Stroke

CLINICAL AND POPULATION SCIENCES

Frequency and Predictors of Major Bleeding in Patients With Embolic Strokes of Undetermined Source

NAVIGATE-ESUS Trial

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BACKGROUND AND PURPOSE: Risks, sites, and predictors of major bleeding during antithrombotic therapies have not been well defined for patients with recent embolic stroke of undetermined source.

METHODS: Exploratory analysis of major bleeds defined by International Society of Thrombosis and Hemostasis criteria occurring among 7213 participants in international NAVIGATE (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial) embolic stroke of undetermined source randomized trial comparing rivaroxaban 15 mg daily with aspirin 100 mg daily.

RESULTS: During a median follow-up of 11 months, 85 major bleeds occurred. The most frequent site was gastrointestinal (38%), followed by intracranial (29%). Assignment to rivaroxaban (hazard ratio [HR], 2.7 [95% CI, 1.7–4.3]), East Asia region (HR, 2.5 [95% CI, 1.6–3.9]), systolic blood pressure ≥160 mm Hg (HR, 2.2 [95% CI, 1.2–3.8]), and reduced estimated glomerular filtration rate (HR, 1.2 per 10 mL/min per 1.73 m^2 decrease, [95% CI, 1.0–1.3]) were independently associated with presence of major bleeds. Five (6%) were fatal. Among 15 patients with intracerebral hemorrhage, 2 (13%) were fatal. There was no evidence of an early high-risk period following initiation of rivaroxaban. The annualized rate of intracerebral hemorrhage was 6-fold higher among East Asian participants (0.67%) versus all other regions (0.11%; HR , 6.3 [95% CI, 2.2–18.0]). Distribution of bleeding sites was similar for rivaroxaban and aspirin.

CONCLUSIONS: Among embolic stroke of undetermined source patients participating in an international randomized trial, independent predictors of major bleeding were assignment to rivaroxaban, East Asia region, increased systolic blood pressure, and impaired renal function. East Asia as a region was strongly associated with risk of intracerebral hemorrhage. Estimated glomerular filtration rate should be a consideration for stratifying bleeding risk.

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Key Words: blood pressure ■ embolism ■ glomerular filtration rate ■ infarction ■ rivaroxaban

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Cryptogenic strokes account for approximately one-third of all ischemic strokes.[1–3] Causes of cryptogenic stroke remain speculative and may include different types and sources of embolism. Embolic strokes of undetermined source (ESUS) are a subset of patients with cryptogenic strokes who have clinical

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features supporting an embolic mechanism and, therefore, exclude patients with small subcortical infarcts.[4]

Several characteristics of patients with ESUS have been defined, for example, patients with ESUS have a substantial rate of recurrent ischemic stroke, averaging about 5% per year.[5,6] However, bleeding during antithrombotic therapies, including bleeding sites and predictors of bleeding, are unknown. Here, we present an analysis of bleeding outcomes in participants in the NAVIGATE ESUS trial (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial Versus Acetylsalicylic Acid to Prevent Embolism in Embolic Stroke of Undetermined Source). The trial was terminated early at interim analysis due to increased bleeding among those assigned to rivaroxaban coupled with absence of efficacy for reduction in recurrent stroke.[7] This is another reason why comprehensive analysis of bleeding outcomes is particularly important for understanding the results of the trial. In addition, understanding predictors of bleeding could help to stratify the risk of antithrombotic treatments for patients with ESUS in routine clinical practice.

METHODS

In accordance with Bayer AG policy, NAVIGATE ESUS data are available by reasonable request. For more information see the Data Supplement.

