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BRIEF COMMUNICATION

Predictors of Recurrent Stroke After Embolic Stroke of Undetermined Source in the RE-SPECT ESUS Trial

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BACKGROUND: We sought to determine recurrent stroke predictors among patients with embolic strokes of undetermined source (ESUS).

METHODS AND RESULTS: We applied Cox proportional hazards models to identify clinical features associated with recurrent stroke among participants enrolled in RE-SPECT ESUS (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source) trial, an international clinical trial evaluating dabigatran versus aspirin for patients with ESUS. During a median follow-up of 19 months, 384 of 5390 participants had recurrent stroke (annual rate, 4.5%). Multivariable models revealed that stroke or transient ischemic attack before the index event (hazard ratio [HR], 2.27 [95% CI, 1.83–2.82]), creatinine clearance <50 mL/min (HR, 1.69 [95% CI, 1.23–2.32]), male sex (HR, 1.60 [95% CI, 1.27–2.02]), and CHA_2DS_2-VASc ≥4 (HR, 1.55 [95% CI, 1.15–2.08] and HR, 1.66 [95% CI, 1.21–2.26] for scores of 4 and ≥5, respectively) versus CHA_2DS_2-VASc of 2 to 3, were independent predictors for recurrent stroke.

CONCLUSIONS: In RE-SPECT ESUS trial, expected risk factors previously linked to other common stroke causes were associated with stroke recurrence. These data help define high-risk groups for subsequent stroke that may be useful for clinicians and for researchers designing trials among patients with ESUS.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02239120.

Key Words: embolic stroke of undetermined source ■ risk factors ■ secondary prevention ■ stroke predictors

Embolic strokes of undetermined source (ESUS) represent a subset of cryptogenic strokes and are defined as nonlacunar infarcts without a definitive cardioembolic source, no significant arterial steno-occlusive disease, and with no other identified stroke cause. About 17% of first-ever brain infarctions meet criteria for ESUS.[1] ESUS generally manifest with milder symptoms, affect a relatively younger population, and have recurrence rates of 4% to 5% per year.[1]

Two recent randomized controlled trials failed to show oral anticoagulation is superior to antiplatelet monotherapy for secondary stroke prevention after ESUS.[2,3] Taking this into consideration, ESUS terminology is now considered to include a heterogeneous group of potential cerebral emboli sources, some of them unlikely to benefit from anticoagulation more than aspirin. Investigating predictors of stroke recurrence among patients with ESUS could potentially expand our

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understanding on the pathogenesis of ESUS and the differential prognosis among patients who meet ESUS criteria. In the current analysis, we evaluated recurrent stroke predictors among participants enrolled in RE-SPECT ESUS (Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source) trial.

METHODS

The data that support the findings of this study are available on reasonable request to the RE-SPECT ESUS trial steering committee.

Design of RE-SPECT ESUS trial has been described elsewhere.[2,4] In brief, this international randomized trial compared dabigatran, 150 mg twice daily (or 110 mg twice daily for patients aged ≥75 years or with creatinine clearance [CrCl] of 30–49 mL/min), with aspirin, 100 mg daily. Enrollment occurred during the period from December 2014 through January 2018. Eligible participants were those aged ≥60 years within 3 months of an ischemic stroke categorized as ESUS. Patients aged 18 to 59 years were eligible if they had at least one additional stroke risk factor. ESUS were defined as nonlacunar ischemic strokes detected by brain imaging, without atherosclerosis of ≥50% stenosis in arteries supplying the affected territory, no atrial fibrillation (AF) or intracardiac thrombus, and no other specific stroke cause.[4] The primary outcome of first recurrent stroke was determined by an adjudication committee and defined as sudden neurological dysfunction caused by brain, spinal cord, or retinal injury as a result of infarction or hemorrhage. The institutional review board at each participating site approved the trial, and all participants provided informed consent.

Variables collected at enrollment comprised demographics, pharmacotherapy, and history of hypertension, hyperlipidemia, diabetes, stroke or transient ischemic attack (TIA), myocardial infarction, coronary artery disease, heart failure, and cancer. Renal function (estimated creatinine clearance), left ventricular ejection fraction, and patent foramen ovale presence were recorded. The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack [TIA], vascular disease, age 65 to 74 years, sex category) was calculated on the basis of baseline information. Candidate recurrent stroke predictors were defined on the basis of medical judgement.

