Cryptogenic Stroke
Research and Practice

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Background: **Cryptogenic stroke accounts for 30% to 40% of ischemic stroke. It is essential to determine the possible culprit because this will improve secondary stroke prevention strategies.**

Methods: **We performed a narrative nonsystematic review of the literature that included randomized trials, exploratory comparative studies, and case series on cryptogenic stroke.**

Results: **There are several possible mechanisms implicated in cryptogenic stroke, including occult paroxysmal atrial fibrillation, patent foramen ovale, aortic arch atherosclerosis, atrial cardiopathy, and substenotic atherosclerosis. The heterogeneity of these mechanisms leads to differences in stroke prevention strategies among cryptogenic stroke patients.**

Conclusions: **A thorough diagnostic evaluation is essential to determine the pathogenesis in cryptogenic stroke. This approach, in addition to risk factor management and lifestyle modifications, will lead to improved stroke prevention strategies in patients with cryptogenic stroke. This will allow for targeted clinical trials to improve stroke prevention strategies in this patient population. (*Circ Res*. 2017;120:527-540. DOI: 10.1161/CIRCRESAHA.116.308447.)**

Key Words: cryptogenic stroke ■ diagnostic testing ■ embolism ■ prevention ■ therapeutic implications

Of the 690000 ischemic strokes that occur in the United States every year, ≤30% are of unknown cause, or cryptogenic. Several possible mechanisms may underlie cryptogenic stroke (CS), including but not limited to occult paroxysmal atrial fibrillation (AF) and other atrial cardiopathies, paradoxical embolism through a patent foramen ovale (PFO), or substenotic atherosclerosis. In the absence of AF, antiplatelet therapy remains the mainstay of treatment in most patients with CS, although the scientific support for this is limited. The aim of this review is to highlight the fact that CS is a heterogeneous disease leading to differences in diagnostic evaluation and therapeutic implications.

Definitions

There are several proposed definitions for CS. The Trial of Org 10172 in Acute Stroke Treatment defines CS as a cerebral infarct not attributed to a definite source of cardioembolism, large-vessel

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ARTESIA	Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation
ASSERT	Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial
CMR	cardiac magnetic resonance imaging
CRYSTAL-AF	Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke
CS	cryptogenic stroke
CT	computed tomography
EMBRACE	30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event
LAA	left atrial appendage
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NOMASS	Northern Manhattan Stroke Study
PFO	patent foramen ovale
ROPE	Risk of Paradoxical Embolism
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography

atherosclerosis, or small-vessel disease, despite (1) extensive cardiac, vascular, hematologic, and serological evaluation; (2) evidence of >1 competing cause, or (3) incomplete diagnostic evaluation.[1] On the contrary, the Causative Classification System definition requires a diagnostic evaluation, including brain and cerebrovascular imaging along with a cardiac evaluation. Causative Classification System divides cryptogenic stroke into 2 categories: cryptogenic embolism and other cryptogenic. Cryptogenic embolism refers to a stroke in which there is angiographic evidence of abrupt cutoff consistent with a blood clot within otherwise angiographically normal-looking intracranial arteries, imaging evidence of complete recanalization of previously occluded artery, or the presence of multiple acute infarctions that have occurred closely related in time without detectable abnormality in the relevant vessels. Other cryptogenic is reserved for those not fulfilling the criteria of cryptogenic embolism.[2]

Nearly 65% of patients with CS have cortical infarcts on brain imaging, a characteristic typically suggestive of embolism.[3,4] In fact, a study from the National Institute of Neurological Disorders and Stroke Databank reported that nearly two thirds of patients with what initially appeared to be cryptogenic stroke were found to have evidence of potential sources of cardioembolism on long-term follow-up.[5] Given the strong circumstantial evidence favoring an embolic pathogenesis of most CS patients, investigators have recently suggested using the term embolic stroke of undetermined source to describe nonlacunar stroke without evidence of ipsilateral extracranial or intracranial large artery stenosis of ≥50%, a major cardioembolic source such as AF or severe left ventricle dysfunction, or other specific mechanism of stroke.[6]

Prevalence and Epidemiology

Ischemic stroke affects nearly 690 000 patients per year in the United States, 30% of which are considered to be of unknown cause. With the exception of AF, the prevalence of risk factors is more or less similar between patients with CS and stroke of known cause. A major limitation of these studies, however, is the use of older definitions for CS and the fact that some strokes were considered as cryptogenic based on incomplete diagnostic evaluation.

Demographic Factors

The NOMASS (Northern Manhattan Stroke Study) observed that CS disproportionately affects younger patients (55% in subjects <45 years old versus 42% in subjects who are ≥45 years old).[7] In contrast, other studies found lower rates of CS in younger versus older patients.[8,9] A meta-analysis of 2 population-based studies showed that the prevalence of CS was lower in patients <50 years of age when compared with patients ≥50 years of age (odds ratio [OR] 0.6, 95% confidence interval [CI] 0.4–1.0).[10] In addition, studies have not shown a sex disparity for CS.[7–9] In NOMASS, blacks and Hispanics had an increased incidence of CS when compared with Caucasians.[11] These findings were also supported by other studies such as Greater Cincinnati/Northern Kentucky Stroke Study and the University of California at San Diego Stroke Data Bank and could not be accounted for by differences in the diagnostic evaluation between the 2 groups.[12,13]

Vascular Risk Factors

Hypertension

Several studies showed that the prevalence of hypertension is lower in patients with CS when compared with other subtypes.[12,14–16] This finding was also supported by a meta-analysis, showing a decreased prevalence of hypertension in CS patients when compared with patients with other stroke subtypes (OR 0.8, 95% CI 0.6–0.9).[10]

Diabetes Mellitus

Two population-based studies showed that the prevalence of diabetes mellitus was similar across stroke subtypes, including CS[17,18] and this was also confirmed by a meta-analysis of 4 population-based studies showing that the odds of diabetes mellitus was similar between patients with CS and those with other stroke subtypes (OR 1.0, 95% CI 0.7–1.2).[10]

Hyperlipidemia

Similar to diabetes mellitus, in population-based studies, the prevalence of hyperlipidemia in CS patients is nearly similar to that among other stroke subtypes.[10,14] Two hospital-based studies, however, showed that patients with CS had a lower prevalence of hypercholesterolemia when compared with those with large artery atherosclerosis and small artery disease but higher when compared with those with cardioembolic stroke.[15,16] A case–control study showed that although CS patients and controls had similar levels of total cholesterol and low-density lipoprotein, patients with CS were more likely to be in the lowest versus highest quartile of high-density lipoprotein (OR 5.36, 95% CI 1.1–12.2).[19]

