ORIGINAL ARTICLE

Edoxaban versus Vitamin K Antagonist for Atrial Fibrillation after TAVR

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ABSTRACT

BACKGROUND

The role of direct oral anticoagulants as compared with vitamin K antagonists for atrial fibrillation after successful transcatheter aortic-valve replacement (TAVR) has not been well studied.

METHODS

We conducted a multicenter, prospective, randomized, open-label, adjudicator-masked trial comparing edoxaban with vitamin K antagonists in patients with prevalent or incident atrial fibrillation as the indication for oral anticoagulation after successful TAVR. The primary efficacy outcome was a composite of adverse events consisting of death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolism, valve thrombosis, or major bleeding. The primary safety outcome was major bleeding. On the basis of a hierarchical testing plan, the primary efficacy and safety outcomes were tested sequentially for noninferiority, with noninferiority of edoxaban established if the upper boundary of the 95% confidence interval for the hazard ratio did not exceed 1.38. Superiority testing of edoxaban for efficacy would follow if noninferiority and superiority were established for major bleeding.

RESULTS

A total of 1426 patients were enrolled (713 in each group). The mean age of the patients was 82.1 years, and 47.5% of the patients were women. Almost all the patients had atrial fibrillation before TAVR. The rate of the composite primary efficacy outcome was 17.3 per 100 person-years in the edoxaban group and 16.5 per 100 person-years in the vitamin K antagonist group (hazard ratio, 1.05; 95% confidence interval [CI], 0.85 to 1.31; P=0.01 for noninferiority). Rates of major bleeding were 9.7 per 100 person-years and 7.0 per 100 person-years, respectively (hazard ratio, 1.40; 95% CI, 1.03 to 1.91; P=0.93 for noninferiority); the difference between groups was mainly due to more gastrointestinal bleeding with edoxaban. Rates of death from any cause or stroke were 10.0 per 100 person-years in the edoxaban group and 11.7 per 100 person-years in the vitamin K antagonist group (hazard ratio, 0.85; 95% CI, 0.66 to 1.11).

CONCLUSIONS

In patients with mainly prevalent atrial fibrillation who underwent successful TAVR, edoxaban was noninferior to vitamin K antagonists as determined by a hazard ratio margin of 38% for a composite primary outcome of adverse clinical events. The incidence of major bleeding was higher with edoxaban than with vitamin K antagonists. (Funded by Daiichi Sankyo; ENVISAGE-TAVI AF ClinicalTrials.gov number, NCT02943785.)

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*The ENVISAGE-TAVI AF Investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Atrial fibrillation occurs in approximately 33% of patients after transcatheter aortic-valve replacement (TAVR),[1-7] and oral anticoagulation is generally recommended as treatment. Non–vitamin K oral anticoagulants are frequently used for this purpose instead of vitamin K antagonists.[8] The effects of various antithrombotic strategies to prevent thromboembolic events with atrial fibrillation after TAVR have not been well studied. A randomized trial[9] showed that the addition of clopidogrel to oral anticoagulation in patients undergoing TAVR who had established indications for anticoagulation, predominantly atrial fibrillation, resulted in more bleeding complications. Non–vitamin K oral anticoagulants were prescribed in less than 33% of the patients in that trial; there was no comparison between regimens, and medications were mostly initiated before TAVR.[9]

Edoxaban is an oral, reversible, direct factor Xa inhibitor that was shown to be noninferior to a vitamin K antagonist (warfarin) in the prevention of stroke and other thromboembolic events, with lower rates of bleeding and death from cardiovascular causes, in a general population of patients with atrial fibrillation who were at moderate-to-high thromboembolic risk, but that trial did not include patients with TAVR.[10] An exploratory subgroup analysis involving 191 patients with previous implantation of a bioprosthetic valve, the results of which are reported in a separate article,[11] suggested that clinical outcomes may have been better with edoxaban than with warfarin. The aim of the current Edoxaban versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation (ENVISAGE-TAVI AF) trial was to compare the efficacy and safety of edoxaban with those of vitamin K antagonists in patients with prevalent or incident atrial fibrillation after successful TAVR.

Methods

Trial Design and Oversight

This was a multinational, multicenter, prospective, randomized, open-label, adjudicator-masked trial.[12] It was conducted in accordance with the International Council for Harmonisation and the Declaration of Helsinki. The protocol (available with the full text of this article at NEJM.org) was approved by the ethics committees and corresponding health authorities for all sites. All the patients provided written informed consent before enrollment.

