

ORIGINAL ARTICLE

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

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ABSTRACT

BACKGROUND

Embolic strokes of undetermined source represent 20% of ischemic strokes and are associated with a high rate of recurrence. Anticoagulant treatment with rivaroxaban, an oral factor Xa inhibitor, may result in a lower risk of recurrent stroke than aspirin.

METHODS

We compared the efficacy and safety of rivaroxaban (at a daily dose of 15 mg) with aspirin (at a daily dose of 100 mg) for the prevention of recurrent stroke in patients with recent ischemic stroke that was presumed to be from cerebral embolism but without arterial stenosis, lacune, or an identified cardioembolic source. The primary efficacy outcome was the first recurrence of ischemic or hemorrhagic stroke or systemic embolism in a time-to-event analysis; the primary safety outcome was the rate of major bleeding.

RESULTS

A total of 7213 participants were enrolled at 459 sites; 3609 patients were randomly assigned to receive rivaroxaban and 3604 to receive aspirin. Patients had been followed for a median of 11 months when the trial was terminated early because of a lack of benefit with regard to stroke risk and because of bleeding associated with rivaroxaban. The primary efficacy outcome occurred in 172 patients in the rivaroxaban group (annualized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (hazard ratio, 1.07; 95% confidence interval [CI], 0.87 to 1.33; $P=0.52$). Recurrent ischemic stroke occurred in 158 patients in the rivaroxaban group (annualized rate, 4.7%) and in 156 in the aspirin group (annualized rate, 4.7%). Major bleeding occurred in 62 patients in the rivaroxaban group (annualized rate, 1.8%) and in 23 in the aspirin group (annualized rate, 0.7%) (hazard ratio, 2.72; 95% CI, 1.68 to 4.39; $P<0.001$).

CONCLUSIONS

Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding. (Funded by Bayer and Janssen Research and Development; NAVIGATE ESUS ClinicalTrials.gov number, NCT02313909.)

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*A complete list of the NAVIGATE ESUS Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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ISCHEMIC STROKES OF UNCERTAIN CAUSE, also called cryptogenic strokes, are frequent despite advances in the diagnostic techniques used to determine the underlying cause and to implement treatment specific to their causes.¹⁻³ Most cryptogenic strokes are presumed to result from emboli originating from cardiac and arterial sources and occasionally from venous thromboembolism due to paradoxical embolism, such as those associated with patent foramen ovale. For the purposes of clinical trials, the term “embolic stroke of undetermined source” has been proposed to describe a group of cryptogenic strokes, representing approximately 20% of ischemic strokes, that are not associated with proximal arterial stenosis or a recognized cardioembolic source, such as atrial fibrillation of left ventricular thrombus, and that are not lacunar.¹

The known efficacy of anticoagulants for the prevention of embolic stroke in patients with atrial fibrillation^{4,5} led us to hypothesize that anticoagulants would be more effective than antiplatelet therapy for the prevention of recurrent stroke in patients with recent embolic stroke of undetermined source.^{1,6} Rivaroxaban is an orally administered, direct factor Xa inhibitor that is effective for the prevention of stroke in patients with atrial fibrillation. We designed the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) trial to compare rivaroxaban with aspirin to test this hypothesis.

METHODS

TRIAL DESIGN

We conducted this international, randomized, event-driven, phase 3 trial at 459 centers in 31 countries. The rationale for the trial, design details, and eligibility features have been published previously.^{6,7}

Patients were randomly assigned in a 1:1 ratio with variable block size, stratified according to country and age of the patient (<60 years vs. ≥60 years), with the use of an interactive Web-response system, to receive either rivaroxaban at a dose of 15 mg (immediate-release, film-coated tablets) plus placebo or aspirin at a dose of 100 mg (enteric coated tablets) plus placebo; in each group, the two tablets (active drug and placebo) were taken orally once daily. Active medication

and identical placebos were taken with food; adherence to assigned therapy was assessed by means of interview and pill counts at each clinic visit. Patients returned for outpatient visits at 1, 6, and 12 months and then every 6 months, during which there was assessment for the occurrence of safety and efficacy events, adherence, and adverse events. Investigators and patients were unaware of the treatment assignments during the trial.

The trial was conducted and reported in accordance with the protocol (available with the full text of this article at NEJM.org) and the statistical analysis plan. The trial was initiated by the two principal investigators, who designed the trial with input from a steering committee (which included representatives of the trial sponsors, Bayer and Janssen Research and Development). The Population Health Research Institute at McMaster University selected the trial sites, collected and managed the data, and performed the data analysis, with financial support from the sponsors. The trial sponsors provided trial medications, contracted with and paid the members of the steering committee and the trial sites, and provided site monitoring.

