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SPECIAL ARTICLE
Thrombosis and antithrombotic treatment

Embolic strokes of undetermined source: a clinical consensus statement of the ESC Council on Stroke, the European Association of Cardiovascular Imaging and the European Heart Rhythm Association of the ESC

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Abstract

One in six ischaemic stroke patients has an embolic stroke of undetermined source (ESUS), defined as a stroke with unclear aetiology despite recommended diagnostic evaluation. The overall cardiovascular risk of ESUS is high and it is important to optimize strategies to prevent recurrent stroke and other cardiovascular events. The aim of clinicians when confronted with a patient not only with ESUS but also with any other medical condition of unclear aetiology is to identify the actual cause amongst a list of potential differential diagnoses, in order to optimize secondary prevention. However, specifically in ESUS, this may be challenging as multiple potential thromboembolic sources frequently coexist. Also, it can be delusively reassuring because despite the implementation of specific treatments for the individual pathology presumed to be the actual thromboembolic source, patients can still be vulnerable to stroke and other cardiovascular events caused by other pathologies already identified during the index diagnostic evaluation but whose thromboembolic potential was underestimated. Therefore, rather than trying to presume which particular mechanism is the actual embolic source in an ESUS patient, it is important to assess the overall thromboembolic risk of the patient through synthesis of the individual risks linked to all pathologies present, regardless if presumed causally associated or not. In this paper, a multi-disciplinary panel of clinicians/researchers from various backgrounds of expertise and specialties (cardiology, internal medicine, neurology, radiology and vascular surgery) proposes a comprehensive multi-dimensional assessment of the overall thromboembolic risk in ESUS patients through the composition of individual risks associated with all prevalent pathologies.

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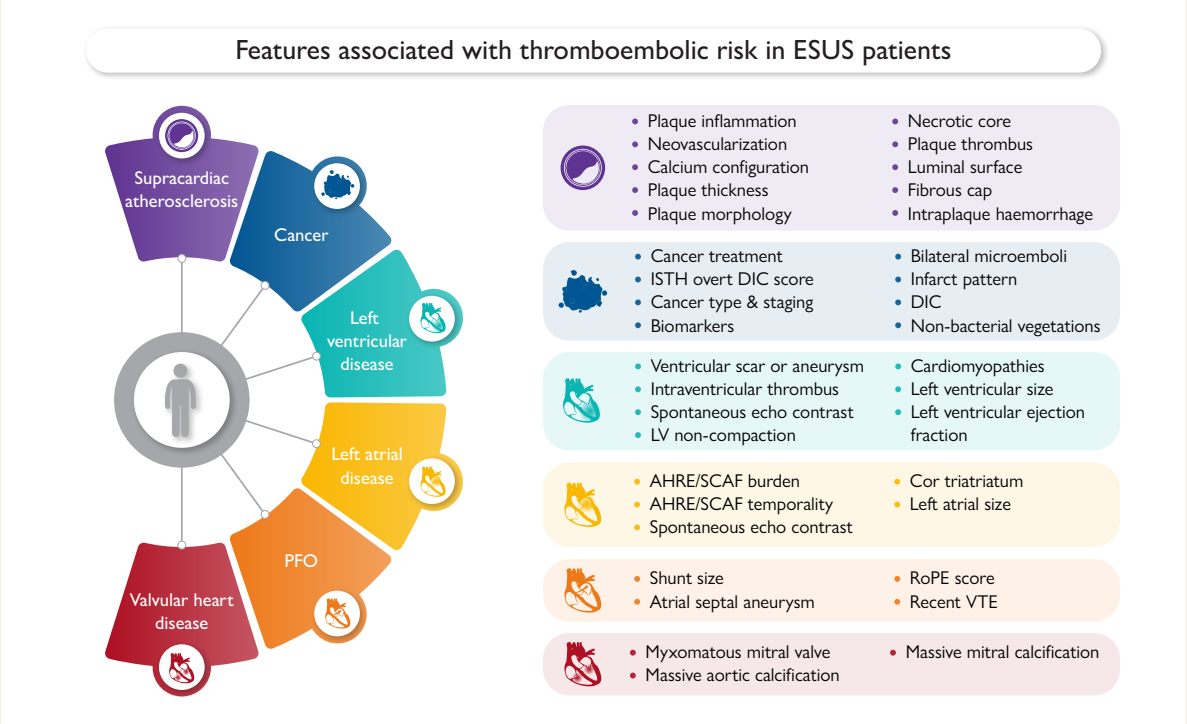
Graphical Abstract



AHRE, atrial high-rate episode; DIC, disseminated intravascular coagulation; ISHT, International Society on Thrombosis and Haemostasis; LV, left ventricular; RoPE, Risk of Paradoxical Embolism; SCAF, subclinical atrial fibrillation; VTE, venous thromboembolism.

Keywords Embolic stroke of undetermined source • Aetiology • Atherosclerosis • Patent foramen ovale • Left atrial disease • Left ventricular disease • Valvular heart disease • Cancer

Introduction

One in six patients with ischaemic stroke has an embolic stroke of undetermined source (ESUS), defined as a stroke that despite recommended diagnostic workup, a convincing underlying cause like atrial fibrillation (AF), atherosclerotic plaque with high-grade stenosis, and others could not be identified.[1–3] The term ESUS is not synonymous with the term 'cryptogenic stroke', as the latter also includes patients with multiple aetiologies, such as patients with both AF and atherosclerotic carotid stenosis ipsilateral to the infarct, and it also includes patients with incomplete diagnostic workup[4] (*Figure 1*). The introduction of the ESUS concept in 2014 was based on explicit definition and diagnostic criteria, facilitated clinical research, and was widely adopted in clinical practice.[1,5] Recently, an update of the ESUS criteria and diagnostic algorithm was published.[5]

Several pathologies can be the source of embolism in an ESUS patient, and they can be broadly categorized into supracardiac atherosclerosis, patent foramen ovale (PFO), and other right-to-left shunts, left atrial (LA) disease (including atrial arrhythmias and atrial cardiomyopathy), left ventricular (LV) disease, valvular heart disease, and cancer.[1–4] The overall cardiovascular risk of ESUS patients is high, and their 5-year cumulative probability for stroke recurrence and other cardiovascular events is 29% and 38%, respectively, which highlights the importance of optimizing secondary preventive strategies to prevent recurrent strokes and other cardiovascular outcomes.[3]

The aim of any physician, when confronted with a patient not only with ESUS but also with any other medical condition of unclear aetiology, is to identify the *actual* cause amongst a list of potential differential diagnoses, in order to optimize strategies of treatment and prevention. However, specifically in patients with ESUS, this may be challenging and delusively reassuring.[6] It can be *challenging* because in the majority of ESUS patients, multiple overlapping potential embolic sources exist, and it is frequently unclear which one was the actual embolic source.[7,8] Also, it can be *delusively reassuring* because despite the establishment of specific secondary preventive measures for the individual pathology presumed to be the actual embolic source, a patient can still be vulnerable to future stroke and other cardiovascular events caused by other pathologies that were already present during the ESUS diagnostic workup but their thromboembolic potential was underestimated. In this context, rather than trying to presume which particular mechanism is the actual embolic source in an ESUS patient, it is of utmost importance to assess the *overall* thromboembolic risk of the patient through the synthesis of the individual risks linked to all prevalent pathologies, regardless if they are deemed to be causally associated with ESUS or not. A paradigm shift is justified, away from the assumption-based and inherently uncertain diagnostic label of *embolic stroke due to [presumed potential cause]* to the more comprehensive diagnostic term of *embolic stroke in a patient with [all potential causes]*.[6] This can facilitate an integrated comprehensive approach to secondary prevention through the initiation of a bundle of therapeutic strategies according to the findings of the diagnostic workup, thereby optimizing the odds of achieving good patient outcomes.

