Cardiogenic and Aortogenic Brain Embolism

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Cardioaortic brain embolism is a potentially devastating condition that presents frequent diagnostic and therapeutic challenges. In this report, we review key aspects of the etiology, clinical presentation, diagnosis, prognosis, and treatment of cardiogenic and aortogenic stroke. Emphasis is on advances in diagnostic imaging capabilities and on recent literature addressing secondary prevention for specific cardioembolic sources, upon which diagnosis and prognosis primarily depend. While early evaluation with modern neuroimaging techniques offers to enhance diagnostic accuracy, additional study is required to define optimal utilization. Appropriate imaging of the heart and aorta is paramount to identifying potential sources of embolism. Secondary prevention for high-risk embolic sources generally involves anticoagulation, but immediate initiation of anticoagulation is not routinely indicated. Medium-risk sources have more modest or undefined risks and little randomized comparative evidence to guide management, but antiplatelet therapy is generally favored. One possible exception is patent foramen ovale, for which high-risk features may warrant anticoagulation or mechanical closure. Definitive recommendations for this and other findings await completion of ongoing clinical trials. (J Am Coll Cardiol 2008; 51:1049–59) © 2008 by the American College of Cardiology Foundation

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Stroke, which is almost 90% ischemic in nature, is a leading cause of mortality and long-term disability worldwide (1). While the etiology of ischemic stroke is often found in the cervicocranial vasculature, approximately 20% result from high-risk cardiac abnormalities (2,3). In another 30%, the etiology cannot be established (2), but most “cryptogenic” ischemic strokes have embolic features (4), suggesting a possible cardioaortic origin (3).

Given the clinical importance of brain embolism arising from the heart and aorta, we prepared a narrative review detailing optimal approaches to diagnosis and secondary prevention based on the latest available evidence and published guidelines.

Pathophysiology

The brain, which receives 15% of cardiac output, is exquisitely sensitive to ischemia. Thus, material dislodged proximally to the great vessels often travels to the cervicocephalic arteries, where impaction tends to manifest in stark clinical terms. Most commonly, the embolic material is thrombus (5), whose propensity for spontaneous dissolution heightens the risk of hemorrhagic conversion (6). While thromboemboli of central origin frequently occlude cerebral artery stems or major branches (5), microemboli, such as air, fat, and cholesterol crystals, may travel to smaller terminal branches, leading to watershed infarction (7).

Symptoms and Signs

Clinical presentation is imperfect in differentiating cardioembolic from noncardioembolic stroke (8). Cardiogenic brain embolism presents characteristically with neurologic deficits that are maximal at onset, reflecting sudden interruption of blood flow (8). This contrasts with the stuttering course attributed to atherothrombotic stroke (9). Yet because emboli can shift or fragment after initial impaction (3), presentation is nonabrupt in at least one-fifth of cardioembolic strokes (8,9). Moreover, large-artery atherothrombosis causes not only hypoperfusion (7), but also artery-to-artery embolism (3). Accordingly, cardioembolic features can occur in more than two-fifths of noncardioembolic strokes (9). Particular neurologic deficits favoring a cardioembolic etiology have been identified, but have suboptimal discriminatory capacity (10). While insensitive, the most specific features for cardioembolism are infarcts in multiple territories and concurrent systemic embolism (8,10).

Diagnosis

Diagnosis of cardio/aortogenic infarction depends on circumstantial evidence provided by detection of proximal emboligenic findings (hereafter “cardiac sources of embolism” [CSEs]) (Table 1) and supportive clinical, neuroimaging, or laboratory features.
Neuroimaging. Magnetic resonance imaging (MRI) affords superior resolution than computed tomography (CT), along with the capacity to detect cerebral ischemia within minutes of onset (11). Cardiac emboli often occlude large arteries or multiple vascular territories (12), more commonly affect certain vessels (10), and frequently lead to hemorrhagic transformation (6). But the utility of infarct features for making a diagnosis of cardioembolism is limited (10).