The two principal investigators wrote the first draft of the manuscript. There were no agreements in place with the sponsors concerning the confidentiality of trial data. The sponsors commented on the manuscript before submission for publication, but sponsor approval was not required for submission. The authors vouch for fidelity of the trial to the protocol and for the accuracy and completeness of the data and the reporting of adverse events. The protocol was approved by the relevant health authorities and the institutional review board at each trial site. Written informed consent was obtained from each participant.

TRIAL POPULATION

Patients who had ischemic stroke, as identified on cerebral imaging, that had occurred between 7 days and 6 months before screening were eligible if the stroke was not lacunar and was not associated with extracranial vessel atherosclerosis causing more than 50% luminal stenosis in arteries supplying the area of ischemia or with identified risk factors for a cardiac source of embolism (atrial fibrillation, left ventricular thrombus, mechanical prosthetic cardiac valve,

or severe mitral stenosis) and if no other cause of stroke could be found.⁶ Intracranial imaging was optional, but if it was performed, a finding of more than 50% stenosis due to atherosclerosis was an exclusion criterion. Participants had to be older than 49 years at the time of the stroke; if participants were 50 to 59 years of age, they were required to have at least one additional vascular risk factor (hypertension, diabetes, previous ischemic stroke, active tobacco smoking, or heart failure).⁶

After the qualifying stroke, at least 20 total hours of cardiac rhythm monitoring were required in order to rule out atrial fibrillation lasting 6 minutes or longer, although investigators could choose to monitor for longer periods. Cardiac rhythm monitoring had to be completed before randomization, and the presence of implantable loop recorders therefore excluded participation. Echocardiography was required, and intracardiac thrombus that was detected by either transthoracic or transesophageal echocardiography was an exclusion criterion. Patients who had received a diagnosis of patent foramen ovale were eligible for entry to the trial unless there were plans for closure of the defect. Additional exclusion criteria were a history of atrial fibrillation, severely disabling stroke (modified Rankin score of ≥ 4 at screening; scores range from 0 to 6, with higher scores representing worse functional deficits), a specific indication for anticoagulation or for antiplatelet therapy, ongoing regular use of conventional nonsteroidal antiinflammatory drugs, major bleeding within the previous 6 months, and previous nontraumatic intracranial hemorrhage.

OUTCOMES

The primary efficacy outcome was the first recurrent stroke (including ischemic, hemorrhagic, or undefined stroke) or systemic embolism in a time-to-event analysis. Ischemic stroke was defined as a focal neurologic deficit of sudden onset that was due to presumed arterial occlusion persisting for more than 24 hours and without evidence of primary hemorrhage on neuroimaging; if there was a neurologic deficit lasting less than 24 hours, evidence of acute brain infarct had to be present on neuroimaging.⁸ Hemorrhagic strokes included symptomatic, nontraumatic intracerebral and subarachnoid hemorrhages. Undefined strokes (based on an

absence of neuroimaging or autopsy features to distinguish ischemic from hemorrhagic stroke) were considered to be ischemic strokes in the analyses unless otherwise noted.

Secondary efficacy outcomes were a composite of death from cardiovascular causes, recurrent stroke, systemic embolism, and myocardial infarction; death from any cause; disabling stroke (modified Rankin scale score of 4 or 5 at hospital discharge) or fatal stroke (modified Rankin scale score of 6); and individual components of the primary and secondary efficacy outcomes. The severity of the stroke at trial entry was estimated with the use of the National Institutes of Health Stroke Scale (NIHSS) score (scores range from 0 to 42, with higher scores representing worse neurologic deficits).

The primary safety outcome was major bleeding at any site in the body according to the criteria of the International Society of Thrombosis and Hemostasis (ISTH).⁹ Secondary safety outcomes were life-threatening or fatal bleeding, clinically relevant nonmajor bleeding, and intracranial hemorrhage (including traumatic and atraumatic intracerebral, subarachnoid, and subdural or epidural hemorrhage).

Outcome events were reported by local investigators through the completion of case-report forms that included questions regarding outcomes and adverse events. Potential outcome events that did not meet all the trial protocol criteria were adjudicated by stroke experts who were fluent in the language of the participating clinical site and who reviewed untranslated source documents and, if there was disagreement with the local investigator, by the secondary review of translated source documents by the chairs of the central adjudication committee, all of whom were unaware of the treatment assignments.

