ORIGINAL ARTICLE

Antithrombotic Therapy after Successful Catheter Ablation for Atrial Fibrillation

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ABSTRACT

BACKGROUND

Whether successful catheter ablation for atrial fibrillation eliminates the need for long-term oral anticoagulant therapy is unknown.

METHODS

We conducted an international, open-label, randomized, blinded-outcome-assessment trial involving 1284 patients who had undergone successful catheter ablation for atrial fibrillation at least 1 year earlier and had a CHA_2DS_2-VASc score (scores range from 0 to 9, with higher scores indicating a higher risk of stroke) of 1 or more (or ≥2 for women or for patients in whom vascular disease was a risk factor). Patients were randomly assigned to receive either aspirin (at a dose of 70 to 120 mg daily, depending on availability in the local jurisdiction) or rivaroxaban (at a dose of 15 mg) and followed for 3 years. Magnetic resonance imaging (MRI) of the head was performed after enrollment and at 3 years. The primary outcome was a composite of stroke, systemic embolism, or new covert embolic stroke (defined by ≥1 new infarct measuring ≥15 mm on MRI) at 3 years.

RESULTS

A total of 641 patients were assigned to the rivaroxaban group and 643 to the aspirin group. A primary-outcome event occurred in 5 patients (0.31 events per 100 patient-years) in the rivaroxaban group and in 9 patients (0.66 events per 100 patient-years) in the aspirin group (relative risk, 0.56; 95% confidence interval [CI], 0.19 to 1.65; absolute risk difference at 3 years, −0.6 percentage points; 95% CI, −1.8 to 0.5; P=0.28). New cerebral infarcts measuring less than 15 mm occurred in 22 of 568 patients (3.9%) in the rivaroxaban group and in 26 of 590 patients (4.4%) in the aspirin group (relative risk, 0.89; 95% CI, 0.51 to 1.55). Fatal or major bleeding (the composite primary safety outcome) had occurred in 10 patients (1.6%) with rivaroxaban and in 4 patients (0.6%) with aspirin (hazard ratio, 2.51; 95% CI, 0.79 to 7.95) at 3 years.

CONCLUSIONS

Among patients who had had successful catheter ablation for atrial fibrillation at least 1 year earlier and had risk factors for stroke, treatment with rivaroxaban did not result in a significantly lower incidence of a composite of stroke, systemic embolism, or new covert embolic stroke than treatment with aspirin. (Funded by Bayer and others; OCEAN ClinicalTrials.gov number, NCT02168829.)

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Catheter ablation is an established therapy for the treatment of atrial fibrillation and is superior to medical therapy in reducing the recurrence and burden of atrial fibrillation.[1] A low burden of atrial fibrillation has been associated with a decreased risk of stroke,[2-4] but it is unclear whether successful catheter ablation reduces the risk of stroke enough that the risk–benefit ratio does not support the need for oral anticoagulant therapy. Consequently, current guidelines state that anticoagulation should be continued indefinitely after atrial fibrillation ablation on the basis of the patient's stroke risk profile and not the apparent success of the procedure.[1,5] These recommendations are based on evidence from small, nonrandomized studies.[6-14]

The risks and benefits of ongoing anticoagulation after successful atrial fibrillation ablation remain unclear. The purpose of this trial was to evaluate whether ongoing anticoagulation with rivaroxaban would be superior to aspirin for the prevention of stroke, systemic embolism, and covert embolic stroke in patients with risk factors for stroke who had undergone successful catheter ablation for atrial fibrillation.

Methods

Design and Oversight

The Optimal Anticoagulation for Enhanced Risk Patients Post-Catheter Ablation for Atrial Fibrillation (OCEAN) trial was an investigator-initiated, prospective, open-label, randomized, blinded-outcome-assessment trial that was conducted at 56 sites in 6 countries. A list of participating sites and committees is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The trial design has been reported previously,[15,16] and the trial protocol is available at NEJM.org. The protocol was approved by the ethics committee at each site and by any required national authorities. An independent data and safety monitoring board monitored the trial conduct, data management, and patient safety. All the patients provided written informed consent.

