# Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes

P. Kirchhof, T. Toennis, A. Goette, A.J. Camm, H.C. Diener, N. Becher, E. Bertaglia, C. Blomstrom Lundqvist, M. Borlich, A. Brandes, N. Cabanelas, M. Calvert, G. Chlouverakis, G.-A. Dan, J.R. de Groot, W. Dichtl, B. Kravchuk, A. Lubiński, E. Marijon, B. Merkely, L. Mont, A.-K. Ozga, K. Rajappan, A. Sarkozy, D. Scherr, R. Sznajder, V. Velchev, D. Wichterle, S. Sehner, E. Simantirakis, G.Y.H. Lip, P. Vardas, U. Schotten, and A. Zapf, for the NOAH-AFNET 6 Investigators*

## ABSTRACT

### BACKGROUND

Device-detected atrial high-rate episodes (AHREs) are atrial arrhythmias detected by implanted cardiac devices. AHREs resemble atrial fibrillation but are rare and brief. Whether the occurrence of AHREs in patients without atrial fibrillation (as documented on a conventional electrocardiogram [ECG]) justifies the initiation of anticoagulants is not known.

### METHODS

We conducted an event-driven, double-blind, double-dummy, randomized trial involving patients 65 years of age or older who had AHREs lasting for at least 6 minutes and who had at least one additional risk factor for stroke. Patients were randomly assigned in a 1:1 ratio to receive edoxaban or placebo. The primary efficacy outcome was a composite of cardiovascular death, stroke, or systemic embolism, evaluated in a time-to-event analysis. The safety outcome was a composite of death from any cause or major bleeding.

### RESULTS

The analysis population consisted of 2536 patients (1270 in the edoxaban group and 1266 in the placebo group). The mean age was 78 years, 37.4% were women, and the median duration of AHREs was 2.8 hours. The trial was terminated early, at a median follow-up of 21 months, on the basis of safety concerns and the results of an independent, informal assessment of futility for the efficacy of edoxaban; at termination, the planned enrollment had been completed. A primary efficacy outcome event occurred in 83 patients (3.2% per patient-year) in the edoxaban group and in 101 patients (4.0% per patient-year) in the placebo group (hazard ratio, 0.81; 95% confidence interval [CI], 0.60 to 1.08; P=0.15). The incidence of stroke was approximately 1% per patient-year in both groups. A safety outcome event occurred in 149 patients (5.9% per patient-year) in the edoxaban group and in 114 patients (4.5% per patient-year) in the placebo group (hazard ratio, 1.31; 95% CI, 1.02 to 1.67; P=0.03). ECG-diagnosed atrial fibrillation developed in 462 of 2536 patients (18.2% total, 8.7% per patient-year).

### CONCLUSIONS

Among patients with AHREs detected by implantable devices, anticoagulation with edoxaban did not significantly reduce the incidence of a composite of cardiovascular death, stroke, or systemic embolism as compared with placebo, but it led to a higher incidence of a composite of death or major bleeding. The incidence of stroke was low in both groups. (Funded by the German Center for Cardiovascular Research and others; NOAH-AFNET 6 ClinicalTrials.gov number, NCT02618577; ISRCTN number, ISRCTN17309850.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Kirchhof can be contacted at p.kirchhof@uke.de or at the Department of Cardiology, University Heart and Vascular Center Hamburg, University Medical Center Hamburg–Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany.

*A complete list of the NOAH-AFNET 6 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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ORAL ANTICOAGULATION WITH THE USE of vitamin K antagonists[1] or direct-acting, non–vitamin K antagonist oral inhibitors of factor II or Xa[2] (NOACs) reduces the risk of ischemic stroke among patients with atrial fibrillation. The non–vitamin K antagonists are currently preferred over vitamin K antagonists, since they are associated with a lower risk of bleeding.[2,3] Oral anticoagulant therapy is often initiated only after a stroke in patients with atrial fibrillation.[4,5] Systematic rhythm monitoring for the detection of atrial fibrillation can enable earlier detection of atrial fibrillation and initiation of anticoagulant therapy.[6,7] Implanted cardiac devices allow the continuous monitoring of cardiac rhythm. They can record short episodes of atrial arrhythmias by means of intracardiac or subcutaneous sensors. Arrhythmias detected by this type of continuous rhythm monitoring are referred to as subclinical atrial fibrillation or atrial high-rate episodes (AHREs). Because cardiac electrical activity recorded during AHREs resembles that recorded during atrial fibrillation,[8] some clinicians have initiated oral anticoagulant therapy in patients with AHREs, especially in those who have several clinical risk factors for stroke or in those who have AHREs that last longer than 24 hours.[8] Owing to their rarity and episodic nature, AHREs typically remain undiagnosed in patients who are not undergoing long-term rhythm monitoring.[9]

In the absence of atrial fibrillation, oral anticoagulation has generally not been effective for the prevention of stroke in patients who have had an embolic stroke of unknown source[10,11] or in those with heart failure.[12,13] We conducted the NOAH-AFNET 6 trial (Non–Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes) to compare the efficacy and safety of oral anticoagulant therapy with the non–vitamin K antagonist edoxaban with the efficacy and safety of no anticoagulation in patients with AHREs who had clinical risk factors for stroke.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

This investigator-initiated, double-blind, double-dummy, randomized trial was conducted in 18 European countries. Details of the trial design have been described previously.[14] The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. The protocol was approved by the institutional review boards at each participating site. All the patients provided written informed consent before enrollment. The trial was designed and overseen by a steering committee. During the trial, the steering committee was supported by a national coordinators committee. The trial was conducted in accordance with the principles of the Declaration of Helsinki and with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Details regarding the participating sites and committee members are provided in the Supplementary Appendix, available at NEJM.org. An independent data and safety monitoring board guided the trial. All reports of serious adverse events were adjudicated by an independent outcome review committee whose members were unaware of the trial-group assignments.

The trial was planned by the steering committee and the Atrial Fibrillation Network (AFNET). AFNET is a nonprofit academic research organization that conducts investigator-initiated clinical research projects with support from public funders and industry partners. AFNET conducted the trial, with support from the trial committees, in collaboration with a contract research organization (CRI — the Clinical Research Institute, Munich, Germany). The contract research organization and the trial sites used the Marvin electronic data management system (XClinical). The Institute of Medical Biometry and Epidemiology at the University Medical Center Hamburg–Eppendorf was the core statistical unit. Daiichi Sankyo Europe, the manufacturer of edoxaban, provided the doses of edoxaban and placebo to AFNET. Daiichi Sankyo Europe and the German Center for Cardiovascular Research funded the trial but did not participate in the trial design, data collection, or data analysis, nor in the decision to submit the manuscript for publication. There were no agreements between the investigators and Daiichi Sankyo Europe. The first author wrote the first draft of the manuscript, and all the authors contributed to the review and revision of subsequent versions of the manuscript. All the voting members of the steering committee (see the Supplementary Appendix) vouch for the accuracy and completeness

of the data and for the fidelity of the trial to the protocol.

