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Cerebrovascular Disease and Stroke (S Silverman, Section Editor)

Cryptogenic Stroke: Diagnostic Workup and Management

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Abstract

Purpose of review Cryptogenic stroke describes a subset of ischemic stroke for which no cause can be found despite a structured investigation. There are a number of putative mechanisms of cryptogenic ischemic stroke including a covert structural cardiac lesion, paroxysmal atrial fibrillation, hypercoagulable state or undiagnosed malignancy. Because many of these proposed mechanisms are embolic – and based on studies of thrombus history showing commonalities between thrombus composition between cardioembolic and cryptogenic strokes – the concept of embolic stroke of undetermined source (ESUS) (Hart et al. Lancet Neurol. 13(4):429–38, 2014; Stroke. 48(4):867–72, 2017) has been proposed to describe cryptogenic strokes that may warrant systemic anticoagulation. In this review, we discuss the phenomena of cryptogenic stroke, ESUS and a proposed management pathway. *Recent findings* 1. The concept of ESUS was proposed in 2014 as a potentially useful therapeutic entity. Two recent trials – NAVIGATE-ESUS (Hart et al. N Engl J Med. 378(23):2191–201, 2018) and RESPECT-ESUS (Diener 2018) were proposed based on this concept. They were negative for their primary endpoint and for the secondary endpoint of ischemic stroke recurrence. Post-hoc analysis of the WARSS trial (Longstreth et al. Stroke. 44(3):714–9, 2013) suggested that people with elevated pro-BNP benefited from systemic anticoagulation whereas those with a normal pro-BNP did not. This led to the hypothesis that a subgroup of patients at higher risk for embolism from the left atrium would benefit

from anticoagulation, even if the WARSS trial was negative for the primary endpoint. Thus, the ARCADIA trial (Kamel et al. Int J Stroke. 14(2):207–14, 2019) was proposed – a randomized, active-control, multi-center trial comparing apixaban with aspirin for secondary stroke prevention in patients with ESUS and biomarkers of left atrial cardiopathy. This trial is actively recruiting. 2. Carotid web – an intimal form of fibromuscular dysplasia – has come to increased prominence in the literature as a cause of embolic stroke. It is a non-stenosis, non-atherosclerotic lesion in the posterior wall of the internal carotid artery that leads to pooling with stasis of blood distal to the lesion and, as a consequence, embolic stroke. It is not usually detected by a standard stroke workup as it masquerades as non-calcified atherosclerosis and does not cause hemodynamically significant stenosis. There have been two major recent papers – a meta-analysis in *Stroke* (Zhang et al. Stroke. 49(12):2872–6, 2018) and narrative review in *JAMA Neurology* (Kim et al. JAMA Neurol. 2018) – that addressed this topic.

Summary Cryptogenic stroke describes a stroke for which no cause has been found. ESUS is a more precisely-defined entity that mandates a specific workup and implicates remote embolism as a cause of stroke. In ESUS, the options for further investigation include long-term cardiac monitoring, transesophageal echocardiography, investigation for occult malignancy or arterial hypercoagulability. Options for management include anti-platelet therapy (the current standard of care), empiric anticoagulation or enrollment in to a clinical trial examining the use of NOACs compared with aspirin for secondary prevention (such as ARCADIA or ATTICUS). In a person less than 60 years old with ESUS and a patent foramen ovale the risk of a recurrent stroke is low but recent trials have suggested that percutaneous device closure reduces this risk further with an acceptable complication rate.

Introduction

Cryptogenic stroke describes a subtype of ischemic stroke for which no cause can definitively be identified. The TOAST criteria [1] assign a likely stroke etiology according to the following classification system: 1) Large artery atherosclerosis; 2) Cardioembolic stroke; 3) Small vessel stroke; 4) Other identified cause and; 5) Cryptogenic stroke. The cryptogenic subtype accounts for 26% of all strokes [2]. According to this classification scheme, cryptogenic includes all strokes without a defined cause; that is strokes with no mechanism, strokes with more than one potential mechanism and strokes in which the workup is incomplete. Thus, a heterogeneous population of patients is included within this group. In order to provide a more useful clinical paradigm, the concept of embolic stroke of undetermined source (ESUS) was proposed [3, 4]. This classification sought to identify a subgroup of patients with cryptogenic stroke, who have an embolic-appearing stroke that is not lacunar and has no high-risk cardioembolic source, nor high-grade arterial stenosis in the arterial supply serving the affected area. The goal in this classification was to identify a population of patients who could potentially benefit from anticoagulation even before a mechanism was identified. Potential causes of ESUS include substenotic atherosclerotic disease, a cardioembolic source (such as a moderately depressed left ventricular ejection fraction, intracardiac mass, paroxysmal atrial tachycardia) or an undiagnosed hypercoagulable tendency.

ESUS accounts for up to 25% of all ischemic strokes [3] and comprises the vast majority of cryptogenic strokes. 200,000 people in the United States experience a cryptogenic stroke every year [5]. The probability of a stroke being cryptogenic decreases with age and in the presence of other vascular risk factors [6] - in young people, half of strokes are cryptogenic [4]. One population-based study [6] examined a cohort of 2555 patients with stroke or transient ischemic attack (TIA) and found that 32% were cryptogenic. The 10-year rate of recurrence was 32%. The risk of recurrent stroke or TIA after ESUS is 5.6% per year [7] and, as in patients

Table 1. Potential mechanisms of stroke

Large artery atherosclerosis	Cardioembolism	Small vessel stroke	Other defined cause
Carotid artery stenosis	Atrial fibrillation	Lipohyalinosis	Arterial dissection
Vertebral artery stenosis	Prosthetic cardiac valve	Branch atheromatous disease	Venous infarct
Intracranial artery stenosis	Left ventricular thrombus		Carotid web
Substenotic atherosclerosis	Atrial myxoma		Toxin exposure
	Fibroelastoma		Venous sinus thrombosis
	Infectious endocarditis		Hypercoagulable state
	Left atrial appendage thrombus		Radiation vasculopathy
	Aortic arch atheroma		Fibromuscular dysplasia
	Left atrial cardiopathy		Takayasu's arteritis
			Giant cell arteritis
			Polyarteritis nodosa
			Primary CNS vasculitis
			Moya Disease
			CADASIL
			Fabry Disease
			Homocystinuria
			MELAS
			Sickle cell disease
			MoyaMoya Disease

with atrial fibrillation, the risk can be stratified based on the CHA_2DS_2VASc score. At present most people with ESUS are treated with anti-platelet therapy alone [4] with only slightly over 10% being treated empirically with anticoagulation.

