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Characteristics of Recurrent Ischemic Stroke After Embolic Stroke of Undetermined Source
Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE The concept of embolic stroke of undetermined source (ESUS) unifies a subgroup of cryptogenic strokes based on neuroimaging, a defined minimum set of diagnostic tests, and exclusion of certain causes. Despite an annual stroke recurrence rate of 5%, little is known about the etiology underlying recurrent stroke after ESUS.

OBJECTIVE To identify the stroke subtype of recurrent ischemic strokes after ESUS, to explore the interaction with treatment assignment in each category, and to examine the consistency of cerebral location of qualifying ESUS and recurrent ischemic stroke.

DESIGN, SETTING, AND PARTICIPANTS The NAVIGATE-ESUS trial was a randomized clinical trial conducted from December 23, 2014, to October 5, 2017. The trial compared the efficacy and safety of rivaroxaban and aspirin in patients with recent ESUS (n = 7213). Ischemic stroke was validated in 309 of the 7213 patients by adjudicators blinded to treatment assignment and classified by local investigators into the categories ESUS or non-ESUS (ie, cardioembolic, atherosclerotic, lacunar, other determined cause, or insufficient testing). Five patients with recurrent strokes that could not be defined as ischemic or hemorrhagic in absence of neuroimaging or autopsy were excluded. Data for this secondary post hoc analysis were analyzed from March to June 2019.

INTERVENTIONS Patients were randomly assigned to receive rivaroxaban, 15 mg/d, or aspirin, 100 mg/d.

MAIN OUTCOMES AND MEASURES Association of recurrent ESUS with stroke characteristics.

RESULTS A total of 309 patients (205 men [66%]; mean [SD] age, 68 [10] years) had ischemic stroke identified during the median follow-up of 11 (interquartile range [IQR], 12) months (annualized rate, 4.6%). Diagnostic testing was insufficient for etiological classification in 39 patients (13%). Of 270 classifiable ischemic strokes, 156 (58%) were ESUS and 114 (42%) were non-ESUS (37 [32%] cardioembolic, 26 [23%] atherosclerotic, 35 [31%] lacunar, and 16 [14%] other determined cause). Atrial fibrillation was found in 27 patients (9%) with recurrent ischemic stroke and was associated with higher morbidity (median change in modified Rankin scale score 2 [IQR, 3] vs 0 (IQR, 1]) and mortality (15% vs 1%) than other causes. Risk of recurrence did not differ significantly by subtype between treatment groups. For both the qualifying and recurrent strokes, location of infarct was more often in the left (46% and 54%, respectively) than right hemisphere (40% and 37%, respectively) or brainstem or cerebellum (14% and 9%, respectively).

CONCLUSIONS AND RELEVANCE In this secondary analysis of randomized clinical trial data, most recurrent strokes after ESUS were embolic and of undetermined source. Recurrences associated with atrial fibrillation were a minority but were more often disabling and fatal. More extensive investigation to identify the embolic source is important toward an effective antithrombotic strategy.

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Supplemental content

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Ischemic strokes are caused by a variety of mechanisms that are conventionally categorized into cardioembolic, extracranial or intracranial large artery atherosclerotic disease, lacunar (ie, small vessel disease), other defined entities, and cryptogenic origin. In most cases, secondary stroke prevention with antithrombotic drugs is performed with antiplatelet agents, but for high-risk cardioembolism, including atrial fibrillation, anticoagulants are preferred because of their superior efficacy compared with antiplatelets.[1,2]

Cryptogenic stroke, representing about 20% of all strokes, has been an ill-defined category for decades. In 2014, Hart and coworkers[3] proposed the concept of embolic stroke of undetermined source (ESUS). The ESUS concept unifies a large subgroup of cryptogenic strokes based on neuroimaging, a defined minimum set of diagnostic tests, and exclusion of specific causes. In several observational studies,[4,5] ESUS carried a substantial annual stroke recurrence rate of 3% to 6% despite antithrombotic therapy. Beyond a clearer mechanistic characterization of strokes of unknown origin, a main purpose of the ESUS concept was to define a group of patients who might benefit from anticoagulants. However, 2 recently reported large randomized clinical trials, NAVIGATE-ESUS (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial vs ASA to Prevent Embolism in Embolic Stroke of Undetermined Source)[6] and RESPECT-ESUS (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate vs Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source),[7] did not find superior efficacy of direct oral anticoagulants over antiplatelets.