### PATIENTS

Eligible patients were 65 years of age or older with AHREs detected by implanted devices and no history of atrial fibrillation as documented on an electrocardiogram (ECG). Qualifying AHREs could be captured by pacemakers, defibrillators, resynchronization devices, or implanted loop recorders with long-term rhythm-monitoring capabilities. Patients had to have AHREs at least 2 months after implantation of the device. A qualifying AHRE had to involve an atrial rate of at least 170 beats per minute and had to last 6 minutes or longer; there was no upper limit of duration of the AHRE.[14] Approximately 10 to 30% of patients with implanted devices are estimated to have AHREs that last longer than 5 or 6 minutes.[8] Patients were also required to have one or more of the following risk factors for stroke: heart failure, hypertension, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease (previous myocardial infarction, aortic plaque, or peripheral, carotid, or cerebral arterial disease), or an age of 75 years or older.[14] Exclusion criteria were atrial fibrillation as documented on an ECG; acute coronary syndrome, percutaneous coronary intervention, or coronary bypass surgery within 30 days before enrollment; a life expectancy of less than 12 months; a contraindication to oral anticoagulation or to edoxaban; an indication for dual antiplatelet therapy; and other indications for oral anticoagulation.

Clinical characteristics, a medical assessment, information on current medications and concomitant conditions, an ECG, information on quality of life and functional status, and eligibility for edoxaban dose reduction and the use of acetylsalicylic acid therapy were obtained at baseline. All serious adverse events were reported by site personnel as soon as they became aware of them. The reporting of such events could be triggered by a hospital admission, by contact with the patient or the patient's relative during the scheduled visits or during a telephone call, or by other sources. The date of each event was determined on the basis of interview of the patient and review of medical records and was adjudicated. Follow-up visits were scheduled every 6 months and included a medical assessment, capturing of AHREs from implantable devices, an ECG, assessment of criteria for edoxaban dose reduction and indication for acetylsalicylic acid, and dispensing of doses of edoxaban or placebo. Trial sites actively sought out patients with AHREs and aimed for rapid enrollment of these patients after documentation of this rhythm disturbance. Because screening logs were available only from some trial sites, the total number of patients screened for enrollment is not known.

### INTERVENTION

Eligible patients were randomly assigned in a 1:1 ratio to receive edoxaban (anticoagulation) or placebo in a double-blind, double-dummy design. Randomization was performed with the use of blocks of variable size and was stratified according to the indication for acetylsalicylic acid therapy.

Anticoagulation consisted of the factor Xa inhibitor edoxaban at the dose approved for the prevention of stroke in patients with atrial fibrillation (60 mg once daily). Criteria for a dose reduction to 30 mg once daily, as approved by European regulatory authorities (a body weight of ≤60 kg, a creatinine clearance of 15 to 50 ml per minute, or the concomitant use of strong P-glycoprotein inhibitors), were assessed at the baseline visit and at each subsequent visit, and appropriate dose adjustments were made. Doses of edoxaban and placebo were dispensed in quantities that were anticipated to be adequate for 6 months. The placebo group received a double-dummy placebo tablet that contained either no active compound or acetylsalicylic acid at a dose of 100 mg daily; the tablet that a patient received was determined on the basis of the accepted indications for the use of acetylsalicylic acid, which included peripheral or coronary artery disease, a previous myocardial infarction, or a previous stroke. Eligibility for the receipt of acetylsalicylic acid therapy was determined by the investigator at the baseline visit and each time the trial drug was dispensed.

### OUTCOMES

The primary efficacy outcome was a first occurrence of a composite of cardiovascular death, stroke, or systemic embolism, evaluated in a time-to-event analysis.[14] The safety outcome was a composite of death from any cause or major

bleeding, as defined by the International Society on Thrombosis and Hemostasis.[14,15] Data on all potential serious adverse events and adverse events of special interest were centrally adjudicated by a committee whose members were unaware of the trial-group assignments.

Key secondary outcomes were the individual components of the primary efficacy outcome and the safety outcome, a composite of stroke or systemic embolism, cognitive function as assessed by the Montreal Cognitive Assessment, quality of life as assessed by the EuroQol Group 5-Dimension 5-Level questionnaire (EQ-5D-5L), patient satisfaction and symptoms as assessed by the Perception of Anticoagulant Treatment questionnaire, and functional status as assessed by the Karnofsky performance-status score.[14] Patient-reported outcomes were recorded on paper by the patients.

### STATISTICAL ANALYSIS

The trial was designed as an event-driven trial.[14] On the basis of event rates reported in previous trials (see the Supplementary Appendix), the primary efficacy outcome was tested for a difference between the groups at an overall two-sided type I error rate of 5%. The sample size was initially estimated to be 3400 patients and was subsequently reduced to 2538 patients on the basis of a planned, blinded interim analysis that was performed after 1000 patient-years of follow-up; no alpha was spent as a result of this analysis.[14] The overall event rate at that time point (4.6% per patient-year) was not markedly different from the expected rate. We estimated that approximately 220 primary efficacy outcome events would need to occur to provide the trial with 80% power to detect a difference between the trial groups. The sample size was calculated on the basis of an enrollment period of 71 months (adjusted from 54 months during the planned interim analysis), a 32% risk reduction in the occurrence of a primary efficacy outcome event with edoxaban as compared with placebo (an assumed hazard ratio of 0.68), a hazard rate of 0.02 for the competing event of noncardiovascular death, and a hazard rate of 0.287 for the development of overt atrial fibrillation.[14] At the outset of the trial, the data and safety monitoring board decided to use the Haybittle–Peto stopping boundary for the assessment of efficacy and to apply a general judgment

of all available evidence for the assessment of safety.

Categorical data are summarized as numbers and percentages. Continuous data are summarized as mean values with standard deviations or as median values with interquartile ranges, as appropriate. The analyses of the primary efficacy outcome and the safety outcome were performed in the modified intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of edoxaban or placebo. For the primary efficacy analysis, data were censored at the time of development of atrial fibrillation (as documented on an ECG), loss to follow-up, withdrawal of consent, or unblinding of the trial-group assignment. All the data from the trial sites in Ukraine were censored on February 24, 2022, the start of the Russian invasion.