Smoking

A meta-analysis showed an inverse association between smoking and CS (when compared with other stroke subtypes; OR 0.8, 95% CI 0.6–1.0).[10]

Stroke Recurrence

Overall, the short-term risk of recurrent stroke after CS is intermediate between the high early risk after large artery atherosclerosis stroke and low risk after small artery disease stroke. In the Oxford meta-analysis of 4 large population-based studies, the risks of recurrent stroke after CS were 1.6% at 7 days, 4.2% at 1 month, and 5.6% at 3 months.[20] In the National Institute of Neurological Disorders and Stroke Data Bank, 3% of CS patients had recurrent events at 1 month.[21] In NOMASS at 3 months, the risk of recurrence for the cryptogenic group was 3.7%,[22] slightly lower than those found in the Oxford meta-analysis.[20]

At 2 years, recurrence risk ranges from 14% to 20%.[18,23,24] In the Stroke Data Bank, CS had the lowest 2-year recurrence risk and was an independent predictor of low recurrence risk.[25] However, data from the Athens stroke registry showed a relatively high recurrence rate in patients with embolic stroke of undetermined source when compared with other subtypes, with a recurrence rate of roughly 10% at 1 year and nearly 20% at 2 years.[26] At 5 years, the long-term recurrence risk was 33% in Olmstead county, Minnesota, not significantly different from the other subtypes.[23]

Diagnostic Evaluation

The diagnostic evaluation in patients with ischemic stroke is widely variable and includes brain imaging, vascular imaging, and a cardiac evaluation (Table 1).

Imaging

Neuroimaging

The initial evaluation of patients with suspected stroke includes a head computed tomography (CT) without contrast, which has a high sensitivity for excluding intracranial hemorrhage.[27] Although head CT is widely available, faster to obtain, and less expensive than other imaging modalities, such as brain magnetic resonance imaging (MRI), it is not as sensitive in detecting small infarcts that may be important to characterize the stroke mechanism. Although MRI and CT have the same sensitivity in excluding hemorrhage, a brain MRI is superior to CT in detecting acute infarction.[28,29] In addition, certain ischemic lesion patterns on MRI can aid in determining the stroke mechanism. For example, the presence of acute ischemic lesions in multiple vascular territories is suggestive of a cardioaortic source (Figure 1), whereas multiple acute ischemic lesions confined to one vascular territory may suggest large-vessel disease (Figure 1).[30] Therefore, in patients with CS and clinical and CT evidence of one lesion, an MRI may identify clinically covert infarctions in other vascular territories, which may point toward a proximal cardioaortic source (Figure 2).[31]

Vascular Imaging

In patients with ischemic stroke, several modalities are used to detect extracranial and intracranial vascular lesions that may constitute the stroke mechanism. Identifying these lesions may help improve stroke prevention strategies, especially given that large-vessel disease is associated with the highest risk of early recurrence among other subtypes. These modalities include conventional angiography, computed tomographic angiography of the head and neck, MRA of the head and neck, and carotid ultrasound and transcranial Doppler. Studies have shown that when compared with conventional angiography, computed tomographic angiography ranges between 76% and 85% sensitivity and 93% and 94% specificity in detecting 70% to 99% carotid stenosis[32,33] and sensitivities between 78% and 100%, with specificities of 82% to 100% in detecting intracranial large artery stenosis.[34] MRA, on the contrary, had 60% to 90% sensitivity and nearly 90% specificity in detecting intracranial large artery stenosis[34] and nearly 90% sensitivity and specificity in detecting 70% to 99% carotid stenosis.[35] Carotid ultrasound has nearly 90% sensitivity and 80% specificity in detecting 70% to 99% carotid stenosis,[36] but there is limited data on the use of transcranial Doppler to detect intracranial large artery stenosis. Cerebral angiography is the gold standard in diagnosing atherosclerotic disease; however, it is an invasive procedure with ≤1% risk of neurological complications, including stroke,[37,38] and therefore, clinicians rely on noninvasive testing to detect extracranial and intracranial atherosclerotic disease.

In patients with ischemic stroke, the presence of an atherosclerotic vascular lesion that is causing >50% narrowing of the lumen of an intracranial or extracranial large vessel supplying the area of infarction makes the subtype large artery disease. Because the sensitivity and specificity of imaging modalities, such as MRA, computed tomography angiography, and ultrasound, in detecting atherosclerotic lesions are significantly lower in patients with <70% to 99% stenosis,[33] these modalities may not be useful in detecting active substenotic lesions that may be causative of the ischemic event. High resolution MRA can identify an intraplaque hyperintense signal on T1-weighted sequences suggestive of intraplaque hemorrhage.[39] In addition, MRA with vessel wall imaging can show contrast enhancement suggestive of active atherosclerosis (Figure 3).[31] This imaging modality, however, is not widely available and only used in certain large tertiary care centers. In addition, MRA with fat-suppressed images is the gold standard noninvasive test to diagnose an arterial dissection, especially in the absence of significant luminal narrowing (Figure 4).[40] Therefore, in patients with CS, these imaging modalities may be useful in identifying a vascular lesion that may be a culprit.

Cardiac Evaluation

Because most of the potential mechanisms in CS are integrally related to the cardiac system, a thorough diagnostic evaluation of this system is necessary to identify the stroke mechanism and improve secondary prevention strategies. This evaluation includes cardiac imaging and cardiac monitoring.