Although these neutral results have led some researchers to suggest abandoning the ESUS concept,[8,9] others have proposed identifying subgroups within the ESUS construct that are likely to benefit from either an anticoagulant or an antiplatelet preventive strategy.[10,11] In any case, to develop a more tailored strategy for stroke prevention after ESUS, a better understanding of the characteristics and the causes of recurrent strokes after ESUS is needed. In the present exploratory analysis of the NAVIGATE-ESUS trial, we aim to describe the stroke subtype of recurrent ischemic strokes after ESUS, to explore the interaction with treatment assignment in each category, and examine the consistency of cerebral location of qualifying ESUS and recurrent ischemic stroke.

Key Points

Question What are the characteristics and the etiology of recurrent strokes after embolic strokes of undetermined source?

Findings In this secondary analysis of a randomized clinical trial, recurrent ischemic stroke occurred in 309 of 7213 patients undergoing randomization. Among 270 classifiable recurrent strokes, 156 (58%) were embolic strokes of undetermined source, and 114 (42%) were not. Atrial fibrillation was found in 27 recurrent strokes (9%) and was associated with higher mortality and disability compared with other causes.

Meaning This trial analysis found that most stroke recurrences after embolic strokes of undetermined source were embolic and often of undetermined source; few were associated with atrial fibrillation, and these had worse outcomes.

Methods

Patients and Procedures

NAVIGATE-ESUS was an international, double-blinded, randomized phase 3 trial conducted at 459 centers in 31 countries and involving 7213 participants from December 23, 2014, to October 5, 2017 (trial protocol in Supplement 1). The study was approved by the relevant health authorities and the institutional review board at each trial site, and all patients provided written informed consent. This secondary post hoc analysis of the NAVIGATE-ESUS data followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

The study rationale, design, participant features, and main results have been previously published.[6,12-14] Briefly, patients with recent (7 days to 6 months) ischemic stroke visualized by neuroimaging were eligible if they met criteria for ESUS[3] with minor modifications.[14] Eligibility required that patients be 50 years or older. Participants who were aged 50 to 59 years were required to have 1 or more additional stroke risk factors consisting of stroke or transient ischemic attack before the qualifying stroke, diabetes, heart failure, hypertension, or tobacco smoking.[14] 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. Transthoracic echo without evidence of major cardioembolic source but not transesophageal echocardiography was required. Participants were randomly assigned to either rivaroxaban (15 mg once daily) or enteric-coated aspirin (100 mg once daily) to be taken with food. Median follow-up was 11 (interquartile range [IQR], 12) months when the trial was stopped at an interim analysis.[6] 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. Expert adjudicators were blinded to assignment of treatment.

For the present analyses concerning 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. Recurrent ischemic strokes were classified by local investigators as ESUS, non-ESUS (specifically atherosclerotic, cardioembolic, lacunar, or of other defined etiology), or indeterminate (ie, mainly because insufficient diagnostic testing was performed). Based on overall clinical assessment, local investigators also determined arterial territory of the qualifying ESUS and the recurrent ischemic stroke, which were then categorized as single vs multiple territory, with single territory further categorized into left hemispheric, right hemispheric, or brainstem and/or cerebellar.

Figure. Trial Profile

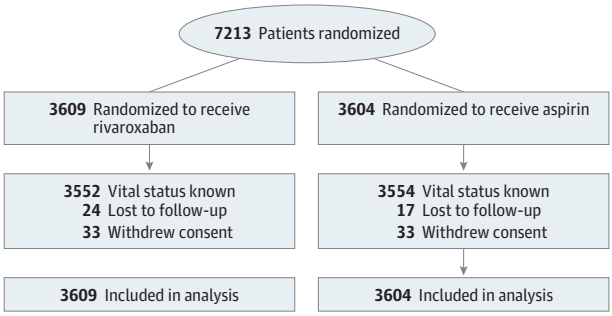

Table 1. Classification of Subtypes of Recurrent Ischemic Stroke

Classification of recurrent ischemic stroke	Classifiable recurrent ischemic stroke, No. (%) (n = 270)[a]
ESUS	156 (58)
Non-ESUS	
Atherosclerosis	26 (10)
Cardioembolism	37 (14)
Lacunar	35 (13)
Other specific causes	16 (6)
Insufficient diagnostic evaluation	NA

Abbreviation: ESUS, embolic stroke of undetermined source.

