Characterization of Patients with Embolic Strokes of Undetermined Source in the NAVIGATE ESUS Randomized Trial

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Abstract

Background: The New Approach riVaroxaban Inhibition of Factor Xa in a Global trial vs. ASA to prevenT Embolism in Embolic Stroke of Undetermined Source (NAVIGATE-ESUS) trial is an international randomized phase III trial comparing rivaroxaban versus aspirin in patients with recent ESUS. While these patients share the common stroke mechanism of ESUS, they likely vary with respect to the underlying potential embolic sources.
Aims: We aimed to describe the baseline characteristics of this large ESUS cohort in order to explore their relationships among key subgroups.
Methods: We enrolled 7214 patients at 459 sites in 31 countries. Pre-specified subgroup analyses for the primary safety and efficacy outcomes included age, sex, race, global region, stroke or TIA prior to qualifying event, time from qualifying stroke to randomization, hypertension, and diabetes mellitus.
Results: The mean age was 66.9±9.8 years, and 24% were <60 years old. Older patients had more hypertension, coronary disease, and cancer. Strokes in older subjects were more frequently cortical and accompanied by radiographic evidence of prior infarction. Women comprised 38% of participants and were older than men. Patients from East Asia were oldest while those from Latin America were youngest. Patients in the Americas more frequently were on aspirin prior to the qualifying stroke. Acute infarction involving the cortex was more common in the U.S.A., Canada, and Western Europe, while prior infarctions in addition to the index stroke were most commonly observed in East Asia. About 45% of subjects were enrolled within 30 days of the qualifying stroke, with the earliest enrollments in Asia and Eastern Europe.
Conclusions: NAVIGATE ESUS is the largest randomized trial comparing antithrombotic strategies for secondary stroke prevention in patients with embolic strokes of undetermined source. The study population encompasses a broad array of patients across multiple continents and these subgroups provide ample opportunities for future research.

Introduction

Embolic stroke of undetermined source (ESUS) is a subset of cryptogenic stroke, and a diagnostic label proposed for an ischemic stroke that occurs without an identifiable and specifically treatable underlying stroke etiology, including >50% stenosis in a large proximal artery in the territory of ischemia, atrial fibrillation or other major-risk cardioembolic source, lacunar (small vessel occlusive) disease, or identified uncommon cause.[1] ESUS accounts for 15 to 30% of all ischemic strokes.[2] A wide range of potential cardiac, arterial, paradoxical, and hematological sources have been proposed that might be amenable to treatment with an anticoagulant.[1, 3, 4] The New Approach riVaroxaban Inhibition of Factor Xa in a Global trial vs. ASA to prevenT Embolism in Embolic Stroke of Undetermined Source (NAVIGATE-ESUS) trial is an international randomized phase III trial comparing rivaroxaban with aspirin in patients with recent ESUS. The design of the trial has previously been reported,[5] enrollment of 7214 subjects has recently been completed, and participant features are reported here.

While the NAVIGATE-ESUS participants share a common diagnosis of ESUS, they likely vary with respect to the underlying potential embolic sources,[6] and therefore subgroup analyses may be especially important.[7, 8] Subgroup analysis in clinical trials is often performed for two key purposes. One major goal is to explore the consistency of a treatment effect among different subpopulations that are defined at baseline. The other is to investigate whether there are specific groups that are more or less likely to receive benefit or harm from the treatment. Together, these assessments of both homogeneity and heterogeneity can yield valuable information for clinicians and future research, but these analyses must be interpreted cautiously, mitigated by reduced statistical power and the play of chance.[9] Subgroup analysis can also help identify populations at greatest risk of a recurrent event. Clinical characteristics of selected subgroups pre-specified in the NAVIGATE ESUS trial statistical analysis plan are provided.

Methods:

NAVIGATE ESUS Study design

The design of NAVIGATE ESUS (clinicaltrials.gov.NCT02313909) has previously been published.[5] In brief, it is an international, double-blinded, randomized phase III superiority trial comparing rivaroxaban 15 mg once daily (immediate-release, film-coated tablets) with aspirin (enteric-coated) 100 mg once daily, both to be taken with food, in patients with recent ESUS. Target enrollment was approximately 7000, and the study was designed to continue until at least 450 primary events have occurred. Key eligibility criteria for NAVIGATE ESUS are summarized in the Appendix (Supplement Table 1). The primary efficacy outcome is time to recurrent stroke, comprising ischemic, hemorrhagic and undefined stroke, including TIAs with positive neuroimaging[10] or systemic embolism. The primary safety outcome is major bleeding as defined by the criteria of the International Society of Thrombosis and Haemostasis.[11] The main efficacy and safety results will be available in 2018.

