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ORIGINAL ARTICLE

Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source

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ABSTRACT

BACKGROUND

Cryptogenic strokes constitute 20 to 30% of ischemic strokes, and most cryptogenic strokes are considered to be embolic and of undetermined source. An earlier randomized trial showed that rivaroxaban is no more effective than aspirin in preventing recurrent stroke after a presumed embolic stroke from an undetermined source. Whether dabigatran would be effective in preventing recurrent strokes after this type of stroke was unclear.

METHODS

We conducted a multicenter, randomized, double-blind trial of dabigatran at a dose of 150 mg or 110 mg twice daily as compared with aspirin at a dose of 100 mg once daily in patients who had had an embolic stroke of undetermined source. The primary outcome was recurrent stroke. The primary safety outcome was major bleeding.

RESULTS

A total of 5390 patients were enrolled at 564 sites and were randomly assigned to receive dabigatran (2695 patients) or aspirin (2695 patients). During a median follow-up of 19 months, recurrent strokes occurred in 177 patients (6.6%) in the dabigatran group (4.1% per year) and in 207 patients (7.7%) in the aspirin group (4.8% per year) (hazard ratio, 0.85; 95% confidence interval [CI], 0.69 to 1.03; P=0.10). Ischemic strokes occurred in 172 patients (4.0% per year) and 203 patients (4.7% per year), respectively (hazard ratio, 0.84; 95% CI, 0.68 to 1.03). Major bleeding occurred in 77 patients (1.7% per year) in the dabigatran group and in 64 patients (1.4% per year) in the aspirin group (hazard ratio, 1.19; 95% CI, 0.85 to 1.66). Clinically relevant nonmajor bleeding occurred in 70 patients (1.6% per year) and 41 patients (0.9% per year), respectively.

CONCLUSIONS

In patients with a recent history of embolic stroke of undetermined source, dabigatran was not superior to aspirin in preventing recurrent stroke. The incidence of major bleeding was not greater in the dabigatran group than in the aspirin group, but there were more clinically relevant nonmajor bleeding events in the dabigatran group. (Funded by Boehringer Ingelheim; RE-SPECT ESUS ClinicalTrials.gov number, NCT02239120.)

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*A complete list of the RE-SPECT ESUS committees and principal investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Ischemic infarctions account for the majority of strokes and are classified by their cause: large-artery extracranial or intracranial atherosclerosis, embolism from a cardiac source, small-artery occlusion, and other, less common causes.[1] However, 20 to 30% of ischemic strokes are categorized as cryptogenic,[2,3] and a proportion of these are further classified as embolic strokes of undetermined source if a pattern of infarction that suggests an embolic (nonlacunar) cause is present on brain imaging but no source for the embolus is identified after a series of tests is performed to try to find the source.[4,5]

Guidelines for secondary prevention of stroke in patients who have had a cryptogenic stroke recommend administration of antiplatelet agents, and treatment may include aspirin, a combination of extended-release dipyridamole and aspirin, or clopidogrel and aspirin.[6] Oral anticoagulants, including dabigatran etexilate, have an established role in reducing the incidence of recurrent strokes among patients with high-risk cardioembolic factors, such as atrial fibrillation.[7,8]

We conducted the RE-SPECT ESUS trial (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source) to compare the efficacy and safety of dabigatran with those of aspirin for the prevention of recurrent stroke.

Methods

Study Design and Oversight

RE-SPECT ESUS was an international, double-blind, parallel-group, randomized trial. Patients were enrolled during the period from December 2014 through January 2018 at 564 sites in 42 countries. The trial was approved by the ethics committee at each participating site. The study rationale, design, and methods have been published previously,[9] and the protocol, including the statistical plan, is available with the full text of this article at NEJM.org.

The executive committee and representatives of the sponsor, Boehringer Ingelheim, developed the protocol and were responsible for supervising the trial and making protocol amendments. An independent data monitoring committee assessed safety outcomes and study conduct. An independent adjudication committee, whose members were unaware of the treatment assignments, reviewed and classified primary and secondary efficacy outcomes and major bleeding events.

The sponsor provided the investigational drugs, collected the data, performed the statistical analysis, and paid for professional editing of an earlier version of the manuscript for submission. Confidentiality agreements were in place between the investigators and authors and the sponsor. The executive committee drafted the manuscript. All the authors vouch for the accuracy and completeness of the data and reporting of adverse events and for the fidelity of the trial to the protocol. All patients provided written informed consent before participating in the trial.

Trial Population

Patients 60 years of age or older were eligible for enrollment if they had had an embolic stroke of undetermined source within the previous 3 months or, if they had at least one vascular risk factor, within the previous 6 months; patients 18 to 59 years of age were eligible if they had had a qualifying stroke within the previous 3 months and had at least one additional vascular risk factor.[9] Exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

Embolic stroke of undetermined source was defined[4] as a nonlacunar ischemic stroke (detected by brain imaging) in a patient in whom no extracranial or intracranial atherosclerosis causing 50% or greater stenosis in arteries supplying the area of the stroke was detected by arterial imaging or cervical and transcranial Doppler ultrasonography, no atrial fibrillation lasting longer than 6 minutes[10] was shown by cardiac rhythm monitoring for 20 hours or longer, no intracardiac thrombus was detected by transthoracic or transesophageal echocardiography, and no other specific cause of stroke was identified.

Trial Treatments

Patients were randomly assigned in a 1:1 ratio, in a double-blind manner, to receive dabigatran and aspirin placebo or aspirin and dabigatran

placebo (Fig. S1 in the Supplementary Appendix). Dabigatran was administered at a dose of 150 mg twice daily, but in patients 75 years of age or older and in patients who had an estimated creatinine clearance of 30 to 50 ml per minute, dabigatran was administered at a dose of 110 mg twice daily. Patients in the aspirin group were given aspirin in nonenteric-coated form at a dose of 100 mg once daily. Patients with coronary heart disease who were assigned to the dabigatran group could receive aspirin for treatment of their coronary heart disease; patients in the aspirin group who had coronary heart disease received aspirin plus placebo. The trial treatment period was planned to be a minimum of 6 months and a maximum of 3.5 years.

OUTCOMES

The primary efficacy outcome was recurrent stroke of ischemic, hemorrhagic, or unspecified type, assessed in a time-to-event analysis. The two key secondary efficacy outcomes were ischemic stroke and a composite of nonfatal stroke, nonfatal myocardial infarction, or death from cardiovascular causes, with both outcomes evaluated in time-to-event analyses. Other secondary efficacy outcomes were disabling recurrent stroke and death from any cause. Disabling recurrent stroke was defined by a score on the modified Rankin scale of 4 or more 3 months after a recurrent stroke; scores on the modified Rankin scale range from 0 to 6, with 0 indicating no deficit and 6 indicating death. Tertiary efficacy outcomes are shown in Table S2 in the Supplementary Appendix. The primary safety outcome was major bleeding according to International Society on Thrombosis and Hemostasis (ISTH) criteria, assessed in a time-to-event analysis.[11] Additional safety outcomes were nonmajor bleeding resulting in hospitalization, medical or surgical intervention, or change, interruption, or discontinuation of the trial drug (i.e., clinically relevant nonmajor bleeding) and a composite of major bleeding or clinically relevant nonmajor bleeding.