[a] Recurrent ischemic strokes were classified as ESUS, non-ESUS (specifically atherosclerotic, cardioembolic, lacunar, or of other defined subtype), or indeterminate, because of insufficient diagnostic evaluation.

Statistical Analysis

Data were analyzed from March to June 2019. All analyses were performed on the intention-to-treat population. Patient characteristics were described using proportions for discrete variables and means with SDs or medians with IQRs for continuous variables. Characteristics were compared between groups using a χ^2 test (or Fisher exact test if minimum expected cell count was <5) for categorical data and a unpaired *t* test (or Mann-Whitney test for nonparametric data) or analysis of variance (or Kruskal-Wallis for nonparametric data) for continuous variables. Time-to-event data were summarized by computing the annualized event rate (ie, the number of patients with an event divided by patient-years of exposure) with 95% CI computed assuming a Poisson distribution. Hazard ratios (HRs) and CIs from a Cox proportional hazards model were used to describe treatment effect within a group. There was no imputation of missing data. All tests were 2 sided, and statistical significance was accepted at the $P < .05$ level. No adjustments were made for multiple comparisons. Statistical analysis was performed using SPSS for Windows, version 24.0.0 (IBM Corp).

Results

The trial profile is presented in the **Figure**. A recurrent ischemic stroke was identified in 309 of the 7213 patients in NAVIGATE-ESUS trial (205 men [66%] and 104 women [34%]; mean [SD] age, 68 [10] years). Of these, stroke subtype was not classified for 39 patients (13%), mainly because the available diagnostic evaluation was incomplete according to the ESUS diagnostic criteria. Of the 270 classifiable recurrent ischemic strokes, 156 (58%) were reported as ESUS and 114 (42%) as non-ESUS (37 [32%] cardioembolic, 26 [23%] atherosclerotic, 35 [31%] lacunar, and 16 [14%] other determined cause). (**Table 1**). Annualized rates of recurrent ischemic stroke were 4.7% and 4.6% in those assigned rivaroxaban and aspirin, respectively.

Patient characteristics at enrollment were similar among the different subtypes of recurrent ischemic stroke with the exception of current tobacco use, which ranged from 5 patients with a cardioembolic subtype (14%) to 18 patients with a lacunar subtype (51%) (**Table 2**). Recurrent ischemic strokes associated with cardioembolic subtype were more disabling as measured by the modified Rankin scale score (median change from baseline, 2 [IQR, 3] vs 0 [IQR, 1]) and were associated with a higher mortality rate than other stroke subtypes including ESUS (11% vs 1%) (Table 2).

Because identification of atrial fibrillation based on patient characteristics would have a major effect on preventive antithrombotic therapy, we compared the features of participants with recurrent ischemic stroke who were diagnosed with atrial fibrillation during study follow-up (27 of 309 [9%]) vs those without AF (282 of 309 [91%]) (**Table 3**). Differences between these groups beyond the severity of the stroke were limited to a larger atrial diameter in patients with atrial fibrillation (mean [SD], 4.1 [0.7] vs 3.7 [0.8] cm) and proportionally fewer patients assigned to rivaroxaban among those with recurrent strokes who were diagnosed with atrial fibrillation after randomization (8 [30%] vs 148 [52%]).

The effect of assigned treatment with rivaroxaban vs aspirin for prevention of recurrent ischemic stroke by stroke subtype is shown in eTable 1 in Supplement 2. Participants assigned to rivaroxaban vs aspirin tended to less frequently have a cardioembolic stroke (HR, 0.54; 95% CI, 0.28-1.1). In contrast, participants not assigned to aspirin tended to have higher risk for atherosclerotic (HR, 1.9; 95% CI, 0.84-4.2) and lacunar (HR, 1.5; 95% CI, 0.76-2.9) stroke, although none of these differences were statistically significant.