Potential mechanisms and diagnostic workup

Mechanisms of stroke sorted according to the TOAST criteria are outlined in Table 1. All patients with a stroke should have imaging of the cervical and cerebral arterial system, as well as a transthoracic echocardiogram (TTE). Additionally, patients should be screened for hypertension, hyperlipidemia and diabetes mellitus and their smoking status identified. In patients with an unrevealing initial workup, further workup is tailored to the individual patient and determined by their age, co-morbidities and imaging characteristics of the stroke. Thrombus histology is almost identical between cardioembolic strokes and cryptogenic strokes [8]. Also, over 55% of patients with cryptogenic strokes have cortically-based as opposed to deep infarcts [9]. These two observations lend credence to the hypothesis that the majority of cryptogenic strokes are embolic in nature and thus the focus of more advanced diagnostic testing is to identify potential occult embolic sources. A scheme for first- and second-line workup in patients presenting with stroke is outlined in Table 2.

a. Paroxysmal atrial fibrillation

Paroxysmal atrial fibrillation (AF) is challenging to diagnose and can easily be missed with only short-term cardiac telemetry. A large proportion of patients with cryptogenic stroke may have AF that has not been detected. Even short bouts of AF increase the risk of stroke [10].

Two recent studies support prolonged cardiac monitoring after cryptogenic stroke:

Table 2. First- and second- line diagnostic workup of ischemic stroke

Category	First line	Second line
Large artery atherosclerosis	CTA Brain/Neck	Diagnostic cerebral angiography
	MRA Brain/Neck	Contrast-enhanced MRA Neck
	Carotid ultrasound Transcranial doppler ultrasonography	Blood-suppressed MR morphologic imaging
Cardioembolism	EKG	Blood cultures
	Cardiac telemetry	Extended cardiac monitoring
	TTE	Transesophageal echocardiorgaphy
		TCD with bubble study
		Cardiac magnetic resonance imaging
		CTA Aortic Arch
Small vessel stroke	Blood pressure measurement LDL Cholesterol	HIV testing
	HbA1C	
Other determined cause	Urine toxicology screen	ESR
		CRP
		Arterial hypercoagulability testing: -Lupus anticoagulant -Anticardiolipin antibodies -B2 glycoprotein antibodies -Homocysteine -Flow cytometry (to look for evidence of Paroxysmal Nocturnal Hemoglobinuria)
		Venous hypercoagulable testing: -Antithrombin activity -Protein C activity -Protein S functional -APC resistance (screening test for Factor V Leiden) -Prothrombin gene mutation
		Magnetic resonance venography
		MRI with T1 fat-suppressed images
		Peripheral blood smear
		CTA Renal Arteries
		PET Scanning
		CSF evaluation
		Brain biopsy

A. EMBRACE [11]: This multi-center study enrolled patients 55 years old or older with no history of AF, who presented with cryptogenic stroke or TIA. The patients were randomized to usual practice

[Electrocardiogram (EKG) and inpatient cardiac telemetry] versus 30-day cardiac event monitoring. The primary outcome was the detection of 30 s of continuous AF. Out of the patients who received usual care, 3.2% were found to have AF, while the arrhythmia was detected in 16.1% of patients who received prolonged cardiac monitoring ($p < 0.001$).

B. CRYSTAL-AF [12]: CRYSTAL-AF enrolled patients with cryptogenic stroke or TIA and randomized them to usual care (consisting of an EKG followed by inpatient cardiac monitoring) or long-term cardiac monitoring by means of an Implantable Loop Recorder (ILR) with the primary outcome being the detection of 30 s of AF. In contrast to EMBRACE, the study enrolled younger patients – age 40 or older. Similar to EMBRACE, the detection of AF increased as the duration of monitoring increased. 1.4% of patients in the control group were found to have AF at 6 months compared to 8.9% in the intervention group. With a follow-up of 3 years, detection of AF in the ILR group exceeded 30%.

EMBRACE had a higher rate of AF detection than CRYSTAL-AF. This may be because EMBRACE enrolled older subjects or there may be a difference in sensitivity for the detection of AF between the ILR and ambulatory cardiac monitoring. Furthermore, both trials used 30 s of AF as an arbitrary threshold when assigning their end points, so they could underestimate the true incidence of paroxysmal AF.

Our usual practice is to perform an electrocardiogram (EKG) and then continuous cardiac telemetry during a person's admission with ischemic stroke. If no cause is evident at the point of discharge (i.e no high-risk cardioembolic source and no large artery stenosis within the arterial territory supplying the region of infarction) and the stroke does not appear definitively lacunar, we refer patients for a 30-day cardiac event monitor. If 30-days of cardiac monitoring does not reveal atrial fibrillation, we then refer patients for ILR implantation.

b. **Left atrial cardiopathy**

Left atrial cardiopathy describes dysfunction of the left atrium as measured by electrocardiographic, serum or imaging markers, in the absence of AF [7, 8]. These include: (1) P wave terminal force in lead V1 on EKG; (2) elevated NT-proBNP (N-terminal pro-B-type natriuretic peptide); (3) and increased left atrial size/ volume. Additionally, recent studies have shown no temporal relationship between subclinical AF and embolic events, arguing that AF is a marker of atrial cardiopathy, which in turn is the direct cause of stroke in most patients with this arrhythmia. An analysis of the Cardiovascular Health Study examined adults without stroke or AF [13] and found that P wave terminal force in lead V-1 and serum NT-proBNP were associated with incident stroke (HR:1.04, 95% CI:1.001–1.08 and HR:1.09, 95% CI:1.03–1.16 respectively). Other electrocardiographic markers of left atrial dysfunction, like prolongation of the PR interval have also been associated with cryptogenic stroke [14]. Atrial fibrosis—as measured via cardiac magnetic resonance imaging—is another putative marker of left atrium/ left atrial appendage (LAA) dysfunction that increases the risk of embolic stroke. A recent study showed that in patients with ischemic stroke, left atrial fibrosis was more frequently detected in patients with cryptogenic stroke versus stroke of determined non-cardioembolic mechanism [15]. An open question is whether or not these mechanisms are independent of AF and whether AF itself may act as a marker of left atrial dysfunction as opposed to the inciting event for embolus formation [16]. There is likely a reciprocal relationship between atrial cardiopathy and AF, whereby AF worsens cardiopathy and visa versa.