For the primary efficacy analysis, we used a cause-specific Cox proportional hazards model, along with the Breslow method to handle tied time points for events, with a frailty term for trial site, the trial-group assignment as a predictor variable, and the randomization strata indication for acetylsalicylic acid as a covariate. This analysis was performed under the assumption of independent censoring. The proportional hazards assumption was confirmed with the use of graphical methods. The outcome results are reported as group-specific event rates in percentage per patient-years and as adjusted estimated cause-specific hazard ratios with a two-sided 95% confidence interval and corresponding P value. Cumulative incidence curves were generated with the use of the Aalen–Johansen estimator, which takes into account competing events; otherwise, Kaplan–Meier curves were used.

The time-to-event secondary outcomes were analyzed in the same way as the primary efficacy outcome. There was no prespecified plan for adjustment of the widths of the confidence intervals with respect to the differences between the groups in the secondary outcomes, and no definitive conclusions can be drawn from these data. The analyses of the continuous secondary outcomes were based on the differences between the baseline values and the follow-up values at 12 and 24 months. Therefore, negative values reflect a decrease from baseline. Mean differences were estimated with the use of a linear mixed-effects regression model with a restricted

maximum-likelihood approach and with the use of the Newton–Raphson algorithm. The interaction between the follow-up time points (12 and 24 months) and the trial-group assignment was estimated if the P value for the interaction was less than 0.05; otherwise, the independent effects of the follow-up time points and the trial-group assignment were estimated, with each adjusted for the respective baseline values and indication for acetylsalicylic acid at randomization. The dependency structure of the time points was modeled by including the trial site as a random effect, and each patient was nested within the trial site. A common unstructured covariance matrix was used to model the variability within a patient. Denominator degrees of freedom were estimated with the use of the containment method.

All the time-to-event outcomes were also analyzed for the safety population (which included all the patients who underwent randomization) and for the per-protocol population. The per-protocol analysis estimated the effect of edoxaban in patients who exactly met all the inclusion and exclusion criteria, took the doses of edoxaban or placebo predominantly as scheduled, and did not take any other oral anticoagulant or antiplatelet agent, under the assumption that the occurrence of protocol deviations was independent from the trial-group assignment. Two sensitivity analyses of the primary efficacy outcome evaluated only patients who met the inclusion criteria regarding AHREs at baseline (as verified by an independent laboratory) and only patients who did not withdraw their consent. The effect of the following causes of censoring of data was assessed in the modified intention-to-treat population: permanent discontinuation of edoxaban or placebo, coronavirus disease 2019, and the Russian invasion in Ukraine [on February 24, 2022]). For the primary efficacy outcome, worst-case imputation was used for missing values (e.g., deaths from an unknown cause were classified as cardiovascular deaths).[16] No other imputation was used for the analyses of the primary efficacy outcome and the safety outcome. Secondary outcomes are reported without imputation. All the analyses were conducted with the use of Stata software, version 17.0 (StataCorp), and R software, version 4.2.3 (R Project for Statistical Computing).

## RESULTS

### PATIENTS

Between June 24, 2016, and September 6, 2022, a total of 2608 patients with AHREs underwent randomization across 206 sites in 18 European countries. The modified intention-to-treat population consisted of 2536 patients, including 1270 patients in the edoxaban group and 1266 patients in the placebo group (Fig. 1). The mean age of the patients was 78 years. The median duration of AHREs was 2.8 hours, and AHREs generally showed atrial rates of greater than 200 beats per minute (Table 1). The median number of AHREs was 2.8 in each group. The median $CHA_2DS_2$-VASc score (which is used to predict the risk of ischemic stroke among patients with atrial fibrillation and ranges from 0 to 9, with higher scores indicating a greater risk of stroke) was 4. The numbers of patients who withdrew from the trial before receiving edoxaban or placebo, as well as the demographic and clinical characteristics of the patients at baseline, were similar in the two groups (Table 1 and Fig. 1). The representativeness of the trial population is shown in Table S1 in the Supplementary Appendix. Ethnic group and race were not systematically recorded; the patients were primarily White in the participating sites and countries.

Among the 1270 patients who received edoxaban, 365 (28.7%) met the criteria for a dose reduction to 30 mg once daily at baseline (Fig. 1). Discontinuation of edoxaban occurred after a median of 16.8 months (interquartile range, 6.1 to 30.0). A total of 134 patients in the edoxaban group withdrew their consent, and atrial fibrillation developed in 232 of 2674 patients (8.7% per patient-year) (Fig. 1). Among the 1266 patients in the placebo group, 683 (53.9%) received acetylsalicylic acid. Discontinuation of placebo occurred after a median of 16.7 months (interquartile range, 6.2 to 31.4). A total of 134 patients in the placebo group withdrew their consent, and atrial fibrillation developed in 230 of 2622 patients (8.8% per patient-year). There were no missing data in the modified intention-to-treat population with respect to the primary efficacy outcome or the safety outcome.