Territories of the qualifying ESUS as well as the recurrent ischemic stroke were classified as left hemispheric, right hemispheric, brainstem and/or cerebellar, or multiple infarcts. Single-territory qualifying infarcts (n = 6445) and single-territory recurrent ischemic strokes (n = 260) were more often located in the left (2983 [46%] and 141 [54%], respectively) than in the right hemisphere (2570 [40%] and 95 [37%], respectively) or brainstem/cerebellum (892 [14%] and 24 [9%], respectively) (**Table 4**). Patients with a recurrent ischemic stroke also had a qualifying ESUS in the left hemisphere more often than those who did not have a recurrent stroke (141 of 260 [54%] vs 2842 of 6185 [46%]). Of those with single-territory qualifying ESUS and recurrent stroke, 61% (95% CI, 54%-68%) of recurrent ischemic stroke (eTable 2 in Supplement 2) and 62% (95% CI, 53%-71%) of recurrent ESUS (eTable 3 in Supplement 2) occurred in the same territory as the qualifying ESUS. Multiple territories were observed in 763 of 7208 (11%) qualifying ESUS and in 24 of 156 (15%) recurrent strokes

Table 2. Participant Features at Baseline by Recurrent Ischemic Stroke Subtype[a]

Characteristic	ESUS (n = 156)	Cardioembolic (n = 37)	Atherosclerosis (n = 26)	Lacunar (n = 35)	Indeterminant (n = 39)	*P* value
Age, mean (SD), y	69 (10)	71 (10)	67 (10)	66 (11)	69 (11)	.50
Aged ≥75 y, No. (%)	44 (28)	13 (35)	5 (19)	8 (23)	14 (36)	.50
Male, No. (%)	100 (64)	27 (73)	17 (65)	25 (71)	24 (62)	.80
BMI, mean (SD)	27 (5)	27 (4)	27 (4)	25 (4)	26 (4)	.50
Blood pressure, SBP/DBP, mean (SD), mm Hg	135 (16)/79 (11)	135 (19)/77 (13)	131 (17)/77 (11)	134 (23)/79 (12)	133 (17)/77 (11)	.90/>.99
No statin use continued after randomization, No. (%)	40 (26)	9 (24)	7 (27)	16 (46)	6 (15)	.06
Hypertension, No. (%)	113 (72)	32 (86)	15 (58)	24 (69)	32 (82)	.07
Diabetes, No. (%)	48 (31)	11 (30)	11 (42)	7 (20)	10 (26)	.40
Current tobacco use, No. (%)	36 (23)	5 (14)	11 (42)	18 (51)	9 (23)	.001
Coronary artery disease, No. (%)	13 (8)	4 (11)	2 (8)	3 (9)	4 (10)	NT
Heart failure, No. (%)	6 (4)	1 (3)	2 (8)	3 (9)	1 (3)	NT
Cancer, No. (%)	16 (10)	4 (11)	3 (12)	3 (9)	7 (18)	NT
Prior stroke or TIA, No. (%)	49 (31)	11 (30)	7 (27)	13 (37)	11 (28)	.90
Qualifying ESUS, No. (%)						
Single acute lesion on imaging	132 (85)	34 (92)	24 (92)	26 (74)	32 (82)	NT
Multiple lesions on imaging	24 (15)	3 (8)	2 (8)	9 (26)	7 (18)	
Clinical TIA with imaging-confirmed infarction, No. (%)	14 (9)	3 (8)	2 (8)	3 (9)	5 (13)	NT
Chronic infarcts on imaging (in addition to qualifying ESUS), No. (%)	70 (45)	18 (49)	9 (35)	21 (60)	11 (28)	.06
Aspirin use prior to qualifying ESUS, No. (%)	38 (24)	10 (27)	7 (27)	10 (29)	7 (18)	.80
Modified Rankin scale score at randomization, median (IQR)[b]	1 (2)	1 (2)	1.5 (1)	1 (2)	1 (1)	.60
Time from qualifying stroke to randomization, d						
Median (IQR)	34 (73)	29 (51)	18 (41)	33 (32)	26 (35)	.50
≤30 d, No. (%)	75 (48)	19 (51)	16 (62)	15 (43)	21 (54)	.60
Left atrial diameter by transthoracic echocardiography, mean (SD), cm[c]	3.7 (0.7)	3.8 (0.9)	3.8 (0.7)	3.7 (0.6)	3.5 (0.9)	.80
Carotid artery plaque, No. (%)	65 (42)	21 (57)	10 (38)	16 (46)	16 (41)	.50
Left ventricular global function, No. (%)						
Normal	133 (88)	30 (81)	21 (81)	26 (74)	31 (79)	NT
Mild dysfunction	7 (4)	3 (8)	1 (4)	0	3 (8)	
Moderate-to-severe dysfunction	2 (1)	2 (5)	0	3 (9)	1 (3)	
Uncertain	9 (6)	2 (5)	4 (15)	6 (17)	4 (10)	
Modified Rankin scale score after recurrent stroke[b,d]						
6, No. (%)	2 (1)	4 (11)	0	0	0	NT
Change from baseline, median (IQR)	0 (1)	2 (3)	1 (2)	0 (2)	0.5 (2)	.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); DBP, diastolic blood pressure; ESUS, embolic stroke of undetermined source; IQR, interquartile range; NT, not tested; SBP, systolic blood pressure; TIA, transient ischemic attack.

