



# Embolic strokes of undetermined source: the case for a new clinical construct

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Cryptogenic (of unknown cause) ischaemic strokes are now thought to comprise about 25% of all ischaemic strokes. Advances in imaging techniques and improved understanding of stroke pathophysiology have prompted a reassessment of cryptogenic stroke. There is persuasive evidence that most cryptogenic strokes are thromboembolic. The thrombus is thought to originate from any of several well established potential embolic sources, including minor-risk or covert cardiac sources, veins via paradoxical embolism, and non-occlusive atherosclerotic plaques in the aortic arch, cervical, or cerebral arteries. Accordingly, we propose that embolic strokes of undetermined source are a therapeutically relevant entity, which are defined as a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources, with a clear indication for anticoagulation. Because emboli consist mainly of thrombus, anticoagulants are likely to reduce recurrent brain ischaemia more effectively than are antiplatelet drugs. Randomised trials testing direct-acting oral anticoagulants for secondary prevention of embolic strokes of undetermined source are warranted.

## Introduction

Despite the high incidence of cryptogenic strokes (which comprise about 25% of ischaemic strokes) and their importance (about 300 000 incident cases annually in North America and Europe), there has been little progress in secondary prevention during the past two decades. No randomised trials devoted specifically to cryptogenic stroke have defined optimum antithrombotic prophylaxis. In this Personal View, we develop the construct that most of these strokes are embolic, and propose the pragmatic clinical construct of embolic stroke of undetermined source (ESUS) as the basis for future randomised trials for secondary prevention.

## Embolic strokes

Ischaemic stroke has long been recognised to result from several different causes of obstruction of the arteries supplying the brain (figure 1). Most non-lacunar ischaemic strokes are embolic; haemodynamic mechanisms, vasospasm, and in-situ thrombotic occlusion are collectively less common causes than embolism.<sup>1,2</sup> Emboli to the brain can originate from the mitral or aortic valves or the left cardiac chambers (cardiogenic embolism), from proximal cerebral arteries or the aortic arch (arteriogenic embolism), and from the veins (paradoxical embolism). Although brain emboli can vary in composition (and can include tumour cells, calcific fragments, and infective thrombi), almost all contain, in whole or in part, a thrombus, which is the pathological basis of the term thromboembolic stroke. Embolic obstructions typically recanalise spontaneously, resulting in open arteries resupplying the infarcted brain—a hallmark of embolic stroke.<sup>3–7</sup> Most strokes are embolic,<sup>8,9</sup> even when ischaemic stroke occurs distal to occlusive atherosclerosis.<sup>10–14</sup>

Embolism underlies most non-lacunar brain infarcts associated with open proximal arteries. In about 20% of

patients who have had ischaemic stroke, a major risk cardiac source, such as atrial fibrillation or left ventricular thrombi, is identified (figure 1). However, in many patients, the specific source might be uncertain because there are often many potential low-risk embolic sources, such as left ventricular dysfunction, mitral annular calcification, patent foramen ovale, left atrial stasis associated with atrial tachycardia, non-stenotic atherosclerotic carotid plaques, and aortic arch atheroma.<sup>15</sup> Non-lacunar strokes without an identified cardioembolic source or due to occlusive atherosclerosis have usually been termed cryptogenic—ie, of unknown cause. We propose that ESUS is a more clinically useful, positively defined construct than is the vague, negatively defined entity of cryptogenic stroke.

## Potential sources of thromboembolism underlying ESUS

### Cardiac sources

Many patients with ESUS have common cardiac abnormalities that are associated with embolic stroke but have a sufficiently low inherent risk of embolism that a causal role of stroke at the patient level is unclear (panel 1, figure 2). For example, patent foramen ovale has a population prevalence of about 25% and is not a risk factor for stroke in the general population;<sup>19</sup> however, this defect has been well documented in some patients with stroke to be the conduit for paradoxical

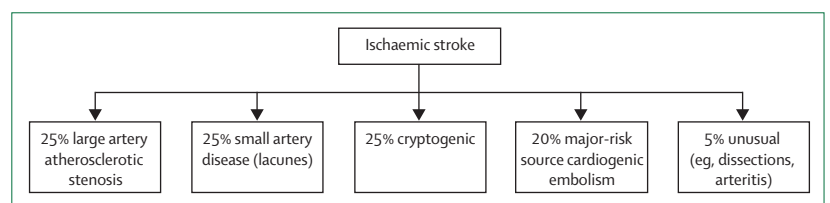


Figure 1: Distribution of ischaemic stroke subtypes in North American and European studies

The distribution in Asian and African populations differs from that in North American and European populations.