The sponsor, Daiichi Sankyo, contributed to the trial design, conduct, and oversight; data analysis; and manuscript writing. The trial was designed by eight academic authors and one author employed by the sponsor. The manuscript was written by the first three authors and the last author. Confidentiality agreements were in place between all the authors and the sponsor. Academic authors were not restricted in publishing the data. The sponsor covered all costs associated with the trial, including the cost of the anticoagulants and all tests for trial purposes that were not otherwise clinically indicated. Most data analyses were performed by a clinical research organization (Covance) and paid for by the sponsor. All events were documented from sources, including, but not limited to, paper and electronic charts, laboratory and imaging test reports, and death certificates, and were adjudicated by an independent clinical events committee, whose members were unaware of the trial-group assignments. Serious adverse events were reviewed by an independent data and safety monitoring board according to a predefined schedule.

Patient Selection and Randomization

Patients 18 years of age or older with either prevalent or incident atrial fibrillation lasting more than 30 seconds after successful TAVR for severe aortic stenosis were eligible for enrollment. Successful TAVR was defined as correct positioning of any approved transcatheter bioprosthetic aortic valve into the proper anatomical location with the intended valve performance and without unresolved periprocedural complications. Among the key exclusion criteria were coexisting conditions that confer a high risk of bleeding (Table S1 in the Supplementary Appendix, available at NEJM.org).

Before the TAVR procedures, use or nonuse of oral anticoagulants was at the discretion of the treating physicians. Randomization was stratified according to placement or no placement of a coronary stent for which the patient required antiplatelet medication and according to whether the patient met criteria (described below) for adjustment of the edoxaban dose; stratification was performed by means of an interactive Web-response system. Patients were randomly assigned in a 1:1 ratio to receive edoxaban or a vitamin K antagonist (any of the following drugs according

to country availability: warfarin, phenprocoumon, acenocoumarol, or fluindione). Randomization occurred 12 hours to 7 days after TAVR.

TRIAL TREATMENT AND FOLLOW-UP

The edoxaban group received 60 mg once daily; a creatinine clearance (Cockcroft–Gault formula) of 15 to 50 ml per minute, a body weight of 60 kg or less, and the use of certain P-glycoprotein inhibitors were indications for dose adjustment to 30 mg once daily. Edoxaban was supplied by the sponsor to the sites, and vitamin K antagonists were supplied according to local practice. The target international normalized ratio (INR) for the vitamin K antagonist regimen was 2.0 to 3.0 (adjusted to 1.6 to 2.6 for patients ≥70 years of age in Japan). Specified antiplatelet therapy in either trial group was allowed at the treating physician's discretion, including dual antiplatelet therapy for up to 3 months after TAVR or single antiplatelet therapy indefinitely. Patients were followed at 3 months after randomization and every 6 months thereafter (minimum of 6 months up to 36 months); details regarding follow-up and concomitant medications are provided in Section 3 in the Supplementary Appendix and in the protocol.

OUTCOMES

The primary efficacy outcome was the incidence of net adverse clinical events, defined as the composite of death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolic event, valve thrombosis, or major bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition).[13] The primary safety outcome was the incidence of major bleeding, designated according to ISTH definitions as clinically overt bleeding associated with a reduced hemoglobin level, blood transfusion, symptomatic bleeding at a critical site, or death.[13] Secondary outcomes were bleeding as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO), Thrombolysis in Myocardial Infarction (TIMI), and Bleeding Academic Research Consortium (BARC), as well as components of the composite primary outcome; secondary efficacy and safety outcomes are listed in Sections 4.1.2 and 4.2.2 in the statistical analysis plan, available with the protocol. Clinically relevant nonmajor bleeding was defined according to ISTH criteria.[13] (Details on outcome and bleeding definitions are provided in Tables S2 and S3.)

STATISTICAL ANALYSIS

We estimated that 320 events would be needed in approximately 1400 patients to show noninferiority of edoxaban to vitamin K antagonists for the primary outcome with 80% power and a two-sided significance level of 0.05; details on power calculation and statistics are provided in the statistical analysis plan. The primary analyses were performed in the intention-to-treat population. A four-step hierarchical testing strategy was used, sequentially testing edoxaban as compared with vitamin K antagonists for noninferiority for the primary outcome, noninferiority for major bleeding, superiority for major bleeding, and superiority for the primary outcome. For both the primary efficacy and major bleeding outcomes, noninferiority would be established if the upper boundary of the 95% confidence interval for the hazard ratio did not exceed 1.38 (Fig. S1). Superiority testing was based on a two-sided significance level of 0.05. The primary analysis period was the time from randomization to an end-of-treatment visit at 36 months, an end-of-trial visit, the patient's last visit, or death, whichever occurred first.

