ORIGINAL ARTICLE

Anticoagulation for Atrial Fibrillation with Intermediate Stroke Risk

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ABSTRACT

BACKGROUND

Current U.S. and European guidelines recommend oral anticoagulation as a class IIa indication in patients with atrial fibrillation at intermediate risk for stroke; however, evidence from randomized trials is needed.

METHODS

We conducted a multicenter, open-label, adjudicator-masked superiority trial in South Korea involving patients with atrial fibrillation and an intermediate risk of stroke (a score of 1 in men and 2 in women on the CHA_2DS_2-VASc scale; range, 0 to 9, with higher scores indicating a greater risk of stroke). Patients were randomly assigned in a 1:1 ratio to receive either direct oral anticoagulant (DOAC) therapy or no anticoagulation. The primary end point was a composite of stroke, systemic embolism, major bleeding, or death from cardiovascular causes at 24 months.

RESULTS

Of 1803 patients who underwent randomization, 902 were assigned to receive DOAC therapy and 901 were assigned to receive no anticoagulant therapy. The mean age of the patients was 60.4 years, and 23.7% were women. At 24 months, a primary end-point event had occurred in 4 patients (cumulative incidence, 0.5%) in the DOAC group and in 13 (cumulative incidence, 1.5%) in the no-anticoagulant group (difference, −1.0 percentage points; 95% confidence interval [CI], −2.0 to −0.1; P=0.03; hazard ratio, 0.31; 95% CI, 0.10 to 0.94). Stroke occurred in 3 patients (cumulative incidence, 0.3%) in the DOAC group and in 10 (cumulative incidence, 1.1%) in the no-anticoagulant group. The incidence of systemic embolism and major bleeding appeared to be similar in the two trial groups, and no deaths from cardiovascular causes occurred in either group. Serious adverse events occurred in 80 patients (8.9%) in the DOAC group and in 84 (9.3%) in the no-anticoagulant group.

CONCLUSIONS

Among patients with atrial fibrillation at intermediate risk for stroke, DOAC therapy led to a lower risk of stroke, systemic embolism, major bleeding, or death from cardiovascular causes at 24 months than no anticoagulation. (Funded by the Ministry of Health and Welfare, South Korea, and others; SINGLE-AF ClinicalTrials.gov number, NCT04437654.)

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*A complete list of the SINGLE-AF investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Atrial fibrillation increases the risk of stroke.[1-4] In patients with higher scores on the CHA_2DS_2-VASc scale (range, 0 to 9, with higher scores indicating a greater risk of stroke),[5] the expected reduction in the risk of thromboembolism with oral anticoagulant therapy generally outweighs the risk of bleeding.[6] Current U.S. and European guidelines strongly recommend therapy with oral anticoagulants for men with a score of 2 or more and for women with a score of 3 or more.[1,2] For patients with an intermediate risk of stroke (defined as a CHA_2DS_2-VASc score of 1 in men and 2 in women), current guidelines provide a class IIa recommendation for consideration of oral anticoagulants; however, evidence from randomized trials supporting this approach is limited.[1,2]

Observational studies have provided conflicting evidence with regard to the net benefit of oral anticoagulants in patients at intermediate risk.[7-10] Direct oral anticoagulants (DOACs) offer a better balance of risks and benefits than vitamin K antagonists in patients with atrial fibrillation, mainly because DOACs confer a lower risk of intracranial hemorrhage.[11,12] Although some phase 3 trials of DOACs included patients at low risk for stroke, they did not directly compare anticoagulation with no treatment in intermediate-risk patients.[13,14] We designed the Efficacy and Safety of Non–Vitamin K Antagonist Oral Anticoagulants for Intermediate Stroke Risk in Patients with Atrial Fibrillation (SINGLE-AF) trial to assess whether the risk of adverse clinical events would be lower with oral anticoagulation than with no anticoagulation among patients with atrial fibrillation who are at intermediate risk for stroke.

Methods

Trial Design

We conducted this investigator-initiated, multicenter, open-label, randomized superiority trial with blinded adjudication of outcome events at 18 centers in South Korea. The rationale and design have been described previously.[15] The trial protocol (available with the full text of this article at NEJM.org) and all subsequent amendments were approved by the institutional review board or ethics committee at each participating site. All the patients provided written informed consent before randomization. All the participating centers and trial personnel are listed in the Supplementary Appendix, available at NEJM.org.

The trial was funded by the Ministry of Health and Welfare in South Korea, Samjin Pharmaceutical, and Hanmi Pharmaceutical. The funders had no role in the design or conduct of the trial; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript. Trial data were reviewed by an independent data and safety monitoring board. The first four authors and the last author wrote the first and subsequent drafts of the manuscript, had full access to the data, and participated in the analysis and interpretation of the data. The authors made the decision to submit the manuscript for publication and vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. Details regarding trial oversight and the responsibilities of individual authors are provided in the Supplementary Appendix.