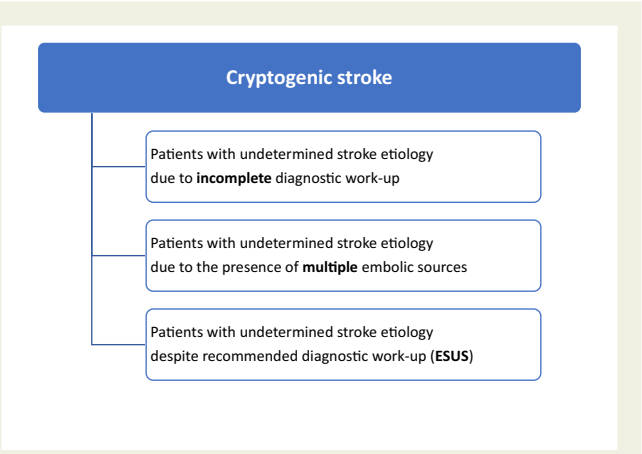


Figure 1 Distinction between the terms *cryptogenic stroke* and *embolic stroke of undetermined source*. ESUS, embolic stroke of undetermined source

In this position paper by the European Society of Cardiology (ESC) Council on Stroke in collaboration with the European Association of Cardiovascular Imaging and the European Heart Rhythm Association of the ESC, a multi-disciplinary panel of clinicians/researchers from various backgrounds of expertise and specialties (cardiology, internal medicine, neurology, radiology, and vascular surgery) proposes a comprehensive multi-dimensional assessment of the overall thromboembolic risk in patients with ESUS through the composition of individual risks associated with each of the six aforementioned broad pathologies (*Graphical Abstract*). It is emphasized that these are based largely on expert opinion and are summarized in *Table 1*. In addition, we discuss the potential implications for clinical practice and research and identify key knowledge gaps that should be addressed in future research.

Supracardiac atherosclerosis

The degree of carotid stenosis is considered the lead parameter for the assessment of a causal relation between the atherosclerotic process and an ischaemic event and for the prediction of the risk of stroke or transient ischaemic attack (TIA). This association was demonstrated >40 years ago in trials that showed the benefit of revascularization in patients with severe stenosis.[9] At that time, the degree of arterial stenosis was the only characteristic of the plaque that could be assessed *in vivo* with angiography. Nowadays, imaging technology not only can visualize the entire supracardiac arterial tree but can also provide detailed information about the structure and composition of the plaque and its potential risk of rupture.[10] Specific features of the plaque are associated with the risk of ischaemic events, regardless of the degree of stenosis.[11] The prevalence of complex carotid artery plaque in patients with ESUS is more than five times higher ipsilateral to the infarct than contralateral.[12–14] Also, the prevalence of complex carotid artery plaque in ESUS is two times higher compared with cardioembolic or small vessel stroke.[15] These findings underline the important association between the risk of ischaemic events and the vulnerability of the plaque, not only in ESUS patients but generally in any patient with carotid plaque, which can be assessed by several parameters, as follows.

Intra-plaque haemorrhage (IPH) is defined by the accumulation of blood components within the atheromatous plaque and is considered the most important feature of plaque vulnerability. In a meta-analysis of seven cohort studies including 560 patients with symptomatic carotid stenosis and 136 patients with asymptomatic carotid stenosis, IPH was a stronger predictor of stroke than any known clinical risk factor. Amongst patients with a <50% stenosis, the annualized rates of ipsilateral stroke were 9.0% amongst patients with IPH and 0.7% amongst patients without.[16] With magnetic resonance imaging (MRI), which is the best imaging technique for its detection, IPH can be classified according to its time of formation, either as fresh/acute (<1 week), recent (1–6 weeks), or remote/old (>6 weeks).[17] The risk of cerebrovascular events is highest with acute/recent IPH but remains elevated for more than 18 months.[18]

The *fibrous cap* (FC), a layer of fibrous connective tissue that separates the core of the plaque from the arterial lumen, is another feature for the assessment of plaque vulnerability, preferably in MRI. A longitudinal prospective MRI-based study in 126 patients with symptomatic carotid stenosis who were followed for an average of 1 year showed that thin and/or ruptured FC was significantly associated with cerebrovascular events.[19] Also, a thin and/or ruptured FC is highly associated with a recent stroke/TIA. For example, in an MRI-based study, patients with ruptured FC were 23 times more likely to have had a recent stroke/TIA compared with patients with thick FC.[20] In another prospective longitudinal study, the disruption of the FC was a risk factor for cerebrovascular events.[21]

Another feature of vulnerability is the presence of carotid *intraluminal thrombus*, which presents with neurologic symptoms in up to 92% of cases.[22] In a retrospective cross-sectional study of 726 carotid-brain MRI examinations, the strongest predictor of a carotid-source stroke was intraluminal thrombus followed by IPH.[23] In another computed tomography angiography (CTA)-based study on 673 patients, the presence of intraluminal thrombi was highly predictive of the symptomatic side in carotid disease.[24]

The *luminal surface* of carotid plaques can be classified as smooth, irregular, or ulcerated.[25] A smooth surface is identified as plain luminal morphology without any sign of ulceration or irregularity. An irregular surface is identified as the presence of small alterations of the luminal surface of the plaque, and its association with cerebrovascular events was described in the Northern Manhattan Study.[26] An ulcerated surface is defined as an intimal defect that is >1 mm in width and exposes the necrotic core of the atheromatous plaque,[27] and its association with cerebrovascular events is well established.[28–30]

The *lipid-rich necrotic core* (LRNC) is a heterogeneous tissue composed, amongst others, of cholesterol crystal, debris of apoptotic cells, and particles of calcium. The LRNC, preferably assessed in MRI, plays a key role in the progression and vulnerability of atherosclerotic plaques. A study of 120 asymptomatic patients with carotid plaque showed that a large LRNC size correlates with ipsilateral cerebrovascular events and that a LRNC > 40% of the wall area was prone to FC rupture in comparison with patients with a LRNC < 40%.[31] In another study of 62 patients, a LRNC within the plaque strongly predicted cerebrovascular events.[32] A systematic review and meta-analysis reported similar results showing that LRNC predicted stroke/TIA in asymptomatic subjects.[33]