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See Comment page 344

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embolism of a venous thrombus.<sup>16,20,21</sup> Results of case-control studies have consistently shown a higher frequency of patent foramen ovale in patients with cryptogenic stroke than in age-matched controls without stroke,<sup>20–24</sup> although it is usually not possible to convincingly establish this as the cause in individual patients.<sup>25</sup>

Minor-risk cardioembolic sources are associated with a low rate of initial stroke, and are more often incidental than the actual cause of stroke.<sup>15</sup> Consequently, antithrombotic therapy is not recommended for primary stroke prevention for patients in whom minor-risk sources have been identified. These include moderate left ventricular systolic dysfunction with or without heart failure,<sup>8</sup> left ventricular diastolic dysfunction that can promote atrial stasis and thrombus formation,<sup>26</sup>

#### Panel 1: Causes of embolic strokes of undetermined source

##### Minor-risk potential cardioembolic sources\*

###### Mitral valve

- Myxomatous valvulopathy with prolapse
- Mitral annular calcification

###### Aortic valve

- Aortic valve stenosis
- Calcific aortic valve

###### Non-atrial fibrillation atrial dysrhythmias and stasis

- Atrial asystole and sick-sinus syndrome
- Atrial high-rate episodes
- Atrial appendage stasis with reduced flow velocities or spontaneous echodensities

###### Atrial structural abnormalities

- Atrial septal aneurysm
- Chiari network

###### Left ventricle

- Moderate systolic or diastolic dysfunction (global or regional)
- Ventricular non-compaction
- Endomyocardial fibrosis

##### Covert paroxysmal atrial fibrillation

###### Cancer-associated

- Covert non-bacterial thrombotic endocarditis
- Tumour emboli from occult cancer

###### Arteriogenic emboli

- Aortic arch atherosclerotic plaques
- Cerebral artery non-stenotic plaques with ulceration

###### Paradoxical embolism

- Patent foramen ovale
- Atrial septal defect
- Pulmonary arteriovenous fistula

\*Minor-risk sources are more often incidentally present than is the stroke cause when identified in an individual stroke patient, are associated with a low or uncertain rate of initial stroke, and consequently cause-effect relation and management implications are usually unclear.

persistent left ventricular regional wall motion abnormalities or aneurysms after myocardial infarction,<sup>27</sup> left ventricular non-compaction,<sup>28</sup> myxomatous mitral valve disease with prolapse,<sup>29</sup> mitral annular calcification,<sup>30–33</sup> atrial septal aneurysms,<sup>21,34–37</sup> and calcific aortic stenosis.<sup>38,39</sup> At least one of these minor-risk cardiac abnormalities is present in about half of patients with ischaemic stroke or transient ischaemic attack.<sup>9,40–45</sup> In summary, common cardiac lesions with low, but well documented, embolic potential are often detected in patients with ESUS. From a population perspective, each lesion has been established as a potential source of embolism. However, at the individual patient level, the lesions might be coincidental, meaning the source of embolism cannot be reliably identified in most patients. In further support of the importance of cardioembolic causes of ESUS, a study of gene expression profiles estimated that cardiogenic embolism accounted for 58% of cryptogenic strokes.<sup>46</sup>

Attention has focused on covert paroxysmal atrial fibrillation as a potential cause of cryptogenic stroke. Researchers in several studies in which patients with cryptogenic ischaemic stroke have undergone extended (7–30 days) cardiac rhythm monitoring have detected paroxysmal atrial fibrillation in 10–20% of patients.<sup>47–55</sup> However, in many patients the duration of paroxysmal atrial fibrillation is short, and whether brief episodes lasting seconds to minutes are thrombogenic and justify anticoagulation is uncertain.<sup>56,57</sup> Other common cardiac rhythm abnormalities are also associated with thromboembolic stroke, including paroxysmal atrial flutter,<sup>58</sup> paroxysmal supraventricular tachycardia,<sup>59–61</sup> sick sinus syndrome,<sup>62,63</sup> and atrial high-rate episodes in patients with cardiac pacemakers.<sup>64</sup> As with the minor-risk cardiac structural abnormalities, these rhythm abnormalities are also common and, although associated with an increased risk of stroke at the population level, whether they have a causal role at the individual patient level is difficult to know. Thromboemboli that originate in the left atrium and its appendage due to covert paroxysmal atrial fibrillation and other stasis-precipitating dysrhythmias are important contributors to ESUS.