STATISTICAL ANALYSIS

We calculated that the trial would have 92% power to detect a 30% lower risk of recurrent stroke (the primary outcome) in the dabigatran group than in the aspirin group. The targeted number of recurrent strokes confirmed by the independent adjudication committee in this event-driven trial was 353 strokes. The original plan was to randomly assign 6000 patients over the course of 2.5 years, with a planned maximum observation period of 3 years. Because recruitment was slower than planned and the primary event rate was higher than expected, the recruitment period was extended to 3 years, which resulted in a total observation period of 3.5 years, and the target total sample size was reduced to 5390 patients.

All analyses were performed in the intention-to-treat population unless otherwise specified; analysis of data from patients who were lost to follow-up was based on the last day their status was known. A Cox proportional-hazards regression model, adjusted for the covariates of age, renal impairment (baseline creatinine clearance <50 or ≥50 ml per minute), and transient ischemic attack or stroke before the index stroke, was the prespecified model for the analysis of outcomes. However, the assumption of proportional hazards was not satisfied for the primary outcome; therefore, we explored whether the treatment effect varied according to time (after inspection of the Kaplan–Meier curves), with additional analyses describing the results separately before and after 1 year in a piecewise Cox model.

To control for type I errors, a hierarchical analysis plan stipulated that if the results for the primary outcome were not statistically significant, key secondary outcomes would be reported without claims of statistical significance. No multiplicity adjustments were planned for other secondary outcomes, and all confidence intervals reported for secondary outcomes were unadjusted for multiple comparisons. On-treatment analyses were performed as sensitivity analyses. No imputation of missing data was performed. Tests for the interaction of treatment with various subgroups were performed to evaluate the consistency of results with respect to the primary outcome and major bleeding. A total of 22 subgroups were prespecified for analysis. Results for 11 prespecified subgroups of greatest clinical interest are presented; 1 subgroup (assignment to dabigatran dose of 110 mg vs. 150 mg) was analyzed post hoc.

RESULTS

PARTICIPANTS AND FOLLOW-UP

A total of 5830 patients were screened, and 5390 were randomly assigned to a treatment group

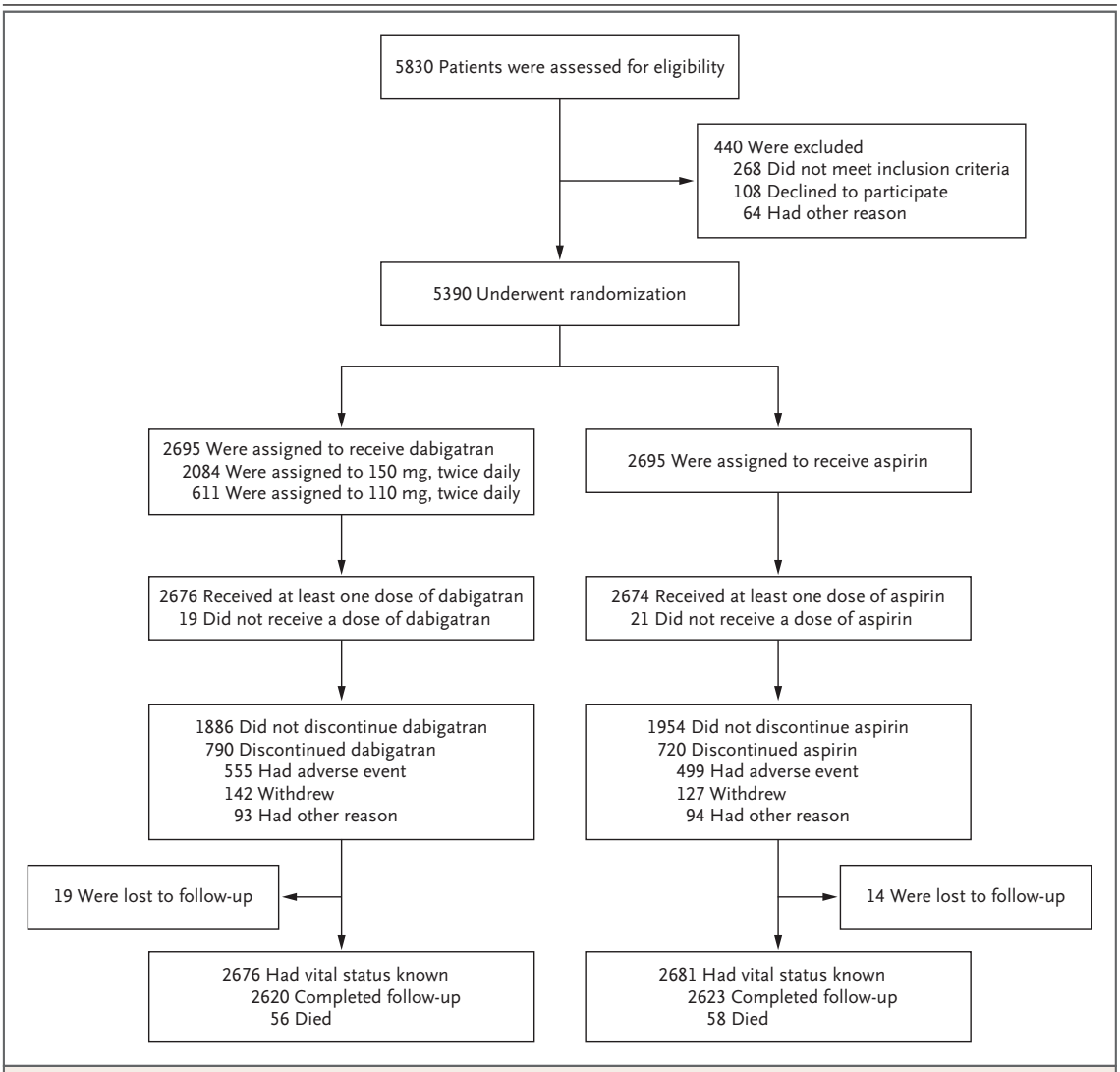

Figure 1. Enrollment, Randomization, and Treatment.

Patients who did not receive the trial medication and those who discontinued the study early were still followed, and vital status was known for nearly all the patients (99.4%) at the end of the trial; data for 33 patients (0.6%) were censored because their vital status could not be verified at the end of the trial.

(2695 in each group) (Fig. 1). Patients were recruited from Europe (58.8%), Asia (22.2%), North America (11.0%), and Latin America (4.2%). The mean age of the patients was 64.2 years, and 36.9% were women. Patients in the two groups had similar baseline clinical and demographic characteristics, except for age; patients in the dabigatran group were a mean of 0.6 years older than those in the aspirin group (Table 1). Patent foramen ovale was diagnosed in 680 patients (12.6%), with similar numbers in the two treatment groups.