Baseline characteristics according to primary outcome occurrence were evaluated using descriptive statistics. Potential recurrent stroke predictors in the combined treatment groups were determined by Cox regression analysis and presented as hazard ratios (HRs) with 95% CIs after adjusting for covariates used for stratification (age and creatinine clearance) and for previous stroke or TIA. Multivariable Cox regression models were developed by selecting variables with $P<0.1$ in univariate analyses (model 1), backward selection based on all candidate predictors (model 2), and Akaike criterion (model 3). All 3 multivariable models have additionally been adjusted for treatment. For the multivariable models, the C-index and a bias-corrected and accelerated bootstrap CI based on 10 000 bootstrap samples are reported as a measure of discrimination. The partial χ^2 minus the predictor degrees of freedom were plotted as a measure of the relative strength of the statistical contribution to the model prediction. Patients with missing categories in any variable were not considered for multivariate regression analysis.

RESULTS

A total of 5390 patients (mean age, 64.2 years; 63.1% men) were enrolled at 564 sites (Europe, 59%; Asia, 22%; North America, 11%; and Latin America, 4%). Median time from the qualifying event to randomization was 44 days (interquartile range, 21–80 days), and the median follow-up time was 19 months (interquartile range, 13–27 months). Recurrent ischemic strokes occurred in 384 participants (97.7% ischemic strokes), and the most common subtype was undetermined cause (66.8%), followed by cardioembolism (9.4%), large-artery atherosclerosis (8.3%), and small-vessel occlusion (6.4%). The overall annual recurrence rate was 4.5%. Annual stroke recurrence was 4.1% in the dabigatran group and 4.8% in the aspirin group (HR, 0.85 [95% CI, 0.69–1.03]). Baseline differences between patients experiencing recurrent stroke and those without recurrent stroke in the combined treatment group are presented in Table S1.

Variables identified as recurrent stroke predictors in the Cox regression analysis are shown in Table 1. Multivariable models consistently showed that previous stroke or TIA (HR, 2.27 [95% CI, 1.83–2.82]), creatinine clearance <50 mL/min (HR, 1.69 [95% CI, 1.23–2.32]), male sex (HR, 1.60 [95% CI, 1.27–2.02]), and CHA_2DS_2-VASc score ≥4 (HR, 1.55 [95% CI, 1.15–2.08] and HR, 1.66 [95% CI, 1.21–2.26] for scores of 4 and ≥5, respectively) versus CHA_2DS_2-VASc score of 2 to 3, were independently associated with recurrent stroke (Table 2). Assessment of variable importance showed that previous stroke or TIA was by far the most important predictor for stroke recurrence (Figure).

DISCUSSION

This exploratory analysis revealed 4 independent predictors of recurrent stroke among ESUS: stroke or

Table 1. HRs for Recurrent Stroke Predictors, Controlling for Age, Renal Impairment, and Prior Stroke or TIA

Variable	HR (95% CI)
Stroke or TIA before index event*	2.35 (1.90–2.90)†
Renal impairment (CrCl <50 mL/min)*	2.07 (1.56–2.74)†
Previous myocardial infarction	1.56 (1.11–2.18)†
Aged ≥75 y*	1.52 (1.22–1.91)†
CHA_2DS_2-VASc score	
4 vs 2–3	1.50 (1.13–2.00)†
≥5 vs 2–3	1.45 (1.08–1.95)†
Male sex	1.43 (1.15–1.78)†
Diabetes	1.25 (1.00–1.57)†
Time from index stroke to randomization, d	
<8 vs ≥91	1.70 (1.03–2.82)†
8–30 vs ≥91	1.26 (0.93–1.69)
31–90 vs ≥91	1.04 (0.78–1.40)
Left ventricular ejection fraction ≤40%	1.85 (0.99–3.48)
Coronary artery disease	1.28 (0.96–1.71)
Proton-pump inhibitor at baseline	1.22 (0.99–1.50)
Hypertension	1.18 (0.92–1.50)
History of cancer	1.18 (0.84–1.65)
Hyperlipidemia	0.95 (0.77–1.16)
Aspirin at baseline	0.95 (0.75–1.20)
Treatment (dabigatran vs aspirin)	0.85 (0.69–1.03)
Heart failure	0.84 (0.49–1.44)
Cardiac monitoring >48 h	0.83 (0.64–1.08)
Patent foramen ovale	0.73 (0.52–1.04)
Body mass index, kg/m^2	
<25 vs ≥35	0.63 (0.43–0.94)†
25–29 vs ≥35	0.75 (0.51–1.10)
30–34 vs ≥35	0.80 (0.52–1.22)

