International
Journal of Stroke WSO

Regional, sex, and age differences in diagnostic testing among participants in the NAVIGATE-ESUS trial

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Abstract

Background and aim: The diagnosis of embolic stroke of undetermined source (ESUS) is based on excluding other more likely stroke etiologies, and therefore diagnostic testing plays an especially crucial role. Our objective was to compare the diagnostic testing by region, sex, and age among the participants of NAVIGATE-ESUS trial.

Methods: Participants were grouped according to five global regions (North America, Latin America, Western Europe, Eastern Europe and East Asia), age (<60, 60–74, and >75 years), and sex. Frequencies of each diagnostic test within areas of echocardiography, cardiac rhythm monitoring, and arterial imaging were described and compared across groups. A multivariable logistic regression model for each diagnostic test was fit to assess the independent influence of each of region, age, and sex and likelihood of testing.

Results: We included 6985 patients in the analysis (918 from North America; 746 from Latin America; 2853 from Western Europe; 1118 from Eastern Europe; 1350 from East Asia). Average age (highest in Western Europe (69 years), lowest in Eastern Europe (65 years)), % females (highest in Latin America (44%) and lowest in East Asia (31%)), and use of each diagnostic test varied significantly across regions. Region, but not sex, was independently associated with use of each diagnostic test examined. Transesophageal echocardiography and either CT or MR angiogram were more often used in younger patients.

Conclusion: Diagnostic testing differed by region, and less frequently by age, but not by sex. Our findings reflect the existing variations in global practice in diagnostic testing in ESUS patients.

Keywords

Embolic stroke of undetermined source, region, age, sex

Introduction

The clinical construct of embolic stroke of undetermined source (ESUS) was proposed to define non-lacunar cryptogenic ischemic stroke likely due to embolism. Because the diagnosis is based on excluding other more likely stroke etiologies, ESUS comprises

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heterogeneous pathologies, and therefore diagnostic testing plays an especially crucial role.[1]

Screening for covert atrial fibrillation (AF) is a key step in the diagnosis of ESUS. The optimal techniques for ECG monitoring are uncertain given the lack of head-to-head trials and recent rapid advances in device design. Three major randomized controlled trials have examined the value of undertaking further monitoring in patients with cryptogenic stroke. The results show significantly higher detection rates with more intensive rhythm monitoring strategies than with standard care.[2–4] In most regions, the first-line method for non-invasive detection of AF in ESUS patients remains via Holter monitoring. Non-invasive monitoring using loop recorders can record cardiac rhythm for several weeks, while other sites prefer longer term monitoring via implanted cardiac monitors.

Recent data suggest that the etiology of ESUS could be beyond cardioembolism, be heterogeneous and have other sources of embolism, or the result of nonstenosing large-artery atherosclerosis, aortic atherosclerosis, or nonatherosclerotic vasculopaties.[5] This suggests that other studies such as transesophageal echocardiography (TEE) and intracranial vascular imaging could be of importance in the study of patients with ESUS. However, many of these diagnostic methods are not readily accessible in many low and middle-income countries. In the ESUS global registry, for up to 14% of the patients who did not meet ESUS criteria, the reason was insufficient diagnostic testing.[6]

Differences in the diagnostic testing in ESUS patients may vary not only from region to region, but also with other factors such as age and sex. Therefore, we compared the diagnostic testing according to region, sex, and age among the participants of NAVIGATE-ESUS trial.

Methods

The methods of the NAVIGATE ESUS trial and baseline characteristics of its participants have been published.[7] The trial enrolled 7213 patients between December 2014 and September 2017 who experienced a recent ischemic stroke and satisfied the criteria for ESUS, specifically, a nonlacunar stroke on brain imaging, open arteries proximal to the infarct, and no major-risk cardioembolic source. In addition to brain computed tomography or magnetic resonance imaging showing the brain infarct, patients required imaging of intracranial and extracranial cerebral arteries, to exclude extracranial vessel atherosclerosis causing more than 50% luminal stenosis in arteries supplying the area of ischemia. Intracranial imaging was otherwise optional, but if performed, a finding of more than 50% stenosis due to atherosclerosis was an exclusion criterion. An electrocardiogram, and at least 20 total hours of cardiac rhythm monitoring were also required in order to rule out AF lasting 6 min or longer, although investigators could choose to monitor for longer periods. Patients with implanted cardiac rhythm monitors were excluded from NAVIGATE ESUS study. No participant had an implantable cardiac rhythm monitor. Non-implantable monitors were used for 7, 14, or 30 days, and the patient could not be randomized until cardiac rhythm monitoring was completed. Echocardiography was required, either transthoracic (TTE) or TEE.

