Intracranial and systemic atherosclerosis in the NAVIGATE ESUS trial: Recurrent stroke risk and response to antithrombotic therapy

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Background: Non-stenotic intracranial and systemic atherosclerosis are associated with ischemic stroke. We report frequency and response to anticoagulant vs. antiplatelet prophylaxis of patients with embolic stroke of undetermined source (ESUS) who have non-stenotic intracranial atherosclerosis and/or systemic atherosclerosis. *Methods:* Exploratory analysis of the international NAVIGATE ESUS randomized trial comparing rivaroxaban 15mg daily with aspirin 100mg daily in 7213 patients with recent ESUS. Among participants with results of intracranial arterial imaging with either computed tomographic angiography (CTA) or magnetic resonance angiography (MRA), the frequency and predictors of non-stenotic intracranial and systemic atherosclerosis and responses to antithrombotic therapy were assessed. *Results:* Among 4723 participants with available intracranial CTA or MRA results (65% of the trial cohort), the prevalence of intracranial atherosclerosis was 16% (n=739). Patient features independently associated with intracranial atherosclerosis included East Asian region (odds ratio 2.7, 95%CI 2.2,3.3) and cervical carotid plaque (odds ratio 2.3, 95%CI 1.9,2.7), among others. The rate of recurrent ischemic stroke averaged 4.8%/year among those with intracranial atherosclerosis vs. 5.0.%/year for those without (HR 0.95, 95%CI 0.65, 1.4). Among those with intracranial atherosclerosis, the recurrent ischemic stroke rate was higher if assigned to rivaroxaban (5.8%/year) vs. aspirin (3.7%/year), but the difference was not

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statistically significant (HR 1.6, 95%CI 0.78, 3.3). There was trend for the effect of antithrombotic treatments to be different according to the presence or absence of intracranial atherosclerosis ($p_{interaction}$=0.09). Among participants with evidence of systemic atherosclerosis by either history or imaging (n=3820), recurrent ischemic stroke rates were similar among those assigned to rivaroxaban (5.5%/year) vs. aspirin (4.9%/year)(HR 1.1, 95%CI 0.84, 1.5). *Conclusions:* East Asia region was the strongest factor associated with intracranial atherosclerosis. There were no statistically significant differences between rivaroxaban and aspirin prophylaxis for recurrent ischemic stroke in patients with non-stenotic intracranial atherosclerosis and/or systemic atherosclerosis.

Keywords: Embolic stroke—ESUS—Rivaroxaban—Cerebrovascular atherosclerosis—Intracranial atherosclerosis—Randomized trial

Introduction

Embolic strokes of undetermined source (ESUS) represent a large subset of cryptogenic ischemic strokes that have clinical features supporting an embolic mechanism.[1] 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) trial, patients with the index ischemic stroke who had intracranial arterial imaging and had ipsilateral intracranial artery stenosis >50% were excluded from participation.[2] However, non-stenotic intracranial atherosclerotic plaques can be a cause of ischemic stroke,[3] and these lesions did not preclude trial participation. For this exploratory analysis, the subgroup of NAVIGATE ESUS participants known to have intracranial atherosclerosis is analyzed, including patient features, independent predictors of intracranial atherosclerosis, recurrent stroke rates, and response to antithrombotic therapies. In addition, the relative effect of antithrombotic therapies among patients with either a clinical history or imaging evidence of systemic atherosclerosis is considered.

