Journal of the Formosan Medical Association (2021) 120, 93–106

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

Review Article

Diagnosis and Treatment for embolic stroke of undetermined source: Consensus statement from the Taiwan stroke society and Taiwan society of cardiology

Li-Kai Tsai [a], I-Hui Lee [b], Yung-Lung Chen [c], Tze-Fan Chao [d], Yu-Wei Chen [a,e], Helen L. Po [f], Li-Ming Lien [g,h], Pao-Hsien Chu [i], Wei-Chun Huang [j], Tsung-Hsien Lin [k], Ming-Tai Lin [l], Jiann-Shing Jeng [a,**], Juey-Jen Hwang [m,*]

[a] *Stroke Center and Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan*
[b] *Department of Neurology, Neurological Institute, Taipei Veteran General Hospital, Taipei, Taiwan*
[c] *Division of Cardiology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*
[d] *Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[e] *Department of Neurology, Landseed International Hospital, Taoyuan, Taiwan*
[f] *Stroke Center and Department of Neurology, MacKay Memorial Hospital, Taipei, Taiwan*
[g] *Department of Neurology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan*
[h] *Department of Neurology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[i] *Department of Cardiology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan*
[j] *Department of Critical Care Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[k] *Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[l] *Division of Pediatric Cardiology, National Taiwan University Hospital, Taipei, Taiwan*
[m] *Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*

Received 28 November 2019; received in revised form 22 April 2020; accepted 18 May 2020

KEYWORDS
Cardiac rhythm monitor;

Cryptogenic stroke comprises about one-quarter of ischemic strokes with high recurrence rate; however, studies specifically investigating the features and treatment of this stroke subtype are rare. The concept of 'embolic stroke of undetermined source' (ESUS) may facilitate the

* Corresponding author. No. 7, Chung-Shan South Road, Taipei, 100, Taiwan.
** Corresponding author. No. 7, Chung-Shan South Road, Taipei, 100, Taiwan.
E-mail addresses: jsjeng@ntu.edu.tw (J.-S. Jeng), jueyhwang@ntu.edu.tw (J.-J. Hwang).

https://doi.org/10.1016/j.jfma.2020.05.026

Cryptogenic stroke;
ESUS;
NOAC;
Transesophageal echocardiography

development of a standardized approach to diagnose cryptogenic stroke and improve clinical trials. Since recent large randomized control trials failed to demonstrate a reduction in stroke recurrence with anticoagulants, anti-platelet agents remain the first-line treatment for ESUS patients. Nevertheless, patients with high risk of stroke recurrence (e.g., those with repeated embolic infarcts despite aspirin treatment) require a more extensive survey of stroke etiology, including cardiac imaging and prolonged cardiac rhythm monitoring. Anticoagulant treatments may still benefit some subgroups of high-risk ESUS patients, such as those with multiple infarcts at different arterial territories without aortic atheroma, the elderly, or patients with high CHA_2D_2-VASc or HOVAC scores, atrial cardiopathy or patent foramen ovale. Several important ESUS clinical trials are ongoing, and the results are anticipated. With rapid progress in our understanding of ESUS pathophysiology, new subcategorizations of ESUS and assignment of optimal treatments for each ESUS subgroup are expected in the near future.

Introduction

Ischemic stroke of undetermined etiology, often called cryptogenic stroke, comprises 20—30% of all ischemic strokes in Taiwan and worldwide.[1,2] Previously, the heterogeneous nature of cryptogenic stroke (including both true cryptogenic stroke and stroke with incomplete investigation or multiple causes)[3] has impeded study of its features and optimal therapy. In 2014, Hart et al. proposed the new clinical entity 'embolic stroke of undetermined source' (ESUS), which has a clear diagnostic definition.[4] Since then, the number of published studies focusing on the mechanism, natural history and therapy of ESUS has increased every year. Recently, the results of two phase 3 clinical trials failed to support the hypothesis that anticoagulants are superior to aspirin for prevention of recurrent stroke in subjects with ESUS.[5,6] The results from these trials imply that patients with ESUS cannot be treated simply as a unified entity, and more research is needed to determine the optimal therapy for each ESUS patient subgroup. In order to standardize the principles of diagnosis and therapy for ESUS, we brought together experts in neurology and cardiology to find a consensus for ESUS management based on currently available evidence. This consensus statement is written with an emphasis on diagnosis and treatment of ESUS, especially for those patients with high risk of stroke recurrence. Cardiac imaging and cardiac rhythm monitoring are two tools that may potentially be used to improve ESUS diagnosis and will be discussed in detail. The consensus used the American College of Cardiology (ACC)/American Heart Association (AHA) Class of Recommendations (COR) and Level of Evidence (LOE) format as described previously.[7]

Diagnosis of ESUS

ESUS concept

Based on the TOAST classification, ischemic stroke can be classified into five subtypes,[3] including large-artery atherosclerosis, small-artery disease, cardioembolism, stroke of other determined etiologies, and stroke of undetermined etiology. Among these subtypes, stroke of undetermined etiology, or cryptogenic stroke, is the least well investigated. Cryptogenic stroke is a heterogeneous classification that consists of (1) true cryptogenic stroke with sufficient survey of etiology, (2) stroke with incomplete investigation, and (3) stroke with multiple causes, such as in patients with both carotid stenosis and atrial fibrillation.[3] In order to develop a clinical construct that can provide a basis for future randomized trials of secondary prevention agents, the ESUS entity was introduced.[4] This construct refines the category of cryptogenic stroke by excluding those patients with incomplete evaluation or multiple causes. Because most cryptogenic strokes show clinical and radiographic appearance of embolic-like stroke of unknown sources,[4] a diagnostic definition of ESUS includes (1) non-lacunar infarction (small vessel occlusion), (2) no $\geq$ 50% large artery atherosclerotic stenosis supplying the ischemic area, (3) no major-risk cardioembolic sources, and (4) no other specific causes of stroke.

Accordingly, ESUS diagnosis requires a basic set of assessments, abbreviated as 'HEAD': (1) Head imaging by computerized tomography (CT) or magnetic resonance imaging (MRI) to rule out lacunar infarcts (less than 1.5 cm in diameter by CT or 2 cm by MRI); (2) Electrocardiogram (ECG) and Echocardiography: 12-lead ECG, 24-hr Holter monitor and transthoracic echocardiography to rule out major-risk cardioembolic sources, including atrial fibrillation (AF), atrial flutter, intracardiac thrombus, valvular heart diseases, atrial myxoma, recent (<4 weeks) myocardial infarction (MI), left ventricular ejection fraction less than 30%, valvular vegetations, infective endocarditis, etc.; (3) Arterial imaging of cervico-cephalic large arteries using Doppler ultrasound, CT or MR angiography to rule out large artery stenosis (>50%); and (4) Differential diagnosis of other specific causes, such as vasculitis, dissection, migraine/vasospasm, drug misuse, etc.[4]

Features and potential etiology of ESUS

Based on meta-analysis, the frequency of ESUS is estimated to be 17% (ranging from 9 to 25%) of ischemic strokes.[8] In a

global registry study, the frequency of ESUS ranged from 13 to 24% in some Asian countries.[9] Patients with ESUS are relatively young (mean age of 65 years) and typically have minor strokes (mean initial NIHSS of 5) compared to those with ischemic strokes of other subtypes. While most ESUS patients (86%) are treated with antiplatelet therapy during follow-up, the annual stroke recurrence rate averages 4.5%. Among ischemic stroke subtypes, the distribution of ischemic lesions from ESUS is more similar to that from cardioembolism.[10] ESUS is associated with a risk of stroke recurrence that is higher than the recurrence risk for non-cardioembolic strokes.[11] Notably, the long-term mortality risk for ESUS patients is lower than that for cardioembolic stroke, despite similar composite cardiovascular endpoints and recurrence rates. Some clinical characteristics are independent determinants for recurrent ischemic stroke in ESUS patients, including prior stroke or transient ischemic attack (TIA) before ESUS, advanced age, current tobacco use, multiple acute infarcts on neuroimaging, and diabetes.[12] Compared with the low-risk CHA_2DS_2-VASc group (men, score 0; women, 1), patients in the high-risk group (men, score ≥ 2; women, ≥ 3) have higher risks of recurrent ischemic stroke or TIA ($\sim$3-fold) and death ($\sim$13-fold).[13]