Cardiac Imaging

Several studies showed that transthoracic echocardiography (TTE) and perhaps transesophageal echocardiography (TEE) are useful in identifying a potential cardiac source in patients with CS.[31] Studies showed the superiority of TEE over TTE in identifying potential mechanisms. One study showed that TEE identified a potential cardiac source in 40% of patients with ischemic stroke, in which TTE was nonrevealing.[41] The vast majority of these abnormalities were aortic arch atheromas and cardiac shunts.[42–44] The advantage of TEE over TTE

Table 1. Diagnostic Evaluation of Ischemic Stroke to Determine Stroke Mechanism

Diagnostic Test	Suggested Algorithm
Brain imaging	Brain MRI in patients with cryptogenic stroke
	Brain CT when stroke mechanism is known
Vascular imaging	Intracranial and extracranial vascular imaging on all patients with ischemic stroke
	MRA with fat-suppressed images when clinical suspicion for cervical artery dissection
Cardiac imaging	TTE on all patients with ischemic stroke to look for evidence of cardiac disease (evidence of prior myocardial infarction warranting ischemic cardiac evaluation or systolic heart failure)
	TEE with bubble study on patients <50 y old to look for cardiac shunts/cardiac tumors if TEE was nonrevealing
Cardiac monitoring	Thirty-day noninvasive cardiac monitoring on patients with cryptogenic stroke and ≥40 y
	Implantable cardiac monitor if 30-day monitor does not reveal AF or flutter
Hypercoagulable testing	Serum hypercoagulable workup in patients with no or minimal risk factors
Screening for malignancy	Age appropriate screening
	CT chest/abdomen/pelvis when systemic symptoms suggestive of cancer are present such as unexplained weight loss or unexplained fever

AF indicates atrial fibrillation; CT, computed tomography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

is in providing better views of the left atrial appendage (LAA), left atrium, and aortic arch and in identifying cardiac shunts.[44] Although TEE is superior to TTE in viewing the left atrium and LAA, <1% of patients are found to have cardiac thrombi, spontaneous echocardiographic contrast, or cardiac tumors, which will lead to change in clinical management. The vast majority of sources identified on TEE only are cardiac shunts and aortic arch plaques, which when identified will not necessarily lead to a change in management in most patients. When compared with TEE, however, TTE is noninvasive, less expensive, and more widely available.[44] Therefore, TEE is infrequently performed after CS[45] because many of the findings best identified on TEE do not have proven treatment implications and potential safety risks.[44]

Recently cardiac MRI (CMR) has emerged as a noninvasive diagnostic modality in cardiovascular medicine[46] and has been used by some centers to identify cardiac sources in patients with CS. In cardiovascular medicine, CMR is considered the gold standard noninvasive test to determine several cardiovascular parameters, such as left ventricular mass and left atrial volume.[47] In addition, when using a contrast-enhanced CMR, clinicians are able to identify areas of scarring or fibrosis in the myocardium,[48] and adding a phase contrast MRA will allow identification of cardiac shunts, such as atrial septal defects. CMR is the imaging modality of choice for diagnosing cardiac tumors and a wide range of cardiomyopathies, including hypertrophic cardiomyopathy and cardiac amyloidosis,[49,50] and provides good views of the aortic arch.[51,52] The literature on the use of CMR in CS is scarce, however, and the added benefit of CMR over a TTE and TEE remains unclear. In one study that included patients with CS undergoing TTE or TEE, CMR reduced the percentage of patients labeled as cryptogenic after echocardiography from 27% to 20%.[53] In another study, CMR showed evidence of a large myocardial infarction in 6% of patients who underwent a TEE that showed only minimal or no hypokinesis.[54] CMR is at least as good as TEE is identifying cardiac thrombi and assessing structural and functional parameters of the left atrium and LAA.[55] Because the data on the use of CMR is scarce, however, more studies are needed to determine the utility of CMR as a noninvasive tool as a replacement for TEE in the diagnostic evaluation of cryptogenic stroke.

Cardiac Monitoring

Outpatient cardiac monitoring for occult AF is now the standard of care after a CS because the detection of AF will lead to anticoagulation therapy that is superior to antiplatelet therapy.[56]

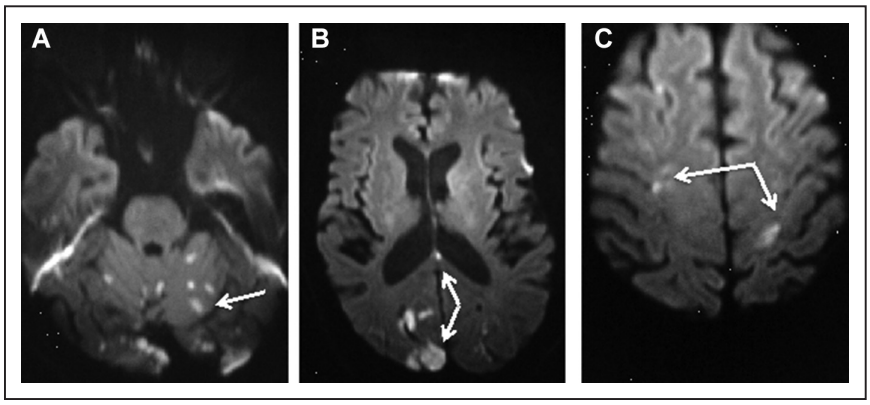

Figure 1. A and **B**, Multiple small infarcts in the posterior circulation in a patient with proximal basilar artery stenosis. **C**, Small infarcts in multiple vascular territories suggestive of a cardioaortic source.

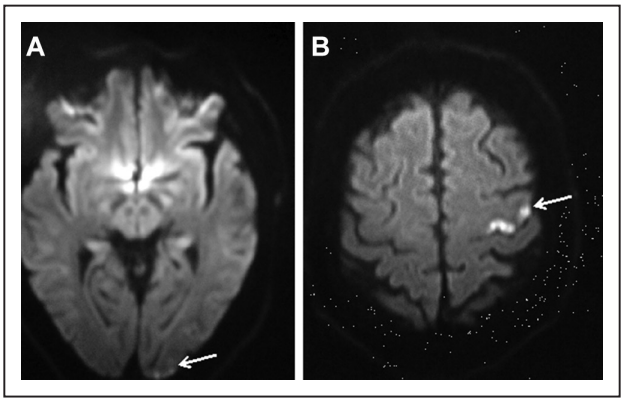

Figure 2. Brain magnetic resonance imaging (MRI; diffusion-weighted imaging sequence) of a patient with acute onset right-hand weakness showing a small infarct in the left frontal showing: (**A**) a clinically covert infarct in the left occipital lobe (posterior cerebral artery territory) and (**B**) a simultaneous small infarct in the left frontal lobe (middle cerebral artery territory) suggesting a cardioaortic source and found to have atrial fibrillation on long-term outpatient cardiac monitoring.