Cumulative event-free survival was estimated by means of Kaplan–Meier analyses. Cox proportional-hazards regression models were used to analyze the time from randomization to the first occurrence of a trial outcome, with treatment regimen as a main factor and two randomization stratification factors (coronary stent for which the patient required antiplatelet medication and characteristics warranting adjustment of the edoxaban dose) as covariates, to estimate the hazard ratios and 95% confidence intervals. The proportionality assumption was tested by visual inspection of the log-minus-log survival curves of the outcomes, and the proportionality assumption was upheld.

Secondary outcomes were analyzed with the use of the same methods as those described above, with comparisons focused on superiority of edoxaban but without hierarchical analysis. Because of the lack of a prespecified plan for adjustment of confidence intervals for multiple comparisons, no conclusions can be drawn from the secondary outcome results. All other safety outcomes were summarized with the use of descriptive statistics (SAS software, version 9.2 or newer; SAS Institute). Detailed descriptions of all statistical analyses are provided in the statistical analysis plan.

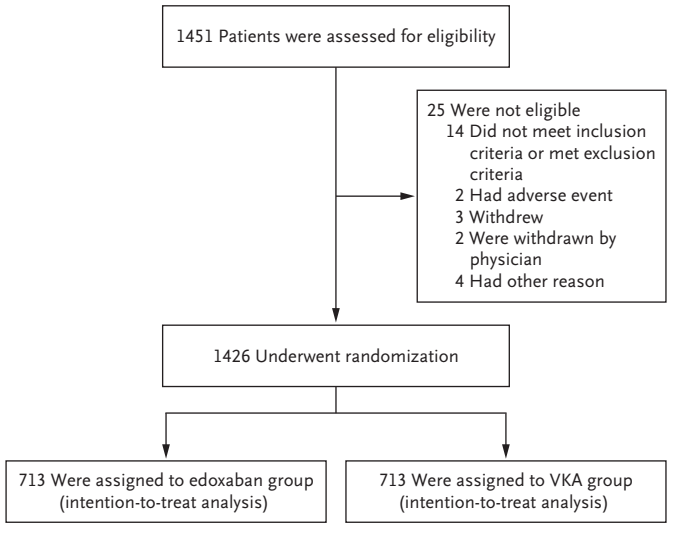

Figure 1. Screening, Randomization, and Treatment.
VKA denotes vitamin K antagonist.

RESULTS

TRIAL POPULATION

From April 2017 through January 2020, a total of 1426 patients with prevalent or incident atrial fibrillation and conventional indications for oral anticoagulants were enrolled after successful TAVR at 173 centers in 14 countries on three continents (Fig. 1 and Table S4). Almost all the patients (99%) had atrial fibrillation before TAVR. A total of 713 patients were assigned to the edoxaban group, and an equal number were assigned to the vitamin K antagonist group. The mean time between TAVR and randomization was 66.6 hours in the edoxaban group and 70.2 hours in the vitamin K antagonist group. The demographic and clinical characteristics of the patients at baseline were similar in the two trial groups (Table 1). The mean age of the patients was 82.1 years, and 47.5% of the patients were women. The mean Society of Thoracic Surgeons

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

Characteristic	Edoxaban (N=713)	Vitamin K Antagonist (N=713)
Age — yr	82.1±5.4	82.1±5.5
Female sex — no. (%)	347 (48.7)	331 (46.4)
Race — no. (%)†		
Asian	92 (12.9)	89 (12.5)
White	593 (83.2)	594 (83.3)
Other	28 (3.9)	30 (4.2)
Weight — kg	74.6±17.9	76.0±17.3
Body-mass index‡	27.5±5.7	27.9±5.4
Creatinine clearance by Cockcroft–Gault formula — ml/min	57.9±24.0	58.6±24.3
Hypertension — no. (%)	647 (90.7)	657 (92.1)
Diabetes mellitus — no. (%)	270 (37.9)	257 (36.0)
Congestive heart failure — no. (%)	591 (82.9)	619 (86.8)
NYHA class III or IV	314 (44.0)	328 (46.0)
Mitral-valve disease — no. (%)	57 (8.0)	60 (8.4)
History of stroke or TIA — no. (%)	123 (17.3)	116 (16.3)
History of coronary artery disease — no. (%)	293 (41.1)	297 (41.7)
Previous CABG	67 (9.4)	60 (8.4)
Previous PCI	176 (24.7)	192 (26.9)
PCI performed within 30 days before TAVR	34 (4.8)	28 (3.9)
Previous myocardial infarction	97 (13.6)	101 (14.2)
Incident (new onset) atrial fibrillation — no. (%)	7 (1.0)	8 (1.1)
CHA_2DS_2-VASc score§		
Mean	4.5±1.4	4.5±1.3
Median (IQR)	4 (4–5)	4 (4–5)