Methods

NAVIGATE ESUS (ClinicalTrials.gov number NCT02313909) was an international, double-blinded, randomized phase III trial conducted at 459 centers in 31 countries that enrolled 7213 participants randomized to receive either rivaroxaban 15mg daily or aspirin 100mg daily. The trial design, participant features, and main results have been previously published.[2,4,5] Patients with recent (7 days to 6 months) ischemic stroke visualized by neuroimaging who met criteria for ESUS as proposed by the Cryptogenic Stroke / ESUS International Working Group were eligible,[1] with a modification related to the mandatory requirement for intracranial arterial imaging.[2] Eligibility required that patients be ≥50 years old, and if between ages 50−59 years, have additional stroke risk factors.[2] Required diagnostic testing to assess for probable stroke causes included carotid artery imaging to exclude stenosis >50% or occlusion, at least 20 h of cardiac rhythm monitoring to exclude occult atrial fibrillation, and echocardiography to exclude intracardiac thrombus. Intracranial arterial imaging was not required in order to facilitate screening and recruitment at clinical sites that did not perform this diagnostic test as part of routine clinical practice in patients with cryptogenic ischemic stroke, but if performed, intracranial stenosis >50% ipsilateral to the index stroke excluded participation. Patients with intracranial arterial occlusions were potentially eligible if the local investigator attributed the occlusion to embolism rather than to atherosclerosis or if not in the territory of the qualifying stroke.

Among the 7213 participants, 4798 (67%) underwent intracranial computed tomography angiography (CTA) and/or magnetic resonance angiography (MRA), 847 (12%) additional participants underwent only transcranial Doppler ultrasonography, and 1568 (21%) had none of these three tests. There were 36 participants who underwent CTA and 39 who underwent MRA for whom no results were available, and these patients are excluded from the analyses, leaving 4723 participants with intracranial CTA or MRA results for the main analyses (Fig. 1). For those undergoing both CTA and MRA, the CTA results regarding intracranial atherosclerosis were used for these analyses. The presence of intracranial atherosclerosis was based on local clinical interpretation of CTA and MRA by local readers with no pre-defined criteria or central oversight. Data were not collected to reliably allow correlation of the site of the qualifying infarct or of recurrent infarct in relation to intracranial atherosclerosis.

To assess the treatment effects among participants with systemic atherosclerosis, two cohorts were assembled: 1) those with observed evidence of cervical, intracranial and/or aortic arch atherosclerotic plaque on diagnostic imaging done for eligibility assessment (labelled as the atherosclerosis by diagnostic imaging cohort) and 2) those with atherosclerosis according to a history of coronary artery disease, carotid revascularization, and/or peripheral vascular disease at study entry (a.k.a. atherosclerosis based on medical history cohort) (Fig. 2). Because most participants did not undergo transesophageal echocardiography to assess for aortic arch atherosclerosis[6] and intracranial arterial imaging, a cohort with no atherosclerosis documented by diagnostic imaging could not be assembled.

