Predictors of Recurrent Ischemic Stroke in Patients with Embolic Strokes of Undetermined Source and Effects of Rivaroxaban Versus Aspirin According to Risk Status: The NAVIGATE ESUS Trial

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Background: Embolic stroke of undetermined source (ESUS) identifies patients with cryptogenic ischemic stroke presumed due to embolism from several unidentified sources. Among patients with recent ESUS, we sought to determine independent predictors of recurrent ischemic stroke during treatment with aspirin or rivaroxaban and to assess the relative effects of these treatments according to risk. *Methods:* Exploratory analyses of 7213 participants in the NAVIGATE ESUS international trial who were randomized to aspirin 100 mg/day or rivaroxaban 15 mg/day and followed for a median of 11 months, during which time there were 309 first recurrent ischemic strokes (4.6% per year). Baseline features were correlated with recurrent stroke by multivariate analysis. *Results:* The 7 independent predictors of recurrent stroke were stroke or transient ischemic attack (TIA) prior to the qualifying stroke (hazard ratio [HR] 2.03 95% confidence internal [CI] 1.58-2.60), current tobacco user (HR 1.62, 95% CI 1.24-2.12), age (HR 1.02 per year increase, 95%CI 1.01-1.03), diabetes (HR 1.28, 95% CI 1.01-1.64), multiple acute infarcts on neuroimaging (HR 1.49, 95% CI 1.09-2.02), aspirin use prior to qualifying stroke (HR 1.34, 95% CI 1.02-1.70), and time from qualifying stroke to randomization (HR .98, 95% CI .97-.99). The rate of recurrent stroke rate was 2.6% per year for participants

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Received March 29, 2019; revision received May 8, 2019; accepted May 14, 2019.

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1052-3057/$ - see front matter

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https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.05.014

without any of these risk factors, and increased by an average of 45% for each independent predictor ($P < .001$). There were no significant interactions between treatment effects and independent stroke predictors or stroke risk status. *Conclusions:* In this large cohort of ESUS patients, several features including prior stroke or TIA, advanced age, current tobacco user, multiple acute infarcts on neuroimaging, and diabetes independently identified those with an increased risk of ischemic stroke recurrence. The relative effects of rivaroxaban and aspirin were similar across the spectrum of independent stroke predictors and recurrent stroke risk status.

Key Words: Embolic stroke—ESUS--rivaroxaban—recurrent stroke—stroke recurrence—prediction of recurrent stroke

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Introduction

Ischemic strokes of uncertain cause (ie, cryptogenic strokes) remain frequent despite diagnostic advances aimed at determining stroke etiology.[1,2] Most nonlacunar cryptogenic ischemic strokes are likely due to emboli originating from one of several potential cardiac and arterial sources and occasionally from venous thromboembolism (ie, via paradoxical embolism),[3] and the construct of embolic strokes of undetermined source (ESUS) has been proposed.[1] ESUS criteria identify patients with a rate of recurrent ischemic stroke that averages about 5% per year.[4-6]

In 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) randomized trial, we compared rivaroxaban (an anticoagulant), a selective direct factor Xa inhibitor, with aspirin (an antiplatelet drug) for prevention of recurrent stroke in ESUS patients.[7] Rates of recurrent ischemic stroke were similar in both treatment arms.[5] Here, we analyze independent predictors of recurrent ischemic stroke and the relative effects of rivaroxaban versus aspirin among high-risk ESUS patients.[8] Because the presumed underlying potential embolic sources were heterogeneous, treatment interactions with individual risk factors for recurrent stroke were explored in order to potentially shed light on the overall neutral trial results. Seeking pathomechanistic insights, we additionally assessed differences in independent predictors between antithrombotic treatment arms and on recurrent strokes classified as recurrent ESUS.