Another important feature of plaque vulnerability is the *maximum plaque thickness* (MPT). This is distinct from stenosis as a thick plaque can occur without necessarily causing severe narrowing of the lumen. In a CTA-based study of 85 ESUS patients, >3 mm plaque thickness of the non-calcified component was present ipsilateral to stroke in 35% of patients and contralateral in 15%.[34] In an MRI cross-sectional study of 1072 subjects, the MPT was more strongly associated with cerebral ischaemic symptoms than was the degree of stenosis.[35]

The role of calcium in atherosclerosis remains controversial, but it is generally agreed that the size, shape, and position of calcification may all affect plaque development.[36] Amongst the different types of calcium configuration, the *positive rim sign*, defined as the presence of thin

Table 1 Features to assess the overall thromboembolic risk in embolic stroke of undetermined source patients

	Moderately increased thromboembolic risk	Slightly increased thromboembolic risk
Supracardiac atherosclerosis	• Acute or recent intra-plaque haemorrhage • Thin/ruptured fibrous cap • Intraluminal thrombus • Ulcerated plaque morphology	• Lipid-rich necrotic core > 40% of the wall area. • Maximum plaque thickness of the non-calcified component > 3 mm • Irregular plaque morphology • Positive rim sign • Healed ulcerated plaque
Patent foramen ovale (*Figure 3*)	• Recent DVT or pulmonary embolism AND presence of ASA or large shunt, regardless of patient age or RoPE score • Presence of ASA or large shunt AND RoPE ≥ 7 and age < 60 years	• Presence of ASA or large shunt AND RoPE < 7, regardless of patient age • Absence of ASA or large shunt AND RoPE ≥ 7, regardless of patient age • Recent DVT or pulmonary embolism, AND absence of ASA or large shunt, regardless of patient age or RoPE score
Left atrial disease	• LA spontaneous echocardiographic contrast • Cor triatriatum	
Atrial arrhythmias	• AHRE or SCAF lasting >24 h and occurring within a month after stroke • Any episode of atrial fibrillation lasting >30 s during stroke unit telemetry.	• AHRE or SCAF lasting <24 h and occurring later than a month after stroke
Atrial cardiomyopathy		• Significant LA enlargement (LA diameter > 4.6 cm)
Left ventricular disease	• large or dyskinetic scar tissue • LV aneurysm • LV non-compaction with deep trabeculations or spongious LV • Severe restrictive cardiomyopathy with decrease in cardiac output despite a preserved LV ejection fraction, e.g. cardiac amyloidosis.	• Moderately decreased LV systolic function and/or very enlarged LV with spontaneous echo-contrast • Cardiomyopathies, e.g. hypertrophic cardiomyopathy or amyloidosis • Acute phase of an ischaemic cardiopathy
Valvular heart disease		• Large redundant Barlow mitral valve disease • Massive mitral valve calcifications • Aortic valve calcifications
Cancer	• Cardiac vegetation(s) with negative blood cultures • ISTH overt DIC score ≥5 with D-dimer > 4000 ng/mL AND fibrinogen < 100 mg/dL AND platelet count < 100 10^3/μL (OR PT prolongation > 3 s)	• Cancer spread beyond primary site OR recent progression of disease OR centrally located primary or metastatic lung cancer • D-dimer > 2500 ng/mL in the absence of an acute DVT or pulmonary embolism • Acute infarction in multiple cerebral arterial territories • Bilateral high-intensity transient signals on transcranial Doppler in the absence of a known central embolic source

AHRE, atrial high-rate episode; ASA, atrial septal aneurysm; DIC, disseminated intravascular coagulation; DVT, deep venous thrombosis; ISTH, International Society on Thrombosis and Haemostasis; LA, left atrial; LV, left ventricle; PFO, patent foramen ovale; RoPE, Risk of Paradoxical Embolism Score; SCAF, subclinical atrial fibrillation.

(<2 mm) adventitial calcifications with internal low attenuation plaque of ≥2 mm in maximum thickness in CTA, is associated with the presence of IPH.[37,38] On the other hand, other calcium configurations such as intimal or superficial calcifications, or type 3, deep, or bulky calcifications, are rarely associated with the occurrence of cerebrovascular events.[39]

Intra-plaque *neovascularization* can be detected with contrast-enhanced ultrasound (CEUS), computed tomography (CT) and MRI, and requires the administration of contrast media for the detection and quantification of neovascularization.[40] It can be seen in advanced atherosclerotic lesions, but, currently, routine clinical practice has not adopted non-invasive imaging assessment of plaque inflammation and neovascularization due to limitations related to the technical complexity of this analysis. A prospective CEUS study of 155 patients showed that intraplaque neovascularization is associated with recurrent cerebrovascular events regardless of the severity of carotid stenosis.[41] An MRI study showed that adventitial enhancement, a marker of neovascularization, was associated with cerebrovascular events.[42] The importance of wall enhancement as an additional marker of stroke risk stratification was also highlighted using CT.[43] Currently, it is also possible to explore the level of *inflammation* within the plaque mainly with fluorodeoxyglucose positron emission tomography,[44] but this parameter is also not currently adopted as a routine non-invasive imaging assessment.

Recently, the Carotid Plaque-RADS stroke risk classification system was introduced, which offers a morphological assessment of the thromboembolic risk associated with carotid plaques in addition to the prevailing quantitative parameter of stenosis.[45]

The proposed features to assess the thromboembolic risk in patients with ESUS and supracardiac atherosclerosis are presented in *Table 1*, and patient cases are illustrated in *Figures 2* and *3*.

We note that this section focuses and discusses the embolic source *per se* (i.e. the atherosclerotic plaque) and not the pathophysiologic entities that contribute to it like diabetes mellitus, arterial hypertension, smoking, dyslipidaemia, and others. The risk assessment and management of these pathologies are covered extensively in the related ESC Clinical Practice Guidelines. This is the case also for the next sessions of this Clinical Consensus Statement.