Trial Population

Patients were eligible to participate in the trial if they were at least 19 years of age, had atrial fibrillation, and were at intermediate risk for stroke (defined as a CHA_2DS_2-VASc score of 1 in men or 2 in women). Key exclusion criteria were clinically significant disease of the kidney (a serum creatinine level of ≥3.5 mg per deciliter or a creatinine clearance of <30 ml per minute) or liver (aspartate aminotransferase or alanine transaminase level of >3 times the upper limit of the normal range or Child–Pugh class B or C disease); the use of anticoagulation owing to the presence of a mechanical prosthetic valve, moderate-to-severe mitral stenosis, or deep-vein thrombosis; and clinically significant structural heart disease (e.g., dilated or hypertrophic cardiomyopathy and cardiac amyloidosis). Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

Randomization and Follow-up

Eligible patients were randomly assigned in a 1:1 ratio to receive DOAC therapy or no anticoagulant therapy. Randomization was performed by means of a Web-based system with a permuted-block design with block sizes of 4 or 6, stratified according to trial site.

Patients assigned to the DOAC group received either apixaban (5 mg twice daily) or rivaroxa-

ban (20 mg once daily), at the treating physician's discretion, with appropriate dose reductions applied for those who met prespecified criteria (see the Supplementary Appendix). If patients had unacceptable side effects with apixaban or rivaroxaban, another DOAC could be prescribed at the investigator's discretion.

Patients assigned to the no-anticoagulant group did not receive routine oral anticoagulation as part of their assigned trial regimen; temporary administration of a DOAC was permitted before and after rhythm-control interventions, such as cardioversion or catheter ablation for atrial fibrillation. In both groups, the use of antiplatelet therapy was permitted if it was clinically indicated (e.g., after coronary intervention or an acute coronary syndrome) or at the physician's discretion; however, routine use was not recommended.

Follow-up assessments were performed at baseline and at 3, 6, 12, 18, and 24 months after randomization. At each visit, we assessed the patients' general health status, the use of cardiovascular medication, and the occurrence of trial end-point events or adverse events.

END POINTS

The primary end point was a composite of stroke, systemic embolism, major bleeding (as defined by the International Society on Thrombosis and Haemostasis), or death from cardiovascular causes at 24 months after randomization. The primary end point originally included death from any cause. In January 2025, the members of the independent data and safety monitoring board, who were unaware of the trial-group assignments, noted that all the deaths that had been reported up to that point were due to noncardiovascular causes and unlikely to be related to treatment. To prevent these unrelated events from diluting the ability to assess the treatment effect, the primary end point was amended to include only death from cardiovascular causes, with death from any cause retained as a secondary outcome.[16] This change, which has been described previously,[15] did not alter the original sample-size or power assumptions.

Secondary end points included the individual components of the primary outcome, death from any cause, transient ischemic attack, clinically relevant nonmajor bleeding, myocardial infarction, and hospitalization for any cause. In post hoc analyses, we evaluated a composite of ischemic stroke or systemic embolism and a composite of major or clinically relevant nonmajor bleeding. Major or clinically relevant nonmajor bleeding was defined primarily in accordance with the criteria of the International Society on Thrombosis and Haemostasis; bleeding events were additionally classified according to the Bleeding Academic Research Consortium definitions. All suspected end-point events were adjudicated by an independent clinical-events committee whose members were unaware of the trial-group assignments. A detailed list of the trial end points and their definitions is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We hypothesized that DOAC therapy would be superior to no anticoagulant therapy with respect to the primary end point. On the basis of previously reported outcomes from a subgroup analysis of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial and from observational data,[7,8,14,17] we assumed that the incidence of the primary end-point events at 24 months would be 2.0% in the DOAC group and 4.5% in the no-anticoagulant group. We calculated that enrollment of 1800 patients, with 900 per group, would provide the trial with 80% power to detect a between-group difference of 2.5 percentage points at a two-sided alpha level of 0.05, with an assumed attrition of 12%.

The primary analyses were conducted in the intention-to-treat population. The cumulative incidence of the primary end point at 24 months was estimated with the Aalen–Johansen method, with death from noncardiovascular causes as a competing event. The cumulative incidence of death from any cause was estimated with the Kaplan–Meier method. Treatment effects were assessed with Fine–Gray subdistribution hazard models.[18] The absolute between-group differences in cumulative incidence at 24 months were calculated from the Aalen–Johansen estimates, with standard errors derived from the corresponding estimated variances. Subgroup analyses of the primary end point were performed according to prespecified clinical characteristics. In addition, we performed a post hoc subgroup analysis according to the type of atrial fibrillation (paroxysmal or nonparoxysmal).