Studies have shown that the longer patients are monitored, the more likely AF is detected. In the CRYSTAL-AF study (Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke), the detection rate was 30% at 3 years of monitoring with implantable cardiac monitors.[57] There is a chance, however, that some of the AF detected may not be causative of the ischemic event. Nevertheless, the presence of AF even in these patients, will lead to anticoagulation therapy to improve stroke prevention strategies. In the EMBRACE study (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event), however, the detection rate was nearly 16% at 30 days, and most AF was detected in the first week after the index event.[58] This may be because patients in the EMBRACE trial were older on average than those in CRYSTAL-AF and had less extensive cardiac evaluation, including cardiac monitoring, prior to enrollment. Although the most cost-effective approach to cardiac monitoring has yet to be determined, it may be reasonable to start with noninvasive 30-day cardiac monitoring as a first step, especially in patients with a high index of suspicion for AF and a high likelihood of compliance with 30-day monitoring. However, a negative 30-day monitor does not exclude the presence of AF, and these patients should be considered to undergo an implantable cardiac monitor for longer monitoring.[59] Although there are no guidelines on how long the implantable monitors are typically left in, as the battery life on the implantable cardiac monitors last >3 years, it makes sense to leave it in for the lifetime of the battery because this information may be useful to assess symptoms related to AF, ventricular rate during AF episodes, possible response to therapy, and assessment for other arrhythmias often associated with AF, such as prolonged sinus pauses, as part of a sick sinus syndrome. As far as the cost issue, a cost-effectiveness analysis of the CRYSTAL-AF trial does show that the implantable cardiac device strategy is cost-effective even when including the removal cost rate.[60]

Hypercoagulable Testing

The prevalence of hypercoagulable states in patients with ischemic stroke ranges between 3% and 21% in ischemic stroke.[61] Most of these are associated with venous rather than arterial events, with the exception of antiphospholipid antibody syndrome that can cause both arterial and venous systems.[62–64] The overall pretest probability for all hypercoagulable states as detecting a potential source for thrombosis has a reported range of 5%.[61] Therefore, given the low diagnostic yield and high cost, it is important that clinicians are judicious in choosing appropriate testing based on pretesting probability. The yield of such tests may be higher in younger patients with minimal or no vascular risk factors, in recurrent venous or arterial thrombotic events, and in the presence of positive family history.[61–64] In addition, levels of some of these tests, such as protein S and protein C, may be falsely abnormal in the acute setting after a stroke, and therefore, it is best to measure them a few weeks after the event.[65] Moreover, the presence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, or anti-β-2-glycoprotien) does not imply the diagnosis of antiphospholipid antibody syndrome because the diagnostic criteria require repeated testing 12 weeks apart.[66]

Evaluation for Malignancy

The incidence of stroke in patients with cancer is nearly 7%,[67] most of which occur in the first few months after cancer diagnosis. This is likely related to hypercoagulability through alterations of the homeostatic cascade, the integrity of the endothelium, and platelet function.[68–70]

Stroke mechanisms in patients with known cancer may differ from those that occur in the general population,[71,72] with cryptogenic stroke subtype being the most common subtype and associated with reduced survival.[73] Cancer-specific

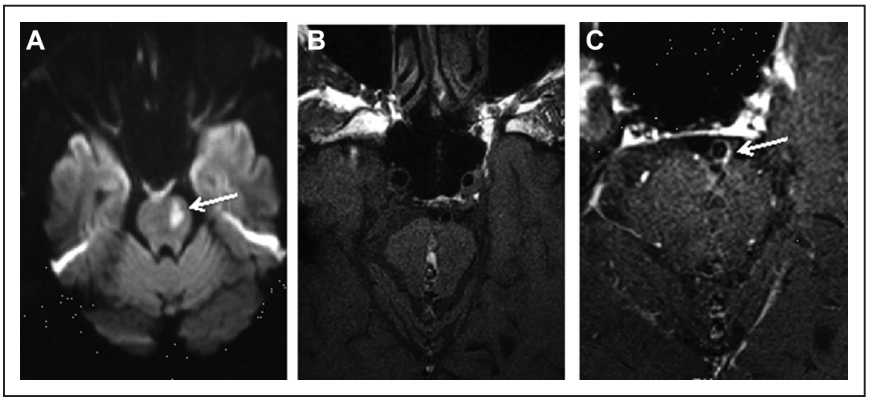

Figure 3. A, Diffusion-weighted imaging sequence showing a left pontine infarct in a patient with stuttering right-sided weakness and dysarthria. **B** and **C**, Displaying high-resolution vessel wall imaging pre- and post-contrast, respectively, showing focal enhancement in the basilar artery possibly related to an active nonstenosing atherosclerotic plaque.

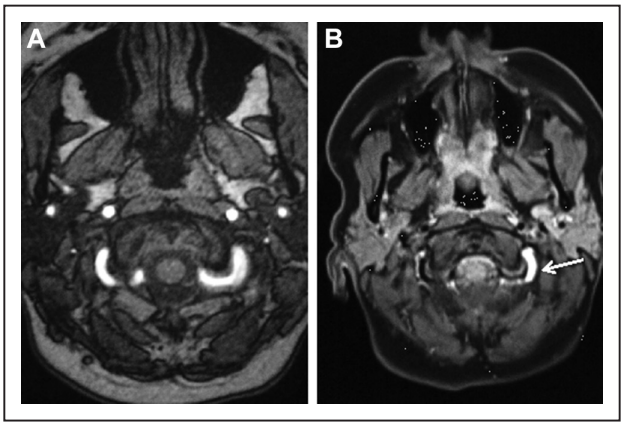

Figure 4. Young patient with acute onset left-sided neck pain with (**A**) magnetic resonance angiography sequence showing normal flow-related signal in bilateral vertebral arteries and (**B**) fat-suppressed sequence showing a hyperintense signal in the left vertebral artery suggestive of a dissection.

mechanisms include marantic endocarditis, intravascular coagulation, and tumor embolism. Of all cancer types, studies have shown an increased incidence of thrombotic events in patients with adenocarcinoma when compared with other types and lung and pancreatic cancer when compared with other locations.[73,74]

An evaluation for occult malignancy as a cause of CS should be considered once other potential mechanisms are excluded, especially in older patients with systemic symptoms suggestive of a cancer diagnosis, such as unexplained weight loss. Patients with cancer are more likely to have infarcts involving multiple vascular territories.[75] There is a relatively low yield of diagnostic testing when looking for an occult malignancy in the absence of systemic symptoms suggestive of cancer. Some of the tests commonly performed include age-appropriate cancer screening modalities, serum inflammatory markers, such as erythrocyte sedimentation rate, and computerized tomography scan of the chest, abdomen, and pelvis.[76]

Mechanisms in Cryptogenic Stroke

Several mechanisms are implicated in patients with CS, including but not limited to occult paroxysmal AF, paradoxical embolism through a PFO, or substenotic atherosclerosis (Table 2).