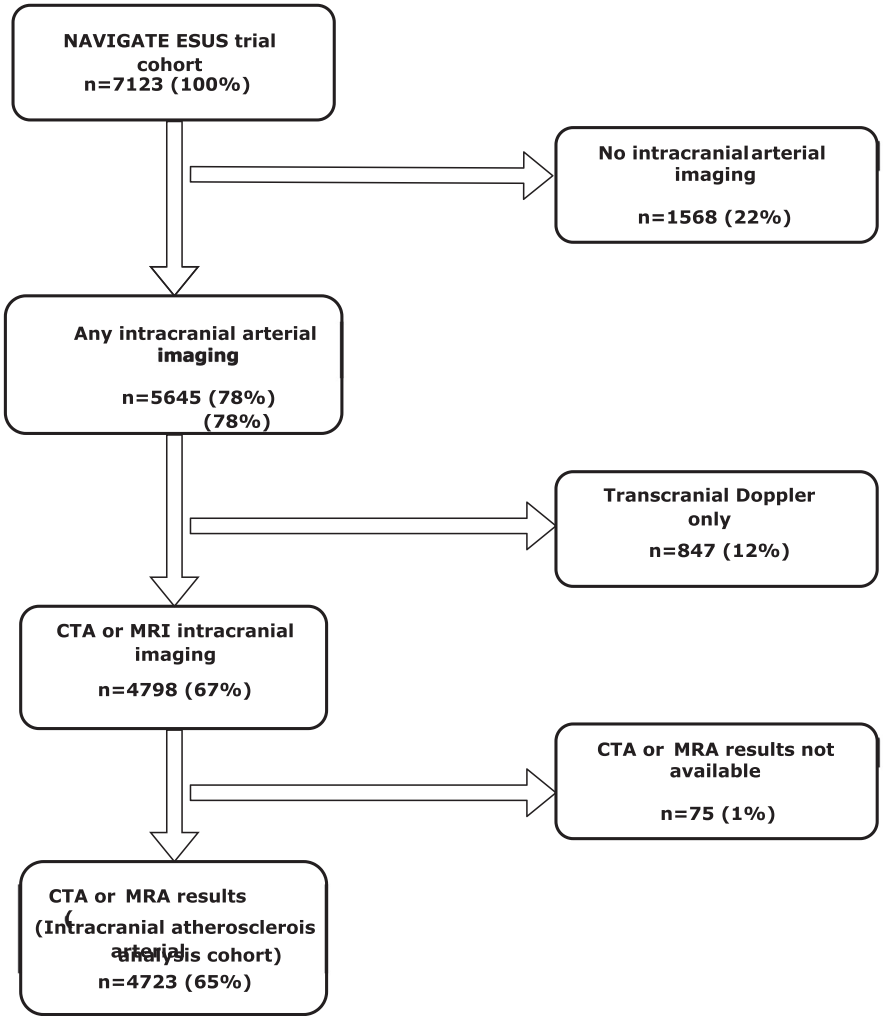

Fig. 1. *Original NAVIGATE ESUS trial cohort and selection of Intracranial atherosclerosis analysis cohort.*

Analyses were performed based on the intent-to-treat population based on the time to first event. Patient characteristics were described using proportions for discrete variables and means with standard deviations (SD) [or medians with interquartile range (IQR)] for continuous variables. Distributions of characteristics were compared across groups using a chi-square test for categorical variables and a t-test for continuous variables. Characteristics, except for qualifying stroke particulars, which were statistically different ($p < 0.10$) between those with versus without intracranial atherosclerosis were included in a forward multivariable logistic regression analysis to identify characteristics independently associated with intracranial atherosclerosis. For the final multivariable model, odds ratios (OR) and their 95% confidence intervals (CI) along with the C-statistics as an estimate of fit are reported. Annualized recurrent stroke rates (% per year) were computed by dividing the number of patients with a stroke by the total number of person-years of exposure and multiplying by 100. A hazard ratio (HR) and the 95% CI from a univariable Cox proportional hazards model was computed to estimate the effect of assigned treatment for a particular group and endpoint. There was no imputation of missing data or adjustment for multiple comparisons. All reported p-values are two-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

Characteristics of the 4723 patients with intracranial CTA or MRA results (65% of participants) (Fig. 1) were similar to those without these results (35%) with the exception that CTA or MRA intracranial imaging was more often undertaken in the East Asia and Canada/USA regions.(Supplement Table 1)

The prevalence of non-stenotic intracranial atherosclerosis was 16% (739/4723). Participants with intracranial atherosclerosis were of the same mean age (67 years) compared with those without it, but had substantially higher