### PRIMARY OUTCOMES

On the basis of recommendations from the data and safety monitoring board and the steering
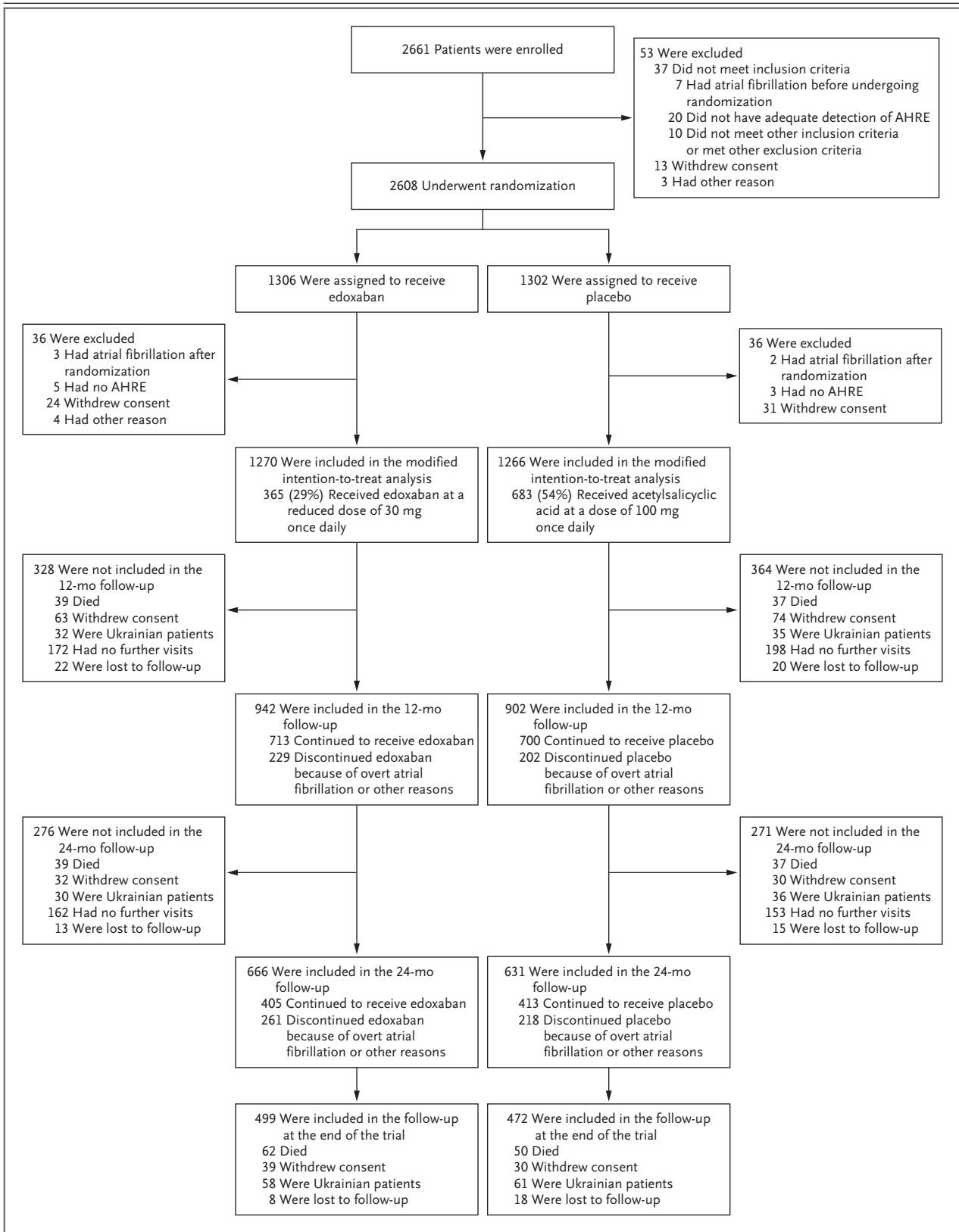
2661 Patients were enrolled

53 Were excluded
  37 Did not meet inclusion criteria
   7 Had atrial fibrillation before undergoing
     randomization
  20 Did not have adequate detection of AHRE
  10 Did not meet other inclusion criteria
     or met other exclusion criteria
  13 Withdrew consent
   3 Had other reason

2608 Underwent randomization

1306 Were assigned to receive edoxaban

1302 Were assigned to receive placebo

36 Were excluded
  3 Had atrial fibrillation after
    randomization
  5 Had no AHRE
 24 Withdrew consent
  4 Had other reason

36 Were excluded
  2 Had atrial fibrillation after
    randomization
  3 Had no AHRE
 31 Withdrew consent

1270 Were included in the modified
    intention-to-treat analysis
 365 (29%) Received edoxaban at a
    reduced dose of 30 mg
    once daily

1266 Were included in the modified
    intention-to-treat analysis
 683 (54%) Received acetylsalicyclic
    acid at a dose of 100 mg
    once daily

328 Were not included in the
    12-mo follow-up
 39 Died
 63 Withdrew consent
 32 Were Ukrainian patients
 172 Had no further visits
 22 Were lost to follow-up

364 Were not included in the
    12-mo follow-up
 37 Died
 74 Withdrew consent
 35 Were Ukrainian patients
 198 Had no further visits
 20 Were lost to follow-up

942 Were included in the 12-mo
    follow-up
 713 Continued to receive edoxaban
 229 Discontinued edoxaban
    because of overt atrial
    fibrillation or other reasons

902 Were included in the 12-mo
    follow-up
 700 Continued to receive placebo
 202 Discontinued placebo
    because of overt atrial
    fibrillation or other reasons

276 Were not included in the
    24-mo follow-up
 39 Died
 32 Withdrew consent
 30 Were Ukrainian patients
 162 Had no further visits
 13 Were lost to follow-up

271 Were not included in the
    24-mo follow-up
 37 Died
 30 Withdrew consent
 36 Were Ukrainian patients
 153 Had no further visits
 15 Were lost to follow-up

666 Were included in the 24-mo
    follow-up
 405 Continued to receive edoxaban
 261 Discontinued edoxaban
    because of overt atrial
    fibrillation or other reasons

631 Were included in the 24-mo
    follow-up
 413 Continued to receive placebo
 218 Discontinued placebo
    because of overt atrial
    fibrillation or other reasons

499 Were included in the follow-up
    at the end of the trial
 62 Died
 39 Withdrew consent
 58 Were Ukrainian patients
  8 Were lost to follow-up

472 Were included in the follow-up
    at the end of the trial
 50 Died
 30 Withdrew consent
 61 Were Ukrainian patients
 18 Were lost to follow-up

committee, the trial was stopped prematurely, at a median follow-up of 21 months, owing to safety concerns and the results of an informal assessment of futility for the efficacy of edoxaban. At the time of termination of the trial, the planned enrollment had been completed, and 184 of the 220 planned primary efficacy outcome events had occurred during a median follow-up of 21 months per patient in both groups (edoxaban group, 21 months [interquartile range, 11 to 38]; placebo group, 21 months [interquartile range, 9 to 38]).

A primary efficacy outcome event occurred in 83 of 1270 patients (3.2% per patient-year) in the edoxaban group and in 101 of 1266 patients (4.0% per patient-year) in the placebo group (hazard ratio, 0.81; 95% confidence interval [CI], 0.60 to 1.08; P=0.15) (Table 2 and Fig. 2A). A safety outcome event occurred in 149 of 1270 patients (5.9% per patient-year) in the edoxaban group and in 114 of 1266 patients (4.5% per patient-year) in the placebo group (hazard ratio, 1.31; 95% CI, 1.02 to 1.67; P=0.03) (Table 3 and Fig. 2B). The results of sensitivity analyses of the primary efficacy outcome and the safety outcome, a subgroup analysis of the primary efficacy outcome, and a per-protocol analysis of the primary efficacy outcome and the safety outcome, as well as the results of the primary efficacy outcome and safety outcome analyses in the safety population (all the patients who underwent randomization) were generally similar to those of the primary efficacy outcome and safety outcome analyses (Fig. S1 and Tables S4, S5, and S6).

