Age- and sex-specific analysis of patients with embolic stroke of undetermined source

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ABSTRACT

Objective: To investigate whether the correlation of age and sex with the risk of recurrence and death seen in patients with previous ischemic stroke is also evident in patients with embolic stroke of undetermined source (ESUS).

Methods: We pooled datasets of 11 stroke registries from Europe and America. ESUS was defined according to the Cryptogenic Stroke/ESUS International Working Group. We performed Cox regression and Kaplan-Meier product limit analyses to investigate whether age (<60, 60–80, >80 years) and sex were independently associated with the risk for ischemic stroke/TIA recurrence or death.

Results: Ischemic stroke/TIA recurrences and deaths per 100 patient-years were 2.46 and 1.01 in patients <60 years old, 5.76 and 5.23 in patients 60 to 80 years old, 7.88 and 11.58 in those >80 years old, 3.53 and 3.48 in women, and 4.49 and 3.98 in men, respectively. Female sex was not associated with increased risk for recurrent ischemic stroke/TIA (hazard ratio [HR] 1.15, 95% confidence interval [CI] 0.84–1.58) or death (HR 1.35, 95% CI 0.97–1.86). Compared with the group <60 years old, the 60- to 80- and >80-year groups had higher 10-year cumulative probability of recurrent ischemic stroke/TIA (14.0%, 47.9%, and 37.0%, respectively, $p < 0.001$) and death (6.4%, 40.6%, and 100%, respectively, $p < 0.001$) and higher risk for recurrent ischemic stroke/TIA (HR 1.90, 95% CI 1.21–2.98 and HR 2.71, 95% CI 1.57–4.70, respectively) and death (HR 4.43, 95% CI 2.32–8.44 and HR 8.01, 95% CI 3.98–16.10, respectively).

Conclusions: Age, but not sex, is a strong predictor of stroke recurrence and death in ESUS. The risk is ≈3- and 8-fold higher in patients >80 years compared with those <60 years of age, respectively. The age distribution in the ongoing ESUS trials may potentially influence their power to detect a significant treatment association. *Neurology*® 2017;89:532–539

GLOSSARY

ATTICUS = Apixaban for Treatment of Embolic Stroke of Undetermined Source; **CI** = confidence interval; **ESUS** = embolic stroke of undetermined source; **HR** = hazard ratio; **IQR** = interquartile range; **NAVIGATE ESUS** = Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (ESUS); **RE-SPECT ESUS** = Randomized Evaluation in Secondary Stroke Prevention Comparing the Thrombin Inhibitor Dabigatran Etexilate Versus Aspirin in Embolic Stroke of Undetermined Source; **STROBE** = Strengthening the Reporting of Observational Studies in Epidemiology; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment.

Age and sex are 2 nonmodifiable factors that have been shown to modify the risk for ischemic stroke. Age is the single most important risk factor for stroke, and studies have shown that the stroke rate increases 2-fold for every decade after the age of 55.[1–3] Female sex is also associated with a moderate increase in stroke risk. The Framingham study found that the lifetime stroke

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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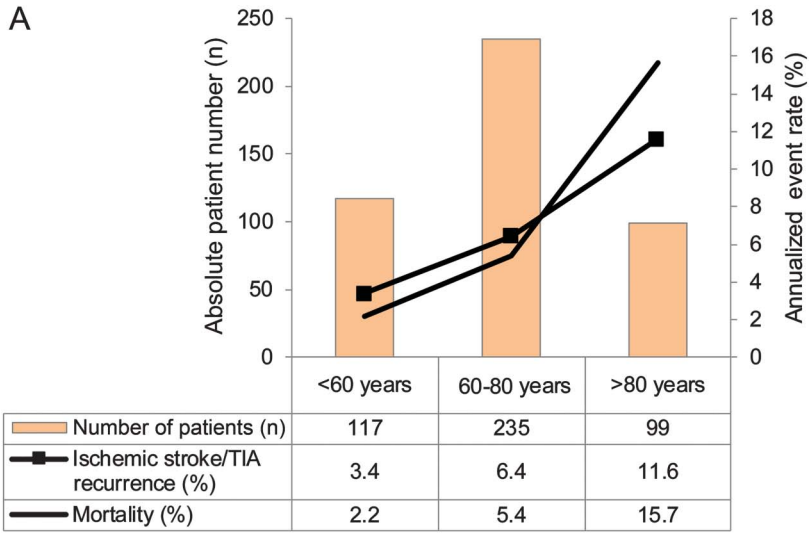
risk among middle-aged women is higher than in middle-aged men.[4] Similar evidence exists for patients with atrial fibrillation.[5]