Table 1 lists some defining etiological features and proposed antithrombotic agents for each ESUS subclass. However, randomized controlled trials are still needed to test optimal therapies for each subclass of ESUS. The potential causes of ESUS include the following. First, paroxysmal AF may cause cardioembolic stroke and then revert back to sinus rhythm, with the AF rhythm remaining undetectable even under prolonged heart rhythm monitoring.[14] In addition, markers of atrial cardiopathy are independently associated with embolic-appearing strokes, and as such, atrial cardiopathy is a likely underlying mechanism of ESUS.[15] Furthermore, while MI has recently been considered a major cardioembolic source, unrecognized subclinical MI comprises at least one-third of all MIs.[16] These silent MIs may be another source of ESUS. The passage of an embolus from venous circulation to arterial circulation via the patent foramen ovale (PFO) may also cause embolic stroke; the clinical benefits seen with specific PFO-targeted treatment support the idea that this process may be a causal mechanism for ESUS.[17] About 50% of cancer-associated strokes are considered ESUS with subsequent multiple infarctions in different vascular territories; these strokes generally result from cancer-related hypercoagulability.[18] Patients with ESUS were more likely to experience non-stenotic (<50%) carotid arterial intraplaque hemorrhage on the ipsilateral side than the contralateral side,[19] which supports a causal role for unstable non-stenotic atherosclerotic plaques in ESUS. Artery-to-artery emboli may originate from aortic arch atherosclerosis, and embolic signals detected using transcranial duplex on middle cerebral arteries are associated with large aortic arch atheroma (>4 mm in thickness).[20] Moreover, other specific causes of ESUS may include nonstenosing arterial dissection, infectious or autoimmune disease-associated vasculitis, hypercoagulable disorders (antiphospholipid syndrome, thrombocytosis, hyperhomocysteinemia), reversible vasoconstriction syndrome, hereditary cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL), mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS), and Fabry's disease, among others.[2]

Essential and advanced diagnostic methods for ESUS

In addition to taking a patient's basic history, physical examination, and laboratory tests, the essential work-up for diagnosis of ESUS includes neuroimaging (CT or MRI), vessel imaging (CT angiography, MR angiography, carotid duplex sonography, and/or transcranial duplex sonography), 12-lead ECG, 24-hr Holter monitoring, and transthoracic echocardiography, according to recent criteria for ESUS.[4] However, in clinical practice, more extensive examinations may be useful for precise diagnosis and selection of preventive treatment strategy for patients with high risk of stroke recurrence or those with special clinical conditions.

Fig. 1 shows a proposed diagnostic algorithm for patients with ESUS. After excluding the stroke etiology of large artery

Table 1 Potential embolic sources of ESUS: possible etiological reclassification and expected responses to antithrombotic drugs.

Classification	Likely response to anticoagulant therapy	Likely response to antiplatelet therapy
Cardioembolism	Subclinical atrial fibrillation Atrial cardiopathy Silent myocardial infarction Valvular heart disease	
Paradoxical embolism	Patent foramen ovale Atrial septal defect Pulmonary arteriovenous fistula	
Large artery atherosclerosis		Nonstenosing (<50%) large artery atherosclerosis Aortic arch atherosclerosis
Other causes	Cancer-related hypercoagulability Hypercoagulable disorders: such as antiphospholipid syndrome, etc.	Nonatherosclerotic arteriopathies: dissection, vasculitis, etc.

The optimal treatment for each potential etiology requires confirmation by randomized trials.

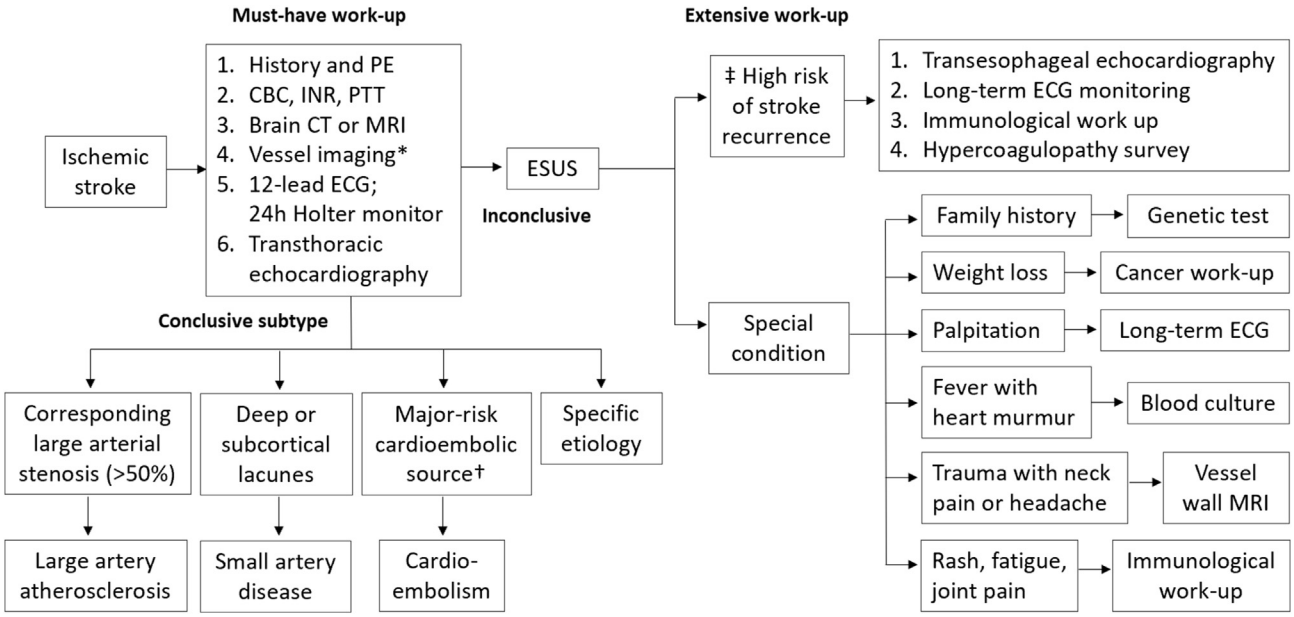

Figure 1 Diagnostic algorithm for ESUS. * CT angiography, MR angiography, carotid duplex sonography and/or transcranial duplex sonography. † Atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic valve, atrial myxoma, mitral stenosis, recent myocardial infarction, left ventricular ejection fraction <30%, valvular vegetation and infective endocarditis. ‡ Recurrent stroke despite aspirin usage, multiple infarcts at different arterial territories, young age, etc. CBC, complete blood count; CT, computerized tomography; ECG, electrocardiogram; ESUS, embolic stroke of undetermined source; INR, international normalized ratio; MRI, magnetic resonance imaging; PE, physical examination; PTT, partial thromboplastin time.

atherosclerosis, small artery disease, cardioembolism and other clear specific causes via the essential work-up, a diagnosis of ESUS can be made. Nevertheless, more extensive examinations are warranted for patients with high risk of stroke recurrence, such as those with repeated embolic events despite aspirin treatment, multiple infarcts at different arterial territories, or young age. These additional exams may include transesophageal echocardiography (TEE; especially for diagnosis of atrial cardiopathy, aortic arch atheroma and PFO), prolonged cardiac rhythm monitoring (long-term event recorder or implanted loop recorder, etc) for paroxysmal AF, immunological studies, and hypercoagulability tests (such as serum levels of anticardiolipin antibody, DRVVT, beta-2 glycoprotein 1 antibody, d-dimer and homocysteine). In addition, patients should be evaluated for underlying conditions in specific cases, e.g., genetic tests in those with stroke family history (CADASIL, MELAS, etc.), cancer work-up in patients with weight loss (tumor markers, d-dimer, and/or whole body CT, etc.), and prolonged cardiac rhythm monitoring in those with intermittent palpitation. Moreover, for ESUS patients with concomitant fever and cardiac murmur, testing for infective endocarditis should be performed by blood culture and/or TEE. In patients with recent trauma followed by headache or neck pain, high-resolution vessel wall MRI is helpful for diagnosis of cervicocephalic arterial dissection.[21] In those with skin rash, fatigue, joint pain and/or low grade fever, immunological work-up for diagnosis of autoimmune disease (erythrocyte sedimentation rate, C-reactive protein, anti-nuclear antibody, rheumatic factor, and anti-neutrophil cytoplasmic antibodies, etc.) may be useful.