STATISTICAL ANALYSIS

We planned to enroll 7000 patients and to follow them for a mean of 2 years to detect a rate of primary efficacy outcome events that was 30% lower with rivaroxaban than with aspirin, with 90% power, on the basis of an estimated rate of the primary outcome of 3.8% per year among patients who had been assigned to the aspirin group. The trial was planned to continue until at least 450 events of the primary efficacy outcome had occurred. All the analyses were based on the intention-to-treat population (which included all

patients who underwent randomization) unless otherwise specified. The annualized event rate represents the average number of events per participant during a 1-year period.

The rivaroxaban group was compared with the aspirin group with the use of a log-rank test, and Kaplan–Meier estimates were used to plot the cumulative-incidence risk over time. Hazard ratios were estimated by the Cox proportional-hazards model. Secondary efficacy outcomes were analyzed with the use of methods similar to those used for the primary efficacy analysis. A hierarchical analysis plan stipulated that if the primary efficacy outcome did not differ significantly between treatment groups, secondary outcomes were to be considered to be exploratory and would be reported without claims of statistical significance. All the reported P values are two-sided. Exploratory analyses of prespecified subgroups were undertaken with the variables of age, sex, geographic region, time from the index stroke to randomization, and renal function, but the trial was not powered for subgroup comparisons. There was no imputation for missing data.

An independent data and safety monitoring committee monitored the safety of the patients on an ongoing basis. Two formal interim analyses were planned when approximately 50% and 67% of the first events of the primary efficacy outcome had occurred, with the use of a prespecified stopping rule that was based on modified Haybittle–Peto cutoff points for efficacy. Details are provided in the statistical analysis plan, which is available with the protocol.

RESULTS

PARTICIPANTS AND FOLLOW-UP

After the second interim analysis, on October 5, 2017, the trial was terminated at the recommendation of the data and safety monitoring committee owing to an excess risk of bleeding among patients assigned to rivaroxaban and an absence of an offsetting benefit regarding a reduction in the rate of stroke, with little estimated chance of a benefit being found if the trial proceeded to its planned completion. All the analyses are reported up to that date.

Recruitment began in December 2014 and ended in September 2017, with 7213 participants being randomly assigned to one of the treatment groups (Fig. S1 in the Supplementary Appendix,

available at NEJM.org). Patients were recruited from Europe (43% of the patients were from Western Europe and 15% from Eastern Europe), East Asia (19%), United States and Canada (13%), and Latin America (10%) (Table 1). At the time of trial termination, participants had been followed for a median of 11 months (range, 1 to 33; interquartile range, 5 to 17).

The mean age of the patients was 67 years, and 62% of the patients were men. In the entire cohort, there was a history of hypertension in 77% of the patients, diabetes mellitus in 25%, and previous stroke or transient ischemic attack in 18% (Table 1). Patent foramen ovale was diagnosed in 5% of the participants (313 of 6883) undergoing transthoracic echocardiography and in 27% of those (379 of 1382) undergoing transesophageal echocardiography (patients may have undergone both procedures). Overall, 7% of the participants (259 patients in the rivaroxaban group and 275 in the aspirin group) had patent foramen ovale. There were no significant differences in the demographic or clinical characteristics between the rivaroxaban group and the aspirin group. Intracranial arterial imaging was performed in 78% of the patients. The median duration of cardiac rhythm monitoring before randomization was 24 hours (interquartile range, 24 to 48), with 34% of participants undergoing monitoring for 48 hours or longer. The median time from the qualifying stroke to randomization was 37 days (interquartile range, 14 to 88); 25% of the patients were entered within 2 weeks. The median NIHSS score after the initial stroke was 1 (interquartile range, 0 to 2) in each group, representing minor residual deficits at trial entry.

The trial drug was discontinued before a primary outcome event in 15% of the patients in the rivaroxaban group and in 12% of those in the aspirin group. Protocol-mandated discontinuation of trial medication due to atrial fibrillation occurred in 155 patients (2%; 80 patients in the rivaroxaban group and 75 in the aspirin group) after a median of 5 months (interquartile range, 2 to 11). A total of 1% of the patients were lost to follow-up after a mean (\pm SD) of 15 ± 9 months, and an additional 1% of the patients withdrew consent for follow-up after a mean of 5 ± 6 months. Vital status was available at the end of trial for 99% of the patients who had undergone randomization and who had not withdrawn consent or been lost to follow-up.