The trial was managed by the University of Ottawa Heart Institute (UOHI) Cardiovascular Research Methods Centre under the supervision of the first two authors and the last author, who vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. An interim analysis was initially planned after all the patients had undergone magnetic resonance imaging (MRI) of the head at 1 year, but the requirement for this imaging study was ultimately removed because of the coronavirus disease 2019 pandemic; therefore, the interim analysis was removed from the protocol in July 2021. All statistical analyses were performed by UOHI statisticians. The first two authors drafted the manuscript, and all the authors made the decision to submit the article for publication and provided review and revisions. Funding was provided by Bayer, Abbott, Biotronik, the Canadian Institutes of Health Research, the UOHI Accelerate funding program, the Canadian Stroke Prevention Intervention Network, the Brain-Heart Interconnectome Canada First Research Excellence Fund, and the Rosenfeld Heart Foundation. None of the funders were involved in the data analysis or the preparation of the manuscript.

Patients

Eligible patients had undergone successful catheter ablation for nonvalvular atrial fibrillation at least 1 year before enrollment. A successful ablation procedure was defined by no clinical evidence of any atrial arrhythmia and no atrial arrhythmia lasting longer than 30 seconds on at least one 24-hour Holter monitor study between 2 and 6 months after the ablation procedure and on at least one 24-hour Holter monitor study at any time after 6 months after the ablation procedure. In accordance with the protocol, patients also underwent additional 48-hour Holter monitoring during the 2 months before enrollment. Patients had to have a CHA_2DS_2-VASc score of 1 or more or a score of 2 or more for women and for patients in whom vascular disease was a risk factor (scores range from 0 to 9, with higher scores indicating a higher risk of stroke).[17]

Patients were excluded if they had a creatinine clearance of less than 30 ml per minute, if they had a contraindication to anticoagulant or antiplatelet therapy, if they had a contraindication to MRI, if they had valvular atrial fibrillation (associated with rheumatic mitral-valve disease or mechanical valve replacement), if they had had a disabling stroke within the past year or any stroke within 14 days before enrollment, if they had a hypercoagulability disorder or a known intracranial vascular anomaly, or if they were older than 85 years of age.

INTERVENTIONS

Patients were randomly assigned in a 1:1 ratio to receive either aspirin at a dose of 70 to 120 mg daily (depending on availability in the local jurisdiction) or rivaroxaban at a dose of 15 mg daily.[15,16] Aspirin was chosen because, although it may provide minimal benefit for a reduction in the risk of stroke in patients with atrial fibrillation who have a very low risk of stroke,[17] it may provide greater benefit in patients with a higher stroke risk.[18] Rivaroxaban at a dose of 15 mg has pharmacokinetic properties that are similar to those of the 20-mg dose but with a lower bleeding risk, and the 15-mg dose has been evaluated in other trials.[19-23]

Randomization was performed by means of a Web-based system with the use of blocks of varying sizes and was stratified according to trial site. For patients who were unable to take aspirin owing to adverse effects, no antiplatelet agent was given; for patients who were unable to take rivaroxaban because of adverse effects, an alternative direct oral anticoagulant was allowed. For cases in which patients underwent cardioversion, acute coronary intervention, or an interventional or surgical procedure, the strategy for the temporary addition, switching, or interruption of anticoagulant or antiplatelet therapy was detailed in the trial protocol and is also provided in the Supplementary Appendix. By design, patients who underwent repeat ablation procedures for atrial fibrillation during the 3-year follow-up period were withdrawn from the trial.

All the patients underwent MRI of the head at baseline, and surviving patients underwent a second MRI at the 3-year follow-up visit to detect covert embolic stroke. The first 658 enrolled patients also underwent MRI at 1 year until the protocol was modified. The methods and techniques for performing MRI of the head are provided in the Supplementary Appendix. The imaging core laboratory was at the University of Calgary.

Patients had in-person follow-up visits at 6 months, 12 months, and then annually through 3 years. However, during the pandemic, telephone follow-up was allowed. Cardiac testing or monitoring was performed as clinically indicated.