Data were analyzed according to five global regions (Figure 1): North America (Canada and United States of America (USA)), Latin America (Argentina, Brazil, Chile, México), Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Portugal, Spain, Sweden, Switzerland, United Kingdom), Eastern Europe (Czech Republic, Hungary, Poland, Russian Federation, Turkey), and East Asia (China, Japan, South Korea). Participants from Australia ($n = 119$), Israel ($n = 60$), and South Africa ($n = 49$) could not be categorized into one of these five geographical regions and were excluded from these analyses. Descriptive statistics summarizing age (mean ± standard deviation (SD)), male sex, and frequency of each diagnostic test were done overall and by each of region, sex, and age (categorized a priori as <60, 60–74, and >75 years), and compared across groups using an ANOVA or Chi-square test as appropriate. A multivariable logistic regression model for each diagnostic test was fit to assess the influence of region (4 degrees of freedom, df), age (2 df), and sex (1 df) on likelihood of that test with Western Europe (largest region), age <60 years (youngest), and male sex serving as reference groups. Results from the models were summarized qualitatively by considering which groups were significantly different from the reference groups. Statistical significance was accepted at the 0.01 level (two-sided), and no adjustment was made for multiple comparisons. Analyses were done using SPSS 24.0.0.0 software.

Results

This analysis included 6985 (97%) of the 7213 NAVIGATE-ESUS clinical trial participants: 918 from North America; 746 from Latin America; 2853 from Western Europe; 1118 from Eastern Europe; 1350 from East Asia. Age (mean + SD) varied across region ($p < 0.001$) with the highest in Western Europe ($69 + 10$ years) and lowest in Eastern Europe ($65 + 8$ years). The fraction of participants who were male also varied ($p < 0.001$) and was highest in East Asia (71%) and lowest in Latin America (56%). (Table 1)

Figure 1. Number of analyzed patients by region.