The median time from the qualifying first stroke to randomization was 44 days (interquartile range, 21 to 80). At the time of randomization, the median score on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating more neurologic deficits) resulting from the qualifying stroke was 1 (interquartile range, 0 to 2). In addition to the minimum required 20 hours of electrocardiogram (ECG) monitoring, extended ECG monitoring with an outpatient monitoring device was performed in 14% of the patients, and 6% of the patients received an implantable loop recorder to monitor cardiac rhythm. A total of 24 patients in the dabigatran group (0.9%) and 20 in the aspirin group (0.7%) were found

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dabigatran Group (N=2695)	Aspirin Group (N=2695)
Mean age — yr	64.5±11.4	63.9±11.4
Female sex — no. (%)	1001 (37.1)	986 (36.6)
Region — no. (%)		
North America	300 (11.1)	294 (10.9)
Central Europe	369 (13.7)	335 (12.4)
Western Europe	1210 (44.9)	1254 (46.5)
Latin America	107 (4.0)	118 (4.4)
Asia	616 (22.9)	582 (21.6)
Other	93 (3.5)	112 (4.2)
Race — no. (%)†		
White	1926 (71.5)	1966 (72.9)
Black	54 (2.0)	40 (1.5)
Asian	631 (23.4)	597 (22.2)
Other or missing	84 (3.1)	92 (3.4)
Mean body-mass index‡	27.2±5.0	27.3±5.0
Current smoker — no. (%)	458 (17.0)	433 (16.1)
Creatinine clearance <50 ml per minute at baseline — no. (%)	227 (8.4)	203 (7.5)
Median time from index stroke to randomization (IQR) — days	46.0 (21.0–82.0)	43.0 (20.0–78.0)
Median score on modified Rankin Scale (IQR)§	1 (0–2)	1 (0–2)
Median NIHSS score (IQR)¶	1 (0–2)	1 (0–2)
Medical history — no. (%)		
Previous TIA or stroke	475 (17.6)	500 (18.6)
Previous myocardial infarction	168 (6.2)	172 (6.4)
Coronary artery disease	301 (11.2)	276 (10.2)
Hypertension	1996 (74.1)	1985 (73.7)
Diabetes mellitus	585 (21.7)	639 (23.7)
Hyperlipidemia	1533 (56.9)	1510 (56.0)
Patent foramen ovale	319 (11.8)	361 (13.4)
Congestive heart failure‖	117 (4.3)	124 (4.6)
LV dysfunction, ejection fraction ≤40%, or both	36 (1.3)	35 (1.3)

* Plus–minus values are means ±SD. There were no significant differences between the groups except with respect to age (P=0.03). P values were calculated with Student's t-tests for continuous variables and chi-square tests for categorical variables. Percentages may not total 100 because of rounding. IQR denotes interquartile range, LV left ventricular, and TIA transient ischemic attack.
† Race was reported by the patient. Patients who identified as more than one race or did not identify their race were classified as other.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating worse functional deficits.
¶ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating worse neurologic deficits.
‖ No patients had New York Heart Association class IV heart failure.

Table 2. Efficacy Outcomes.*

Outcome	Dabigatran Group (N=2695)	Aspirin Group (N=2695)	Hazard Ratio (95% CI)†
	no. of patients (annualized rate)		
Primary outcome: first recurrent stroke	177 (4.1)	207 (4.8)	0.85 (0.69–1.03)‡
Key secondary outcomes§			
Ischemic stroke	172 (4.0)	203 (4.7)	0.84 (0.68–1.03)
Composite of nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death	207 (4.8)	232 (5.4)	0.88 (0.73–1.06)
Other secondary outcomes			
Disabling stroke	25 (0.6)	42 (0.9)	0.59 (0.36–0.96)
Death from any cause	56 (1.2)	58 (1.3)	0.96 (0.66–1.38)
Tertiary outcomes			
Death from cardiovascular causes	19 (0.4)	24 (0.5)	0.78 (0.43–1.43)
Hemorrhagic stroke	6 (0.1)	7 (0.2)	0.86 (0.29–2.55)
TIA	43 (1.0)	37 (0.8)	1.14 (0.73–1.77)
Systemic embolism	6 (0.1)	11 (0.2)	0.54 (0.20–1.46)
Myocardial infarction	23 (0.5)	18 (0.4)	1.28 (0.69–2.38)
Venous thromboembolism	9 (0.2)	15 (0.3)	0.59 (0.26–1.34)
Net clinical outcome: disabling stroke, life-threatening bleeding, myocardial infarction, venous thromboembolism, or death from cardiovascular causes	98 (2.2)	109 (2.5)	0.88 (0.67–1.16)

* All outcomes were confirmed by an independent adjudication committee, except the score on the modified Rankin scale, which determines disabling stroke.
† Hazard ratios have not been adjusted for multiple comparisons.
‡ P=0.10 for the primary outcome of first recurrent stroke.
§ Because no adjustment for multiple comparisons was made for secondary outcomes and because the result of the primary outcome was not statistically significant, P values were not computed for secondary outcomes, and only confidence intervals unadjusted for multiplicity are shown.

after randomization to have atrial fibrillation (defined as cumulative duration of atrial fibrillation of more than 6 minutes during the extended monitoring period).

The median duration of follow-up was 19 months (interquartile range, 13 to 27). Trial medication was discontinued in 671 patients in the dabigatran group (24.9%) and in 568 in the aspirin group (21.1%) before a primary outcome was reached. Adverse events were the main reason for discontinuation in both groups; 555 patients in the dabigatran group and 499 patients in the aspirin group had adverse events leading to discontinuation (Fig. 1). The vital status of 19 patients in the dabigatran group and 14 patients in the aspirin group could not be established.

EFFICACY OUTCOMES

A recurrent stroke of any type (the primary outcome) occurred in 177 patients (6.6%) in the dabigatran group (a rate of 4.1% per year) and in 207 patients (7.7%) in the aspirin group (a rate of 4.8% per year) (hazard ratio, 0.85; 95% confidence interval [CI], 0.69 to 1.03; P=0.10) (Table 2 and Figs. 2A and 3). Results for secondary outcomes are shown in Table 2. Ischemic strokes occurred in 172 patients (6.4%) in the dabigatran group (a rate of 4.0% per year) and in 203 patients (7.5%) in the aspirin group (a rate of 4.7% per year) (hazard ratio, 0.84; 95% CI, 0.68 to 1.03). A composite outcome event of nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death occurred in 207 patients (7.7%) in