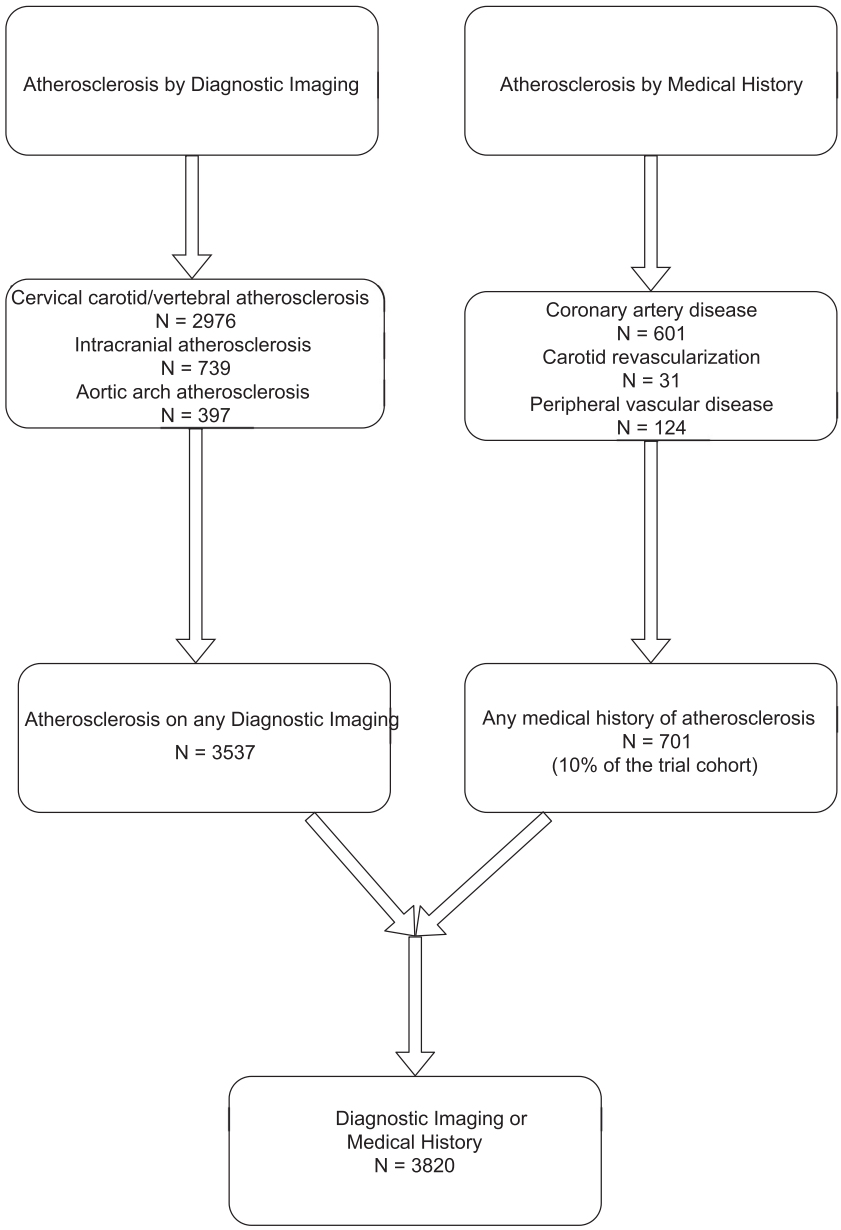

Fig. 2. *Systemic atherosclerosis cohorts.*

frequencies of diabetes (32% vs 23%, respectively), coronary artery disease (12% vs. 7% respectively), and carotid artery plaque (54% vs 32%, respectively) (Table 1). Statins were used after randomization in 87% of those with non-stenotic intracranial atherosclerosis and by 83% of those without (p=0.01). Intracranial atherosclerosis was more frequently reported if imaged by CTA (17%) than by MRA (14%)($p<0.001$).

By multivariable analysis, participants with carotid artery plaque (OR 2.3) and those randomized in either Canada/USA (OR 2.4) or East Asia (OR 2.7) had substantially higher odds of having intracranial atherosclerosis (Table 2). Diabetes, coronary artery disease, aortic valve disease, statin use prior to randomization, CTA, and chronic brain infarcts on baseline brain imaging were also independently associated with intracranial atherosclerosis though the associations were less robust . Lower estimated glomerular filtration rate at baseline was modestly associated with a lower likelihood of intracranial atherosclerosis) (Table 2).

The rate of recurrent ischemic stroke averaged 4.8%/year among those with intracranial atherosclerosis vs. 5.0%/year for those without (HR 0.95, 95%CI 0.65, 1.4). The effect of antithrombotic treatment on recurrent ischemic stroke was qualitatively different for those with intracranial atherosclerosis versus without intracranial atherosclerosis, although this difference was not statistically significant ($p_{\text{interaction}} = 0.09$) (Table 3). Participants with intracranial atherosclerosis had fewer recurrent ischemic strokes if assigned to aspirin, while those

Table 1. *Patient features according to the presence or absence of intracranial atherosclerosis detected by CTA or MRA*[*].