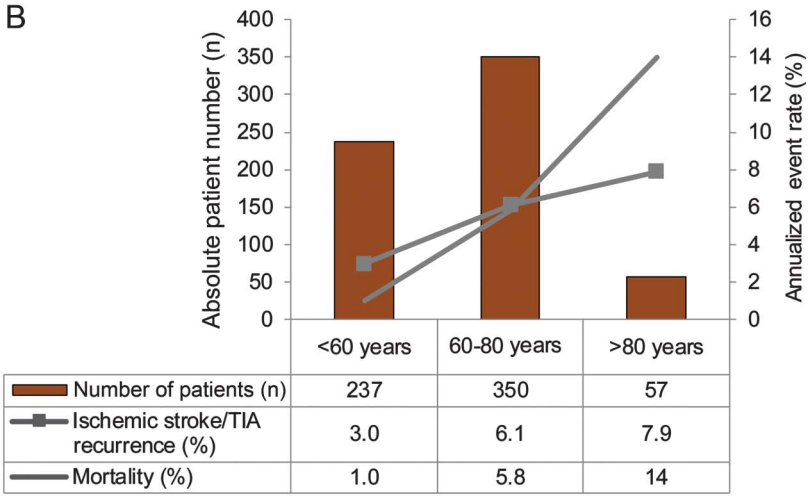
The term embolic stroke of undetermined source (ESUS) was introduced recently by the Cryptogenic Stroke/ESUS International Working Group to include ischemic stroke patients for whom the source of embolism remains unidentified despite recommended investigation.[6] Currently, 3 ongoing randomized trials are investigating the optimal antithrombotic strategy in these patients.[7–9] The eligibility criteria differ between these trials, and different age thresholds have been implemented. If the stepwise association between age and stroke risk is true also for ESUS, this could have implications for the power of the trials to identify a significant treatment effect. For example, a trial population with a preponderance of younger patients may show a reduced rate of stroke recurrences and thus a diluted potential treatment effect.

In this context, we aimed to assess whether age and sex are associated with the risk for ischemic stroke/TIA risk and death in patients with ESUS.

Figure 1 Age- and sex-specific frequency distribution and annualized event rates for ischemic stroke/TIA recurrence and mortality



	<60 years	60-80 years	>80 years
Number of patients (n)	117	235	99
Ischemic stroke/TIA recurrence (%)	3.4	6.4	11.6
Mortality (%)	2.2	5.4	15.7



	<60 years	60-80 years	>80 years
Number of patients (n)	237	350	57
Ischemic stroke/TIA recurrence (%)	3.0	6.1	7.9
Mortality (%)	1.0	5.8	14

(A) Female patients; (B) male patients.

METHODS The study population was derived from 11 stroke registries from Buenos Aires (Argentina), San José (Costa Rica), Helsinki (Finland), Athens and Larissa (Greece), Perugia and Savona (Italy), Mexico City (Mexico), and Barcelona and Madrid (Spain). Details about the methodology followed for the collection and pooling of the data have been previously published.[10] In particular, prospectively collected data of consecutive patients from all centers were pooled with the use of a standardized form with prespecified parameters and merged at the coordinating center (Larissa, Greece) where the pooled analysis was performed. The use of these registry data for research has been approved by the local ethics committees when necessary.

ESUS was defined according to the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group as a visualized nonlacunar brain infarct in the absence of the following: extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia; major-risk cardioembolic source, and any other specific cause of stroke (e.g., arteritis, dissection, migraine/vasospasm, drug misuse).[6] Lacunar strokes were defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[11]

Stroke severity was assessed with the NIH Stroke Scale score on admission.[12] The outcomes of interest were ischemic stroke/TIA recurrence and all-cause death. Assessment of outcomes during follow-up was performed by onsite patient visits or by contact with the patient, patient's family, or primary physician. The report of the analysis follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines.

Statistical analysis. We defined 3 age groups: <60, 60 to 80, and >80 years; the selection of these cutoffs was arbitrary and prespecified. We also performed a secondary analysis of age as a continuous covariate. Univariate and multivariate Cox regression analyses were performed to investigate whether sex and age (using the <60-year group as the comparator) were independently associated with the risk for ischemic stroke/TIA recurrence or all-cause death. Besides age and sex, other covariates included in the analyses were prestroke disability, stroke severity (evaluated by the NIH Stroke Scale score), arterial hypertension, diabetes mellitus, smoking, dyslipidemia, coronary artery disease, peripheral artery disease, heart failure, history of ischemic stroke/TIA/thromboembolism, acute treatment (no specific recanalization treatment, intravenous thrombolysis, pure acute endovascular, bridging, other acute recanalization treatment), and antithrombotic treatment at discharge (no treatment, antiplatelet, oral anticoagulant, combination of antiplatelet with anticoagulant). The covariates that were significant in the univariate analyses were included in the multivariate Cox model. For the univariate analysis, the level of significance was set at 10% to reduce the risk of a type II error. For the multivariate analyses, the level of significance was set at 5%. Associations are presented as hazard ratios (HRs) with their corresponding 95% confidence intervals (95% CIs).

