Prevalence and Overlap of Potential Embolic Sources in Patients With Embolic Stroke of Undetermined Source

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Background—We aimed to assess the prevalence and degree of overlap of potential embolic sources (PES) in patients with embolic stroke of undetermined source (ESUS).

Methods and Results—In a pooled data set derived from 3 prospective stroke registries, patients were categorized in ≥1 groups according to the PES that was/were identified. We categorized PES as follows: atrial cardiopathy, atrial fibrillation diagnosed during follow-up, arterial disease, left ventricular disease, cardiac valvular disease, patent foramen ovale, and cancer. In 800 patients with ESUS (43.1% women; median age, 67.0 years), 3 most prevalent PES were left ventricular disease, arterial disease, and atrial cardiopathy, which were present in 54.4%, 48.5%, and 45.0% of patients, respectively. Most patients (65.5%) had >1 PES, whereas only 29.7% and 4.8% of patients had a single or no PES, respectively. In 31.1% of patients, there were ≥3 PES present. On average, each patient had 2 PES (median, 2). During a median follow-up of 3.7 years, stroke recurrence occurred in 101 (12.6%) of patients (23.3 recurrences per 100 patient–years). In multivariate analysis, the risk of stroke recurrence was higher in the atrial fibrillation group compared with other PES, but not statistically different between patients with 0 to 1, 2, or ≥3 PES.

Conclusions—There is major overlap of PES in patients with ESUS. This may possibly explain the negative results of the recent large randomized controlled trials of secondary prevention in patients with ESUS and offer a rationale for a randomized controlled trial of combination of anticoagulation and aspirin for the prevention of stroke recurrence in patients with ESUS.

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Key Words: atrial fibrillation • embolic stroke • embolic stroke of undetermined source • embolism

T he term embolic stroke of undetermined source (ESUS) was introduced by the Cryptogenic Stroke/ESUS International Working Group to describe patients with stroke of undetermined cause despite adequate diagnostic workup (ie, nonlacunar strokes without proximal arterial stenosis or a major cardiac source of embolism, like intracardiac thrombus, atrial fibrillation [AF], mechanical heart valves, and others).[1,2] Approximately 17% of all patients with ischemic stroke are classified as having ESUS, which is associated with a considerable rate of stroke recurrence (≈5% per year).[1,3,4]

Embolism in patients with ESUS may be causally related to a large number of conditions, like covert AF, other non–AF supraventricular arrhythmias, structural abnormalities of the left atrium or the left ventricle (LV), aortic atherosclerotic plaques, carotid atherosclerotic plaques causing low-degree stenosis (ie, <50%), paradoxical embolism through patent foramen ovale (PFO), atrial septal defect or pulmonary arteriovenous fistula, cardiac valvular pathological conditions, cancer, and others.[1,2] As it may be the case also for the non–ESUS ischemic stroke population, >1 potential embolic source (PES) may be present in a single patient, rendering it challenging to conclude on the actual cause.[5] There is scarce information about the prevalence and, in particular, the degree of PES overlap in the ESUS population. This information may be important as it could assist in the interpretation of the recent trials of secondary prevention in patients with

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Clinical Perspective

What Is New?

- In this large multicenter data set of 800 consecutive patients with embolic stroke of undetermined source (ESUS), there was major overlap of potential embolic sources: two thirds of patients with ESUS had at least 2, whereas one third of patients had at least 3, with the most prevalent being left ventricular disease, arterial disease, and atrial cardiopathy (each one of which was present in nearly half of the study population).

What Are the Clinical Implications?

- These results may possibly explain the negative results of the NAVIGATE ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) and RE-SPECT ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With ESUS) trials, which showed that anticoagulation is not superior to aspirin for prevention of stroke recurrence in patients with ESUS and offer a rationale for a randomized controlled trial of combination of anticoagulation and aspirin for the prevention of stroke recurrence in patients with ESUS.

ESUS and generate hypotheses that could be tested in future research.

The objective of the study was to assess the prevalence and the degree of overlap of PES in patients with ESUS. In addition, we aimed to provide information about the rates of stroke recurrence associated with each PES, as well as with the number of PES per patient.

Methods

We will make the data, methods used in the analysis, and materials used to conduct the research available to any researcher for purposes of reproducing the results or replicating the procedure on reasonable request.