Noninvasive vascular imaging has largely supplanted conventional angiography, and can help impugn a cardioaortic source, especially when used early (13). The finding of a hyperdense cerebral artery by noncontrast CT (14), denoting thrombus (Fig. 1), or its hyperintense counterpart by MRI (15), confirms the diagnosis in the absence of proximal arterial pathology. Early use of thin-section noncontrast CT in acute stroke outperforms conventional sectionsing, identifying intracranial thrombi in almost 90% of cases (16). The presence of intracranial thrombi may also be detected noninvasively with MRI angiography (17), CT angiography (18), or transcranial Doppler (19). Lately, MRI has been applied to identify erythrocyte-rich thrombi, whose detection provides direct support for cardioembolism (20). There are no published guidelines regarding the optimal neuroimaging approach, but contemporary techniques promise substantial improvement in diagnostic accuracy. Ultimately, however, the diagnosis of cardio/aortogenic stroke rests with detection of the embolic source itself, which requires electrocardiographic monitoring and cardioaortic imaging.

Echocardiography. In patients with clinically apparent heart disease, the yield for CSEs of conventional transthoracic echocardiography (TTE) with agitated-saline injection may exceed 25% (21), but falls below 10% otherwise (13). By contrast, the superior image resolution of transesophageal echocardiography (TEE) permits identification of possible CSEs in more than 50% of patients without clinically overt heart disease (21) or otherwise unexplained cerebrovascular events (22). In particular, TEE allows the diagnosis of “complex” aortic atheroma (CAA), consisting of protruding, mobile, or ulcerated plaque (23). Newer techniques, however, have brought the diagnostic accuracy of TEE for right-to-left interatrial shunts closer to TEE (24–26). Second-harmonic TTE can attain sensitivities of 62.5% to 90% compared with TEE (24,25).

There are scant data regarding the optimal echocardiographic approach in suspected cardioembolic stroke. In a study of unexplained stroke evaluated by both TTE and TEE, the latter technique yielded findings (patent foramen ovale [PFO], aortic thrombus) that prompted a change from antiplatelet to anticoagulant therapy in 30% of cases (27). Therapeutic decisions were based on clinical judgment, however, and randomized data supporting anticoagulant therapy for these findings are lacking. Published guidelines reflect the shortfall in available evidence and, while acknowledging the superiority of TEE for detecting selected CSEs (Table 2) (28), do not make specific recommendations regarding imaging strategy (28,29).

Ongoing uncertainties notwithstanding, the higher yield of TTE in patients with clinically overt heart disease supports its use as the initial imaging technique in this setting. Contrariwise, the higher prevalence of potential CSEs that are difficult to detect by TTE in younger patients with unexplained stroke, together with the potentially serious consequences of occult pathology in this population, makes TEE the modality of choice. Although transcranial Doppler with contrast injection can offer comparable diagnostic accuracy to TEE for right-to-left shunts (30), it cannot provide direct information on cardiac structure. The case for cardioaortic embolism depends chiefly on detection of a presumptive proximal culprit. Absent an alternative explanation, identification of high-risk CSEs makes a diagnosis of cardioembolic stroke likely, if not definite. Because the link of medium-risk CSEs to cerebral infarction is more modest or uncertain, their detection does not, in isolation, permit assignment of a cardioembolic etiology. Adjunctive clinical and imaging findings, however, such as deep-vein thrombosis accompanying PFO, can implicate a medium-risk source as the likely offender. Yet

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**Table 1** Proximal Sources of Embolism