Table 1. (Continued.)

Characteristic	Edoxaban (N=713)	Vitamin K Antagonist (N=713)
STS risk score¶		
Mean	4.8±3.5	5.0±4.1
Distribution — %‖		
<4	53.0	51.5
4–8	34.7	35.5
>8	12.3	13.0
Gastrointestinal disorder — no. (%)	264 (37.0)	242 (33.9)
Previous PPI use — no. (%)	406 (56.9)	393 (55.1)
Pre-TAVR use of non–vitamin K oral anticoagulant — no. (%)**	206 (28.9)	198 (27.8)
Pre-TAVR use of vitamin K antagonist — no. (%)	311 (43.6)	337 (47.3)
No pre-TAVR use of non–vitamin K oral anticoagulant or vitamin K antagonist — no. (%)	196 (27.5)	178 (25.0)
History of labile INR — no. (%)	53 (7.4)	61 (8.6)
Indication for dose adjustment — no. (%)††	330 (46.3)	331 (46.4)
Valve type — no. (%)‡‡		
Any balloon-expandable valve	342 (48.0)	335 (47.0)
Intraannular self-expanding valve	46 (6.5)	49 (6.9)
Supraannular self-expanding valve	325 (45.6)	328 (46.0)

* Plus–minus values are means ±SD. Medical history was coded with the use of the Medical Dictionary for Regulatory Activities. Percentages may not total 100 because of rounding. CABG denotes coronary-artery bypass grafting, INR international normalized ratio, IQR interquartile range, NYHA New York Heart Association, PCI percutaneous coronary intervention, PPI proton-pump inhibitor, TAVR transcatheter aortic-valve replacement, and TIA transient ischemic attack.
† Race was reported by the investigator from information obtained from patient history. "Other" includes patients of another race and those who chose not to report race.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The CHA_2DS_2-VASc is a measure of the risk of stroke among persons with atrial fibrillation. Weighted scores are based on the presence of congestive heart failure, hypertension, diabetes mellitus, or vascular disease; a history of stroke or TIA; 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.
¶ Scoring on the risk model of the Society of Thoracic Surgeons (STS) uses an algorithm that is based on the presence of coexisting illnesses in order to predict 30-day operative mortality. The STS score equals the predicted mortality expressed as a percentage.
‖ Percentages of patients were calculated on the basis of the total number of patients with data available on the STS score.
** Non–vitamin K oral anticoagulants included rivaroxaban, apixaban, dabigatran, and edoxaban.
†† Indications for adjustment of the edoxaban dose included a creatinine clearance of 50 ml or less per minute, a body weight of 60 kg or less (not used as an indication in U.S. patients), and concomitant therapy with a P-glycoprotein inhibitor (not used as an indication in U.S. patients).
‡‡ Valve type was not reported for one patient in the vitamin K antagonist group.

risk score (predicted 30-day mortality) was 4.9%, and the mean CHA_2DS_2-VASc score (range, 0 to 9, with higher scores indicating greater risk of embolic events) was 4.5. There was concomitant use of oral antiplatelet agents before randomization in 328 patients (46.0%) in the edoxaban group and in 359 patients (50.4%) in the vitamin K antagonist group. At trial entry, 46.4% of the overall trial population met any of the criteria for adjustment of the edoxaban dose and received reduced doses.

