

# Frequency and features of embolic stroke of undetermined source in young adults

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## Abstract

**Introduction:** The sources of emboli in those with embolic stroke of undetermined source may differ in old and young. We assessed the frequency, features and potential embolic sources of younger vs. older embolic stroke of undetermined source patients in the embolic stroke of undetermined source Global Registry.

**Patients and methods:** Cross-sectional study of consecutive patients over age 18 years, with recent ischaemic strokes at 19 centres conducted in 2013–2014. Characteristics of embolic stroke of undetermined source patients who aged  $\leq 50$  years were analysed and compared with embolic stroke of undetermined source patients who aged  $>50$  years.

**Results:** Among 2144 patients with ischaemic stroke, 323 (15.1%, 95% confidence interval: 13.6–16.7%) were  $\leq 50$  years old and, 1821  $>50$  years. 24% ( $n = 78$ ) of young vs. 15% ( $n = 273$ ) of older patients met embolic stroke of undetermined source criteria. The mean age of young embolic stroke of undetermined source patients was 40 years (standard deviation  $+/-9$ ), 33% were women and the most prevalent vascular risk factor was hypertension (38%). Conventional vascular risk factors were less frequent in younger embolic stroke of undetermined source patients. Fewer young embolic stroke of undetermined source patients (63%) had potential minor risk embolic sources identified vs. older embolic stroke of undetermined source patients (77%) ( $p = 0.02$ ). Stroke severity on admission was similar in younger vs. older patients (National Institute of Health Stroke Scale (NIHSS) 3 vs. 4,  $p = 0.06$ ).

**Discussion:** Young embolic stroke of undetermined source patients comprise an important subset of ischaemic stroke patients around the world. Severity of stroke on admission and 30-day mortality rates are similar among young and older patients. However, there are important differences between younger vs. older embolic stroke of undetermined source patients with respect to risk factors, and potential embolic sources that could affect response to anticoagulants vs. antiplatelet therapies.

**Conclusion:** This study provides a benchmark for the global frequency and characteristics of young embolic stroke of undetermined source patients and shows consistent high frequency of embolic stroke of undetermined source in young adults.

## Keywords

Embolic stroke of undetermined source, stroke in young

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## Introduction

In 2014, the clinical construct of embolic stroke of undetermined source (ESUS) was introduced to identify patients with non-lacunar cryptogenic ischaemic strokes in whom embolism was the likely mechanism.<sup>1</sup> The underlying embolic sources in ESUS patients are heterogeneous. As it is hypothesized that most emboli are thrombotic, and that anticoagulants might be more efficacious than antiplatelet agents for secondary prevention of stroke in ESUS patients, the ESUS construct is the basis for three ongoing randomized controlled trials (RCTs) comparing non-vitamin K antagonist direct-acting oral anticoagulants with aspirin for secondary stroke prevention.<sup>2–4</sup> In total, these trials will recruit about 13,500 ESUS patients. However, there will be a limited number of ESUS patients under the age of 50 years enrolled in these studies because younger patients were excluded based on an assumption that they are at lower risk of outcome events and may thus compromise the statistical power of the studies. Although these trials are likely to provide valuable information about older ESUS patients, there will likely be a relative gap in the knowledge concerning the clinical characteristics of young ESUS patients even at their conclusion.

We sought to determine the clinical characteristics of young ESUS patients and to compare them with older ESUS patients in order to elucidate potential differences in embolic sources.

## Patients and methods

The methods of the ESUS Global Registry Project have been previously reported.<sup>5</sup> Briefly, data from consecutive patients with recent ischaemic stroke were sought at 19 stroke research centres in 19 different countries, in 2013–2014. This retrospective registry aimed to review 100 patients with acute ischaemic stroke at each site or until 25 patients meeting ESUS criteria (Table 1) were identified. Sites retrospectively

identified consecutive inpatients evaluated for recent stroke either from hospital discharge diagnosis codes or from databases associated with acute stroke units. The study was compliant with local institutional research board regulations.