OUTCOMES

The primary outcome was a composite of stroke, systemic embolism, or new covert embolic stroke detected by MRI of the head at 3 years. Covert embolic stroke was defined by at least one new cerebral infarct measuring at least 15 mm that was detected between the baseline MRI and the MRI at 3 years.[24] The primary safety outcome, a composite of fatal bleeding or major bleeding, was defined in accordance with the International Society on Thrombosis and Haemostasis.[25] Data for all clinical outcomes were adjudicated by a committee whose members were unaware of the treatment assignments. All MRI scans of the head were independently reviewed by two core laboratory readers who were unaware of the treatment assignments. Discrepancies were resolved by consensus.

Key secondary outcomes were the individual components of the primary efficacy outcome; the composite of stroke or systemic embolism; major, minor, and clinically relevant nonmajor bleeding; intracranial hemorrhage; transient ischemic attack; new cerebral infarcts measuring less than 15 mm; and death from any cause. A full list of the secondary outcomes is provided in Table S1 in the Supplementary Appendix.

STATISTICAL ANALYSIS

We calculated a sample size of 1572 patients. This number was based on a risk of stroke and systemic embolism of 1.6% per year and a risk of covert embolic stroke of 1.9% per year, resulting in a combined risk of a primary-outcome event of 3.5% per year. Patients who underwent repeat ablation for atrial fibrillation during follow-up were withdrawn from the trial; the percentage of patients who were expected to be withdrawn for this reason was assumed to be 1.25% per year. We assumed a 2% loss to follow-up over the course of 3 years. Crossovers were defined as patients who switched from their assigned treatment to the other treatment for more than 3 months. Patients who temporarily switched to the other therapy in accordance with the trial protocol because of undergoing cardioversion, coronary intervention, or an invasive procedure were not considered to be crossovers. Given the current guidelines favoring anticoagulation, we assumed that the incidence of crossovers would be 3.75% in the aspirin group and 1.5% in the rivaroxaban group over the course of 3 years. On the basis of these assumptions, the trial had 80% power to detect a relative reduction of 40% in the risk of a primary-outcome event in the rivaroxaban group with a two-sided alpha level of 0.05.

An interim analysis was initially planned but later removed from the protocol when the requirement for MRI at 1 year was removed. Therefore, there were no formal rules for stopping the trial for efficacy or futility beyond the judgment of the data and safety monitoring board.

The primary efficacy and safety outcomes were analyzed in the intention-to-treat population, which was defined as all the patients who had undergone randomization. The primary efficacy outcome was analyzed with the use of a chi-square test and reported with a relative risk and an absolute risk difference with 95% confidence intervals. A logistic-regression model that included key variables was used to assess the consistency of the treatment effect. The primary safety outcome was assessed in a time-to-event analysis with the use of the Kaplan–Meier method with a hazard ratio and 95% confidence interval. A nonparametric log-rank test was used to compare the primary safety outcome in the two groups.

Dichotomous secondary outcomes were analyzed in the intention-to-treat population with the same methods that were used for the primary efficacy outcome. Time-to-event secondary outcomes, such as stroke or systemic embolism and the bleeding outcomes, were analyzed by means of the Kaplan–Meier method with a nonparametric log-rank test. A Cox proportional-hazards model was used to assess the consistency of the treatment effect. In the event that death was a competing risk, the Fine–Gray subdistribution hazard model was used to compare cumulative incidence curves. The treatment effect on the primary outcome was also compared in prespecified subgroups. For the secondary outcomes, the widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

Analyses of the primary and secondary outcomes were repeated for the per-protocol population, which was defined as patients who received the intended treatment, did not have any major protocol violations, and were not lost to follow-up. Categorical data are presented as numbers and percentages. Continuous data are presented as means with standard deviations or as medians with interquartile ranges. All the analyses were conducted with the use of SAS software, version 9.4 (SAS Institute). Additional details regarding the statistical methods are provided in the statistical analysis plan (available with the protocol).