Regions (Patients)
- Canada & USA (918)
- Latin America (746)
- Western Europe (2853)
- Eastern Europe (1118)
- East Asia (1350)
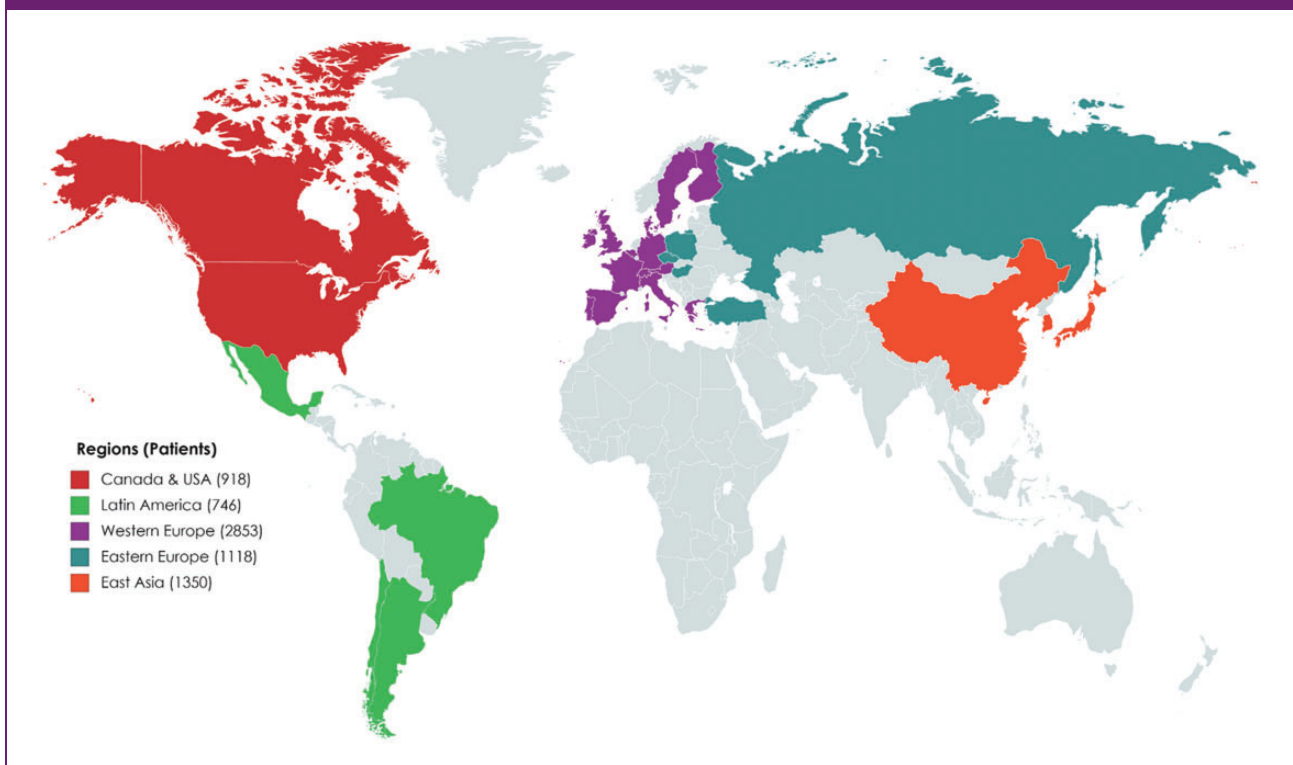
Diagnostic testing by region

The relative frequencies of all diagnostic tests varied by region (Table 1). TTE was common across all regions (range 93–99%), while TEE was nearly twice as frequent in East Asia (26%) and Western Europe (23%) as in Eastern Europe (12%) or Latin America (13%). Participants in East Asia were more likely to have both TTE and TEE (25%).

For cardiac rhythm monitoring, in-hospital telemetry was most frequent in Western Europe (53%) and infrequently used in Latin America (7%), whereas ambulatory ECG (Holter) was most common in East Asia (98%), Latin America (96%) and Eastern Europe (93%) where in-hospital telemetry was less common (range 7 to 13%). Prolonged cardiac rhythm monitoring was frequently done in Canada/USA (39% of participants) but uncommon elsewhere (range <1 to 8%). Arterial imaging via CT angiogram was frequent in Canada/USA (75%) but much less frequent elsewhere (range 23 to 38%), and was frequent via MRI angiogram in East Asia (62%) but about half as common elsewhere (range 10 to 36%). CT or MR angiography was done in 89% of participants from Canada/USA versus 33% of those from Eastern Europe. Sonography was widely used in Eastern Europe (82%), East Asia (79%), Western Europe (68%), and Latin America (62%), but infrequently used in Canada/USA (19%).

Diagnostic testing by age and sex

Fewer differences in frequencies of diagnostic tests were apparent considering patient age and sex (Table 2). Notably, TEE was done more frequently in patients under age 60 years (24%) vs. those age 75 years or older (14%). Both studies (TTE and TEE) were performed in a fewer patients, although more frequently in those under 60 years of age (18%) vs. those age 75 years or older (11%). Other absolute differences in frequencies were smaller.

Multivariable analysis of the influence of region, age, and sex

Region was independently associated (each $p < 0.001$, 4 df) with likelihood of each of the diagnostic tests and combinations considered, whereas sex was not independently associated (each $p > 0.18$, 1 df) with any of them. Age was independently associated with each of the echocardiography tests and the combination (each $p < 0.001$, 2 df), but not any of the rhythm monitoring tests (each $p > 0.19$). Age was also associated with likelihood of CT angiogram ($p < 0.001$, 2 df) and CT