NAVIGATE ESUS was an international, double-blinded, randomized phase III trial conducted at 459 centers in 31 countries that enrolled 7213 participants. The study rationale, design, participant features, and main results have been previously published,[6–8] including bleeding rates and the effects of treatment on major bleeding outcomes (see Table I in the Data Supplement).[7] Patients with recent (7 days to 6 months) ischemic stroke visualized by neuroimaging were eligible for enrollment if they met criteria for ESUS as proposed by the Cryptogenic Stroke/ESUS International Working Group, with minor modifications.[8] Eligibility required that patients be ≥50 years old, and if between ages 50 to 59 years, have additional stroke risk factors.[6] Required diagnostic testing to assess for probable stroke causes included carotid artery imaging to exclude stenosis >50% or occlusion, at least 20 hours of cardiac rhythm monitoring to exclude occult atrial fibrillation, and echocardiography to exclude intracardiac thrombus. Exclusion criteria related to bleeding included prior primary intracranial hemorrhage, active bleeding, major bleeding within the past 6 months, or deemed by local clinicians to have a high risk for serious bleeding if given rivaroxaban or aspirin.[6] Patients were then randomized to rivaroxaban 15 mg once daily or aspirin 100 mg once daily. The relevant health authorities and the institutional review board at each trial site approved NAVIGATE ESUS. Written informed consent was obtained from each participant. The authors declare that all supporting data are available within the article and in the Data Supplement.

The primary safety outcome for the trial was major bleeding. Major bleeding was defined by the International Society of Thrombosis and Hemostasis (ISTH) criteria[9] and required that at least one of the following were met: (1) fatal bleeding, (2) symptomatic bleeding in a critical area or organ (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), (3) clinically overt bleeding associated with a recent decrease in the hemoglobin level of ≥2 g/dL compared with the most recent hemoglobin value available before the event, (4) clinically overt bleeding leading to transfusion of ≥2 units of packed red blood cells or whole blood. Major bleeds were centrally adjudicated by those unaware of treatment allocation and other patient characteristics.

In NAVIGATE ESUS, clinically relevant nonmajor bleedings (CRNMB) were also reported but we chose not to include them in these analyses for the following reasons: (1) CRNMB were not centrally adjudicated as opposed to major bleedings, (2) intracranial bleeds that make up about 25% of ISTH major bleeds and that have their own independent predictors, are not included in CRNMBs, (3) some clinically less relevant bleeds, for example, nose-bleeds requiring medical attention are CRNMBs and not ISTH major bleeds, and hence analysis of independent predictors of ISTH major bleeds and CRNMBs together would be potentially misleading.

Analyses were performed based on the intent-to-treat population unless otherwise noted. Only the first major bleed for a patient was included in these analyses. Patient characteristics were described using proportions for discrete variables and means with SD for continuous. Missing data (patient characteristic) were rare except as noted. The hazard ratio (HR) and 95% CI from the Cox proportional hazards model were computed to describe risk of major bleed for each characteristic with the proportional hazards assumption checked by evaluating an interaction term between time and the characteristic. Continuous variables were empirically checked for linearity by evaluating if the changes in the beta (ln HR) between quartiles were similar; alternatively HRs for clinically important groups were reported. Characteristics statistically different ($P<0.10$) between groups by univariable analyses (with the exception of race due to missing values) were included in forward stepwise multivariable analyses using a Cox proportional hazards model to identify independent predictors of major bleeding. Fit of the final multivariable model was estimated by computing the C statistic. Kaplan-Meier curves were fit to display time to event data. Potential for competing risks was assessed by evaluating the fit of the final multivariable model for bleeding for the end point of all cause death and the combined end point of major bleed and death. Distribution of major bleeds was compared across treatment groups after first collapsing sites into 3 locations: gastrointestinal, intracranial hemorrhage, and all others. There was no imputation of missing data or adjustment for multiple comparisons. All reported P values were 2-sided. Statistical analysis was done using SPSS for Windows version 25.0.0 (IBM Corp, Armonk, NY) and MedCalc Statistical Software version 19 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019).

RESULTS

The 7213 participants were recruited from Europe (58%), East Asia (19%), North America (13%), and Latin America (10%) between December 2014 and September 2017. The mean participant age was 67 years and

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62% were men. Previous gastrointestinal bleeding (>6 months before randomization) was prevalent in 2%, regular aspirin use before the qualifying stroke in 17%, and in 6% the estimated glomerular filtration rate (eGFR) was <50 mL/min per 1.73 m^2. Detailed baseline characteristics are shown in Table 1.