c. **Occult structural cardiac lesion**

One possible cause of cryptogenic stroke is a cardiac lesion that is not always evident on TTE. Such lesions include aortic arch/ descending aorta atheroma (Fig. 1), papillary fibroelastoma (Fig. 2), LAA thrombus (Fig. 3) or atrial myxoma (Fig. 4). If a person has an embolic stroke of undetermined source, options for further work-up include a transesophageal echocardiogram (TEE), cardiac computed tomography (CT) or Cardiac Magnetic Resonance Imaging (CMR). TEE provides excellent pictures of the left atrium and LAA and can identify the presence of spontaneous echo contrast, sludge or thrombus in it. Spontaneous echo contrast describes increased echogenicity in the left atrial appendage due to blood stasis and it is associated with increased likelihood of thrombus formation [11]. TEE also provides direct visualization of the aortic arch and the descending aorta and can identify the presence of atheroma, which can serve as a potential embolic source. Finally the TEE has higher resolution and accuracy in the identification of valvular lesions such as fibroelastomas and valvular vegetations, which may be missed in a transthoracic study. Katsanos et al. [17] found that in 52% of patients with ESUS, a new cardiac finding was identified by TEE. In 16.2% of all patients, this resulted in a change in management including anticoagulation, institution of antibiotics or

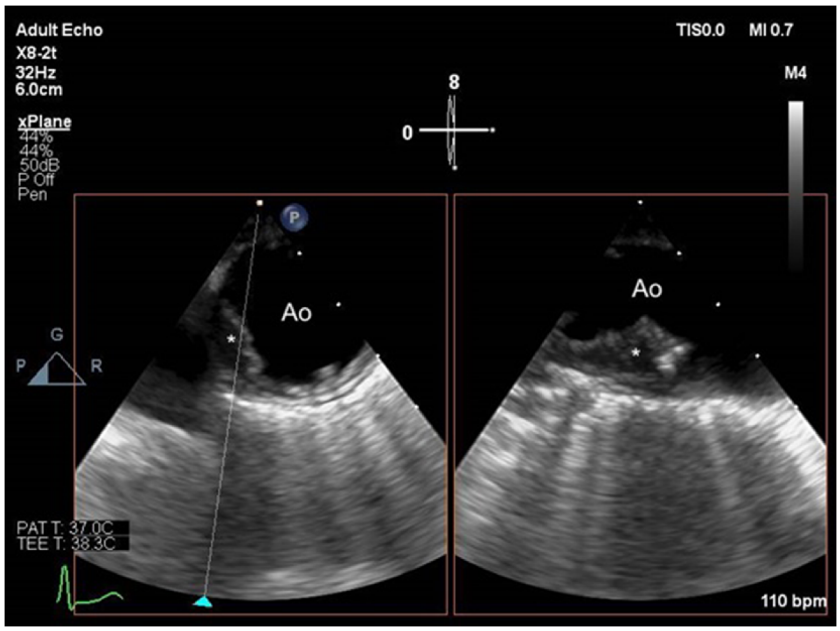

Fig. 1. Short and long axis views of the descending aorta obtained by transesophageal echocardiogram, demonstrating a large, mobile and ulcerated atheroma (grade V). Atheroma (*), Ao = Aorta.

closure of a previously unidentified PFO. Our practice is to pursue TEE in a patient with an embolic stroke of undetermined source who is younger than 50 years old or in those patients with a specific clinical concern for cardioembolism that is not addressed by TTE. Because TEE requires conscious sedation and thus the use of

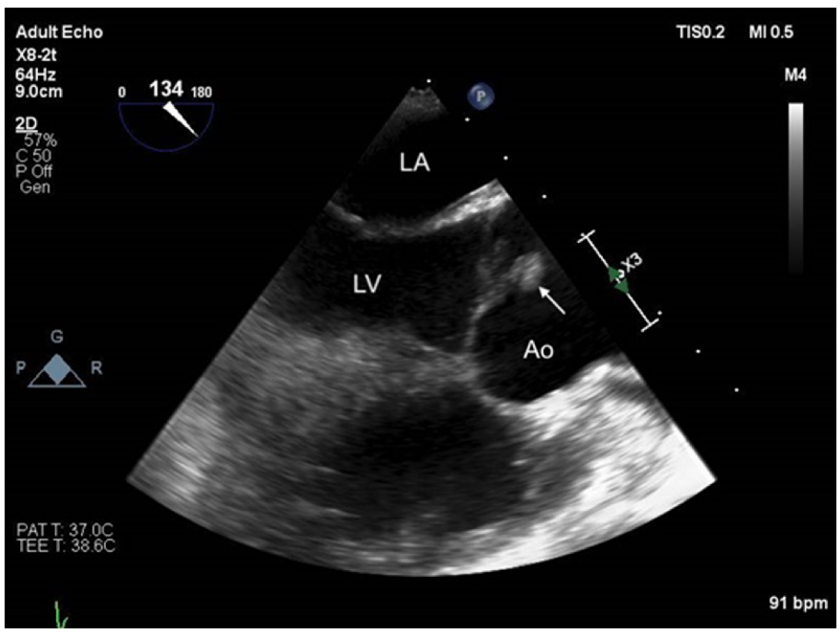

Fig. 2. Transesophageal echocardiogram mid-esophageal view at 120–135^0 demonstrating a long axis view of the aortic valve with a pedunculated mass arising from the mid portion of the aortic valve (arrow), consistent with a papillary fibroelastoma. Ao = aorta, LA = left atrium, LV = left ventricle.

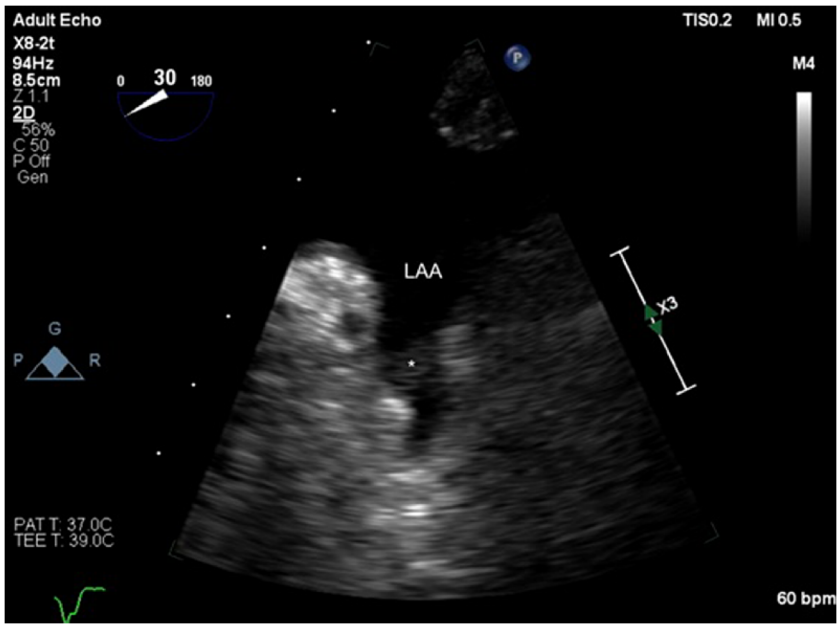

Fig. 3. Transesophageal echocardiogram zoomed mid-esophageal view of the LAA showing thrombus (*) in the left atrial appendage. LAA = left atrial appendage.

agents that may lower blood pressure and hinder a neurological examination, we do not obtain TEE in someone with a pressure-dependent examination or perfusion delay by imaging.