Patent Foramen Ovale

Paradoxical embolism through a PFO is hypothesized to be one of the possible mechanisms leading to CS. Prior retrospective studies showed an increase in prevalence of PFO in patients with ischemic stroke,[77] particularly of the CS.[78] However, recent data suggest a weak association between PFO and CS.[79] In pooled cross-sectional study from multiple population-based cohorts, PFO was not associated with an increased risk of stroke recurrence in patients with CS.[80]

Recently, investigators designed the Risk of Paradoxical Embolism (ROPE) score that provides insight into the degree of causality between PFO and stroke in patients with cryptogenic stroke found to have a PFO. The ROPE score is a 10-point score, where a high ROPE score suggests that PFO is the likely mechanism (observed in a young patient with little or no vascular risk factors and superficially located infarcts), while a low ROPE score argues that the PFO is incidental (eg, an elderly patient with deep infarcts and vascular risk factors). Interestingly, the estimated 2-year risk of recurrent stroke or transient ischemic attack was as low as 2% in patients with high ROPE scores and as high as 20% in patients with low ROPE scores.[80] In addition, predictors of stroke recurrence differed based on the ROPE scores, that is, in patients with ROPE scores >6, factors related to the PFO such as a minimal degree of shunting and the presence of an atrial septal aneurysm were predictive of recurrent stroke risk, whereas in patients with ROPE scores ≤6, predictors of recurrent stroke

Table 2. Diagnostic Evaluation and Therapeutic Implications in Ischemic Stroke

	Diagnostic Tests	Therapeutic Implications
Cardiac causes		
Paroxysmal occult AF	Noninvasive cardiac monitoring, and if no AF or flutter detected, then implantable cardiac monitoring	Anticoagulation therapy
Atrial cardiopathy	Serum NT-proBNP, echocardiography, ECG	Treatment with antiplatelet vs anticoagulation is unknown, but empirical treatment with anticoagulation may be reasonable
Atrial septal defect	Echocardiography (TEE superior to TTE)	Venous imaging if atrial septal defect detected
Atherosclerotic causes		
Aortic arch disease	Echocardiography (TEE superior to TTE)	Antiplatelet and statin therapy
Substenotic atherosclerosis	Vessel wall imaging, plaque MRI	Antiplatelet and statin therapy
Other causes		
Cancer	CT chest, abdomen, and pelvis	Antiplatelet vs. anticoagulation treatment of underlying cancer
Hypercoagulable state	Hypercoagulable work-up, including antiphospholipid antibodies	Anticoagulation therapy based on findings
Arterial dissection	MRA with fat-suppressed images	Antiplatelet therapy

AF indicates atrial fibrillation; CT, computed tomography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

were older age and antiplatelet versus anticoagulation therapy.[81] The ROPE score represents a summary of the patient's traditional vascular risk factors. Because there is no gold standard for determining the true relevance of a PFO, the ROPE score merely quantitates widespread assumptions about stroke causation.

Paradoxical embolization is the most commonly proposed mechanism for ischemic stroke in patients with PFO; thus, investigating for venous thrombi not only will confirm the cause–effect relationship but will also lead to a change in clinical management. The reported frequency of deep venous thrombosis (DVT) detection in patients with PFO and stroke has been 10% to 22%.[82–84] Of major importance, in one study, 80% of DVTs detected were asymptomatic, emphasizing the need of ultrasound phlebography in patients with PFO and stroke of unknown source.[82] With a diagnostic advantage over ultrasound, magnetic resonance venography can help detect isolated pelvic DVTs. Although considered a rare entity, isolated pelvic thrombi have been seen in 8% to 20% of patients with suspected DVT.[84,85]

Therefore, patients with CS and evidence of a PFO may particularly benefit from venography to look for asymptomatic venous thrombi. In the absence of venous thrombi, however, antiplatelet therapy remains the mainstay of treatment for patients with cryptogenic stroke and PFO, especially in light of a trial and recent meta-analyses showing no benefit of anticoagulation over antiplatelet therapy[86,87] and marginal benefit of PFO closure over medical treatment in secondary stroke prevention.[88,89]

Aortic Arch Disease

Aortic arch atherosclerosis is a marker of systemic atherosclerotic disease. However, there is evidence to suggest that mobile aortic plaques, especially those >4 mm in size, are associated with risk of spontaneous embolization or following mechanical manipulation, such as cardiac catheterization or cardiac surgery.[90,91] Although some studies showed that TTE can detect aortic arch plaques,[92] this technique has a limited resolution in detecting plaque thickness, which correlates with embolic risk. On the contrary, TEE is the gold standard test to grade aortic arch plaques, with a 73% agreement with pathological grading and over 90% sensitivity and specificity in detecting aortic arch thrombus.[93] Recently, CMR has been used in detecting aortic arch plaque; however, the data are limited and have not been validated in large studies.[94]

There is an association between atheromas of the aortic arch and ischemic stroke.[95] In case–control study of patients undergoing transesophageal echocardiogram, complex thoracic aortic plaque is seen much more frequently in stroke patients compared with controls without stroke in both TEE and autopsy studies (21%–27% versus 5%–9%).[95–98]

Complex thoracic aortic plaques are associated with a high frequency of embolization.[99–101] In a prospective observational cohort study of >500 patients who underwent TEE, 42 patients were identified as having a complex thoracic aortic plaque and no other detected source of emboli.[100] Among these patients, strokes occurred in 12% and peripheral emboli in 21%, compared with embolization in only 7% in patients without plaque during a mean follow-up of 14 months.

There are several factors associated with stroke risk in patients with aortic arch disease. In a case–control study (250 with ischemic stroke and 250 controls), compared with plaque thickness <1 mm, patients with plaques thickness >4 mm were more likely to have ischemic stroke (OR 4.2).[95] In addition, a prospective study of 331 patients with ischemic stroke who underwent TEE showed that when compared with patients with aortic arch plaque thickness <1 mm, patients with aortic arch plaque thickness >4 mm were more likely to have recurrent ischemic stroke (11.9% versus 2.8%; $P<0.05$). In multivariate models adjusting for several confounders, aortic arch plaque thickness >4 mm was an independent predictor of ischemic stroke risk (relative risk 3.8; 95% CI 1.8–7.8).[99] In addition to plaque thickness, plaque ulceration and mobility have been associated with risk of ischemic stroke and embolic events.[98,100,102,103] Furthermore, in one study, the risk of ischemic stroke was higher in patients with ascending aortic plaques than in patients with descending aortic plaques (13.8% versus 1.8%; $P<0.05$),[95] suggesting that descending aortic plaques are likely a marker of systemic atherosclerosis, whereas ascending plaques may constitute a mechanism for stroke and systemic embolism.