In a sensitivity analysis, follow-up data were censored when a patient's CHA_2DS_2-VASc score increased to 2 or higher in men or 3 or higher in women, at which point oral anticoagulant therapy was allowed in accordance with class I guideline recommendations. In an additional sensitivity analysis, we calculated the win ratio using an unmatched-pairs approach.[19] All possible pairs consisting of one patient from the DOAC group and one patient from the no-anticoagulant group were compared sequentially according to the following prespecified hierarchical sequence: death from cardiovascular causes, intracranial hemorrhage, ischemic stroke or systemic embolism, and major bleeding excluding intracranial hemorrhage. No imputation was performed for missing baseline variables. The statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary end points and in subgroup analyses; therefore, the widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

All statistical analyses were performed with the use of R software, version 4.2.2 (R Foundation for Statistical Computing). The statistical analysis plan is available with the trial protocol.

RESULTS

PATIENTS

From July 27, 2020, through June 29, 2023, a total of 1803 patients underwent randomization; 902 were assigned to the DOAC group and 901 to the no-anticoagulant group (Fig. 1). The characteristics of the patients at baseline appeared to be well balanced between the two trial groups (Table 1). The mean (±SD) age of the patients was 60.4±7.9 years, 23.7% were women, and 71.8% had paroxysmal atrial fibrillation. The median time from the diagnosis of atrial fibrillation to randomization was 21 months (interquartile range, 2 to 59).

TREATMENTS AND FOLLOW-UP

Details regarding the antithrombotic regimens administered after randomization are provided in Table S1 in the Supplementary Appendix. During the trial period, 902 patients (100%) in the DOAC group and 50 of 901 patients (5.5%) in the no-anticoagulant group received a DOAC. Details regarding protocol violations are provided in Table S2. The most commonly prescribed therapy in the DOAC group was apixaban at a dose of 5 mg (used in 67.4% of the patients), followed by rivaroxaban at doses of 20 mg (in 14.1%) and 15 mg (in 13.9%). DOACs were administered at full doses in 81.6% of these patients and at reduced doses in 18.4%. Antiplatelet therapy was used in 0.4% of the patients in the DOAC group and in 36.5% of those in the no-anticoagulant group.

The median follow-up was 730 days. At 24 months, 94.6% of the patients in both groups had completed follow-up. Details regarding adherence to the trial regimen during the trial period are provided in Figure S1.

PRIMARY AND SECONDARY END POINTS

At 24 months after randomization, a primary end-point event had occurred in 4 of 902 patients (cumulative incidence, 0.5%) in the DOAC group and in 13 of 901 patients (cumulative incidence, 1.5%) in the no-anticoagulant group, for a difference of −1.0 percentage points (95% confidence interval [CI], −2.0 to −0.1; P=0.03) and a hazard ratio of 0.31 (95% CI, 0.10 to 0.94) (Table 2 and Fig. 2). The proportional subdistribution hazards and proportional-hazards assumptions for the primary end point were tested with the use of a time-by-treatment interaction term and Schoenfeld residuals, which showed no evidence of violation (P=0.18 for Cox proportional-hazards model).

At 24 months, stroke had occurred in 3 patients (cumulative incidence, 0.3%) in the DOAC group and in 10 patients (cumulative incidence, 1.1%) in the no-anticoagulant group (hazard ratio, 0.30; 95% CI, 0.08 to 1.08) (Fig. S2). Detailed data regarding stroke events are provided in Table S3. Systemic embolism occurred in no patients in the DOAC group and in 1 patient (cumulative incidence, 0.1%) in the no-anticoagulant group. Major bleeding occurred in 3 patients (cumulative incidence, 0.3%) in the DOAC group and in 4 patients (cumulative incidence, 0.5%) in the no-anticoagulant group (hazard ratio, 0.75; 95% CI, 0.17 to 3.35). Clinically relevant nonmajor bleeding occurred in 22 patients (cumulative incidence, 2.5%) in the DOAC group and in 14 patients (cumulative incidence, 1.6%)

in the no-anticoagulant group (hazard ratio, 1.58; 95% CI, 0.81 to 3.08). Detailed data regarding bleeding events are provided in Table S4.