Baseline characteristics and subgroup analyses

Baseline characteristics collected in the trial include demographic features, medical history, qualifying stroke information, and baseline functional and cognitive status. Pre-specified participant subgroup analyses for which the treatment effects will be presented in the main results publication were chosen for presentation here, in accord with the statistical analysis plan. These included the following, based on the data collected at the time of randomization: age, sex, race, global region, stroke or TIA prior to qualifying event, time from qualifying stroke to randomization, hypertension, and diabetes mellitus.

Statistical analysis

We describe the features of all subjects and compare the baseline characteristics for selected pre-specified subgroups. Descriptive statistics use mean ± standard deviation, median (interquartile range [IQR]), or proportion as appropriate. Univariate comparisons were made using t-tests for continuous variables and chi- squared tests for categorical variables, and we present nominal two-sided p-values. For comparisons within subgroups, we consider only p values <0.01 to be significant to account for the multiple comparisons.

Results

A total of 7214 subjects were randomized in the NAVIGATE ESUS trial between December 24, 2014 and September 20, 2017. The major baseline characteristics for the entire study population are summarized in Table 1. The mean age was 66.9 ± 9.8 years, and 62% were men. Median baseline NIHSS score was 1 (IQR 0, 2) and was ≤5 in 96% of patients. All subjects had extracranial vascular imaging, echocardiography, and initial cardiac rhythm monitoring as required by protocol, and 78% had intracranial vascular imaging. Forty-three percent (43%) of patients were enrolled from Western Europe (Figure). Characteristics of pre-specified selected subgroups are summarized in Tables 2 to 4 and the Supplemental Tables. Key differences among subgroups are described below. Of note, only 7% of participants had a history of coronary artery disease due to protocol stipulation excluding patients who require single or dual antiplatelet therapy.

Age. As summarized in Table 2, 24% of patients were under 60 and 21% were older than 75 years. Older subjects were more likely to be women, of white race, and had lower weight and BMI values as well as lower estimated glomerular filtration rates. Older subjects had a greater burden of hypertension, coronary artery disease, cancer, but there were fewer smokers and less diabetes. Cognitive function as assessed by the Montreal Cognitive Assessment (MoCA) was more impaired with increasing age. Aspirin use prior to the qualifying stroke was more common with increasing age. The qualifying strokes in older subjects more frequently involved the cerebral cortex and were more often accompanied by evidence of prior or chronic infarcts observed on neuroimaging.

Sex. As shown in Table 3, compared to men, the 39% of subjects who were women were older, more likely to be white and less likely to be Asian. Women had lower weight but slightly greater BMI than men. Women had modestly more hypertension but were less likely to be current smokers. Women were more commonly treated with acute thrombolysis or endovascular therapy.

Region. As summarized in Table 4, patients enrolled in Western Europe tended to be the oldest. Smoking was more common in Eastern Europe and East Asia. Patients in the Americas were more likely to be on aspirin prior to the qualifying stroke than those from Europe and East Asia. Patients were less likely to be treated with thrombolysis for the qualifying stroke in Latin America and East Asia. Acute cortical infarction was more common in North America and Western Europe, while chronic infarctions in addition to the index stroke were most commonly observed in East Asia.

Race. The majority of subjects were white (72%) or Asian (20%). Variability in baseline characteristics by race are shown in Supplemental Table 2, with notably lower BMI values among Asians and more current tobacco use. Asians also appeared more likely to have subcortical infarctions, more chronic infarctions, and suffered less disability from their strokes (mRS 0-1). Blacks were enrolled mainly in the Americas and had the highest prevalence of hypertension.

Hypertension. A history of hypertension was reported in 77% of subjects, and was associated with older age and the presence of diabetes and coronary artery disease, as shown in Supplemental table 3. Patients with hypertension were more likely to be taking aspirin prior to the qualifying stroke, had more evidence of chronic radiographic infarction, and mildly lower MoCA scores.