Table 1. Characteristics of the Patients at Trial Entry.*

Characteristic	Rivaroxaban Group (N=3609)	Aspirin Group (N=3604)
Age — yr	66.9±9.8	66.9±9.8
Male sex — no. (%)	2232 (62)	2204 (61)
Race — no. (%)†		
White only	2612 (72)	2604 (72)
Black only	51 (1)	60 (2)
Asian only	716 (20)	698 (19)
Other	230 (6)	242 (7)
Body-mass index‡	27.1±4.9	27.3±5.1
Blood pressure — mm Hg		
Systolic	135.1±17.0	134.9±16.6
Diastolic	79.0±10.8	78.9±10.8
Statin use after randomization — no. (%)	2815 (78)	2789 (77)
Hypertension — no. (%)	2782 (77)	2803 (78)
Diabetes mellitus — no. (%)	889 (25)	917 (25)
Current tobacco use — no. (%)	756 (21)	728 (20)
Previous stroke or TIA — no. (%)	620 (17)	643 (18)
Geographic region — no. (%)		
United States or Canada	461 (13)	457 (13)
Latin America	372 (10)	374 (10)
Western Europe	1541 (43)	1540 (43)
Eastern Europe	560 (16)	558 (15)
East Asia	675 (19)	675 (19)
Qualifying stroke — no./total no. (%)		
Single acute lesion on imaging	3231/3606 (90)	3214/3602 (89)
Multiple lesions on imaging	375/3606 (10)	388/3602 (11)
Aspirin use before qualifying stroke — no. (%)	624 (17)	629 (17)
Median NIHSS score at randomization (IQR)§	1 (0–2)	1 (0–2)
Median modified Rankin scale score at randomization (IQR)¶	1 (0–2)	1 (0–2)
Median time from qualifying stroke to randomization (IQR) — days	38.0 (15.0–89.0)	36.0 (14.0–86.5)
Intracranial vascular imaging — no. (%)	2821 (78)	2824 (78)
Cardiac rhythm monitoring ≥48 hr — no. (%)	1218 (34)	1217 (34)

* Plus–minus values are means ±SD. There were no significant differences between the treatment groups with regard to any characteristic. Percentages may not total 100 because of rounding. IQR denotes interquartile range, and TIA transient ischemic attack.

† Race was reported by the participant. Other race includes unreported data and multiracial.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores representing worse neurologic deficits.

¶ Scores on the modified Rankin scale range from 0 to 6, with higher scores representing worse functional deficits.

|| Computed tomographic angiography was used in 36% of the patients, and transcranial Doppler imaging was the only intracranial imaging in 12% of the patients.

OUTCOMES

The primary efficacy outcome of recurrent stroke of any type or systemic embolism occurred in 172 patients in the rivaroxaban group (annual-

ized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (hazard ratio, 1.07; 95% confidence interval [CI], 0.87 to 1.33; P=0.52). (Table 2 and Fig. 1A). This represented 332 (74%)

Table 2. Efficacy Outcomes.*

Outcome	Rivaroxaban Group (N=3609)	Aspirin Group (N=3604)	Hazard Ratio (95% CI)†
	<i>no. of patients (annualized rate)</i>		
Primary efficacy outcome: any recurrent stroke or systemic embolism	172 (5.1)	160 (4.8)	1.07 (0.87–1.33)
Secondary efficacy outcomes			
Any recurrent stroke‡	171 (5.1)	158 (4.7)	1.08 (0.87–1.34)
Ischemic stroke‡	158 (4.7)	156 (4.7)	1.01 (0.81–1.26)
Hemorrhagic stroke§	13 (0.4)	2 (0.1)	6.50 (1.47–28.8)
Systemic embolism	1 (<0.1)	2 (0.1)	0.50 (0.05–5.51)
Any recurrent stroke, myocardial infarction, death from cardiovascular causes, or systemic embolism¶	207 (6.2)	195 (5.8)	1.06 (0.87–1.29)
Any disabling stroke	41 (1.2)	29 (0.8)	1.42 (0.88–2.28)
Myocardial infarction	17 (0.5)	23 (0.7)	0.74 (0.39–1.38)
Death from any cause	65 (1.9)	52 (1.5)	1.26 (0.87–1.81)
Death from cardiovascular causes¶	34 (1.0)	23 (0.7)	1.48 (0.87–2.52)

* The annualized event rate represents the average number of events per participant during a 1-year period. Event rates are unadjusted.