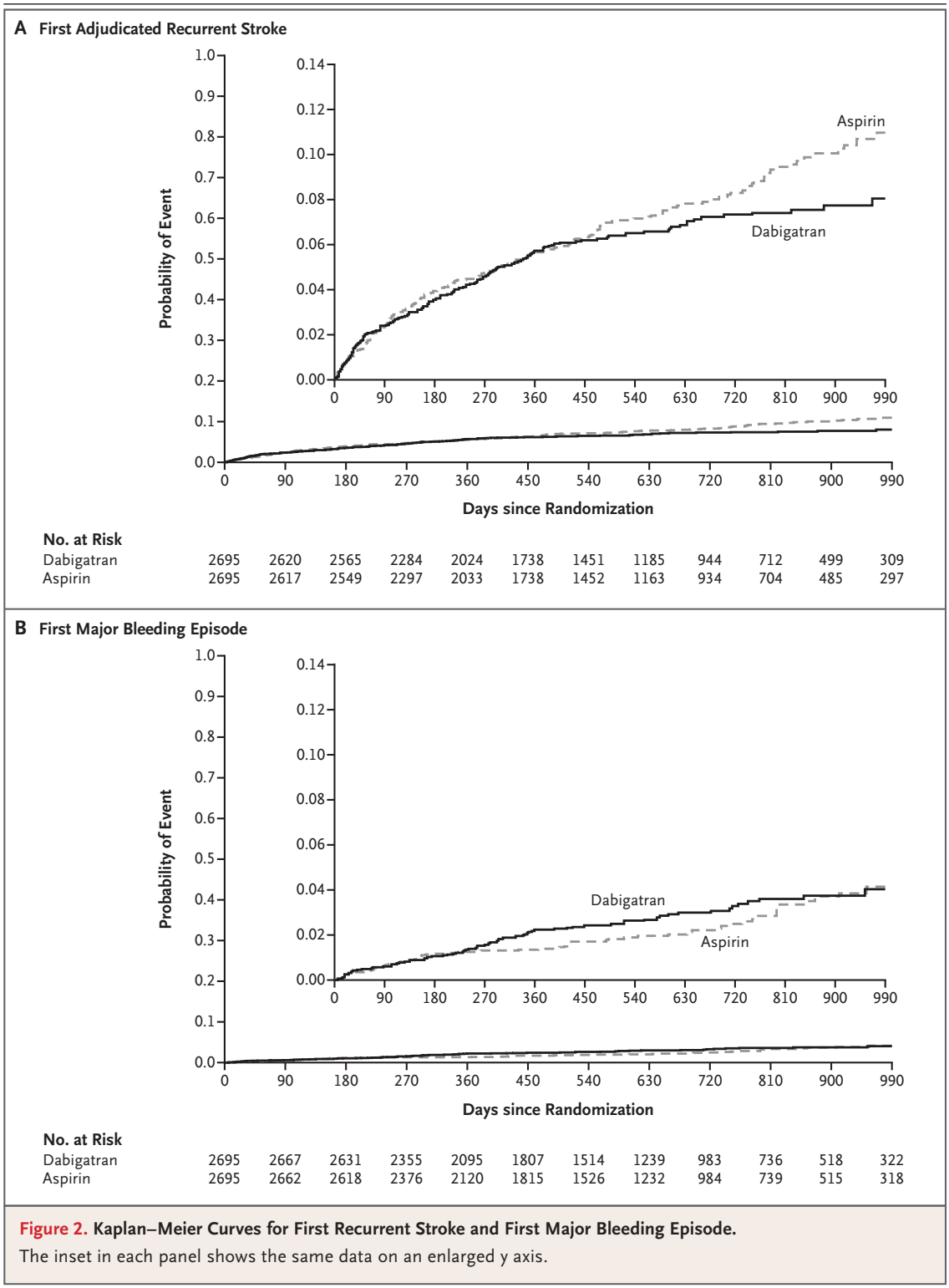

Figure 2. Kaplan–Meier Curves for First Recurrent Stroke and First Major Bleeding Episode.
The inset in each panel shows the same data on an enlarged y axis.

the dabigatran group (a rate of 4.8% per year) and in 232 patients (8.6%) in the aspirin group (a rate of 5.4% per year) (hazard ratio, 0.88; 95% CI, 0.73 to 1.06). Hemorrhagic strokes occurred in 6 patients (0.2%) in the dabigatran group (a rate of 0.1% per year) and in 7 patients (0.3%) in the

Subgroup	Dabigatran	Aspirin	Hazard Ratio (95% CI)
	no. of events/total no. (%)		
Overall	177/2695 (6.6)	207/2695 (7.7)	0.85 (0.69–1.03)
Age classification			
<50 yr	11/285 (3.9)	10/320 (3.1)	1.31 (0.55–3.15)
50 to <65 yr	57/961 (5.9)	58/965 (6.0)	0.99 (0.69–1.43)
65 to <75 yr	66/901 (7.3)	79/928 (8.5)	0.85 (0.62–1.19)
≥75 yr	43/548 (7.8)	60/482 (12.4)	0.63 (0.43–0.94)
Sex			
Male	123/1694 (7.3)	144/1709 (8.4)	0.87 (0.68–1.11)
Female	54/1001 (5.4)	63/986 (6.4)	0.81 (0.56–1.17)
Geographic region			
North America	24/300 (8.0)	18/294 (6.1)	1.26 (0.68–2.33)
Central Europe	16/369 (4.3)	25/335 (7.5)	0.56 (0.30–1.06)
Western Europe	87/1210 (7.2)	94/1254 (7.5)	0.94 (0.70–1.26)
Latin America	9/107 (8.4)	7/118 (5.9)	1.39 (0.51–3.75)
Asia	37/616 (6.0)	54/582 (9.3)	0.68 (0.44–1.03)
Other	4/93 (4.3)	9/112 (8.0)	0.46 (0.14–1.51)
Dose assignment			
110 mg	45/611 (7.4)	71/546 (13.0)	0.57 (0.39–0.83)
150 mg	132/2084 (6.3)	136/2149 (6.3)	0.99 (0.78–1.26)
Proton-pump inhibitors			
No	113/1748 (6.5)	117/1797 (6.5)	1.00 (0.77–1.29)
Yes	58/876 (6.6)	87/827 (10.5)	0.61 (0.44–0.86)
Days from index stroke to randomization			
<8	14/95 (14.7)	6/97 (6.2)	2.02 (0.76–5.38)
8–30	72/892 (8.1)	75/937 (8.0)	1.00 (0.72–1.38)
31–90	67/1219 (5.5)	89/1200 (7.4)	0.73 (0.53–1.00)
≥91	24/489 (4.9)	37/460 (8.0)	0.62 (0.37–1.04)
Creatinine clearance at baseline			
30 to <50 ml/min	23/226 (10.2)	33/201 (16.4)	0.63 (0.37–1.07)
50 to <80 ml/min	59/1041 (5.7)	80/965 (8.3)	0.68 (0.48–0.95)
≥80 ml/min	95/1424 (6.7)	93/1525 (6.1)	1.10 (0.83–1.46)
Add-on aspirin at baseline			
No	165/2526 (6.5)	191/2557 (7.5)	0.88 (0.71–1.08)
Yes	12/169 (7.1)	16/138 (11.6)	0.50 (0.24–1.07)
History of stroke or TIA before index stroke			
No	124/2220 (5.6)	132/2195 (6.0)	0.92 (0.72–1.18)
Yes	53/475 (11.2)	75/500 (15.0)	0.71 (0.50–1.01)
Cardiac monitoring at baseline			
≤48 hr	139/2220 (6.3)	174/2263 (7.7)	0.80 (0.64–1.00)
>48 hr	38/474 (8.0)	33/432 (7.6)	1.07 (0.67–1.71)
CHA_2DS_2–VASc score			
2–3	41/836 (4.9)	40/840 (4.8)	1.06 (0.69–1.65)
4	50/743 (6.7)	64/779 (8.2)	0.82 (0.56–1.18)
≥5	86/1116 (7.7)	103/1076 (9.6)	0.79 (0.59–1.06)
Patent foramen ovale			
No	160/2375 (6.7)	188/2333 (8.1)	0.83 (0.68–1.03)
Yes	16/319 (5.0)	19/361 (5.3)	0.88 (0.45–1.71)

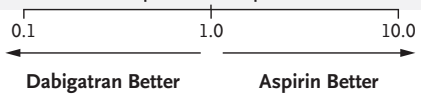

Figure 3. Analyses of Treatment Effects on Recurrent Stroke in Subgroups.

The trial may be underpowered to assess these subgroups. All subgroups were prespecified except dose assignment, which was post hoc. The CHA_2DS_2–VASc score reflects the risk of stroke among patients with atrial fibrillation. Scores range from 0 to 9, with higher scores indicating greater risk. TIA denotes transient ischemic attack.