Death from any cause occurred in 3 patients (cumulative incidence, 0.3%) in the DOAC group and in 5 patients (cumulative incidence, 0.6%) in the no-anticoagulant group (hazard ratio, 0.60; 95% CI, 0.14 to 2.51). Details regarding the causes of death are provided in Table S5. No myocardial infarction or deaths from cardiovascular causes occurred in either group. A transient ischemic attack occurred in no patients in the DOAC group and in 3 patients (cumulative incidence, 0.3%) in the no-anticoagulant group. In post hoc analyses, ischemic stroke or systemic embolism had occurred by 24 months in 1 patient (cumulative incidence, 0.1%) in the DOAC group and in 10 patients (cumulative incidence, 1.1%) in the no-anticoagulant group (hazard ratio, 0.10; 95% CI, 0.01 to 0.77) (Fig. S3).

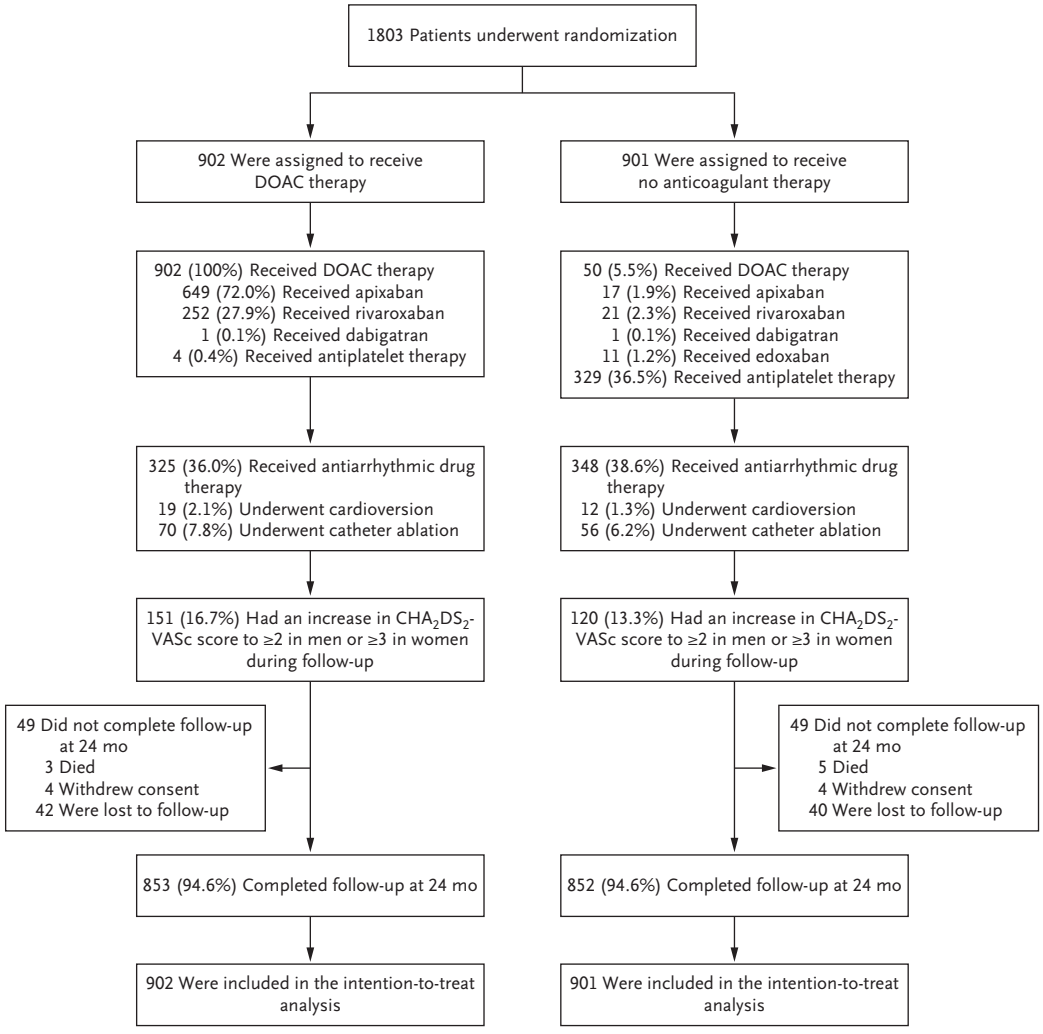


Figure 1. Randomization, Treatment, and Follow-up.

Patients were randomly assigned in a 1:1 ratio to receive direct oral anticoagulant (DOAC) therapy or no anticoagulant therapy. In the no-anticoagulant group, 50 patients crossed over and received DOAC therapy. Separately, protocol-permitted temporary DOAC therapy was administered for a median duration of 2.8 months before and after cardioversion or catheter ablation. The CHA_2DS_2-VASc score (an assessment of the risk of stroke among patients with atrial fibrillation) ranges from 0 to 9, with higher scores indicating a higher risk of stroke.