We pooled the data of all consecutive patients with ESUS registered in 3 prospective stroke registries: the ASTRAL (Acute Stroke Registry and Analysis of Lausanne), the Athens Stroke Registry, and the Larissa Stroke Registry.[6–8] We used a standardized form with prespecified parameters to collect data. The use of these registry data for research was approved by the local Institutional Review Boards. Study participants provided written or verbal informed consent for the research use of their deidentified data. The study is registered at Clinicaltrials.gov (NCT02766205), and its methods were previously described.[9]

Definition of ESUS

ESUS was defined according to the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group as a nonlacunar brain infarct in the absence of the following: (1) extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia; (2) major-risk cardioembolic source; and (3) any other specific cause of stroke (eg, arteritis, dissection, migraine/vasospasm, or drug misuse).[2] For pragmatic reasons, imaging of the intracranial arteries was not required for the definition of ESUS, similar to the approach followed in the NAVIGATE ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) trial.[10]

Classification of potential embolic sources

Patients were categorized in ≥1 groups according to the PES that was/were identified. We categorized PES as follows: atrial cardiopathy (AC), AF diagnosed during follow-up, arterial disease, LV disease, cardiac valvular disease, PFO, and cancer. When >1 PES was identified in a single patient, the patient was categorized in all applicable PES groups. Hence, the overall sum of the number of patients (calculated by adding the number of patients in each PES group) is higher than the total number of patients in our population.

Definitions of potential embolic sources

On the basis of previously published associations with the risk of stroke, AC was diagnosed if the echocardiogram reported left atrial dilatation or increased left atrial diameter (>38 mm for women and >40 mm for men)[11] or if supraventricular extrasystoles were present at the 12-lead ECGs performed during hospitalization.[12] We diagnosed arterial disease in case of presence of any ipsilateral atherosclerotic carotid plaque causing luminal stenosis of <50%[13] or aortic arch atherosclerosis[14–16] based on the imaging reports. We did not review the images. We did not include contralateral carotid atherosclerosis in this PES. LV disease was diagnosed if low LV ejection fraction (<35%), LV hypertrophy, or left-sided heart failure was reported at the echocardiogram, or if LV hypertrophy was identified at the ECG (Sokolow index ≥35 mm). We diagnosed cardiac valvular disease if moderate-to-severe stenosis or regurgitation of the mitral or aortic valve was reported at the echocardiogram. AF was assessed during on-site patient visits at the outpatient clinic and/or by contact with the patient and/or the next of kin or the patient's primary physician; it was considered present if
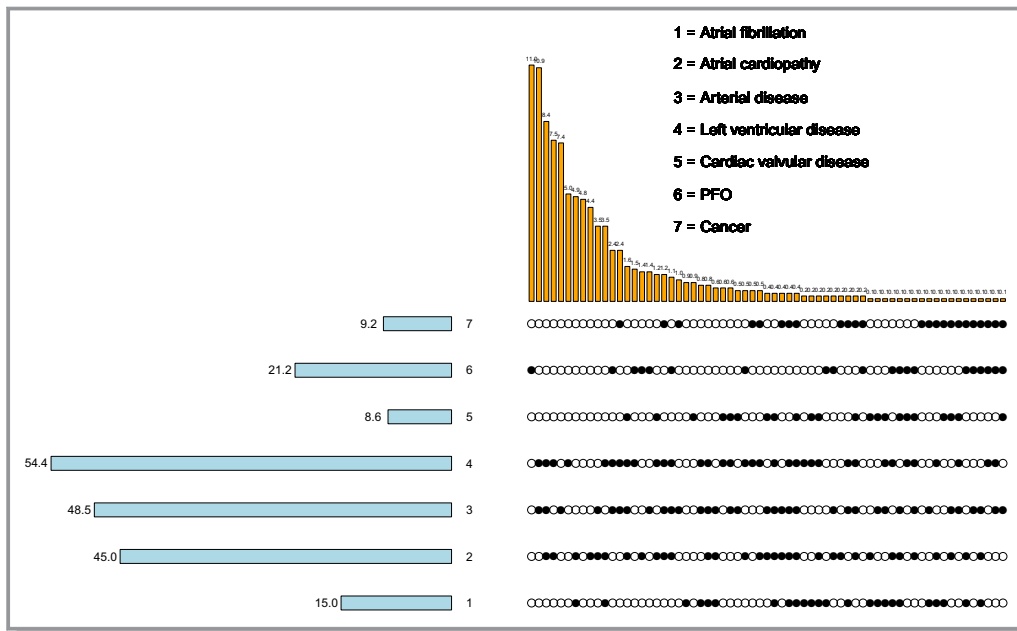
Figure 1. Prevalence of potential embolic sources (PES) and degree of their overlap. Each row corresponds to a specific PES, as described in the legend. Empty cells indicate absence of the specific PES, whereas filled cells correspond to the presence of the specific PES. Each column corresponds to a specific combination of PES. The numbers in the plot correspond to the proportion of patients in the overall population who have a specific PES (for the numbers shown at the rows) or a specific combination of PES (for the numbers shown at the columns). PFO indicates patent foramen ovale.