† Hazard ratios and 95% confidence intervals were estimated on the basis of age group (<60 years vs. ≥60 years) with stratified Cox proportional-hazards models. P=0.52 for the comparison of the primary outcome.

‡ Data include undefined strokes with no neuroimaging or autopsy (in five patients). Secondary hemorrhagic transformation is included as ischemic stroke.

§ Atraumatic primary intracerebral hemorrhage (in 13 patients) and subarachnoid hemorrhage (in 2) were included as primary outcomes; one additional intracerebral hemorrhage that occurred after an ischemic stroke is not included here but is reported with the safety outcomes.

¶ Nine deaths that could not be reliably classified owing to insufficient information were counted as deaths from cardiovascular causes.

of the anticipated 450 efficacy events that were expected to occur in order for the trial to have adequate power. A total of 314 events (95%) were ischemic strokes, 158 of which occurred in the rivaroxaban group and 156 in the aspirin group (hazard ratio, 1.01; 95% CI, 0.81 to 1.26); 15 events (5%) were hemorrhagic strokes and 3 (1%) were systemic emboli. Of the 314 recurrent ischemic strokes, 36 (11%) were associated with symptoms lasting less than 24 hours but also with neuroimaging evidence of brain infarction, and 5 (2%) could not be classified as ischemic or hemorrhagic because brain imaging was not performed. There were 13 hemorrhagic strokes in the rivaroxaban group, as compared with 2 in the aspirin group. The severity of recurrent ischemic strokes as indicated by the modified Rankin scale score at hospital discharge was similar in the two treatment groups (Fig. S2 in the Supplementary Appendix).

There was no difference in the effect of rivaroxaban as compared with aspirin with regard to the other secondary efficacy outcomes, including disabling stroke, myocardial infarction, death from any cause, or death from cardiovascular causes (Table 2). There was evidence of heterogeneity of treatment effect for two prespecified exploratory subgroups; patients from East Asia (China, Japan, and South Korea) and those with an estimated glomerular filtration rate of more than 80 ml per minute had lower rates of the primary efficacy outcome in the aspirin group than in the rivaroxaban group (Fig. 2), but the number of events may not have provided adequate power for determining the significance of these findings. Efficacy outcomes regarding first unrefuted events that occurred between randomization and 2 days after receipt of the last dose of trial medication are provided in Table S1 in the Supplementary Appendix.

SAFETY OUTCOMES

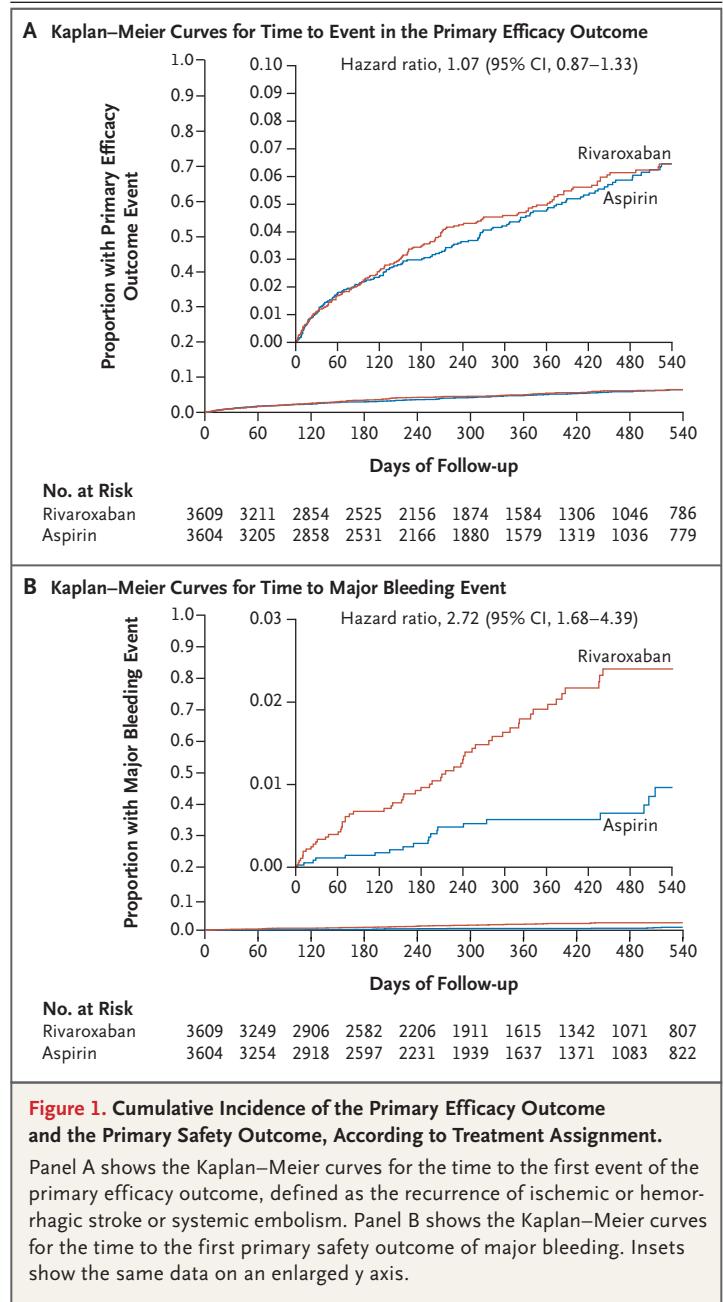
Major bleeding occurred in 62 patients in the rivaroxaban group (annualized rate, 1.8%), as compared with 23 in the aspirin group (annualized rate, 0.7%) (hazard ratio, 2.72; 95% CI, 1.68 to 4.39; $P < 0.001$) (Table 3 and Fig. 1B). The rate of life-threatening or fatal bleeding was significantly higher in the rivaroxaban group than in the aspirin group (hazard ratio, 2.34; 95% CI, 1.28 to 4.29; $P = 0.004$), as were the rates of symptomatic intracranial hemorrhage (hazard ratio, 4.02; 95% CI, 1.51 to 10.7; $P = 0.003$) and clinically relevant nonmajor bleeding (hazard ratio, 1.51; 95% CI, 1.13 to 2.00; $P = 0.004$) (Table 3). Safety outcomes regarding first unrefuted events that occurred between randomization and 2 days after receipt of the last dose of trial medication are provided in Table S2 in the Supplementary Appendix.