Recommendations

- To make a diagnosis of ESUS, essential tests include brain CT or MRI, vascular imaging (CT angiography, MR angiography, carotid duplex sonography and/or transcranial duplex sonography), transthoracic echocardiography, and cardiac rhythm study (12-lead ECG and 24-hr Holter ECG). (COR I; LOE C-LD)
- For ESUS patients with high risk of stroke recurrence, TEE (especially for diagnosis of atrial cardiopathy, aortic arch atheroma and PFO), prolonged cardiac rhythm monitoring (long-term event recorder or implanted loop recorder, etc) for paroxysmal AF, immunological studies, and hypercoagulability tests are useful to determine stroke etiology. (COR IIa; LOE C-LD)

Cardiac imaging

Atrial cardiopathy, aortic arch atheroma, and ESUS

Left atrium (LA) abnormalities in the absence of AF may still cause cardioembolic stroke,[22] either as a precursor to AF or as an independent risk factor for the formation of a LA thrombus. Markers of atrial disease are significant risk factors for ischemic stroke and have been used to define a new clinical entity, atrial cardiopathy. Atrial cardiopathy means "any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations".[23] It is usually defined as at least one of the

following: P-wave terminal force velocity in lead V1 (PTFV1) on ECG > 5000 μVms, severe left atrial enlargement on echocardiogram (≥3 cm/m^2), or serum levels of N-terminal probrain natriuretic peptide (NT-proBNP) > 250 pg/mL.[24] Atrial cardiopathy may result from aging, obesity, diabetes mellitus, hypertension and sleep apnea, which result in the degeneration and apoptosis of myocytes, fibroblast proliferation, extracellular matrix remodeling and atrial fibrosis.[25] LA dilatation and dysfunction may further cause atrial blood stasis, a prothrombotic state and subsequent cardioembolic stroke. PTFV1 is a marker of LA pathophysiological changes, such as hypertrophy and elevated filling pressures.[26] Studies have indicated that LA enlargement and increased PTFV1 hold stronger associations with cryptogenic or cardioembolic stroke than other stroke types.[27,28] These associations remain unchanged or are even stronger when AF patients are excluded, indicating that atrial cardiopathy may lead to thromboembolism without AF and cause a cryptogenic or cardioembolic stroke.

Cardiac MRI has been used to characterize tissue changes, such as fibrosis and scarring. Recently, the presence of late gadolinium enhancement on cardiac MRI has been shown to be useful for evaluating the severity of cardiac fibrosis in AF patients.[29,30] A study comparing cardiac MRI and TEE showed atrial fibrosis is independently associated with LA appendage thrombus and spontaneous echo contrast on echocardiography,[31] which again supports the idea that atrial cardiopathy may have an independent role in cardioembolic stroke.

Atheroma in the aortic arch is a major cause of cerebral embolism, particularly if the thickness of the atherosclerotic plaque is ≥ 4 mm.[32,33] The prevalence of large aortic arch atheroma (≥4–5 mm) ranges from 4.6% to 25.2% in patients with cryptogenic stroke detected by TEE.[34,35] In patients with prior stroke, the risks of recurrent stroke, long term neurologic events and mortality are consistently 2- to 4-fold higher in patients with large aortic arch plaque (≥4 mm) than those with small (<4 mm) or no plaque.[36,37] A recent study showed that antiplatelet therapy was superior to anticoagulants for stroke prevention in patients with cryptogenic stroke and large aortic arch atheroma (≥4 mm).[38]

Survey of ESUS etiology by TEE

TEE is superior to transthoracic echocardiography in terms of diagnostic performance for patients with ischemic stroke of unknown etiology[39]; a potential cardiac embolic source was detected by both transthoracic echocardiography and TEE in 17% of patients and by TEE alone in 39% of patients. In patients with cryptogenic stroke, the most common findings by TEE surveys include PFO/atrial septal defect, atrial septal aneurysm, LA spontaneous echo contrast or thrombus, valvular vegetation, mitral valve strands, and aortic arch atheroma. Notably, in up to one-third of patients with cryptogenic stroke, TEE results are used to justify anticoagulant therapy or to guide further treatment.[40] A TEE may be also helpful for evaluating LA appendage morphology. Patients with chicken wing LA appendage morphology are less likely to experience an embolic event than those with other LA appendage morphologies (cactus, windsock or cauliflower) after controlling for comorbidities and $CHADS_2$ score, possibly owing to differences in flow velocity, trabeculae or orifice size of the LA appendage, and number of appendage lobes.[41,42] Severe complications (e.g., bronchospasm, hypoxia, non-sustained ventricular tachycardia and transient AF) of TEE occur in less than 1 out of 5000 patients and are rarely fatal.[43] Therefore, in ESUS patients, a TEE study is useful for probing stroke etiology with an emphasis on examining the potential presence of right-to-left shunt, LA thrombus/spontaneous echo contrast, valvular vegetation, and large aortic arch atheroma, as well as evaluation of morphology and flow velocity of the LA appendage.

Recommendation

- In patients with ESUS, a TEE study may be utilized to examine stroke etiology, with an emphasis on determining the presence of right-to-left shunt, LA thrombus/spontaneous echo contrast, valvular vegetation, and large aortic arch atheroma, as well as evaluating morphology and flow velocity of the LA appendage. (COR IIa; LOE C-LD)

Cardiac rhythm monitoring

Cardiac arrhythmia and ESUS

An important risk factor for ischemic stroke is AF, which was associated with a 3.34-fold increase in stroke risk according to a study conducted in Taiwan.[44] However, AF is sometimes paroxysmal in nature and therefore difficult to detect. A sub-analysis of the ACTIVE W trial showed that the risk of stroke or systemic embolism did not differ significantly between patients with paroxysmal and sustained AF (annual risk: paroxysmal AF, 2.0%; sustained AF, 2.2%; $P = 0.50$).[45] In addition, even a short duration of subclinical AF could be associated with increased risk of ischemic stroke or systemic embolism. In the ASSERT trial, subclinical atrial tachyarrhythmias, which are defined as episodes of atrial rate >190 beats per min for more than 6 min, could be detected by implanted devices in 10.1% patients without AF.[46] Notably, these subclinical atrial tachyarrhythmias were associated with an increased risk of ischemic stroke or systemic embolism (hazard ratio, 2.49; $P = 0.007$) during a mean follow-up of 2.5 years. Therefore, it is important to screen for AF among patients with ESUS, and long-term oral anticoagulants should be considered if AF is detected.

Methods for cardiac rhythm monitoring

Generally, tools for cardiac rhythm monitoring are classified as external or implantable cardiac monitors (ICMs). The advantages of external cardiac monitors (e.g., 24-hr Holter ECG) are convenience and non-invasiveness. However, external cardiac monitors are limited by relatively short monitoring durations (usually on the order of days). In contrast, ICMs (e.g., implantable loop recorder) can

continuously monitor heart rhythm for years, but their widespread use is prohibited by cost and the invasiveness of implantation.

Prior studies have reported a variety of different AF detection rates, depending on the monitoring modalities used for screen, selection of patient population and definition of AF.[47] In general, AF detection rates were higher for longer durations of monitoring, in patients with higher clinical probability of AF-related stroke, and when shorter arrhythmic episodes were defined as AF. In a meta-analysis of 11,658 patients with ischemic stroke or TIA,[48] the cardiac monitoring methods for AF diagnosis could be stratified into four sequential phases of screening: phase 1 (emergency room) consisted of 12-lead ECG; phase 2 (in hospital) included serial ECG, continuous inpatient ECG monitoring or cardiac telemetry, and in-hospital Holter monitoring; phase 3 (first ambulatory period) consisted of ambulatory Holter; and phase 4 (second ambulatory period) consisted of mobile cardiac outpatient telemetry, external loop recording, and implantable loop recording. The proportions of patients diagnosed with post-stroke AF were 7.7%, 5.1%, 10.7%, and 16.9% in phases 1 to 4, respectively, with an overall AF detection rate of 23.7%.[47] In another meta-analysis, the pooled AF detection rate after cryptogenic stroke was 10.7% for 24-hr Holter monitoring and 14.7% for >24 h monitoring.[49]

Studies that have detected AF using external cardiac monitors with a longer duration are summarized in Table 2. Among these investigations, the EMBRACE study was a randomized trial that included 572 patients without known AF who had experienced cryptogenic ischemic stroke or TIA within the previous 6 months. Patients were assigned to undergo additional noninvasive ambulatory electrocardiography monitoring with either a 30-day event-triggered recorder (intervention group) or a conventional 24-hr monitoring protocol (control group).[56] After the monitoring period, AF (longer than 30 s) was detected in 16.1% of patients in the intervention group compared to only 3.2% in the control group.