confirmed by an ECG performed for any reason, including palpitations, irregular pulse on clinical examination, in-hospital surveillance, or portable outpatient monitoring.

Assessment of outcome

The assessment of stroke recurrence was performed by on-site patient visits at the outpatient clinic and/or by contact with the patient and/or the next of kin or the patient's primary physician and was ascertained by reviewing the patient's medical chart and imaging, whenever possible.

Statistical Analysis

Continuous covariates are summarized as median and interquartile range. All comparisons were performed using the Cochran-Mantel-Haenszel χ^2 test. The rates of stroke recurrence are reported per 100 patient-years.

To enhance the visualization of the prevalence of PES and the degree of their overlap, we used UpSet (Caleydo, https://caleydo.org) to draw a matrix layout (Figure 1). The plot has 7 rows, each one of which corresponds to a specific PES, as described in the plot legend. Cells may be either empty (indicating absence of the specific PES) or filled (indicating presence of the specific PES). Each column corresponds to a specific combination of PES. The numbers in the plot correspond to the proportion of patients in the overall population with a specific

PES (for the numbers shown at the rows) or with a specific combination of PES (for the numbers shown at the columns).

To assess the association between time to stroke recurrence and PES, which were fitted using a separate indicator, a Cox model was implemented. Adjustment was allowed for demographics (age and sex), medical history (hypertension, dyslipidemia, diabetes mellitus, smoking status, coronary artery disease, and prosthetic valve history), and National Institute of Health Stroke Scale score at admission. A similar model was used to quantify the relationship between time to stroke recurrence and number of PES per patient. In both models, stepwise methods were used to select significant covariates. Associations are presented as hazard ratios (HRs) with their corresponding 95% CIs, and the level of significance was set at 5%.

Graphical display of the results was produced using the Kaplan-Meier product limit method, where adjusted estimation of the 10-year cumulative probabilities of stroke recurrence for a specific PES or the number of PES per patient was derived. For patients lost during follow-up, survival data were censored at the last time known to be alive. For patients who experienced >1 recurrence during the follow-up period, the time of the first event was used in the analysis. Differences in Kaplan-Meier curves were evaluated with the likelihood ratio test, and the level of significance was set at 5%. Missing data were not imputed. Statistical analyses were performed with the R package (version 3.5.1).

Table. Baseline Characteristics and Outcomes of Patients per PES

Variable	Atrial Fibrillation (n=120)	Atrial Cardiopathy (n=360)	Arterial Disease (n=388)	Left Ventricular Disease (n=435)	Cardiac Valvular Disease (n=69)	Patent Foramen Ovale (n=170)	Cancer (n=74)	P Value
Female sex	57 (47.5)	142 (39.4)	178 (45.9)	185 (42.5)	35 (50.7)	75 (44.1)	36 (48.6)	0.49
Age, y	73.7 (65.3–79.0)	72.0 (63.3–79.3)	72.2 (63.7–80.5)	72.0 (63.0–79.5)	74.2 (64.1–79.3)	48.6 (37.2–63.9)	74.5 (65.4–80.1)	0.00
NIHSS score	5.0 (2.0–9.0)	6.0 (3.0–13.0)	7.0 (3.0–12.0)	6.0 (3.0–12.0)	7.0 (3.0–14.0)	5.0 (2.0–11.8)	7.0 (4.0–11.0)	0.40
Hypertension	98 (81.7)	269 (74.7)	289 (74.5)	332 (76.3)	57 (82.6)	53 (31.2)	57 (77.0)	0.00
Dyslipidemia	73 (60.8)	241 (66.9)	300 (77.3)	307 (70.6)	46 (66.7)	96 (56.5)	57 (77.0)	0.00
Diabetes mellitus	32 (26.7)	84 (23.3)	68 (17.5)	98 (22.5)	9 (13.0)	10 (5.9)	16 (21.6)	0.65
Smoking	41 (34.2)	121 (33.6)	179 (46.1)	167 (38.4)	28 (40.6)	64 (37.6)	31 (41.9)	0.44
Coronary artery disease	27 (22.7)	76 (21.2)	53 (13.7)	69 (15.9)	9 (13.0)	7 (4.1)	10 (13.5)	0.21
Previous stroke	21 (17.5)	59 (16.4)	89 (22.9)	83 (19.1)	19 (27.5)	19 (11.2)	14 (18.9)	0.00
Antiplatelet at discharge	112 (94.9)	323 (91.8)	370 (96.1)	396 (93.0)	60 (89.6)	154 (91.1)	70 (94.6)	0.36
Anticoagulant at discharge	5 (4.2)	31 (8.8)	19 (4.9)	35 (8.2)	6 (9.0)	16 (9.5)	5 (6.8)	0.28
Stroke recurrence*	25.20	23.62	22.42	23.90	21.70	17.91	20.61	0.37