### SECONDARY OUTCOMES

Strokes occurred in 22 patients (0.9% per patient-year) in the edoxaban group and in 27 patients (1.1% per patient-year) in the placebo group (Table 2). Systemic embolism occurred in 14 patients (0.5% per patient-year) in the edoxaban group and in 28 patients (1.1% per patient-year) in the placebo group. A composite of stroke or systemic embolism occurred in 25 patients (1.0% per patient-year) in the edoxaban group and in 38 patients (1.5% per patient-year) in the placebo group (hazard ratio, 0.65; 95% CI, 0.39 to 1.07). Cardiovascular death occurred in 52 patients (2.0% per patient-year) in the edoxaban group and in 57 patients (2.2% per patient-year) in the placebo group (Table 2). Major bleeding was reported in 53 patients in the edoxaban group and in 25 patients in the placebo group (hazard ratio, 2.10; 95% CI, 1.30 to 3.38). Death from any cause occurred in 111 patients in the edoxaban group and in 94 patients in the placebo group (hazard ratio, 1.16; 95% CI, 0.88 to 1.53) (Table 3).

The mean score on the EQ-5D-5L visual analogue scale worsened over time without a substantial difference between the trial groups. Other patient-reported outcomes, cognitive function, and functional status did not change appreciably over time and were similar in the two groups (Table S3).

## DISCUSSION

In this double-blind, double-dummy, randomized trial, oral anticoagulation with edoxaban, administered at doses approved for the treatment of atrial fibrillation, did not result in a lower incidence of a composite outcome of cardiovascular death, stroke, or systemic embolism than no anticoagulation in patients with AHREs. However, edoxaban led to a higher incidence of a composite of death from any cause or major bleeding. The incidences of events were generally within expected ranges, with the exception of a low incidence of stroke in both trial groups.

The clinical characteristics of the population studied in this trial, including age and clinical risk factors for stroke, are consistent with those of patients with atrial fibrillation who are at a high risk for stroke and are not being treated with anticoagulants. Despite the enrollment of a high-risk population, the observed incidence of stroke among patients who were not treated with oral anticoagulation was lower than expected. The incidence of stroke observed in our trial was considerably lower than the incidence reported in a cohort study involving Swedish patients with atrial fibrillation and a $CHA_2DS_2$-VASc score of 4 who were not being treated with oral anticoagulation.[17] The incidence of stroke

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

| Characteristic | Edoxaban (N=1270) | Placebo (N=1266) | Total (N=2536) |
|---|---|---|---|
| Age — yr | 77.4±6.5 | 77.5±6.8 | 77.5±6.7 |
| Age ≥75 yr — no./total no. (%) | 845/1270 (66.5) | 855/1266 (67.5) | 1700/2536 (67.0) |
| Female sex — no./total no. (%) | 469/1270 (36.9) | 480/1266 (37.9) | 949/2536 (37.4) |
| Device used to record AHREs — no./total no. (%) | | | |
|    Pacemaker | 1017/1270 (80.1) | 1055/1266 (83.3) | 2072/2536 (81.7) |
|    Defibrillator | 100/1270 (7.9) | 88/1266 (7.0) | 188/2536 (7.4) |
|    Cardiac resynchronization device | 138/1270 (10.9) | 113/1266 (8.9) | 251/2536 (9.9) |
|    Implanted loop recorder | 15/1270 (1.2) | 10/1266 (0.8) | 25/2536 (1.0) |
| Median duration of AHREs (IQR) — hr† | 2.8 (0.8–9.2) | 2.8 (0.7–9.5) | 2.8 (0.8–9.4) |
| AHREs with atrial rates >200 beats/ min — no./total no. (%) | 918/944 (97.2) | 896/925 (96.9) | 1814/1869 (97.1) |
| Median $CHA_2DS_2$-VASc score (IQR)‡ | 4 (3–5) | 4 (3–5) | 4 (3–5) |
| Median $CHA_2DS_2$-VA score (IQR)‡ | 3 (3–4) | 3 (3–4) | 3 (3–4) |
| Heart failure — no./total no. (%)§ | 361/1270 (28.4) | 335/1266 (26.5) | 696/2536 (27.4) |
| Hypertension — no./total no. (%)¶ | 1096/1270 (86.3) | 1109/1266 (87.6) | 2205/2536 (86.9) |
| Diabetes mellitus — no./total no. (%) | 350/1270 (27.6) | 331/1266 (26.1) | 681/2536 (26.9) |
| Previous stroke or transient ischemic attack — no./total no. (%) | 122/1270 (9.6) | 131/1266 (10.3) | 253/2536 (10.0) |
| Previous myocardial infarction, PCI, or CABG — no./total no. (%) | 353/1270 (27.8) | 316/1266 (25.0) | 669/2536 (26.4) |
| Indication for acetylsalicylic acid at random-ization — no./total no. (%)‖ | 684/1270 (53.9) | 683/1266 (53.9) | 1367/2536 (53.9) |
| Indication for edoxaban dose reduction to 30 mg once daily — no./total no. (%)‖ | 365/1270 (28.7) | 382/1266 (30.2) | 747/2536 (29.5) |
| Estimated creatinine clearance — ml/min | 66.4±23.6 | 65.7±23.2 | 66.0±23.4 |
| Hemoglobin — g/liter** | 138.9±17.5 | 138.6±16.9 | 138.8±17.2 |
| Heart rate — beats/min†† | 68.9±10.8 | 68.4±10.8 | 68.6±10.8 |
| Cardiovascular therapies — no./total no. (%) | | | |
|    Beta-blockers | 741/1263 (58.7) | 735/1250 (58.8) | 1476/2513 (58.7) |
|    Antihypertensive therapy | 1155/1263 (91.4) | 1141/1250 (91.3) | 2296/2513 (91.4) |
|    ACE inhibitors, ARBs, or sacubitril–valsartan | 889/1263 (70.4) | 869/1250 (69.5) | 1758/2513 (70.0) |
|    Loop diuretics | 325/1263 (25.7) | 331/1250 (26.5) | 656/2513 (26.1) |
|    Mineralocorticoid-receptor antagonists | 209/1263 (16. 5) | 189/1250 (15.1) | 398/2513 (15.8) |
|    Statins | 762/1263 (60.3) | 732/1250 (58.6) | 1494/2513 (59.5) |