##### Arterial sources

Non-stenotic (<50% diameter stenosis) atherosclerotic carotid artery plaques are common (about 15%) in the elderly population and carry a low absolute risk of stroke.<sup>14</sup> However, non-stenotic carotid and vertebral artery plaques can be a source of arteriogenic thromboembolism, especially if ulcerated and irregular (figure 2).<sup>14,65–71</sup> For example, in 32 patients with cryptogenic stroke and non-stenotic carotid artery plaques undergoing high-resolution carotid MRI, type VI complicated plaques were present in 38% of carotid arteries ipsilateral to the stroke versus 0% contralateral.<sup>65</sup> Consistent results of case-control and pathological studies have firmly linked aortic arch atheroma (present

in about 30% of the stroke-prone age group) with thromboembolic stroke (figure 2).<sup>17,72–83</sup> A widely accepted notion is that aortic arch atheroma is an underdiagnosed cause of ischaemic stroke, the mechanism of which is thromboembolic.<sup>81</sup> Imaging of the aortic arch via transoesophageal echocardiography or CT angiography is not routinely done in most patients with stroke because there are no evidence-based management implications.

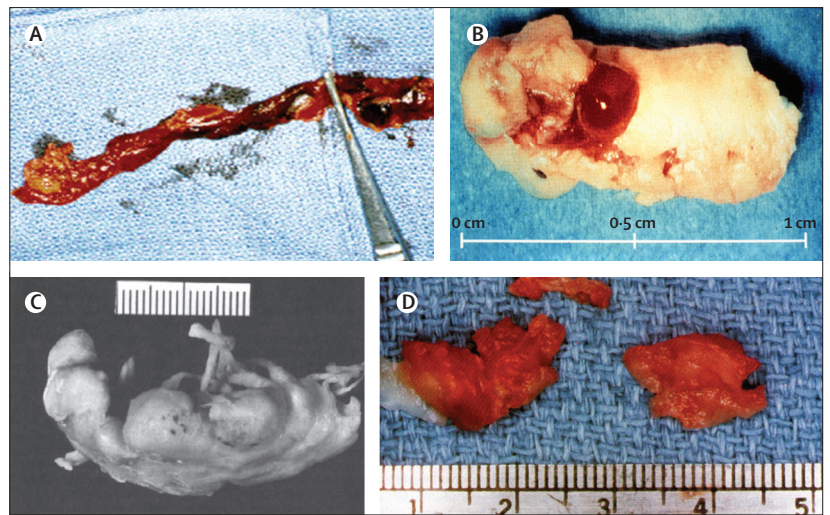
Although small, deep infarcts can sometimes result from embolism from proximal sources, most seem to be due to local microatheroma, non-thrombotic occlusion (eg, lipohyalinosis), or endothelial failure, and are defined as lacunar infarcts.<sup>84–86</sup> Recurrent strokes are usually lacunar,<sup>87,88</sup> but whether antithrombotic agents effectively prevent recurrent lacunar stroke and could exacerbate the particularly high risk of intracerebral haemorrhage associated with lacunar strokes is unclear.<sup>87,88</sup> Although small, deep infarcts occasionally result from embolism, exclusion of such patients from a diagnosis of ESUS is sensible.

### Diagnosis of ESUS

Investigations to establish a diagnosis of ESUS must be sufficient to exclude major-risk cardioembolic sources, proximal occlusive atherosclerosis, and lacunar strokes due to cerebral small artery disease (panel 2). The proposed approach is informed partly by the response of these excluded stroke causes to specific interventions, such as revascularisation for secondary prevention in patients with ipsilateral occlusive carotid artery stenosis, and anticoagulation for patients with stroke associated with major-risk cardioembolic sources such as atrial fibrillation, based on the results of randomised clinical trials.