Data are given as number (percentage), unless otherwise indicated. Continuous covariates are summarized as median (interquartile range). NIHSS indicates National Institute of Health Stroke Scale; PES, potential embolic sources.

*(Per 100 patient-years). All comparisons were performed using Cochran-Mantel-Haenszel χ^2 test.

Results

Baseline Characteristics of the Overall Population

Among 839 consecutive patients with ESUS, 800 (43.1% women; median age, 67.0 years) with complete data were included in the final analysis. The baseline characteristics of patients are summarized in the Table. The prevalence of the classic cardiovascular risk factors did not have major differences across different PES, except for patients with PFO who were younger and had a lower prevalence of arterial hypertension, dyslipidemia, and previous stroke.

Prevalence and Overlap of PES

The prevalence of each PES and the degree of their overlap is summarized in Figure 1. The 5 most prevalent PES were LV disease, arterial disease, AC, PFO, and AF, which were present in 54.4%, 48.5%, 45.0%, 21.3%, and 15.0% of patients, respectively. Most patients (65.5%) had >1 PES, whereas only 29.7% and 4.8% of patients had a single or no PES, respectively. In 31.1% of patients, there were ≥3 PES present. On average, each patient had 2 PES (median, 2).

Stroke Recurrence per Specific PES and Degree of PES Overlap

The median follow-up was 3.7 years. Stroke recurrence occurred in 101 (12.6%) of patients in the overall population, corresponding to 23.3 recurrences per 100 patient-years.

The rates of stroke recurrence according to PES are presented in the Table. In multivariate analysis, the risk of stroke recurrence was higher in the AF group compared with other PES groups (Figure 2). In Kaplan-Meier analysis, the cumulative probabilities of stroke recurrence were borderline statistically different across PES groups (likelihood ratio test, 14.12; P=0.05) (Figure 3) because of the higher cumulative probability of recurrence in the AF group relatively to the other PES groups.

The rates of stroke recurrence for patients with 0 to 1, 2, or ≥3 PES were 20.8, 27.6, and 21.9 per patient-years, respectively. In multivariate analysis, the risk of stroke recurrence was not statistically different between patients with 0 to 1, 2, or ≥3 PES (Figure 2). In Kaplan-Meier analysis, the cumulative probability of stroke recurrence was not statistically different between patients with 0 to 1, 2, or ≥3 PES (likelihood ratio test, 2.54; P=0.28) (Figure 3).