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, AHRE atrial high-rate episode, ARB angiotensin-receptor blocker, CABG coronary-artery bypass graft, IQR interquartile range, and PCI percutaneous coronary intervention.
† This category includes AHREs with atrial rates of at least 170 beats per minute that lasted for at least 6 minutes per episode, as documented by the implanted device.
‡ $CHA_2DS_2$-VASc scores range from 0 to 9, with higher scores indicating a greater risk of stroke. All the patients in the trial had a $CHA_2DS_2$-VASc score of 2 or higher. $CHA_2DS_2$-VA scores range from 0 to 8, with higher scores indicating a greater risk of stroke.
§ Heart failure was either clinically overt or was defined by a left ventricular ejection fraction less than 45%.
¶ Patients were considered to have hypertension if they were receiving regular treatment for hypertension, if continuous antihypertensive therapy was warranted (as determined by the investigator), or if they had a resting blood pressure higher than 145/90 mm Hg.
‖ Indications for acetylsalicylic acid included previous myocardial infarction, PCI, or CABG and secondary prevention of stroke. Acetylsalicylic acid was administered only to patients randomly assigned to no anticoagulation, and the dose of edoxaban was reduced only in patients randomly assigned to anticoagulation with edoxaban.
** Data were missing for 65 patients in the edoxaban group and for 52 patients in the placebo group.
†† Data were missing for 74 patients in the edoxaban group and for 66 patients in the placebo group.

**Table 2. Efficacy Outcomes.***

| Outcome | Edoxaban (N = 1270) | Placebo (N = 1266) | Adjusted Hazard Ratio (95% CI) |
|---|---|---|---|
| | no. of patients with event/patient-yr (% per patient-yr) | | |
| Primary composite efficacy outcome† | 83/2557 (3.2) | 101/2495 (4.0) | 0.81 (0.60 to 1.08)‡ |
| Ischemic stroke | 22/2573 (0.9) | 27/2519 (1.1) | 0.79 (0.45 to 1.39) |
| Systemic embolism | 14/2579 (0.5) | 28/2515 (1.1) | 0.51 (0.27 to 0.96) |
|     Myocardial infarction | 10/2589 (0.4) | 16/2524 (0.6) | — |
|     Pulmonary embolism | 3/2589 (0.1) | 9/2533 (0.4) | — |
|     Peripheral limb embolism | 1/2592 (<0.1) | 3/2536 (0.1) | — |
|     Abdominal embolism | 0 | 1/2540 (<0.1) | — |
| Cardiovascular death | 52/2595 (2.0) | 57/2540 (2.2) | 0.90 (0.62 to 1.31) |
|     Death due to acute myocardial infarction | 1/2595 (<0.1) | 4/2540 (0.2) | — |
|     Sudden cardiac death | 18/2595 (0.7) | 13/2540 (0.5) | — |
|     Death due to heart failure | 13/2595 (0.5) | 15/2540 (0.6) | — |
|     Death due to stroke | 1/2595 (<0.1) | 3/2540 (0.1) | — |
|     Death due to cardiovascular hemorrhage | 2/2595 (0.1) | 1/2540 (<0.1) | — |
|     Death due to other cardiovascular cause | 1/2595 (<0.1) | 4/2540 (0.2) | — |
|     Death of unknown cause, counted as cardiovascular cause | 16/2595 (0.6) | 17/2540 (0.7) | — |
| Major adverse cardiovascular event§ | 92/2532 (3.6) | 102/2485 (4.1) | 0.89 (0.67 to 1.18) |
| Ischemic stroke or systemic embolism | 25/2566 (1.0) | 38/2509 (1.5) | 0.65 (0.39 to 1.07) |

\* The numbers of patients summarized here indicate patients with a first occurrence of an event. The widths of the confidence intervals for the differences between the trial groups with respect to the secondary outcomes have not been adjusted for multiple comparisons.
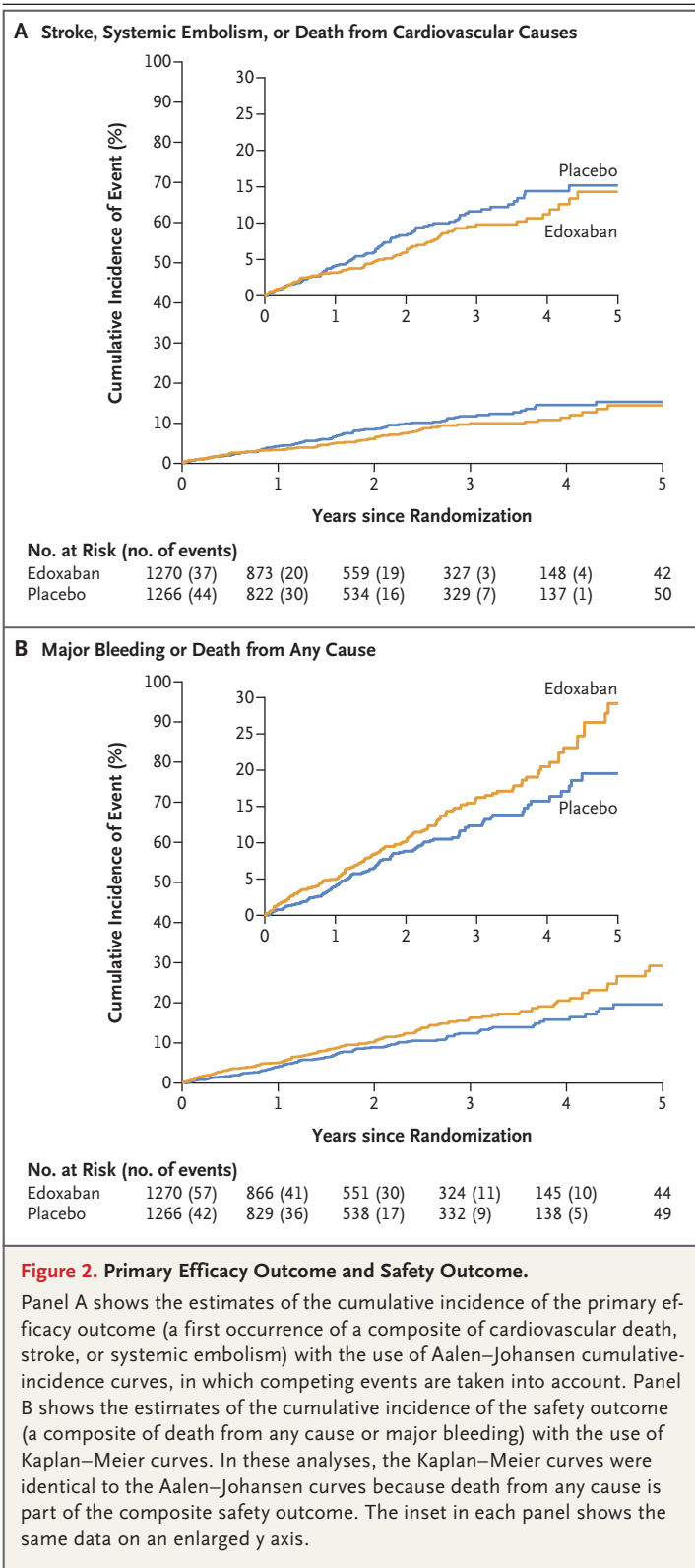
† The primary efficacy outcome was a first occurrence of a composite of cardiovascular death, stroke (including ischemic and hemorrhagic stroke), or systemic embolism.