RESULTS

PATIENTS

On May 19, 2022, the data and safety monitoring board recommended stopping enrollment in the trial because of a high likelihood that completion of the trial would not show a benefit of rivaroxaban for the primary outcome; an increased risk of nonmajor bleeding was also noted. All the patients who had already provided written informed consent were allowed to undergo randomization, and follow-up of all the patients who had undergone randomization was permitted while they continued to receive their assigned treatment, with ongoing oversight by the data and safety monitoring board. Investigators were not made aware of any interim trial results.

Between March 30, 2016, and July 25, 2022, a total of 1284 patients underwent randomization, and all were included in the intention-to-treat analysis (Fig. 1). Because of unacceptable adverse effects from the assigned trial medication, 34 patients received an alternative direct oral anticoagulant instead of rivaroxaban and 7 patients received no antiplatelet therapy instead of aspirin, as allowed by the trial protocol. Death occurred in 10 patients in the rivaroxaban group and in 7 patients in the aspirin group. Only 4 patients in each group were lost to follow-up. In accordance with the protocol, a total of 71 patients were withdrawn from the trial owing to repeat ablation for atrial fibrillation during the follow-up period. Excluding withdrawals from the trial, 1104 of 1134 patients (97.4%) underwent MRI of the head at 3 years. The median duration of follow-up was 36.0 months (interquartile range, 35.5 to 36.9).

The characteristics of the patients at baseline are shown in Table 1 and Table S2, and the representativeness of the trial population is shown in Table S3. Patients were enrolled a median of 16.4 months (interquartile range, 13.5 to 25.2) after their last ablation procedure. The mean (±SD) age of the patients was 66.3±7.3 years, and 28.6% were women. The mean CHA_2DS_2-VASc score was 2.2±1.1, and 31.9% of the patients had a score of 3 or higher.

PRIMARY EFFICACY OUTCOME

A primary-outcome event occurred in 5 patients (0.8%) in the rivaroxaban group and in 9 patients (1.4%) in the aspirin group (relative risk, 0.56; 95% confidence interval [CI], 0.19 to 1.65; absolute risk difference at 3 years, −0.6 percentage

points; 95% CI, −1.8 to 0.5; P=0.28) (Table 2), corresponding to an annualized rate of 0.31 events per 100 patient-years with rivaroxaban and 0.66 events per 100 patient-years with aspirin. The results of a sensitivity analysis of the primary outcome with adjustment for key variables appeared to be similar to those of the unadjusted analysis (Table S4). The number of patients that would need to be treated to prevent one primary-outcome event or one individual component of the primary outcome is shown in Table S5. The results of analyses of the primary efficacy outcome in prespecified subgroups seemed to be consistent with those of the main analysis (Fig. S1 and Table S6).

SECONDARY EFFICACY OUTCOMES

The incidence of the individual components of the primary efficacy outcome is shown in Table 2. Stroke or systemic embolism occurred in 0.8% of the patients in the rivaroxaban group and in 1.1% of those in the aspirin group (relative risk, 0.72; 95% CI, 0.23 to 2.25) (Fig. 2). The incidence of new covert embolic stroke also was not substantially different in the two groups, occurring in no patients in the rivaroxaban group and in 0.3% of those in the aspirin group. New cerebral infarcts measuring less than 15 mm occurred in 22 of 568 patients (3.9%) in the rivaroxaban group and in 26 of 590 patients (4.4%) in the aspirin group (relative risk, 0.89; 95% CI, 0.51 to 1.55) (Table S7).

SAFETY OUTCOMES

Fatal or major bleeding (the primary safety outcome) occurred in 10 patients (1.6%) in the rivaroxaban group and in 4 patients (0.6%) in the aspirin group (hazard ratio, 2.51; 95% CI, 0.79 to 7.95) (Table 3 and Fig. S2). The incidence of the individual components of the safety outcome, specifically fatal bleeding and major bleeding, did not appear to be substantially different in the two groups (Table 3). Clinically relevant nonmajor bleeding occurred in 5.5% of the patients in the rivaroxaban group, as compared with 1.6% of those in the aspirin group (hazard ratio, 3.51; 95% CI, 1.75 to 7.03) (Fig. S3). The incidence of minor bleeding was also higher in the rivaroxaban group. The numbers of patients that would need to be treated to result in harm are shown in Table S8. Summaries of all major adverse events that occurred during the trial are provided in Tables S9 and S10.