[a] Of 309 patients with recurrent ischemic stroke, 16 with other specific causes are not considered in this Table.

[b] Indicates modified Rankin score at 7 days or hospital discharge (whichever earlier). Scores range from 0 to 6, with 6 indicating death.

[c] Includes 177 patients.

[d] Includes 282 patients.

classified as ESUS (Table 4). Multiple-territory qualifying ESUS occurred in 49 of 309 patients with a recurrent stroke (16%) and 714 of 6899 qualifying ESUS without recurrence (10%) (eTable 4 in Supplement 2).

Discussion

These exploratory analyses of the NAVIGATE-ESUS trial yield 3 major new findings. First, most of the recurrent ischemic strokes after ESUS met the criteria for ESUS. No source of embolus was identified in about three-quarters of cases, despite repeated diagnostic workup at the time of recurrent stroke. Second, analysis of location of recurrent ischemic strokes underscores the coexistence of several embolic mechanisms for recurrent strokes. Third, recurrences were rarely associated with atrial fibrillation, but atrial fibrillation–related recurrent ischemic strokes had particularly grave consequences and were prevented by rivaroxaban better than by aspirin.

The predominance of embolic features in most of the recurrent strokes after ESUS found in our analysis supports the validity of the ESUS construct in terms of embolism as the

Table 3. Baseline Participant Features and Functional Outcome Based on Identification of Atrial Fibrillation (AF) During Study Follow-Up[a]

Characteristic	Recurrent ischemic stroke, No. (%)	
	With identification of atrial fibrillation (n = 27)	Without identification of atrial fibrillation (n = 282)
Age, mean (SD), y	71 (10)	68 (10)
Aged ≥75 y, No. (%)	9 (33)	78 (28)
Male sex, No. (%)	17 (63)	188 (67)
Race, No. (%)		
White only	19 (70)	192 (68)
Black only	1 (4)	5 (2)
Asian only	7 (26)	71 (25)
Other or multiracial	0	0
Not reported	0	14 (5)
BMI, mean (SD)[b]	27 (4)	27 (5)
SBP/DBP, mean (SD), mm Hg	136 (16)/80 (12)	134 (18)/78 (11)
No statin use continued after randomization, No. (%)	10 (37)	72 (26)
Hypertension, No. (%)	23 (85)	207 (73)
Diabetes, No. (%)	6 (22)	86 (30)
Current tobacco use, No. (%)	3 (11)	79 (28)
Coronary artery disease, No. (%)	4 (15)	22 (8)
Heart failure, No. (%)	2 (7)	11 (4)
Cancer, No. (%)	2 (7)	33 (12)
Prior stroke or TIA, No. (%)	6 (22)	89 (32)
Qualifying ESUS, No. (%)		
Single acute lesion on imaging	23 (85)	237 (84)
Multiple lesions on imaging	4 (15)	45 (16)
Clinical TIA with imaging-confirmed infarction, No. (%)	1 (4)	28 (10)
Chronic infarct on imaging (in addition to qualifying stroke), No. (%)	12 (44)	125 (44)
Aspirin use before qualifying ESUS, No. (%)	9 (33)	67 (24)
Modified Rankin scale score at randomization, No. (%)[c]		
0	8 (30)	78 (28)
1	6 (22)	94 (33)
2	8 (30)	73 (26)
3	5 (19)	37 (13)
Time from qualifying ESUS to randomization, d		
Median (IQR)	31 (56)	30 (56)
≤30 d, No. (%)	13 (48)	142 (50)
eGFR, mL/min/1.73 m^2, No. (%)		
<50	4 (15)	17 (6)
50-80	16 (59)	154 (55)
>80	7 (26)	111 (39)
Left atrial diameter by transthoracic echocardiography, mean (SD), cm[d]	4.1 (0.7)	3.7 (0.8)
Abnormal mitral valve, No. (%)	14 (52)	127 (47)
Abnormal aortic valve, No. (%)	9 (33)	102 (38)
Carotid artery plaque, No. (%)	14 (52)	122 (43)
Left ventricular global function, No. (%)		
Normal	24 (89)	236 (84)
Mild dysfunction	0	14 (5)
Moderate-to-severe dysfunction	1 (4)	7 (2)
Uncertain	2 (7)	25 (9)
Modified Rankin scale score after recurrent stroke[c,e]		
Change from baseline, median (IQR)	2 (3)	0 (1)
Score of 6 (fatal), No. (%)	4 (15)	2 (1)
Assigned rivaroxaban, No. (%)	8 (30)	148 (52)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by square of height of meters); DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESUS, embolic stroke of underdetermined source; IQR, interquartile range; SBP, systolic blood pressure; TIA, transient ischemic attack.