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Medium or Uncertain Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial dysrhythmias</td>
<td>Interal atrial septal abnormalities</td>
</tr>
<tr>
<td>· Atrial fibrillation</td>
<td>· Patent foramen ovale</td>
</tr>
<tr>
<td>· Sick sinus syndrome</td>
<td>· Atrial septal defect*</td>
</tr>
<tr>
<td>· Atrial flutter</td>
<td>· Atrial septal aneurysm</td>
</tr>
<tr>
<td>Left atrial thrombus</td>
<td>Pulmonary arteriovenous malformation</td>
</tr>
<tr>
<td>· Atrial dysrhythmias</td>
<td></td>
</tr>
<tr>
<td>· Mitral valve stenosis</td>
<td></td>
</tr>
<tr>
<td>Left ventricular thrombus</td>
<td>Spontaneous echo contrast (“smoke”)</td>
</tr>
<tr>
<td>· Acute myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>· Dilated cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Primary cardiac tumors</td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>· Myxoma</td>
<td></td>
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<tr>
<td>· Papillary fibroelastoma</td>
<td></td>
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<tr>
<td>Metastatic tumors to the heart*</td>
<td>Valvular calcification</td>
</tr>
<tr>
<td>· Valvular calcification</td>
<td>· Mitral annular calcification</td>
</tr>
<tr>
<td>· Aortic valve sclerosis/stenosis</td>
<td>· Aortic valve sclerosis/stenosis</td>
</tr>
<tr>
<td>Vegetations</td>
<td>Valvular strands</td>
</tr>
<tr>
<td>· Infective</td>
<td></td>
</tr>
<tr>
<td>· Noninfected (marantic)</td>
<td></td>
</tr>
<tr>
<td>Prosthetic cardiac valve</td>
<td></td>
</tr>
<tr>
<td>Complex aortic atheroma</td>
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</tbody>
</table>

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*Not discussed in this review.

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**Abbreviations and Acronyms**

AF = atrial fibrillation
ASA = atrial septal aneurysm
CAA = complex aortic atheroma
CSE = cardiac source of embolism
CT = computed tomography
INR = international normalized ratio
LV = left ventricle/ventricular
MRI = magnetic resonance imaging
PFO = patent foramen ovale
TEE = transesophageal echocardiography
TTE = transthoracic echocardiography

identification of even a high-risk source does not necessarily confirm cardioaortic embolism because CSEs often coexist with other potential stroke etiologies. Failure to detect a potential CSE for a large-vessel infarct lacking another explanation leads to a designation of cryptogenic embolism.

**Prognosis and Treatment**

Cardioembolic stroke is associated with a worse outcome than other stroke subtypes (31). Clinical trials of acute cardioembolic stroke have failed to demonstrate the benefit of acute intravenous anticoagulation, while showing greater symptomatic intracranial hemorrhage compared with antiplatelet therapy (32). Current guidelines (2,33) do not recommend routine immediate anticoagulation, but favor early antiplatelet treatment for cardioembolic stroke.

In acute as in chronic management, choice of an antithrombotic agent depends on the balance between thromboembolic and hemorrhagic risk. Incidence of hemorrhagic transformation for cardioembolic stroke, ranging from petechiae to intrainfarct hematoma, averages 42% (6). Peak onset is 2 to 4 days, leading to the proposition that, for atrial fibrillation (AF), anticoagulation should be started 4 days post-stroke (34). Long-term anticoagulation doubles the risk of intracranial hemorrhage (from 0.3% to 0.6% annually) compared with antiplatelet treatment (35). Whereas acute hemorrhagic risk correlates with infarct size (6), both acute and chronic risks are determined by age, blood pressure, and intensity and stability of anticoagulation (35).

Although thromboembolic risk varies with embolicogenic substrate, existing literature addressing the risk of individual CSEs is predominantly observational and subject to bias (36). Nevertheless, available data permit useful categorization of proximal sources based on their known propensity for embolism (Table 1). Published treatment guidelines by professional societies center on individual cardioembolic findings (Table 3), but the paucity of existing randomized data is an acknowledged limitation.