In a case–control study from NOMASS, there was increased prevalence of aortic atheromas >4 mm in size in patients with ischemic stroke (26% versus 13%; OR 2.4, 95% CI 1.2–4.7). In this study, in patients aged ≥60 years, the frequency of ulcerated or mobile atheromas was particularly high among CS patients (22% versus 8% in control subjects; OR 3.4, 95% CI 1.1–11.2).[104] Despite all this, it remains unclear whether aortic arch atheroma is the direct cause of the stroke or it is just a marker of systemic atherosclerosis and ischemic stroke risk.

Substenotic Atherosclerosis

Substenotic atherosclerotic plaques in the extracranial or intracranial cerebral blood vessels are considered to be another potential stroke mechanism. Extracranial substenotic plaques are thought to cause stroke by artery-to-artery embolism, whereas intracranial substenotic plaques are thought to cause by either artery-to-artery embolism or by plaque extension into the ostium of small perforators. Recent evidence suggests that patients with cryptogenic stroke are more likely to have complex or active internal carotid plaques ipsilateral as opposed to contralateral to the side of the infarct.[105] In one study using high-resolution carotid plaque MRA in patients with cryptogenic stroke, 22% of patients had evidence of intraplaque hemorrhage ipsilateral to the stroke, whereas none had this in the contralateral carotid artery.[39] In addition, advanced vessel imaging modalities, such as vessel wall imaging, have been used in some instances to detect nonstenosing active intracranial atherosclerotic plaque that is a potential cause of the infarct.[31]

Clinical trials showed no benefit of anticoagulation therapy over antiplatelet therapy in secondary stroke prevention in patients with intracranial atherosclerosis.[106] In addition, surgical treatment of nonstenosing carotid plaque was not superior to medical treatment for secondary stroke prevention.[107] Thus, similar to aortic arch disease, antiplatelet agents are the

mainstay therapy to reduce the risk of recurrent stroke in patients with intracranial or extracranial atherosclerosis.[108]

Paroxysmal Occult AF

Identification of AF after a cryptogenic stroke is of paramount importance because it leads to anticoagulation therapy that is likely superior to antiplatelet therapy in secondary stroke prevention.[56] Because AF can be paroxysmal, there has been growing evidence supporting the use of outpatient cardiac monitoring. Previous retrospective studies showed a relatively high yield of detection of paroxysmal AF after CS ranging from 3% to 7% on inpatient ECG and telemetry and from 3% to 25% on mobile cardiac outpatient telemetry. In these studies, the rate of detection of AF increased with the duration of monitoring and reached 30% at 3 years using implantable loop recorders. This culminated in 2 randomized trials proving an increase in detection rates with prolonged monitoring when compared with routine clinical follow-up. The EMBRACE trial showed that a 30-day outpatient event–triggered external loop recorder was superior to 24-hour Holter monitoring in detecting episodes of AF lasting ≥30 seconds (16.1% versus 3.2%; $P<0.001$).[58] In addition, the CRYSTAL-AF study showed that long-term monitoring with an implantable loop recorder was superior to standard-of-care clinical follow-up in detecting episodes of AF at 6 months (8.9% versus 1.4%; $P<0.001$), yielding a hazard ratio (HR) of 6.4 (95% CI 1.9–21.7; $P<0.001$) at 6 months and a HR of 8.78 (95% CI 3.47–22.19) at 3 years.[57] These trials show that longer periods of heart rhythm monitoring result in higher yields of AF detection after cryptogenic stroke. Although episodes of AF lasting ≥5 minutes have been shown to be associated with a 2-fold increase in risk of stroke or death,[109] the benefit of chronic anticoagulation in patients with brief runs of AF remains unclear. The ongoing ARTESIA trial (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation) will look at this issue in patients with high CHADSVASC score (though not specifically post-stroke; NCT01938248).

Several predictors of AF were identified in retrospective studies, including advanced age,[110] left atrial dilatation on echocardiogram, and prior embolic infarcts.[110,111] In addition, post hoc analyses of CRYSTAL-AF showed that the main predictors of AF detection were age, prolonged PR interval on ECG, chronic brain infarctions, and leukoaraiosis. Interestingly, the pattern and topography of the index infarct were not associated with detection of AF detection. On the contrary, a post hoc analysis of the EMBRACE trial showed that the main predictor of AF was the presence of atrial premature beats on 24-hour Holter ECG.[112,113] Although these predictors, when present, increase the chances of detecting AF, there are still a substantial number of patients who had AF detected in the absence of these predictors, and therefore, they conclude that cardiac monitoring should still be performed in the absence of these predictors in patients meeting the inclusion criteria for these studies.

Atrial Cardiopathy and LAA Dysfunction

AF with its implied intracavitary stasis in the setting of irregular atrial wall contractile function has been long considered to provide a direct mechanistic explanation for embolism where anticoagulation has been shown to reduce the risk of ischemic stroke.[114] There is a challenge, however, in detecting episodes of paroxysmal AF, especially when these episodes are subclinical. The ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) that enrolled subjects aged ≥65 years with hypertension and no history of AF showed that episodes of subclinical AF were detected in ≈35% of patients at 2.5 years, and only 16% of them had clinical AF. In addition, subclinical AF was associated with increased stroke risk (HR 2.5; 95% CI, 1.3–4.9).[109] In addition, this study and another study[115] showed lack of a temporal relationship between AF and stroke where only 25% to 30% of patients were found to be in AF in the 30 days prior to the stroke, challenging the concept that AF rather than an underlying atrial cardiopathy is the sole cause of stroke in most of these patients.