Methods

NAVIGATE ESUS (ClinicalTrials.gov number NCT02313909) was an international, double-blinded, randomized phase III trial conducted at 459 centers in 31 countries and involved 7213 participants. The study rationale, design, participant features, and main results have been previously published.[1,5,7,9] Patients with recent (7 days to 6 months) ischemic stroke visualized by neuroimaging were eligible if they met criteria for ESUS as proposed by the Cryptogenic Stroke/ESUS International Working group,[1] with minor modifications.[7] Eligibility required that patients be ≥50 year old, and if between ages 50 and 59 years, have additional stroke risk factors.[7] Ischemic stroke was defined as a focal neurological deficit of sudden origin due to presumed arterial occlusion persisting for more than 24 hours and without evidence of primary hemorrhage on neuroimaging; if lasting fewer than 24 hours, neuroimaging evidence of brain infarction must have been present. Transesophageal echocardiography was not required. For these analyses of recurrent ischemic stroke during follow-up, patients with recurrent strokes that could not be defined as ischemic or hemorrhagic in the absence of relevant neuroimaging or autopsy (n = 5) were excluded. Stroke outcome events observed during follow-up were verified centrally using a 2-tier process consisting of an algorithm linking reports by local physician investigators (overwhelmingly stroke neurologists) with criteria for stroke diagnosis, followed by conventional expert adjudication if all diagnostic criteria were not met. The subset of recurrent ischemic strokes classified as ESUS by local physician investigators was analyzed separately regarding independent predictors and relative effects of treatment.

We correlated participant features at time of study entry with the occurrence of first recurrent ischemic stroke during follow-up. Prior stroke or transient ischemic attack (TIA) refers to events prior to the qualifying stroke. Mitral valve disease (13% of the cohort) included annular calcification or regurgitation if rated as moderate to severe, valve thickening or prolapse, while aortic valve disease (20% of the cohort) included stenosis or regurgitation if rated moderate to severe or aortic valve thickening based on transthoracic echocardiography. A subset of 19% of participants was investigated with transesophageal echocardiography regarding the presence of patent foramen ovale and associations are reported separately.[10] In order to explore potential interactions of assigned antithrombotic therapy with predictors of recurrence, clinical features associated with recurrent ischemic stroke were analyzed separately according to assigned therapy.

Patient features that were included in multivariable models (using stepwise Cox proportional hazards) were

those in Table 1 that were univariably associated with recurrent stroke at a $p < 0.15$ level.

Annualized stroke rates represent the average number of events per participant during a 1-year period. The significance of stroke predictors was assessed using Cox proportional hazards models. All analyses followed an intention-to-treat paradigm. All tests were 2-sided; no adjustments were made for multiple comparisons, and statistical significance was accepted at the ≤.05 level.

The NAVIGATE ESUS trial was sponsored by Bayer AG and Janssen Research and Development LLC.

Results

The 7213 participants were recruited from Europe (59%), East Asia (19%), North America (13%), and Latin America (10%). The mean participant age was 67 years, 62% were men, and history of hypertension, diabetes, and prior stroke or TIA was present in 77%, 25%, and 17%, respectively. Participants were randomized, on average, 37 days after the qualifying ESUS. During a median follow-up of 11 months, first recurrent ischemic strokes occurred in 309 participants (annualized rate 4.6% per year), with no difference between assigned treatment arms (Fig 1). Of first recurrent ischemic strokes, 36 (12%) were clinical TIAs with positive neuroimaging. The mean (SD) National Institutes of Health Stroke Scale score at the time of stroke onset was 4.6 (5.2), and the median (interquartile range) was 3.0 (1.0-6.0).

Factors Associated With Recurrent Ischemic Stroke

By bivariate analysis, participants experiencing recurrent ischemic stroke were significantly older compared with those who did not (68.4 versus 66.9 years, respectively; Table 1). Other features significantly associated with recurrent ischemic stroke were current tobacco use, stroke or TIA prior to the qualifying stroke, diabetes mellitus, Asian race, multiple acute infarcts on neuroimaging, time from qualifying stroke to randomization, and aspirin use prior to the qualifying stroke (Table 1).