**High-risk sources.** **ATRIAL DYSRHYTHMIAS.** Atrial fibrillation is the most common cause of cardioembolic stroke, and its close link to age augurs marked increases in prevalence in coming decades (37,38). Valvular AF is associated with higher stroke risk than nonvalvular AF (37). Thromboembolic risk is similar for paroxysmal and persistent nonvalvular AF, but is strongly determined by associated cardiovascular risk factors (37). The severity and duration of these risk factors, through their effects on left ventricular (LV) function, influence the extent of left atrial enlargement.
<table>
<thead>
<tr>
<th>Individual Disorders</th>
<th>ACC/AHA*</th>
<th>American College of Chest Physicians†</th>
<th>American Stroke Association/AHA (1)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF/atrial flutter</td>
<td>Chronic oral anticoagulant therapy to achieve a target intensity INR of 2 to 3, unless contraindicated (Class I, Level of Evidence: A); aspirin in a dose of 325 mg daily as an alternative in those with certain contraindications to oral anticoagulation (Class I, Level of Evidence: A) (46).</td>
<td>Anticoagulation with an oral vitamin K antagonist, such as warfarin (target INR 2.5; range 2.0 to 3.0) (Grade 1C) (62); if INR is therapeutic, add aspirin 75 to 100 mg/day, or if unable to take aspirin, dipyridamole 400 mg/day, or clopidogrel (Grade 1C) (62).</td>
<td>Anticoagulation with adjusted-dose warfarin (target INR 2.5; range 2.0 to 3.0) (Class IA); if unable to take oral anticoagulants, aspirin 325 mg/day (Class IA).</td>
</tr>
<tr>
<td>Rheumatic mitral valve disease</td>
<td>Anticoagulation is indicated in patients with mitral stenosis, even in sinus rhythm (63).</td>
<td>Long-term anticoagulation therapy (target INR 2.5; range 2.0 to 3.0) (Grade 1C) (62); if INR is therapeutic, add aspirin 75 to 100 mg/day, or if unable to take aspirin, dipyridamole 400 mg/day, or clopidogrel (Grade 1C) (62).</td>
<td>Long-term warfarin therapy is reasonable, with a target INR of 2.5 (range 2.0 to 3.0) (Class IIa, Level of Evidence: C); antiplatelet agents should not routinely be added to warfarin to avoid the additional bleeding risk (Class III, Level of Evidence: C).</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>If cardiogenic source of embolism (AF, LV mural thrombus, LV akinesic segment) present, moderate intensity (INR 2 to 3) warfarin anticoagulation (in addition to aspirin) or variable duration depending on underlying source. For LV thrombus or akinesic segment, warfarin administered for 3 months, unless follow-up echocardiography shows new, enlarging, or mobile thrombus, wherein anticoagulation is continued long term (Class I, Level of Evidence: B); if no cardiogenic source of embolism detected, in patients undergoing stenting, clopidogrel 75 mg/day is added to aspirin 75 to 162 mg/day for a minimum of 12 months. In patients not undergoing stenting, aspirin/extended-release dipyridamole 25/200 mg plus aspirin 81 mg/day (60).</td>
<td>—</td>
<td>When LV mural thrombus is identified, oral anticoagulation is reasonable, aiming for an INR of 2.0 to 3.0 for at least 3 months and up to 1 year (Class IIa, Level of Evidence: B). Aspirin should be used concurrently for ischemic coronary artery disease during oral anticoagulant therapy in doses up to 162 mg/day (Class IIa, Level of Evidence: C).</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>Absence of definitive trials cited, but anticoagulation with warfarin ‘most justified’ in patients with heart failure and an embolic event (61).</td>
<td>—</td>
<td>Either warfarin (INR 2.0 to 3.0) or antiplatelet therapy may be considered for prevention of recurrent events (Class IIb, Level of Evidence: C).</td>
</tr>
<tr>
<td>Valvular prosthesis—mechanical</td>
<td>If within INR range indicated for specific prosthesis, addition of aspirin 75 to 100 mg/day and maintenance of INR at target of 3.0 (range 2.5 to 3.5) (Grade 1C) (62).</td>
<td>Oral anticoagulation for 3 to 12 months (Grade 1C) (62).</td>
<td>Anticoagulation with warfarin (INR 2.0 to 3.0) may be considered (Class IIb, Level of Evidence: C).</td>
</tr>
<tr>
<td>Valvular prosthesis—biological</td>
<td>—</td>
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<tr>
<td>Infective vegetations</td>
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<tr>
<td>Noninfective (marantic) vegetations</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>—</td>
<td>—</td>
<td>Antiplatelet therapy is reasonable to prevent a recurrent event (Class IIa, Level of Evidence: B). Insufficient data exist to make a recommendation about closure in patients with a first stroke and patent foramen ovale. Closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (Class IIb, Level of Evidence: C).</td>
</tr>
<tr>
<td>Alone</td>
<td>—</td>
<td>—</td>
<td>Recommend antiplatelet therapy over no therapy (Grade 1C) and suggest antiplatelet therapy over warfarin (Grade 2A) (2).</td>
</tr>
</tbody>
</table>
and, consequently, the likelihood of AF-associated thrombus formation (38). They also foster aortic and carotid atherosclerosis and small-vessel disease, which along with structural heart disease can themselves cause cerebral ischemia in AF patients (37). In this context, the interplay of atherosclerotic, inflammatory, and prothrombotic factors has received attention (38).