Table 3. Safety Outcomes.*

Outcome	Dabigatran Group (N = 2695)	Aspirin Group (N = 2695)	Hazard Ratio (95% CI)†
	no. of patients (annualized rate)		
Major bleeding	77 (1.7)	64 (1.4)	1.19 (0.85–1.66)
Intracranial hemorrhage	32 (0.7)	32 (0.7)	0.98 (0.60–1.60)
Gastrointestinal bleeding	27 (0.6)	22 (0.5)	1.22 (0.70–2.15)
Life-threatening bleeding	38 (0.8)	45 (1.0)	0.83 (0.54–1.28)
Fatal bleeding and fatal hemorrhagic stroke‡	1 (0.02)	6 (0.1)	0.17 (0.02–1.39)
Clinically relevant nonmajor bleeding	70 (1.6)	41 (0.9)	1.73 (1.17–2.54)
Major or clinically relevant nonmajor bleeding	145 (3.3)	101 (2.3)	1.44 (1.12–1.85)

* All outcomes except clinically relevant nonmajor bleeding were confirmed by an independent adjudication committee.
† Hazard ratios have not been adjusted for multiple comparisons.
‡ Three deaths were confirmed by the adjudication committee as fatal intracranial hemorrhage (all three in the aspirin group), and four deaths were confirmed by the adjudication committee as fatal hemorrhagic stroke (one in the dabigatran group and three in the aspirin group).

aspirin group (a rate of 0.2% per year) (hazard ratio, 0.86; 95% CI, 0.29 to 2.55). Disabling strokes occurred in 25 patients (0.9%) in the dabigatran group (a rate of 0.6% per year) and in 42 patients (1.6%) in the aspirin group (a rate of 0.9% per year) (hazard ratio, 0.59; 95% CI, 0.36 to 0.96) (Fig. S2 in the Supplementary Appendix). Efficacy outcomes during the on-treatment period for the treated population, which included all randomly assigned patients who received one or more doses of the assigned trial treatment, are shown in Table S3 in the Supplementary Appendix. The results of a post hoc exploratory analysis comparing the incidence of first recurrent strokes before 1 year and after 1 year are shown in Table S4 in the Supplementary Appendix.

The absence of a treatment effect on the primary outcome was consistent across most prespecified subgroups (Fig. 3). Patients with patent foramen ovale showed a treatment effect consistent with the overall trial results; 16 of 319 patients (5.0%) with foramen ovale in the dabigatran group and 19 of 361 patients (5.3%) with foramen ovale in the aspirin group had recurrent stroke (hazard ratio, 0.88; 95% CI, 0.45 to 1.71). Potential treatment interactions that were exploratory, and from which inferences cannot be made, were observed in two subgroups — those defined according to the use of proton-pump inhibitors and according to the number of days from the index stroke to randomization (Fig. 3).

SAFETY OUTCOMES

Major bleeding occurred in 77 patients (2.9%) in the dabigatran group (a rate of 1.7% per year) and in 64 patients (2.4%) in the aspirin group (a rate of 1.4% per year) (hazard ratio, 1.19; 95% CI, 0.85 to 1.66) (Table 3 and Fig. 2B). The composite outcome event of major or clinically relevant nonmajor bleeding occurred more frequently with dabigatran than with aspirin (hazard ratio, 1.44; 95% CI, 1.12 to 1.85) because of the excess of clinically relevant nonmajor bleeding episodes with dabigatran (hazard ratio, 1.73; 95% CI, 1.17 to 2.54).

Intracranial hemorrhage occurred in 32 patients (1.2%) in both the dabigatran group and the aspirin group (a rate of 0.7% per year) (hazard ratio, 0.98; 95% CI, 0.60 to 1.60). The incidence of life-threatening bleeding did not differ between the two treatment groups (hazard ratio, 0.83; 95% CI, 0.54 to 1.28) (Table 3). The treatment effect on major bleeding was consistent across subgroups. Other safety outcomes are shown in Figure S3 and Tables S3, S5, and S6 in the Supplementary Appendix.

DISCUSSION

The RE-SPECT ESUS trial showed no significant difference between the effect of dabigatran and that of aspirin on the risk of recurrent stroke among patients with embolic stroke of undeter-

mined source. The rate of recurrent stroke was 4.1% per year among patients in the dabigatran group and 4.8% per year among patients in the aspirin group. Dabigatran was associated with major bleeding in 1.7% of the patients per year, and aspirin was associated with major bleeding in 1.4% of the patients per year. The percentages were similar in the two groups in all subcategories of major bleeding, but more patients in the dabigatran group than in the aspirin group had clinically relevant nonmajor bleeding.

Our hypothesis was that dabigatran would be more effective than aspirin for stroke prevention in patients with embolic stroke of undetermined source because many of these patients might have had an unrecognized source of cardiac embolism, including atrial fibrillation. Post hoc analysis suggested that dabigatran may have had an effect on stroke recurrence after 1 year, but no inferences can be made because of the post hoc nature of the analysis. A possible explanation for this temporal pattern might be a progressive increase in the occurrence of asymptomatic, undetected atrial fibrillation and other cardiac sources of embolism over time. The CRYSTAL-AF (Cryptogenic Stroke and Underlying Atrial Fibrillation)[12] and FIND-AF (Finding Atrial Fibrillation in Stroke)[13] trials in patients with cryptogenic stroke showed detection rates of atrial fibrillation of approximately 10 to 15% per year in populations that were similar to the RE-SPECT ESUS population. In our trial, extended ECG monitoring after randomization was performed in only 14% of patients; therefore, we do not have a systematic assessment of the occurrence of atrial fibrillation. Whether patients with cryptogenic stroke who have atrial cardiopathy and are at a high risk for atrial fibrillation could benefit from anticoagulation is being investigated in the ongoing ARCADIA trial (Atrial Cardiopathy and Antithrombotic Drugs In Prevention after Cryptogenic Stroke).[14]

Our trial design differed from that of NAVIGATE ESUS (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source).[15] NAVIGATE ESUS used a lower dose of rivaroxaban than has been used for stroke prophylaxis in patients with atrial fibrillation. In RE-SPECT ESUS, for patients 75 years of age or older or patients who had impaired renal function, we used the lower dose of dabigatran (110 mg twice daily) according to slightly modified criteria from the European approved labeling for atrial fibrillation. The median follow-up was 11 months in NAVIGATE ESUS as compared with 19 months in RE-SPECT ESUS. The overall number of bleeding events in patients in the aspirin group was lower in NAVIGATE ESUS than in RE-SPECT ESUS. Aspirin was used in an enteric-coated form in NAVIGATE ESUS and in plain form in RE-SPECT ESUS.

The strengths of RE-SPECT ESUS are the large sample size and the broad distribution of international trial centers that may allow the results to be generalized. The stroke event rates matched the expectations that were used in the power calculation for the trial, and we reached the prespecified target number of recurrent strokes in this event-driven trial.

In conclusion, we found that dabigatran was not superior to aspirin in preventing recurrent stroke in patients who had had an embolic stroke of undetermined source. The incidence of major bleeding was not greater in the dabigatran group than in the aspirin group, but there were more clinically relevant nonmajor bleeding events in the dabigatran group.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