Factors Independently Associated With Recurrent Stroke by Multivariate Analysis

Among all participants, 7 independent factors emerged as significantly predictive of first recurrent ischemic stroke by stepwise multivariate analysis: prior stroke or TIA (hazard ratio [HR] 2.03 95% confidence internal [CI] 1.58-2.60), current tobacco user (HR 1.62, 95% CI 1.24-2.12), age (HR 1.02 per year increase, 95% CI 1.01-1.03), diabetes (HR 1.28, 95% CI 1.01-1.64), multiple acute infarcts on neuroimaging (HR 1.49, 95% CI 1.09-2.02), aspirin use prior to qualifying stroke (HR 1.34, 95% CI 1.02-1.70), and time from qualifying stroke to randomization (HR per 5 days .98, 95% CI .97-.99; Table 2).

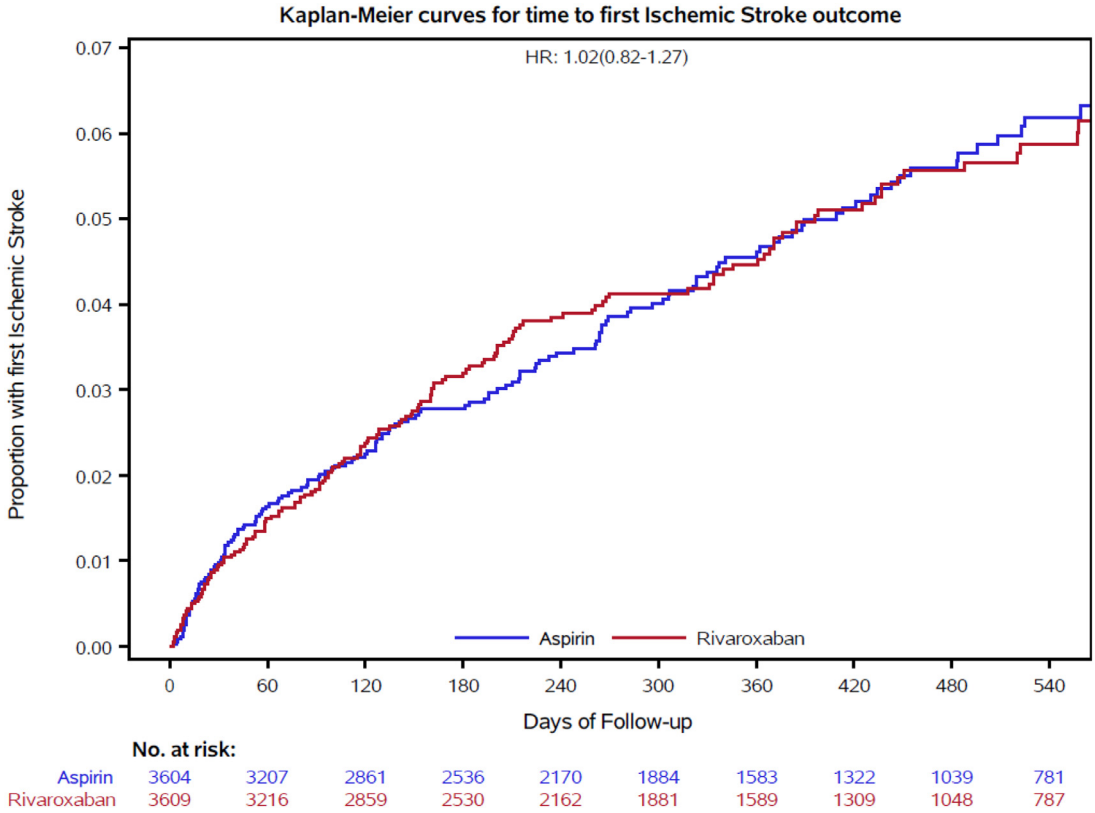

Figure 1. *Kaplan-Meier plot of first recurrent ischemic stroke according to treatment assignment.*

Table 1. *Features evaluated for association with first recurrent ischemic stroke*