Predictors of Major Bleeding

During the median follow-up of 11 months, 85 first major bleeds occurred. Older participant age, East Asian region (and Asian race), systolic blood pressure (SBP) ≥160 mm Hg, reduced eGFR, and assignment to rivaroxaban were associated with bleeds in univariable analyses (Table 1 and Table II in the Data Supplement). By multivariable analysis, features independently associated with major bleeding were East Asia region (HR, 2.5 [95% CI, 1.6–3.9]), SBP ≥160 mm Hg (HR, 2.2 [95% CI, 1.2–3.8]), reduced eGFR (HR, 1.2 per 10 mL/min per 1.73 m^2 decrease, [95% CI, 1.0–1.3]), and assignment to rivaroxaban (HR, 2.7 [95% CI, 1.7–4.3]; C statistic, 0.71 [CI, 0.66–0.77]; Table 2 and Table III in the Data Supplement). None of the interaction terms between treatment and any feature in the model was statistically significant. Within rivaroxaban-assigned as well as aspirin-assigned group, baseline characteristics in patients with and without major bleed were similar (Table II in the Data Supplement). Substitution of Asian race for East Asian region resulted in the same multivariable model with Asian race being an independent predictor (multivariable HR, 2.4 [95% CI, 1.6–3.8]). While race was reported for all participants from East Asian region (1347/1350 Asian only), it was not reported for 399 participants from other regions, including 3 who had a major bleed. Sixty-seven participants from other regions reported being Asian only. Major bleeding occurred in 25 (2.1%) of 1177 East Asian region participants and 39 (0.8%) of the 5045 others with neither SBP >160 mm Hg nor eGFR <50 mL/min per 1.73 m^2, as well as in 14 of the 173 (8.1%) East Asian region participants and 6 (0.7%) of the 802 others with either SBP ≥160 mm Hg and eGFR<50 mL/min per 1.73 m^2.

Location of Bleeds and Associated Mortality

Considering major bleeds, 38% were gastrointestinal and 29% intracranial, while the remainder were scattered among multiple sites (Table 3). The relative distributions of sites of major bleeding were similar between treatment arms (P=0.5, χ^2, 2 df; Table 3). Major bleeds were fatal in 5 of the 85 (6%) patients; 4 of 62 (6%) rivaroxaban-assigned and 1 of 23 aspirin-assigned.

Factors Associated With Symptomatic Intracerebral Hemorrhage

In univariable analyses, region, diastolic blood pressure, prior stroke/transient ischemic attack, and hemorrhagic transformation of the qualifying stroke were associated with the occurrence of nontraumatic intracerebral hemorrhages (n=15; 12 on rivaroxaban, 3 on aspirin; Table 4), with the limited number of events precluding multivariable analysis. The annualized rate of intracerebral hemorrhage was 6-fold higher among East Asian participants (0.67%/y) versus all other regions (0.11%/y) although the CI was wide (HR, 6.3 [95% CI, 2.2–18]). Of the 15 intracerebral hemorrhages, 2 (13%) were fatal versus 3 (4%) of the 70 nonintracerebral major bleeds.

Regarding the relationship to the qualifying ischemic stroke, of 10 hemispheric intracerebral hemorrhages, 7 were ipsilateral to the qualifying infarct, while in 3 the bleeding was either contralateral or the qualifying infarct involved the brain stem/cerebellum only. Of 4 intracerebral hemorrhages involving the brain stem or cerebellum, the qualifying infarct involved the brain stem/cerebellum in one (in one patient the location of intracerebral hemorrhage was not reported).

Timing of Symptomatic Intracerebral Hemorrhage

Four (33%) of 12 intracerebral hemorrhages in rivaroxaban-assigned patients occurred within the initial 30 days after randomization versus 1 (33%) of 3 in aspirin-assigned (Figure). In a Cox proportional hazards model fit for the outcome of intracerebral hemorrhage, the assumption of proportional hazards was not violated (P=0.6), supporting that the risk of intracerebral hemorrhage with rivaroxaban versus aspirin remained proportional over time within chance.