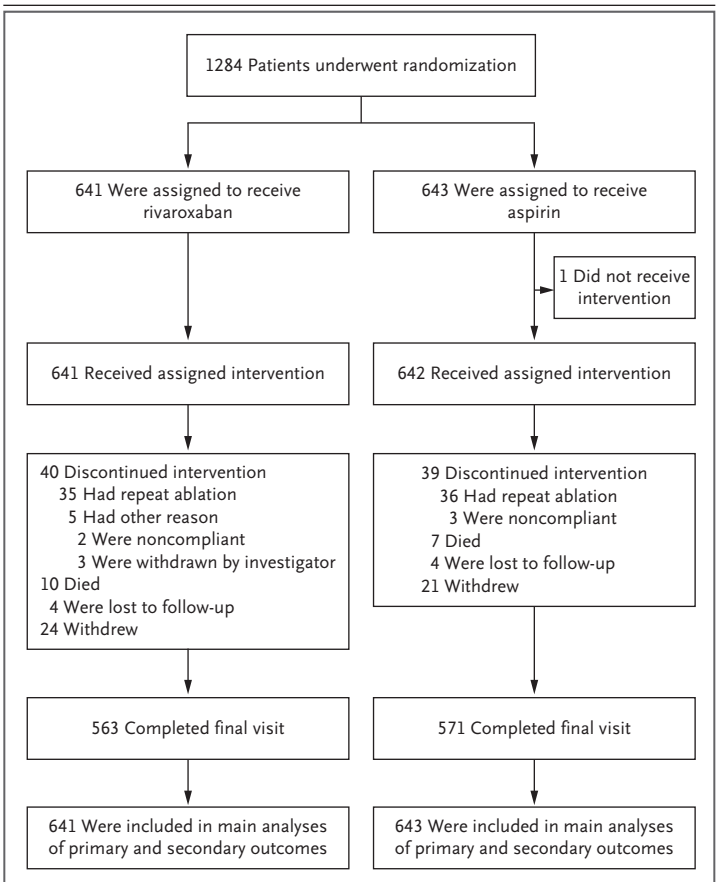

Figure 1. Randomization and Follow-up.

PER-PROTOCOL ANALYSES

Analyses of the primary efficacy and safety outcomes were performed in the per-protocol population. The results did not appear to differ markedly from those of the analyses performed in the intention-to-treat population (Tables S11 and S12).

DISCUSSION

Among patients who had undergone ablation for atrial fibrillation at least 1 year before enrollment and did not have recurrent atrial tachyarrhythmia, treatment with rivaroxaban did not lead to a significantly lower incidence of stroke, systemic embolism, or new covert embolic stroke (the primary composite outcome) than treatment with aspirin. The incidence of stroke or new covert embolic stroke in both groups was much lower than anticipated. Overall, 96% of the patients in both groups had no evidence of new cerebral infarcts on MRI at 3 years. The incidence of fatal bleeding and major bleeding was similar in the