Data were analysed according to five global regions: Europe, North America, Latin America, East Asia and Pacific. Descriptive analyses regarding the frequency of key features were done using *t* test and Chi-square; and data were compared for patients aged  $\leq 50$  (termed young ESUS) and over 50 years.

## Results

Among 2144 patients with recent ischaemic stroke from 19 stroke research centres in 19 countries, 323 (15.1%, 95% confidence interval (CI): 13.6–16.7%) were  $\leq 50$  years old and 1821 were older than 50 years.

### Frequency of ESUS by country and global region

Of the 323 patients aged  $\leq 50$  years, 78 (24%, 95% CI 20–29%) met ESUS criteria (Table 2).

The highest frequency was found in East Asia (49%) and the lowest in Latin America (13%) (Table 3).

### Reasons for not ESUS

One of the frequent reasons that young patients with ischaemic stroke did not meet the criteria for ESUS was lack of diagnostic tests done to meet the ESUS criteria. Of note, 24-h cardiac rhythm monitoring (required for ESUS diagnosis) was not routinely carried out in 48%, and echocardiography (required for ESUS diagnosis) was not routinely done in 28% of young ischaemic stroke patients. Other reasons that ischaemic stroke patients did not meet the ESUS criteria were: other stroke causes such as dissection, arteritis and major risk cardioembolic sources (except Atrial Fibrillation (AF)) 27%, lacunar strokes (12%), non-visualized strokes 6% (stroke visualization required

**Table 1.** Criteria for diagnosis of embolic stroke of undetermined source (ESUS).<sup>a</sup>

1. Ischaemic stroke detected by CT or MRI that is not lacunar.<sup>b</sup>
2. Absence of extracranial or intracranial atherosclerosis causing  $>50\%$  luminal stenosis in arteries supplying the area of ischaemia.
3. No major-risk cardioembolic source of embolism.<sup>c</sup>
4. No other specific cause of stroke identified (e.g. arteritis, dissection, migraine/vasospasm, drug abuse).

<sup>a</sup>Requires minimum diagnostic evaluation that includes cardiac rhythm monitoring for  $>24$  h with automated rhythm detection.<sup>1</sup>

<sup>b</sup>Lacunar defined as a subcortical infarct  $<1.5$  cm ( $<2.0$  cm on MRI diffusion images) in largest dimension, including on MRI diffusion-weighted images, and in the distribution of the small, penetrating cerebral arteries of the cerebral hemispheres and pons.

<sup>c</sup>Permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, recent ( $<4$  weeks) myocardial infarction, left ventricular ejection fraction  $<30\%$ , valvular vegetations or infective endocarditis.

CT: computed tomography; MRI: magnetic resonance imaging.

**Table 2.** Frequency of young ESUS patients in 19 centres of different countries.

Site	No. of ischaemic stroke patients age $\leq 50$ yrs	ESUS <sup>a</sup> n (%)
Buenos Aires, Argentina	7	3 (43)
Perth, Australia	21	7 (33)
Brussels, Belgium	5	1 (20)
Sao Paulo, Brazil	23	1 (4)
Hamilton, Canada	14	5 (36)
Beijing, China	20	9 (45)
Paris, France	8	5 (63)
Heidelberg, Germany	3	0 (0)
Galway, Ireland	8	3 (38)
Rome, Italy	10	2 (20)
Tokyo, Japan	12	5 (42)
Mexico City, Mexico	86	11 (13)
Amsterdam, Netherlands	11	0 (0)
Manila, Philippines	32	4 (13)
Coimbra, Portugal	10	3 (30)
Moscow, Russia	11	5 (45)
Seoul, South Korea	13	8 (62)
Glasgow, United Kingdom	12	2 (17)
Philadelphia, United States	17	4 (24)
Total	323	78 (24)

Yrs: years.