Additional covariates in the Cox regression model are age (<75 or ≥75 years), renal impairment (CrCl <50 or ≥50 mL/min), and prior stroke or TIA (yes or no). Patients with missing information in any variable were excluded. CrCl indicates creatinine clearance; HR, hazard ratio; and TIA, transient ischemic attack.

*Model is calculated without additional covariates.

†$P<0.05$.

TIA before index event, higher CHA_2DS_2-VASc score, renal impairment, and male sex. Our findings confirm that history of stroke or TIA is the strongest predictor for recurrence among patients with ESUS.[5] Although stroke history is nonspecific for a particular cause, it is often a marker of underlying cerebrovascular risk from the same or other competing mechanisms of cerebral ischemia.

CHA_2DS_2-VASc score is a stratification tool developed to guide antithrombotic therapy for patients with AF and represents a combination of multiple vascular risk factors. In addition, CHA_2DS_2-VASc score has shown to predict stroke in individuals without AF.[6] In ESUS, higher CHA_2DS_2-VASc score is associated with AF detection during follow-up,[7] as well as with large aortic arch plaques.[8] Similar to our findings, a pooled analysis of 11 registries showed that recurrence risk after ESUS is reliably stratified by CHA_2DS_2-VASc score.[9] We also identified renal impairment as an independent predictor for stroke recurrence. A previous report focused on ESUS failed to demonstrate such association.[10] The link between renal impairment and vascular risk is likely multifactorial and probably related to increased oxidative stress, proinflammatory mediators, and renin-angiotensin-aldosterone system activation, resulting in an increased risk of atherosclerosis and incident AF.[11]

The ESUS concept was constructed to favor cardiac embolism, in particular covert paroxysmal AF, as the most likely pathogenic stroke mechanism. This concept has been challenged by the neutral results of 2 randomized clinical trials evaluating oral anticoagulation compared with aspirin therapy,[2,3] as well as by the lower rate of AF detection during follow-up in this population.[12] Therefore, multiple potential embolic sources, including nonstenotic plaques, nonatherosclerotic vasculopathies, and atrial cardiopathy, likely play a pathogenic role in an important fraction of patients with ESUS. On the other hand, a recent trial showed that a significant fraction of individuals with stroke secondary to small-vessel disease and large-artery atherosclerosis developed AF during follow-up, thus evidencing that overlap among stroke causes is common.[13] These observations suggest that revising stroke cause classification might be necessary to guide future secondary prevention trials.

In our study, we found that factors known to predict stroke recurrence in AF and atherosclerotic disease were also independent stroke recurrence predictors after ESUS. Alternatively, a recent analysis of patients with ESUS across 3 stroke registries showed that those with a lower vascular risk profile, as determined by an elevated Risk of Paradoxical Embolism score, were less likely to have incident AF during follow-up and showed a trend toward lower stroke recurrence rate.[14] Our results in conjunction with previous analyses may assist physicians not just for prognostication, but also for tailoring diagnostic workup. Patients with ESUS with high vascular risk profiles may benefit from advanced vascular imaging to investigate culprit nonstenotic plaques or prolonged cardiac monitoring to rule out covert AF, whereas those with lower vascular risk profiles may need a more sensitive investigation for detecting a patent foramen ovale, as well as the consideration of other, less frequent, stroke causes. Finally, our results are of potential value for researchers to guide inclusion criteria for future ESUS trials to select subgroups with a greater risk of outcome events.[15]

Study limitations relate to the exploratory nature of our analyses. For example, we may lack adequate power to assess cardioembolic-related features, such as left

Table 2. Multivariable Analyses of Clinical Predictors for Recurrent Stroke: Randomized Set