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

Characteristic	Rivaroxaban (N=641)	Aspirin (N=643)
Demographics		
Age — yr	66.3±7.1	66.3±7.6
Male sex — no. (%)	458 (71.5)	459 (71.4)
Atrial fibrillation history		
Median time since first atrial fibrillation ablation (IQR) — mo	19.3 (13.9–35.7)	19.3 (14.2–31.3)
Median time since most recent atrial fibrillation ablation (IQR) — mo	16.4 (13.4–25.2)	16.5 (13.6–25.2)
Total no. of ablations for atrial fibrillation or atrial tachyarrhythmia — no. (%)		
1	484 (75.5)	504 (78.4)
2	133 (20.7)	105 (16.3)
≥3	24 (3.7)	34 (5.3)
Type of atrial fibrillation — no. (%)		
Paroxysmal	431 (67.2)	421 (65.5)
Persistent	204 (31.8)	212 (33.0)
Long-standing persistent	6 (0.9)	10 (1.6)
Total HAS-BLED score†	1.4±0.9	1.3±0.8
Coexisting conditions		
Hypertension — (%)	442 (69.0)	434 (67.5)
Diabetes — (%)	96 (15.0)	77 (12.0)
Stroke — (%)		
Ischemic	7 (1.1)	17 (2.6)
Hemorrhagic	0	2 (0.3)
Uncertain	3 (0.5)	6 (0.9)
Transient ischemic attack — (%)	18 (2.8)	25 (3.9)
Coronary artery disease — (%)	74 (11.5)	68 (10.6)
Ischemic cardiomyopathy — (%)	9 (1.4)	6 (0.9)
Nonischemic cardiomyopathy — (%)	15 (2.3)	20 (3.1)
Peripheral vascular disease — (%)	9 (1.4)	9 (1.4)
Clinically significant carotid artery disease — (%)	2 (0.3)	4 (0.6)
CHA_2DS_2VASc score‡		
Mean	2.2±1.1	2.2±1.1
Distribution — no. (%)		
1	194 (30.3)	196 (30.5)
2	241 (37.6)	243 (37.8)
3	138 (21.5)	127 (19.8)
≥4	68 (10.6)	77 (12.0)
Echocardiography§		
Ejection fraction — %	61.8±7.1	61.5±7.3
Left ventricular function — no. (%)		
Normal	476 (99.2)	453 (97.8)
Abnormal	4 (0.8)	10 (2.2)
Mild impairment	4 (0.8)	6 (1.3)
Moderate impairment	0	3 (0.6)
Severe impairment	0	1 (0.2)
Left atrial diameter — mm¶	40.7±16.0	40.4±19.2

* Plus–minus values are means ±SD. Baseline data were collected at the time of randomization. Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† HAS-BLED scores reflect the risk of major bleeding. Scores range from 0 to 9, with higher scores indicating a higher risk of major bleeding.
‡ Scores range from 0 to 9, with higher scores indicating a higher risk of stroke. For women and for patients in whom vascular disease was a risk factor, a score of 2 or higher was required for inclusion in the trial.
§ A total of 161 patients in the rivaroxaban group and 180 patients in the aspirin group had missing data.
¶ The normal diameter is less than 40 mm.

two groups, whereas the incidence of minor and clinically relevant nonmajor bleeding was higher with rivaroxaban than with aspirin.

Current guidelines recommend continuing anticoagulant therapy indefinitely in patients with risk factors for stroke after ablation regardless of the success of the procedure.[1,5] This is because ablation may reduce the burden of atrial fibrillation but does not eliminate it[1,26]; even brief durations of atrial fibrillation may increase the risk of stroke,[2] and stroke risk among patients with atrial fibrillation is assessed on the basis of risk factors and not the duration of atrial fibrillation.[17] Among the patients with risk factors for stroke after successful ablation for atrial fibrillation in our trial, strokes were rare, and we could not detect a benefit of continuing anticoagulation.

The rates of a primary-outcome event were much lower than anticipated, with an annualized rate of a composite of stroke, systemic embolism, or new covert embolic stroke detected by head MRI at 3 years of 0.31 events per 100 patient-years in the rivaroxaban group and 0.66 events per 100 patient-years in the aspirin group. In contrast, in a trial involving patients with clinical atrial fibrillation who had not undergone ablation but had a stroke risk similar to that seen in our trial population, annualized rates of stroke of 1.6% for anticoagulant therapy and 3.7% for aspirin were observed.[27] Furthermore, in a population of patients with subclinical atrial fibrillation, the annualized rate of stroke was 0.85% with anticoagulant therapy and 0.97% with aspirin.[28] The annualized rate of stroke in our trial is similar to that of patients with a CHA_2DS_2-VASc risk score of 2 and no history of atrial fibrillation.[29]

One explanation for the low stroke risk is that it is plausible that catheter ablation reduces the