DISCUSSION

The major findings of these exploratory analyses were the identification of independent predictors of major bleeding, the similar distributions of bleeding sites in patients assigned rivaroxaban 15 mg daily or aspirin 100 mg daily, and the strong association of intracerebral hemorrhage with East Asia region. The independent predictors of major bleeding were assignment to rivaroxaban, East Asia region, SBP ≥160 mm Hg, and reduced eGFR.

Asia region was reported to be an independent predictor of major bleeding also in another international clinical trial cohort of patients with ESUS.[10] Also in 2 studies S_2TOP-BLEED and B_2LEED$_3$S, analyzing predictors of bleeding in patients treated with antiplatelets, Asians had more major and intracerebral bleeding, respectively.[11] Higher bleeding risk due to antithrombotic treatment in Asians was described also in ST-segment–elevation myocardial infarction, thus it

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Table 1. Baseline Characteristics in Participants With and Without Major Bleeding and Hazard Ratios for Major Bleed

	No Major Bleed (N=7128) N (%)	Major Bleed (N=85) N (%)	Unadjusted (HR; 95% CI)	*P* Value
Age, y, mean±SD	67±10	69±11	NC	
Age, y				0.05
<60	1696 (24)	20 (24)	Reference group	
60–74	3769 (53)	35 (41)	0.79 (0.46–1.4)	
≥75	1663 (23)	30 (35)	1.5 (0.83–2.6)	
Male sex	4388 (62)	48 (56)	0.79 (0.51–1.2)	0.3
Global region				0.001
USA and Canada	906 (13)	12 (14)	1.3 (0.65–2.4)	
Latin America	743 (10)	3 (4)	0.46 (1.4–1.5)	
Western Europe	3048 (43)	33 (39)	Reference group	
Eastern Europe	1112 (16)	6 (7)	0.54 (0.23–1.3)	
East Asia	1319 (19)	31 (36)	2.1 (1.3–3.4)	
Assignment to rivaroxaban	3547 (50)	62 (73)	2.7 (1.7–4.4)	<0.001
Race			HR vs all others	
White only	5170 (73)	48 (56)	0.51 (0.33–0.78)	NC
Asian only	1382 (19)	32 (38)	2.3 (1.5–3.6)	NC
Other/multiracial	180 (3)	2 (2)	NC	
Not reported	396 (6)	3 (4)	NC	
BMI, kg/m^2, mean±SD, HR/5 units	27±5	27±7	0.90 (0.72–1.1)	0.3
Blood pressure, mm Hg, mean±SD, HR/10 units	135±17/79±11	137±20/80±12	NC/1.1 (0.88–1.3)	0.5
Systolic blood pressure, mm Hg				0.05
<140	4288 (60)	45 (54)	reference group	
140–159	2239 (31)	25 (30)	1.1 (0.65–1.7)	
≥160	588 (8)	14 (17)	2.3 (1.2–4.1)	
NIHSS score at randomization				0.3
0	3077 (43)	38 (45)	Reference group	
1	1567 (22)	13 (15)	0.69 (0.37–1.3)	
2	1010 (14)	16 (19)	1.4 (0.76–2.4)	
≥3	1470 (21)	18 (21)	1.1 (0.63–1.9)	
Prior stroke or TIA	1243 (17)	20 (24)	1.4 (0.87–2.4)	0.2
Hypertension	5518 (77)	67 (79)	1.1 (0.66–1.9)	0.7
Diabetes mellitus	1787 (25)	19 (22)	0.90 (0.54–1.5)	0.9
Heart failure	236 (3)	2 (2)	0.71 (0.18–2.9)	0.6
Coronary artery disease	464 (7)	8 (9)	1.4 (0.70–3.0)	0.3
Current tobacco use	1469 (21)	15 (18)	0.85 (0.49–1.5)	0.6
History of gastrointestinal bleeding	110 (2)	2 (2)	1.4 (0.35–5.8)	0.7
Liver disease	111 (2)	2 (2)	1.5 (0.36–5.9)	0.6
Aspirin use before qualifying stroke	1239 (17)	14 (16)	0.99 (0.56–1.8)	1.0
Statin use after randomization	5540 (78)	64 (75)	0.93 (0.57–1.5)	0.8
Cancer	609 (9)	11 (13)	1.6 (0.84–3.0)	0.2
Qualifying stroke arterial territory				0.4
Anterior circulation	4799 (67)	56 (66)	Reference group	
Posterior circulation	1916 (27)	21 (25)	0.96 (0.58–1.6)	
Anterior and posterior	325 (5)	7 (8)	1.8 (0.80–3.9)	
Unable to determine	86 (1)	1 (1)	NC	
Qualifying stroke–tPA and endovascular treatment	1342 (19)	15 (18)	0.92 (0.53–1.6)	0.8
PFO or interatrial shunting (n=6394)	528 (8)	9 (12)	1.4 (0.68–2.8)	0.4