The Kaplan-Meier product limit method was used to estimate the 10-year cumulative probability of ischemic stroke/TIA recurrence and all-cause death in the aforementioned age and sex groups. For patients lost during follow-up, survival data were censored at the last time known to be alive. Patients who experienced >1 recurrences during the follow-up period were censored at the time of the first event. Differences in Kaplan-Meier curves were evaluated with the log-rank test, and the level of significance was set at 5%. Differences in continuous variables were identified with the Mann-Whitney *U* test. The Pearson χ^2 test was used to compare binary variables between sexes and to assess the relation between death and stroke recurrence.

Statistical analyses were performed with the Statistical Package for Social Science (SPSS Inc, version 20.0 for Windows, Chicago, IL).

RESULTS We analyzed 1,095 patients with ESUS with a median age of 68 years (interquartile range [IQR] 54–77 years). There were 354 patients (32.3%) <60 years of age, 585 (53.4%) between 60 and 80 years of age, and 156 (14.2%) >80 years of age; 451 (41.2%) were women and 644 (58.8%) men. The age- and sex-specific distribution of patients with ESUS is summarized in figure 1. The median follow-up was 31 (interquartile range, 14–59) months, corresponding to 3285 patient-years.

The age- and sex-specific baseline characteristics of the patients are summarized in table 1 and figure 1. Women were older than men (72 vs 65 years, $p < 0.001$), whereas men were more frequently smokers (18.4% vs 47.1%, $p < 0.001$) and more frequently had coronary artery disease (10.7% vs 18.5%, $p < 0.001$). The age- and sex-specific comorbidities of patients are summarized in figure 2. All-cause mortality was related to stroke recurrence (Pearson χ^2 <0.001, likelihood ratio <0.001).

Age-specific analysis of event rates during follow-up. In patients with ESUS <60 years of age, the median follow-up was 33 (IQR 14–60) months, corresponding to 1180 patient-years. There were 29 ischemic stroke/TIA recurrences (8.2%) and 12 deaths (3.4%), which correspond to 2.46 ischemic stroke/TIA recurrences and 1.02 deaths per 100 patient-years.

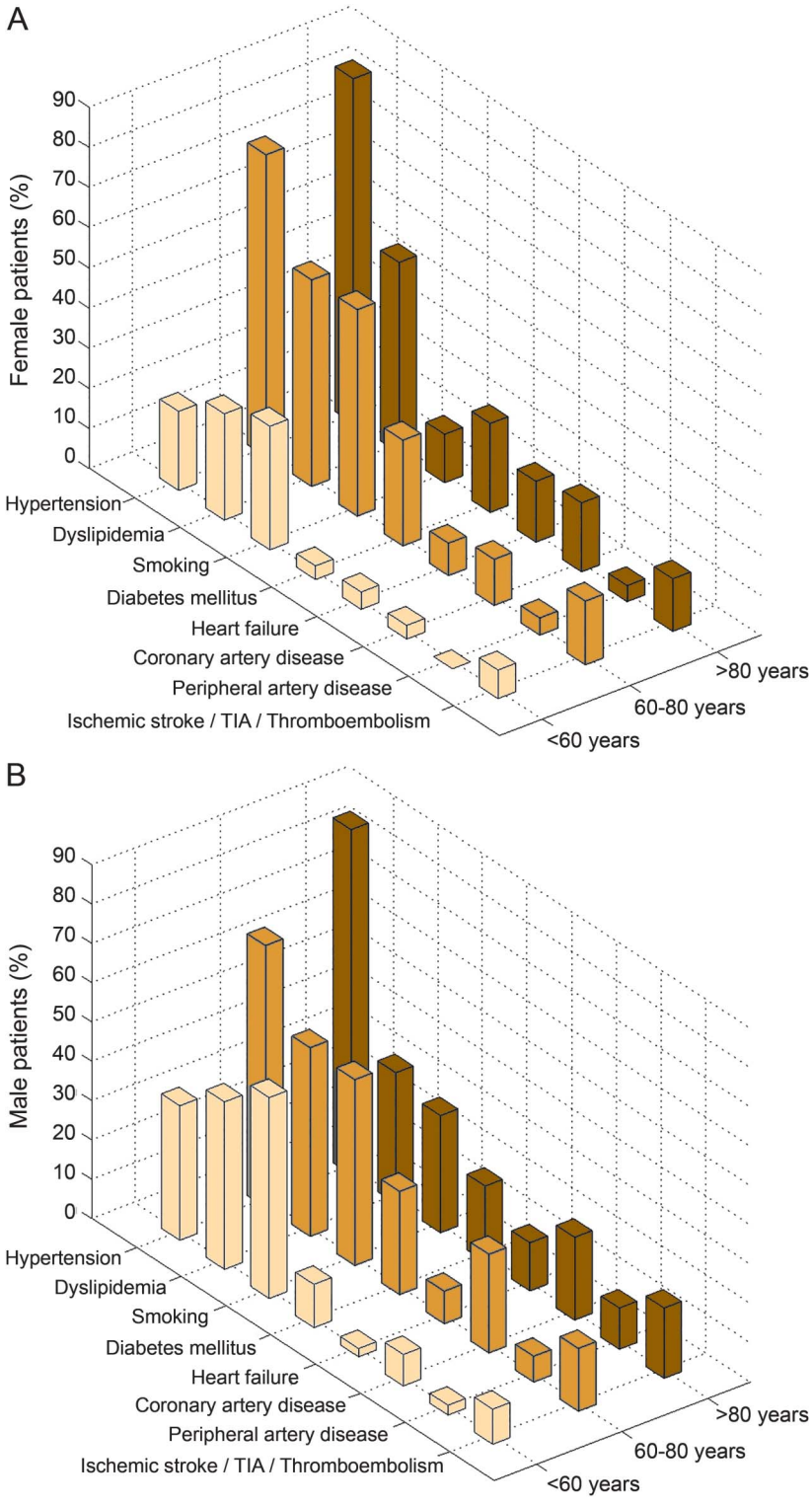
In patients with ESUS between 60 and 80 years of age, the median follow-up was 32 (IQR 14–57) months, corresponding to 1702 patient-years. There were 98 ischemic stroke/TIA recurrences (16.7%) and 89 deaths (15.2%), which correspond to 5.76