Risk stratification can be accomplished with clinical prediction instruments such as CHADS2, which assigns 1 point each for Congestive heart failure, Hypertension, Age ≥75 years, and Diabetes, and 2 points for prior Stroke or transient ischemic attack (39). While identification of dense smoke or CAA by TEE also predicts AF-associated thromboembolic risk, its additive prognostic value to clinical measures requires further investigation (23).

Atrial flutter and sick sinus syndrome are often associated with AF and structural heart disease (40–42). Thromboembolic risk is generally lower, if less well characterized, than for AF, but is influenced by these relations (40,41,43,44).

Available guidelines (2,45,46) highlight the preeminence of prior stroke in amplifying thromboembolic risk in AF. While the annual risk of thromboembolism is 0.5% in lone AF, it soars to 12% in AF associated with prior
thromboembolism (37). Given the magnitude of this risk and the strength of randomized data favoring warfarin over aspirin for thromboembolism prevention (47), guidelines concur in recommending adjusted-dose warfarin (international normalized ratio [INR] 2.0 to 3.0) for patients with cerebral ischemia unless contraindications to anticoagulation exist (Table 3) (1,2,45,46). (Strategies for rate and rhythm control are beyond the scope of this review, but clinical trials have not shown advantage to the latter [46].) Although less evidence is available, a similar approach is advocated for atrial flutter (46), and, in proportion to the likelihood of associated AF, warrants consideration for sick sinus syndrome.

LEFT HEART THROMBUS. Since stasis is the principal determinant of left atrial (appendage) thrombus formation, thrombosis in this chamber (Fig. 2) is primarily observed with AF or mitral stenosis (48). Left atrial thrombus also occurs in sinus rhythm when myocardial or valvular disease is present, but is exceedingly rare in their absence (48).

Myocardial infarction and dilated cardiomyopathy are most frequently associated with LV thrombus formation attributable to stasis caused by regional or global myocardial dysfunction (49,50). Approximately 1% to 2.5% of patients with acute myocardial infarction will suffer a stroke within 4 weeks, one-half in the first 5 days (51,52). Infarct location and severity of systolic dysfunction determine the propensity for thromboembolism (53). Dyskinetic segments that remodel into aneurysms remain chronic foci for potential thrombosis (54,55).

Dilated cardiomyopathy is also associated with LV thrombus. Annual risk of embolization ranges approximately from 1.0% to 3.5% (50,56), paralleling the severity of systolic dysfunction (56–58), but climbs to 9% once stroke has occurred (59).