(*Continued*)

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Table 1. Continued

	No Major Bleed (N=7128) N (%)	Major Bleed (N=85) N (%)	Unadjusted (HR; 95% CI)	*P* Value
Left ventricular ejection fraction (n=5936)				0.5
≥55	5318 (91)	64 (86)	Reference group	
40–54	464 (8)	8 (11)	1.4 (0.66–2.9)	
<40%	80 (1)	2 (3)	2.1 (0.52–8.6)	
eGFR, mL/min per 1.73 m² mean±SD	79±21	72±21	0.86 (0.77–0.97)	0.009
eGFR, mL/min per 1.73 m²				0.04
<50	410 (6)	9 (11)	2.5 (1.2–5.3)	
50–80	3482 (49)	49 (58)	1.6 (0.99–2.5)	
>80	3234 (45)	27 (32)	Reference group	
Time from qualifying stroke to randomization, days				0.8
≤14	1780 (25)	25 (29)	Reference group	
15–30	1412 (20)	15 (18)	0.76 (0.40–1.4)	
31–89	2183 (31)	24 (28)	0.77 (0.44–1.3)	
≥90	1753 (25)	21 (25)	0.78 (0.44–1.4)	

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NC, not calculated; NIHSS, National Institutes of Health Stroke Scale; PFO, patent foramen ovale; TIA, transient ischemic attack; and tPA, tissue-type plasminogen activator.

seems not to be specific to stroke. Many reasons have been hypothesized including higher prevalence of underlying and occult sources of gastrointestinal bleeding like gastric cancer or ulcer due to higher prevalence of *Helicobacter pylori* in Asians.[12–14] In our study, we could not differentiate the effect of the East Asia region versus Asian race because only 70 participants were classified differently by region versus race, that is, 67 Asians were randomized outside the East Asia region and 3 non-Asians were randomized in the East Asia region.

Because rivaroxaban is partially excreted by the kidneys, the association of major bleeding with reduced renal function could be due to more sustained anti-Xa levels among participants with renal impairment. Reduced kidney function as an independent risk factor for bleeding in trial where rivaroxaban was tested against coumarin for secondary stroke prevention in patients with atrial fibrillation.[15] Although the dosage in the present trial was lower than the regular dose used for secondary prevention in patients with stroke increased bleeding occurred. However, explanation between bleeding risk and eGFR in patients on aspirin is less clear. First of all, eGFR was not analyzed as predictor of bleeding in S_2TOP-BLEED or B_2LEED$_3$S, so data in neurological patients are not available. Second, in cardiology patients, eGFR was actually found to be related to bleeding risk in patients on aspirin in a sub-analysis of a large primary prevention study.[16] This higher bleeding risk was, however, offset by greater absolute reduction in major cardiovascular events and mortality in patients with lower eGFR, which is explained by higher cardiovascular risk in patients with chronic kidney disease.

Of note, our simple 4-item model has a similar predictive ability for bleeding in our cohort (C statistic, 0.71 [CI, 0.66–0.77]) as previously published models such as S_2TOP-BLEED (C statistic, 0.63 [CI, 0.60–0.64]) or B_2LEED$_3$S score (C statistic, 0.64 [CI, 0.61–0.68]) found in their derivation cohorts, although we used continuous variables in our model and not dichotomized variables as in the other models. Given these findings in cardiology literature and the findings in our study, eGFR seems to be an important predictor of bleeding in patients with stroke, including those taking aspirin and should be included in predictive scores.