Cardiac CT permits non-invasive visualization of heart structure with excellent spatial resolution of the atria, ventricles, myocardium and cardiac valves. Cardiac CT can be exploited to image the ascending aorta with excellent

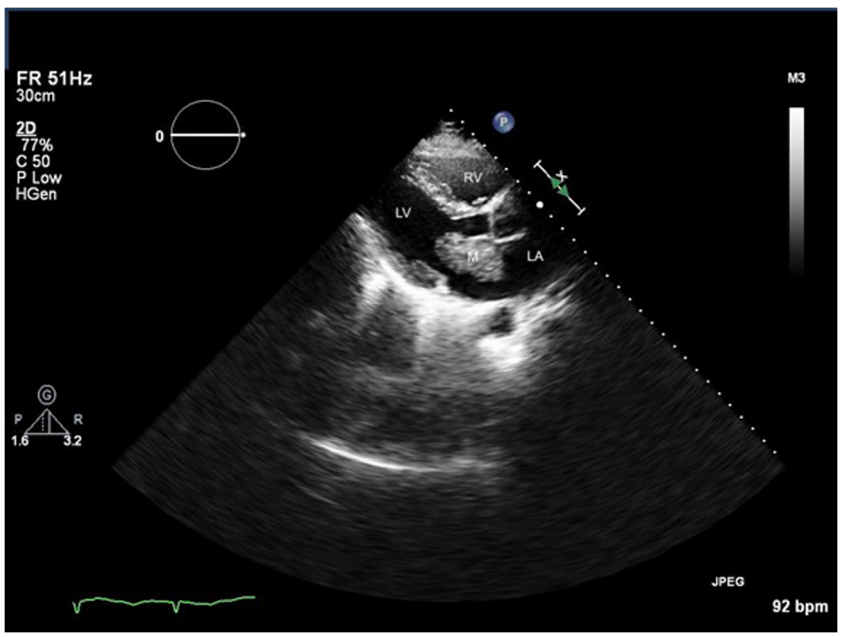

Fig. 4. Transthoracic echocardiogram parasternal long axis view showing a large mass in the left atrium, attached in the interatrial septum and prolapsing across the mitral valve into the left ventricle, consistent with a myxoma (M). LA = left atrium, LV = left ventricle, RV = right ventricle.

resolution and (with a modified protocol) the coronary circulation. Current imaging protocols are rapid, require only momentary breath-holding from the patient and do not require the use of anesthesia. Additionally, cardiac CT can be obtained in patients with MRI-incompatible cardiac devices and is less vulnerable to artifact from such devices. Cardiac CT necessitates the administration of iodinated contrast and a high radiation dose, though this is a property of CT in general. It permits detection of left atrial thrombi and can delineate the morphology of the left atrium and left atrial appendage [18]. It has comparable diagnostic accuracy for detecting left atrial and left atrial appendage thrombi when compared with TEE [19, 20]. Cardiac CT can also detect circulatory stasis within the left atrial appendage [20] – the imaging phenomenon referred to as spontaneous echo contrast on TEE – and reliably distinguish thrombi from circulatory stasis [21]. However, it has a lower sensitivity than echocardiography for PFO [22]. We utilize cardiac CT when it is not feasible to perform a TEE and when cardiac MRI is not feasible (either due to inability to participate or the presence of an MRI incompatible device).

CMR also permits non-invasive visualization of the chambers of the heart with excellent spatial resolution and allows tissue characterization [23]. Contrast-enhanced CMR is the method of choice to distinguish intracardiac tumors from thrombi [23]. It permits three-dimensional visualization of the left atrium and is the gold standard for establishing the volume of the left atrium [24, 25]. It permits characterization of atrial fibrosis, ventricular scarring or focal ventricular hypokinesis, implicating the left ventricle as the source of thrombus even in the presence of a preserved ejection fraction [26]. It has at least equivalent sensitivity of the presence of left ventricular thrombus (Fig. 5) to TEE in the presence of a depressed ejection fraction [27] (though the most sensitive modality for this specific question is TTE with the use of contrast). Novel applications of this technique include characterization of the morphology of the left atrial appendage (LAA) and the degree of fibrosis in the LA [15].

d. **Patent foramen ovale**

Patent foramen ovale is a potential cause of embolic stroke via thrombus formation at the foramen or via paradoxical embolization from the venous system to the cerebral arteries. Transthoracic echocardiography with an agitated saline bubble study is used as an initial study to examine for the presence of a PFO. TEE is less sensitive than TTE [28, 29] - this may be because the presence of the echo probe in the throat renders it more difficult to perform a valsalva maneuver, which is necessary for a bubble study. However, in the presence of a known PFO, TEE can determine the size and presence/absence of an interatrial septal aneurysm (Fig. 6). These two features speak to a higher potential benefit from intervention on a PFO and were entry criteria in to the recent clinical trial Closure of Patent Foramen Ovale or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) [30]. The most sensitive modality is trans-cranial Doppler ultrasonography with an agitated saline bubble study [31] and should be pursued in patients in whom a PFO is strongly suspected but not present on TTE.

e. **Atherosclerosis**

Although surgical intervention is generally not performed when there is less than 50% stenosis of the extracranial carotid arteries, substenotic atherosclerosis (with friable plaque or superimposed thrombus) remains a likely stroke mechanism. This likely causes strokes due to artery-to-artery embolization as opposed to hypoperfusion or focal occlusion, as occurs with high-grade stenosis. Intracranial substenotic atherosclerosis may also cause infarcts by occluding the origins of small, perforating vessels. One study using high-resolution carotid plaque magnetic resonance angiography showed that 22% of patients with cryptogenic stroke had intra-plaque hemorrhage ipsilateral to the infarct [32]. Large but non-stenotic atherosclerotic plaque is more common ipsilateral to a cryptogenic stroke and contralateral to it [33].