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Rivaroxaban (N=641)	Aspirin (N=643)	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)†
Primary composite outcome: stroke, systemic embolism, or new covert embolic stroke				
No. of patients (%)	5 (0.8)	9 (1.4)	0.56 (0.19 to 1.65)	−0.6 (−1.8 to 0.5)‡
Annualized rate — events per 100 patient-yr	0.31	0.66	—	—
Components of primary outcome				
All stroke				
No. of patients (%)	5 (0.8)	7 (1.1)	0.72 (0.23 to 2.25)	−0.3 (−1.4 to 0.7)
Annualized rate — events per 100 patient-yr	0.31	0.58	—	—
Systemic embolism				
No. of patients (%)	0	0	—	—
Annualized rate — events per 100 patient-yr	0	0	—	—
New covert embolic stroke				
No. of patients (%)	0	2 (0.3)	0	−0.3 (−0.7 to 0.1)
Annualized rate — events per 100 patient-yr	0	0.08	—	—
Other secondary outcomes				
All stroke or systemic embolism				
No. of patients (%)	5 (0.8)	7 (1.1)	0.72 (0.23 to 2.25)	−0.3 (−1.4 to 0.7)
Annualized rate — events per 100 patient-yr	0.29	0.58	—	—
Transient ischemic attack				
No. of patients (%)	1 (0.2)	5 (0.8)	0.20 (0.02 to 1.71)	−0.6 (−1.4 to 0.1)
Annualized rate — events per 100 patient-yr	0.05	0.26	—	—

* The widths of the confidence intervals for the components of the primary outcome and secondary outcomes have not been adjusted for multiplicity and should not be used to infer a treatment effect.
† Differences are expressed as percentage points.
‡ P=0.28.

Table 3. Safety Outcomes.*

Outcome	Rivaroxaban (N=641)	Aspirin (N=643)	Hazard Ratio (95% CI)
	no. of patients (%)		
Primary composite safety outcome: fatal bleeding or major bleeding	10 (1.6)	4 (0.6)	2.51 (0.79–7.95)
Secondary safety outcomes			
Fatal bleeding	0	0	—
Major bleeding	10 (1.6)	4 (0.6)	2.51 (0.79–7.95)
Intracranial bleeding	5 (0.8)	1 (0.2)	5.02 (0.59–42.81)
Gastrointestinal bleeding	3 (0.5)	2 (0.3)	1.50 (0.25–8.97)
Other major bleeding	2 (0.3)	1 (0.2)	2.01 (0.18–22.07)
Minor bleeding	74 (11.5)	20 (3.1)	3.71 (2.29–6.01)
Clinically relevant nonmajor bleeding	35 (5.5)	10 (1.6)	3.51 (1.75–7.03)
Composite of major bleeding or minor bleeding	83 (12.9)	23 (3.6)	3.62 (2.31–5.67)
Death from any cause	10 (1.6)	7 (1.1)	1.43 (0.55–3.74)

* The widths of the confidence intervals for the primary and secondary safety outcomes have not been adjusted for multiplicity and should not be used to infer a treatment effect.

burden of atrial fibrillation to the point where the risk of stroke is similar to that in a population of patients without atrial fibrillation in whom stroke is predominantly caused by nonembolic events. It is also possible that, because of selection bias, patients who undergo atrial fibrillation ablation are at lower risk of stroke than their risk score would suggest. For example, our trial included few patients with a history of stroke. Given such low event rates, a sample size of more than 11,000 patients would have been needed to detect a relative reduction of 40% in the risk of stroke in the rivaroxaban group.

We included the use of head MRI to ensure that subtle embolic cerebral events were not missed. The fact that 96% of the patients in our trial had no evidence of new infarcts over the course of 3 years provides confidence in the low event rate observed in this trial. Covert embolic stroke was included as part of the primary composite outcome because it is associated with an increased risk of clinical stroke, cognitive decline, and death,[30,31] and it has been used as an outcome in previous clinical trials.[32-34] The ratio of covert embolic stroke to clinical stroke has been reported to be 1:1 to 3:1 among anticoagulant-treated and untreated patients,[32,34] so inclusion of new covert embolic stroke in our primary outcome reduced our calculated sample size. However, the rates of new covert embolic stroke were so low in our trial population that we still could not detect any benefit for anticoagulation.