Table 1. Frequency of diagnostic testing by global region

	Overall (n = 6985)	North America (n = 918)	Latin America (n = 746)	Western Europe (n = 2853)	Eastern Europe (n = 1118)	East Asia (n = 1350)	p-value*
Age, mean ± SD	67 ± 10	66 ± 10	66 ± 10	69 ± 10	65 ± 8	66 ± 10	<0.001
Male, %	61	58	56	60	61	69	<0.001
Echocardiography							
Transthoracic, %	95	97	93	94	94	99	<0.001
Transesophageal, %	20	15	13	23	12	26	<0.001
Both, %	15	12	6	17	6	25	<0.001
Cardiac Rhythm Monitoring							
In-hospital telemetry, %	31	34	7	53	12	13	<0.001
If yes, duration, %							
<24 hr	7	5	18	5	31	7	
24–<48 hr	36	34	41	38	52	17	
≥48 hr	54	55	41	55	16	72	
Uncertain/unknown	3	7	0	2	1	3	
Ambulatory ECG (Holter), %	79	64	96	64	93	98	<0.001
Duration, hours, median (IQR)	24 (1)	24 (24)	24 (1)	24 (1)	24 (1)	24 (1)	
Other prolonged (>24 hr), %	9	39	<1	8	1	1	<0.001
Duration, days, median (IQR)	16 (23)	30 (16)		7 (8)	7 (9)	7 (4)	
Arterial imaging							
CT angiogram, %	37	75	34	38	24	23	<0.001
MR angiogram, %	34	20	24	36	10	62	<0.001
CT and/or MR angiogram, %	64	89	56	65	33	77	<0.001
Sonography, %	64	19	62	68	82	71	<0.001

*Statistical significance for comparison across regions.
CT: computed tomography; MR: magnetic resonance; IQR: interquartile range; hr: hour; ECG: electrocardiography.

and/or MR angiogram ($p < 0.001$, 2 df), but not with MR angiogram only ($p = 0.53$, 2 df). Table 3 summarizes these differences qualitatively with exact results reported in the Online Supplemental Appendix.

Discussion

NAVIGATE-ESUS was a randomized clinical trial that compared different antithrombotic treatments in patients meeting the diagnostic criteria for ESUS.[8]

The study included a large cohort of patients across multiple continents. Despite the fact that minimum diagnostic studies were required for its inclusion, the trial cohort provides ample opportunity to assess the differences in diagnostic testing in four continents.

Prolonged cardiac rhythm monitoring is infrequently used in all regions. In Latin America, Eastern Europe, and East Asia it was reported for less than 1% of patients, while in Canada/USA, where it was most frequently done, the percentage reached 39%.

Table 2. Frequency of diagnostic testing by age and sex

		Age categories				Sex		
	Overall (n = 6985)	<60 years (n = 1660)	60–74 years (n = 3679)	≥75 years (n = 1646)	p-value*	Male (n = 4290)	Female (n = 2695)	p-value#
Echocardiography								
Transthoracic, %	95	94	95	97	<0.001	96	95	0.5
Transesophageal, %	20	24	20	14	<0.001	20	18	0.01
Both, %	15	18	15	11	<0.001	16	13	0.001
Cardiac rhythm monitoring								
In-hospital telemetry, %	31	28	31	35	<0.001	31	33	0.1
If yes, duration, %								
<24 hr	7	8	8	5		8	7	
24–<48 hr	36	33	39	34		38	34	
≥48 hr	54	56	50	59		52	57	
Uncertain/unknown	3	3	3	2		3	2	
Ambulatory ECG (Holter), %	79	81	79	76	0.003	79	78	0.3
Duration, hours, median (IQR)	24 (1)	24 (1)	24 (1)	24 (1)		24 (1)	24 (1)	
Other prolonged (>24 hr), %	9	9	9	9	0.9	9	9	0.6
Duration, days, median (IQR)	16 (23)	22 (23)	19 (23)	14 (26)		14 (23)	21 (23)	
Arterial imaging								
CT angiogram, %	37	40	38	33	<0.001	37	38	0.3
MR angiogram, %	34	33	33	35	0.5	35	32	0.02
CT and/or MR angiogram, %	64	65	65	62	0.05	65	64	0.5
Sonography, %	64	64	63	65	0.2	64	63	0.2

*Statistical significance for comparison across age categories.
#Statistical significance for comparison between male and females.
CT: computed tomography; MR: magnetic resonance; IQR: interquartile range; hr: hour; ECG: electrocardiography.