Atherosclerosis of the aortic arch is an underappreciated stroke mechanism that is not accounted for in the standard ischemic stroke workup. Atherosclerotic plaques of the thoracic aorta greater than 4 mm in depth are more common in patients with stroke than control patients [34]. Even plaques of the proximal descending aorta are speculated to relate to ischemic stroke risk [35]. Patients with protruding plaques or plaques with mobile components have a high risk of subsequent vascular events [36] and this risk is increased in the absence of plaque calcifications [37]. HITS are associated with AAs in elderly stroke patients [38] and aortic arch atherothrombosis increases the risk of early ischemic lesion recurrence [39]. CT angiography of the aorta is superior to TEE for examining for the presence of aortic arch atheromatous disease [40].

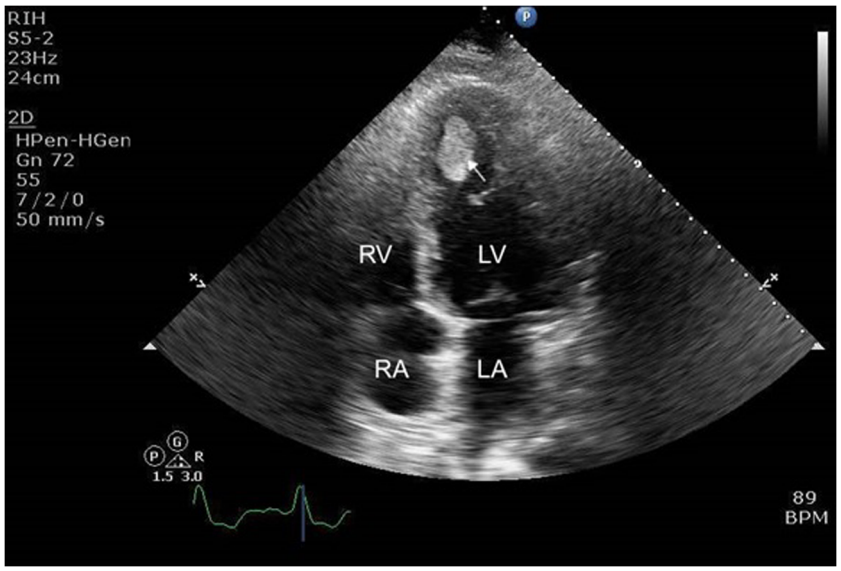

Fig. 5. Transthoracic echocardiogram apical 4-chamber view in a patient with severely reduced left ventricular ejection fraction showing a large left ventricular apical thrombus (arrow). LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle.

f. **Hypercoagulability**

Hypercoagulability is a potential mechanism of stroke and can lead to thrombus formation even in the presence of normal cardiac structure/function and in the absence of atherosclerosis in the pre-cerebral or cerebral arteries. Hypercoagulable testing is of low yield in patients with ischemic stroke [41]. However it should be pursued in patients younger than 50 without another identified cause. In particular, hypercoagulability needs to be ruled out before PFO closure is pursued. Arterial hypercoagulability can result from disorders including antiphospholipid antibody syndrome, disseminated

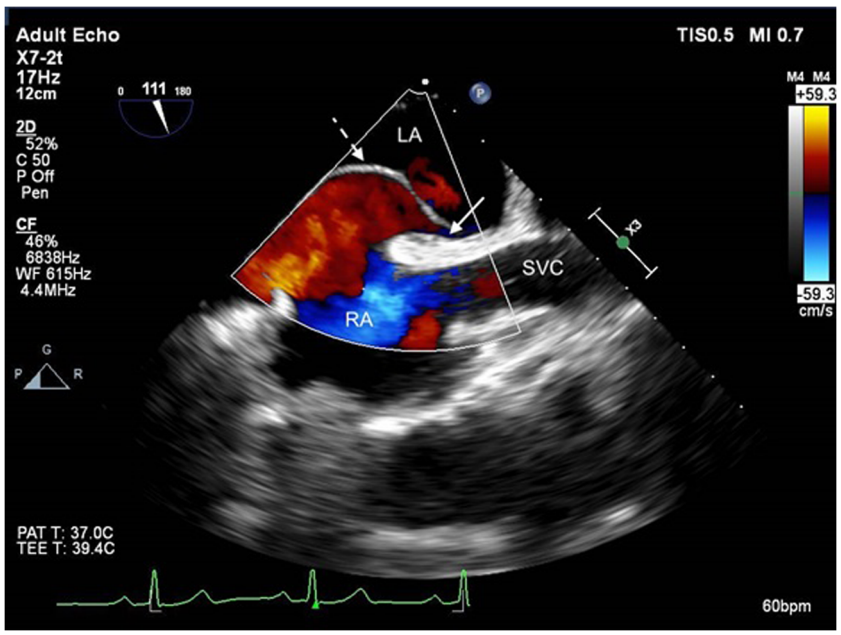

Fig. 6. Transesophageal echocardiogram bicaval view showing a patent foramen ovale (solid arrow) with left to right shunt demonstrated by color Doppler, and an atrial septal aneurysm (dashed arrow). LA = left atrium, RA = right atrium, SVC = superior vena cava.

intravascular coagulation or an occult malignancy. Venous hypercoagulability can be implicated as a cause of stroke in the presence of a PFO or atrial septal defect (ASD). Disorders of venous hypercoagulability include protein C deficiency, protein S deficiency, antithrombin III deficiency, factor V Leiden mutation, prothrombin gene mutation, hyperhomocystinemia or polycythemia rubra vera. Occult malignancy should be suspected in patients with B-symptoms, abnormalities on physical examination (such as lymphadenopathy) or in an older person who has not undergone age-appropriate cancer screening or when there is high clinical suspicion for familial cancer syndrome.