<sup>a</sup>ESUS: embolic stroke of undetermined source per criteria in Table 1.**Table 3.** Frequency of young ESUS patients by global region.<sup>a</sup>

Region	No. of ischaemic stroke patients $\leq 50$ yrs	ESUS n (%)
Europe (9 sites)	78	21 (27)
North America (2 sites)	31	9 (29)
Latin America (3 sites)	116	15 (13)
East Asia (3 sites)	45	22 (49)

<sup>a</sup>One site each in Australia and the Philippines are not considered.

for ESUS diagnosis) and carotid artery stenosis (6%). Atrial fibrillation only accounted for 5% of ischaemic stroke in the young (Figure 1). All young ESUS patients in the registry had undergone intracranial vessel imaging either by Computed Tomography Angiogram (CTA), Magnetic Resonance Angiogram (MRA) or transcranial Doppler and was deemed not to have  $\geq 50\%$  stenosis of the intracranial arteries.

### Demographic risk factors and clinical features of ESUS patients

The mean age of the young ESUS patients was 40 years and 33% were women.

Among the 78 young ESUS patients, hypertension, diabetes and coronary artery disease were present in 36,

21 and 7%, respectively; 11% were taking antiplatelet therapy at stroke onset. A history of stroke or TIA prior to the index stroke was present in 5% of the patients. Median (interquartile range) NIHSS score near hospital admission was 3 (1–7); 9% received intravenous tissue plasminogen activator at the time of the index stroke (Table 4).

Magnetic resonance imaging (MRI) scans of the brain were done in 94%, with a previous stroke (i.e. prior to index stroke) present on MRI in 30%. Transoesophageal echocardiography (TEE) was undertaken in 49% of young ESUS patients, with patent foramen ovale (PFO) present in 32% and complex aortic arch plaque reported in 3% of those undergoing TEE.

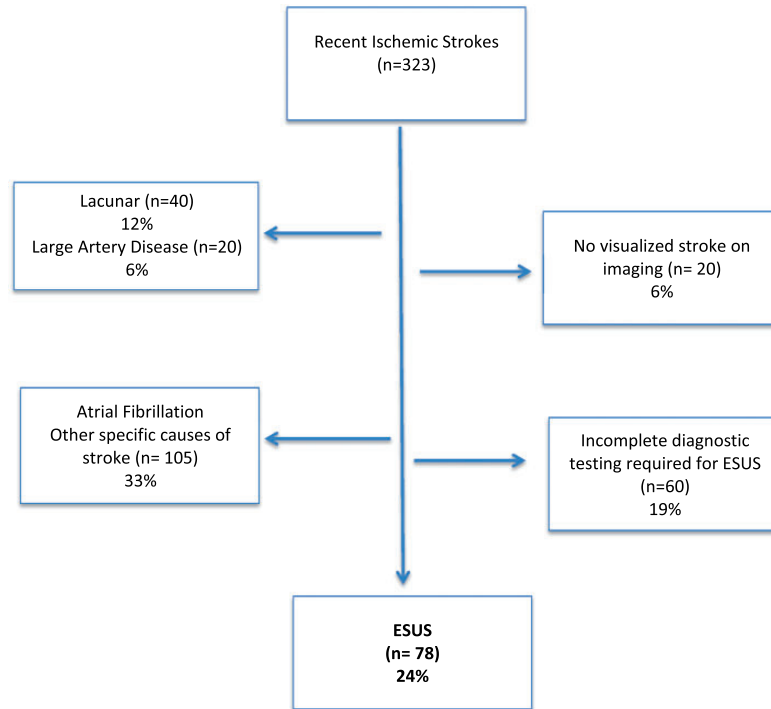
At hospital discharge, 77% of young ESUS patients received antiplatelet monotherapy, 9% anticoagulant therapy and the remainder (13%) were discharged on dual antiplatelet therapy (Table 4). The vascular risk factor profile of young ESUS patients was significantly different from older ESUS patients. In contrast, there was no statistically significant difference in the presenting NIHSS score or the 30-day mortality rate among younger and older ESUS patients (1% in young ESUS patients compared with 2% in the older ESUS patients) (Table 4).