Subclinical AF is the leading occult mechanism for ESUS. Multiple studies show that prolonged heart-rhythm monitoring establishes a new diagnosis of AF in 10% to 20% of patients with recent stroke.[4,9] The yield increases with the duration of monitoring and approaches 30% after three years of continuous monitoring.[2,10] In our study, the difference in the other types of cardiac rhythm monitoring was also evident: in Latin America, in-hospital telemetry was done in only 7% of the patients, whereas ambulatory ECG Holter (with median duration of 24 h) was widely done in Latin America, Eastern Europe, and East Asia. These differences can be explained by the access to the different diagnostic methods in the different regions. In low- and middle-income countries, the prolonged monitoring via implanted cardiac monitor is infrequently used and underdiagnosed AF is likely to contribute significantly to cryptogenic stroke and ESUS.[11]

Diagnostic testing may affect the trial outcome as patients with more extensive investigation probably represent a slightly different ESUS cohort. The value of TEE in patients with ESUS was previously evaluated in a small cohort.[12] Abnormal TEE findings may decisively affect the selection of appropriate therapeutic strategy in one of seven patients with ESUS. Given that the diagnostic criteria of ESUS allows TTE,

Table 3. Qualitative summary of factors independently associated with undergoing diagnostic testing after multivariate analysis.[a]

	Age	Sex	Region
Echocardiography			
Transthoracic	↑ with older age	No	↑ in East Asia and USA and Canada
Transesophageal	↓ with older age	No	↑ in East Asia and Western Europe
Both	↓ with older age	No	↑ in East Asia and Western Europe
Cardiac rhythm monitoring			
In-hospital telemetry	No	No	↑ in Western Europe
Ambulatory ECG (Holter)	No	No	↑ in East Asia, Latin America, and Eastern Europe
Other prolonged (>24 hr)	No	No	↑↑ in USA and Canada; ↑ in Western Europe
Arterial imaging			
CT angiogram	↓ with age ≥75	No	↑↑ in USA and Canada; ↑ Western Europe
MR angiogram	No	No	↑↑ in East Asia; ↑ Western Europe
CT and/or MR angiogram	↓ with age ≥75	No	↑↑ in USA and Canada; ↑ East Asia and Western Europe
Sonography	No	No	↑↑ in Eastern Europe; ↑ East Asia and Western Europe

CT: computed tomography; MR: magnetic resonance; ECG: electrocardiography; hr: hour.
[a]Likelihood of testing is reflected by arrows. Three levels are possible depending on results of multivariable logistic regression. A test with only a single arrow for a region indicates an increased odds for the listed region(s) relative to the other regions not listed, i.e. high ↑ and reference (not listed). A test with both double and single arrows indicates three groups, i.e. highest odds ↑↑, higher ↑, and reference (not listed). See Supplemental Appendix for the specific numbers.

the TEE was only used in 20% of NAVIGATE-ESUS patients, and in Latin America and Eastern Europe was done in only 13% and 12%, respectively. Extensive evaluation including TEE and cardiac monitoring for longer periods may help to identify the etiology of the stroke in these patients. Using routine TTE, it is possible to identify only a small subset of patients with ESUS without known AF who might benefit from treatment with anticoagulants. A secondary analysis of NAVIGATE-ESUS[13] found that in patients with at least moderate left atrial enlargement, there was a significant reduction in ischemic stroke with rivaroxaban. These results suggest that left atrial volume would have been a better marker of left atrial size; however, this was not available for a large number of ESUS patients.