The results of a sensitivity analysis that censored follow-up when the CHA_2DS_2-VASc score increased to a guideline-based class I indication for anticoagulation were consistent with the primary analysis (Table S6). The win-ratio comparison of DOAC therapy to no anticoagulant therapy was 3.31 (95% CI, 1.15 to 9.54) (Fig. S4). With regard to the primary end point, the effect of DOAC therapy as compared with no anticoagulant therapy appeared to be consistent across the subgroups (Fig. 3).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	DOAC Therapy (N=902)	No Anticoagulant Therapy (N=901)
Age		
Mean — yr	60.7±7.8	60.0±8.1
≥65 yr — no. (%)	304 (33.7)	282 (31.3)
Male sex — no. (%)	682 (75.6)	694 (77.0)
Type of atrial fibrillation — no. (%)		
Paroxysmal	636 (70.5)	658 (73.0)
Nonparoxysmal	266 (29.5)	243 (27.0)
Median time since atrial fibrillation diagnosis (IQR) — mo	21 (2–60)	21 (2–58)
Medical history — no. (%)		
Hypertension	435 (48.2)	482 (53.5)
Diabetes mellitus	67 (7.4)	70 (7.8)
Heart failure	93 (10.3)	72 (8.0)
Stroke or transient ischemic attack	0 (0)	2 (0.2)
Dyslipidemia	224 (24.8)	193 (21.4)
Myocardial infarction	3 (0.3)	2 (0.2)
Peripheral artery disease	8 (0.9)	4 (0.4)
Previous ablation for atrial fibrillation — no. (%)	266 (29.5)	285 (31.6)
Previous cardioversion — no. (%)	162 (18.0)	137 (15.2)
Current alcohol use — no. (%)	253 (28.0)	265 (29.4)
Current smoker — no. (%)	97 (10.8)	123 (13.7)
CHA_2DS_2-VASc score†		
Mean	1.3±0.5	1.3±0.5
Median (IQR)	1 (1–1)	1 (1–1)
CHA_2DS_2-VA score‡		
Mean	1.0±0.1	1.0±0.2
Median (IQR)	1 (1–1)	1 (1–1)
$CHADS_2$ score§		
Mean	0.7±0.5	0.7±0.5
Median (IQR)	1 (0–1)	1 (0–1)
HAS-BLED score¶		
Mean	0.5±0.6	0.5±0.7
Median (IQR)	0 (0–1)	0 (0–1)
Blood pressure — mm Hg		
Systolic	125.6±15.4	127.1±14.4
Diastolic	76.6±12.4	77.2±11.8

Table 1. (Continued.)

Characteristic	DOAC Therapy (N=902)	No Anticoagulant Therapy (N=901)
Body-mass index‖	25.2±3.2	25.3±3.2
Creatinine clearance — ml/min**	88.7±24.8	90.5±25.8

* Plus–minus values are means ±SD. DOAC denotes direct oral anticoagulant, and IQR interquartile range.
† The CHA_2DS_2-VASc score (an assessment of the risk of stroke among patients with atrial fibrillation) ranges from 0 to 9, with higher scores indicating a higher risk of stroke. 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 female sex.
‡ The CHA_2DS_2-VA score (an assessment of the risk of stroke among patients with atrial fibrillation) ranges from 0 to 8, with higher scores indicating a higher risk of stroke. 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; and an age of 65 to 74 years or 75 years or older.
§ The $CHADS_2$ score (a measure of the risk of stroke among persons with atrial fibrillation) ranges from 0 to 6, with higher scores indicating a greater risk. 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.
¶ The HAS-BLED score (an assessment of the risk of bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy) ranges from 0 to 9, with higher scores indicating a greater risk of bleeding. Scores are weighted according to the presence of hypertension, abnormal kidney function or abnormal liver function (or both), a history of stroke or bleeding, the labile international normalized ratio, an age older than 65 years, and the use of medications or consumption of alcohol at a level that increases the risk of bleeding.
‖ 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.

SAFETY

Serious adverse events occurred in 80 patients (8.9%) in the DOAC group and in 84 (9.3%) in the no-anticoagulant group. The most common serious adverse event was hospitalization related to atrial fibrillation (34 events in the DOAC group and 15 in the no-anticoagulant group). Further details regarding adverse events are provided in Table S7.