### Frequency of minor-risk potential embolic sources in ESUS patients

Of young ESUS patients with anterior circulation stroke, 69% had non-stenotic cervical carotid artery plaque either of ipsilateral or contralateral carotid arteries; this was less than in patients over the age of 50 years (82%) and was statistically significant ( $p=0.0393$ ). Among those who underwent transthoracic (precordial) echocardiography, mitral annular calcification or myxomatous changes (0%), and aortic valve stenosis or calcification (1%), were not commonly seen (Table 5). The prevalence of PFO among this young ESUS population who had TEE was 32%. At least one minor-risk potential embolic source was identified in 63% of young ESUS patients compared to 77% of older ESUS patients ( $p=0.0197$ ), 14% of young ESUS patients had two or more potential minor risk embolic sources compared to 26% of older ESUS patients (Table 5).

### Discussion

Following the completion of the large randomized trials testing anticoagulants in ESUS patients in 2018, clinical interest in the ESUS construct is likely to increase exponentially. There will be intense interest to know whether the results of these trials are generalizable to young adults with ESUS: are these patients



**Figure 1.** Frequency of embolic stroke of undetermined source (ESUS) in patients under 50 years as a proportion of all ischaemic strokes under 50 years.

**Table 4.** Features of ESUS patients ≤ 50 years vs. >50 years.

	ESUS patients				
	Age ≤50 yrs (N=78)		Age >50 yrs (N=273)		P value <sup>b</sup>
	N <sup>a</sup>	% or Mean	N <sup>a</sup>	% or Mean	
Mean age (yrs)	78	40 (9)	273	68 (10)	<0.0001
Men (%)	78	67	272	54	0.0688
Diabetes (%)	78	21	273	26	0.3755
Hypertension (%)	78	36	270	73	<0.0001
Current tobacco use (%)	78	28	273	21	0.1707
Coronary artery disease (%)	74	7	258	11	0.3812
History of stroke or TIA prior to index stroke (%)	78	5	270	21	0.0006
Heart failure (%)	73	0	258	2	0.3452
Hyperlipidemia (%)	72	28	254	43	0.0285
Peripheral vascular disease (%)	71	0	236	4	0.1240
Antiplatelet therapy at the time of index stroke (%)	76	11	270	36	<0.0001
Anticoagulant therapy at the time of index stroke (%)	72	3	255	1	0.2117
Median NIHSS score near admission (IQR)	58	3 (1, 7)	228	4 (2, 9)	0.0553
IV TPA for index stroke (%)	78	9	269	19	0.0551
Death within 30 days (%)	67	1	208	2	>0.90
Antithrombotic therapy at discharge					
ASA (%)	78	59	263	53	0.3669
Clopidogrel (%)	78	18	263	19	>0.90
Dual antiplatelet (%)	78	13	263	20	0.1835
Warfarin/vitamin K antagonist only (%)	78	8	263	3	0.0980
Rivaroxaban, dabigatran or apixaban only (%)	78	1	263	2	>0.90
None only (%)	78	0	263	2	0.5776

ASA: aspirin; ESUS: embolic strokes of undetermined source; IQR: interquartile range; TIA: Transient Ischemic Attack; IV: Intra venous; TPA: Tissue plasminogen activator; yrs: years.

<sup>a</sup>Only complete cases used to calculate the percentages.

<sup>b</sup>P values for categorical comparison – Fisher’s exact test; P values for continuous comparison – Wilcoxon rank-sum test.

**Table 5.** Frequency of potential minor risk embolic sources among ESUS patients  $\leq 50$  years vs.  $> 50$  years.

Minor risk potential embolic sources	Age $\leq 50$ N (%)	Age $> 50$ N (%)	P value <sup>a</sup>
Carotid artery non-stenotic plaques <sup>b</sup>	37 (69)	171 (82)	0.0393
Mitral annular calcification and thickening with myxomatous changes <sup>c</sup>	0 (0)	17 (7)	0.0296
Aortic valve stenosis and calcification <sup>c</sup>	1 (1)	23 (9)	0.0367
Hypokinetic/akinetic left ventricle <sup>c</sup>	3 (4)	10 (4)	$> 0.90$
Moderate-to-severely dilated left atrium <sup>c</sup>	6 (8)	13 (5)	0.3894
Aortic arch atherosclerotic plaques <sup>d</sup>	1 (3)	34 (40)	$< 0.0001$
Patent foramen ovale <sup>c</sup>	7 (10)	12 (5)	0.1487
Patent foramen ovale <sup>d</sup>	12 (32)	19 (22)	0.2605
Any minor risk potential embolic sources	49 (63)	209 (77)	0.0197
$\geq 2$ minor-risk embolic sources	11 (14)	72 (26)	0.0240