	Intracranial atherosclerosis (n = 739)	No intracranial atherosclerosis (n = 3984)
Age, years, mean ± SD	67 ± 10	67 ± 10
Age ≥ 75 years, n (%)	172 (23)	889 (22)
Male sex, n (%)	486 (66)	2458 (62)
Region, n (%)		
Canada and USA	184 (25)	579 (15)
Latin America	39[5]	300[8]
Western Europe	201 (27)	1797 (45)
Eastern Europe	52[7]	384 (10)
East Asia	263 (36)	924 (23)
Body mass index, kg/m^2, mean ± SD	27 ± 5	27 ± 5
eGFR, mL/min per 1.73 m^2, mean ± SD	81 ± 22	79 ± 20
Hypertension, n (%)	584 (79)	2970 (75)
Diabetes mellitus, n (%)	236 (32)	918 (23)
Tobacco use, n (%)		
Never	352 (48)	1989 (50)
Former	208 (28)	1197 (30)
Current	178 (24)	797 (20)
Coronary artery disease, n (%)	90 (12)	288[7]
Heart failure, n (%)	18[2]	89[2]
Cancer, n (%)	60[8]	391 (10)
Prior stroke or TIA, n (%)	152 (21)	686 (17)
Hyperlipidemia, n (%)	405 (55)	2227 (56)
Mitral valve disease, n (%)	108 (15)	513 (13)
Aortic valve disease, n (%)	185 (25)	723 (18)
Left ventricular dysfunction moderate-severe, n (%)	8[1]	44[1]
Carotid artery plaque, n (%)	399 (54)	1285 (32)
Aspirin use prior to qualifying stroke, n (%)	127 (17)	648 (16)
Statin use prior to randomization, n (%)	503 (68)	2390 (60)
Chronic infarct on imaging (in addition to qualifying stroke), n (%)	299 (40)	1247 (31)
CTA (vs. MRA), n (%)	444 (60)	2114 (53)
Clinical TIA with imaging-confirmed infarction, n (%)	48[7]	330[8]
Arterial territory, n (%)		
Anterior circulation	461 (62)	
Posterior circulation	216 (29)	
Both	60[8]	
Unable to determine	2 (<1)	
Multiple vs. single territory, n (%)		
Multiple	102 (14)	495 (12)
Single location	636 (86)	3485 (88)
If single, location, n (%):		
Hemispheric with cortical involvement	353 (58)	2213 (65)
Hemispheric, subcortical only	170 (28)	718 (21)
Brainstem only	41[7]	149[4]
Cerebellum only	46[8]	336 (10)
Treated with intravenous tPA for qualifying stroke, n (%)	132 (18)	859 (22)
Treated with endovascular intervention for qualifying stroke	54[7]	206[5]

(*Continued*)

Table 1 (*Continued*)

	Intracranial atherosclerosis (n = 739)	No intracranial atherosclerosis (n = 3984)
NIHSS score at randomization, median (IQR)	1[2]	1[2]
NIHSS score ≥ 3, n (%)	165 (22	634 (16)
Time from qualifying stroke to randomization, days, median (IQR)	30 (58)	39 (80)
Time < 30 days, n (%)	369 (50)	1724 (43)
Atrial fibrillation identified during follow-up, n (%)	13[2]	134[3]
Recurrent ischemic stroke during follow-up, % per year	4.8	5.0

CTA = computed tomography angiography; eGFR= estimated glomerular filtration rate; IQR = interquartile range; MRA = magnetic resonance angiography; NIHSS = National Institutes of Health Stroke Scale; NT = not tested; TIA = transient ischemic attack; tPA = tissue plasminogen activator.

*An additional 36 participants underwent CTA and 39 underwent MRA, but no results were available, and they are excluded from these analyses (Fig. 1).