Table 1 Baseline characteristics

	Women				Men			
	All (n = 451)	<60 y (n = 117)	60–80 y (n = 235)	>80 y (n = 99)	All (n = 644)	<60 y (n = 237)	60–80 y (n = 350)	>80 y (n = 57)
Demographics								
Age, y	72 (58–80)	46 (37–52)	72 (67–76)	84 (82–86)	65 (53–75)	47 (37.5–55)	70 (65–75)	84 (82–85)
Prestroke mRS ≤2, n (%)	421 (94.4)	116 (100)	221 (95.3)	84 (85.7)	615 (96.1)	229 (97.4)	337 (96.8)	49 (86.0)
NIHSS score at admission	6 (2–12)	6 (2–12)	6 (2–13)	6 (3–12)	4 (2–9)	5 (2–9)	4 (2–8)	6 (3–14)
Follow-up, mo	26 (14–55)	24 (13–60)	31 (14–56)	24 (12–43)	33.5 (14–60)	35 (15–60)	33 (14–58)	24 (12.5–48.5)
Acute treatment, n (%)								
Antiplatelet only	368 (81.6)	102 (87.2)	185 (84.1)	87 (87.9)	547 (84.9)	198 (84.6)	299 (85.4)	50 (87.7)
Intravenous thrombolysis	75 (16.6)	12 (10.3)	51 (21.7)	12 (12.1)	90 (14.0)	35 (14.8)	48 (13.7)	7 (12.3)
Acute endovascular (pure)	3 (0.7)	1 (0.9)	2 (0.9)	0 (0.0)	3 (0.5)	2 (0.8)	1 (0.3)	0 (0.0)
Bridging	4 (0.9)	2 (1.7)	2 (0.9)	0 (0.0)	4 (0.6)	2 (0.8)	2 (0.6)	0 (0.0)
Treatment on discharge, n (%)								
No antithrombotic	4 (0.9)	0 (0.0)	3 (1.3)	1 (1.0)	7 (1.1)	1 (0.4)	4 (1.2)	2 (3.6)
Antiplatelet	387 (88.2)	94 (84.7)	202 (87.4)	91 (93.8)	550 (86.9)	198 (84.6)	299 (87.2)	53 (94.6)
Oral anticoagulant	45 (10.3)	16 (14.4)	24 (10.4)	5 (5.2)	58 (9.2)	30 (12.8)	28 (8.2)	0 (0.0)
Antiplatelet and oral anticoagulant	3 (0.7)	1 (0.9)	2 (0.9)	0 (0.0)	18 (2.8)	5 (2.1)	12 (3.5)	1 (1.8)
Outcome, n (%)								
Ischemic stroke/TIA recurrence	70 (15.5)	8 (6.8)	39 (16.6)	23 (23.2)	89 (13.8)	21 (8.9)	59 (16.9)	9 (15.8)
All-cause death	69 (15.3)	5 (4.3)	33 (14.0)	31 (31.3)	79 (12.3)	7 (3.0)	56 (16.0)	16 (28.1)

Abbreviations: ESUS = embolic stroke of undetermined source; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.
Continuous variables are presented as median ± interquartile range. Nominal variables are presented as absolute number and percent (percent refers to recorded values only; missing values have been excluded).