Patent foramen ovale and other right-to-left shunts

Stroke due to paradoxical embolism may occur when a thrombus traverses a right-to-left shunt from the venous circulation into the arterial system and subsequently causes occlusion and infarction. The most common right-to-left shunt associated with stroke is PFO, but also other pathologies may exist such as other septal defects or intrapulmonary shunts. Alternatively, the thrombus may be formed *de novo* within the PFO tunnel. Epidemiologic studies have demonstrated a consistent relationship between ischaemic stroke and PFO in patients without another identifiable stroke aetiology. However, as PFO is a relatively common congenital anomaly found in about one-quarter of adults, its pathogenic role in stroke was contested for decades. Strokes occurring in patients with PFO were labelled as cryptogenic owing to this uncertainty, and the implementation of ESUS criteria in 2014 maintained the status of PFO as an undetermined source.[1] Since 2017, several trials demonstrated that percutaneous closure of PFO reduced the risk of subsequent stroke amongst patients who otherwise met ESUS criteria.[47] A meta-analysis using individual patient data from all trials reported a hazard ratio (HR) of 0.41 [95% confidence interval (CI) 0.28–0.60] for closure compared with medical therapy alone.[48]

These persuasive efficacy data underline that PFO can have significant thromboembolic risk in ESUS patients, the magnitude of which can be further evaluated by clinical and anatomic data, as well as clinical judgement after a thorough diagnostic workup.[49] A classification has been proposed using the PFO-Associated Stroke CAusal Likelihood (PASCAL) algorithm.[50] PASCAL combines the Risk of Paradoxical Embolism (RoPE) score, based on clinical characteristics, with key cardiac anatomic features of the PFO such as large right-to-left shunt and atrial septal aneurysm, both of which are associated with increased stroke risk[51] and with signs of concurrent venous thromboembolism.[50]

The PASCAL algorithm was initially proposed based on inferences from epidemiology and pathophysiology, but the aforementioned individual patient data meta-analysis provided compelling retrospective validation.[50] However, PASCAL was derived solely from clinical trial populations, nearly all patients were <60 years, and it has not been prospectively validated. The relative efficacy of closure compared with medical therapy alone was greater for patients in the PASCAL category 'probably related' (HR 0.10; 95% CI 0.03–0.35) compared with the category 'possibly related' (HR 0.38; 95% CI 0.22–0.65), and no benefit was observed for those in the category 'relation unlikely' (HR 1.14; 95% CI 0.53–2.46).[50] The PASCAL classification is a rational and practical tool to aid in clinical decision-making. There are many other factors that have been reported to be associated with a causal role of PFO, including clinical features such as deep vein thrombosis, pulmonary or systemic embolism occurring close to the ischaemic stroke (within 48–72 h of stroke onset), stroke occurring at awakening in patients with sleep apnoea, circumstances that promote venous thrombotic events (e.g. prolonged travel, dehydration, or hypercoagulable state), stroke onset coincident with a Valsalva manoeuvre, a permanently increased right-to-left pressure gradient (due to chronic arterial pulmonary hypertension or right heart diseases), a history of non-cerebral embolism, a history of migraine with aura, and decompression illness, and anatomic features including the presence of a Eustachian valve or Chiari network, but these were not integrated into the PASCAL tool and require further research. Also, there is no quality evidence to support that ESUS patients should have venous ultrasound to detect potential embolic sources.

In patients < 60 years with 'possible' or 'probable' PFO-related stroke according to PASCAL who have no other probable embolic source, the PFO could be considered as the actual cause of stroke and hence, not considered as an ESUS. Accordingly, this is also proposed in the updated ESUS criteria.[5] Moreover, the role of other simultaneously additional or alternative pathways for right-to-left shunt, including other cardiac septal defects or pulmonary arteriovenous malformations, deserves further investigation.

Therefore, the proposed criteria for assessing the thromboembolic risk in patients with ESUS and PFO expand beyond the PASCAL classification, which largely applies to younger patients and does not include all related clinical features. Instead, a broader set of criteria also including age and venous thrombotic events is proposed in *Table 1* and *Figure 4*, and patient cases are illustrated in *Figures 2* and *3*.

Left atrial disease

The presence of thrombus in the LA or the LA appendage (LAA) carries a very high embolic risk.[52] Thrombi have a prevalence of approximately 3% in anticoagulated persons with AF,[53] which is higher in non-paroxysmal than in paroxysmal AF (approximately 4.8% and 1%, respectively).[53] The risk is even higher, approximately 9%, in non-anticoagulated persons with AF.[54] Conversely, in persons without an AF diagnosis, its prevalence is low but can be associated with mitral valve disease,[55] atrial cardiomyopathy,[55,56] or covert AF. In a patient with stroke, the presence of LA thrombus is a convincing aetiology of cardioembolic stroke, and such patients should not be classified as ESUS. *Spontaneous echocardiographic contrast* in the LA is the cardiac factor which is most strongly related to LAA thrombus.[57]

Cor triatriatum sinistrum is a congenital cardiac anomaly in which the LA is divided into two chambers by a membrane. It is a rare finding as it represents only 0.4% of all congenital heart defects.[58] Given its rarity, finding a cor triatriatum sinistrum in a patient with ESUS should be regarded as a probable stroke aetiology.

Atrial arrhythmias

The strong association of AF with thromboembolic events in observational studies, coupled with the profound effect of oral anticoagulation (OAC) on stroke prevention in persons with AF, provided undisputed evidence about the role of AF in stroke.[59] However, it should be emphasized that the beneficial role of OAC is proven only in AF detected with the standard 12-lead ECG (frequently termed as clinical AF) and not AF detected after stroke (frequently termed as AFDAS) such as AF detected during telemetry at the stroke unit or during non-invasive monitoring like Holter ECG or 14-day patch ECG soon after

Figure 2 Examples of graphical illustration of the overall thromboembolic risk in embolic stroke of undetermined source patients. (Left upper panel) Patient with embolic stroke of undetermined source and metastatic lung cancer and vegetations at the aortic valve with sterile cultures and an ipsilateral-to-the-infarct atherosclerotic plaque in the common carotid artery causing 40% stenosis with smooth plaque surface and thick fibrous cap. (Right upper panel) A 68-year-old patient with embolic stroke of undetermined source and an ipsilateral-to-the-infarct atherosclerotic plaque in the internal carotid artery causing 40% stenosis with acute intra-plaque haemorrhage on magnetic resonance imaging; aortic valve calcification; and a patent foramen ovale with small shunt and no atrial septal aneurysm. (Left middle panel) Patient with embolic stroke of undetermined source and coronary artery disease with a large dyskinetic scar tissue in the left ventricular wall due to previous myocardial infarction and aortic valve stenosis with thin leaflets and no calcification. (Right middle panel) Patient with embolic stroke of undetermined source and an ipsilateral-to-the-infarct atherosclerotic plaque in the carotid bulb causing 40% stenosis with thick fibrous cap and irregular plaque morphology, but without intra-plaque haemorrhage or superimposed thrombus; heart failure with left ventricular ejection fraction 40%; and a large redundant Barlow mitral valve disease. (Left lower panel) patient with embolic stroke of undetermined source and spontaneous echocardiographic contrast in the left atrium; an ipsilateral-to-the-infarct non-ulcerated atherosclerotic plaque in the common carotid artery with thick plaque, lipid-rich necrotic core > 40% of the wall area without intra-plaque haemorrhage, or superimposed thrombus; and a calcified aortic valve. (Right lower panel) A 56-year-old patient with embolic stroke of undetermined source and a patent foramen ovale with atrial septal aneurysm and Risk of Paradoxical Embolism score 7 and an ipsilateral-to-the-infarct atherosclerotic plaque in the internal carotid artery causing 30% stenosis with significant calcification

stroke. New-onset AF is identified in approximately 13% of stroke patients during the in-hospital phase,[60] and such patients should not be classified as ESUS.[1] More episodes of asymptomatic AF may be detected in the outpatient setting with the use of cardiac rhythm monitoring devices.[60] With the use of prolonged, continuous cardiac monitoring in patients following stroke, short-lasting episodes (minutes to hours) of asymptomatic AF with a very low burden of AF (defined as <1% of AF over monitoring time) are often detected, and this entity