	No recurrent ischemic stroke (N = 6904)	Recurrent ischemic stroke (N = 309)	Unadjusted hazard ratio (95% CI)
Age, years (mean ± s.d.)	66.9 ± 9.8	68.4 ± 10.2	1.02 (1.00-1.03)
Male sex	61%	66%	1.21 (.96-1.53)
Race:			
White	72%	68%	.84 (.66-1.07)
Black	2%	2%	1.25 (.56-2.81)
Asian	19%	25%	1.33 (1.03-1.72)
Others (includes not reported or multiracial)	7%	5%	.71 (.41-1.21)
Body mass index, kg/m^2 (mean ± s.d.)	27.3 ± 5.0	26.6 ± 4.6	.97 (.95-1.00)
Systolic blood pressure, mmHg (mean ± s.d.)	135.1 ± 16.8	134.3 ± 17.4	1.00 (.99-1.00)
Diastolic blood pressure, mmHg (mean ± s.d.)	79.0 ± 10.8	78.2 ± 11.5	.99 (.98-1.01)
No statin use at the time of randomization	22%	27%	1.21 (.94-1.56)
Hypertension	78%	74%	.86 (.66-1.11)
Diabetes mellitus	25%	30%	1.32 (01.03-1.68)
Current tobacco user	20%	27%	1.43 (1.11-1.85)
Coronary artery disease	6%	8%	1.30 (.87-1.95)
Heart failure	3%	4%	1.30 (.75-2.27)
Cancer	8%	11%	1.38 (.97-1.96)
Prior stroke or TIA (prior to the qualifying stroke)	17%	31%	2.14 (1.68-2.72)
Global region:			
U.S. and Canada	13%	13%	1.05 (.76-1.46)
Latin America	11%	7%	.73 (.47-1.13)
Western Europe	43%	42%	.92 (.73-1.16)
Eastern Europe	16%	15%	.96 (.70-1.32)
East Asia	18%	24%	1.29 (.99-1.67)
Qualifying stroke: Multiple lesions on imaging	10%	16%	1.58 (1.16-2.14)
Clinical TIA with imaging-confirmed infarction	7%	9%	1.29 (.88-1.90)
Chronic infarct on imaging (in addition to index stroke)	32%	44%	1.65 (1.32-2.07)
Aspirin use prior to qualifying stroke	17%	25%	1.65 (1.27-2.14)
Modified Rankin Score at randomization (median, IQR)	1.0 (.0, 2.0)	1.0 (.0, 2.0)	1.10 (.99-1.23)
Time from qualifying stroke to randomization, per 5 days (median, IQR)	37 (15,89)	30 (12,68)	.98 (.97-.99)
eGFR (mL/min)			
<50	6%	7%	1.18 (.76-1.83)
50-80	49%	55%	1.23 (.99-1.54)
>80	46%	38%	.77 (.61-.97)
Left atrial diameter by transthoracic echocardiography, per cm (mean ± s.d.)	3.8 ± 1.4	3.8 ± 1.3	1.01 (.92-1.12)
Mitral valve disease	13%	14%	1.02 (.74-1.42)
Aortic valve disease	20%	20%	1.00 (.76-1.33)
Carotid artery plaque	40%	44%	1.23 (.98-1.54)
Left ventricular ejection fraction <=40%	2%	3%	1.46 (.69-3.09)
Left dysfunction classified as moderate to severe	1%	3%	1.96 (.97-3.95)

CI, confidence interval; eGFR, estimated glomerular filtration rate; IQR, interquartile range; TIA, transient ischemic attack.

When analyzed separately by treatment assignment, there were no statistically significant interactions between independent predictors and treatment assignment (Table 2). Qualitatively, eGFR less than or equal to 80 mL/min was independently associated with higher stroke recurrence among those assigned aspirin (HR 1.89, 95% CI 1.33-2.70), but not among those allocated to rivaroxaban (HR .89, 95% CI .65-1.22).