g. **Carotid web**

"Carotid web" describes a form of focal fibromuscular dysplasia which manifests as a nonatheromatous strand of tissue that protrudes in to the lumen of the carotid artery. It is usually observed immediately distal to the bifurcation of the common carotid artery and derives from the posterolateral wall of the internal carotid artery. It can cause ischemic stroke in the absence of a hemodynamically significant stenosis. The imaging modality of choice is a computed tomography angiography (CTA) study with contrast as it permits the distinction between vascular tissue, calcium, atherosclerotic plaque and thrombus [42]. It is best seen on oblique sagittal CTA where it appears to jut in to the lumen of the vessel and it also appears as septum on axial CTA. The presence of this strand of tissue in the vessel lumen causes altered hemodynamics and leads to stasis in the vessel immediately distal to the web [43]. This stasis can appear as contrast stagnation - immediately above the web - in the venous phase of diagnostic angiography [44]. One series of patients with carotid web showed that 58% of patients had an asymptomatic one contralateral to the symptomatic lesion [44]. A recent report [45] identified an internal carotid artery web that developed from the site of an intimal dissection suggesting that these are not congenital lesions but arise from dissections in predisposed individuals. One case-control study found that in patients under the age of 60, 6% had an ipsilateral carotid web compared with <1% of age-matched controls giving an odds ratio of 8 (95% CI 1.2–6.7). A post-hoc analysis of the patients from MR-CLEAN found that 13 out of 500 patients had a carotid web present on re-examination of their cervical vessel imaging [46]. Joux et al. [47] examined carotid webs in a cohort of patients of afro-Caribbean ethnicity and found a recurrence rate of 30% after a mean follow up of 25 months. The incidence of stroke associated with carotid web is 3.8/100,000 years in a population of people from Martinique under the age of 55 [48]. In almost all cases, webs cause less than 50% stenosis [44, 49••].

Management

a. Anti-thrombotic therapy

At present, the standard of care for patients with an embolic stroke of undetermined source is anti-platelet therapy and modification of concurrent vascular risk factors. The Warfarin-Aspirin Recurrent Stroke Study Group Trial [50] enrolled patient with non-cardioembolic stroke and randomized them to warfarin (target INR of 1.4–2.8) or aspirin 325 mg per day. There was no significant difference over two year follow up in the outcome of recurrent ischemic stroke or death between the two groups. However this trial included patients each of lacunar strokes (56% of enrolled patients) and strokes arising from large artery atherosclerotic stenosis (12% of enrolled patients). The construct of ESUS was proposed in order to refine a population of patients who may benefit from systemic anticoagulation, even before a precise etiology is determined. The hypothesis is that in this condition there is an undiagnosed cardiac lesion or hypercoagulable tendency. Given that most mechanisms are felt to involve fibrin-based thrombi as opposed to platelet, cholesterol or calcium aggregates it was hypothesized that anticoagulation would be the treatment of choice as opposed to anti-platelet therapy. Two clinical trials have been completed thus

far comparing anti-platelet therapy to anticoagulation for secondary stroke prevention in patients with ESUS, NAVIGATE-ESUS [51••] and RESPECT-ESUS [52]. They were both negative for their primary endpoints of stroke or systemic embolism (NAVIGATE) and recurrent stroke (RESPECT). ATTICUS [53] is an ongoing trial comparing apixaban and aspirin in patients with ESUS and 1 additional risk factor for cardiac embolism. ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke; NCT03192215) [54] is enrolling patients with an embolic stroke and evidence of left atrial cardiopathy. ARCADIA will compare anticoagulation (apixaban) with anti-platelet therapy (aspirin 81 mg daily) for secondary stroke prevention in patients with recent ESUS and evidence of atrial cardiopathy. Part of the impetus for this trial is the retrospective analysis of the WARSS Study (Warfarin-Aspirin Recurrent Stroke Study), which suggested that anticoagulation was superior to antiplatelet therapy for secondary stroke prevention in those patients with an elevated NT-proBNP (>750 mg/dL) [55]. Trials of anti-platelet versus anticoagulant therapy in ESUS are summarized in Table 3.

b. Patent foramen ovale

Treatment options for secondary stroke prevention in patients with a PFO include anti-platelet therapy, anticoagulation, percutaneous closure and open closure. Recent randomized trials have provided evidence that percutaneous closure reduces the risk of recurrent stroke in selected patients [30, 56–61]. Study of stroke secondary prevention in patients with PFO is difficult because the rate of recurrent stroke is so low and thus large trials are required to obtain power to determine efficacy.

Table 3. Trials of anti-platelet versus anticoagulation in patients with embolic stroke of undetermined source

Name	Agent	Enrollment criteria	Enrollment	Intervention	Primary endpoint	Results
NAVIGATE-ESUS [51••]	Rivaroxaban	ESUS	7213	Rivaroxaban vs. Aspirin	Stroke or systemic embolism	5.1%/year in treatment vs. 4.8%/year in control
RESPECT-ESUS [52]	Dabigatran	ESUS	5390	Dabigatran vs. Aspirin	Recurrent stroke	4.1% in treatment vs. 4.8% in control
ATTICUS [53]	Apixaban	ESUS and 1 risk factor for cardiac embolism	500 (target)	Apixaban vs. Aspirin	New ischemic lesion on MRI	Ongoing
ARCADIA [54]	Apixaban	ESUS and left atrial cardiopathy	1100 (target)	Apixaban vs. Aspirin	Recurrent stroke	Ongoing

There are 6 recent trials comparing percutaneous closure versus medical therapy in patients with PFO and a cryptogenic stroke. These are summarized in Table 4.

1) CLOSURE [59]: This trial randomized 909 patients to medical therapy versus closure with the STARFlex device (CardioSEAL, NMT Medical, Boston, MA) and followed them for 2 years. The primary endpoint of stroke or TIA occurred in 5.5% of patients in the device closure group compared to 6.8% of patients treated with medical therapy (adjusted HR, 0.78; 95% CI: 0.45–1.35; $p = .37$). This trial likely failed to attain significance because it enrolled patients with lacunar infarcts (i.e likely not related to embolization), which likely diluted the effect size of the intervention.
2) PC [56]: It randomized 414 patients to medical treatment versus closure with the AMPLATZER device and followed them for a median of 4.1 years. This trial also did not show a significant benefit of closure when compared to medical treatment (HR 0.63; 95% CI: 0.24–1.62; $p = .34$).
3) GORE-REDUCE [57••]: GORE® HELEX® Septal Occluder / GORE® CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients With Patent Foramen Ovale (PFO) compared percutaneous PFO closure and anti-platelet therapy with anti-platelet therapy alone and enrolled patients in a 2:1 (treatment:control) randomization strategy. 664 patients were randomized in the study with a median follow-up of 3.2 years. There was a recurrent stroke in 1.4% of patients in the PFO closure group compared with 5.5% of subjects in the medical therapy group (HR 0.23, CI:0.29–0.91, $p = 0.04$). The rate of serious adverse events did not differ between the two groups, however 6% of patients in the percutaneous closure group developed AF compared with only 0.4% of patients in the medical therapy arm.
4) CLOSE [30]: The CLOSE trial (Closure of Patent Foramen Ovale or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence) enrolled patients with cryptogenic stroke and at least one high-risk feature associated with the PFO (a large inter-atrial shunt or an interatrial septal aneurysm). Subjects were randomized to one of three groups: 1) Device closure; 2) Antiplatelet therapy alone or 3) Anticoagulation alone. The primary end-point was recurrent ischemic stroke. 663 patients were randomized in this trial with a mean follow up of 5.3 years. In this trial, no patients in the PFO closure group had a stroke. By contrast, 14 out of 235 patients in the antiplatelet therapy alone group had a stroke (HR 0.03, 95% CI: 0–0.26, $p < 0.001$). As in GORE-REDUCE, the rate of AF was increased in the device-closure group (4.6% vs. 0.9%).
5) RESPECT [60, 61]: This trial randomized patients between 18 and 60 years of age with cryptogenic stroke within 270 days of stroke onset, to medical treatment ($n = 481$) versus closure with the AMPLATZER device ($n = 499$). Results were published at a median 2.1 years after enrollment. The event rate was 0.61%/year in the closure arm compared with 1.25%/year in the medical treatment arm, which did not achieve statistical significance on the first analysis [60]. When followed for a median of 5.9 years, there was a hazard ratio of 0.55 (CI 0.31–0.999, $p = 0.046$) in the PFO closure group (for the primary end point representing a composite of recurrent ischemic