Table 2. *Patient characteristics independently associated with non-stenotic intracranial atherosclerosis*

	Odds ratio* (95% CI)
Region	
Western Europe	Reference group
Canada/USA	2.4 (1.9, 3.0)
Latin America	1.1 (0.74, 1.5)
Eastern Europe	1.0 (0.72, 1.4)
East Asia	2.7 (2.2, 3.3)
Diabetes	1.4 (1.2, 1.7)
Coronary artery disease	1.5 (1.1, 1.9)
Aortic valve disease	1.4 (1.1, 1.7)
Carotid artery plaque	2.3 (1.9, 2.7)
Chronic infarcts on imaging	1.3 (1.1, 1.5)
Statin use prior to randomization	1.2 (1.0, 1.5)
CTA vs. MRA	1.5 (1.2,1.8)
eGFR, mL/min/1.73m^2	
> 80	Reference group
50-80	0.86 (0.73, 1.0)
< 50	0.66 (0.44, 0.99)

CTA = computed tomographic angiography; eGFR = estimated glomerular filtration rate; MRA = magnetic resonance angiography.

*All characteristics from Table 1 with $p<0.1$ were considered except for qualifying stroke particulars; c-statistic for fit of model 0.70 (95% CI 0.68, 0.72).

without intracranial atherosclerosis had fewer if assigned to rivaroxaban (Table 3). These differences in treatment effects were magnified when participants with concomitant carotid artery plaque were excluded (Table 3).

Considering participants with cerebrovascular atherosclerosis involving the cervical carotid arteries, intracranial arteries and/or aortic arch (n=3537) (Fig. 2), the recurrent ischemic stroke rates were non-significantly higher (HR 1.2, 95%CI 0.87, 1.6) if assigned to rivaroxaban vs. aspirin (Table 4). Considering systemic atherosclerosis that additionally included a history of coronary artery, carotid artery revascularization, or peripheral vascular disease (Supplement Table 2, Fig. 2), recurrent ischemic stroke rates were non-significantly higher (HR 1.1, 95%CI 0.84,1.5) if assigned to rivaroxaban vs. aspirin.(Table 4)

Discussion

The multiple underlying causes of ischemic stroke respond differently to antithrombotic therapies.[7] In a recent randomized trial, patients with atherosclerosis with acute ischemic stroke responded differently to antiplatelet therapies compared with other stroke causes.[8] In these exploratory analyses of the NAVIGATE ESUS trial, we assessed the relative effects of anticoagulant vs. antiplatelet therapies for secondary prevention of ischemic stroke among participants with intracranial and systemic atherosclerosis. Importantly, not all recurrent ischemic strokes occurring in ESUS patients with intracranial atherosclerosis were likely to be due to the intracranial atherosclerotic lesion since multiple potential sources of embolic stroke can coexist in individual patients.

East Asian region was strongly associated with non-stenotic intracranial atherosclerosis (odds ratios 2.7, Table 2). Other characteristics independently associated with non-stenotic intracranial atherosclerosis included a traditional risk factor for atherosclerosis (diabetes mellitus), atherosclerosis in other arteries (carotid artery plaque, coronary artery disease), and markers of previous vascular disease (chronic infarcts on baseline neuroimaging, statin use prior to randomization) (Table 2). Aortic valve disease was also independently associated with intracranial atherosclerosis whereas age was not, and as both are associated with advancing age, we speculate that aortic valve disease weakened the expected association between age and intracranial atherosclerosis.

Table 3. *Effect of antithrombotic therapies according to presence of non-stenotic intracranial atherosclerosis*

	Intracranial atherosclerosis (n = 739)			No intracranial atherosclerosis (n = 3984)		
	Rivaroxaban-assigned annualized rate (n)	Aspirin-assigned annualized rate (n)	Hazard ratio (95% CI)	Rivaroxaban-assigned annualized rate (n)	Aspirin-assigned annualized rate (n)	Hazard ratio (95% CI)
All participants with intracranial imaging						
Ischemic strokes (n)	5.8 (20)	3.7 (12)	1.6 (0.78, 3.3)	4.5 (86)	5.4 (102)	0.83 (0.62, 1.1)*
Excluding participants with concomitant cervical carotid artery plaque[#]						
Ischemic strokes (n)	5.7 (10)	2.6[4]	2.2 (0.69, 7.1)	4.1 (53)	5.2 (68)	0.77 (0.54, 1.1)^

*Treatment interaction $p = 0.09$.
[#]Excludes 1684 patients with concomitant cervical carotid artery plaque, leaving 340 patients with intracranial atherosclerosis and 2699 without intracranial atherosclerosis.
^Treatment interaction $p = 0.07$.