ESUS: embolic strokes of undetermined source; TTE: Transthoracic Echocardiogram; POCS: Posterior Circulation Stroke; CTA: Computed Tomography Angiogram; MRA: Magnetic Resonance Angiogram.

<sup>a</sup>P values for categorical comparison – Fisher's exact test.

<sup>b</sup>In all ESUS patients excluding POCS either on CTA, MRA or carotid ultrasonography.

<sup>c</sup>ESUS patients who had TTE.

<sup>d</sup>ESUS patients who had TEE.

similar to those enrolled in the trials (i.e. older patients) or are they quite different in their clinical characteristics and embolic sources. Approximately 10% of ischaemic strokes occur in people under the age of 50 years, the age threshold most often used to define 'young-onset stroke'.<sup>6</sup> While the age cut off is biologically arbitrary, it is based on the differing clinical characteristics, risk factors and stroke aetiologies between younger and older stroke patients. By available estimates, 15–20% of ESUS patients will be under 50 years of age and not included in the RCTs. To our knowledge, there is only one study published that reports the clinical characteristics of young ESUS patients (age  $< 55$  years) and this study is limited by the small sample size.<sup>7</sup> Our multicentre study found that young ESUS patients comprise about one in four ischaemic strokes in patients aged 50 years and under with a varying proportion between centres. The most likely reason for the varying proportion of young ESUS patients between centres is the extent of diagnostic tests performed at each centre and this reflects the existing variations in global practice in diagnostic testing at major stroke research centres. For example, one in five young ischaemic stroke patients was not considered to be ESUS due to lack of diagnostic testing to meet the ESUS criteria. 24-holter monitoring and echocardiography required for the diagnosis of ESUS was not routinely done in young ischaemic stroke patients at many centres, so only a small fraction could be categorized as ESUS. Therefore, this rate is likely to be higher at centres that routinely undertake the complete diagnostic evaluation required to meet

ESUS criteria. In contrast, the frequency of ESUS patients might be lower in centres that perform more extensive examinations for stroke aetiology (e.g. 30-day Electrocardiogram (ECG) monitoring, cardiac MRI, advanced intracranial vessel imaging, advanced carotid plaque imaging and routine TEE). The frequency seen in our study is consistent with the frequency of ESUS noted in the most recent systematic review of ESUS patients.<sup>8</sup> In our study, when those patients who did not undergo the complete diagnostic investigation required for ESUS diagnosis were excluded ( $n = 60$ , most often lack of cardiac investigations), the frequency of ESUS was 30%. Considering an estimated 40–45% frequency of cryptogenic ischaemic strokes in young adults based on the recent literature,<sup>6,8</sup> this frequency of ESUS supports the notion that most (but not all) non-lacunar cryptogenic ischaemic strokes are likely due to embolism.

Young ESUS patients on average had relatively minor strokes (median NIHSS 3) with a low 30-day mortality rate (1%). Their mean age (40 years) was similar to non-ESUS ischaemic stroke patients without AF, but significantly lower than, that of non-ESUS stroke patients with atrial fibrillation (43 years). The mild severity of stroke in ESUS patients is consistent with smaller emboli, e.g. originating from cardiac valves and arterial sources, in contrast to larger emboli that typically originate in the cardiac chambers (e.g. left atrial thrombus in patients with atrial fibrillation).<sup>9</sup> Our observations regarding stroke severity are consistent with those regarding ESUS patients from the Athens Stroke Registry.<sup>10</sup> The substantially

younger age and milder strokes of ESUS patients compared with patients with AF-associated stroke support different embolic origins in the majority of patients (i.e. that undiagnosed paroxysmal atrial fibrillation is unlikely to underlie most ESUS).