‡ P = 0.15.

§ Major adverse cardiovascular events included cardiovascular death, myocardial infarction, acute coronary syndrome, PCI, and CABG. This composite outcome is reported in order to simplify the comparison of the outcomes in this trial with those in other cardiovascular trials.

without anticoagulation in our trial was also lower than that reported among patients with atrial fibrillation who were randomly assigned to receive acetylsalicylic acid in the AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) study,[18] in patients randomly assigned to receive no anticoagulation in the ELDERCARE-AF (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) trial,[19] and in patients randomly assigned to receive no anticoagulation (aspirin) in trials of vitamin K antagonists.[1,20] Furthermore, the incidence of stroke among patients who did not receive oral anticoagulation in our trial was lower than that reported among patients with atrial fibrillation who received edoxaban in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) trial.[21] The higher incidence of major bleeding among patients in the edoxaban group in our trial was an expected side effect of anticoagulant therapy.[1,17,18,20] These observed major bleeding incidences are also consistent with major bleeding

**Figure 2. Primary Efficacy Outcome and Safety Outcome.**

Panel A shows the estimates of the cumulative incidence of the primary efficacy outcome (a first occurrence of a composite of cardiovascular death, stroke, or systemic embolism) with the use of Aalen–Johansen cumulative-incidence curves, in which competing events are taken into account. Panel B shows the estimates of the cumulative incidence of the safety outcome (a composite of death from any cause or major bleeding) with the use of Kaplan–Meier curves. In these analyses, the Kaplan–Meier curves were identical to the Aalen–Johansen curves because death from any cause is part of the composite safety outcome. The inset in each panel shows the same data on an enlarged y axis.

incidences among patients who received edoxaban in the ENGAGE AF-TIMI 48 trial,[21] in the ELDERCARE-AF trial,[19] and in clinical practice.[22]

The findings of this trial — the low incidence of stroke that was not further reduced by treatment with edoxaban — may make it appropriate to withhold anticoagulant therapy in patients with AHREs.[8,23] The main difference between the population studied in this trial and patients with atrial fibrillation as documented on an ECG appears to be the paucity and brevity of atrial arrhythmias in patients with AHREs (termed low arrhythmia burden).[8] Published reports show that a low arrhythmia burden contributes to a low incidence of stroke among patients with atrial fibrillation: paroxysmal atrial fibrillation is associated with a lower incidence of stroke than persistent or permanent atrial fibrillation.[24,25] Early rhythm control reduces the risk of cardiovascular events, including stroke,[26] and this effect is mediated by attaining sinus rhythm, which reflects a reduced arrhythmia burden.[27] These results may support the conclusion from our trial that, in patients with AHREs but without ECG-documented atrial fibrillation, AHREs are better managed without anticoagulation.

This trial has several limitations. First, owing to the premature termination of the trial after the accrual of 184 of the 220 originally planned primary efficacy outcome events, the trial does not have sufficient power to detect or rule out a small beneficial effect of oral anticoagulation on the prevention of stroke. Second, the generalizability of these findings with edoxaban to other NOACs is not known. Ongoing trials have been designed to determine the efficacy and safety of NOAC therapy after successful rhythm-control therapy and to evaluate the safety and efficacy of apixaban in patients with AHREs.[28,29] Similar trials may be warranted to evaluate the efficacy and safety of oral anticoagulation in patients who have rare atrial arrhythmias as detected by consumer electronics but do not have atrial fibrillation as documented on an ECG.[6,30] Our trial enrolled predominantly White patients in Europe; results may differ in other racial and ethnic groups. Third, the low incidences of stroke that were observed in this trial and in the LOOP study[9] suggest that, in addition to clinical

**Table 3. Safety Outcomes.***

| Outcome | Edoxaban (N = 1270) | Placebo (N = 1266) | Adjusted Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | no. of patients with event/patient-yr (% per patient-yr) | | | |
| Composite safety outcome† | 149/2534 (5.9) | 114/2508 (4.5) | 1.31 (1.02 to 1.67) | 0.03 |
| Death from any cause | 111/2595 (4.3) | 94/2540 (3.7) | 1.16 (0.88 to 1.53) | 0.28 |
|     Cardiovascular death | 52/2595 (2.0) | 57/2540 (2.2) | — | — |
|     Cancer-related death | 22/2595 (0.8) | 9/2540 (0.4) | — | — |
|     Covid-19–associated death | 15/2595 (0.6) | 12/2540 (0.5) | — | — |
|     Death due to acute infection or sepsis | 12/2595 (0.5) | 9/2540 (0.4) | — | — |
|     Death due to frailty or old age | 3/2595 (0.1) | 2/2540 (0.1) | — | — |
|     Death due to accident or poly-trauma | 3/2595 (0.1) | 1/2540 (<0.1) | — | — |
|     Death due to lung disease | 2/2595 (0.1) | 1/2540 (<0.1) | — | — |
|     Death due to acute abdomen | 0 | 2/2540 (0.1) | — | — |
|     Kidney-related death | 1/2595 (<0.1) | 0 | — | — |
|     Dementia-related death | 0 | 1/2540 (<0.1) | — | — |
|     Suicide | 1/2595 (<0.1) | 0 | — | — |
| Major bleeding | 53/2534 (2.1) | 25/2508 (1.0) | 2.10 (1.30 to 3.38) | 0.002 |
| Mean no. of major bleeding events per patient | 0.06±0.35 | 0.02±0.16 | 3.06 (1.74 to 5.36)‡ | <0.001 |

* The numbers of patients summarized here indicate patients with a first occurrence of an event. All the deaths were adjudicated by the outcome review committee as being due to cardiovascular or noncardiovascular causes. The specific causes of deaths from noncardiovascular causes shown here were classified on the basis of the *Medical Dictionary for Regulatory Activities*, version 19.1. Covid-19 denotes coronavirus disease 2019.
† The safety outcome was a composite of death from any cause or major bleeding, as defined by the International Society on Thrombosis and Hemostasis.[14,15]
‡ These data are the adjusted rate ratio and 95% confidence interval.

risk prediction formulas for stroke, methods to improve the estimation of stroke risk among patients with infrequent atrial arrhythmias detected by long-term monitoring are needed to guide decision making on the use of anticoagulation. Finally, although the protocol did not define a time limit between the detection of AHREs and randomization, the intention was that patients would be enrolled soon after the detection of the rhythm disturbance and that any imbalances between the trial groups would presumably be obviated by the randomization process.