Intracerebral hemorrhage, the most serious complication of antithrombotic therapy, made up 18% of major bleeds (19% in rivaroxaban-assigned, 13% in aspirin-assigned). In clinical trials, testing vitamin K antagonists, the fraction of major bleeds that were intracranial averages 25%[16] and is lower during anticoagulation with oral factor Xa inhibitors.[17] The rate of symptomatic intracerebral bleeding was low in both treatment arms for a post-stroke cohort treated with antithrombotic therapy (0.3%/y with rivaroxaban, 0.1%/y with aspirin), supporting that patients with ESUS are not at special risk compared with other patients who have suffered an ischemic stroke.[18–20] The small number of intracerebral hemorrhages precluded multivariable analysis to identify independent predictors of

Table 2. Independent Predictors of Major Bleeding in the Multivariable Analysis

	HR (95% CI)	*P* Value
East Asia region*	2.5 (1.6–3.9)	<0.001
eGFR, per 10 mL/min per 1.73 m² increase	0.86 (0.77–0.97)	0.01
Systolic blood pressure ≥160 mm Hg	2.2 (1.2–3.8)	0.009
Assignment to rivaroxaban	2.7 (1.7–4.3)	<0.001

The final model included 7197 patients with 84 first major bleed events. eGFR indicates estimated glomerular filtration rate; and HR, hazard ratio.

*HR (95%CI) for Asian race when substituted for East Asian region: 2.5 (1.6–3.8).

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Table 3. Sites of Major Bleeding by Assigned Treatment*

	All Participants, N=85		Aspirin-Assigned, N=23		Rivaroxaban-Assigned, N=62	
Bleeding Sites	N	%	N	%	N	%
Gastrointestinal - all	32	38	11	48	21	34
Upper	19	22	6	26	13	21
Lower	7	8	4	17	3	5
Unknown	6	7	1	4	5	8
Intracranial	25	29	5	22	20	32
Intracerebral	15	18	3	13	12	19
Subarachnoid	6	7	1	4	5	8
Subdural	4	5	1	4	3	5
Skin	1	1	0	0	1	2
Nasal	0	0	0	0	0	0
Urinary	2	2	1	4	1	2
Respiratory	1	1	0	0	1	2
Eye	5	6	2	9	3	5
Genital	7	8	1	4	6	10
Other sites	8	9	2	9	6	10
Uncertain	4	5	1	4	3	5

ISTH indicates International Society of Thrombosis and Hemostasis.
*Only the first ISTH major bleed per patient was considered.

this complication, but it was notable that East Asian region was associated with a 6-fold higher risk and accounted for 9 (60%) of the 15 intracerebral hemorrhages (East Asians made up 19% of the trial cohort). In the international RE-SPECT ESUS trial (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety), the rate of intracranial hemorrhage was increased by 2.5× among Asian participants versus all others.[20] Asians have higher rates of intracranial hemorrhage compared with non-Asians,[21] and Asian ethnicity is associated with an increased risk of intracranial hemorrhage during antiplatelet therapy.[22]

Assignment to rivaroxaban was previously reported to be associated with major bleeding in the NAVIGATE ESUS trial[7] (Table I in the Data Supplement), but interpretation of this observation requires additional context. Early stopping of the NAVIGATE ESUS trial at an interim analysis was prompted by the relative increase in major bleeds among participants assigned to rivaroxaban versus aspirin that was not offset by treatment benefits.[7] Early termination at interim analysis likely exaggerated the point estimate of the increased relative risk of bleeding associated with assignment to rivaroxaban. The observed rate of bleeding among those assigned to rivaroxaban (1.8%/y) was less than anticipated when the trial was designed (2.0%/y), and the observed rate of major bleeding among those assigned aspirin (0.7%/y) was also lower than anticipated (1.0%/y).[23] Hence, the absolute increase in major bleeding of 1.1% per year among those assigned rivaroxaban 15 mg daily compared with aspirin was consistent with that anticipated when the trial was designed (1% per year) and with that observed in the recent COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) comparing rivaroxaban 5 mg twice daily with aspirin in patients of similar age with atherosclerosis (0.9% per year).[24] In another large, international randomized trial, the RE-SPECT ESUS trial, that involved a similar cohort of patients with ESUS, the rate of ISTH major bleeding (ie, the same criteria) was 1.7%/y with dabigatran and 1.4%/y with aspirin.[20] In summary, the observed major bleeding rate among those assigned to rivaroxaban in NAVIGATE ESUS was that expected for the participant population and was similar to that seen with use of another nonvitamin-K-agonist anticoagulant (dabigatran) in a second, similar trial.[20]