Detection of intracavitary thrombus, especially when mobile, moves the benefit–risk calculus in favor of early post-stroke anticoagulation. In sinus rhythm, anticoagulation should be instituted for at least 3 months, unless contraindicated, with demonstration of thrombus resolution by echocardiography (1,60). Absent detectable thrombus, opinion is divided regarding anticoagulation for secondary stroke prevention in acute myocardial infarction or dilated cardiomyopathy (1,61), but it is recommended for rheumatic mitral stenosis (1,62,63).

CARDIAC TUMORS. Primary cardiac tumors are rare, accounting for a small minority of cerebrovascular events in reported series (21). Detachment of tumor fragments or superimposed thrombi underlies embolic risk (64). Myxoma is the most common, exceeding 50% of all benign cardiac tumors (64), while papillary fibroelastoma accounts for another 30% (65). Secondary stroke prevention entails surgical resection of myxoma or large, mobile fibroelastomas (2,64,65). This is usually definitive, but myxoma recurrences can occur (64).

VALVULAR VEGETATIONS. The incidence of ischemic stroke associated with infective endocarditis is 15% to 20% (66), with the highest risk in the first 7 to 10 days after presentation. Mitral valve involvement carries greater stroke risk than aortic valve involvement (67). Embolic risk is also increased by mobility, consistency, extent, and size (67–69). Marantic endocarditis, characterized by noninfective valvular vegetations, is seen in neoplastic or other debilitating disorders and also confers a high risk of embolism (69,70).

Treatment must be directed at the underlying cause. Infective endocarditis requires administration of systemic antibiotics and, if indicated, surgery (66). Noninfective endocarditis is treated with tumor-suppressive, antiretroviral, or immunosuppressive therapy with systemic anticoagulation, preferably heparin based (62), as appropriate. Sterile vegetations, especially when large and mobile, make immediate post-stroke anticoagulation compelling unless hemorrhagic risk is excessive.

PROSTHETIC VALVES. Systemic embolization occurs as a complication of both bioprosthetic and mechanical heart valves at 1% to 4% annually (62). Eighty percent of clinical thromboemboli associated with prosthetic valves involve the brain. The absolute yearly risk of cerebral embolism is higher for prosthetic valves in the mitral (2% to 3.5%) than aortic position (1% to 2%), and this risk is amplified by AF (62).
High-intensity anticoagulation (INR 2.5 to 3.5) is recommended for modern mechanical prostheses when cerebral ischemia occurs, with addition of low-dose aspirin when the event occurs despite a therapeutic INR (1,62). Moderate-intensity anticoagulation can be considered in the case of bioprostheses (1,62). Early initiation/intensification of antithrombotic therapy should be entertained.

CAA. Various studies in populations with cerebral ischemia have established a link between protruding aortic atheroma and systemic embolism (71), although an independent relation was not demonstrated in a community-based study with a modest number of outcomes (72). In a prospective investigation of stroke patients age >60 years, the presence of proximal aortic atheroma ≥ 4 mm in thickness conferred a recurrence risk of 11.9 per 100 person-years, compared with 3.5 per 100 person-years or less observed for atheroma <4.0 mm (73). A TEE substudy in AF, which defined CAA as ≥4 mm or containing ulceration or mobile components (23), demonstrated a 4-fold greater risk of thromboembolism with than without CAA. Taken together, available data in patients with cerebral ischemia or AF show CAA to heighten thromboembolic risk, either directly or through associated cardiovascular disease (71).

Although CAA-associated thrombi would be expected to be platelet-rich, some small-scale observational data suggest that secondary prevention with anticoagulation may be superior to antiplatelet therapy (71). Still, current guidelines do not recommend routine anticoagulation (2). In the presence of mobile atheroma, however, early systemic anticoagulation can be considered (Table 3) (2,62). The best antithrombotic strategy awaits completion of clinical trials, but aggressive lipid lowering and renin-angiotensin antagonism are indicated (74).