DISCUSSION

Treatment with rivaroxaban did not result in a lower rate of stroke recurrence than aspirin among patients with recent ischemic stroke who had met criteria for an embolic stroke of undetermined source. Rivaroxaban was also not found to have a benefit with regard to the secondary efficacy outcomes in this population of patients. The risk of recurrent ischemic stroke was approximately 5% per year in each treatment group.

The incidence of major bleeding was 1.1 percentage points per year higher among patients in the rivaroxaban group than among those in the aspirin group. The rate of intracerebral hemorrhage, the most serious category of major hemorrhage relevant to stroke, was 0.3% per year in the rivaroxaban group versus 0.1% per year in the aspirin group. The rate of intracerebral hemorrhage among patients in the aspirin group in this trial was lower than rates in previously reported cohorts of patients with ischemic stroke.¹⁰

All the patients underwent cardiac rhythm monitoring for at least 20 hours before randomization to screen for covert paroxysmal atrial fibrillation lasting 6 minutes or longer. Atrial fibrillation was identified during follow-up in 3% of the patients, at a median of 5 months after entry, although systematic screening for arrhythmia was not undertaken during the trial period. A previous prospective study with con-



tinuous cardiac rhythm monitoring showed that 12% of patients with cryptogenic stroke had undiagnosed atrial fibrillation, often of short duration.¹¹ Rivaroxaban, including the 15-mg daily dose that was used in the current trial, has been effective for the prevention of recurrent stroke in patients with atrial fibrillation,^{12–14} and the absence of an observed lower rate of recurrent