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United States: Pramod Sethi, Aneesh Singhal, Navdeep Sangha, Truman Milling, Fan Caprio, Lance Lee, Mahmoud Rayes, Norman Lepor, Fenwick Nichols, David Rose, Fazeel Siddiqui, Ali Saad, Pierre Fayad, Austin Hake, David Chiu, James Conners, Kumiko Owada, Andrei Alexandrov, Ali Malek, Carmelo Graffagnino, Aboubakar Sharaf, James Welker, Sidney Mallenbaum, Nils Mueller-Kronast, Mark Goldstein, Warren Felton, Mark Young, Daniel Gzesh, Jeffrey Katz, John Ip, Haitham Hussein, Robert Yapundich, Muhammad Farooq, Edward Bradbury, David Wang, Karl Meisel, Dennis Finkielstein, Sebastian Koch, Angelos Katramados, Richard Zweifler, Helmi Lutsep, Gerald McIntosh, Rony Salem, Mutaz Tabbaa, Abhay Kumar, Muhib Khan, Vivien Lee, Stuart Shafer, Raj Rajan, Elaine Skalabrin, Kerri Remmel, Raymond Reichwein, Eugene Francis LaFranchise, Justin Nolte, Allyn Sher, Ritesh Kaushal, Sushant Kale, Helmi Lutsep, Carol Pappas, Gregory Anderson, Guy Rordorf, James Brorson, Rolando Ania, Larry Blankenship, John Freiberg, Naseem Jaffrani, Nirav Shah, Logan McDaneld, Harvey Serota, Bhupesh Dihenia, Andrew Xavier, Karen Porth, Amre Nouh, Donald Tamulonis, Latisha Sharma, Royya Modir, Amir Khan, Adrian Jarquin-Valdivia, Aniel Majjhoo, Ziad Darkhabani, Jonathan Harris, Michael Jacoby, Christopher Commichau, Aamir Rasheed, William Jones, Vasileios Lioutas, Amanda Mack, Diana Tzeng, Brandi French, Justin Stahl, Jay Yasen, Nirav Patel, Bronislava Shafran, Jeffrey Wagner, Ahmad Mohammad, Glenn Hamroff, Seemant Chaturvedi, Michael Puente, Christine Boutwell, Arbi Ohanian, Steven Lupovitch, Terry Heiman-Patterson, George Juang, Omar Almousalli, B. Judson Colley, Nada El Husseini.

Supplementary Table S1. Main Exclusion Criteria in RE-SPECT ESUS.

- Modified Rankin Scale score of ≥4 at the time of randomization
- Major-risk cardioembolic source of embolism such as history of atrial fibrillation, intracardiac thrombus, prosthetic cardiac valve (mitral or aortic, bioprosthetic or mechanical), atrial myxoma or other cardiac tumors, moderate or severe mitral stenosis, recent (<4 weeks) myocardial infarction, valvular vegetations, or infective endocarditis
- Other specific stroke etiology (e.g., cerebral arteritis or arterial dissection, migraine/vasospasm, drug abuse)
- Intracerebral hemorrhage on qualifying neuroimaging, and/or history of symptomatic nontraumatic intracranial hemorrhage
- Increased risk of bleeding
- Estimated creatinine clearance <30 ml per min
- Indication for antiplatelet therapy with a P2Y12 antagonist or with dipyridamole, or indication for aspirin (acetylsalicylic acid) other than for embolic stroke of undetermined source (with the exception of coronary artery disease, where open-label aspirin at a dose of 100 mg once daily could be assigned, in addition to the blinded aspirin regimen, at the discretion of the investigator)

Supplementary Table S2. Other/Tertiary Efficacy Outcomes in RE-SPECT ESUS.

- Cardiovascular death
- Hemorrhagic stroke
- Transient ischemic attack
- Systemic embolism
- Myocardial infarction
- Venous thromboembolism
- Cardiovascular hospitalization
- Recurrent stroke or systemic embolism (composite)
- Recurrent stroke or death (composite)
- Net clinical benefit as measured by the composite clinical end point of disabling stroke (modified Rankin Scale score ≥4, as determined 3 months after recurrent stroke), life-threatening bleed, venous thromboembolism, myocardial infarction, and cardiovascular death
- Composite of myocardial infarction, ischemic stroke, cardiovascular death, venous thromboembolism, or cardiovascular hospitalization
- Change in cognitive status from baseline to end of treatment in all patients as assessed by the MoCA questionnaire
- Modified Rankin Scale at three months post-stroke

MoCA denotes Montreal Cognitive Assessment.

Supplementary Table S3. Efficacy and Safety Outcomes for the Treated Set.

Outcome	Dabigatran Group (N=2676)	Aspirin Group (N=2674)	Hazard Ratio (95% CI)
	No. of Patients (Annualized Rate)		
Primary outcome: first recurrent stroke	154 (4.4)	179 (5.0)	0.87 (0.70–1.08)
Key secondary outcomes			
Ischemic stroke	149 (4.2)	177 (4.9)	0.85 (0.69–1.06)
Composite of nonfatal stroke, nonfatal MI, or cardiovascular death	172 (4.9)	197 (5.5)	0.89 (0.72–1.09)
Secondary outcomes			
Disabling stroke	16 (0.4)	26 (0.7)	0.61 (0.33–1.14)
Death from any cause	14 (0.4)	23 (0.6)	0.61 (0.31–1.19)
Safety outcomes			
Major bleed	65 (1.8)	48 (1.3)	1.36 (0.94–1.97)
Intracranial hemorrhage	24 (0.7)	23 (0.6)	1.03 (0.58–1.83)
Gastrointestinal	25 (0.7)	17 (0.5)	1.48 (0.80–2.74)
Life-threatening bleed	27 (0.8)	33 (0.9)	0.82 (0.49–1.36)
Fatal bleed and fatal hemorrhagic stroke*	1 (0.0)	2 (0.1)	0.53 (0.05–5.85)
Major or clinically relevant non-major bleed	127 (3.6)	82 (2.3)	1.57 (1.19–2.07)

* Includes 2 deaths confirmed by adjudication as fatal ICH (0 dabigatran and 2 aspirin), plus 1 death confirmed by adjudication as fatal hemorrhagic stroke (1 dabigatran and 0 aspirin)

On-treatment outcome events are included if they occurred between the first intake of trial medication and the last intake of trial medication plus 6 days.

CI denotes confidence interval, MI myocardial infarction.

Supplementary Table S4. Post hoc Exploratory Analysis of Time to First Recurrent Stroke by Time for the Randomized Set.

	Dabigatran Group	Aspirin Group
Randomised patients, N	2695	2695
Patients with recurrent stroke 0 to 12 months after randomisation, n	146	146
Annualised event rate, %/yr	6.0	6.0
Hazard ratio vs. aspirin (95% CI)	0.99 (0.79, 1.25)	
Number of patients in the trial ≥366 days since randomisation, N	2013	2018
Patients with recurrent stroke >12 months after randomisation, n	31	61
Annualised event rate, %/yr	1.6	3.2
Hazard ratio vs. aspirin (95% CI)	0.50 (0.32, 0.77)	

CI denotes confidence interval.

Supplementary Table S5. Serious Adverse Events (SAEs) for the Treated Set.

System organ class (MedDRA 21.0)	Dabigatran Group (N=2676)	Aspirin Group (N=2674)	Overall (N=5350)
Total number of patients with SAEs	724 (27.1)	740 (27.7)	1464 (27.4)
Blood and lymphatic system disorders	10 (0.4)	6 (0.2)	16 (0.3)
Cardiac disorders	91 (3.4)	94 (3.5)	185 (3.5)
Congenital, familial and genetic disorders	9 (0.3)	8 (0.3)	17 (0.3)
Ear and labyrinth disorders	20 (0.7)	12 (0.4)	32 (0.6)
Endocrine disorders	5 (0.2)	2 (0.1)	7 (0.1)
Eye disorders	31 (1.2)	25 (0.9)	56 (1.0)
Gastrointestinal disorders	45 (1.7)	49 (1.8)	94 (1.8)
General disorders and administration site conditions	20 (0.7)	23 (0.9)	43 (0.8)
Hepatobiliary disorders	11 (0.4)	11 (0.4)	22 (0.4)
Immune system disorders	2 (0.1)	0 (0.0)	2 (0.0)
Infections and infestations	77 (2.9)	61 (2.3)	138 (2.6)
Injury, poisoning, and procedural complications	68 (2.5)	59 (2.2)	127 (2.4)
Investigations	4 (0.1)	8 (0.3)	12 (0.2)
Metabolism and nutrition disorders	13 (0.5)	12 (0.4)	25 (0.5)
Musculoskeletal and connective tissue disorders	44 (1.6)	48 (1.8)	92 (1.7)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	69 (2.6)	73 (2.7)	142 (2.7)
Nervous system disorders	298 (11.1)	322 (12.0)	620 (11.6)

Product issues	0	1 (0.0)	1 (0.0)
Psychiatric disorders	22 (0.8)	22 (0.8)	44 (0.8)
Renal and urinary disorders	33 (1.2)	30 (1.1)	63 (1.2)
Reproductive system and breast disorders	14 (0.5)	7 (0.3)	21 (0.4)
Respiratory, thoracic, and mediastinal disorders	25 (0.9)	28 (1.0)	53 (1.0)
Skin and subcutaneous tissue disorders	7 (0.3)	3 (0.1)	10 (0.2)
Social circumstances	1 (0.0)	0 (0.0)	1 (0.0)
Surgical and medical procedures	2 (0.1)	2 (0.1)	4 (0.1)
Vascular disorders	29 (1.1)	40 (1.5)	69 (1.3)

Data shown are no. (%)

On-treatment AEs are included if they occurred between the first intake of trial medication and the last intake of trial medication plus 6 days.