Diabetes mellitus. Diabetes mellitus was present in 25% of subjects at enrollment and characteristics are summarized in Supplemental Table 4. Patients with diabetes were younger, had greater BMI values, and were more likely to have hypertension, coronary disease, prior stroke as well as chronic radiographic infarction, and mildly lower MoCA scores. Aspirin use prior to the index stroke was more common and thrombolysis use less common in patients with diabetes.

Stroke or TIA prior to index event. As shown in Supplemental Table 5, 17% of subjects had a prior clinical stroke or TIA. These patients were similar with respect to demographic features, but had a greater burden of coronary artery disease. Aspirin use prior to the index stroke and chronic infarcts on imaging were more than twice as common in this group, and they had slightly lower MoCA scores.

Time from qualifying stroke to randomization. As indicated in Supplemental Table 6, 45% of subjects were enrolled within 30 days of the qualifying stroke, 31% between 30 and 90 days, and 24% between 3 and 6 months. Patients in East Asia and Eastern Europe were enrolled earlier than in other regions.

Discussion

NAVIGATE ESUS is the largest randomized trial comparing antithrombotic therapeutic strategies for secondary stroke prevention in patients with ESUS. The study population encompasses a wide spectrum of patients across multiple continents. Moreover, the population is similar to published smaller cohorts of patients with cryptogenic stroke or ESUS,[2, 12-15] supporting the external validity and generalizability of the ESUS concept and its implementation in this trial.

The hypothesis of the NAVIGATE-ESUS trial is that rivaroxaban would be associated with a substantially lower risk of recurrent embolic events without a clinically unacceptable increase of major hemorrhages relative to aspirin, with relatively consistent treatment effects across the subgroups described here. However, higher event rates would be anticipated for older patients, women, and those with stroke or TIA prior to qualifying event, hypertension, and diabetes. Observed baseline differences across subgroups may be important in the assessment of treatment effects within these groups. Some of these are potentially relevant confounders, such as the relationships between older age and prior antiplatelet agent use, or between global region and time from qualifying event to randomization, because those relationships within subgroups could also be associated with outcome events. Others are statistically significant relationships that are unlikely to confound a treatment effect, such as the apparent relationship between smoking and time from the qualifying event, but nevertheless provide important descriptions of the cohort. The relevance of these factors will need to be weighed in the context of the overall and subgroup analyses of treatment effects in NAVIGATE ESUS, which are anticipated in the near future. Further, these data will provide a robust opportunity to determine if different ESUS subgroups have varying risks of recurrent stroke and other major vascular events. ESUS is a broad definition and description of the full cohort across multiple baseline characteristics helps to understand the inherent heterogeneity and perhaps guide future trials about optimal patient selection.

This study has potential limitations. Despite the large size of NAVIGATE cohort, it represents

patients who are willing and able to participate in a clinical trial and therefore may be subject to limitations on generalizability, both overall and within these subgroups. Differences in the acute treatment of stroke and variations in risk factors based on racial and genetic predispositions may introduce heterogeneity among these subgroups. Further, diagnostic testing may affect outcome analysis as patients in higher income countries may have undergone more extensive pre-enrollment investigation than those in middle or lower income countries.

NAVIGATE ESUS is the largest randomized trial in ESUS and the first to address new paradigms for stroke diagnosis and prevention. The results, particularly in key subgroups, are expected to shed new light on the treatment and prognosis of ESUS.

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Table 1. Baseline characteristics of the complete NAVIGATE-ESUS study population

Characteristic	N with Data	Summary (N=7214)
Age, years (mean ± s.d.)	7214	66.9 ± 9.8
Age<60 years		24%
Male sex	7214	62%
Race:	7206	
White only		72%
Black only		2%
Asian only		20%
Others (includes not reported/multiracial)		6%
BMI, kg/m^2 (mean ± s.d.)	7179	27.2 ± 5.0
<25 kg/m^2		35%
≥25 - <30 kg/m^2		41%
≥30 kg/m^2		24%
<30 kg/m^2		76%
≥30 kg/m^2		24%
Weight, kg (mean ± s.d.)	7186	76.2 ± 16.6
<70 kg		35%
70 - 90 kg		48%
>90 kg		16%
<50 kg		3%
50 - 100 kg		90%
>100 kg		7%
Estimated glomerular filtration rate (eGFR), mL/min per 1.73 m^2	7190	78.6 ± 20.6
<50 mL/min		6%
50 - 80 mL/min		49%
>80 mL/min		45%
Medical history:		
Hypertension	7209	77%
Diabetes mellitus	7209	25%
Current tobacco use	7206	21%
Coronary artery disease	7209	7%
Heart failure	7209	3%
Cancer	7209	9%
Prior stroke or TIA	7209	17%
Global region:		