Medium- or Uncertain-Risk Sources

PFO. This fetal remnant constitutes a potential conduit for right-to-left shunting in 25% to 30% of adults (36). Many (75), but not all (76,77), studies have documented an association between PFO and ischemic stroke, particularly in adults ≤55 years of age, in whom the prevalence rises to 50%. This relation is stronger for cryptogenic stroke, suggesting that PFO may be important in the pathogenesis of cerebral infarction. The putative mechanism, based on rare instances of thrombus “in transit” across the foramen in patients with stroke (Fig. 3), is paradoxical embolism (78). Joint occurrence of venous thromboembolism and PFO suffices for a circumstantial diagnosis of paradoxical embolism (78), and autopsy series have identified paradoxical embolism as the culprit in as many as 4% of brain infarcts in this manner (79). In such reports, however, cases with major pulmonary embolism have predominated, leading to ascertainment bias. By contrast, antemortem stroke studies seldom uncover clinically overt pulmonary embolism or sonographic deep-vein thrombosis (36). This has prompted consideration of alternative mechanisms for the PFO-stroke association, including in situ thrombosis and atrial dysrhythmias, but these are also rarely documented (36). Nevertheless, a 1-mm thrombus sufficient to produce a clinical stroke can well elude detection by existing venous imaging modalities. Moreover, more extensive evaluation with conventional venography (80) and MRI venography (81) has documented frequent calf-vein and pelvic-vein thrombosis in patients with unexplained systemic embolism and interatrial shunts.

Population estimates suggest that PFOs generally have low pathogenicity (36). Additional factors must, therefore, act to increase thromboembolic risk. Intrinsic PFO features such as anatomical degree of patency (82), magnitude of microbubble passage (83), septum-primum hypermobility (84), or presence of atrial septal aneurysm (ASA) (85) have been reported to amplify risk. Moreover, an individual’s propensity to venous thrombosis, either from immobility or hypercoagulable state, influences the associated risk of paradoxical embolism (78).

ASA. Defined as exaggerated excursion of the septum into the atrial chambers, ASA occurs more frequently in patients
with ischemic stroke than in the general population (7.9% vs. 2.2%) (86). The precise mechanism underlying this association is unclear. An interatrial shunt is present in 50% to 90% of ASAs, suggesting paradoxical embolism as the pathophysiological basis (36). Additional potential mechanisms include in situ thrombosis (87) and associated atrial dysrhythmias (88).

**PFO and ASA.** There is no consensus regarding optimal secondary stroke prevention for PFO (36). Treatment options include antiplatelet or anticoagulant agents, and percutaneous or surgical closure. A substudy of patients with noncardioembolic stroke randomized to aspirin versus warfarin who underwent TEE found no difference in recurrent stroke or death, irrespective of PFO size or presence of ASA (89). In a subgroup with cryptogenic stroke, however, warfarin reduced by one-half the risk of stroke or death, but this analysis was underpowered (89). In a separate study of younger patients with cryptogenic stroke receiving aspirin, prospective follow-up showed a similar 4-year risk of stroke recurrence for patients with isolated PFO and without PFO (85). For patients with both PFO and ASA, however, the risk of recurrence was 4-fold greater than without either abnormality (85). (Larger shunt size was associated with ASA, but it did not influence the risk of stroke recurrence.) This observation, though at variance with findings in older adults (89), suggests that aspirin affords insufficient protection for young cryptogenic stroke patients with combined PFO and ASA.

Patent foramen ovale closure has been traditionally accomplished by open thoracotomy, but percutaneous closure represents an attractive alternative (36). Nevertheless, there are no available randomized data on the relative merits of anticoagulation for accompanying mitral valve disease. Accordingly, antiplatelet therapy is favored for PFO unless concurrent venous thromboembolism or hypercoagulable state requiring anticoagulation is detected (1,2). In the setting of cryptogenic stroke and PFO with high-risk features—large shunt (>50 bubbles), ASA, antecedent Valsalva, multiple infarcts—especially in younger adults, long-term anticoagulation may be a preferred strategy. This is in keeping with the fibrin-rich composition of venous-source thrombi (36). Patients interested in percutaneous closure should be encouraged to participate in clinical trials. Surgical closure is an alternative when anticoagulation is contraindicated. Optimal secondary prevention for isolated ASA remains uncertain.