The main study limitation is that these analyses were exploratory (ie, not predefined), increasing the likelihood of chance associations. The limited number of patients with major bleeds (n=85) threatens the stability of multivariable models. In addition, most trial participants had relatively minor ischemic strokes as patients with large, disabling strokes were excluded per protocol from the trial. Another limitation was that due to missing and unverifiable data we could not analyze some related important clinical questions such as if differences in size of the infarction influenced bleeding risk or if some intracerebral hemorrhages were due to hemorrhagic transformation of brain infarction.

In summary, the absolute rates of major bleeding in the NAVIGATE ESUS trial were slightly lower than expected, but the relative increase in major bleeding among those assigned to rivaroxaban contributed to early stopping of the trial at interim analysis. In addition to assignment to rivaroxaban, other independent predictors of major bleeding were increased SBP, impaired renal function,

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Table 4. Baseline Characteristics in Participants With and Without Intracerebral Hemorrhage and Hazard Ratios for Intracerebral Hemorrhage

	No Intracerebral Bleed (N=7198), N (%)	Intracerebral Bleed (N=15), N (%)	Unadjusted HR (95% CI)
Age, y			
<60	1710 (24)	6 (40)	Reference group
60–74	3799 (53)	5 (33)	0.38 (0.12–1.3)
≥75	1689 (23)	4 (27)	0.66 (0.19–2.3)
Male sex	4424 (61)	12 (80)	2.4 (0.69–8.7)
Global region			HR vs. all others
USA and Canada	918 (13)	0 (0)	NC
Latin America	746 (10)	0 (0)	NC
Western Europe	3076 (43)	5 (33)	0.63 (0.22–1.9)
Eastern Europe	1117 (16)	1 (7)	0.41 (0.05–3.1)
East Asia	1341 (19)	9 (60)	6.3 (2.2–18)
BMI, kg/m^2, mean±SD, HR per 5 units	27±5	26±5	0.79 (0.45–1.4)
Blood pressure, mm Hg, mean±SD, HR per 10 mm Hg increase	135±17/79±11	140±15/87±14	1.2 (0.90–1.6)/1.9 (1.2–2.9)
Systolic blood pressure, mm Hg			
<140	4326 (60)	7 (47)	Reference group
140–159	2258 (31)	6 (40)	1.6 (0.55–4.9)
≥160	600 (8)	2 (13)	2.1 (0.43–9.9)
NIHSS score at randomization			
0	3109 (43)	6 (40)	Reference group
1	1579 (22)	1 (7)	0.33 (0.04,2.8)
2	1023 (14)	3 (20)	1.6 (0.40–6.4)
≥3	1483 (21)	5 (33)	1.9 (0.58–6.2)
Prior stroke or TIA	1256 (17)	7 (47)	4.1 (1.5–11)
Hypertension	5573 (77)	12 (80)	1.2 (0.33–4.2)
Diabetes mellitus	1802 (25)	4 (27)	1.1 (0.36–3.5)
Heart failure	238 (3)	0 (0)	NC
Coronary artery disease	472 (7)	0 (0)	NC
Current tobacco use	1481 (21)	3 (20)	1.0 (0.28–3.5)
History of GI bleeding	111 (2)	1 (7)	4.3 (0.56–32)
Liver disease	112 (2)	1 (7)	4.3 (0.57–33)
Aspirin use before qualifying stroke	1249 (17)	4 (27)	1.8 (0.58–5.7)
Statin use after randomization	5594 (78)	10 (67)	0.60 (0.21–1.8)
Cancer	619 (9)	1 (7)	0.77 (0.10–5.8)
Qualifying stroke arterial territory			NC
Anterior circulation	4845 (67)	10 (67)	
Posterior circulation	1934 (27)	3 (20)	
Anterior and posterior circulation	331 (5)	1 (7)	
Unable to determine	86 (1)	1 (7)	
Qualifying stroke– tPA and endovascular treatment	1355 (19)	2 (13)	0.66 (0.15–2.9)
Qualifying stroke–Hemorrhagic transformation	435 (6)	4 (27)	5.1 (1.6–16)
eGFR, mean±SD, HR per 10 mL/min per 1.73 m^2 increase	79±21	83±23	1.1 (0.88–1.4)
Time from qualifying stroke to randomization, d			
≤14	1800 (25)	5 (33)	Reference group
15–30	1423 (20)	4 (27)	1.0 (0.27–3.7)
31–89	2203 (31)	4 (27)	0.6 (0.17–2.4)
≥90	1772 (25)	2 (13)	0.37 (0.07–1.9)