Characteristic	N with Data	Summary (N=7214)
U.S.A. and Canada	7214	13%
Latin America		10%
Western Europe		43%
Eastern Europe		16%
East Asia		19%
Qualifying stroke:		
Clinical TIA with imaging-confirmed infarction as qualifying event:	7214	7%
Arterial territory of qualifying stroke:*	7214	
Anterior circulation		72%
Posterior circulation		31%
Location of qualifying stroke:	7214	
Single Location:		
Cerebral hemisphere with cortical involvement		56%
Cerebral hemisphere, subcortical only		21%
Brainstem only		5%
Cerebellum only		8%
Multiple Locations:		10%
Chronic infarct on imaging (in addition to index stroke)	7200	32%
Aspirin use prior to qualifying stroke	7214	17%
Treated with intravenous tPA for qualifying stroke	7206	17%
Treated with endovascular intervention for qualifying stroke	7206	4%
NIHSS score at randomization (median, IQR)	7201	1.0 (0.0, 2.0)
NIHSS score ≤5		96%
Modified Rankin Scale (mRS) at randomization:	7203	
mRS 0 or 1		65%
mRS 2		23%
mRS ≥3		12%
MoCA score at randomization (median, IQR)	5787	25.0 (21.0, 27.0)
Time from qualifying stroke to randomization, days (median, IQR)	7202	37.0 (14.0, 88.0)
Extracranial vascular imaging completed:		
CTA	7206	38%
MRA	7203	33%
Carotid ultrasound	7205	63%
Conventional angiography	5576	2%
Intracranial vascular imaging completed:	7214	
CTA but not MRA or Transcranial Doppler		36%
MRA but not Transcranial Doppler		30%

Characteristic	N with Data	Summary (N=7214)
Transcranial Doppler		12%
None		22%
Transthoracic echocardiography:	7203	95%
Left atrial diameter, cm (mean ± s.d.)	3973	3.8 ± 1.9
Left ventricular ejection fraction, % (mean ± s.d.)	5744	62.3 ± 8.1
Transesophageal echocardiography	7201	19%
Patent foramen ovale present	1383	27%
Duration of cardiac rhythm monitoring ≥48 hours	7187	34%

*Arterial territory could be multiple, resulting in a total>100%

Table 2. Comparisons by Age

Characteristic	<60 yrs (N=1716)	60 - 75 yrs (N=4013)	>75 yrs (N=1485)	p^
Age, years (mean ± s.d.)	54.1 ± 4.5	67.4 ± 4.4	80.5 ± 3.7	
Male sex	71%	63%	47%	<.001
Race:				
White only	67%	73%	77%	<.001
Black only	3%	1%	1%	<.001
Asian only	24%	19%	16%	<.001
Others (includes not reported/multiracial)	7%	6%	6%	0.38
BMI, kg/m^2 (mean ± s.d.)	27.9 ± 5.5	27.3 ± 5.0	26.3 ± 4.5	<.001
Weight, kg (mean ± s.d.)	80.5 ± 17.3	76.7 ± 16.3	69.9 ± 14.5	<.001
Estimated glomerular filtration rate (eGFR), mL/min per 1.73 m^2	88.1 ± 21.0	78.7 ± 19.4	67.5 ± 17.4	<.001
Medical history:				
Hypertension	78%	75%	83%	0.001
Diabetes mellitus	26%	25%	22%	0.009
Current tobacco use	38	19%	5%	<.001
Coronary artery disease	5%	6%	9%	<.001
Heart failure	4%	3%	4%	0.80
Cancer	3%	9%	15%	<.001
Prior stroke or TIA	19%	16%	21%	0.40
Global region:				
U.S.A. and Canada	15%	13%	11%	0.003
Latin America	10%	11%	9%	0.45
Western Europe	35%	42%	55%	<.001
Eastern Europe	18%	17%	9%	<.001
East Asia	23%	18%	16%	<.001
Qualifying stroke:				
Clinical TIA with imaging-confirmed infarction as qualifying event:	6%	8%	8%	0.03
Arterial territory of qualifying stroke:*				
Anterior circulation	71%	71%	74%	0.15
Posterior circulation	31%	31%	30%	0.54
Location of qualifying stroke:				
Single Location:				
Cerebral hemisphere with cortical involvement	48%	56%	62%	<.001
Cerebral hemisphere, subcortical only	27%	21%	15%	<.001
Brainstem only	5%	5%	3%	0.003