Figure 2 Age- and sex-specific comorbidities in patients with ESUS



(A) Female patients; (B) male patients. ESUS = embolic stroke of undetermined source.

ischemic stroke/TIA recurrences and 5.23 deaths per 100 patient-years.

In patients with ESUS >80 years of age, the median follow-up was 24 (IQR 12–47) months, corresponding to 406 patient-years. There were 32 ischemic stroke/TIA recurrences (20.5%) and 47 deaths (30.1%), which correspond to 7.88 ischemic stroke/TIA recurrences and 11.58 deaths per 100 patient-years.

The annualized event rates for ischemic stroke/TIA recurrence and mortality per age group of patients with ESUS are presented in figure 1.

Sex-specific analysis of event rates during follow-up. In female patients with ESUS, the median follow-up was 26 (IQR 14–55) months, corresponding to 1305 patient-years. There were 70 ischemic stroke/TIA recurrences (15.5%) and 69 deaths (15.3%), which correspond to 3.53 ischemic stroke/TIA recurrences and 3.48 deaths per 100 patient-years.

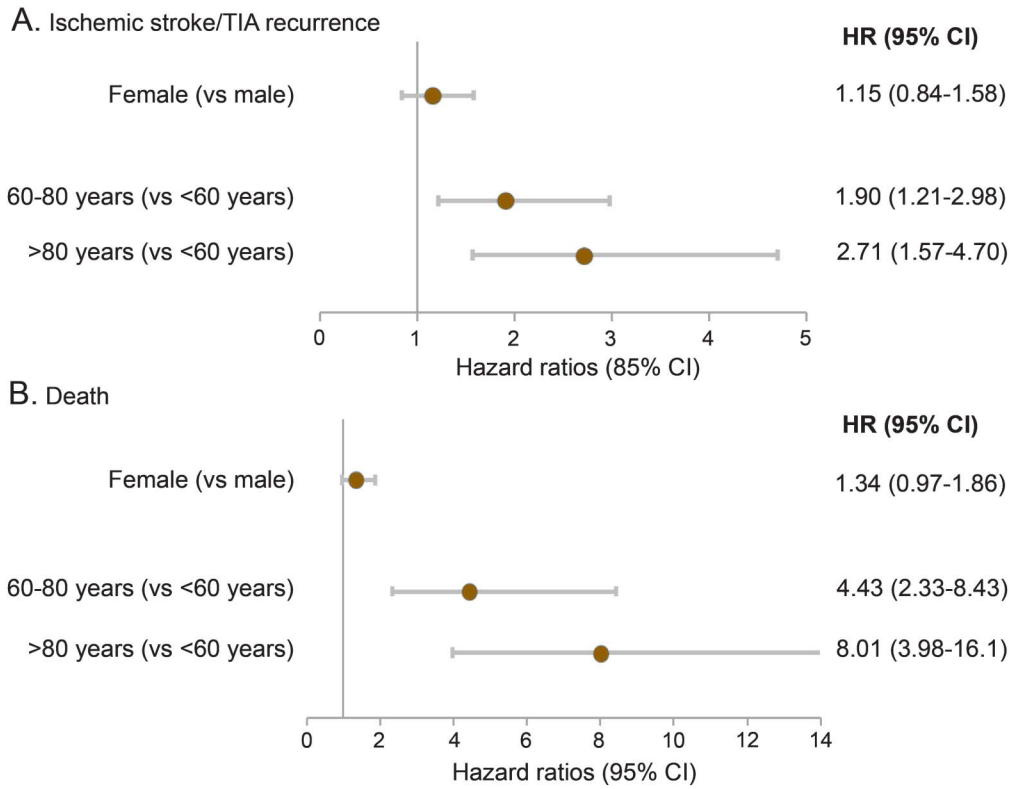
In male patients with ESUS, the median follow-up was 33.5 (IQR 14–60) months, corresponding to 1984 patient-years. There were 89 ischemic stroke/TIA recurrences (13.8%) and 79 deaths (12.3%), which correspond to 4.49 ischemic stroke/TIA recurrences and 3.98 deaths per 100 patient-years.

The annualized event rates for ischemic stroke/TIA recurrence and mortality in both sexes are presented in figure 1.

Age and risk for recurrent ischemic stroke/TIA or all-cause death. In the multivariate Cox regression analysis, age was associated with the risk of recurrent ischemic stroke/TIA. Compared with patients <60 years of age, patients between 60 and 80 years of age had a higher risk (HR 1.90, 95% CI 1.21–2.98, $p = 0.005$) (figure 3). The association was even stronger for patients >80 years of age (HR 2.71 compared to patients <60 years of age, 95% CI 1.57–4.70, $p < 0.001$) (figure 3). Similarly, the multivariate Cox regression analysis for mortality showed increased risk of all-cause death for patients 60 to 80 years (HR 4.43, 95% CI 2.32–8.44, $p < 0.001$) and patients >80 years (HR 8.01, 95% CI 3.98–16.10, $p < 0.001$) compared to those <60 years of age (figure 3). In a secondary analysis including age as a continuous covariate, age was a significant predictor of stroke recurrence and death (table e-1 at Neurology.org).