Discussion

The present analysis of a large multicenter data set of 800 consecutive patients shows that there was major overlap of
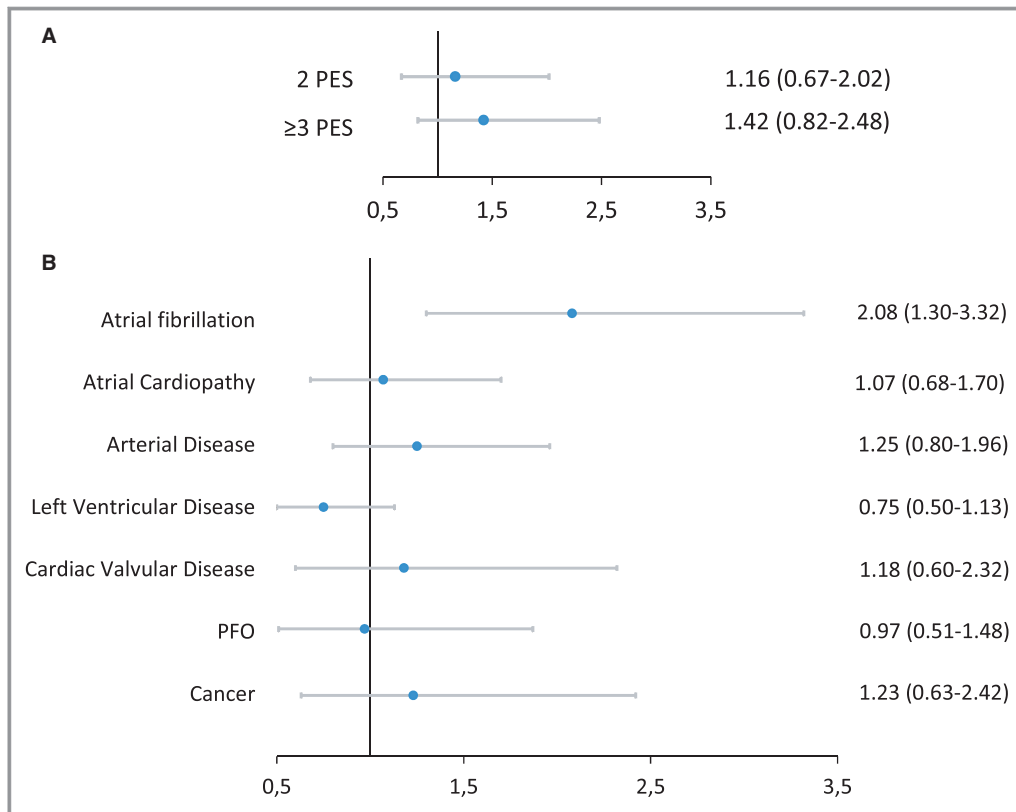
Figure 2. Top: Multivariable regression analysis of the association between the presence of each potential embolic source (PES) and stroke recurrence (for each PES, the comparison is made to patients without the specific PES). **Bottom:** Multivariable regression analysis of the association between the number of PES per patient and stroke recurrence (the comparisons are made to patients with 0 to 1 PES). Associations are presented as hazard ratios and 95% CIs. For both analyses, associations are adjusted for sex, age, hypertension, dyslipidemia, diabetes mellitus, smoking, coronary artery disease, and National Institute of Health Stroke Scale score at admission. For the **top** analysis, associations are also adjusted for other concomitant PES. PFO indicates patent foramen ovale.

PES in patients with ESUS: two thirds of patients with ESUS had at least 2 PES, whereas one third of patients had at least 3 PES. The most prevalent PES were LV disease, arterial disease, and AC, each one of which was present in nearly half of the study population.

It is likely that our estimate for the degree of overlap of PES is only an underestimate of the actual degree of overlap. Given the pragmatic nature of this study, the identification of PES relied on investigations that are routinely performed in clinical practice, like standard 12-lead ECG, transthoracic echocardiogram, extracranial vascular imaging, and automated cardiac rhythm monitoring. It is likely that a larger number of PES might have been identified if all our patients had an exhaustive panel of investigations that are currently not routinely used in most patients with ESUS. For example, biomarkers (eg, NT-proBNP [N-terminal pro–B-type natriuretic peptide][17,18] and high-sensitivity cardiac troponin T[19]), cardiac magnetic resonance imaging (for the assessment of atrial fibrosis[20]), ECG indexes (eg, P-wave terminal force in V1[21–24]), and transesophageal echocardiogram (for the assessment of

spontaneous echocardiographic contrast[25] and the morphological features of the left atrial appendage[26]) could have lead to more diagnoses of AC; intracranial vascular imaging and transesophageal echocardiogram could have lead to more diagnoses of intracranial and aortic atherosclerosis, respectively[14–16]; and transesophageal echocardiogram could have identified a larger number of patients with PFO, if performed in all patients regardless of their age. If patients were investigated with such an exhaustive diagnostic workup, it is highly likely that the degree of overlap of PES would be much higher and only a small minority of patients would be considered to have a single or no PES. However, such a diagnostic panel would be considered unrealistic to apply to the entire population with ESUS, even in high-resource settings.