Cerebellum only	9%	8%	8%	0.50
Multiple Locations:	11%	10%	12%	0.32
Chronic infarct on imaging (in addition to index stroke)	31%	32%	37%	<.001
Aspirin use prior to qualifying stroke	13%	17%	24%	<.001
Treated with intravenous tPA for qualifying stroke	16%	18%	17%	0.35
Treated with endovascular intervention for qualifying stroke	4%	4%	4%	0.83
NIHSS score at randomization (median, IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	<.001
Modified Rankin Scale (mRS) at randomization:				
mRS 0 or 1	63%	67%	59%	0.02
mRS 2	25%	22%	24%	0.33
mRS ≥3	11%	11%	17%	<.001
MoCA score at randomization (median, IQR)	26.0 (22.0, 28.0)	25.0 (21.0, 27.0)	22.0 (18.0, 26.0)	<.001
Time from qualifying stroke to randomization, days (median, IQR)	35.0 (14.0, 87.0)	38.0 (15.0, 90.0)	35.5 (13.5, 85.5)	0.43

*Arterial territory could be multiple, resulting in a total>100%

Table 3. Comparisons by Sex

Characteristic	Male (N=4437)	Female (N=2777)	p value^
Age, years (mean ± s.d.)	65.6 ± 9.4	69.1 ± 10.0	<.001
Age<60 years	27%	18%	<.001
Race:			
White only	70%	76%	<.001
Black only	1%	2%	0.40
Asian only	22%	16%	<.001
Others (includes not reported/multiracial)	6%	7%	0.64
BMI, kg/m^2 (mean ± s.d.)	27.1 ± 4.6	27.5 ± 5.7	<.001
Weight, kg (mean ± s.d.)	80.2 ± 15.7	69.7 ± 15.8	<.001
Estimated glomerular filtration rate (eGFR), mL/min per 1.73 m^2	80.7 ± 20.6	75.4 ± 20.0	<.001
Medical history:			
Hypertension	75%	81%	<.001
Diabetes mellitus	26%	23%	0.009
Current tobacco use	26%	12%	<.001
Coronary artery disease	7%	5%	0.004
Heart failure	3%	3%	0.26
Cancer	8%	9%	0.22
Prior stroke or TIA	17%	19%	0.01
Global region:			
U.S.A. and Canada	12%	14%	0.02
Latin America	9%	12%	<.001
Western Europe	42%	44%	0.20
Eastern Europe	15%	16%	0.93
East Asia	21%	15%	<.001
Qualifying stroke:			
Clinical TIA with imaging-confirmed infarction as qualifying event:	8%	7%	0.57
Arterial territory of qualifying stroke:*			
Anterior circulation	71%	74%	0.001
Posterior circulation	33%	29%	<.001
Location of qualifying stroke:			
Single Location:			
Cerebral hemisphere with cortical involvement	55%	57%	0.07
Cerebral hemisphere, subcortical only	21%	21%	0.77
Brainstem only	5%	4%	0.30
Cerebellum only	8%	8%	0.32
Multiple Locations:	11%	10%	0.11
Chronic infarct on imaging (in addition to index stroke)	33%	31%	0.06
Aspirin use prior to qualifying stroke	17%	18%	0.18
Treated with intravenous tPA for qualifying stroke	16%	19%	0.005

Characteristic	Male (N=4437)	Female (N=2777)	p value^
Treated with endovascular intervention for qualifying stroke	3%	5%	<.001
NIHSS score at randomization (median, IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	0.77
Modified Rankin Scale (mRS) at randomization:			
mRS 0 or 1	67%	62%	<.001
mRS 2	22%	24%	0.05
mRS ≥3	11%	14%	0.002
MoCA score at randomization (median, IQR)	25.0 (21.0, 27.0)	24.0 (20.0, 27.0)	<.001
Time from qualifying stroke to randomization, days (median, IQR)	36.0 (14.0, 90.0)	37.0 (15.0, 85.0)	0.77