Variable	Model 1	Model 2	Model 3
Stroke or TIA before index event	2.25 (1.82–2.80)*	2.27 (1.83–2.81)*	2.27 (1.83–2.82)*
Renal impairment (CrCl <50 mL/min)	1.69 (1.23–2.33)*	1.67 (1.22–2.29)*	1.69 (1.23–2.32)*
Male sex	1.54 (1.21–1.96)*	1.59 (1.26–2.00)*	1.60 (1.27–2.02)*
CHA_2DS_2-VASc score			
4 vs 2–3	1.53 (1.13–2.07)*	1.59 (1.19–2.13)*	1.55 (1.15–2.08)*
≥5 vs 2–3	1.55 (1.08–2.22)*	1.70 (1.25–2.32)*	1.66 (1.21–2.26)*
Aged ≥75 y	1.11 (0.82–1.50)	1.09 (0.82–1.45)	1.07 (0.81–1.43)
Proton-pump inhibitor at baseline	1.21 (0.98–1.49)	1.21 (0.98–1.50)	1.23 (1.00–1.52)
Patent foramen ovale	0.79 (0.55–1.13)		0.77 (0.53–1.10)
Previous myocardial infarction	1.28 (0.81–2.04)		
Coronary artery disease	0.93 (0.62–1.38)		
Diabetes	1.04 (0.80–1.34)		
Left ventricular ejection fraction ≤40%	1.53 (0.80–2.96)		
Time from index stroke to randomization, d			
<8 vs ≥91	1.65 (0.97–2.80)		
8–30 vs ≥91	1.27 (0.94–1.72)		
31–90 vs ≥91	1.09 (0.81–1.48)		
Treatment (dabigatran vs aspirin)	0.83 (0.68–1.02)	0.83 (0.68–1.02)	0.82 (0.67–1.01)
Cardiac monitoring >48 h			0.80 (0.61–1.04)

Data are given as hazard ratio (95% CI). Model 1: predictors with $P<0.1$ in univariate analyses; Harrell's C-statistic (95% CI), 0.65 (0.62–0.67). Model 2: backward selection using SLSTAY=0.1; Harrell's C-statistic (95% CI), 0.64 (0.61–0.67). Model 3: Akaike criterion (best model); Harrell's C-statistic (95% CI), 0.65 (0.61–0.67). For all models, additional constant covariates are age (<75 or ≥75 years), renal impairment (CrCl <50 or ≥50 mL/min), prior stroke or TIA (yes or no), and treatment. For the C-statistic, a bias-corrected and accelerated bootstrap CI based on 10 000 bootstrap samples is calculated. Patients with missing information in any variable were excluded. CrCl indicates creatinine clearance; and TIA, transient ischemic attack.

*$P<0.05$.

ventricular dysfunction attributable to its low prevalence. Patent foramen ovale frequency in our cohort was lower than previously reported in ESUS,[16] and notably did not vary between those with and without stroke recurrence. Because age and diabetes are linked to the estimated creatinine clearance and CHADS-VASc score, it is possible that an independent relationship between these variables and recurrent stroke is incorporated into renal impairment and CHADS-VASc. The role of nonstenosing atherosclerotic plaques, as well as other recognized predictors of recurrent stroke in ESUS, such as left atrial enlargement, NT-proBNP (N-terminal pro-B-type natriuretic peptide), multiterritorial infarcts, and leukoaraiosis, was not systematically assessed at study entry.[8,15] Finally, because enrollment criteria included enrichment factors, it is possible that associations seen in an unselected population could be distorted.

In summary, we found that several risk factors previously linked to other common stroke causes were also associated with stroke recurrence in patients with