In Kaplan-Meier analysis, compared with patients with ESUS <60 years of age, the 10-year cumulative probability of ischemic stroke/TIA recurrence was higher in patients between 60 and 80 and in those >80 years of age (14.0%, 47.9%, and 37.0% respectively, log-rank test $p < 0.001$, $\chi^2 = 22.792$). Similarly, compared with patients with ESUS <60 years of age, the 10-year cumulative probability of death was higher in patients with ESUS between 60 and 80 and those >80 years of age (6.4%, 40.6%, and 100%, respectively, log-rank test $p < 0.001$, $\chi^2 = 80.800$). The age-specific Kaplan-Meier analyses in the female and male subgroups are presented in figure 4. In both women and men, the 10-year cumulative probability of ischemic stroke/TIA recurrence and death was higher in the older groups.

Figure 3 Cox regression analyses of the association between age, sex, and ischemic stroke/TIA recurrence



(A) Adjusted for age, coronary artery disease, arterial hypertension, dyslipidemia and previous stroke/TIA/thromboembolism, and mortality. (B) Adjusted for age, sex, NIHSS score, diabetes mellitus, arterial hypertension, smoking heart failure, peripheral artery disease, acute treatment, and coronary artery disease. Associations are presented as HRs and 95% CIs. The full models are presented in table e-2. CI = confidence interval; HR = hazard ratio; NIHSS = NIH Stroke Scale.

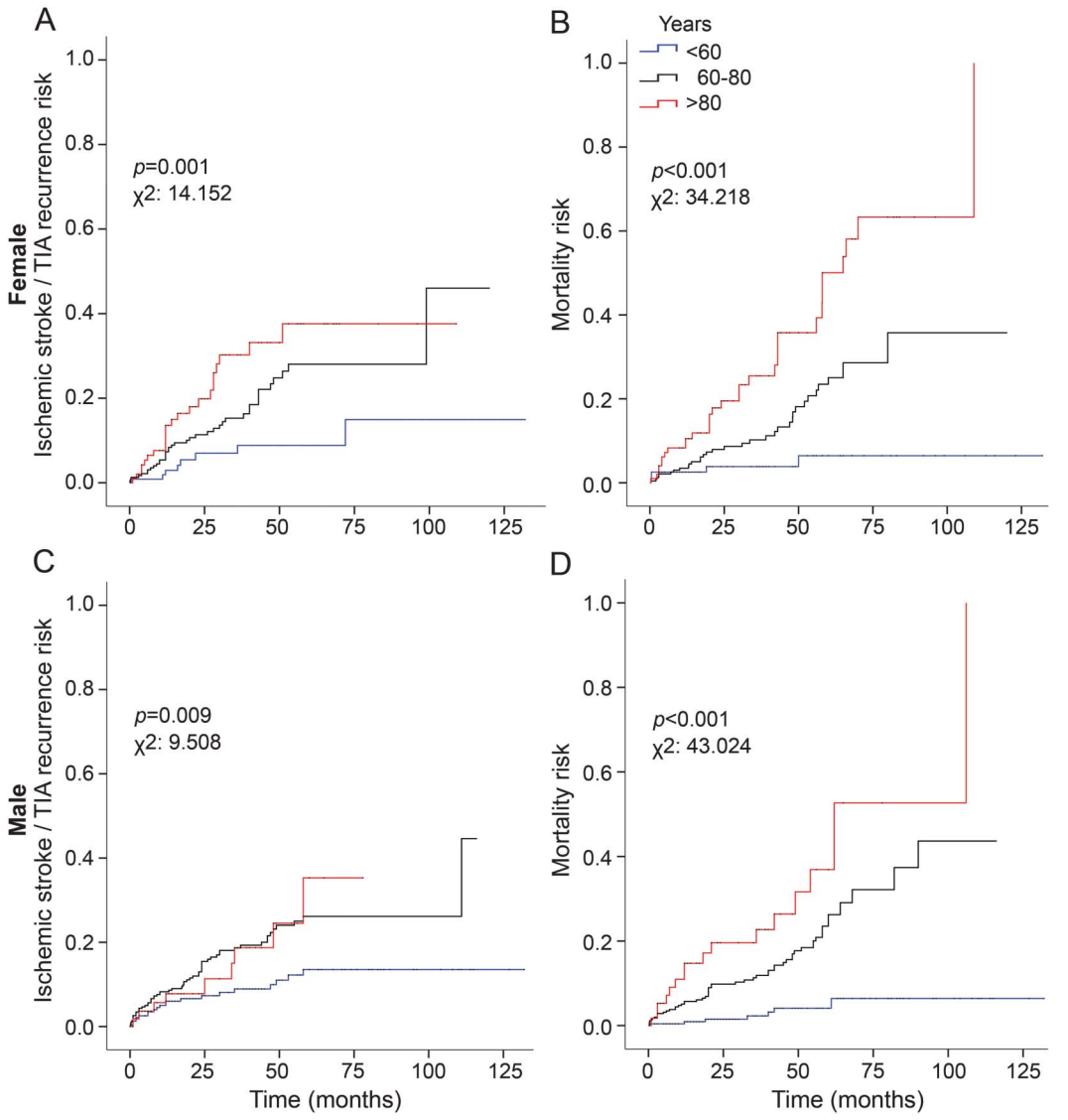
Sex and risk for recurrent ischemic stroke/TIA or all-cause death. In the univariate Cox regression analysis, compared to male sex, female sex was not associated with the risk for recurrent ischemic stroke/TIA (HR 1.15, 95% CI 0.84–1.58, $p = 0.370$) or death (HR 1.35, 95% CI 0.97–1.86, $p = 0.072$) (figure 3).