We propose a step-wise approach to the diagnosis of ESUS (panel 3). The initial step is visualisation of the brain infarct by neuroimaging to confirm the diagnosis of ischaemic stroke (stroke mimics are not rare) and to exclude lacunar infarcts based on infarct topography. The second step is to exclude major-risk cardioembolic sources with ECG and Holter monitoring to detect atrial fibrillation, and with echocardiography to detect intraventricular thrombus. Vascular imaging by MR or CT angiography or ultrasonography must be done to exclude occlusive proximal atherosclerosis. Finally, other uncommon causes of brain ischaemia—eg, migraine-related, arteritis, arterial dissection, reversible cerebral artery vasoconstriction syndrome—must be absent. These disorders are uncommon except in young patients with stroke and are suggested by concomitant systemic features. This diagnostic assessment is routinely done at many stroke centres and could be applied widely if effective interventions for secondary stroke prevention in patients with ESUS were established.

Covert paroxysmal atrial fibrillation can be detected in 10–20% of patients with cryptogenic ischaemic stroke, but many detected episodes of atrial fibrillation are of



**Figure 2: Causes of embolic stroke**

Thrombus trapped in a patent foramen ovale (A). Thrombus overlying an ulceration on a carotid artery plaque (B). Myxomatous mitral valve with small thrombi attached to a roughened surface (C). Thrombus removed from aortic arch during surgery from a patient with leg embolus (D). Reprinted, with permission, from Srivastava and Payment,<sup>16</sup> Kronzon and Tunick,<sup>17</sup> and Barnett.<sup>18</sup>

short (ie, seconds to minutes) duration.<sup>47–55</sup> Few data are available to define what duration is needed to substantially increase the risk of stroke and thus merit anticoagulation. Furthermore, few of the available monitoring studies have included a non-stroke control group of similarly aged patients;<sup>37</sup> nor is there a strong consensus on the appropriate duration of monitoring after stroke to exclude atrial fibrillation. Guidelines have been scarce on this important issue; the two available guidelines recommend Holter cardiac monitoring for at least 24 h.<sup>89,90</sup> There is as yet no persuasive evidence that prolonged cardiac rhythm monitoring of patients with cryptogenic stroke leads to reduced stroke recurrence.

### Cryptogenic stroke versus ESUS

About 25% of ischaemic strokes have been categorised in studies as cryptogenic (figure 1, table).<sup>8,54,91–116</sup> This proportion varies according to the patient population (largest in young stroke and transient ischaemic attack cohorts), the criteria for classification as cryptogenic (no generally accepted definition exists), and the extent of diagnostic assessment (not specified and often not reported). The most widely used criteria for ischaemic stroke subtype classification have been those of the Trial of Org10172 in Acute Stroke Treatment (TOAST), developed in the early 1990s.<sup>115</sup> The TOAST definition includes three circumstances for categorisation as stroke of undetermined cause, or cryptogenic stroke: the diagnostic assessment is incomplete, no cause is found despite an extensive assessment, or, most likely, a cause cannot be established because more than one plausible cause is found. Alternative classification schemes for ischaemic stroke have been proposed that seek to assign a specific cause to individual patients.<sup>103,104,110,117,118</sup> Inter-rater

### Panel 2: Criteria for diagnosis of embolic stroke of undetermined source\*

- Stroke detected by CT or MRI that is not lacunar†
- Absence of extracranial or intracranial atherosclerosis causing  $\geq 50\%$  luminal stenosis in arteries supplying the area of ischaemia
- No major-risk cardioembolic source of embolism‡
- No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, drug misuse)

\*Requires minimum diagnostic assessment (panel 3). †Lacunar defined as a subcortical infarct smaller than or equal to 1.5 cm ( $\leq 2.0$  cm on MRI diffusion images) in largest dimension, including on MRI diffusion-weighted images, and in the distribution of the small, penetrating cerebral arteries; visualisation by CT usually needs delayed imaging greater than 24–48 h after stroke onset. ‡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 less than 30%, valvular vegetations, or infective endocarditis.

### Panel 3: Proposed diagnostic assessment for embolic stroke of undetermined source\*

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for  $\geq 24$  h with automated rhythm detection†
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)

\*Imaging of the proximal aortic arch is not needed; special blood tests for prothrombotic states only if the patient has a personal or family history of unusual thrombosis or associated systematic signs or disorder. †Cardiac telemetry is not sufficient.

agreement is especially poor for strokes of unknown cause using the TOAST criteria.<sup>119</sup> With any of these classification schemes, a substantial proportion of ischaemic strokes were categorised as cryptogenic in recent studies (table).