The studies of AF detection using ICMs are summarized in Table 3. Although the durations of AF events were defined at longer than 2 min (sometimes even 6 min) in these studies, the AF detection rates were generally higher than those found using external cardiac monitors. Studies using external cardiac monitors typically defined the durations of AF events to be more than 30 s. These data nicely illustrate the importance of continuous and long-term monitoring after ESUS. In the CRYSTAL trial, 441 patients who experienced cryptogenic stroke were randomized to receive long-term monitoring with an ICM or conventional follow-up (control) for detection of AF.[62] Patients without evidence of AF during at least 24 h of ECG monitoring underwent randomization within 90 days of the index event. By 6 months, AF was detected in 8.9% of patients in the ICM group, as compared to 1.4% of patients in the control group (hazard ratio, 6.4; $P < 0.001$). By 12 months, AF had been detected in 12.4% of patients in the ICM group, compared to 2.0% in the control group (hazard ratio, 7.3; $P < 0.001$).[62] Notably, among patients in the ICM group with AF detected, the median value for the mean time of AF per day was only 4.3 min, which could be difficult to detect without an ICM. In summary, continuous external cardiac monitoring for at least 24 h is crucial for detection of AF and ESUS diagnosis; external cardiac monitors with a longer duration (>24 h) or even ICMs may be considered for patients at high risk of recurrent stroke to maximize the likelihood of detecting AF.

Recommendations

- Continuous external cardiac monitoring for at least 24 h is crucial for detection of AF and ESUS diagnosis. (COR I; LOE B-R)
- External cardiac monitors with a longer duration (>24 h) or even ICMs may be considered to increase the likelihood of detecting AF in patients at high risk of recurrent stroke. (COR IIa; LOE B-R)

Treatment of ESUS

Antiplatelet treatments

Before the introduction of ESUS, there were no large studies specifically focused on optimal treatment of cryptogenic stroke. According to the results from a large meta-analysis of 18,270 patients with prior TIA or stroke of any kind across 21 trials, patients receiving antiplatelet therapy had lower risk than untreated controls for recurrent stroke, myocardial infarction or vascular death within a mean follow-up duration of 29 months.[66] In addition, for patients with major risk of cardioembolic stroke, such as those with AF or mechanical valve replacement, further studies demonstrated that anticoagulants but not antiplatelet agents significantly reduced the risk of recurrent stroke.[67,68] Together, these studies suggest that patients with non-cardioembolic stroke (including cryptogenic stroke) but not cardioembolic stroke should receive antiplatelet therapy to prevent stroke recurrence.

To compare the effects of warfarin and aspirin on stroke prevention in patients with non-cardioembolic stroke, the WARSS trial was conducted on 2206 subjects. The primary efficacy outcome (recurrent ischemic stroke or death) and safety outcome (major bleeding) were similar between two groups.[69] However, warfarin treatment significantly increased the risk of minor bleeding events compared to aspirin (warfarin, 20.8%; aspirin, 12.9%; $P < 0.001$). A Cochrane meta-analysis further showed that warfarin at any dose was not more efficacious than antiplatelet therapy in patients with minor stroke or TIA from presumed arterial origin,[70] while high intensity warfarin treatment significantly increased the risk of bleeding complications. Therefore, the American Stroke Association and the Taiwan Stroke Association both recommend antiplatelet agents rather than oral anticoagulants to reduce the risk of recurrent stroke in patients with non-cardioembolic ischemic stroke (including cryptogenic stroke) or TIA.[71,72]

Rationale for use of anticoagulants for ESUS

In the cryptogenic stroke subgroup of the WARSS trial, warfarin was better than aspirin for stroke prevention in patients without hypertension, with low initial NIHSS, or who had posterior circulation strokes,[73] all of which may be

Table 2 Studies of atrial fibrillation detection using external cardiac monitors.

Authors	Year	No. of Patients	Monitoring Modality	Monitoring Duration	AF Definition	AF Detection, %	Number needed to detect	Other findings
Tayal et al.[50]	2008	56	Mobile cardiac outpatient telemetry	21 d	< or >30 s >30 s	23% 5.3%	4 19	
Gaillard et al.[51]	2010	98	Transtelephonic ECG monitoring	30 d	32 s	9.2%	11	
Bhatt et al.[52]	2011	62	Mobile cardiac outpatient telemetry	28 d	30 s ≥5 min	24% 9%	4 11	
Flint et al.[53] SMART Registry	2012	239	Mobile cardiac outpatient telemetry	30 d	>5 s >30 s	12.1% 6.7%	8 15	Only 6 of 98 (6.1%) of PAF events were symptomatic
Miller et al.[54]	2013	156	Mobile cardiac outpatient telemetry	Up to 30 d	<30 s >30 s	11.6% 4.5%	9 22	Detection rates during the first 48 h, 7 d, 14 d and 21 d were 3.9, 9.2, 15.1 and 19.5%, respectively.
Higgins et al.[55]*	2013	100	7-day Holter ECG vs standard care	7 d	>20 s	After 14 days, 18% vs 2%	6 vs 50	
Gladstone et al.[56]* EMBRACE trial	2014	572	30-day event recorder vs 24-hr Holter ECG	30 d	>30 s >2.5 min	16.1% vs 3.2% 9.9% vs 2.5%	6 vs 31 10 vs 40	
Wachter et al.[57]* Find-AF trial	2017	398	10-day Holter-ECG-monitoring at baseline, and at 3 months and 6 months vs standard care	10 d, 3 times vs at least 24 h	>30 s	14% vs 5%	7 vs 20	

The table was modified from Sanna et al.[46]
AF, atrial fibrillation; ECG, electrocardiogram; PAF, paroxysmal AF.
*Randomized study.

features of embolic stroke. One recent pathological study analyzed 145 thrombus samples collected via endovascular thrombectomy from patients with acute ischemic stroke, finding that the portions of thrombus collected from patients with cardioembolic stroke or cryptogenic stroke were similar.[74] Another study used late-gadolinium-enhancement MRI to detect atrial fibrosis and showed that patients with ESUS exhibit similar atrial fibrosis compared with patients who had AF and more fibrosis than healthy controls.[75] In the Crystal-AF clinical trial, long-term cardiac rhythm monitoring in patients with cryptogenic stroke was performed with implanted loop recorder. During 1-year and 3-year follow-up periods, AF was detected in 12.4% and 30% of subjects, respectively.[62] Taken together, these studies indicate a strong association between cardioembolic and cryptogenic stroke, which suggests anticoagulants might be effective secondary treatments for both subgroups of ischemic stroke.

Based on the common potential etiologies of ESUS,[4] it would be reasonable to administer antiplatelet therapy to patients with arteriogenic emboli resulting from aortic arch atheroma or cervico-cephalic arterial non-stenotic plaques for long-term stroke prevention.[76] On the other hand, anticoagulants might benefit patients with other potential ESUS etiologies, such as paroxysmal AF, cancer-related hypercoagulability, PFO associated with paradoxical embolism, or minor embolic risk of heart disease (e.g., non-AF atrial dysrhythmias and stasis).[76] In light of the relatively low risk of major bleeding when using non-vitamin K antagonist oral anticoagulants (NOACs) instead of warfarin,[77] NOACs might also be considered as a potential treatment for future stroke prevention in patients with ESUS.

Recent phase 3 clinical trials

Two recent phase 3 randomized placebo-control trials compared the effectiveness and safety of NOACs and aspirin in patients with ESUS.[5,6] The NAVIGATE ESUS trial included 7213 ESUS patients over 50 years old at 7 days to 6 months post-stroke.[5] The primary efficacy outcome (ischemic and hemorrhagic stroke or systemic embolism) and primary safety outcome (major bleeding) were compared between rivaroxaban (15 mg once daily) and aspirin (100 mg once daily) groups. The trial was terminated

Table 3 Studies of atrial fibrillation detection using implantable cardiac monitors.