The incidence of major bleeding and fatal bleeding was also low and did not appear to be markedly different in the two groups. As expected, clinically relevant nonmajor bleeding and minor bleeding were more common with anticoagulation. For patients with atrial fibrillation after successful ablation who have a risk of stroke that is similar to that of the patients in this trial, continuation of either aspirin or anticoagulation may be reasonable, but patients should be aware that anticoagulation carries an increased risk of clinically relevant bleeding.

Our findings are similar to those of the ALONE-AF (Anticoagulation One Year after Ablation of Atrial Fibrillation in Patients with Atrial Fibrillation) trial — another trial that involved patients who had undergone ablation; the annualized rate of stroke among patients with a median CHA_2DS_2-VASc score of 2 was approximately 0.4%.[35] Key differences between the ALONE-AF trial and our trial are that our trial included more randomly assigned patients, the duration of follow-up was longer in our trial, and all the patients in our trial underwent MRI of the head. In

the OPTION (Comparison of Anticoagulation with Left Atrial Appendage Closure after Atrial Fibrillation Ablation) trial, occlusion of the left atrial appendage after atrial fibrillation ablation and discontinuation of anticoagulation was noninferior to the use of continued anticoagulation for stroke and major bleeding[36] (annualized event rate of approximately 0.6 in both groups). However, among patients who were enrolled in the OPTION trial, the mean CHA_2DS_2-VASc score was 3.5, whereas 32% of the patients in our trial had a CHA_2DS_2-VASc score of 3 or higher.

Together, these three trials (ALONE-AF, OPTION, and our trial) examined four approaches to antithrombotic management after ablation for atrial fibrillation: appendage occlusion, continued anticoagulation, treatment with aspirin, and no treatment. Which of the strategies is best after ablation for atrial fibrillation is unclear, but all the approaches were associated with an annualized rate of stroke of less than 1%, which is commonly regarded as the threshold for anticoagulation.[1]

Our trial has limitations. A placebo could have been chosen over aspirin as a comparator. However, if we assume that aspirin had no benefit with respect to stroke, the results of the primary outcome would have been similar with placebo. The incidence of events was so low that the use of a 20-mg dose of rivaroxaban would have been unlikely to yield a result that differed from that seen with the 15-mg dose. The trial did not mandate any extended monitoring of atrial fibrillation before enrollment or during follow-up, so the precise incidence of recurrence of asymptomatic atrial fibrillation is unknown. However, the trial was meant to be practical, and the approach for monitoring resembled clinical practice worldwide, which allowed broad application of the results. Finally, our trial included patients with a moderate risk of stroke and minimal cardiac disease, so for patients with a very high stroke risk, the findings of our trial are not directly relevant.

Among patients who had risk factors for stroke and had undergone successful catheter ablation for atrial fibrillation at least 1 year earlier, treatment with rivaroxaban did not result in a significantly lower incidence of a composite of stroke, systemic embolism, or new covert embolic stroke than treatment with aspirin. The incidence of major bleeding appeared to be similar in the two groups, although the incidence of minor bleeding and clinically relevant nonmajor bleeding was higher with rivaroxaban than with aspirin.

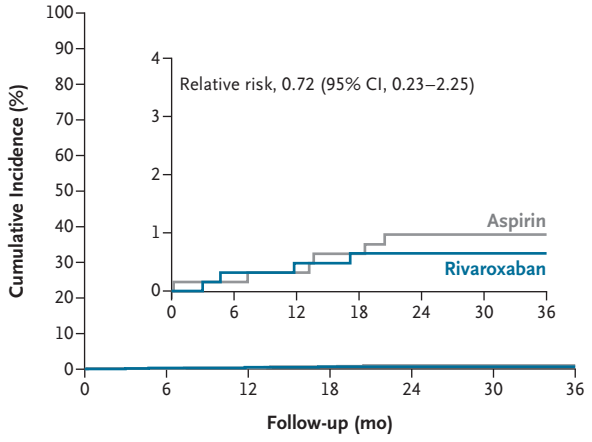

Figure 2. Cumulative Incidence of Stroke or Systemic Embolism.
The inset shows the same data on an expanded y axis.

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