Patients with ESUS are a subset of patients with cryptogenic stroke who have embolic strokes and sufficient diagnostic assessment to exclude major-risk cardioembolic sources, occlusive atherosclerosis, and lacunar stroke (panel 4). In a study of 274 consecutive stroke unit patients,<sup>8</sup> 89 (32%) met these criteria. In studies in which the necessary diagnostic assessment for ESUS has been done, patients with stroke meeting criteria for ESUS had a mean age of about 70 years, 45% were women, and, on average, 66% had hypertension, 35% had diabetes mellitus, and 30% had previous stroke (appendix p 1).<sup>8</sup> An unknown proportion of patients with ESUS, defined by the proposed criteria, are likely to have non-embolic stroke mechanisms (eg, in-situ thrombosis with recanalisation, vasospasm). Most studies used to develop the ESUS construct were done in predominantly white populations, and the

frequency and patient features might differ substantially in predominantly Chinese, African, or south Asian populations.

### Stroke recurrence rates

The reported rate of recurrent stroke in studies of patients with cryptogenic stroke varies widely, because of varying criteria for diagnosis, non-standardised antithrombotic treatment, and varying prognostic factors (particularly mean patient age), but is an average of 3–6% per year (appendix pp 2–5). Young patients (average age mid-40s) with cryptogenic stroke associated with patent foramen ovale have stroke recurrence rates averaging 1–2% per year when given aspirin,<sup>20,120–123</sup> but the recurrence rate is substantially higher in older patients with stroke associated with patent foramen ovale stroke (14% per year in one report),<sup>121</sup> probably indicating the roles of other causes in addition to paradoxical embolism.

### Antithrombotic therapy for secondary stroke prevention in ESUS

The only randomised assessment of anticoagulation in cryptogenic stroke is the subgroup analysis of the Warfarin-Aspirin Recurrent Stroke Study (WARSS) done between 1993 and 2000.<sup>94,124</sup> Among 2206 patients aged between 30 and 85 years with recent (<30 days) ischaemic stroke who were randomly assigned to aspirin 325 mg per day or adjusted-dose warfarin (target international normalised ratio [INR] 1.4–2.8, median achieved INR 1.9), 576 (26%) strokes were deemed cryptogenic on the basis of the TOAST criteria. For patients with cryptogenic stroke, the primary outcome of ischaemic stroke or death occurred in 15.0% of those assigned to warfarin versus 16.5% of those assigned to aspirin over 2 years (hazard ratio [HR] 0.92, 95% CI 0.6–1.4); results limited to recurrent stroke have not been published.<sup>94</sup> For 338 participants with cryptogenic stroke whose CT showed an embolic topography—ie, superficial, cortical or cerebellar, large deep, or superficial and deep combined infarcts, which exclude a diagnosis of lacunar strokes—the 2 year rate of recurrent ischaemic stroke or death was 12% with warfarin versus 18% with aspirin (HR 0.66, 95% CI 0.4–1.2).<sup>124</sup>

In the Patent Foramen Ovale in Cryptogenic Stroke Study,<sup>125</sup> a substudy of WARSS, 260 of the 576 patients (45%) with cryptogenic stroke consented to undergo transoesophageal echocardiography as part of the study protocol. In this subset of participants, the primary outcome (2 year rate of recurrent ischaemic stroke or death) was halved in those assigned to warfarin (9% warfarin vs 17% aspirin). Despite the low achieved INR, data from the WARSS subgroup support the notion that anticoagulation might be more efficacious than aspirin for patients with cryptogenic ischaemic stroke when those with lacunar stroke topography are excluded. The occurrence of recurrent stroke in participants with increased N-terminal pro-brain natriuretic peptide

See Online for appendix

concentrations, a marker of cardioembolic stroke, was reduced by 70% ( $p=0.02$ ) with warfarin compared with aspirin in the WARSS trial, from which patients with major-risk cardioembolic sources were excluded.<sup>126</sup>