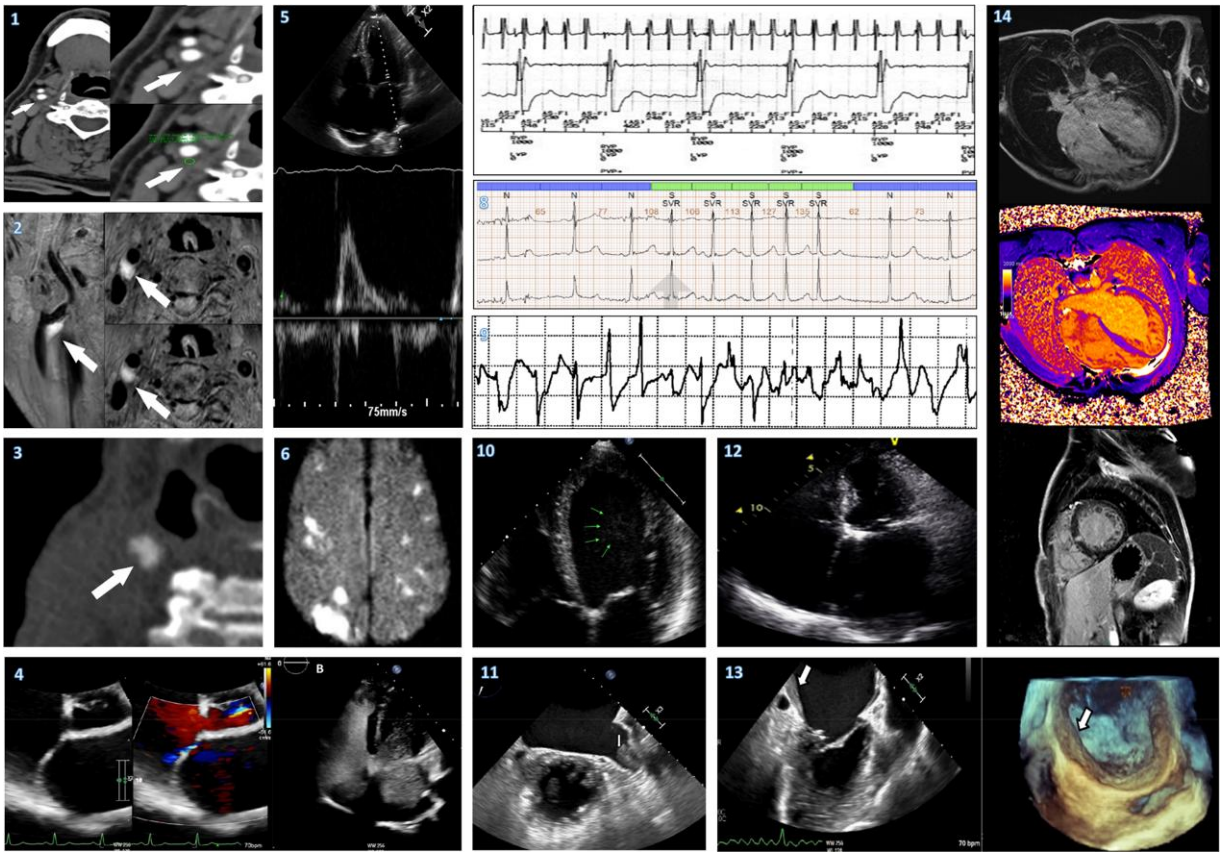


Figure 3 Features associated with thromboembolic risk in embolic stroke of undetermined source patients. (Panel 1) Computed tomography angiography axial scan of the right internal carotid artery in a 73-year-old symptomatic male patient with a 45% stenosis according to the NASCET criteria. A hypodense plaque is visible (arrow) with very low attenuation (<30 Hounsfield units). (Panel 2) MR shows intra-plaque haemorrhage at the bifurcation of the right carotid artery in a 75-year-old symptomatic male patient. (Panel 3) Computed tomography angiography axial scan of the right common carotid artery with a floating thrombus in a 69-year-old female patient. (Panel 4) Patent foramen ovale. (Left) Aneurysm of inter-atrial septum with small inter-atrial shunt in colour Doppler (transthoracic echocardiography, parasternal short-axis view). (Right) Massive right-to-left interatrial shunt during contrast echo with Valsalva manoeuvre. (Panel 5) A mitral inflow Doppler in a restrictive cardiomyopathy (amyloid) showing restrictive physiology, *E/A* > 3, Deceleration time < 120 ms and a short isovolumetric relaxation time. (Panel 6) Brain infarcts in all three cerebral arterial territories (three-territory sign) in a patient with advanced ceacal adenocarcinoma. (Panel 7) Pacemaker recording of an episode of atrial flutter with ventricular pacing. From top to bottom, tracings show atrial electrogram, ventricular electrogram, surface electrocardiogram (ECG), and pacemaker marker channels. (Panel 8) Surface electrocardiographic recording of a short run of non-sustained atrial tachycardia. (Panel 9) Pacemaker atrial electrogram showing an irregular atrial high-rate episode. (Panel 10) Spontaneous echo contrast in the left ventricle (arrows) of a patient with known dilated cardiomyopathy and left ventricular ejection fraction of 12%. (Panel 11) Thrombus (arrow) of the left atrial appendage in a patient with rheumatic mitral stenosis in transoesophageal echocardiography. (Panel 12) Echocardiography demonstrating a severely dilated left atrium in an ESUS patient without known atrial fibrillation. Reprinted from Kamel *et al.*[46] with permission. (Panel 13) Extensive parietal thrombus of left atrium (arrow) in a patient with rheumatic mitral stenosis at 2D transoesophageal echocardiography (left) and 3D transoesophageal echocardiography (right). (Panel 14) Left ventricular non compaction at four-channel late gadolinium enhancement, T1 mapping, and short-axis view in cardiac magnetic resonance imaging

is termed as *subclinical atrial fibrillation* (SCAF) or *atrial high-rate episodes* (AHRE) if ECG/electrograms are not available.[61] The risk of stroke is higher in persons with SCAF/AHRE than in patients without, but lower than in patients with clinical AF.[61,62] In the non-anticoagulated groups of the ARTESIA and NOAH-AFNET 6 trials, the rate of ischaemic stroke was 1.1–1.2/100 person-years.[62,63] It seems plausible that a causal association between SCAF/AHRE and ESUS is stronger in patients with episodes that last longer (e.g. >24 h[64,65]) or occur proximal to the stroke,[64,66] rather than in patients with shorter episodes occurring distally. The role of OAC in individuals with SCAF/AHRE was recently tested in the ARTESIA and NOAH-AFNET 6 trials.[62,63] In the study-level meta-analysis of these two trials, there was significant reduction in the rate of ischaemic stroke with OAC [relative risk (RR) 0.68; 95% CI 0.50–0.92, with no sign of heterogeneity) and significant increase in the rate of major bleeding (RR 1.62; 95% CI 1.05–2.5).[67] The duration of AHRE did not interact with the efficacy or safety of anticoagulation, either using the 24-h threshold or as a continuous covariate in the NOAH-AFNET 6 trial.[68] Only 9.4% of included patients had previous stroke/TIA or systemic embolism. Further analyses of the trials are warranted to identify which parameters, clinical and non-clinical (like the burden of arrhythmia, imaging findings, and biomarkers), can provide a better estimate of the risk of stroke.