The results of NAVIGATE-ESUS and RESPECT-ESUS[14] suggest that ESUS is not a single entity that can be approached with a single antithrombotic treatment strategy. Recent studies indicate that some ESUS cases result from subclinical cardioembolism (atrial cardiomyopathy, unrecognized myocardial infarction, patent foramen ovale), while other cases result from nonstenosing large-artery atherosclerosis (aortic atherosclerosis or nonatherosclerotic vasculopathies).[14]

In this sense, some extension of diagnostic studies could be useful, especially arterial imaging. Recently, Singh et al. reported that among patients with ESUS, one in five had carotid intraplaque hemorrhage identified by MRI of the vessel wall ipsilateral to the ischemic stroke. This observation raises the possibility that mildly stenotic atherosclerotic plaque may be the stroke etiology in many ESUS patients.[15] Our results show 64% of the patients had CT and/or MR angiogram; however, in Eastern Europe, this diagnostic testing was done in only 33% of the cases, versus 89% and 77% in North America and East Asia, respectively.

Although the disparities in the stroke quality of care between women and men have been well documented,[16] we did not find an influence of the patient's sex on diagnostic testing independent of region. This result is encouraging but should be taken with caution, since it is a clinical trial that requires a minimum protocol of diagnostic tests as an inclusion criteria and may not reflect the daily practice of the countries participating in the trial.

We found preference for some diagnostic tests such a TEE and CT/MR angiogram in younger patients. Based on age, it is likely that younger patients with ESUS may have different causes (e.g. patent foramen ovale),

which is better characterized with TEE. There are important differences between younger versus older patients with ESUS regarding risk factors and potential causes. Alternatively, younger stroke patients may more often undergo a more complete evaluation. The ongoing young ESUS registry could provide the global frequency and characteristics of younger patients with ESUS.[17]

Our results reflect the existing variation in global practice in diagnostic testing at major stroke research centers. In many centers, many stroke patients were not considered to be ESUS due to lack of diagnostic testing to meet ESUS criteria. The lack of diagnostic studies and the variation in their use are likely to be different in daily practice, mainly in low- and middle-income countries, where prolonged monitoring of heart rate and echocardiography is not routinely used for patients outside of clinical trials. In a Mexican registry of 1246 patients with cerebral infarction, etiology was unknown in 41% due to the lack of appropriate studies.[18]

Our study has potential limitations. This clinical trial cohort represents patients who are willing and able to participate in a clinical trial, which may limit the generalizability of our findings. A single site in each country also may not accurately reflect the practice in the country or the region. However, the study sites represented many global regions. In addition, NAVIGATE-ESUS required a minimum of diagnostic studies for its inclusion.

Characterizing patients with ESUS and developing therapies for specific mechanisms, can only be achieved with adequate and complete diagnostic testing. Our results highlight the variability of diagnostic testing. Some studies[19] suggest a benefit of antiplatelet therapy in a subgroup of patients with ESUS, perhaps due to different predominant mechanism of stroke.

Although the ESUS definition alone cannot serve as a therapeutic indication for anticoagulation, it may provide a useful basis for further diagnostic advances that in turn could allow for more effective and personalized treatment for stroke prevention. Future trials will need to investigate various antiplatelet drugs, including the combination therapies of antiplatelet agents or antiplatelet therapies combined with low dose of anticoagulants. A recent secondary analysis of the Cardiovascular OutComes for People using Anticoagulation StrategieS (COMPASS) trial found that among patients with systemic atherosclerosis, low-dose rivaroxaban-plus-aspirin was associated with significant reductions in ESUS.[20]

In view of the fact that two large, recent randomized trials failed to demonstrate the superiority of anticoagulants over aspirin in patients with ESUS, our findings support a strategy of extending the diagnosis evaluation of patients with ESUS, in an attempt to more precisely categorize the cause of the stroke and to individualize secondary prevention.

The identification of ESUS patients at high risk for stroke recurrence is a challenge. In a recently proposed tool, age, leukoaraiosis, and multiterritorial infarct were identified as independent predictors. The tool allows classifying patients with low risk (2.1 per 100 patients-years), intermediate risk (3.74 per patient-years), and high risk (8.23 per 100 patients-years).[21]

Conclusion

We found that relative frequencies of all diagnostic tests varied by region, and less frequently age, but not by sex. Our results reflect the existing variations in global practice of diagnostic testing in ESUS patients that likely extend to clinical practice as well. Our findings support that diagnostic evaluation should be expanded in patients with ESUS, trying to more accurately categorize the cause of stroke in order to individualize secondary prevention.

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