DISCUSSION

In this multicenter, open-label, randomized trial involving patients with atrial fibrillation and an intermediate risk of stroke, the risk of a composite of stroke, systemic embolism, major bleeding, or death from cardiovascular causes at 24 months was lower with DOAC therapy than with no anticoagulant therapy. The cumulative incidence of stroke among patients assigned to the no-anticoagulant group was 1.1% over the course of 24 months, which corresponds to an annual incidence of approximately 0.6%. Although this annual incidence of events is lower than that reported in previous nationwide observational studies in Denmark (1.55%) and Taiwan (2.75%),[8,20,21] it is consistent with the 0.7% observed in a more contemporary multinational observational study in Europe.[22] This finding underscores that, even with modern clinical management, this intermediate-risk population retains a residual thromboembolic vulnerability that may benefit from targeted risk reduction through oral anticoagulation. However, the lower incidence of primary end-point events observed in the DOAC group than in the no-anticoagulant group was based on very few events and may overestimate the true magnitude of benefit. Therefore, although this randomized trial supports the benefit of anticoagulant therapy in this population, confirmatory trials or pooled analyses are needed to refine the precision and magnitude of the treatment effect.

The observed incidence of stroke can be interpreted in the context of atrial fibrillation burden, which is increasingly recognized as a determinant of stroke risk.[23] In the current trial, approximately 30% of patients had nonparoxysmal atrial fibrillation, a finding that suggests that patients with this phenotype have a higher burden of disease than patients without recurrent atrial fibrillation after catheter ablation, such as those in the ALONE-AF (Anticoagulation One Year after Ablation of Atrial Fibrillation in Patients with Atrial Fibrillation) or OCEAN (Optimal Anticoagulation for Enhanced Risk Patients Post-Catheter Ablation for Atrial Fibrillation) trials.[24,25]

Table 2. Primary, Secondary, and Exploratory End Points at 24 Months.*

End Point	DOAC Therapy (N=902)	No Anticoagulant Therapy (N=901)	Difference (95% CI)	Hazard Ratio (95% CI)
	no. of patients (estimated %)†		*percentage points*	
Primary end point				
Composite of stroke, systemic embolism, major bleeding, or death from cardiovascular causes	4 (0.5)	13 (1.5)	−1.0 (−2.0 to −0.1)‡	0.31 (0.10 to 0.94)
Secondary end points§				
Stroke	3 (0.3)	10 (1.1)	−0.8 (−1.6 to 0.0)	0.30 (0.08 to 1.08)
Ischemic event	1 (0.1)	10 (1.1)	−1.0 (−1.8 to −0.3)	0.10 (0.01 to 0.77)
Hemorrhagic event	2 (0.2)	0	0.2 (−0.1 to 0.6)	—
Systemic embolism	0	1 (0.1)	−0.1 (−0.3 to 0.1)	—
Major bleeding¶	3 (0.3)	4 (0.5)	−0.1 (−0.7 to 0.5)	0.75 (0.17 to 3.35)
Intracranial hemorrhage‖	2 (0.2)	1 (0.1)	0.1 (−0.3 to 0.5)	2.00 (0.18 to 22.05)
Gastrointestinal hemorrhage	1 (0.1)	2 (0.2)	−0.1 (−0.5 to 0.3)	0.50 (0.05 to 5.51)
Fatal bleeding	0	0	—	—
Death from cardiovascular causes	0	0	—	—
Clinically relevant nonmajor bleeding¶	22 (2.5)	14 (1.6)	0.9 (−0.4 to 2.2)	1.58 (0.81 to 3.08)
Death from any cause	3 (0.3)	5 (0.6)	−0.2 (−0.9 to 0.4)	0.60 (0.14 to 2.51)
Transient ischemic attack	0	3 (0.3)	−0.3 (−0.7 to 0.0)	—
Myocardial infarction	0	0	—	—
Hospitalization for any cause	163 (18.6)	154 (17.6)	0.9 (−2.7 to 4.6)	1.07 (0.86 to 1.33)
Exploratory end points§				
Composite of ischemic stroke or systemic embolism**	1 (0.1)	10 (1.1)	−1.0 (−1.8 to −0.3)	0.10 (0.01 to 0.77)
Composite of major bleeding or clinically relevant nonmajor bleeding¶	24 (2.7)	17 (2.0)	0.8 (−0.6 to 2.2)	1.42 (0.76 to 2.63)

* The analyses were performed in the intention-to-treat population, which included all the patients who underwent randomization, grouped according to their assigned trial group; the start time of follow-up for the intention-to-treat analysis was the day of randomization. For end points that included death from cardiovascular causes as a component, including the primary end point, death from noncardiovascular causes was treated as a competing event. For other end points that do not include death from any cause, death from any cause was treated as a competing event. The hazard ratios were calculated with the use of subdistribution-hazard models from a competing risk analysis.

† The 24-month cumulative incidence of end-point events subject to competing risks was estimated with the cumulative-incidence function, whereas the cumulative incidence of death from any cause was estimated with the Kaplan–Meier method. Therefore, the reported percentages may not correspond directly to the ratio of the numerator to the denominator.