The median duration of follow-up was 554 days in the edoxaban group and 530 days in the vitamin K antagonist group. The mean and median percent of time of INR within the therapeutic range in the vitamin K antagonist group were 63.5% and 68.2%, respectively (Fig. S2). During the entire trial period, 215 patients (30.2%) in the edoxaban group discontinued the trial drug, as compared with 289 patients (40.5%) in the vitamin K antagonist group (Table S5 and Fig. S3). Use of con-

Table 2. Efficacy and Safety Outcomes (Intention-to-Treat Population).*

Outcome	Edoxaban (N=713)	Vitamin K Antagonist (N=713)	Hazard Ratio (95% CI)
	no. of patients (rate per 100 person-yr)		
Primary efficacy outcome: net adverse clinical events†	170 (17.3)	157 (16.5)	1.05 (0.85–1.31)‡
Primary safety outcome: major bleeding§	98 (9.7)	68 (7.0)	1.40 (1.03–1.91)¶
Secondary outcomes			
Death from any cause	85 (7.8)	93 (9.1)	0.86 (0.64–1.15)
Death from cardiovascular causes	49 (4.5)	46 (4.5)	1.00 (0.67–1.50)
Ischemic stroke	22 (2.1)	28 (2.8)	0.75 (0.43–1.30)
Myocardial infarction	12 (1.1)	7 (0.7)	1.65 (0.65–4.14)
Systemic thromboembolic event	2 (0.2)	3 (0.3)	Not calculated
Valve thrombosis§	0	0	Not calculated
Any stroke	29 (2.7)	35 (3.5)	0.78 (0.48–1.28)
Major adverse cardiac or cerebrovascular event‖	86 (8.2)	80 (8.1)	1.02 (0.76–1.39)
Major adverse cardiac event**	61 (5.7)	53 (5.2)	1.10 (0.76–1.58)
Fatal bleeding§	11 (1.0)	10 (1.0)	Not calculated
Life-threatening bleeding	17 (1.6)	19 (1.9)	Not calculated
Intracranial hemorrhage	16 (1.5)	21 (2.1)	0.72 (0.38–1.39)
Clinically relevant nonmajor bleeding§	164 (18.2)	142 (16.4)	1.13 (0.90–1.14)

* The two noninferiority tests with respect to net adverse clinical events (primary efficacy outcome) and major bleeding (primary safety outcome) were the initial two steps of hierarchical testing. Because the second step failed, no further testing for superiority was performed.
† Net adverse clinical events were defined as a composite of death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolic event, valve thrombosis, or major bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition).
‡ P=0.01 for noninferiority.
§ The ISTH definition was used.
¶ P=0.93 for noninferiority.
‖ Major adverse cardiac and cerebrovascular events were defined as the composite of death from cardiovascular causes (including sudden, unexplained, and unwitnessed death), myocardial infarction, stroke (ischemic, hemorrhagic, or undetermined), or repeat coronary revascularization of the target lesion.
** Major adverse cardiac events were defined as the composite of death from cardiovascular causes (including sudden, unexplained, and unwitnessed death), myocardial infarction, or repeat coronary revascularization of the target lesion.

comitant antiplatelet therapy is summarized in Table S6.

EFFICACY AND SAFETY OUTCOMES

In the intention-to-treat analysis, a net adverse clinical event (primary efficacy outcome) occurred in 170 patients (17.3 per 100 person-years) in the edoxaban group and in 157 patients (16.5 per 100 person-years) in the vitamin K antagonist group (hazard ratio, 1.05; 95% confidence interval [CI], 0.85 to 1.31; noninferiority margin, 1.38; P=0.01 for noninferiority) (Table 2 and Figs. 2 and 3). Major bleeding (primary safety outcome) occurred in 98 patients (9.7 per 100 person-years) in the edoxaban group and in 68 patients (7.0 per 100 person-years) in the vitamin K antagonist group (hazard ratio, 1.40; 95% CI, 1.03 to 1.91; noninferiority margin, 1.38; P=0.93 for noninferiority). The hierarchical testing failed at this step; hence, formal testing for superiority was not performed.

The rate of intracranial hemorrhage was 1.5 per 100 person-years in the edoxaban group and 2.1 per 100 person-years in the vitamin K antagonist group, and the rate of fatal bleeding was 1.0 per 100 person-years in both trial groups (Table 2). More patients in the edoxaban group than in the vitamin K antagonist group had major