[a] Of 309 patients with recurrent ischemic stroke, 16 with other specific causes are not considered in this Table.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Scores range from 0 to 6, with 6 indicating death.

[d] Includes 177 patients.

[e] Includes 27 patients with atrial fibrillation and 270 without.

pathogenic mechanism. However, even with the additional knowledge of recurrent stroke subtype in the present analysis, it is not possible to identify patient characteristics that are associated with the mechanism of recurrence at the time of the qualifying ESUS. A previous analysis of NAVIGATE-ESUS data[15] reported prior stroke or transient ischemic attack, current tobacco use, higher age, diabetes, multiple acute infarcts on neuroimaging, and aspirin use before the qualifying stroke as independently predictive of all recurrent stroke, but covariates associated with specific stroke subtypes were not investigated. The persisting uncertainty regarding the embolic source after stroke recurrence in a large proportion of our patients with ESUS suggests that the search for an underlying source may remain futile in many cases with ESUS, given the limitations of widely used diagnostic testing at present. Consequently, addressing a specific embolic source by targeted antithrombotic stroke prevention remains an unresolved dilemma for many patients with ESUS.

The NAVIGATE-ESUS trial did not show an overall benefit for stroke prevention with rivaroxaban vs aspirin. Subsequent exploratory subgroup analyses suggested that patients with ESUS and a patent foramen ovale or with a dilated left atrium at baseline were less likely to have a stroke when allocated to rivaroxaban, but independent confirmation of these findings is needed.[12,13] Based on the classification of the recurrent event taken in the present analysis, only statistically nonsignificant trends for better prevention of cardioembolic events with rivaroxaban and for more effective prevention of

Table 4. Location of Qualifying ESUS and Recurrent Ischemic Stroke

	Patient group, No. (%)							
	With qualifying ESUS				Recurrent ischemic stroke			
	All		With recurrent ischemic stroke		All		With ESUS only	
Territory	All	Single territory	All	Single territory	All	Single territory	All	Single territory
Left hemisphere	2983 (41)	2983 (46)	141 (46)	141 (54)	122 (39)	122 (51)	69 (44)	69 (52)
Right hemisphere	2570 (36)	2570 (40)	95 (31)	95 (37)	96 (31)	96 (40)	51 (33)	51 (39)
Brainstem/cerebellum	892 (12)	892 (14)	24 (8)	24 (9)	22 (7)	22 (9)	12 (8)	12 (9)
Multiple	763 (11)	NA	49 (16)	NA	34 (11)	NA	24 (15)	NA
Not determined	5 (<1)	NA	0	NA	35 (11)	NA	0	NA
Total	7213 (100)	6445 (100)	309 (100)	260 (100)	309 (100)	240 (100)	156 (100)	132 (100)

Abbreviations: ESUS, embolic stroke of undetermined source; NA, not applicable.

atherosclerotic and lacunar strokes by aspirin, respectively, were observed. Corresponding to the analysis by Healey and colleagues,[12] atrial diameter was larger in patients who experienced recurrent ischemic stroke associated with atrial fibrillation than those without atrial fibrillation in our analysis.