The ESUS concept has been criticized that it promotes the lumping approach (ie, a standardized, one-size-fits-all diagnostic approach aiming to detect the major-risk embolic sources for which there is strong evidence to guide secondary prevention).[27] The results of the present study offer support
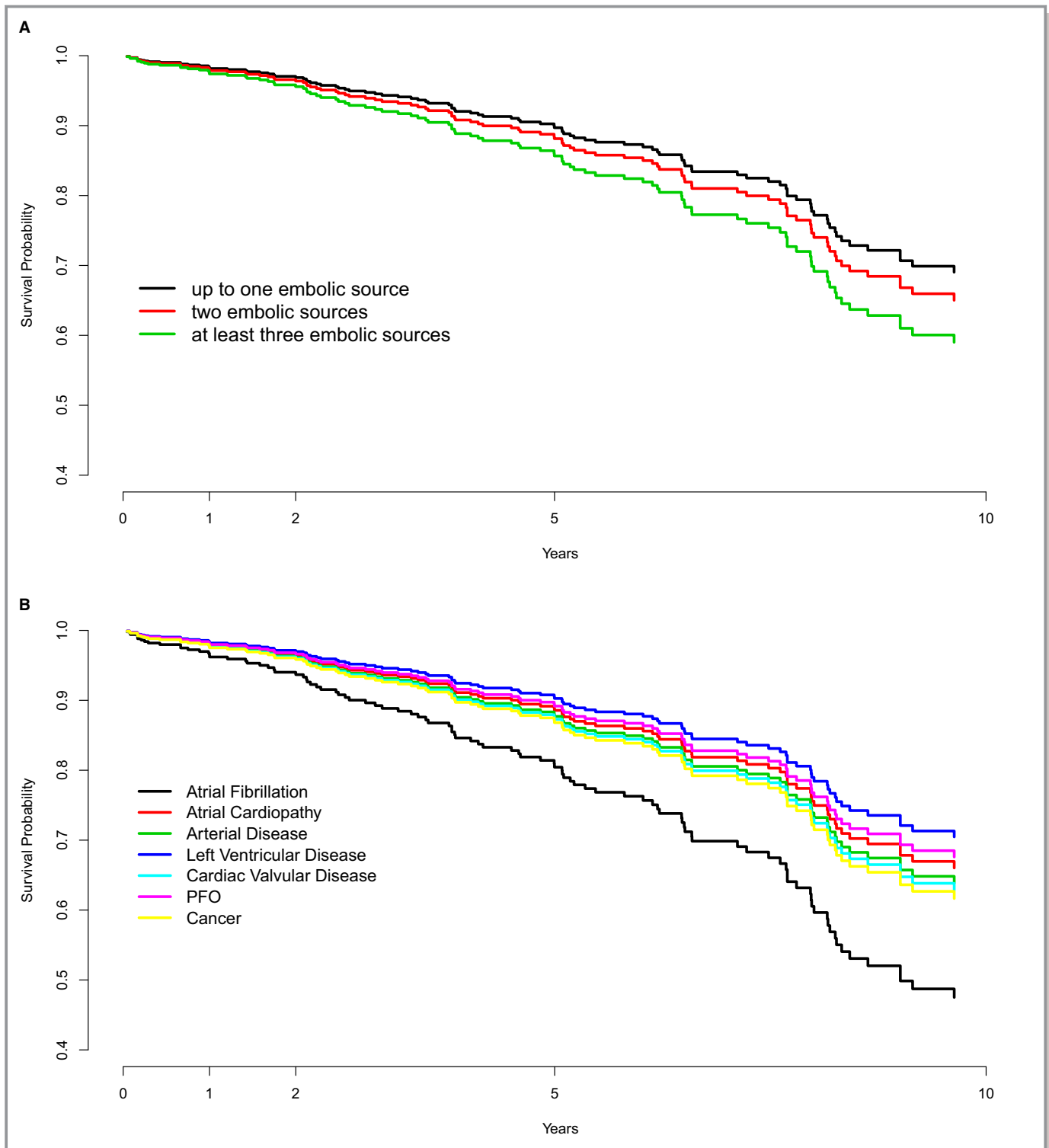
Figure 3. Ten-year survival estimates of stroke recurrence in patients with embolic stroke of undetermined source, according to each potential embolic source (PES; **top**) and the number of PES per patient (**bottom**). PFO indicates patent foramen ovale.