Supplementary Table S6. Adverse Events (AEs) Leading to Discontinuation for the Treated Set.

System organ class (MedDRA 21.0)	Dabigatran Group (N=2676)	Aspirin Group (N=2674)	Overall (N=5350)
Total number of patients with AEs	550 (20.6)	490 (18.3)	1040 (19.4)
Blood and lymphatic system disorders	8 (0.3)	3 (0.1)	11 (0.2)
Cardiac disorders	185 (6.9)	171 (6.4)	356 (6.7)
Congenital, familial, and genetic disorders	3 (0.1)	3 (0.1)	6 (0.1)
Ear and labyrinth disorders	1 (0.0)	4 (0.1)	5 (0.1)
Endocrine disorders	1 (0.0)	0 (0.0)	1 (0.0)
Eye disorders	8 (0.3)	4 (0.1)	12 (0.2)
Gastrointestinal disorders	72 (2.7)	44 (1.6)	116 (2.2)
General disorders and administration site conditions	17 (0.6)	16 (0.6)	33 (0.6)
Hepatobiliary disorders	3 (0.1)	2 (0.1)	5 (0.1)
Infections and infestations	13 (0.5)	12 (0.4)	25 (0.5)
Injury, poisoning, and procedural complications	26 (1.0)	10 (0.4)	36 (0.7)
Investigations	13 (0.5)	10 (0.4)	23 (0.4)
Metabolism and nutrition disorders	1 (0.0)	3 (0.1)	4 (0.1)
Musculoskeletal and connective tissue disorders	8 (0.3)	9 (0.3)	17 (0.3)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	16 (0.6)	17 (0.6)	33 (0.6)
Nervous system disorders	141 (5.3)	157 (5.9)	298 (5.6)

Pregnancy, puerperium, and perinatal conditions	1 (0.0)	1 (0.0)	2 (0.0)
Psychiatric disorders	6 (0.2)	6 (0.2)	12 (0.2)
Renal and urinary disorders	26 (1.0)	10 (0.4)	36 (0.7)
Reproductive system and breast disorders	6 (0.2)	2 (0.1)	8 (0.1)
Respiratory, thoracic, and mediastinal disorders	8 (0.3)	14 (0.5)	22 (0.4)
Skin and subcutaneous tissue disorders	17 (0.6)	9 (0.3)	26 (0.5)
Vascular disorders	7 (0.3)	24 (0.9)	31 (0.6)

Data shown are no. (%)

On-treatment AEs are included if they occurred between the first intake of trial medication and the last intake of trial medication plus 6 days.

Supplementary Table S7. Definition of Lacunar Infarcts (Adapted from*).

Location	• In the deep parts of the brain, in the territories of small penetrating arteries • Absent from the cerebral and cerebellar cortex
Sites of predilection	• Lenticular nucleus, thalamus, central white matter, internal capsule, centrum ovale, corpus callosum, basis pontis; and, rarely, the cerebellum, midbrain, and medulla
Size of infarct	• Of restricted size: on brain CT or MRI: <1.5 cm in largest diameter or <2.0 cm if measured on MRI diffusion sequences
What is *not* a lacunar stroke?	• Infarcts <1.5 cm in largest diameter, or <2.0 cm if measured on MRI diffusion sequences • Located in the dorsal or lateral areas of the brain stem, in the territory of circumferential, rather than deep-penetrating arteries

CT denotes computed tomography and MRI magnetic resonance imaging.

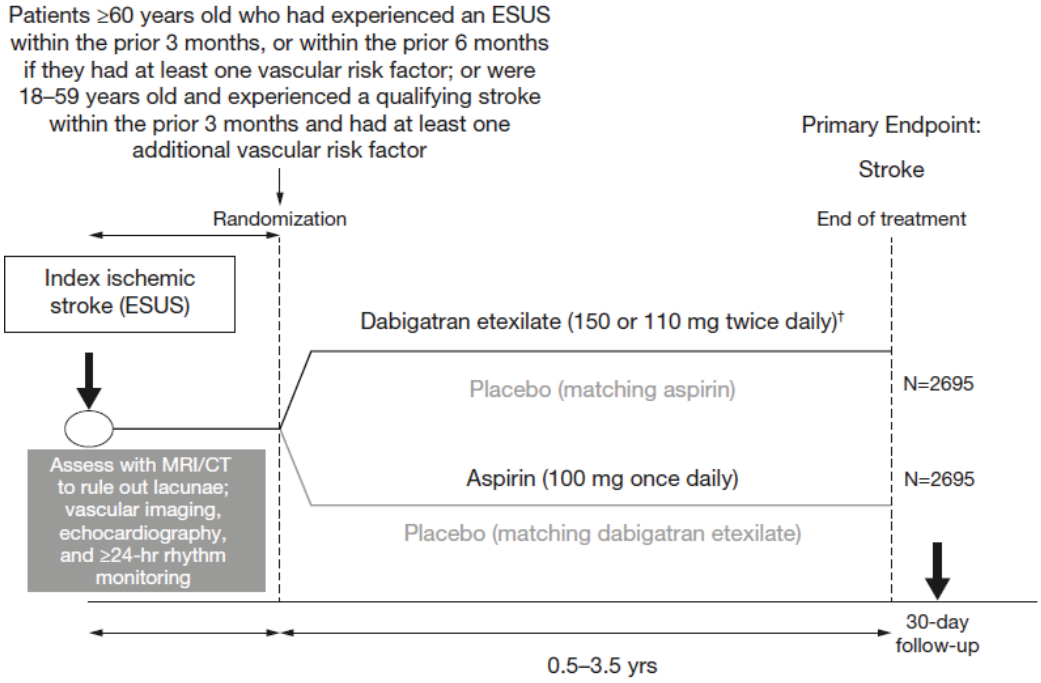
*Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013;12:822-38.

Supplementary Table S8. Possible Embolic Sources among ESUS Cases.

Heart — cardiac thrombi	Rhythm	• Subclinical AF • Atrial asystole • Paroxysmal atrial tachycardia • Sick sinus syndrome
	Structural	• Left atrial enlargement • Left atrial spontaneous echo contrast • Moderate left ventricular systolic dysfunction • Heart failure • Left ventricular diastolic dysfunction • Myocardial infarction with left ventricular regional wall motion abnormalities • Myxomatous mitral valves • Mitral valve prolapse • Mitral annular calcification • Mitral stenosis • Calcific aortic stenosis • Patent foramen ovale • Atrial septal aneurysm • Chiari network
Large vessels		• Aortic arch atheroma • Nonstenotic ulcerated cervical or intracranial plaques • Fibromuscular dysplasia
Hypercoagulable states		

AF denotes atrial fibrillation and ESUS embolic stroke of undetermined source.