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HR, hazard ratio; NC, not computed; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue-type plasminogen activator; and TIA, transient ischemic attack.

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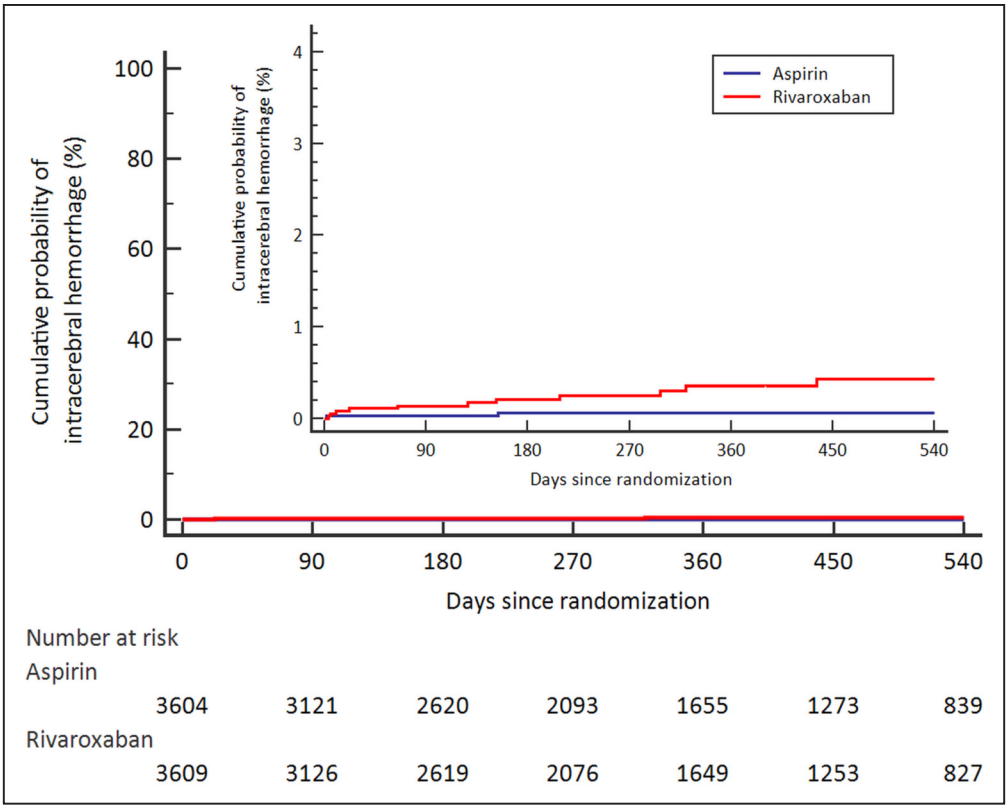

Figure. Kaplan Meier curve of the occurrence of intracerebral hemorrhage according to assigned treatment. Days from randomization to intracerebral hemorrhage for individual patients: rivaroxaban-assigned: 3, 5, 10, 22, 65, 127, 152, 208, 297, 320, 436, 573; aspirin-assigned: 2, 154, 600.

and East Asia region. East Asia region was strongly associated with intracerebral hemorrhage. eGFR should be a consideration of bleeding risk in patients treated with antithrombotic medications, including aspirin.

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