In a trial involving patients who had AHREs without atrial fibrillation detected by ECG and who were 65 years of age or older and had other risk factors for stroke, the incidence of a composite of cardiovascular death, stroke, or systemic embolism with edoxaban was not significantly different from that with placebo, but treatment with edoxaban led to a higher incidence of a composite of death or major bleeding.

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## APPENDIX

The authors' full names and academic degrees are as follows: Paulus Kirchhof, M.D., Tobias Toennis, M.D., Andreas Goette, M.D., A. John Camm, M.D., Hans Christoph Diener, M.D., Nina Becher, M.D., Emanuele Bertaglia, M.D., Carina Blomstrom Lundqvist, M.D., Martin Borlich, M.D., Axel Brandes, M.D., Nuno Cabanelas, M.D., Melanie Calvert, Ph.D., Gregory Chlouverakis, Ph.D., Gheorghe-Andrei Dan, M.D., Ph.D., Joris R. de Groot, M.D., Ph.D., Wolfgang Dichtl, M.D., Ph.D., Borys Kravchuk, M.D., Andrzej Lubiński, M.D., Ph.D., Eloi Marijon, M.D., Ph.D., Béla Merkely, M.D., Ph.D., Lluís Mont, Ph.D., Ann-Kathrin Ozga, Ph.D., Kim Rajappan, M.D., Andrea Sarkozy, M.D., Daniel Scherr, M.D., Rafał Sznajder, M.D., Vasil Velchev, M.D., Dan Wichterle, M.D., Ph.D., Susanne Sehner, M.Sc., Emmanuel Simantirakis, M.D., Ph.D., Gregory Y.H. Lip, M.D., Panos Vardas, M.D., Ph.D., Ulrich Schotten, M.D., Ph.D., and Antonia Zapf, Ph.D.

The authors' affiliations are as follows: the Atrial Fibrillation Network, Münster (P.K., A.G., U.S.), the Department of Cardiology, University Heart and Vascular Center Hamburg (P.K., T.T., N.B.), and the Institute of Medical Biometry and Epidemiology (A.-K.O., S.S., A.Z.), University Medical Center Hamburg–Eppendorf, and the German Center for Cardiovascular Research (DZHK) Partner Site Hamburg–Kiel–Lübeck (P.K., T.T., N.B.), Hamburg, the Department of Cardiology and Intensive Care Medicine, St. Vincenz Hospital Paderborn, Paderborn (A.G.), the Department of Neuroepidemiology, Institute for Medical Informatics, Biometry, and Epidemiology, University Duisburg–Essen, Essen (H.C.D.), and the Heart Center, Segeberger Kliniken, Bad Segeberg (M.B.) — all in Germany; the Institute of Cardiovascular Sciences (P.K.) and the Centre for Patient Reported Outcome Research, Institute of Applied Health Research, the National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre, and the NIHR Applied Research Collaboration West Midlands (M.C.), University of Birmingham, Birmingham, the Cardiovascular and Cell Sciences Research Institute, St. George's University of London, and Imperial College London, London (A.J.C.), the Cardiac Department, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford (K.R.), and Liverpool Centre for Cardiovascular Science at University of Liverpool, John Moores University, and Liverpool Heart and Chest Hospital, Liverpool (G.Y.H.L.) — all in the United Kingdom; Unità Operativa Complessa Cardiologia–Azienda Ospedale Università di Padova, Padua, Italy (E.B.); the Department of Medical Science, Uppsala University, Uppsala, and the Department of Cardiology, School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro — both in Sweden (C.B.L.); the Department of Cardiology, Odense University Hospital, Odense, and the Department of Cardiology, Esbjerg Hospital–University Hospital of Southern Denmark, Esbjerg (A.B.), and the Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg (G.Y.H.L.) — all in Denmark; the Cardiology Department, Fernando Fonseca Hospital, Amadora, Portugal (N.C.); the Biostatistics Lab, School of Medicine, University of Crete (G.C.), and the Department of Cardiology, Heraklion University Hospital (E.S.), Heraklion, and the Biomedical Research Foundation Academy of Athens and Hygeia Hospitals Group, Athens (P.V.) — all in Greece; Medicine University Carol Davila, Colentina University Hospital, Bucharest, Romania (G.-A.D.); the Heart Center, Department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam (J.R.G.), and the Departments of Cardiology and Physiology, Maastricht University, Maastricht (U.S.) — both in the Netherlands; the Department of Internal Medicine III, Cardiology and Angiology, Innsbruck Medical University, Innsbruck (W.D.), and the Department of Cardiology, Medical University of Graz, Graz (D.S.) — both in Austria; the National Institute of Cardiovascular Surgery, Academy of Medical Sciences of Ukraine, Kyiv (B.K.); the Department of Cardiology and Internal Disease, Medical University of Gdansk, Gdansk (A.L.), and the Department of Electrocardiology and Heart Failure, Leszek Giec Upper Silesian Medical Center, Katowice (R.S.) — both in Poland; the Cardiology Division, European Georges Pompidou Hospital, Paris (E.M.); the Heart and Vascular Center, Semmelweis University, Budapest, Hungary (B.M.); the Hospital Clinic, Universtitat de Barcelona, Barcelona, Institut d'Investigacions Biomèdiques August Pi Sunyer, Barcelona, and Centro de Investigacion Biomedica en Red Cardiovascular, Madrid — all in Spain (L.M.); the Department of Cardiology, University Hospital Antwerp, Edegem, Belgium (A.S.); the Cardiology Clinic, St. Anna University Hospital Sofia, Sofia Medical University, Sofia, Bulgaria (V.V.); and the Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic (D.W.).

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