Of interest, AF was identified only in 5% of consecutive young ischaemic stroke patients compared to 20–30% of older ischaemic stroke patients.<sup>5</sup> Recent studies suggest that prolonged (>1 month) cardiac rhythm monitoring identifies additional patients with cryptogenic stroke who have episodes of paroxysmal atrial fibrillation,<sup>11,12</sup> often brief and of uncertain aetiological relevance.<sup>13</sup> More recent studies have shown a strong and significant correlation between the mean age of the stroke cohort and the frequency of AF.<sup>14</sup> These possibly could be the reasons for the lack of routine prolonged cardiac monitoring seen in these patients.

Interestingly, there was a relatively high frequency of conventional vascular risk factors and prior brain infarction in ESUS patients with a mean age of 40 years. Since ours is the first study assessing these factors, it is difficult to know whether this potentially represents patient selection or accurate characterization of young ESUS patients. Further studies are needed to clarify this. The relatively high frequency of prior brain infarction on MRI hints at a high stroke recurrence risk in young ESUS patients. It is known from the ongoing large randomized trials that the stroke recurrence risk among older ESUS patients is higher than expected.

However, the frequency of conventional vascular risk factors was less frequent among young ESUS patients than older ESUS patients. Most (63%) young ESUS patients had at least one minor-risk embolic source identified that could have been the cause of stroke, and nearly one in six (14%) had two or more potential embolic sources identified. However, the majority of the minor embolic sources were carotid artery non-stenotic plaques, a condition that is often thought to be only a marker of atherosclerotic disease but not the cause of ischaemic stroke. Interestingly, the frequency of PFO among young ESUS patients undergoing TEE (32%) was not significantly increased over that expected in the general population. This may be explained by the small sample size plus the fact that TEE is not mandatory according to ESUS criteria and was used selectively, as only 38% of the young stroke patients had a TEE. The prevalence of PFO has been described in cryptogenic stroke patients but has not yet been described in an ESUS population and the significance of PFO in a younger ESUS population is yet to be determined.

Antiplatelet therapy was used for secondary stroke prevention in two-thirds of young ESUS patients, in line with recent guideline recommendations.<sup>15–17</sup>

Interestingly, close to one in six patients were discharged on dual antiplatelet therapy even though there is no evidence to suggest a clear benefit of dual antiplatelet therapy over monotherapy in this situation. This may reflect the clinical equipoise that exist among physicians about best management of these patients. Although emboli vary in composition, almost all include thrombus, and it has been proposed that anticoagulants could offer more protection against recurrent stroke for ESUS patients than antiplatelet agents.<sup>1</sup> Ongoing trials will show whether novel anticoagulant drugs will be superior to aspirin in ESUS patients.<sup>2–4</sup>

Limitations of this study include participation of selected, high-volume stroke centres. A single site in each country may not accurately reflect the spectrum of stroke. However, the study sites represented many global regions allowing characterization of ESUS patients around the world. To ensure data quality in this retrospective study, standardized data collection forms were used along with specific definitions. The cross-sectional design of the study is another limitation, which did not allow us to gather data on prognosis and treatment effects of young ESUS patients. This limits our ability in this study to assess whether the younger patients with ESUS are at a lower risk of future stroke than older patients and the treatment responses.

## Conclusion

In summary, this study provides a benchmark for the global frequency and clinical features of young patients with ESUS. Young ESUS patients comprise an important subset of ischaemic stroke patients around the world. Severity of stroke on admission and 30-day mortality rates are similar among young and older patients. However, there are important differences between younger vs. older ESUS patients with respect to risk factors, and potential embolic sources that could affect response to anticoagulants vs. antiplatelet therapies.

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### Informed consent

Informed consent was waived by all involved Ethics Boards for this retrospective chart review.

### Ethical approval

The study was approved by an institutional review committee at each participating centre.

### Guarantor

KSP.

### Contributorship

KSP and RH researched literature and conceived the study. BS was involved in data analysis. KSP wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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