For patients with major-risk cardiogenic sources of embolism (eg, atrial fibrillation, severe left ventricular dysfunction), results of randomised trials have shown that anticoagulants notably reduce embolic strokes compared with antiplatelets.<sup>127–129</sup> Adjusted-dose warfarin halved the stroke rate in patients with reduced left ventricular dysfunction without atrial fibrillation.<sup>129</sup> The oral factor Xa inhibitors apixaban and rivaroxaban, and the oral direct thrombin inhibitor dabigatran, are at least as efficacious as warfarin for prevention of stroke in patients with atrial fibrillation, and have significantly lower rates of intracranial bleeding.<sup>130</sup> In view of the common mechanism of thromboembolism, a reasonable hypothesis is that oral vitamin K antagonists and the direct-acting oral anticoagulants would reduce recurrent brain ischaemia more effectively than would antiplatelets in patients with ESUS who have minor-risk cardioembolic sources.

No randomised trials have tested anticoagulants in patients with cryptogenic strokes associated with patent foramen ovale. In the subgroup of these patients with paradoxical embolism of venous origin, anticoagulants are likely to be highly efficacious, on the basis of consistent results in prevention and treatment of venous thromboembolism.<sup>131</sup>

Little is known about the relative efficacy of anticoagulant versus antiplatelet therapy for secondary stroke prevention for arteriogenic embolism to the brain, but available data support greater efficacy of anticoagulants. The conventional dichotomy between antiplatelet-responsive white clot (platelet-rich), arterial origin embolism versus anticoagulant-responsive red clot (fibrin-rich), venous-precipitated, or stasis-precipitated embolism is not absolute. Results of double-blind randomised trials show that aspirin reduces venous thromboembolism (ie, red clot) by 30% for many patients,<sup>132</sup> whereas clots on the surface of complicated aortic arch plaques and carotid artery plaques can be red and thrombin-rich (figure 2). Warfarin and aspirin have equal efficacy for prevention of myocardial infarct in patients with coronary artery

	Population	N	Mean age (years)	Criteria for cryptogenic stroke	Frequency
Besancon Stroke Registry (2000) <sup>91</sup>	Prospective registry	1776	71	Study specific	18%†
Athens Stroke Registry (2000) <sup>92</sup>	Prospective registry of first-ever strokes	885	70	Not specified	21%
German Stroke Data Bank (2001) <sup>93</sup>	Prospective registry	5017	66	Modified TOAST criteria	23%
WARSS (2001) <sup>94</sup>	Randomised trial	2206	63	TOAST criteria	26%
Erlangen Study (2001) <sup>95</sup>	Population-based	583	73	TOAST criteria	32%
Ankara (2002) <sup>96</sup>	Prospective registry	264	66	TOAST criteria	33%
Suwon (2003) <sup>97</sup>	Prospective registry	204	62	TOAST criteria	18%
TULIPS (Japan) (2004) <sup>98</sup>	Prospective registry	831	72	NINDS SDB	23%
Perugia (2006) <sup>99</sup>	Prospective stroke unit	358	NR	TOAST criteria	17%
PRoFESS (2008) <sup>100</sup>	Randomised trial	20 332	66	TOAST criteria	16%‡
Bern (2008) <sup>101</sup>	Prospective registry	1288	NR	TOAST criteria	39%
Buenos Aires (2010) <sup>90</sup>	Retrospective case series of stroke and TIA	155	67	TOAST criteria	27%
ASTRAL (2010) <sup>102</sup>	Prospective inpatient registry	1633	73	Modified TOAST criteria	12%§
North Dublin (2010) <sup>103</sup>	Population-based registry	381	NR	Causative Classification System <sup>104</sup>	26%
VITATOPS (2010) <sup>105</sup>	Randomised trial	8164	63	Study specific <sup>106</sup>	14%
PERFORM (2011) <sup>107</sup>	Randomised trial	19 100	67	Study specific <sup>108</sup>	22%
Mannheim Stroke Center (2012) <sup>109</sup>	Prospective case series	103	69	TOAST criteria	30%
Hebi, China (2012) <sup>110</sup>	Retrospective case series	425	65	TOAST criteria	16%
South Korea (2012) <sup>111</sup>	Prospective hospital-based registry	3278	64	TOAST criteria	21%
Miami/Mexico City (2012) <sup>112</sup>	Prospective registry of Hispanics	671	NR	Modified TOAST criteria	17%
Santiago, Chile (2012) <sup>113</sup>	Prospective stroke unit	380	66	TOAST criteria	20%
Barcelona (2012) <sup>8</sup>	Prospective stroke unit	274	NR	TOAST criteria	32%
Santiago de Compostela (2013) <sup>114</sup>	Prospective case series	1050	NR	TOAST criteria	35%
Bavaria (2013) <sup>54</sup>	Prospective stroke unit	..	NR	TOAST criteria	17%