Supplementary Figure S1. Overview of the Design of the RE-SPECT ESUS study.



The dabigatran dose was 150 mg twice daily, and 110 mg twice daily in patients ≥75 years or with an estimated creatinine clearance of ≥30 to ≤50 ml per min.

CT denotes computerized tomography; ESUS embolic stroke of undetermined source; MRI magnetic resonance imaging.

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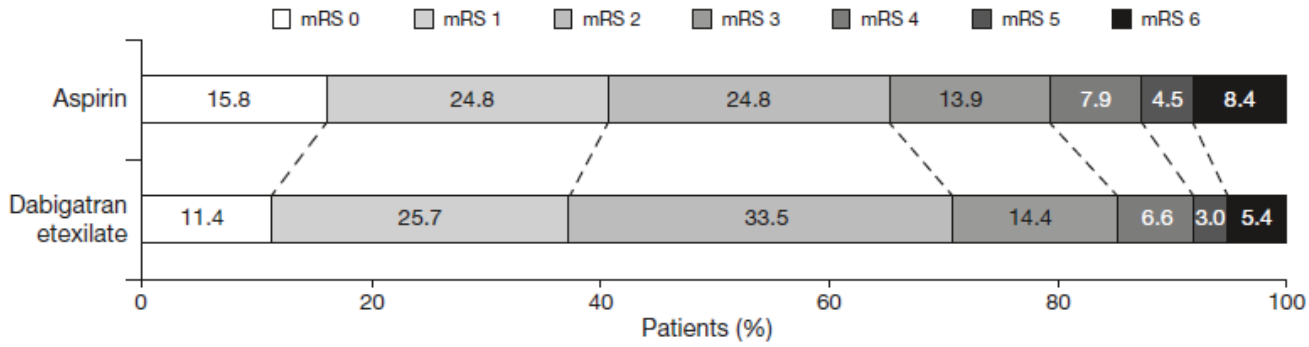
Supplementary Figure S2. Recurrent Stroke Severity in the Randomized Set.

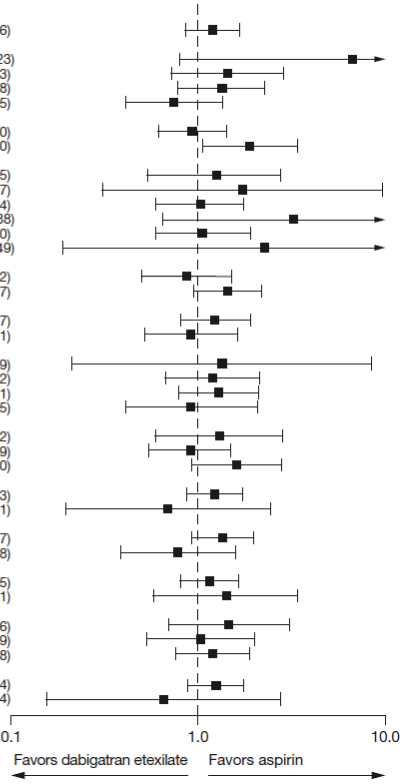
Evaluated using the modified Rankin Scale at 3 months post recurrent stroke.



mRS denotes modified Rankin Scale.

Supplementary Figure S3. Primary Safety Outcome (ISTH Major Bleeding) Overall and by Subgroups in the Randomized S

Subgroup	Dabigatran etexilate n/N (%)	Aspirin n/N (%)	HR (95% CI)
Overall	77/2695 (2.9)	64/2695 (2.4)	1.19 (0.85, 1.66)
Age classification			
<50	6/285 (2.1)	1/320 (0.3)	6.65 (0.80, 55.23)
50–<65	20/961 (2.1)	14/965 (1.5)	1.43 (0.72, 2.83)
65–<75	31/901 (3.4)	24/928 (2.6)	1.34 (0.78, 2.28)
≥75	20/548 (3.6)	25/482 (5.2)	0.75 (0.42, 1.35)
Sex			
Male	43/1694 (2.5)	47/1709 (2.8)	0.93 (0.61, 1.40)
Female	34/1001 (3.4)	17/986 (1.7)	1.90 (1.06, 3.40)
Region			
North America	14/300 (4.7)	10/294 (3.4)	1.22 (0.54, 2.75)
Central Europe	4/369 (1.1)	2/335 (0.6)	1.73 (0.31, 9.57)
Western Europe	27/1210 (2.2)	27/1254 (2.2)	1.02 (0.60, 1.74)
Latin America	6/107 (5.6)	2/118 (1.7)	3.20 (0.65, 15.88)
Asia	24/616 (3.9)	22/582 (3.8)	1.07 (0.60, 1.90)
Other	2/93 (2.2)	1/112 (0.9)	2.24 (0.19, 26.49)
Dose assignment			
110 mg	24/611 (3.9)	26/546 (4.8)	0.87 (0.50, 1.52)
150 mg	53/2084 (2.5)	38/2149 (1.8)	1.43 (0.94, 2.17)
Proton pump inhibitors			
No	47/1748 (2.7)	39/1797 (2.2)	1.22 (0.80, 1.87)
Yes	24/876 (2.7)	24/827 (2.9)	0.91 (0.52, 1.61)
Days from index stroke to randomization			
<8	3/95 (3.2)	2/97 (2.1)	1.34 (0.21, 8.49)
8–30	25/892 (2.8)	22/937 (2.3)	1.20 (0.67, 2.12)
31–90	37/1219 (3.0)	28/1200 (2.3)	1.29 (0.79, 2.11)
≥91	12/489 (2.5)	12/460 (2.6)	0.92 (0.41, 2.05)
Creatinine clearance at baseline (ml/min)			
30–<50	15/226 (6.6)	11/201 (5.5)	1.30 (0.59, 2.82)
50–<80	30/1041 (2.9)	31/965 (3.2)	0.90 (0.55, 1.49)
≥80	32/1424 (2.2)	21/1525 (1.4)	1.61 (0.93, 2.80)
Add-on aspirin at baseline			
No	72/2526 (2.9)	59/2557 (2.3)	1.23 (0.87, 1.73)
Yes	5/169 (3.0)	5/138 (3.6)	0.69 (0.20, 2.41)
Previous stroke/TIA prior to index stroke			
No	63/2220 (2.8)	46/2195 (2.1)	1.35 (0.92, 1.97)
Yes	14/475 (2.9)	18/500 (3.6)	0.78 (0.39, 1.58)
Cardiac monitoring at baseline (hrs)			
≤48	64/2220 (2.9)	56/2263 (2.5)	1.15 (0.80, 1.65)
>48	13/474 (2.7)	8/432 (1.9)	1.41 (0.58, 3.41)
CHA_2DS_2-Vasc score category			
2–3	17/836 (2.0)	12/840 (1.4)	1.46 (0.70, 3.06)
4	18/743 (2.4)	18/779 (2.3)	1.03 (0.54, 1.99)
5+	42/1116 (3.8)	34/1076 (3.2)	1.20 (0.76, 1.88)
Patent foramen ovale			
No	74/2375 (3.1)	59/2333 (2.5)	1.23 (0.88, 1.74)
Yes	3/319 (0.9)	5/361 (1.4)	0.65 (0.15, 2.74)



CI denotes confidence interval; HR hazard ratio TIA, transient ischemic attack.

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