In Kaplan-Meier analysis, the 10-year cumulative probability of ischemic stroke/TIA recurrence was similar between female and male patients with ESUS (32.4% vs 27.9%, respectively, log-rank test $p = 0.369$, $\chi^2 = 0.807$) (figure 4). There was a strong trend of a higher cumulative probability of death in female vs male patients with ESUS (41.6% vs 31.4% respectively, log-rank test $p = 0.070$, $\chi^2 = 3.283$).

DISCUSSION The present study shows that age is a significant predictor of long-term stroke recurrence and all-cause death in patients with ESUS, with the risk of stroke recurrence and death being ≈3- and 8-fold higher in patients >80 years compared to those <60 years of age, respectively. Sex was not associated with the risk of stroke recurrence; however, we identified a strong trend of higher mortality in women.

The association of age with stroke recurrence has implications for stroke research and may inform ongoing and future studies of secondary prevention in patients with ESUS. Currently, there are 3 ongoing trials of oral anticoagulants vs aspirin in patients with ESUS: the Randomized Evaluation in Secondary Stroke Prevention Comparing the Thrombin Inhibitor Dabigatran Etexilate Versus Aspirin in Embolic Stroke of Undetermined Source (RE-SPECT ESUS) trial, the Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (ESUS) (NAVIGATE ESUS), and the Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS) that compare dabigatran etexilate, rivaroxaban, and apixaban, respectively, to aspirin.[7–9] Age distribution of the recruited patients may potentially influence the results of the trials. If, for example, the proportion of young patients is relatively high, there is a possibility that the number of outcome events might be lower than expected, which may result in the dilution of a possible treatment effect. In this context, the inclusion of older patients or patients with higher $CHADS_2$ and CHA_2DS_2-VASc scores (given that these patients are associated with a higher risk for ischemic stroke/TIA recurrence[10]) may allow these trials to provide

Figure 4 Age- and sex-specific cumulative probability of recurrent ischemic stroke/TIA and mortality in patients with ESUS



(A) Female ischemic stroke/TIA recurrence, (B) female mortality, (C) male ischemic stroke/TIA recurrence, and (D) male mortality. ESUS = embolic stroke of undetermined source.

more informative results because this would be associated with a higher rate of endpoints. Toward this end, the NAVIGATE ESUS protocol was amended in late 2015 so that patients <50 years of age are no longer eligible and patients 50 to 59 years of age are eligible only if one or more additional stroke risk factors (hypertension, tobacco smoking at the time of the qualifying stroke, ischemic stroke or TIA before the qualifying stroke, heart failure, or diabetes mellitus) are present.[9] In the same context, in the RESPECT ESUS trial, eligible patients are those ≥60 years of age who have experienced an ESUS within the previous 3 months or within the previous 6 months if they also have at least one stroke risk factor, whereas patients 18 to 59 years of age with at least one stroke risk factor are also eligible if their qualifying stroke was within the previous 3 months.[8] Finally, in the ATTICUS trial, the lower age limit for eligibility is 18 years, but patients must have at least one of the following nonmajor but suggestive risk factors for cardiac embolism: left atrial diameter >45 mm, spontaneous echo contrast in the left atrial appendage, left atrial appendage flow velocity ≤0.2 m/s, atrial high-rate episodes, CHA_2DS_2-VASc score ≥4, or persistent foramen ovale.[7] Finally, the results of our study may also have implications for clinical practice recommendations on secondary stroke prevention in patients with ESUS, especially if the ongoing trials show an interaction between age and treatment effect.