Table 2. *Features independently associated with first recurrent ischemic stroke**

Predictive factor	Hazard ratio (95%CI)	*P* value*
All participants (n = 7213)		
Age (per year increase)	1.02 (1.01-1.03)	.001
Current tobacco user	1.62 (1.24-2.12)	.001
Diabetes mellitus	1.28 (1.01-1.64)	.05
Prior stroke or TIA^	2.03 (1.58-2.60)	<.001
Qualifying stroke: Multiple lesions on brain imaging	1.49 (1.09-2.02)	.01
Aspirin use prior to the qualifying stroke	1.34 (1.02-1.70)	.03
Time from qualifying stroke to randomization (per 5 days)	.98 (.97-.99)	.003
Aspirin-assigned participants (n = 3605)		
Prior stroke or TIA^	2.08 (1.47-2.95)	<.001
Aspirin use prior to the qualifying stroke	1.53 (1.05-2.22)	.03
Body mass index (kg/m^2)	.96 (.93-.99)	.02
eGFR ≤ 80 mL/min	1.89 (1.33-2.70)	<.001
Rivaroxaban-assigned participants (n = 3608)		
Prior stroke or TIA†	2.07 (1.46-2.92)	<.001
Current tobacco user	1.57 (1.10-2.23)	.01
Cancer diagnosis at entry	1.66 (1.02-2.70)	.04
Time from qualifying stroke to randomization	1.00 (.99-1.00)	.03
Modified Rankin Scale score at randomization	1.28 (1.10-1.49)	.002
Global region: U.S. and Canada	1.75 (1.13-2.70)	.01
Race: Asian	1.56 (1.08-2.24)	.02

CI, confidence interval; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack.
*Features that were significant $P \leq .05$ in the forward step-wise multivariate analysis.
†Prior to the qualifying stroke.

Relative Effects of Antithrombotic Interventions According to Independent Risk Predictors and Risk Status

The relative effects of antithrombotic therapies on recurrent ischemic stroke did not differ depending on the presence of the 7 independent risk factors (Table 3). Using a Cox model for the association between the number of independent predictors with first recurrent ischemic stroke, HR = 1.45 (95% CI 1.32-1.59; $P < .0001$). There was no statistically significant interaction between treatment effect and risk status comparing high-risk participants (those with 3 or more risk factors) to other participants.

Factors Independently Associated With Recurrent ESUS

Of first recurrent ischemic strokes, 161 (52%) were classified by local investigators as recurrent ESUS. First recurrent ESUS occurred at an annualized rate of 2.4% per year. Two independent predictors of recurrent ESUS were identified: age (HR 1.02 per year, 95% CI 1.00-1.03) and prior stroke or TIA (HR 2.20, 95% CI 1.58-3.07; Table 4). There were no significant interactions between these 2 independent predictors of first recurrent ESUS and treatment effects.

Discussion

In undertaking these exploratory analyses, we sought to identify a distinctive pattern of recurrent stroke predictors that would be relatively specific to ESUS patients and that would offer pathomechanistic insights into the heterogeneous underlying embolic sources and to their responses to antiplatelet versus anticoagulant therapy. Prior stroke or TIA was the strongest and most consistent predictor of recurrent ischemic stroke (and also of recurrent ESUS), but this feature does not offer clues about etiological mechanisms. No significant treatment interactions with risk factors or risk status emerged to provide understanding of the overall neutral comparison of rivaroxaban with aspirin on recurrent ischemic stroke in the NAVIGATE ESUS trial.

Potential etiological risk factors for recurrent ischemic stroke that emerged from these analyses were those related to atherosclerosis (ie, current tobacco use and diabetes mellitus). Of note, there was inadequate power to adequately assess the contribution of left ventricular dysfunction because of its infrequency in the study cohort (Table 1).

Analysis of independent predictors of stroke recurrence by treatment assignment was undertaken to assess potential differences related to antiplatelet versus anticoagulant therapy (Table 2). Dividing the cohort for such analyses resulted in reduced power (with marginally significant *P* values) and less stable estimates. Differences in independent predictors that emerged were mostly likely due to play of chance since there were no statistically significant interactions.