These analyses suggest that aspirin might have offered more protection against recurrent ischemic stroke than did rivaroxaban among participants with intracranial atherosclerosis compared with those without intracranial atherosclerosis, but this result was not statistically significant ($p_{interaction} = 0.09$) (Table 3). Moreover, the protective effect of aspirin over rivaroxaban on recurrent ischemic stroke was weaker when additional evidence of systemic atherosclerosis was considered (Table 4).

Major methodologic limitations are the exploratory nature of these analyses (i.e. not pre-specified), incomplete assessment of intracranial atherosclerosis across study sites, and alpha values that are unadjusted for multiple comparisons. Consequently, these findings must be considered as hypothesis-generating, requiring independent confirmation before being credible. Patients with high-grade intracranial artery stenosis in arteries supplying the qualifying stroke were excluded from trial participation, so these results are restricted to intracranial atherosclerosis of minor severity. The presence of intracranial atherosclerosis was based on the reports of local clinical interpretation of CTAs and MRAs with no pre-defined criteria or quality-control assessment. Data were not collected to relate the vascular territory of qualifying or recurrent ischemic stroke to intracranial atherosclerotic lesions.

In the COMPASS trial, patients with a history of stable coronary artery or peripheral vascular disease (i.e. with clinical atherosclerosis) who were assigned the combination of low-dose rivaroxaban (2.5mg twice daily) plus aspirin had a reduced risk of ischemic stroke by nearly 50% and by one-third among those assigned to rivaroxaban alone (5mg twice daily) compared with those assigned aspirin alone.[9] The effect of rivaroxaban vs. aspirin among NAVIGATE ESUS participants with a medical history of systemic atherosclerosis (10% of the trial cohort) that most closely approximates COMPASS entry criteria showed a similar large reduction in ischemic stroke (Table 4). Among NAVIGATE ESUS participants, there were no major differences in patient characteristics between those with a medical history of atherosclerosis vs. those with imaging evidence of atherosclerosis that would readily account for the observed directional difference in treatment effect, (Supplement Table 2) and the play of chance due to the small numbers in the NAVIGATE ESUS cohort may be likely.

In conclusion, these exploratory analyses suggest that the treatment effects on recurrent ischemic stroke of rivaroxaban compared with aspirin may be different for ESUS patients with non-stenotic intracranial atherosclerosis vs. those without. However, there were no statistically significant differences between rivaroxaban and aspirin prophylaxis for recurrent ischemic stroke in patients with non-stenotic intracranial atherosclerosis and/or systemic atherosclerosis. East Asian region was the strongest independent predictor of the frequency of non-stenotic intracranial atherosclerosis.

Table 4. *Effect of treatment on recurrent ischemic strokes in patients with systemic atherosclerosis*

	Annualized rate (%/year) by assigned treatment (# of strokes)		Hazard ratio (95% CI)
	Rivaroxaban	Aspirin	
Atherosclerosis by diagnostic imaging* (n=3537)	5.6 (91)	4.7 (75)	1.2 (0.87, 1.6)
Atherosclerosis by medical history^ (n=701)	3.9 (12)	7.1 (25)	0.56 (0.28, 1.1)
Atherosclerosis by diagnostic imaging* and/or medical history^ (n = 3820)	5.5 (96)	4.9 (85)	1.1 (0.84, 1.5)

*Based on available cervical carotid and vertebral imaging, CTA/MRA intracranial imaging, aortic arch imaging by transesophageal echocardiography. Atherosclerosis location was cervical carotid and/or vertebral artery for 2976 patients, intracranial for 739, and aortic arch for 397 with multiple locations possible.

^History of coronary artery disease (n=601), carotid artery revascularization (n=31), or peripheral vascular disease (n=124) at study entry, with multiple sites possible.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2020.104936.

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