Previous studies and the present one have reported that women are older than men at the time of stroke. This finding may explain the strong trend of higher

mortality in women found in the present ESUS population, which was identified also by a meta-analysis of >30,000 stroke patients that reported that the 1-month case fatality was higher in women than men (24.7% vs 9.7%, respectively).[13] In addition, we found that the index strokes were more severe in women, which again confirms the results of previous studies.[13–16] We did not manage to identify any association between sex and the risk for ischemic stroke/TIA recurrence among patients with ESUS, unlike patients with atrial fibrillation, among whom women have a higher risk for stroke.[17]

The main strengths of this analysis are the large size of the study population involving >1,000 consecutive patients with ESUS from 11 stroke registries from 7 countries in Europe and America, the long follow-up of ≈3 years, and the standardized definition of ESUS based on the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group.[6] On the other hand, it is characterized by the inherent limitations of any retrospective multicenter analysis of prospectively collected multicenter data such as collection and registration bias and unregistered confounding factors such as baseline infarct volume or leukoaraiosis, which were shown to be associated with outcome in stroke patients.[18]

Age, but not sex, is a significant predictor of long-term stroke recurrence and all-cause death in patients with ESUS, with the risk of ischemic stroke/TIA recurrence and all-cause death being ≈3- and 8-fold higher, respectively, in patients >80 compared to those <60 years of age. The age distribution of the recruited patients in the ongoing secondary prevention trials in patients with ESUS may potentially have an effect on the power of the trials to detect a significant treatment effect.

AUTHOR CONTRIBUTIONS

George Ntaios: study concept, study design, data acquisition, statistical analysis and interpretation, preparation of manuscript, study supervision. Gregory Y.H. Lip: study concept, critical revision of the manuscript. Konstantinos Vemmos: study concept, study design, data acquisition, critical revision of manuscript. Fotios Gioulekas: statistical analysis, critical revision of the manuscript. Vasileios Papavasileiou: study concept, study design, statistical analysis and interpretation, critical revision of the manuscript, study supervision. All other authors: data acquisition, critical revision of the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

G. Ntaios: member of the Steering Committee of the NAVIGATE ESUS trial; speaker fees from Sanofi, Boehringer Ingelheim, Galenica, Elpen, BMS/Pfizer, and Bayer; advisory board for Amgen, Boehringer Ingelheim, and Galenica. G. Lip: consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo; speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. K. Vemmos and E. Koroboki report no disclosures relevant to the manuscript. E. Manios: participation in the NAVIGATE ESUS trial. A. Vemmou reports no disclosures relevant to the manuscript. A. Rodríguez-Campello, E. Cuadrado-Godia, and J. Roquer: participation in the NAVIGATE ESUS and RE-SPECT ESUS trials. V. Arnao reports no disclosures relevant to the manuscript. V. Caso: speaker bureau: BI, BMS, and Pfizer; advisory board: BI; member of Safety Board in RE-SPECT ESUS; investigator in NAVIGATE ESUS. M. Paciaroni: personal fees from Bayer, Pfizer, Sanofi Aventis, Bristol Meyer Squibb, and Boehringer Ingelheim. E. Diez-Tejedor and B. Fuentes: participation in the NAVIGATE ESUS and RE-SPECT ESUS trials; other from Bayer and Boehringer Ingelheim. J. Pérez Lucas reports no disclosures relevant to the manuscript. A. Arauz: member of the steering committee of NAVIGATE ESUS trial; speaker for Pfizer and Boehringer Ingelheim. S. Ameriso: member of the Steering Committee and site principal investigator of the NAVIGATE ESUS trial; other from Bayer, Boehringer Ingelheim, and Pfizer. L. \Pertierra and M. Gómez-Schneider: participation in the NAVIGATE ESUS trial. M. Hawkes, F. Bandini, and B. Chavarria Cano report no disclosures relevant to the manuscript. A. Iglesias Mohedano, A. García Pastor, and A. Gil-Núñez: participation in the NAVIGATE ESUS and RE-SPECT ESUS trials. J. Putaala: consultant for BMS-Pfizer, Boehringer Ingelheim, Medtronic, and St. Jude Medical; speaker for Orion, Bayer, BMS-Pfizer, Boehringer Ingelheim, and St. Jude Medical; research collaboration with Nokia Technologies, Mega Electronics, Bayer, and Vital Signum. T. Tatlisumak: grants from Helsinki University Central Hospital, University of Gothenburg, and Sahlgrenska University Hospital during the conduct of the study; grants from Boehringer Ingelheim; personal fees from Bayer, Pfizer, and Lumosa Therapeutics; grants from H. Lundbeck A/S, Sanofi Aventis, BrainsGate, Bayer, and Pfizer; member of steering committee of the NAVIGATE ESUS trial. M. Barboza, G. Athanasakis, and F. Gioulekas report no disclosures relevant to the manuscript. K. Makaritsis and V. Papavasileiou: participation in the NAVIGATE ESUS trial. Go to Neurology.org for full disclosures.

Received October 9, 2016. Accepted in final form March 30, 2017.

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