Left atrial enlargement is associated with ischemic stroke risk[116] and subclinical cardiovascular disease.[117] It also carries a thrombogenic potential likely by promoting stasis, endothelial injury, and thrombus formation. Data from TEE studies showed a relationship between severe left atrial enlargement, spontaneous echocardiographic contrast, and LAA thrombi.[118] In addition, recent evidence supports the association between left atrial enlargement and recurrent embolic stroke subtype independent of several confounders, including AF.[119]

In addition, ECG parameters, such as P wave abnormality and supraventricular tachycardia, are other biomarkers of left atrial dysfunction that are associated with ischemic stroke risk. A prolonged P wave terminal force in lead V1 is associated with pathophysiological changes, such as hypertrophy and elevated filling pressures.[120] Evidence from neuroepidemiological cohorts suggests that elevated P wave terminal force in lead V1 is associated with the risk of ischemic stroke,[121] particularly those related to embolism (cryptogenic or cardioembolic)[120] and covert nonlacunar brain infarcts.[122] Furthermore, a study using a nationwide database showed that paroxysmal supraventricular tachycardia was associated with increased risk of ischemic stroke after adjusting for potential confounders, such as paroxysmal AF.[123]

Elevated N-terminal pro-B-type natriuretic peptide, in addition, is a measure of cardiac dysfunction and stretch, volume overload, and a predictor of incident AF.[124] Studies have shown an association between elevated N-terminal pro-B-type natriuretic peptide and ischemic stroke, particularly of the embolic subtype.[125]

LAA morphology and dysfunction have also been shown to be associated with stroke risk.[55] LAA morphology can be assessed by CMR and is categorized into 4 different categories: chicken wing, cactus, windsock, and cauliflower. In addition, measures of LAA function, such as LAA peak systolic flow velocity, can be assessed by echocardiography.[55] Studies have shown that in patients with AF, lower LAA peak flow velocities have been correlated with thrombus formation and ischemic stroke.[55] In addition, studies have shown an inverse association between chicken-wing morphology with ischemic stroke[126,127] and covert brain infarcts.[128] Furthermore, cauliflower LAA morphology was an independent predictor of stroke, which is possibly related to extensive LAA trabeculations.[129] LAA flow velocity was highest among patients with chicken-wing as opposed to

nonchicken-wing morphology,[130–132] which may explain why chicken-wing morphology has the lowest risk of ischemic stroke. Late gadolinium enhancement CMR may also be used to detect LAA structural dysfunction. Recent evidence showed that LAA fibrosis on CMR is associated with reduced LAA flow velocities,[133] indicating that fibrotic changes of the LAA appendage are linked to stasis, thrombus formation, and stroke risk.

In fact, results from the LAA closure trials demonstrate that occlusion of the LAA reduces the risk of ischemic stroke to 1.7% per year, which is lower than the predicted rates based on CHADS2 scores,[134] suggesting that left atrial and LAA structural and functional abnormalities, and not just AF, are the major determinants of stroke risk in this class of patients.

A study from the SPOTRIAS (Specialized Programs of Translational Research in Acute Stroke) data set showed that ≈65% of patients with cryptogenic stroke had evidence of atrial cardiopathy.[135] Because outpatient cardiac monitoring was not routinely performed in this study, allowing a 20% to 30% detection rate of AF suggests that 35% to 45% of patients with cryptogenic stroke may have atrial cardiopathy without AF.

Therapeutic Implications

Patent Foramen Ovale

Several studies showed no benefit of anticoagulation therapy over antiplatelet therapy in patients with ischemic stroke and PFO.[86,136] A substudy of WARSS (Warfarin Aspirin Recurrent Stroke Study) showed that risk of recurrent stroke or death at 2 years was similar in patients with ischemic stroke between aspirin and warfarin.[87] Therefore, in the absence of a DVT or pelvic DVT that warrants anticoagulation treatment, antiplatelet therapy remains the mainstay of treatment in patients with ischemic stroke and evidence of PFO.[108] In addition, clinical trials showed no benefit of PFO closure over medical treatment for secondary stroke prevention.[88] These trials had several limitations. First, because these studies were performed before the ROPE score was designed, they included a proportion of patients whose PFO was incidental and not causative of the stroke. Second, because the event rate was low in these trials, the studies may possibly be underpowered to detect a difference between the 2 arms. Therefore, a trial targeting a group of patients whose PFO was the likely cause of the stroke and are at a particularly higher risk of recurrent events is needed to resolve the issue of whether PFO closure is superior to optimal medical management. Third, the primary outcome of these trails included transient ischemic attack whose diagnosis can be challenging. In fact, a meta-analysis of the closure trials showed that PFO closure was shown to be superior to medical therapy in reducing the risk of recurrent ischemic stroke.[137] Therefore, clinical trials selecting a targeted patient population that may potentially benefit from PFO closure and using hard outcomes, such as recurrent stroke or death, are needed to improve stroke prevention strategies in this patient population.

Substenotic and Aortic Arch Atherosclerosis

A recent randomized clinical trial showed that anticoagulation therapy is not superior to antiplatelet therapy in patients with CS and thick aortic plaque (>4 mm).[138] Thus, antiplatelet agents remain the mainstay of treatment in patients with cryptogenic stroke and evidence of thick aortic arch plaque.[108] The role of anticoagulation specifically in patients with mobile elements in the plaque, thought to represent fresh thrombus, remains unclear.

Clinical trials also showed no benefit of anticoagulation therapy over antiplatelet therapy in secondary stroke prevention in patients with intracranial atherosclerosis.[106] Surgical treatment of nonstenosing carotid plaque was not superior to medical treatment for secondary stroke prevention.[107] Thus, as with aortic arch disease, antiplatelet agents are the mainstay therapy to reduce the risk of recurrent stroke in patients with intracranial or extracranial atherosclerosis.[108]

Anticoagulation Therapy for Atrial Cardiopathy

The LAA has been shown to be the site of the majority of cardiac thrombi in patients with AF. In a pooled analysis that included 4792 patients with AF, left atrial thrombi were detected in ≈14% of patients, and the majority of these occurred in the LAA.[139] Because patients with atrial cardiopathy and AF likely share similar ischemic stroke mechanisms, it is likely that a major mechanism of stroke in patients with atrial cardiopathy is thrombus formation in the LAA.[55,140]

Anticoagulation therapy has been shown to be superior to antiplatelet therapy to prevent cardiac thrombi and cardioembolic stroke in several prototypes of cardiac disease. In patients with AF, a meta-analysis that included patients followed for a mean of 1.9 years showed that warfarin was associated with a nearly 65% reduction in ischemic stroke risk when compared with aspirin (HR 0.55; 95% CI 0.43–0.71), and the novel oral anticoagulants are at least as good if not better than warfarin at preventing stroke.[141,142] Moreover, the AVEROES trial (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) randomized patients considered to be poor warfarin candidates to aspirin versus apixaban and showed that apixaban was associated with a 55% reduction in risk of stroke or systemic embolism when compared with aspirin (0.45; 95% CI 0.32–0.62; $P<0.001$), with similar rates of major bleeding.[56] This effect was seen across all subgroups of patients even in patients with paroxysmal AF.