‡ P=0.03 for superiority of DOAC therapy to no anticoagulant therapy, calculated with Gray's test.

§ Analyses of the exploratory end points were performed post hoc. The widths of the 95% confidence intervals have not been adjusted for multiple comparisons and should therefore not be used to infer treatment effects.

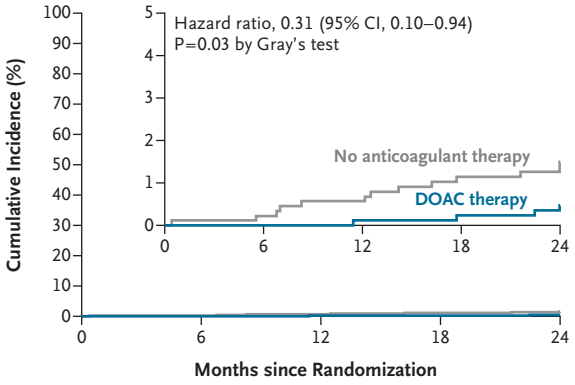
¶ Bleeding events were defined in accordance with the criteria of the International Society on Thrombosis and Haemostasis.

‖ One patient in the no-anticoagulant group had a subdural hemorrhage, which was classified as intracranial hemorrhage but not as hemorrhagic stroke.

** One patient in the no-anticoagulant group had both an ischemic stroke and systemic embolism.

Accordingly, the annual incidence of stroke in the no-anticoagulant group in this trial (approximately 0.6%) was higher than that reported in the no-anticoagulant group in the ALONE-AF trial (0.1%) and the same as that reported in the aspirin group in the OCEAN trial (0.6%), despite the higher mean CHA_2DS_2-VASc scores in those trials. In contrast, the annual incidence of stroke in the current trial was lower than that observed in the control groups in the NOAH-AFNET 6 (Non–Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes) trial (1.1% with placebo) and the ARTESIA (Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Subclinical Atrial Fibrillation) trial (1.2% with aspirin), which enrolled patients with a lower burden of device-detected atrial fibrillation but a higher clinical risk.[26,27] However, these cross-trial comparisons should be interpreted cautiously because of substantial differences in the patient populations, atrial fibrillation burden, and clinical risk profiles of the patients at baseline.

The 24-month cumulative incidence of major bleeding among patients assigned to the DOAC group was 0.3%, which corresponds to an annual incidence of approximately 0.2%. The patients enrolled in this trial had an intermediate risk of stroke and a low risk of bleeding at baseline, with a mean HAS-BLED score (a measure of the risk of bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy) of 0.5 (range, 0 to 9, with higher scores indicating a greater risk of bleeding) — all features that may have influenced the overall net clinical benefit. The findings in this trial contrast with those of trials involving patients at higher risk (median CHA_2DS_2-VASc score of 4), including the ARTESIA and NOAH-AFNET 6 trials.[26,27] In these trials, the use of DOAC therapy was associated with an increased incidence of major bleeding (2.1% per patient-year and 1.5% per patient-year, respectively) as compared with control therapy. Although the incidence of major bleeding events was low, intracranial hemorrhage occurred in two patients in the DOAC group, both of whom had hemorrhagic stroke, and in one patient in the no-anticoagulant group, who did not have hemorrhagic stroke. Given the small number of events, no definitive conclusions can be drawn from this numerical imbalance. Nevertheless, these events should be interpreted with caution because of their clinical severity and possible prognostic implications.



No. at Risk					
No anticoagulant therapy	901	877	856	843	840
DOAC therapy	902	885	859	853	849

Figure 2. Cumulative Incidence of Primary End-Point Events (Intention-to-Treat Population).

Shown is the cumulative incidence of primary end-point events. The primary end point was a composite of stroke, systemic embolism, major bleeding (as defined by the International Society on Thrombosis and Haemostasis), or death from cardiovascular causes at 24 months. The hazard ratio was calculated as a subhazard ratio with the use of the Fine–Gray method to adjust for death from noncardiovascular causes as a competing risk, and the cumulative incidence was estimated with the cumulative-incidence function. The inset displays the same data on an expanded y axis.