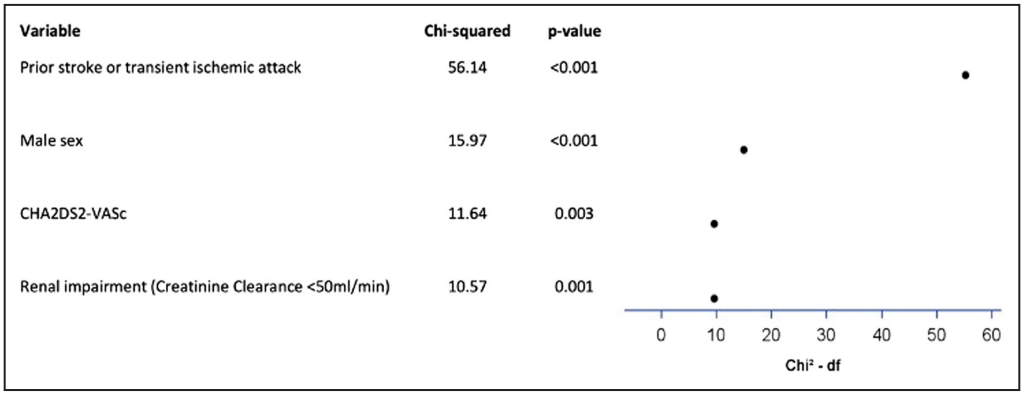

Figure. Factor importance of multivariable regression analysis of clinical predictors for recurrent stroke.
Selection of variables by Akaike criterion.

ESUS. No treatment interactions of dabigatran versus aspirin across high-risk groups were observed in the primary analysis,[2] thus providing no evidence that a particular antithrombotic therapy is beneficial according to risk. Optimizing risk factor control may be especially important in those at high risk of recurrent stroke. Our results could potentially be useful to design future trials exploring novel stroke prevention strategies in this population, as well as to clinicians to better understand subsequent risk in this high-risk population. Furthermore, our results may be a basis for the development of a risk score and nomogram to facilitate the identification of high-risk patients for clinicians in their daily routine.

ARTICLE INFORMATION

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Supplemental Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of patients according to the occurrence of recurrent stroke.

	No recurrent Stroke	Recurrent Stroke	*p value*
Number of patients	5006 (100)	384 (100)	
Age in years, mean ±SD	64.0 ±11.5	67.2 ±10.3	*< 0.01**
Renal impairment, CrCl < 50 mL/min	373 (7.5)	57 (14.8)	*< 0.01*
Prior stroke or TIA	847 (16.9)	128 (33.3)	*< 0.01*
CHA_2DS_2-VASc score			*< 0.01*
2–3	1595 (31.9)	81 (21.1)	
4	1408 (28.1)	114 (29.7)	
≥ 5	2003 (40.0)	189 (49.2)	
Male sex	3136 (62.6)	267 (69.5)	*<0.01*
Previous MI	302 (6.0)	38 (9.9)	*<0.01*
Proton pump inhibitor at baseline	1558 (31.1)	145 (37.8)	*<0.01*
Left ventricular dysfunction and/or ejection fraction ≤ 40%	61 (1.2)	10 (2.6)	*0.02*
Follow-up time, median (IQR)	19.0 (14.7)	21.7 (13.3)	*0.02*
Diabetes mellitus	1120 (22.4)	104 (27.1)	*0.03*
Patent Foramen Ovale	645 (12.9)	35 (9.1)	*0.03*
Coronary artery disease	523 (10.4)	54 (14.1)	*0.03*
Time from index stroke to randomization in days			*0.05*
< 8	172 (3.4)	20 (5.2)	
8–30	1682 (33.6)	147 (38.3)	
31–90	2263 (45.2)	156 (40.6)	
≥ 91	888 (17.7)	61 (15.9)	
Hypertension	3683 (73.6)	298 (77.6)	*0.08*
History of cancer	375 (7.5)	38 (9.9)	*0.09*
Cardiac monitoring at baseline > 48 hours	835 (16.7)	71 (18.5)	*0.36*
Heart failure	227 (4.5)	14 (3.6)	*0.42*
BMI, kg/m2			*0.53*
< 25	1757 (35.1)	125 (32.6)	
25 to < 30	2041 (40.8)	159 (41.4)	
30 to < 35	837 (16.7)	65 (16.9)	
≥ 35	333 (6.7)	32 (8.3)	
Aspirin at baseline	1227 (24.5)	89 (23.2)	*0.56*
Hyperlipidemia	2829 (56.5)	214 (55.7)	*0.77*

All data represents number (%), unless otherwise indicated
All p-values were calculated from chi-squared test, unless otherwise indicated
* From t-test
BMI was missing for 41 patients; renal function, patent foramen ovale, left ventricular dysfunction and/or ejection fraction ≤ 40%, time from index stroke to randomization and cardiac monitoring at baseline were missing for five, two, one, one and one patients, respectively. Patients with missing information are not considered for calculating the p values from a chi-squared test in the respective variable.
BMI, body mass index; CrCl, creatinine clearance; MI, myocardial infarction; TIA, transient ischemic attack.