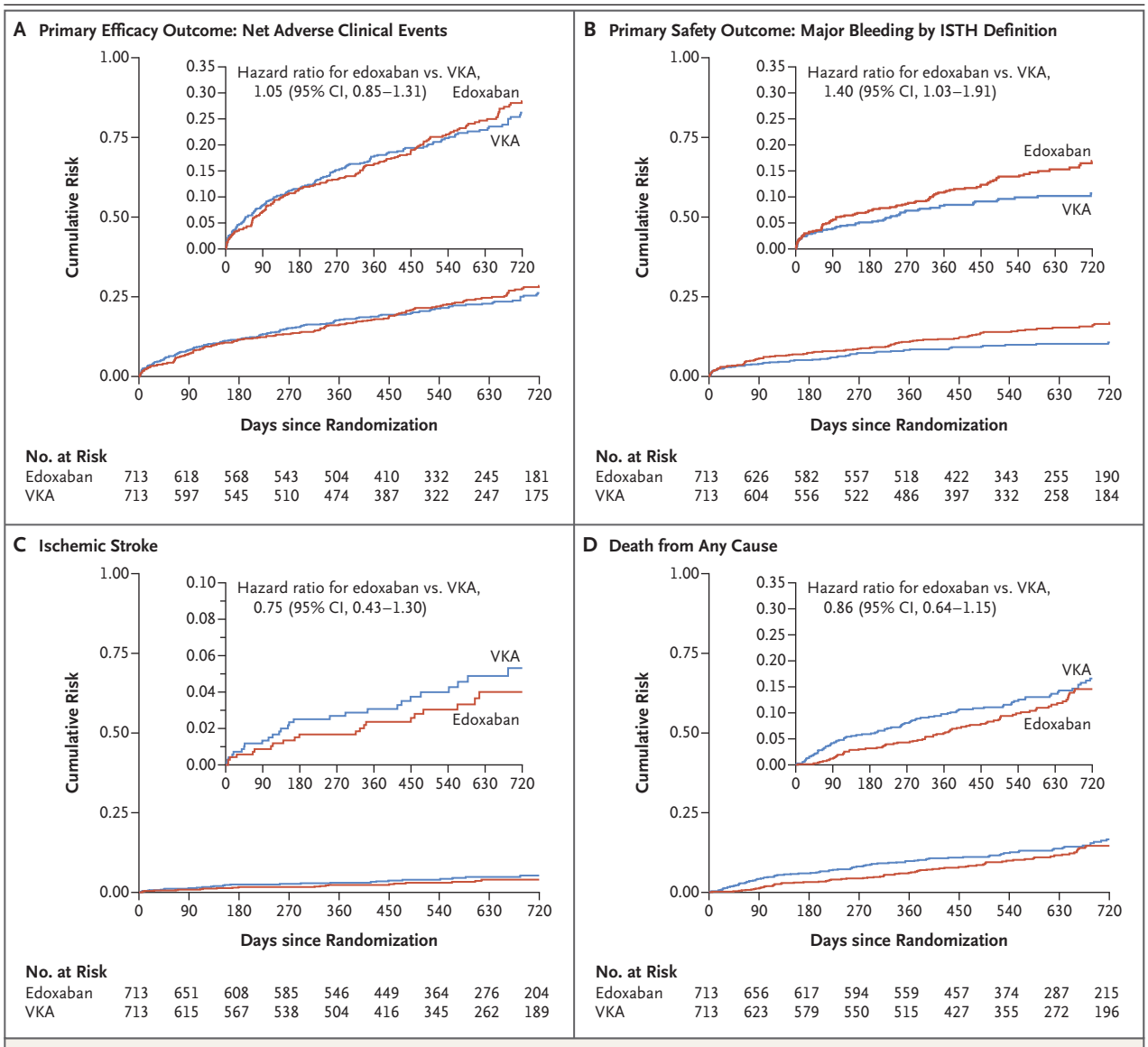

Figure 2. Kaplan–Meier Curves for the Primary Outcomes and Other Outcomes (Intention-to-Treat Population).

Net adverse clinical events were defined as a composite of death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolic event, valve thrombosis, or major bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition). Insets show the same data on an enlarged y axis.

gastrointestinal bleeding (56 [5.4 per 100 person-years] vs. 27 [2.7 per 100 person-years]; hazard ratio, 2.03; 95% CI, 1.28 to 3.22), despite similar incidences of administration of proton-pump inhibitors (71.7% and 69.0%, respectively); one case of major gastrointestinal bleeding was fatal in the edoxaban group. Among patients with major gastrointestinal bleeding, 46 of 56 (82%) in the edoxaban group and 26 of 27 (96%) in the vitamin K antagonist group received proton-pump inhibitors.