In addition, there is a potential benefit of anticoagulation use in stroke prevention in patients with low ejection fraction. The WARCEF trial (Warfarin vs Aspirin in Reduced Cardiac Ejection Fraction) randomized patients with low ejection fraction and no AF to warfarin versus aspirin and showed that there was no difference between warfarin and aspirin in the composite end point (stroke, intracerebral hemorrhage, or death) after a mean follow-up of 3.5 years (HR 0.93, 95% CI 0.79–1.10; $P=0.40$).[143] However, in this trial, warfarin was associated with a reduction in ischemic stroke when compared with aspirin (HR 0.52, 95% CI 0.33–0.88, $P=0.0055$).[143]

Similarly, in patients with anterior myocardial infarction and evidence of left ventricular thrombus, a meta-analysis that included 7 observational studies that included 270 patients with anterior myocardial infarction and documented left ventricle thrombus showed that warfarin was associated with an 86% reduction in embolic events (OR 0.14, 95% CI 0.04–0.52).[144] In patients with mechanical heart valves, the efficacy of anticoagulation therapy has not been tested in randomized trials. A pooled analysis that included 46 studies and

over 130 000 patients with mechanical heart valves, however, showed that in patients with mechanical valves, the risk of embolic events was lower in patients on anticoagulation therapy versus Those on antiplatelet therapy (1.4% versus 8.0%).[145]

These data provide strong evidence that anticoagulation therapy is efficacious in prevention of cardiac thrombi and cardiac embolism in several prototypes of cardiac disease. Therefore, patients with cryptogenic stroke and evidence of atrial cardiopathy may constitute a subgroup of patients who may also benefit from anticoagulation therapy for secondary stroke prevention in a similar manner to those with occult AF. In fact, although the WARSS study showed no difference between warfarin and aspirin in the primary end point of stroke or death at 2 years, a post hoc analysis showed that warfarin was superior to aspirin in patients with N-terminal pro-B-type natriuretic peptide >750 pg/mL, which is one of the markers of atrial cardiopathy (HR 0.30, 95% CI 0.12–0.84; P=0.021).[146]

Therefore, there is compelling suggestive evidence that patients with atrial cardiopathy and CS may constitute a subgroup of patients for future clinical trials comparing antiplatelet therapy to anticoagulation therapy in secondary stroke prevention; however, it has yet to be tested.

Antiphospholipid Antibodies

Serum antiphospholipid antibodies are present in nearly 17% to 42% of patients with ischemic stroke.[147,148] Although anticoagulation therapy is the treatment of choice in patients with antiphospholipid antibody syndrome, in patients with ischemic stroke and presence of antiphospholipid antibodies, clinical trials showed that anticoagulation therapy is as efficacious as antiplatelet therapy for secondary stroke prevention.[108] A subset study of the WARSS trial showed no difference in recurrent stroke or death between warfarin and aspirin in patients with ischemic stroke and antiphospholipid antibodies.[148] The major drawback of this study is that some patients with ischemic stroke and presence of antiphospholipid antibodies may have an alternate mechanism, such as small-vessel disease or large-vessel disease, where antiplatelet therapy is known to be the mainstay of treatment. Therefore, it remains unclear whether anticoagulation therapy may be superior to antiplatelet therapy in patients with CS and evidence of antiphospholipid antibodies, especially with the advent of the non-vitamin K antagonist oral anticoagulants that tend to have better safety profiles when compared with warfarin.

Occult Malignancy

Stroke prevention strategies in patients with cancer remain controversial. Although treating the underlying cancer may help reduce the risk of stroke recurrence, the optimal medical regimen in terms of anticoagulation versus antiplatelet agents remains controversial. Because of the assumed hypercoagulability as a cause of ischemic events in patients with cancer, some experts and guidelines recommend anticoagulation as the first-line treatment for secondary stroke prevention in patients with cancer and ischemic stroke.[149] Furthermore, physicians favor low molecular weight heparin over warfarin because of data from small case series and extrapolation from a trial on venous thromboembolic disease.[67]

Conversely, most modern clinical series of patients with systemic cancer and ischemic stroke have not supported a prominent role of hypercoagulability in stroke pathophysiology. In fact, one large observational study found coagulopathy and marantic endocarditis to account for only 12% and 3% of all strokes, respectively.[150]

Another similar study found atherosclerosis to be the most common cause of ischemic stroke in patients with malignancy and, thus, proposed antiplatelet agents to be sufficient therapy for most patients with cancer and stroke.[151] Therefore, there are conflicting data on the efficacy of anticoagulant therapy when compared with antiplatelet therapy, especially with the increased bleeding risk in cancer patients from bone marrow suppression and frequent invasive procedures. Clinical trials are needed to determine the optimal secondary stroke prevention regiment (eg, anticoagulants or antiplatelet agents) for these patients.

Ongoing Trials

There are several ongoing stroke prevention trials in the cryptogenic stroke population.

The RESPECT ESUS trial (Dabigatran Etexilate for Secondary Stroke Prevention in Patients with Embolic Stroke of Undetermined Source) aims to randomize 6000 patients with CS to dabigatran versus aspirin. The primary outcome is time to first recurrent stroke (ischemic or hemorrhagic) over a 3-year follow-up (NCT02239120). The NAVIGATE ESUS trial (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) is randomizing patients to rivaroxaban versus aspirin, and the primary end points are time to recurrent stroke (ischemic or hemorrhagic) or systemic embolism and time to first occurrence of major bleeding over a 3-year follow-up (NCT02313909).

Conclusion

CS patients constitute a heterogeneous group of patients leading to therapeutic implications based on the potential mechanism. This approach, in addition to risk factor management and lifestyle modifications, will lead to improved stroke prevention strategies in patients with CS. This will allow for targeted clinical trials to improve stroke prevention strategies in this patient population.

Disclosures

R.A. Bernstein provides consulting services and sits on the advisory committee for Medtronic, Beohringer Ingelheim, and Pfizer/BMS. R. Passman reports grant support and personal fees from Medtronic and personal fees from Pfizer, Bristol-Myers Squibb, and Janssen outside the submitted work. The other authors report no conflicts.

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