to this strategy by showing that in a remarkable majority of patients, the strategy of an exhaustive diagnostic workup may be not only unrealistic in terms of availability of resources but also futile, as it would rarely lead to a single PES (for most of which there is low quality of evidence to guide management),

but rather to multiple PES and subsequent frustration in the attempt to conclude on the causal one.[5]

The NAVIGATE ESUS and the RE-SPECT ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With ESUS) trials showed that anticoagulation is not superior to

aspirin for prevention of stroke recurrence in patients with ESUS, indicating that the lumping therapeutic approach of oral anticoagulation for the unselected population with ESUS was not the optimal strategy and indirectly validating the ESUS concept as an etiologically heterogeneous entity. The heterogeneity of embolic sources and their remarkable overlap, as estimated in the present study, could possibly explain these negative results: for some of the embolic sources (like AC, AF, LV disease, PFO, and cancer), the main pathophysiologic mechanism for thrombogenesis is low blood flow, which predisposes to formation of red thrombi that may respond better to anticoagulation. On the other hand, for other embolic sources, like aortic and nonstenotic carotid atherosclerosis, the ulceration of a plaque triggers the formation of white thrombi that may respond better to aspirin. In this context, it may be hypothesized that treating an patients with ESUS with anticoagulation rather than aspirin would just result in exchanging red thrombi for white, with the overall burden remaining largely unchanged. If this hypothesis is correct, it would be rational to expect that simultaneous inhibition of red and white thrombi with a combination of anticoagulation and aspirin would be associated with a significant reduction of stroke recurrences in patients with ESUS. The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial showed that a combination of low-dose rivaroxaban and aspirin was associated with a large reduction of stroke risk compared with aspirin as monotherapy. These thoughts provide a rationale for a randomized controlled trial of combination of anticoagulation and aspirin for the prevention of stroke recurrence in the unselected population with ESUS. Also, this rationale does not apply to patients who are detected with AF who should be anticoagulated. Furthermore, it may not apply to patients with AC if, in the meanwhile, the ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke) trial, which is currently investigating whether oral anticoagulation with apixaban is a better strategy compared with aspirin in patients with AC, reports positive results.[28]

Among all potential PES, the AF group was associated with the highest risk of stroke recurrence. Although it is debatable how strong is the causative association between ESUS and episodes of AF detected during follow up, especially if they occur late or are of short duration,[29] still it is important that these episodes are detected on time as they may warrant oral anticoagulation, which could reduce the risk of stroke recurrence. Given the large prevalence of ESUS and the restricted resources for prolonged cardiac monitoring, it is important to develop prognostic tools that may aid to the stratification of the likelihood of AF detection in patients with ESUS.

A limitation of the present study is that the estimated degree of PES overlap may be an underestimate of the actual overlap, as it might have been higher if a more extensive panel of diagnostic investigations had been performed, as argued above. However, at the same time, this strengthens further the conclusion of this study that there is remarkable overlap of PES in patients with ESUS. Other strengths of the study include the large number of consecutive, well-defined patients with ESUS and its multicenter design. Limitations include the risk of registration bias within and between the participating registries, the retrospective design of the analysis, and differences in the workup of patients during the in-hospital phase.

The present analysis concludes that there is major overlap of PES in patients with ESUS. This may possibly explain the negative results of the NAVIGATE ESUS and RE-SPECT ESUS trials and offer a rationale for a randomized controlled trial of combination of anticoagulation and aspirin for the prevention of stroke recurrence in patients with ESUS.

Author Contributions

Dr Ntaios: study concept, study design, statistical analysis and interpretation, preparation of manuscript, study supervision. Dr Perlepe: data collection, study design, statistical analysis and interpretation, critical revision of the manuscript. Dr Lambrou: statistical analysis and interpretation, critical revision of the manuscript. Dr Sirimarco: data collection, critical revision of the manuscript. Dr Strambo: data collection, critical revision of the manuscript. Dr Eskandari: data collection, critical revision of the manuscript. E. Karagkiozi: data collection, critical revision of the manuscript. Dr Vemmou: data collection, critical revision of the manuscript. Dr Koroboki: data collection, critical revision of the manuscript. Dr Manios: data collection, critical revision of the manuscript. Dr Makaritsis: data collection, critical revision of the manuscript. Dr Vemmos: data collection, study design, statistical analysis and interpretation, critical revision of the manuscript. Dr Michel: data collection, study design, critical revision of the manuscript.

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Disclosures

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