TOAST=Trials of Org 10172 in Acute Stroke Treatment.<sup>115</sup> NR=not reported. TIA=transient ischaemic attack. NINDS SDB=National Institute of Neurological Disorders and Stroke Data Bank. \*English-language studies published since 2000, reporting the frequency of cryptogenic stroke. Petty and colleagues<sup>116</sup> not included; although published in 2000, data were from the 1980s. †An additional 15% had non-stenotic carotid artery atheroma that would be deemed cryptogenic by TOAST criteria.<sup>115</sup> ‡The high proportion with presumed small artery disease (52%) supports a selected stroke population, consistent with the trial exclusion criteria. §TOAST modifications: "likely atherothrombotic" based on risk factors less than 50% stenoses. An additional 4% had "likely patent foramen ovale", and most of the 13% with "likely atherothrombotic" would be cryptogenic by other criteria, and hence more than 20% were cryptogenic by TOAST criteria.<sup>115</sup>

**Table: Frequency of cryptogenic ischaemic stroke in studies\***

disease,<sup>133</sup> and the direct-acting oral anticoagulants prevent arterial thrombosis in acute coronary syndromes.<sup>134,135</sup> In the ESPRIT trial<sup>136</sup> of 1068 patients with non-cardioembolic ischaemic stroke—ie, not restricted to cryptogenic stroke—random allocation to an oral vitamin K antagonist (mean achieved INR 2.6) was associated with a non-significant reduction in recurrent ischaemic stroke by 24% (HR 0.76, 95% 0.51–1.15) compared with aspirin. Clearly, anticoagulants reduce thrombotic events in the arterial circulation.

Investigators of two non-randomised comparisons<sup>82,83</sup> reported reductions in recurrent stroke with anticoagulation in patients with initial stroke attributed to aortic arch atherosclerosis, but this finding was not supported by results of subgroup analysis of the WARSS randomised trial, albeit with the caveat of the low INR achieved in WARSS.<sup>74</sup>

Although anticoagulation is likely to be more effective than aspirin for secondary prevention of stroke in patients with ESUS, some embolic sources included

under the ESUS umbrella might have a variable response to anticoagulation. Separation of relative effects in subgroups will be challenging because of the presence of several potential embolic sources overlapping in many patients, but nevertheless it will be an important aspect of initial clinical trials.

### Net clinical benefit of anticoagulation in patients with ESUS

In randomised trials of secondary prevention of ischaemic stroke that compared warfarin with antiplatelet therapies in patients with a range of ischaemic stroke mechanisms,<sup>136,137</sup> trends toward reduction in ischaemic strokes were offset by increases in major intracranial and extracranial haemorrhages. Patients with ESUS selected because of an embolic stroke mechanism are likely to respond especially well to anticoagulants, as discussed. The novel oral anticoagulants all have greatly reduced risks of intracranial bleeding compared with warfarin anticoagulation.<sup>130</sup> Furthermore, the risk of extracranial haemorrhage with some of the novel oral anticoagulants<sup>138</sup> seems to be lower than with warfarin and depends on dose.<sup>139</sup> Consequently, in terms of net clinical benefit that combines stroke and major haemorrhage (and particularly intracranial haemorrhage), novel oral anticoagulants seem likely to be of overall benefit in patients with ESUS.

### Guideline recommendations for secondary prevention

The 2008 American College of Chest Physicians guideline<sup>140</sup> and 2008 American Heart Association guideline specifically recommend antiplatelet therapy for patients with cryptogenic ischaemic stroke.<sup>141</sup> The European Stroke Organisation guideline,<sup>90</sup> the 2011 American Heart Association revised guideline,<sup>142</sup> the 2012 American College of Chest Physicians guideline,<sup>143</sup> and the 2010 Canadian Best Practice Recommendations for Stroke Care<sup>89</sup> do not comment specifically on cryptogenic stroke, but recommend antiplatelet therapy for patients with non-cardioembolic ischaemic stroke.