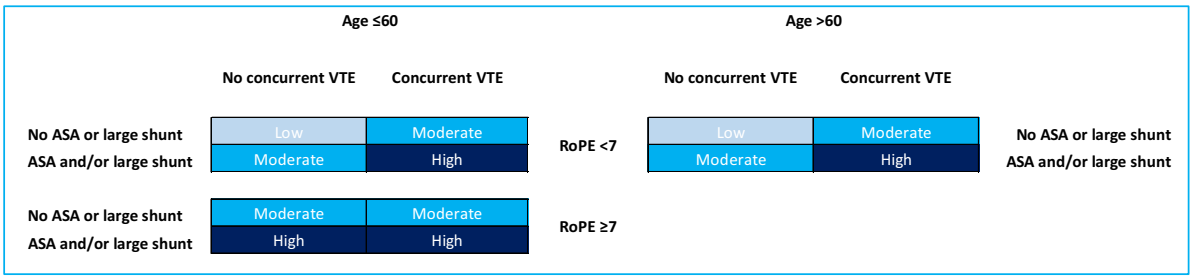


Figure 4 Assessment of thromboembolic risk related to patent foramen ovale in embolic stroke of undetermined source patients based on the morphological features of the patent foramen ovale, the Risk of Paradoxical Embolism score, patient age, and history of recent venous thromboembolism. The right lower part of the figure is blank because the maximum Risk of Paradoxical Embolism score that a patient > 60 years can have is 6. ASA, atrial septal aneurysm; VTE, venous thromboembolism

Atrial cardiomyopathy

The size of the LA has been consistently associated with a higher risk of AF[69] and stroke.[70,71] *Enlargement of the LA* may be associated with age-related progressive remodelling, stretch from pressure and volume overload, and oxidative stress and inflammation and could form an arrhythmogenic and thrombogenic milieu.[72,73] The possible role of LA dilatation in ESUS is supported by a *post hoc* analysis of the NAVIGATE-ESUS trial that showed that oral rivaroxaban was associated with a reduced risk of recurrent stroke amongst patients with ESUS and a LA diameter of >4.6 cm.[74] The ARCADIA trial assessed the role of OAC with apixaban in patients with ESUS and signs of atrial cardiopathy.[75] The trial was stopped after its planned interim analysis for futility as there was no difference in stroke recurrence rate between apixaban- and aspirin-assigned patients.

The proposed features to assess the thromboembolic risk in patients with ESUS and LA disease are presented in *Table 1*, and patient cases are illustrated in *Figures 2* and *3*.

Left ventricular disease

Left ventricular systolic dysfunction is commonly related to stroke, and it is important to diagnose LV disease (including heart failure with preserved ejection fraction) and initiate state-of-the-art heart failure therapy.[76] Ischaemic heart disease and dilated cardiomyopathies with reduced LV ejection fraction (LVEF) are the most common causes of LV dysfunction which may cause stroke.[77] Per the ESUS definition, patients with LVEF < 30% are not classified as ESUS given the well-established association between severely reduced LVEF and stroke. Several studies assessed the role of OAC in patients with reduced LVEF. The WARCEF trial reported that OAC in persons in sinus rhythm and severely reduced LVEF reduced the rate of ischaemic stroke compared with warfarin but increased the risk of major bleeding.[78] Similar conclusions were drawn by a recent meta-analysis of all related trials in which OAC in persons with heart failure and sinus rhythm was associated with a 43% RR reduction of stroke or systemic embolism, which was offset by a 92% RR increase of major bleeding.[79]

Other forms of LV disease may be also the underlying source of ESUS. *Cardiac amyloidosis* can lead to severe restrictive cardiomyopathy with reduced cardiac output despite preserved LVEF and subsequent thrombus in the LV and also in the LA.[80] Thrombus formation may develop in case of *large or dyskinetic scars* or *LV aneurysms* in the chronic phase of myocardial infarction, in *hypertrophic, LV non-compaction and other cardiomyopathies*, as well as in patients with *reduced LV function in valvular heart disease*.[81] In patients with stroke and LV thrombus, the causal association should be regarded as definite cardioembolism and such patients should not be classified as ESUS. The management of LV thrombi was recently reviewed.[82] Oral anticoagulation is recommended in patients with LV non-compaction cardiomyopathy and prior embolic event.[83] Left ventricular *spontaneous echo-contrast* can be seen in patients with low cardiac output and is highly associated with the occurrence of thrombi and potential systemic emboli. The acute phase of ischaemic heart diseases is also associated with an increased risk of stroke.[84] Although the incidence of LV thrombus after acute anterior myocardial infarction with new-onset wall motion abnormalities is low, an increased RR persists in the present era despite current revascularization strategies and dual antiplatelet therapy.[85]

The proposed features to assess the thromboembolic risk in patients with ESUS and LV disease are presented in *Table 1*, and patient cases are illustrated in *Figures 2* and *3*.

Valvular heart disease

Prosthetic cardiac valves, mitral stenosis, and vegetations due to infective endocarditis are considered as major risk sources of cardioembolism, and in their presence, a patient with stroke should not be classified as ESUS.[1] Beyond these entities, the association between valvular pathologies and stroke is weak. The native valvular heart diseases are rare sources of cardiac emboli if we exclude the specific context of endocarditis[86,87] and cardiac tumours.[77,88] In persons with AF, significant aortic valve disease and mitral regurgitation are associated with an increased risk of systemic embolism as compared with patients without valvular disease.[89]

Highly redundant myxomatous mitral valves (Barlow disease) and massive valvular calcifications are two valvular pathologies that are associated with increased embolic risk.[90] These calcifications are becoming more prevalent.[91] They are found on the aortic valve[92] and also on the mitral valve, especially the posterior mitral valve leaflet and the annulus. The valvular calcifications can be associated with more diffuse atherosclerotic disease, such as complex aortic atheroma.[93]

Lambl's excrescences, or else valvular strands, are thin filiform mobile processes that can be found in the mitral and aortic valves. Although it was hypothesized that they are associated with increased stroke risk, observational studies reported inconsistent results.[94,95] In a recent analysis, Lambl's excrescences were not associated with ESUS.[95]

The proposed features to assess the thromboembolic risk in patients with ESUS and valvular heart disease are presented in *Table 1*, and patient cases are illustrated in *Figures 2* and *3*.