Limitations and caveats of these analyses include those common to exploratory analyses of clinical trials, especially spurious associations that are nominally statistically

Table 3. *Absolute rates of recurrent ischemic stroke associated with independent predictors and treatment effects**

		Recurrent ischemic stroke rate (annualized)				
	% of all participants (n = 7213)	All participants	Rivaroxaban assigned	Aspirin assigned	Hazard ratio‡ (95% CI)	*P* value
Individual independent predictors						
Age ≥ 75 years	23%	5.4	5.1	5.6	.91 (.60-1.38)	.65
Diabetes mellitus	25%	5.7	6.3	5.1	1.23 (.82-1.86)	.32
Prior stroke or TIA†	17%	8.2	8.1	8.4	.97 (.65-1.46)	.90
Current tobacco user	20%	6.7	6.7	5.6	1.20 (.77-1.85)	.42
Qualifying stroke: multiple lesions on imaging	10%	6.8	7.3	6.3	1.21 (.69-2.13)	.50
Aspirin use prior to the qualifying stroke	17%	7.0	6.7	7.2	.94 (.60-1.47)	.77
Time from qualifying stroke to randomization <30 d	43%	5.4	5.6	5.2	1.09 (.79-1.49)	.61
According to numbers of independent predictors§						
No independent predictor	16%	2.6	1.9	3.2	.63 (.31-1.31)	.22
Any single independent predictor	33%	3.4	3.2	3.6	.87 (.56-1.37)	.56
Any two independent predictors	30%	5.1	6.2	4.1	1.51 (1.02-2.24)	.04
Three or four independent predictors	18%	7.0	7.3	6.8	1.07 (.70-1.65)	.74
Five or more independent predictors	1%	26.3	13.6	42	.36 (.11-1.14)	.08

CI, confidence interval; TIA, transient ischemic attack.
*Independent predictors of recurrent ischemic stroke with $P \leq .05$ from Table 2.
†Prior to the qualifying stroke.
‡Hazard ratio comparing stroke rates for rivaroxaban-assigned versus those aspirin-assigned by Cox proportional hazards.
§Cox model for the association between the number of independent predictors with first recurrent ischemic stroke: hazard ratio (95% CI) = 1.45(1.32-1.59) $P < .0001$.

Table 4. *Features independently associated with recurrent ESUS**

Predictive factor	Hazard ratio (95%CI)	*P* value*
Age (per year increase)	1.02 (1.00-1.03)	.03
Prior stroke or TIA†	2.20 (1.58-3.07)	<.001

CI, confidence interval; ESUS, embolic stroke of undetermined source as classified by local investigators; TIA, transient ischemic attack.
*Features that are significant $P \leq .05$ by multivariate analysis.
†Prior to the qualifying stroke.

significant due to multiple comparisons. Because of multiple comparisons, we regard correlations that are $P \geq .01$ as of dubious reliability. On the other hand, requiring stringent *P* values risks overlooking true associations for variables that are less frequent (ie, heart failure). Assessment of treatment effects according to post hoc risk stratification is generally accepted for hypothesis generation.[8] A strength of these analyses is the prospectively applied definition of ESUS requiring a standardized diagnostic evaluation, the large numbers of participants and stroke outcomes, and nearly complete follow-up.

Seeking insights into predictors of recurrent ischemic stroke in ESUS patients, no distinctive pattern emerged from these exploratory analyses. Potential etiological predictors of recurrent ischemic stroke were more related to atherosclerotic mechanisms than to cardioembolic causes. There was no convincing evidence of differential treatment effects by individual predictors of risk or by risk status for stroke recurrence.

Conflict of Interest

All authors received payments for participating in the NAVIGATE ESUS randomized trial except for HM, SDB and GP who were employed by the trial sponsors (Bayer AG, Janssen Research and Development LLC).

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