Death from any cause occurred in 85 patients (7.8 per 100 person-years) in the edoxaban group and in 93 patients (9.1 per 100 person-years) in the vitamin K antagonist group (hazard ratio, 0.86; 95% CI, 0.64 to 1.15). The rate of ischemic stroke was 2.1 per 100 person-years and 2.8 per 100 person-years, respectively (hazard ratio, 0.75;

Event	Edoxaban	VKA
	rate per 100 person-yr (no. of patients/total no.)	
Net adverse clinical events	17.3 (170/713)	16.5 (157/713)
Major bleeding	9.7 (98/713)	7.0 (68/713)
Ischemic stroke	2.1 (22/713)	2.8 (28/713)
Myocardial infarction	1.1 (12/713)	0.7 (7/713)
Death from any cause	7.8 (85/713)	9.1 (93/713)

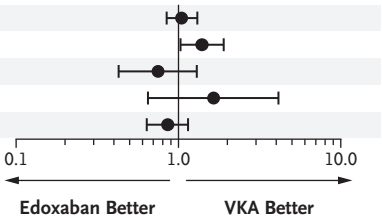

Figure 3. Hazard Ratio for the Primary Efficacy Outcome and Its Components (Intention-to-Treat Population).

Hazard ratios and confidence intervals for the comparison of edoxaban with VKA are based on the Cox proportional-hazards regression model including treatment group, transcatheter aortic-valve replacement procedure undergone with stenting (yes or no), and indication for dose adjustment (yes or no) as covariates. Major bleeding was defined according to ISTH criteria. Two components of the composite outcome of net adverse clinical events — systemic thromboembolic event and valve thrombosis — are not shown because fewer than five patients had an event in each treatment group.

95% CI, 0.43 to 1.30). The rate of myocardial infarction was 1.1 per 100 person-years and 0.7 per 100 person-years, respectively. Systemic thromboembolic events were rare (0.2 per 100 person-years in the edoxaban group and 0.3 per 100 person-years in the vitamin K antagonist group), and no cases of valve thrombosis occurred (Table 2). The rate of death from any cause or stroke was 10.0 per 100 person-years in the edoxaban group and 11.7 per 100 person-years in the vitamin K antagonist group (hazard ratio, 0.85; 95% CI, 0.66 to 1.11). Composite outcome measures, including major adverse cardiac and cerebrovascular events, are reported in Table 2.

The results of prespecified subgroup analyses are provided in Figures S4 and S5; however, the trial was underpowered for these analyses, and results are exploratory. Secondary efficacy and safety results are shown in Tables S7 and S10, respectively. The results regarding the two primary outcomes were concordant when other bleeding scales were applied; anticoagulation after trial treatment is summarized in Table S8. Causes of death are reported in Table S9.

CONCOMITANT ANTIPLATELET DRUGS AND EDOXABAN DOSE ADJUSTMENT

A prespecified exploratory analysis compared treatment effects of edoxaban with those of vitamin K antagonists in patients with or without criteria for adjustment of the edoxaban dose. Rates of net adverse clinical events were similar in the edoxaban group and the vitamin K antagonist group, regardless of whether these criteria were met (Fig. S6). Among patients who met these criteria, rates of major bleeding were similar in the edoxaban group and the vitamin K antagonist group (9.7 per 100 person-years and 7.9 per 100 person-years, respectively; hazard ratio, 1.25; 95% CI, 0.80 to 1.97). Rates of death from any cause were 8.1 per 100 person-years in the edoxaban group and 12.7 per 100 person-years in the vitamin K antagonist group (hazard ratio, 0.64; 95% CI, 0.43 to 0.96); rates of death from noncardiovascular causes were 3.3 per 100 person-years and 6.4 per 100 person-years, respectively (hazard ratio, 0.52; 95% CI, 0.28 to 0.96). Among patients who did not meet these criteria, rates of major bleeding were 9.7 per 100 person-years in the edoxaban group and 6.3 per 100 person-years in the vitamin K antagonist group (hazard ratio, 1.54; 95% CI, 1.00 to 2.35); rates of death from any cause were 7.6 per 100 person-years and 6.3 per 100 person-years, respectively (hazard ratio, 1.20; 95% CI, 0.78 to 1.85). Results of exploratory 90-day landmark analyses are presented in Figs. S7 through S9. Post hoc analyses of rates of the primary efficacy and safety outcomes in the two trial groups according to antiplatelet therapy as prescribed at randomization are shown in Fig. S10.