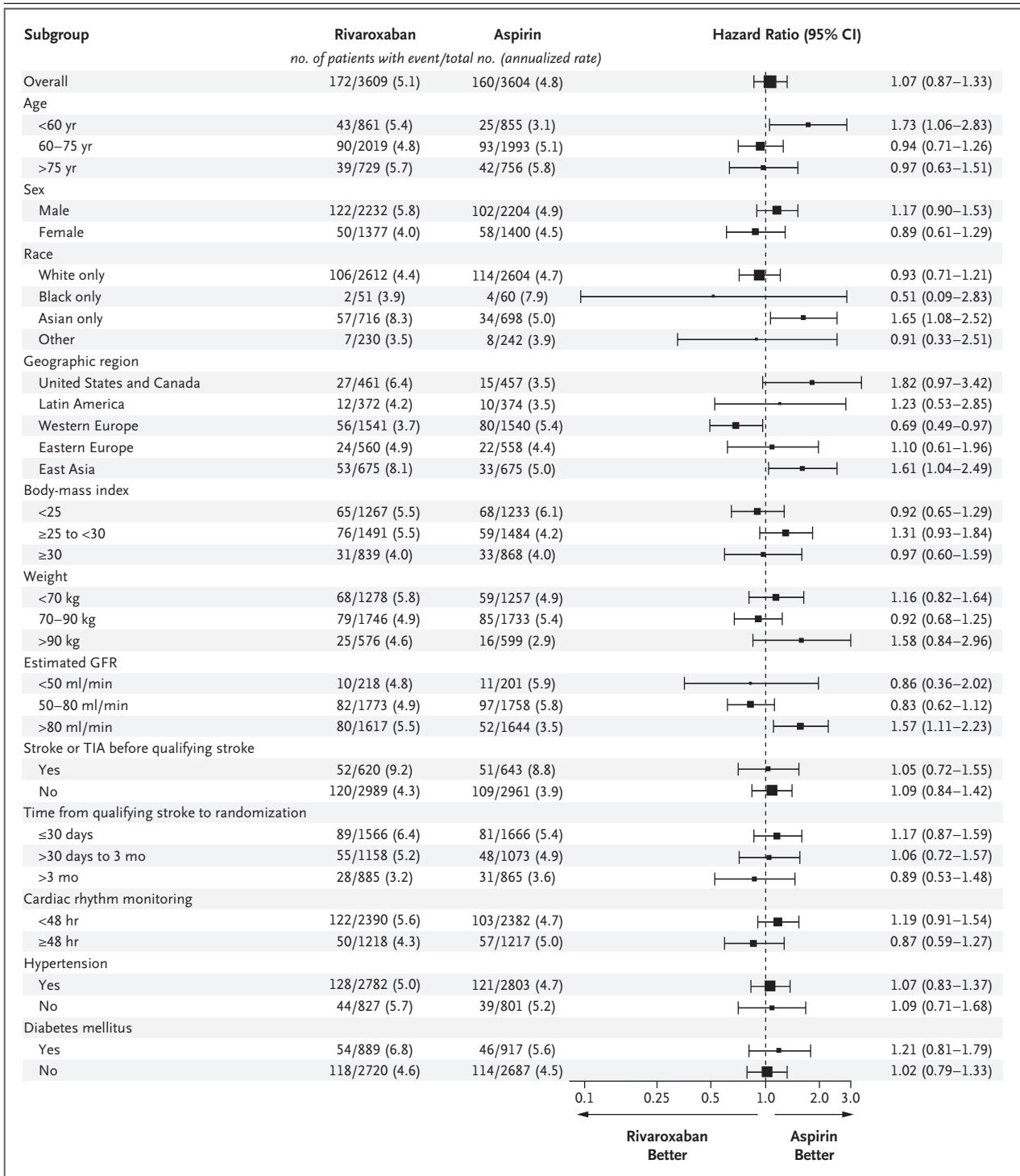


Figure 2. Exploratory Analyses of Treatment Effects on the Primary Efficacy Outcome in Prespecified Subgroups.

The trial may be underpowered to assess these subgroups. The annualized event rate represents the average number of events per participant during a 1-year period. The size of the square is proportional to the number of participants in the subgroup. Race was reported by the participant; other race includes unreported data and multiracial. The body-mass index is the weight in kilograms divided by the square of the height in meters. GFR denotes glomerular filtration rate, and TIA transient ischemic attack.

Table 3. Safety Outcomes.*

Outcome	Rivaroxaban Group (N = 3609)	Aspirin Group (N = 3604)	Hazard Ratio (95% CI)†	P Value
	<i>no. of patients (annualized rate)</i>			
Primary safety outcome: ISTH major bleeding‡	62 (1.8)	23 (0.7)	2.72 (1.68–4.39)	<0.001
Secondary safety outcomes				
Life-threatening or fatal bleeding	35 (1.0)	15 (0.4)	2.34 (1.28–4.29)	0.004
Clinically relevant nonmajor bleeding	118 (3.5)	79 (2.3)	1.51 (1.13–2.00)	0.004
Symptomatic intracranial hemorrhage§	20 (0.6)	5 (0.1)	4.02 (1.51–10.7)	0.003
Intracerebral hemorrhage	12 (0.3)	3 (0.1)	4.01 (1.13–14.2)	0.02
Subarachnoid hemorrhage¶	5 (0.1)	1 (0.0)	5.03 (0.59–43.0)	0.10
Subdural or epidural hematoma¶	3 (0.1)	2 (0.1)	1.51 (0.25–9.02)	0.65

* Event rates are unadjusted.