### Conclusions

Findings from recent monitoring and imaging studies show the many potential sources of embolism present in most patients with ischaemic stroke that potentially cause ESUS. When identified in individual patients, the causal association with stroke is usually not possible to prove. Quite often, more than one potential source is present in the same patient. Yet, an embolic mechanism is common to most of these strokes, with potential implications for secondary prevention.

Randomised clinical trials have addressed secondary prevention for patients with all major ischaemic stroke subtypes except cryptogenic stroke. Clinical research into cryptogenic stroke has been inhibited by the absence of standard diagnostic criteria and inadequate assessment.

#### Panel 4: Comparison of cryptogenic stroke versus embolic stroke of undetermined source

##### Diagnostic criteria

###### *Cryptogenic ischaemic stroke\**

- No arterial stenosis (>50%) or occlusion coupled with non-lacunar infarct on imaging
- No clinical lacunar syndrome if imaging shows no infarct or small (<1.5 cm) subcortical infarct
- No major-risk or medium-risk cardioembolic sources

###### *Embolic stroke of undetermined source (ESUS)*

- Non-lacunar brain infarct on imaging
- Open arteries (<50% stenosis) proximal to the infarct
- No major-risk cardioembolic source

##### Necessary diagnostic assessment

###### *Cryptogenic ischaemic stroke\**

Not specified†

###### *Embolic stroke of undetermined source (ESUS)*

- Brain CT or MRI showing non-lacunar infarct
- Precordial echocardiography
- ECG and cardiac monitoring for ≥24 h
- Imaging of the extracranial and intracranial arteries supplying the area of the brain infarct

##### Limitations

###### *Cryptogenic ischaemic stroke\**

- Inclusion of variable fraction of lacunar infarcts and intracranial arterial stenosis dependent on extent of diagnostic assessment (varies from study to study, and usually not described in detail)

###### *Embolic stroke of undetermined source (ESUS)*

- Transoesophageal echocardiography not recommended, and hence aortic arch atherosclerosis not characterised

ECG=electrocardiogram. \*Criteria for cryptogenic stroke are not standardised; TOAST criteria for stroke of undetermined cause are considered here, excluding those with two or more potential causes.<sup>135</sup> †Some patients will have no likely cause established despite an extensive assessment. In others, no cause is found but the assessment was cursory.<sup>135</sup> In most studies of cryptogenic stroke, the extent of diagnostic imaging is not reported.

We hypothesise that the dominant underlying mechanism of cryptogenic stroke is embolism from an unestablished source. Additional advanced diagnostic testing is unlikely to be a pragmatic solution for cryptogenic stroke because of the expense, additional diagnostic delays, and poor general availability, whereas the ESUS construct enables randomised trials for secondary prevention. We do not regard ESUS as a diagnosis of exclusion, but rather a diagnosis based on visualised non-lacunar infarct in the absence of proximal occlusive atherosclerosis or major-risk cardioembolic source. The validity of ESUS must ultimately be justified by the response to therapy—eg, anticoagulation. Randomised trials comparing oral anticoagulants with antiplatelet therapy for secondary prevention in patients with ESUS are warranted by the magnitude of the problem, and are justified by the effectiveness of warfarin for stroke prevention in patients with major-risk cardioembolic sources such as atrial fibrillation, subgroup analyses from previous warfarin trials, and the introduction of safer and more efficacious oral anticoagulants.

#### Contributors

RGH wrote the initial draft of the Review and supervised revisions. SJC and H-CD contributed to extensive revisions of the initial and subsequent drafts. SBC, JDE, CBG, MJO'D, and RLS each contributed substantially to the content and reviewed all drafts, providing edits and revisions.

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#### Declaration of interests

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own stocks of any pharmaceutical company. JDE has received consulting compensation and research support from AstraZeneca for the SOCRATES trial, and Sanofi provides drug and placebo for the POINT trial, for which JDE is coprincipal investigator, which is funded by the US National Institutes of Health. MJO'D has received honoraria from Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer for lecture presentations. RLS receives consulting income for participation in two academically run and pharmaceutically sponsored Data Safety and Monitoring Boards for clinical trials of antiplatelet agents in stroke and cardiovascular disease treatment (AstraZeneca). SJC declares that he has no competing interests.

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