**Intrapulmonary shunt.** Pulmonary arteriovenous malformations, which constitute a conduit for paradoxical embolization, can be isolated or associated with liver disease or hereditary hemorrhagic telangiectasia (90). Among referrals for endovascular occlusion, cerebral infarction was documented in 32% of patients with single, and 60% with multiple, malformations (91).

Transcatheter embolotherapy is favored for secondary stroke prevention for malformations ≥3 mm in diameter (91).

**Spontaneous echo contrast ("smoke").** This swirling cloud visible within cardiac chambers by echocardiography reflects rouleaux formation from low flow, increased fibrinogen, or high hematocrit (92). Hence, it is common in disorders such as AF and mitral stenosis, as well as prosthetic heart valves and severe ventricular dysfunction.

In AF, smoke typically occurs in the left atrial appendage, where it correlates with reduced contractility (93). Dense smoke in the appendage is not only associated with thrombus, but also predicts incidence of AF-related thromboembolism (23).

Because dense smoke represents a pre-thrombotic condition and is a marker of thromboembolic risk in AF, mitral stenosis, or valvular replacement (94), systemic anticoagulation may be contemplated in cryptogenic stroke patients in sinus rhythm with this finding.

**Mitral valve prolapse.** Early studies reported an association between mitral valve prolapse and stroke, especially in patients <45 years of age (95). Such studies applied echocardiographic criteria that did not take into account the saddle-like shape of the mitral annulus. Subsequent revision of these criteria yielded greater specificity, and several studies, albeit of limited power, have since failed to document an association (96,97).

Guidelines do not recommend post-stroke anticoagulation (1,2,63), except when leaflet thickening or mitral regurgitation is present (63) (Table 3).

**Valvular calcification.** Mitral annular calcification and aortic valve sclerosis are associated with atherosclerotic vascular disease (98,99). Prospective studies have shown mitral annular calcification to increase the risk of stroke (100), but the same has been documented for aortic valve sclerosis only when stenosis is present (101). While the association of mitral annular calcification with stroke reflects its status as a marker for atherosclerotic disease, several reports attest to mitral annular calcification’s potential as a direct source of calcific or thrombotic debris (98).

Recognizing the scant available data, published guidelines (1,62) suggest different general approaches to cerebral embolism not documented to be calcific in association with mitral annular calcification (Table 3), but urge consideration of anticoagulation for accompanying mitral valve disease.

**Valvular strands.** These mobile filaments represent endothelialized fibrin deposits arising from microabrasions of valvular endothelium (102). Associations between valvular excrescences and stroke, ostensibly from embolization, have been reported in cross-sectional studies (102), but failure of longitudinal studies to replicate the findings (103–105) makes a causal association suspect.
Comparison of aspirin versus warfarin therapy in stroke patients with strands showed no difference in outcome (105), and anticoagulation is not recommended (2).

Conclusions

The diagnosis of cardio/aortogenic stroke relies on detection of potential embolicigenic sources in the absence of another etiology of equal or greater plausibility. Early application of modern neuroimaging techniques stands to bolster diagnostic accuracy. Transesophageal echocardiography is the favored screening modality for CSE when clinical heart disease is absent. Treatment for high-risk sources, whether anticoagulation or surgery, is better established than for disease is absent. Treatment for high-risk sources, whether anticoagulation or surgery, is better established than for disease is absent. Treatment for high-risk sources, whether anticoagulation or surgery, is better established than for disease is absent. Treatment for high-risk sources, whether anticoagulation or surgery, is better established than for disease.

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