† Hazard ratios and 95% confidence intervals were estimated on the basis of age group (<60 years vs. ≥60 years) in stratified Cox proportional-hazards models.

‡ Criteria are from the International Society on Thrombosis and Hemostasis (ISTH).⁹

§ These events were included as ISTH major bleeding events and life-threatening or fatal bleeding events. Traumatic intracerebral and subarachnoid hemorrhages were included here.

¶ One patient in the aspirin group had both a traumatic subarachnoid hemorrhage and a separate subdural hematoma; both events are included here.

ischemic stroke with rivaroxaban than with aspirin in the current trial suggests that undetected paroxysmal atrial fibrillation was not a major cause of recurrent stroke.

This trial included patients with patent foramen ovale. The end of recruitment was coincident with the publication of three randomized trials that showed a benefit of closure of patent foramen ovale, as compared with medical therapy, in the treatment of patients with cryptogenic stroke and patent foramen ovale.¹⁵⁻¹⁷ In our trial, it is not known whether patients with patent foramen ovale had characteristics that made them at risk for stroke. The influence of including patients with patent foramen ovale (identified in 7% of the participants) on the outcome of our trial is uncertain.

The effect of the 15-mg daily dose of rivaroxaban on stroke prevention substantially overlaps the effect of the 20-mg daily dose.¹⁸ The latter dose is approved in most countries for the prevention of stroke in patients with atrial fibrillation. Consequently, the use of the 15-mg dose of rivaroxaban in our trial was unlikely to account for the lack of benefit in stroke prevention.

Another possible reason for the absence of a difference between anticoagulant and antiplate-

let therapy in our trial was that the evaluation for eligibility may not have identified strokes due to embolism that would be subject to the prevention of recurrent stroke by rivaroxaban. However, a comprehensive diagnostic evaluation for a source of embolus was required for eligibility. Alternatively, the heterogeneous underlying sources of the embolic strokes (arterial, cardiogenic, or paradoxical) with variation in the composition of emboli may have resulted in the trial enrolling a population that would not have a response to rivaroxaban.

In conclusion, there was no benefit with rivaroxaban at a daily dose of 15 mg, as compared with aspirin at a daily dose of 100 mg, for the prevention of stroke recurrence in patients with embolic stroke of undetermined source. Patients with ischemic stroke who met the eligibility criteria for this trial had a risk of stroke recurrence of approximately 5% per year with either treatment. Ongoing randomized trials are testing alternative anticoagulants versus aspirin in similar groups of patients (ClinicalTrials.gov numbers, NCT02239120 and NCT02427126).^{19,20}

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

APPENDIX

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REFERENCES

- Hart RG, Diener H-C, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13:429-38.
- Li L, Yiin GS, Geraghty OC, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol* 2015;14:903-13.
- Saver JL. Cryptogenic stroke. *N Engl J Med* 2016;374:2065-74.
- Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955-62.
- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857-67.
- Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for secondary stroke prevention in patients with embolic strokes of undetermined source: design of the NAVIGATE ESUS randomized trial. *Eur Stroke J* 2016;1:146-54.
- Kasner SE, Lavados P, Sharma M, et al. Characterization of patients with embolic strokes of undetermined source in the NAVIGATE ESUS randomized trial. *J Stroke Cerebrovasc Dis* 2018;27:1673-82.
- Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol* 2015;66:403-69.
- Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692-4.
- Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. *Stroke* 2005;36:1588-93.
- Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;370:2478-86.
- Hankey GJ, Patel MR, Stevens SR, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol* 2012;11:315-22.
- Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japa-

- nese patients with atrial fibrillation — the J-ROCKET AF study. *Circ J* 2012;76: 2104-11.
14. López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ* 2017; 359:j5058.
15. Mas J-L, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs antiplatelets after stroke. *N Engl J Med* 2017;377:1011-21.
16. Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017;377:1022-32.
17. Søndergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017;377:1033-42.
18. Stampfuss J, Kubitzka D, Becka M, Mueck W. The effect of food on the absorption and pharmacokinetics of rivaroxaban. *Int J Clin Pharmacol Ther* 2013; 51:549-61.
19. Diener HC, Easton JD, Granger CB, et al. Design of Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the Efficacy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS). *Int J Stroke* 2015;10: 1309-12.
20. Geisler T, Poli S, Meisner C, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): rationale and study design. *Int J Stroke* 2017;12:985-90.

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