Table 4. Trials comparing percutaneous closure of patent foramen ovale with best medical therapy

Name	Year	Enrollment criteria	Intervention	Medical therapy	Primary endpoint	No.	Results
CLOSURE [59]	2012	Age 18–60 Cryptogenic stroke or TIA Any PFO	Percutaneous closure STARFLEX	Aspirin, warfarin or both	Stroke or TIA in following 2 years	909	No benefit observed
PC [56]	2013	Age 18–60 Crytogenic stroke or TIA Any PFO	Percutaneous closure AMPLATZER	Any anti-thrombotic agent	Stroke, TIA, peripheral embolism or death	414	No benefit observed
GORE-REDUCE [57••]	2017	Age 18–60 Cryptogenic stroke PFO with right-to-left shunt	GORE-HELEX or GORE-CARDIOFORM Septal Occluder	Anti-platelet therapy	#1 Freedom from recurrent stroke #2 New infarction	664	1.4% stroke recurrence in closure group vs. 5.4% in medical therapy group.
RESPECT [60, 61]	2017	Age 18–60 Cryptogenic stroke Any PFO	Percutaneous closure AMPLATZER	Aspirin, clopidogrel, warfarin or aspirin/dipyiridamole	Stroke or death	980	3.6% recurrence in PFO closure vs. 5.8% recurrence in medical therapy.
CLOSE [30]	2017	Age 16–60 Cryptogenic stroke PFO with atrial septal aneurysm or large interatrial shunt	Percutaneous closure device	Anti-platelet therapy or anticoagulation	Stroke	663	Lower rate of stroke in PFO closure group than in anti-thrombotic therapy.
DEFENSE-PFO [58]	2018	PFO with ASA, hypermobility or large size	Percutaneous closure AMPLATZER	Any anti-thrombotic agent	Stroke, death or major bleeding	120	0% primary endpoint in PFO group vs. 12.9% in medical group.

stroke or death). There was a lower rate of recurrent ischemic stroke in the percutaneous closure group (HR: 0.38, 95% CI:0.18–0.79, $p = 0.007$).

6) DEFENSE-PFO [58]: This trial randomized patients with cryptogenic stroke to percutaneous PFO closure with medical therapy compared to medical therapy alone. Like the CLOSE trial, they enrolled patients with high-risk features associated with the PFO (large size, presence of an interatrial septal aneurysm and hypermobility of the interatrial septum on TEE). 120 patients were enrolled in the trial, 60 in each arm. 12.9% in the medical therapy group reached the primary endpoint of stroke, death attributed to a vascular cause or major bleeding while no patients in the intervention arm reached this primary endpoint.

Mir et al. [62] conducted a meta-analysis of 10 randomized trials, comparing percutaneous closure with medical therapy in patients with PFO and cryptogenic stroke. Their analysis suggested a reduction in recurrent stroke of 87 per 1000 patient-years per 5-year period. This effect was smaller when device closure was compared with anticoagulation as opposed to when compared with anti-platelet therapy, however the rate of major bleeding was higher in patients with anticoagulation. On this basis, our recommendation is to pursue percutaneous PFO closure in parallel with anti-platelet therapy in patients aged 18–60 with a cryptogenic stroke. The decision to pursue closure rests on excluding other potential causes of stroke including large artery atherosclerotic disease, high risk sources of cardioembolism (including paroxysmal atrial fibrillation) and hypercoagulable disorders.

c. Substenotic atherosclerosis

The mainstay of treatment for substenotic atherosclerosis of either the extracranial or intracranial vasculature is anti-platelet therapy, statin therapy and risk factor modification. In the case of symptomatic carotid stenosis of less than 50%, there is no level I evidence showing a benefit to surgical intervention in the form of carotid artery stenting or carotid endarterectomy [63]. We would consider intervention (CAS or CEA) in this setting only if no other stroke mechanism was identified and there were recurrent events despite medical optimization (effective anti-platelet therapy, high-dose statin use, smoking cessation and tight glycemic control).

The SAMMPRIS study [64] identified no net benefit to endovascular stenting for symptomatic intracranial atherosclerotic stenosis but a robust recurrent stroke risk reduction with dual-anti platelet therapy and aggressive lifestyle modification – this trial enrolled people only with hemodynamically-significant, symptomatic intracranial stenosis. Extrapolating, we assume that those patients with substenotic intracranial atherosclerosis do not benefit from intracranial stenting. In patients with substenotic atherosclerosis who have plaque ulceration or mobile plaque elements, the optimal treatment strategy is unclear. The ARCH trial [65] examined anticoagulation (with coumadin) vs. dual anti-platelet therapy and enrolled patients with aortic arch plaque of > = 4 mm and no other embolic source identified. The primary outcome was ischemic stroke, myocardial infarction, peripheral embolism, vascular death or intracranial hemorrhage. It was stopped for futility – with the primary end point arising in 7.6% of people treated with dual anti-platelet therapy and 11.3% of people on coumadin.