DISCUSSION

The ENVISAGE-TAVI AF trial compared the efficacy and safety of edoxaban with those of vitamin K antagonists in patients with prevalent or

incident atrial fibrillation after successful TAVR. Edoxaban was noninferior to vitamin K antagonists with respect to the composite primary efficacy outcome on the basis of an upper boundary of the 95% confidence interval for the hazard ratio that was less than the protocol-defined noninferiority margin of 1.38. However, edoxaban failed noninferiority testing regarding the rate of major bleeding, which was due mainly to more major gastrointestinal bleeding in the edoxaban group. The incidences of intracranial hemorrhage or fatal bleeding were low and were similar in the two trial groups. Because of the hierarchical design of our statistical analysis, the failure to show noninferiority for major bleeding precluded formal testing for superiority of edoxaban, but the point estimate for the hazard ratio favored vitamin K antagonists and the confidence interval included 1, indicating that superiority of edoxaban would not have been shown. Results for composite outcome measures including major adverse cardiac and cerebrovascular events were similar in the two trial groups. The patients in our trial did not have valve thrombosis, which may be compatible with the low incidence observed in recent trials of TAVR in low-risk patients.[6,7] Among patients who received specified concomitant antiplatelet therapy, edoxaban was associated with a higher incidence of major bleeding than vitamin K antagonists.

The 2020 American Heart Association–American College of Cardiology guideline for the management of valvular heart disease acknowledged the paucity of data to support non–vitamin K oral anticoagulants for atrial fibrillation within 3 months after implantation of a surgical or transcatheter bioprosthetic valve.[14] Antithrombotic regimens after TAVR have been investigated in randomized, controlled trials.[9,15-17] A trial of intermediate-dose rivaroxaban in patients without an indication for oral anticoagulation but who were receiving antiplatelet therapy showed increased risks of major bleeding and death as compared with control.[16,17] A randomized trial that evaluated clopidogrel in addition to oral anticoagulation after TAVR in patients with an indication for oral anticoagulation showed that the combination regimen was associated with more bleeding than oral anticoagulation monotherapy and had no clinical benefits.[9,18] Overall, in the current trial, edoxaban was associated with more cases of major bleeding than vitamin K antagonists. Subtherapeutic INR values and a higher incidence of drug discontinuation in the vitamin K antagonist group may have affected the bleeding outcomes. Concomitant antiplatelet therapy was specified before randomization in approximately 50% of the patients. A post hoc analysis showed that patients who received antiplatelet therapy may have had higher bleeding rates with edoxaban than with vitamin K antagonists, as opposed to similar bleeding rates among patients without specified antiplatelet therapy, but these comments are exploratory only. The routine use of concomitant antiplatelet therapy in addition to oral anticoagulant therapy is no longer recommended.[19] Patients who met the criteria for dose adjustment during the trial and received edoxaban at a dose of 30 mg once daily had similar incidences of net adverse clinical events and major bleeding as those who received vitamin K antagonists.

Trials and studies have shown a better benefit–risk profile with non–vitamin K oral anticoagulants than with vitamin K antagonists in patients with nonvalvular atrial fibrillation.[10,20-22] However, the patient populations of these trials differed from that of the ENVISAGE-TAVI AF trial with respect to factors such as a younger mean age by approximately a decade, a lower prevalence of heart failure, and a limited number of patients with bioprosthetic valves; therefore, no direct comparisons of edoxaban and vitamin K antagonists can be made between these trials and ours. Acquired von Willebrand's disease and arteriovenous malformations may also contribute to gastrointestinal bleeding in patients with severe aortic stenosis.[23]

Our trial had an open-label design that entailed a risk of reporting bias regarding the trial outcomes. The coronavirus disease 2019 pandemic affected the outpatient clinic follow-up routine and may have resulted in underassessment of laboratory data and mild-to-moderate clinical events. The outcomes of death and trial-drug discontinuation may have been competing risks in relation to the outcomes we studied, and we did not perform competing-risk analyses. Our trial results apply only to patients with atrial fibrillation, intermediate operative risk, and symptomatic aortic stenosis, and the trial involved a population of older adults who were undergoing TAVR. These results may not apply to younger patients at lower operative risk, patients with asymptomatic aortic stenosis, and those undergoing concomitant percutaneous coronary in-

tervention. Almost all the patients who were enrolled in the trial had atrial fibrillation before TAVR.

In our trial involving patients who had an indication for oral anticoagulation for atrial fibrillation after successful TAVR, edoxaban was noninferior to vitamin K antagonists for the composite primary outcome of adverse clinical events. Edoxaban was associated with a higher risk of major bleeding than vitamin K antagonists.

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APPENDIX

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