*Arterial territory could be multiple, resulting in a total>100%

Table 4. Comparisons by global region

Characteristic	U.S.A. & Canada (N=918)	Latin America (N=746)	Western Europe (N=3081)	Eastern Europe (N=1119)	East Asia (N=1350)	p value^
Age, years (mean ± s.d.)	66.2 ± 9.8	66.4 ± 10.0	68.7 ± 9.8	64.7 ± 8.5	65.6 ± 10.1	<.001
Age<60 years	27%	24%	19%	27%	29%	<.001
Male sex	58%	56%	61%	61%	69%	<.001
Race:						
White only	85%	82%	88%	100%	0%	<.001
Black only	6%	4%	1%	0%	0%	<.001
Asian only	5%	0%	1%	0%	100%	<.001
Others (includes not reported/multiracial)	4%	14%	10%	0%	0%	<.001
BMI, kg/m^2 (mean ± s.d.)	29.3 ± 6.4	28.1 ± 4.6	27.5 ± 4.8	28.3 ± 4.5	23.9 ± 3.5	<.001
Weight, kg (mean ± s.d.)	83.4 ± 19.2	74.5 ± 14.5	78.1 ± 15.7	81.1 ± 14.6	63.8 ± 11.7	<.001
Estimated glomerular filtration rate (eGFR), mL/min per 1.73 m^2	73.3 ± 17.8	81.2 ± 22.1	77.5 ± 19.2	78.6 ± 20.1	83.5 ± 23.4	<.001
Medical history:						
Hypertension	73%	83%	76%	89%	71%	<.001
Diabetes mellitus	24%	31%	22%	27%	26%	<.001
Current tobacco use	17%	13%	18%	25%	29%	<.001
Coronary artery disease	13%	4%	5%	10%	4%	<.001
Heart failure	3%	2%	3%	9%	1%	<.001
Cancer	13%	5%	10%	4%	7%	<.001
Prior stroke or TIA	23%	18%	16%	14%	18%	<.001
Qualifying stroke:						
Clinical TIA with imaging-confirmed infarction as qualifying event:	8%	6%	9%	3%	7%	<.001
Arterial territory of qualifying stroke:*						
Anterior circulation	71%	71%	72%	70%	73%	0.46

Characteristic	U.S.A. & Canada (N=918)	Latin America (N=746)	Western Europe (N=3081)	Eastern Europe (N=1119)	East Asia (N=1350)	p value^
Posterior circulation	33%	31%	30%	30%	35%	0.01
Location of qualifying stroke:						
Single Location:						
Cerebral hemisphere with cortical involvement	65%	55%	64%	46%	39%	<.001
Cerebral hemisphere, subcortical only	13%	25%	14%	33%	30%	<.001
Brainstem only	2%	8%	3%	7%	6%	<.001
Cerebellum only	8%	7%	9%	8%	8%	0.58
Multiple Locations:	12%	5%	10%	6%	17%	<.001
Chronic infarct on imaging (in addition to index stroke)	28%	34%	27%	37%	43%	<.001
Aspirin use prior to qualifying stroke	21%	23%	18%	16%	11%	<.001
Treated with intravenous tPA for qualifying stroke	21%	8%	22%	18%	8%	<.001
Treated with endovascular intervention for qualifying stroke	8%	1%	5%	2%	3%	<.001
NIHSS score at randomization (median, IQR)	0.0 (0.0, 1.0)	2.0 (1.0, 4.0)	0.0 (0.0, 2.0)	2.0 (0.0, 3.0)	1.0 (0.0, 2.0)	<.001
Modified Rankin Scale (mRS) at randomization:						
mRS 0 or 1	69%	55%	67%	57%	70%	<.001
mRS 2	22%	29%	22%	28%	19%	<.001
mRS ≥3	8%	16%	11%	16%	11%	<.001
MoCA score at randomization (median, IQR)	26.0 (23.0, 28.0)	23.0 (17.0, 26.0)	25.0 (21.0, 27.0)	25.0 (22.0, 27.0)	23.0 (20.0, 26.0)	<.001
Time from qualifying stroke to randomization, days (median, IQR)	70.0 (41.0, 123.0)	54.0 (31.0, 102.0)	42.0 (14.0, 101.0)	23.0 (13.0, 56.5)	18.0 (11.0, 38.0)	<.001

*Arterial territory could be multiple, resulting in a total>100%

Figure Legend.

Figure 1. Enrollment by global region in the NAVIGATE-ESUS trial.

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