Authors	Year	No. of Patients	AF Definition	Monitoring Duration	AF Detection, %	Number needed to detect	Other findings
Ritter et al.[58]	2013	60	2 min	382 (89—670) d	17%	6	
Etgen et al.[59]	2013	22	6 min	1 year	27.3%	4	
Rojo-Martinez et al.[60]	2013	101	2 min	281 ± 212 d	33.7%	3	Frequency of false positives: 22.8%. Median time from implant to arrhythmia detection was 102 days (range: 26 —240 days). The majority of events (75%) were detected during the first six months of monitoring.
Christensen et al.[61] SURPRISE study	2014	85	2 min	569 ± 310 d	16.1%	6	The first PAF event was documented at a mean of 109 days after stroke onset. PAF was asymptomatic in all cases and predominantly lasted between 1 and 4 h.
Sanna et al.[62]*	2014	441	2 min	6 months	8.9% vs 1.4%	11 vs 71	By 12 months of follow-up (for patients in the ICM group with AF detected), the median value for the maximum time in AF in a single day was 11.2 h (interquartile range, 0.7 to 19.6), and the median value for the mean time in AF per day was 4.3 min (interquartile range, 0.7 to 34.5).
ICM vs routine care				12 months	12.4% vs 2.0%	8 vs 50	
CRYSTAL AF				36 months	30.0% vs 3.0%	3 vs 33	
Poli et al.[63]	2015	75	2 min	6 months	28%	4	92% of AF episodes were asymptomatic. Left atrial size >45 mm and presence of atrial runs were independently associated with AF detection.
				12 months	33.3%	3	
Ziegler et al.[64]	2017	1247	2 min	579 ± 222 d	21.5%	5	Intermittent monitoring for AF detection was

Table 3 (*continued*)

Authors	Year	No. of Patients	AF Definition	Monitoring Duration	AF Detection, %	Number needed to detect	Other findings
							inferior to continuous ICM monitoring, with sensitivities ranging from 2.9% (annual 24-hr Holter) to 29.9% (quarterly 7-d Holters). $P < 0.001$.
Israel et al.[65]	2017	123	2 min	12.7 ± 5.5 months	23.6%	4	Patients with AF were older, had a higher CHA_2DS_2-VASc score and more frequent cerebral microangiopathy, on average.

The table was modified from Sanna et al.[44]
AF, atrial fibrillation; ECG, electrocardiogram; ICM, implantable cardiac monitor; PAF, paroxysmal AF.
*Randomized study.

early due to lack of benefit with regard to stroke risk and bleeding associated with rivaroxaban. During a median follow-up of 11 months, the primary efficacy outcome was similar between rivaroxaban and aspirin groups (annualized rate: rivaroxaban, 5.1%; aspirin, 4.8%; $P = 0.52$) while rivaroxaban was associated with a higher risk of major bleeding (annualized rate: rivaroxaban, 1.8%; aspirin, 0.7%; $P < 0.001$).

The RE-SPECT ESUS trial enrolled 5390 ESUS patients over 18 years old within 6 months post-stroke.[6] The trial compared the efficacy and safety of dabigatran (110 or 150 mg twice daily) with aspirin (100 mg once daily). The primary outcome was recurrent stroke and the primary safety outcome was major bleeding. During a median follow-up of 19 months, both primary efficacy outcome (annualized rate: dabigatran, 4.1%; aspirin, 4.8%; $P = 0.1$) and safety outcome (annualized rate: dabigatran, 1.7%; aspirin, 1.4%; $P = 0.3$) were similar between groups. Thus, the two trials both showed that NOACs had similar effect with aspirin on stroke prevention for patients with ESUS, but bleeding risk might be increased when compared with aspirin.

Proposed clinical management

Because recent studies did not confirm the superiority of NOACs over aspirin in stroke prevention after ESUS, aspirin is still the first-line treatment for ESUS patients. However, for those patients with high risk of stroke recurrence (e.g., patients with repeated embolic infarcts despite aspirin usage, multiple infarcts at different arterial territories, or young age), it is necessary to perform a more extensive survey for stroke etiology, such as prolonged cardiac rhythm monitoring, TEE, and exams for coagulopathy, immunological disease or malignancy. If a diagnosis of paroxysmal AF, coagulopathy or cancer-related hypercoagulability is made, anticoagulants may be used instead of anti-platelet agents for long-term stroke prevention.[71,78] On the other hand, some subgroups of patients with ESUS might still benefit from anticoagulant treatment (Fig. 2). Among different anticoagulants, a NOAC might be a better choice than warfarin; dabigatran and aspirin treatments carried similar risks of major bleeding in ESUS patients, and patients with AF had less major bleeding on NOACs compared to warfarin.[6,77]

In ESUS patients with multiple infarcts at different territories of cerebral arteries (such as infarcts at bilateral hemispheres or involving both anterior and posterior circulation), the thromboembolism is likely to have originated from heart or aortic arch atheroma. Notably, multiple infarcts indicate high embolic burden leading to multiple cerebral embolization. Therefore, for patients with multiple ESUS at different territories of cerebral arteries (after excluding the presence of large aortic arch atheroma by TEE), the possibility of cardioembolism is high and the usage of anticoagulants may thus be reasonable.

The Crystal-AF trial demonstrated that about one-third of patients with cryptogenic stroke or ESUS have paroxysmal AF (detected by ICM) for up to three years.[62,79] Moreover, in patients with high $CHADS_2$ score ($\geq$4), the AF detection rate was increased to around 50%.[79] Age is an important risk factor of AF,[80] and in the subgroup analysis of RE-SPECT ESUS trial, patients with ESUS that were older than 75 years showed a trend toward better outcome with dabigatran instead of aspirin.[6] The HAVOC score has been developed (1 point each for peripheral vascular disease and obesity; 2 points each for hypertension, age $\geq$ 75, valvular

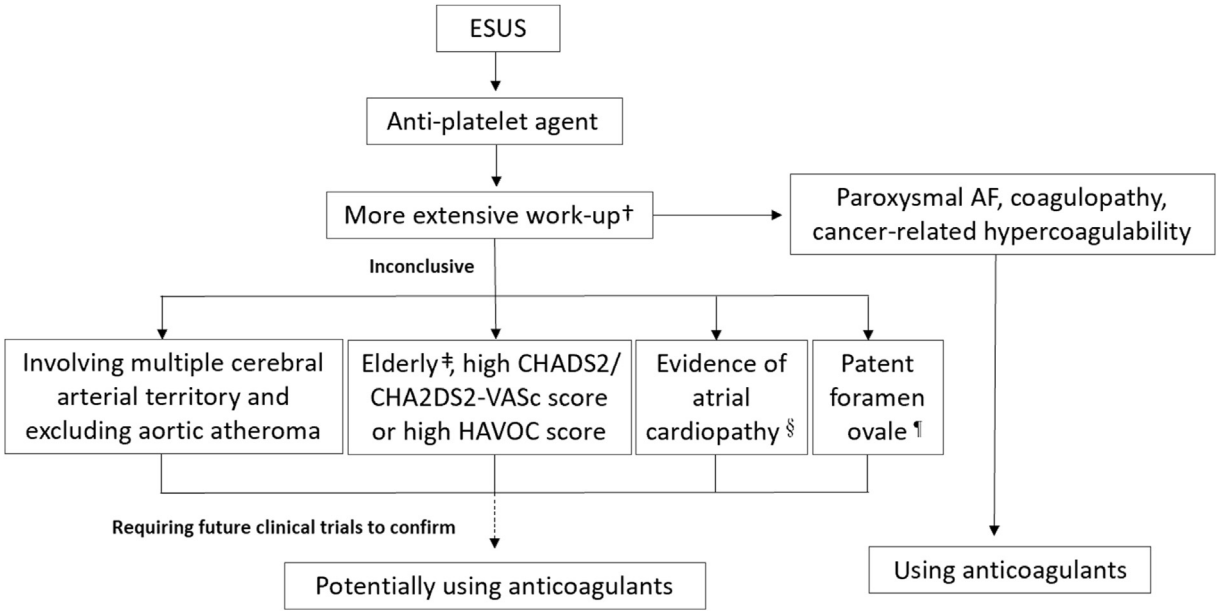

Figure 2 Treatment algorithm for ESUS. † Especially for those with recurrent stroke despite usage of antiplatelet agents, multiple infarcts at different arterial territories, or young age, etc. Studies including transesophageal echocardiography, long-term rhythm monitoring, or exam for coagulopathy, immunology, cancer, etc. ‡ Elderly, eg. more than 75 years old. § Atrial cardiopathy is defined as at least one of the following: PTFV1 on ECG >5000 μVms, severe left atrial enlargement on echocardiogram (≥3 cm/m^2), or serum levels of NT-proBNP > 250 pg/mL ¶ Patent foramen ovale (PFO) is detected by transthoracic or transesophageal echocardiography. Anticoagulants may be reasonable to use especially for those with large shunt or atrial septal aneurysm and unable to receive transcatheter PFO closure. ESUS, embolic stroke of undetermined source; AF, atrial fibrillation.