d. Carotid web

The mainstay of therapy for carotid webs is medical treatment in the form of anti-platelet therapy or anticoagulation. Other management options include carotid endarterectomy or endovascular stent placement. Given that carotid webs almost universally cause less than 50% stenosis, the major barrier to stroke risk reduction in this patient population is identification and recognition of the carotid web. Based on the flow dynamics in the vicinity of a carotid web [43], it is likely that thrombi form as a result of stasis distal to the carotid web and thus anti-platelet therapy is insufficient in terms of stroke risk reduction. Haussen et al. [44] reported a series of 24 patients with carotid web associated with ipsilateral ischemic stroke. In one year 3/8 patients managed with medical therapy had a recurrent stroke, whereas 16 patients who underwent stenting were recurrence-free at a median follow up of 4 months. Zhang et al. [49••] reported a meta-analysis of the published literature until 2018 and found a 56% recurrence rate in a patient with a carotid web treated medically with a median time to recurrence of 12 months. This recurrence rate was higher in patients treated with anticoagulation (75%) but only 4 patients in the world

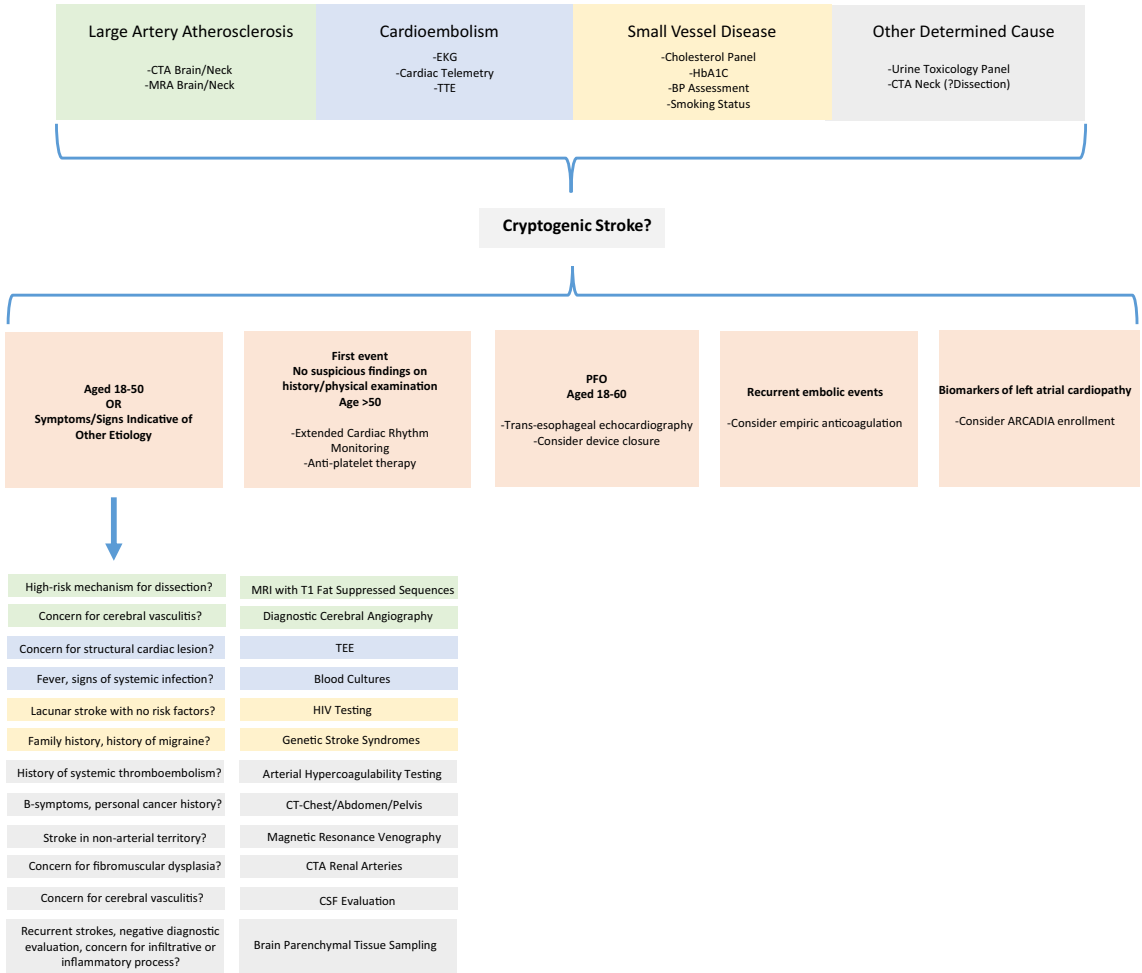

Fig. 7. Proposed investigative and management pathway for patients with cryptogenic stroke.

literature have been reported to have received anticoagulation as secondary prevention, so this finding is of unclear significance. By contrast, at a median follow up of 14 months no patients have been reported to have a recurrent stroke after either carotid artery stenting or carotid endarterectomy.

Conclusion and future directions

Cryptogenic stroke poses a difficult clinical conundrum for the neurologist. A proposed management algorithm is outlined in Fig. 7. The concept of embolic stroke of undetermined source is a potentially useful construct that allows identification of patients who require further workup to look for an occult cardioembolic source. Further research will be needed to identify other risk factors for thromboembolism including left atrial fibrosis and other markers of left atrial dysfunction.

One enticing direction of future investigation is stratifying patients' stroke risk by the morphology of the LAA. The LAA is the most common location for thrombus formation in patients with AF [66]. It is felt to be a vestigial component of the heart with no contribution to cardiac output, though it may modulate left atrial pressures. Studies have shown that spontaneous echocardiographic contrast, reduced LAA peak flow velocity, and LAA fibrosis have been associated with embolic risk [66]. The morphology of the LAA varies from person to person and it differs in terms of its geometry, size and relationship to the left atrium. Its morphology can be determined using TEE as well as cardiac CT or MRI. It has been classified in to 4 morphologies based on its appearance on TEE/cardiac CT – chicken wing, cactus, windsock and cauliflower. The morphology of the LAA has been shown to be associated with the risk of embolization with pilot data suggesting that a nonchicken-wing morphology is most closely associated with embolic stroke (either ESUS or cardioembolic stroke) [67].

In summary, cryptogenic stroke is an important clinical problem that requires a structured workup, tailored to the individual patient. The standard of care for stroke secondary prevention is anti-platelet therapy with careful attention to modifiable vascular risk factors. There is clinical equipoise as to the optimal anti-thrombotic strategy in patients with embolic stroke and markers of left atrial cardiopathy thus such patients can be enrolled in clinical trials attempting to address this question.

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Compliance with Ethical Standards

Conflict of Interest

Brian Mac Grory, Shane Flood, Eirini Apostolidou, and Shadi Yaghi each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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