This trial has several limitations. First, although the end-point events were adjudicated by members of an independent clinical-events committee who were unaware of the trial-group assignments, the open-label design may have introduced bias. Second, the lower-than-anticipated incidence of primary end-point events limited the precision of the treatment-effect estimate, and the results should be interpreted with caution. Third, since 5.4% of the patients in each group did not complete the 2-year follow-up, the results should be interpreted with caution, despite similar baseline characteristics among those with and without complete follow-up (Table S8). Fourth, antiplatelet therapy was used in approximately one third of the patients in the no-anticoagulant group, which may have increased the risk of bleeding and put this group at a disadvantage with regard to the safety comparison. Fifth, generalizability may be limited because this trial included only East Asian patients from a single country,[28-31] and women and patients

Subgroup	No. of Patients	DOAC Therapy	No Anticoagulant Therapy	Hazard Ratio (95% CI)
		no. of patients with event/total no. (estimated %)		
All patients	1803	4/902 (0.5)	13/901 (1.5)	0.31 (0.10–0.94)
Age				
<65 yr	1217	2/598 (0.3)	8/619 (1.4)	0.26 (0.05–1.20)
≥65 yr	586	2/304 (0.7)	5/282 (1.8)	0.37 (0.07–1.91)
Sex				
Female	427	0/220 (0)	2/207 (1.0)	—
Male	1376	4/682 (0.6)	11/694 (1.6)	0.37 (0.12–1.16)
Congestive heart failure				
Yes	165	0/93 (0)	1/72 (1.5)	—
No	1638	4/809 (0.5)	12/829 (1.5)	0.34 (0.11–1.05)
Hypertension				
Yes	917	1/435 (0.2)	3/482 (0.6)	0.37 (0.04–3.50)
No	886	3/467 (0.7)	10/419 (2.5)	0.27 (0.07–0.97)
Diabetes mellitus				
Yes	137	1/67 (1.5)	4/70 (6.1)	0.24 (0.03–2.13)
No	1666	3/835 (0.4)	9/831 (1.1)	0.33 (0.09–1.22)
Vascular disease				
Yes	17	0/11 (0)	0/6 (0)	—
No	1786	4/891 (0.5)	13/895 (1.5)	0.31 (0.10–0.94)
HAS-BLED score				
0	1053	1/556 (0.2)	4/497 (0.8)	0.22 (0.02–1.96)
≥1	750	3/346 (0.9)	9/404 (2.3)	0.39 (0.11–1.45)
Type of atrial fibrillation				
Paroxysmal	1294	3/636 (0.5)	7/658 (1.1)	0.44 (0.11–1.69)
Nonparoxysmal	509	1/266 (0.4)	6/243 (2.6)	0.15 (0.02–1.27)

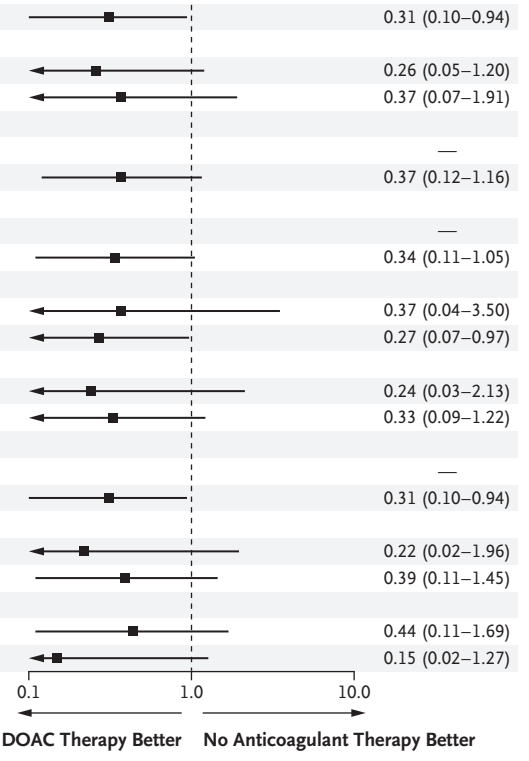


Figure 3. Subgroup Analyses of the Primary End Point.

Shown are hazard ratios for the comparison between DOAC therapy and no anticoagulant therapy for a primary end-point event according to prespecified subgroups. Death from noncardiovascular causes was treated as a competing event. Hazard ratios were estimated with the use of subdistribution-hazard models, and the cumulative incidence was estimated with the cumulative-incidence function. 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). Because the statistical analysis plan did not include a provision for correcting for multiplicity in tests for subgroup analyses, the widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. A subgroup analysis according to the type of atrial fibrillation (paroxysmal or nonparoxysmal) was performed post hoc.

with nonparoxysmal atrial fibrillation might be underrepresented (Table S9).

In the SINGLE-AF trial involving patients with atrial fibrillation at intermediate risk for stroke, DOAC therapy resulted in a lower risk of a composite of stroke, systemic embolism, major bleeding, or death from cardiovascular causes than no anticoagulant therapy at 24 months. Given the lower-than-expected number of end-point events, the precision of the estimated treatment effect is limited, and these findings should be interpreted with caution.

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