When the ESUS construct was originally proposed, common thinking was that covert atrial fibrillation may frequently underlie ESUS and that anticoagulation may be beneficial for stroke prevention after ESUS because of this association. In the meantime, several observational studies have shown that the characteristics of ESUS differ from those of stroke in patients with atrial fibrillation. On average, patients with ESUS are younger and have lower baseline stroke severity, lower burden of cardiovascular risk factors, and lower mortality compared with patients with cardioembolism.[4,5,16,17] Moreover, the lack of success of anticoagulation in the NAVIGATE-ESUS[6] and RESPECT-ESUS[7] trials contradicts the assumption of a major quantitative role of atrial fibrillation–related cardioembolism in ESUS. However, an important finding of our analysis is that recurrent ischemic strokes after ESUS in patients with a first diagnosis of atrial fibrillation during follow-up in the NAVIGATE-ESUS trial had much more severe consequences in terms of disability and mortality than other recurrent stroke types. Therefore, although covert atrial fibrillation may not underlie most recurrent strokes after ESUS, its particularly grave consequences warrant a more extensive search for atrial fibrillation in patients with ESUS than mandated in the originally proposed criteria for ESUS.

Our finding that qualifying ESUS and recurrent ischemic stroke were more frequently located in the left than in the right hemisphere is probably the result of more sensitive recognition of left hemispheric symptoms.[18,19] Less likely, there may be a predilection of cerebral blood flow carrying emboli from the heart to the brain via the left than via the right carotid territory.[20] Interestingly, after excluding recurrences in multiple locations, 62% (95% CI, 53%-71%) of recurrent ESUS in our study occurred in the same location as the qualifying stroke. This was significantly more frequent than expected if the recurrent stroke emboli had originated from a cardiac source where random distribution of emboli follow cerebral blood flow distribution (ie, a ratio of left carotid vs right carotid vs vertebrobasilar of 40:40:20). In that case, the theoretically expected consistency of location following from the observed distribution of the qualifying ESUS would be 38% (eResults in Supplement 2). Instead, recurrent strokes in some cases may have originated from the same vascular, originally nonstenotic culprit lesion in a carotid or vertebrobasilar artery in qualifying and recurrent strokes.[21] One possibility is that lesion progression to a hemodynamically relevant stenosis may have occurred, although this is not likely in most cases during a median follow-up of 11 months.[22] Alternatively, even without progression of the degree of stenosis, a nonstenotic plaque may cause recurrent stroke.[23,24] Although the degree of stenosis can be easily defined by conventional luminal imaging, it seems to have limited predictive value compared with alternative markers of plaque instability, such as ulceration, intraplaque hemorrhage, vessel wall inflammation, and microemboli signal detection, that may identify a culprit lesion. In the setting of ESUS, thrombogenesis triggered by other ESUS-related constellations, such as cancer or atrial cardiomyopathy, may activate a vulnerable plaque.[25,26] However, although a consistency of location in 62% of ESUS recurrent strokes differs from the expected distribution in case of a cardiac source, it does not support an overwhelming pathogenetic role of atherosclerosis in stroke recurrence but rather underscores the competition and interaction of various potential embolic sources in patients with ESUS. Some evidence suggests that different sources of emboli may have a negative association serving as competitors.[27,28] In a recent study,[27] atrial fibrillation was less frequently detected in patients with ESUS and nonstenotic carotid plaques compared with those without ESUS and such plaques. Another study[28] showed a negative association between patent foramen ovale and nonstenotic lesions in young patients with cryptogenic stroke.

Strengths and Limitations

Our present analysis has limitations and strengths. First, this was an exploratory analysis of the large, randomized NAVIGATE-ESUS trial, which was halted early and yielded neutral results. Moreover, the classification of subtypes of recurrent ischemic events and the location of infarcts on brain imaging relied on information provided by site investigators and was based on routine assessment rather than a defined set of diagnostic tests based on specific guidance. For example, a more extensive search for atrial fibrillation may have yielded a larger preva-

lence of the arrhythmia than reported in this paper. On the other hand, all incident strokes during the trial were adjudicated by a panel of experts who were blinded to treatment allocation. Another limitation is that 13% of stroke recurrences were unclassifiable because of insufficient diagnostic evaluation, and location of recurrent infarcts was not reported in 11% of all recurrent strokes. Finally, the number of ischemic strokes for each of the non-ESUS stroke subtypes was somewhat small, which limited our ability to detect differences in patient characteristics and effect of treatment.

Conclusions

This secondary analysis found that most of the recurrent ischemic strokes after ESUS in the NAVIGATE-ESUS trial were embolic in nature and frequently of undetermined source. This finding emphasizes the need for a more extensive search for specific sources of embolism in individual patients or, alternatively, the establishment of another unifying strategy for antithrombotic therapy addressing different pathways of embolus formation.

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