Cancer

Cancer is a complex disease that can cause ischaemic stroke through several mechanisms, including hypercoagulable processes such as non-bacterial thrombotic endocarditis (NBTE) and intravascular coagulation, direct vascular injury such as tumour emboli and external compression, and treatment complications such as radiation vasculopathy and chemotherapy-induced cardiomyopathy.[96,97] In the year before cancer is diagnosed, there is a 59% increased risk of ischaemic stroke.[98] Looking in reverse, 2%–10% of patients with ischaemic stroke are diagnosed with cancer in the subsequent year.[99–102] Once cancer is diagnosed, stroke risk remains elevated and is doubled in the 6 months thereafter.[103] The increased stroke risk in patients with cancer follows a U-shaped curve, with risks peaking near the time of cancer diagnosis and then many years later, and the later peak driven by cumulative deleterious effects of cancer treatments.[96] In the USA, 14% of patients hospitalized with ischaemic stroke in 2019 had active or prior cancer.[104] About 50% of cancer-related strokes are classified as ESUS after standard evaluation.[105] Many cancer patients with strokes classified as ESUS have a distinctive phenotype with advanced or progressive cancer, very elevated clotting markers, and evidence for a central embolic process on imaging.[106] These observations highlight the important link between cancer and stroke and raise the question of whether cancer-related stroke should be considered its own stroke subtype.

According to autopsy data from a cancer centre in the 1980s, NBTE is a leading cause of stroke in patients with cancer.[107] Non-bacterial thrombotic endocarditis is characterized by sterile platelet-fibrin vegetations on cardiac valves. Vegetations are generally small and friable, and therefore, definitive diagnosis antemortem is rare, even with transoesophageal echocardiography.[108,109] Immunohistochemical analyses of thrombectomy specimens have demonstrated similar clot profiles between cancer patients with non-infectious cardiac vegetations and those with ESUS, suggesting that NBTE is an underappreciated cause of cancer-related stroke.[110]

Advanced solid or haematological cancer can cause *disseminated intravascular coagulation* (DIC) leading to stroke. The International Society on Thrombosis and Haemostasis (ISTH) has established criteria, based on levels of D-dimer, fibrinogen, platelet count, and prothrombin time, to diagnose overt DIC in patients with malignancy.[111] While D-dimer elevations are common in patients with cancer and stroke, overt DIC fulfilling ISTH criteria is rare.[97]

Embolic stroke of undetermined source in cancer patients often has a *distinctive clinical phenotype* with fewer prevalent vascular risk factors; cancer types associated with increased risks of thromboembolism (e.g. lung, pancreas, gastric, colorectal, ovarian, bladder, and non-Hodgkin's lymphoma); cancers that are newly diagnosed, metastatic, or progressing through treatment; and multi-territory embolic-appearing infarct patterns.[105] Cancer patients with ESUS also often have activation of multiple pathways promoting thrombosis, including platelets, coagulation factors, endothelium, neutrophil extracellular traps, and extracellular vesicles.[105,106,112] The most consistent markers routinely available in practice are the multi-territorial infarct pattern and D-dimer.

Small, diffuse, predominantly cortical, acute infarcts involving multiple cerebral arterial territories occur in 30%–70% of patients with active cancer and ESUS.[106,113,114] This infarct pattern, while not specific, can help identify previously occult cancer in patients with ESUS[100] and is associated with an increased risk of early neurological deterioration.[115] When involving all three cerebral arterial territories, it has been termed the *three-territory sign*.[116]

Transcranial Doppler (TCD) high-intensity transient signals (HITS), surrogates for circulating microemboli, are present in 38%–58% of patients with cancer and ESUS, a rate much higher than in stroke patients without cancer, correlate with plasma D-dimer levels, and are associated with adenocarcinoma histology and an increased risk of recurrent stroke or death.[117,118] If bilateral, HITS suggest a central embolic process.

Extreme elevations of thrombotic end-products such as *plasma D-dimer* are common in patients with cancer and ESUS.[100] In a prospective study of 50 patients with solid cancer and acute ischaemic stroke, the median D-dimer value was 2.552 ng/mL, compared with median values of 405 and 670 ng/mL in matched patients with stroke only and cancer only, respectively.[106] In this study, D-dimer levels were associated with an increased risk of recurrent stroke and death.[117] The optimal threshold to identify an occult cancer or posit causation to a known cancer is uncertain, with reported cut-offs ranging from 820 to 10 000 ng/mL.[102,119,120] We chose a cut-off of 2500 ng/mL for our proposed criteria, as it is close to most published cut-offs and is five times the upper limit of normal. It is worth noting that D-dimer is not specific and can be increased by thromboembolic events besides stroke, AF, prosthetic heart valves, trauma, surgery, and poor sample collection. Many other haematological, inflammatory, and tumour markers are also increased in cancer-related stroke, including P-selectin, thrombin–antithrombin, thrombomodulin, soluble intercellular adhesion molecule, vascular cellular adhesion molecule, CA19-9, CA125, and C-reactive peptide.[106,121,122] However, the relative difference for these markers between cancer and non-cancer patients is not as large as for D-dimer, and many are costly and not routinely available in practice.[106] It is emphasized that plasma D-dimer and TCD HITS are not specific to cancer as an ESUS aetiology but rather serve as quantitative surrogate markers for central embolic processes, which may contribute to ESUS, including atrial cardiomyopathy and atrial arrhythmias.

Tumour embolism is likely an under-recognized cause of stroke in patients with cancer. *Centrally located primary or metastatic lung cancers* can invade the pulmonary veins or cardiac chambers and embolize to the brain causing stroke.[123] Patients with tumour embolism who survive long enough may develop metastases at the site of their stroke.

Nearly all cancer treatments have been associated with increased stroke risk, particularly platinum-based chemotherapy, tyrosine kinase inhibitors, vascular endothelial growth factor inhibitors, and hormonal therapy.[96] However, these associations are often confounded by indication and disappear after adjustment for cancer status,[124] and in most cases, cancer treatments are probably innocent bystanders or triggers for stroke and not the actual cause. The exceptions to this are surgery causing perioperative stroke through direct injury to the heart or cervicocephalic vessels and radiation causing delayed vasculopathy or heart disease, although in these scenarios, patients' stroke mechanism is known.[125] For this position paper, we have restricted thromboembolism risk to the cancer itself and not its treatments, which we believe are separate entities with differing characteristics and outcomes.

The criteria that we proposed for the assessment of thromboembolic risk amongst patients with cancer and ESUS should not affect management decisions, as the prothrombotic effects seen in cancer and stroke are multi-fold and involve platelets as much as coagulation factors, and bleeding risks in these patients are exceedingly high.[117]

The proposed features to assess the thromboembolic risk in patients with ESUS and cancer are presented in *Table 1*, and patient cases are illustrated in *Figures 2* and *3*.