heart disease, and coronary artery disease; 4 points for congestive heart failure) to predict the risk of AF after cryptogenic stroke or TIA.[79] Patients with high HAVOC score (≥4) had higher risk of measurable AF than those with low score (0—1) during a 1 year follow-up (high score, 32%; low score, 11%), as indicated by post-hoc analysis of the Crystal-AF trial.[81] In patients participating in NAVIGATE ESUS trial, detection of AF during follow-up increased along with increased HAVOC score: 2.3% (score 0—2), 3.0% (score 3), and 5.8% (score >3).[82] Taken together, patients with high $CHADS_2/CHA_2DS_2$-VASc score, high HAVOC score, and/or the elderly may benefit from anticoagulant treatment, considering their high risk for paroxysmal AF.

Atrial cardiography is highly associated with AF, and LA enlargement is a predisposal factor for AF.[83] Increased PTFV1 on ECG reflects LA abnormalities and has been reported to be associated with ischemic stroke, especially non-lacunar infarcts.[15] The parameters of atrial cardiography, such as LA size and PTFV1, are independently associated with stroke and AF.[84] In subgroup analysis of NAVIGATE ESUS trial, rivaroxaban treatment was associated with a reduced risk of recurrent stroke compared to aspirin (rivaroxaban, 1.7%; aspirin, 6.5% per year; hazard ratio, 0.26; confidence interval, 0.07—0.94) in patients with ESUS and moderate or severe LA enlargement.[83] Therefore, for ESUS with high burden of stroke recurrence, the presence of atrial cardiography by echocardiography (for atrial size) or 12-lead ECG (for PTFV1) may imply high risk of cardioembolism. As such, use of anticoagulants may be preferable for future stroke prevention in these patients.

The prevalence of PFO in patients with cryptogenic stroke was reported to be as high as 50%; such a strong association implies that paradoxical emboli through a PFO may be an important mechanism of ESUS.[85] Transcatheter closure of the PFO is associated with a significant reduction in the risk of recurrence following cryptogenic stroke,[86] reflecting the critical role of PFO in cardioembolism. The reduction of recurrent stroke risk was more prominent in patients with atrial septal aneurysms or with large shunts (hazard ratio: septal aneurysm, 0.2; large shunt, 0.26; $P = 0.005$).[87,88] With the novel designs of improved devices, all-cause serious adverse events (including major bleeding) were similar between patients receiving percutaneous PFO closure and those with medicinal therapy. In Taiwan, PFO closure is covered by National Health Insurance for patients with right-to-left shunt and stroke or TIA. On the other hand, subgroup analysis of the NAVIGATE ESUS trial showed a trend toward reduced risk of recurrent stroke for rivaroxaban compared to aspirin in patients with ESUS and PFO.[89] Moreover, a meta-analysis of NAVIGATE ESUS and two PFO trials (PICSS and CLOSE trials; comparisons were made mainly between warfarin and aspirin)[90,91] further demonstrated that anticoagulants reduced recurrent stroke in patients with PFO and ESUS by about half (odds ratio, 0.48; confidence interval, 0.24—0.96). Therefore, in ESUS patients with PFO, especially those having large shunt or atrial septal aneurysm,[85] anticoagulants may be a reasonable alternative for long-term stroke prevention in addition to transcatheter PFO closure.

Recommendations

- In general, anti-platelet agents remain the first-line treatment for patients with ESUS. (COR I; LOE A)
- Anticoagulant treatment may benefit subgroups of high-risk patients with ESUS, such as those with multiple infarcts at different arterial territories without aortic atheroma, the elderly, or patients with high CHA_2D_2-VASc score, high HAVOC score, atrial cardiopathy or PFO. (COR IIb; LOE C-EO)

Future perspectives

In light of the overall negative results from the NAVIGATE and RE-SPECT ESUS trials, the definition of ESUS seems to be still too broad to guide management with a unified approach. The embolic stroke of *possible* source (ESPS) might be an even more pragmatic construct than ESUS. Each patient with ESUS should receive appropriate history taking and work-ups to categorize ESUS into subgroups of *possible* etiology, e.g., cardioembolism (atrial cardiopathy, PFO, etc.), arterial atherosclerosis (aortic arch atheroma and cervico-cephalic artery non-stenotic plaques, etc.) and atypical small artery disease (paramedian pontine infarct, anterior choroidal artery infarct, etc.). Cardiac imaging, such as TEE and prolonged cardiac rhythm monitoring, should be investigated thoroughly for practicality of use in determining potential ESUS etiology. Future clinical trials may also benefit from enrolling ESUS patients within specific subgroups to determine optimal therapies.

In accordance with this notion of subcategorizing ESUS patients, two large ongoing clinical trials are focused on ESUS patients with high risk of cardioembolism.[24,92] The ATTICUS trial is a prospective, randomized, blinded, open-label, phase 3 trial on approximately 500 ESUS patients.[92] The trial is designed to determine whether a NOAC (apixaban) is superior to aspirin for prevention of new MRI-documented ischemic lesions within 12 months of the index stroke. A key inclusion criterion in this trial is the presence of ESUS with at least one of the following non-major but suggestive risk factors for cardioembolism: LA size $>$45 mm, spontaneous echo contrast in LA appendage, flow velocity in LA appendage $\leq$0.2 m/s, atrial high rate episodes, CHA_2DS_2-VASc score $\geq$4, or presence of PFO. The ARCADIA trial is a prospective, randomized, double-blind, phase 3 trial enrolling about 1100 ESUS patients.[24] The aim of this trial is to test the hypothesis that apixaban is superior to aspirin for the prevention of recurrent stroke in subjects with ESUS and atrial cardiopathy. The definition of atrial cardiopathy includes PTFV1 $>$ 5000 μVms, LV diameter index $\geq$3 cm/m^2 on echocardiogram or serum NT-proBNP $>$ 250 pg/mL.

Conclusion

Cryptogenic stroke comprises about one-quarter of ischemic strokes with high recurrence rate[1,2]; however, studies specifically investigating the features and treatment of this stroke subtype are rare. The introduction of the ESUS classification in 2014 has facilitated the development of a standardized approach to diagnosing cryptogenic stroke and initiating clinical trials for optimal therapy.[4] Since neither the NAVIGATE ESUS nor RE-SPECT ESUS trials demonstrated a reduction in stroke recurrence with anticoagulants,[5,6] anti-platelet agents remain the first-line treatment for patients with ESUS. However, the results of these trials raise two important issues about future ESUS management: (1) more extensive diagnostic work-ups are required for ESUS patients, and (2) ESUS should be categorized into different subgroups. In addition to the essential diagnostic requirements for ESUS, TEE, prolonged cardiac rhythm monitoring, and exams for coagulopathy, immune disease and malignancy can further assign patients to various subgroups that will not only guide treatment but also allow better design of clinical trials. Some important ESUS clinical trials are ongoing, and the results are anticipated. With the rapid advancement of our understanding of ESUS, development of new ESUS subcategories and validation of optimal treatments for each subgroup are expected in the near future.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

Acknowledgement

The consensus conference was supported by Boehringer Ingelheim.