Diagnostic evaluation

It is evident that the complexity of ESUS precludes a one-size-fits-all approach in the diagnostic evaluation of patients. Diagnostic algorithms for ESUS have been proposed,[126] but the large number of associated pathologies, the even larger number of risk factors that contribute to these pathologies, and the availability of several diagnostic methods to assess the heart and the arteries require an individualized approach. This should be guided by specific patient characteristics, scalable quantifiable proxies of these pathologies, as well as availability and expertise in imaging techniques. These could include age, comorbidities, and smoking/diet habits, lipid profile, and other organ-specific blood biomarkers as discussed throughout the previous sections, estimation of the cardiovascular risk of the patient using validated risk scores, estimation of the likelihood of covert AF using validated prognostic scores like the AF-ESUS score,[127,128] vascular ultrasound, CT/CTA, and MRI/magnetic resonance angiography to visualize the arterial circulation and the heart, and others. This highly personalized integrated strategy warrants broad expertise in several fields and calls for clinicians who care for stroke patients to broaden their skills across these domains. We need stroke specialists to take ownership of all these facets, rather than just diffusing responsibility across a whole bunch of consulting specialists.[129]

Implications for clinical practice and research

Patients with ESUS have a considerable risk for stroke recurrence and other cardiovascular events, which highlights the importance to optimize preventive strategies to mitigate this risk. For several decades, there were no clear criteria to define the term 'cryptogenic stroke', which hindered clinical research in this field. In 2014, the introduction of the ESUS concept with explicit definition and criteria led to an improved standardization of this population and hence potentiated clinical research with several randomized trials assessing the role of preventive strategies.[1] The first intervention that was tested in the general ESUS population was OAC with direct oral anticoagulants. However, the results of three randomized trials were disappointing.[130–132] Consequently, it was suggested that future research on ESUS should be tailored to patients with specific characteristics that point towards specific embolic sources.[46] The present position paper has the potential to further enhance research in this population, as it can support a more accurate and homogeneous phenotypic clustering of patients according to their characteristics and consequently facilitate randomized trials of targeted preventive strategies.

Table 2 Key knowledge gaps

• In patients with ESUS and supracardiac atherosclerosis, is intensive lipid-lowering treatment superior compared with standard of care for the prevention of stroke recurrence?
• In patients with ESUS and supracardiac atherosclerosis, is intensive antithrombotic treatment superior compared with currently recommended antiplatelet treatment for the prevention of stroke recurrence?
• In patients with ESUS and supracardiac atherosclerosis and increased levels of lipoprotein(a), is lowering of lipoprotein(a) beneficial for the prevention of stroke recurrence?
• In patients with ESUS and supracardiac atherosclerosis and increased markers of inflammation, is anti-inflammatory treatment beneficial for the prevention of stroke recurrence?
• In patients with ESUS and supracardiac atherosclerosis, is intervention with endarterectomy or stenting superior compared with medical-only treatment for the prevention of stroke recurrence?
• In patients with ESUS and PFO who are >60 years of age, is percutaneous PFO closure superior compared with medical-only treatment for the prevention of stroke recurrence?
• In patients with ESUS and LA spontaneous echo contrast, is OAC superior compared with antiplatelet treatment for the prevention of stroke recurrence?
• In which subgroups of patients with AHRE/SCAF does the benefit of OAC clearly outweigh the harm of associated bleeding?
• How can we improve the prediction of stroke risk in patients with AHRE/SCAF?
• What is the optimal definition of AF burden?
• What is the minimal AF burden which merits OAC in ESUS patients?
• In patients with ESUS and significant LA enlargement, is OAC superior compared with antiplatelet treatment for the prevention of stroke recurrence?
• In patients with ESUS and LV disease, is OAC superior compared with antiplatelet treatment for the prevention of stroke recurrence?
• In patients with ESUS and valvular heart disease, is valvular intervention superior compared with medical-only treatment for the prevention of stroke recurrence?
• In patients with ESUS and cancer, is OAC superior compared with antiplatelet treatment for the prevention of stroke recurrence?

AF, atrial fibrillation; AHRE, atrial high-rate episode; ESUS, embolic stroke of undetermined source; LA, left atrial; LV, left ventricle; OAC, oral anticoagulation; PFO, patent foramen ovale; SCAF, subclinical atrial fibrillation.

Key knowledge gaps

Further evidence is needed to optimize secondary prevention in ESUS. Future secondary prevention trials in ESUS could provide this, as it has been the case for trials of percutaneous PFO closure, which, through their positive results, provided practice-changing evidence for patients < 60 years. *Table 2* presents a list of open questions. For example, in patients with ESUS and supracardiac atherosclerosis, trials of intensive antithrombotic treatment (e.g. addition of a factor XIa inhibitor or low-dose rivaroxaban to standard antiplatelet treatment); intensive lipid-lowering treatment to more aggressive targets than currently recommended; anti-inflammatory drugs; lowering of lipoprotein(a); and intervention with endarterectomy or stenting are warranted. Also, in patients with ESUS and PFO who are >60 years of age, trials of percutaneous PFO closure are needed. In addition, for specific populations of patients with LA, LV disease, or with SCAF/AHRE, further trials of OAC are necessary. The minimal AF burden that merits OAC is unknown. Also, in patients with ESUS and cancer, trials of OAC alone or a combination of OAC and antiplatelet therapy are warranted.

Synthesis and concluding remarks

When the negative results of the trials of OAC compared with aspirin in the general ESUS population were published,[130–132] criticism was addressed towards the ESUS concept. It was suggested that ESUS is not a useful concept and has failed. This is far from the truth: on the contrary, what has actually failed by the results of these trials is not the ESUS concept itself, but the hypothesis that OAC is beneficial in all of these patients and, consequently, the hypothesis that the majority of ESUS is due to covert AF. As clearly stated in the landmark paper that introduced ESUS,[1] in the publication that introduced the updated ESUS criteria and diagnostic algorithm,[5] in the present position paper and elsewhere,[4,46] the underlying aetiologies in ESUS are numerous and frequently overlapping. The failure of the hypothesis that covert AF is a leading aetiology of ESUS as emphatically implied by the results of the NAVIGATE-ESUS[130] and RE-SPECT ESUS[131] trials, urges the research community to redirect focus on assessing the role of other preventive strategies in ESUS, as discussed above, which could potentially improve the prognosis in this patient population.

The high prevalence of ESUS, the considerable risk for stroke recurrence, the modern diagnostic imaging techniques, and the availability of several medical and interventional strategies that could potentially reduce stroke risk in ESUS-associated pathologies like supracardiac atherosclerosis, PFO, LA, or LV disease, valvular heart disease, and cancer identify ESUS as an important priority in stroke research in the coming years, which may hopefully improve outcomes in this large patient population.

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Declarations

Disclosure of Interest

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