References

1. Hsieh FI, Lien LM, Chen ST, Bai CH, Sun MC, Tseng HP, et al. Get with the guidelines-stroke performance indicators: surveillance of stroke care in the taiwan stroke registry: get with the guidelines-stroke in taiwan. *Circulation* 2010;**122**:1116–23.
2. Saver JL. Cryptogenic stroke. *N Engl J Med* 2016;**374**:2065–74.
3. Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;**24**:35–41.
4. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;**13**:429–38.
5. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;**378**:2191–201.
6. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019;**380**:1906–17.
7. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018;**49**:e46–110.
8. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. *Stroke* 2017;**48**:867–72.

9. Perera KS, Vanassche T, Bosch J, Giruparajah M, Swaminathan B, Mattina KR, et al. Embolic strokes of undetermined source: prevalence and patient features in the ESUS Global Registry. *Int J Stroke* 2016;**11**:526—33.
10. Wang W, Tang X, Liu W, Jia K, Zhao X, Yu F. Clinical features of embolic stroke of undetermined source. *Font Neurol* 2020;**11**:58.
11. Ntaios G, Papavasileiou V, Milionis H, Makaritsis K, Vemmou A, Koroboki E, et al. Embolic strokes of undetermined source in the Athens Stroke Registry: an outcome analysis. *Stroke* 2015;**46**:2087—93.
12. Hart RG, Veltkamp RC, Sheridan P, Sharma M, Kasner SE, Bangdiwala SI, et al. Predictors of recurrent ischemic stroke in patients with embolic strokes of undetermined source and effects of rivaroxaban versus aspirin according to risk status: the NAVIGATE ESUS Trial. *J Stroke Cerebrovasc Dis* 2019;**28**:2273—9.
13. Ntaios G, Vemmos K, Lip GY, Koroboki E, Manios E, Vemmou A, et al. Risk stratification for recurrence and mortality in embolic stroke of undetermined source. *Stroke* 2016;**47**:2278—85.
14. Sposato LA, Cipriano LE, Saposnik G, Ruíz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol* 2015;**14**:377—87.
15. Kamel H, O'Neal WT, Okin PM, Loehr LR, Alonso A, Soliman EZ. Electrocardiographic left atrial abnormality and stroke subtype in the atherosclerosis risk in communities study. *Ann Neurol* 2015;**78**:670—8.
16. Sigurdsson E, Thorgeirsson G, Sigvaldason H, Sigfusson N. Unrecognized myocardial infarction: epidemiology, clinical characteristics, and the prognostic role of angina pectoris: the Reykjavik study. *Ann Intern Med* 1995;**122**:96—102.
17. Ahmad Y, Howard JP, Arnold A, Shin MS, Cook C, Petraco R, et al. Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials. *Eur Heart J* 2018;**39**:1638—49.
18. Navi BB, Singer S, Merkler AE, Cheng NT, Stone JB, Kamel H, et al. Recurrent thromboembolic events after ischemic stroke in patients with cancer. *Neurology* 2014;**83**:26—33.
19. Singh N, Moody AR, Panzov V, Gladstone DJ. Carotid intraplaque hemorrhage in patients with embolic stroke of undetermined source. *J Stroke Cerebrovasc Dis* 2018;**27**:1956—9.
20. Rundek T, Di Tullio MR, Sciacca RR, Titova IV, Mohr JP, Homma S, et al. Association between large aortic arch atheromas and high-intensity transient signals in elderly stroke patients. *Stroke* 1999;**30**:2683—6.
21. Wu Y, Wu F, Liu Y, Fan Z, Fisher M, Li D, et al. High-resolution magnetic resonance imaging of cervicocranial artery dissection: imaging features associated with stroke. *Stroke* 2019. https://doi.org/10.1161/STROKEAHA.119.026362. STROKEAHA119026362.
22. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics-2014 update: a report from the American Heart Association. *Circulation* 2014;**129**:e28—292.
23. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;**18**:1455—90.
24. Kamel H, Longstreth Jr WT, Tirschwell DL, Kronmal RA, Broderick JP, Palesch YY, et al. The AtRial Cardiopathy and Antithrombotic Drugs in prevention after cryptogenic stroke randomized trial: rationale and methods. *Int J Stroke* 2019;**14**:207—14.
25. Acampa M, Lazzerini PE, Martini G. Atrial cardiopathy and sympatho-vagal imbalance in cryptogenic stroke: pathogenic mechanisms and effects on electrocardiographic markers. *Front Neurol* 2018;**9**:469.
26. Hancock EW, Deal BJ, Mirvis DM, Okin P, Kligfield P, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part V: electrocardiogram changes associated with cardiac chamber hypertrophy. *Circulation* 2009;**119**:e251—61.
27. Kamel H, Hunter M, Moon YP, Yaghi S, Cheung K, Di Tullio MR, et al. Electrocardiographic left atrial abnormality and risk of stroke: northern Manhattan Study. *Stroke* 2015;**46**:3208—12.
28. Jalini S, Rajalingam R, Nisenbaum R, Javier AD, Woo A, Pikula A. Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies. *Neurology* 2019;**92**:e288—94.
29. Akoum N, Marrouche N. Assessment and impact of cardiac fibrosis on atrial fibrillation. *Curr Cardiol Rep* 2014;**16**:518.
30. Daccarett M, Badger TJ, Akoum N, Burgon NS, Mahnkopf C, Vergara G, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:831—8.
31. Akoum N, Fernandez G, Wilson B, Mcgann C, Kholmovski E, Marrouche N. Association of atrial fibrosis quantified using LGE-MRI with atrial appendage thrombus and spontaneous contrast on transesophageal echocardiography in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 2013;**24**:1104—9.
32. Amarenco P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med* 1994;**331**:1474—9.
33. Di Tullio MR, Sacco RL, Gersony D, Nayak H, Weslow RG, Kargman DE, et al. Aortic atheromas and acute ischemic stroke: a transesophageal echocardiographic study in an ethnically mixed population. *Neurology* 1996;**46**:1560—6.
34. Censori B, Colombo F, Valsecchi MG, Clivati L, Zonca A, Camerlingo M, et al. Early transoesophageal echocardiography in cryptogenic and lacunar stroke and transient ischaemic attack. *J Neurol Neurosurg Psychiatry* 1998;**64**:624—7.
35. Gu X, He Y, Li Z, Kontos MC, Paulsen WH, Arrowood JA, et al. Comparison of frequencies of patent foramen ovale and thoracic aortic atherosclerosis in patients with cryptogenic ischemic stroke undergoing transesophageal echocardiography. *Am J Cardiol* 2011;**108**:1815—9.
36. Dávila-Román VG, Murphy SF, Nickerson NJ, Kouchoukos NT, Schechtman KB, Barzilai B. Atherosclerosis of the ascending aorta is an independent predictor of long-term neurologic events and mortality. *J Am Coll Cardiol* 1999;**33**:1308—16.
37. Cohen A, Tzourio C, Bertrand B, Chauvel C, Bousser M-G, Amarenco P, et al. Aortic plaque morphology and vascular events. A follow-up study in patients with ischemic stroke. *Circulation* 1997;**96**:3838—41.
38. Amarenco P, Davis S, Jones EF, Cohen AA, Heiss W, Kaste M, et al. Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. *Stroke* 2014;**45**:1248—57.
39. De Bruijn SF, Agema WR, Lammers GJ, van der Wall EE, Wolterbeek R, Holman ER, et al. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. *Stroke* 2006;**37**:2531—4.
40. McGrath ER, Paikin JS, Motlagh B, Salehian O, Kapral MK, O'Donnell MJ. Transesophageal echocardiography in patients with cryptogenic ischemic stroke: a systematic review. *Am Heart J* 2014;**168**:706—12.
41. Di Biase L, Santangeli P, Anselmino M, Mohanty P, Salvetti I, Gili S, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial

fibrillation? Results from a multicenter study. *J Am Coll Cardiol* 2012;**60**:531–8.
42. Khurram IM, Dewire J, Mager M, Maqbool F, Zimmerman SL, Zipunnikov V, et al. Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation. *Heart Rhythm* 2013;**10**:184–9.
43. Daniel WG, Erbel R, Kasper W, Visser CA, Engberding R, Sutherland GR, et al. Safety of transesophageal echocardiography. A multicenter survey of 10,419 examinations. *Circulation* 1991;**83**:817–21.
44. Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH, et al. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan Nationwide AF Cohort Study. *Chest* 2018;**153**:453–66.
45. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, et al. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *J Am Coll Cardiol* 2007;**50**:2156–61.
46. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–9.
47. Sanna T, Ziegler PD, Crea F. Detection and management of atrial fibrillation after cryptogenic stroke or embolic stroke of undetermined source. *Clin Cardiol* 2018;**41**:426–32.
48. Sposato LA, Cipriano LE, Saposnik G, Ruíz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol* 2015;**14**:377–87.
49. Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ, et al. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke* 2014;**45**:520–6.
50. Tayal AH, Tian M, Kelly KM, Jones SC, Wright DG, Singh D, et al. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. *Neurology* 2008;**71**:1696–701.
51. Gaillard N, Deltour S, Vilotijevic B, Hornych A, Crozier S, Leger A, et al. Detection of paroxysmal atrial fibrillation with transtelephonic EKG in TIA or stroke patients. *Neurology* 2010;**74**:1666–70.
52. Bhatt A, Majid A, Razak A, Kassab M, Hussain S, Safdar A. Predictors of occult paroxysmal atrial fibrillation in cryptogenic strokes detected by long-term noninvasive cardiac monitoring. *Stroke Res Treat* 2011;**2011**:172074.
53. Flint AC1, Banki NM, Ren X, Rao VA, Go AS. Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. *Stroke* 2012;**43**:2788–90.
54. Miller DJ, Khan MA, Schultz LR, Simpson JR, Katramados AM, Russman AN, et al. Outpatient cardiac telemetry detects a high rate of atrial fibrillation in cryptogenic stroke. *J Neurol Sci* 2013;**324**:57–61.
55. Higgins P, MacFarlane PW, Dawson J, McInnes GT, Langhorne P, Lees KR. Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: a randomized, controlled trial. *Stroke* 2013;**44**:2525–31.
56. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;**370**:2467–77.
57. Wachter R, Gröschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, et al. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFRANDOMISED): an open-label randomised controlled trial. *Lancet Neurol* 2017;**16**:282–90.
58. Ritter MA, Kochhäuser S, Duning T, Reinke F, Pott C, Dechering DG, et al. Occult atrial fibrillation in cryptogenic stroke: detection by 7-day electrocardiogram versus implantable cardiac monitors. *Stroke* 2013;**44**:1449–52.
59. Etgen T, Hochreiter M, Mundel M, Freudenberger T. Insertable cardiac event recorder in detection of atrial fibrillation after cryptogenic stroke: an audit report. *Stroke* 2013;**44**:2007–9.
60. Rojo-Martinez E, Sandín-Fuentes M, Calleja-Sanz AI, Cortijo-García E, García-Bermejo P, Ruiz-Piñero M, et al. High performance of an implantable Holter monitor in the detection of concealed paroxysmal atrial fibrillation in patients with cryptogenic stroke and a suspected embolic mechanism. *Rev Neurol* 2013;**57**:251–7.
61. Christensen LM, Krieger DW, Højberg S, Pedersen OD, Karlsen FM, Jacobsen MD. Paroxysmal atrial fibrillation occurs often in cryptogenic ischaemic stroke. Final results from the SURPRISE study. *Eur J Neurol* 2014;**21**:884–9.
62. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478–86.
63. Poli S, Diedler J, Härtig F, Götz N, Bauer A, Sachse T, et al. Insertable cardiac monitors after cryptogenic stroke–a risk factor based approach to enhance the detection rate for paroxysmal atrial fibrillation. *Eur J Neurol* 2016;**23**:375–81.
64. Ziegler PD, Rogers JD, Ferreira SW, Nichols AJ, Richards M, Koehler JL, et al. Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population. *Int J Cardiol* 2017;**244**:175–9.
65. Israel C, Kitsiou A, Kalyani M, Deelawar S, Ejangue LE, Rogalewski A, et al. Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders. *Thromb Haemostasis* 2017;**117**:1962–9.
66. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
67. Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, et al. Antithrombotic therapy in atrial fibrillation: American College of chest physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;**133**. 546S-92S.
68. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation* 1994;**89**:635–41.
69. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;**345**:1444–51.
70. De Schryver EL, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ. Vitamin K antagonists versus antiplatelet therapy after transient ischaemic attack or minor ischaemic stroke of presumed arterial origin. *Cochrane Database Syst Rev* 2012;**9**:Cd001342.
71. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:2160–236.
72. The Taiwan Stroke Association. *Guidelines for antiplatelet therapy in ischemic stroke*. 2016. http://www.stroke.org.tw/GoWeb2/include/pdf/03%20guideline_缺血性腦中風的抗血小板藥物治療指引_20160520.pdf.
73. Sacco RL, Prabhakaran S, Thompson JL, Murphy A, Sciacca RR, Levin B, et al. Comparison of warfarin versus aspirin for the prevention of recurrent stroke or death: subgroup analyses from the Warfarin-Aspirin Recurrent Stroke Study. *Cerebrovasc Dis* 2006;**22**:4–12.

74. Boeckh-Behrens T, Kleine JF, Zimmer C, Neff F, Scheipl F, Pelisek J, et al. Thrombus histology suggests cardioembolic cause in cryptogenic stroke. *Stroke* 2016;**47**:1864—71.
75. Tandon K, Tirschwell D, Longstreth Jr WT, Smith B, Akoum N. Embolic stroke of undetermined source correlates to atrial fibrosis without atrial fibrillation. *Neurology* 2019;**93**:e381—7.
76. Kamel H, Merkler AE, Iadecola C, Gupta A, Navi BB. Tailoring the approach to embolic stroke of undetermined source: a review. *JAMA Neurol* 2019;**76**:855—61.
77. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;**39**:1330—93.
78. Dardiotis E, Aloizou AM, Markoula S, Siokas V, Tsarouhas K, Tzanakakis G, et al. Cancer-associated stroke: pathophysiology, detection and management. *Int J Oncol* 2019;**54**:779—96.
79. Verma N, Ziegler PD, Liu S, Passman RS. Incidence of atrial fibrillation among patients with an embolic stroke of undetermined source: insights from insertable cardiac monitors. *Int J Stroke* 2019;**14**:146—53.
80. Kwong C, Ling AY, Crawford MH, Zhao SX, Shah NH. A clinical score for predicting atrial fibrillation in patients with cryptogenic stroke or transient ischemic attack. *Cardiology* 2017;**138**:133—40.
81. Zhao SX, Ziegler PD, Crawford MH, Kwong C, Koehler JL, Passman RS. Evaluation of a clinical score for predicting atrial fibrillation in cryptogenic stroke patients with insertable cardiac monitors: results from the CRYSTAL AF study. *Ther Adv Neurol Disord* 2019;**12**. 1756286419842698.
82. Healey JS, Gladstone DJ, Swaminathan B, Eckstein J, Mundl H, Epstein AE, et al. Recurrent stroke with rivaroxaban compared with aspirin according to predictors of atrial fibrillation: secondary analysis of the NAVIGATE ESUS randomized clinical trial. *JAMA Neurol* 2019;**76**:764—73.
83. Oikonomou E, Zografos T, Papamikroulis GA, Siasos G, Vogiatzi G, Theofilis P, et al. Biomarkers in atrial fibrillation and heart failure. *Curr Med Chem* 2019;**26**:873—87.
84. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke* 2016;**47**:895—900.
85. Abdelghani M, El-Shedoudy SAO, Nassif M, Bouma BJ, de Winter RJ. Management of patients with patent foramen ovale and cryptogenic stroke: an update. *Cardiology* 2019;**15**:1—11.
86. Riaz H, Khan MS, Schenone AL, Waheed AA, Khan AR, Krasuski RA. Transcatheter closure of patent foramen ovale following cryptogenic stroke: an updated meta-analysis of randomized controlled trials. *Am Heart J* 2018;**199**:44—50.
87. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017;**377**:1022—32.
88. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017;**377**:1011—21.
89. Kasner SE, Swaminathan B, Lavados P, Sharma M, Muir K, Veltkamp R, et al. Rivaroxaban or aspirin for patent foramen ovale and embolic stroke of undetermined source: a prespecified subgroup analysis from the NAVIGATE ESUS trial. *Lancet Neurol* 2018;**17**:1053—60.
90. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002;**105**:2625—31.
91. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017;**377**:1011—21.
92. Geisler T, Poli S, Meisner C, Schreieck J, Zuern CS, Nägele T, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): rationale and study design. *Int J Stroke* 2017;**12**:985—90.