Clinical management of patients with acute stroke and the approach used for secondary prevention depends upon clarification of pathogenesis. Although most strokes are a consequence of cerebrovascular disease, ∼15% to 20% of ischemic (nonhemorrhagic) strokes have been attributed to cardiogenic embolism. In practice, determination of the stroke mechanism is fraught with uncertainty, particularly when the possibility of thromboembolism emanating from atherosclerotic lesions in the aorta or cervical arteries is considered. When cardiogenic embolism is suspected, cardiac ultrasound is the principal method used to identify the potential source. The finding of left atrial enlargement has been shown to bear a significant relationship to the risk of stroke in a multivariate analysis of population-based data from the Framingham Heart Study. The most frequent confounding variable is atrial fibrillation, occurring in >2 million patients in North America and in over half of all patients with cardiogenic embolism. Criteria for selection of patients with acute ischemic stroke for transesophageal echocardiography (TEE) to search for a potential cardiac source of embolism are controversial, particularly because cardiogenic embolism is often an uncertain diagnosis that is inferred merely on the basis of the finding of potential cardiac source. Even after extensive investigation, ∼40% of ischemic stroke patients have no clearly identifiable pathogenesis (cryptogenic stroke). In one study, 62% of patients younger than 60 years of age without an obvious source of cerebral infarction and 23% of those with arterial lesions had potential sources of cardiogenic embolism identified by TEE (P = 0.0007 for the difference).

Among the cardiac anomalies detected by TEE that have been implicated as risk factors for stroke are patent foramen ovale (PFO) and atrial septal aneurysm (ASA). The foramen ovale, a remnant of the fetal circulation, remains patent through adulthood in ∼1 in 4 individuals, allowing right-to-left interatrial shunting whenever the pressure in the right atrium exceeds that in the left atrium. In case-control studies involving patients younger than 55 years of age, the prevalence of PFO was ∼3 times greater (95% CI 2.3 to 4.2) and ASA ∼6 times greater (95% CI 2.5 to 15.2) in patients with unexplained cerebral ischemic events than in the general population. In patients with PFO identified after an episode of symptomatic cerebral ischemia, the combined rate of recurrent stroke and transient ischemic attack is ∼3% per year. A causal relationship between PFO and stroke is not clear, and potential mechanistic links are complex and include paradoxical embolism of thrombus from the peripheral venous system, direct arterial embolism of thrombus from the endocardial surface of the atrial septum, cerebral ischemia related to occult paroxysmal atrial fibrillation, and associated vascular pathology. Patients who have experienced a stroke and in whom PFO and ASA are found tend to be younger, and the neurological deficits they experience tend to be milder than those in stroke patients without these anomalies, suggesting that different stroke mechanisms are involved. Although paradoxical embolism is a favored hypothesis, the relatively low rate of detectable deep venous thrombosis in patients with PFO who suffer stroke argues that another mechanism is operant in many cases.

The Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) by Homma et al. reported in this issue of Circulation is particularly valuable because of its large cohort and prospective design. Patients with a recent ischemic stroke enrolled in the Warfarin-Aspirin Recurrent Stroke Study (WARSS) were randomized to treatment with warfarin or aspirin, and TEE was performed in a subgroup after an alternative cardiogenic source and severe carotid stenosis were excluded. The prevalence of PFO was greater among those with cryptogenic stroke (39.2%) than among those in whom a potential pathogenesis of stroke could be identified (29.9%; P < 0.02); this was particularly true with respect to large PFOs (20.0% versus 9.7%, P < 0.001). No significant difference was found, however, in the rate of recurrent stroke or death over 2 years between those with PFOs of any size and those without PFOs. Furthermore, there were no significant differences in primary event rates between patients randomized to warfarin (mean international normalized ratio [INR] around 2) or aspirin (325 mg/d), regardless of whether the pathogenesis of the index stroke was cryptic or defined. The authors conclude that medical therapy (with either warfarin or aspirin) is protective against death and recurrent stroke in stroke patients with PFO, independent of the size of the defect or the presence of ASA.

In the absence of a placebo control, there is need to interpret the results cautiously in terms of treatment efficacy. Although no superiority of one antithrombotic agent over another was found, the study was not designed to evaluate their therapeutic equivalence. This was true as well for the primary analysis of the main WARSS trial, from which the
PICSS cohort was derived. There was no advantage of warfarin over aspirin for prevention of recurrent strokes that were predominantly of arterial origin. Death was a key end-point variable, and the mortality rate was high in this population of stroke victims, indicating that the causes of death were not generally responsive to either of the anti-thrombotic strategies employed. The reader is left without information about the relative efficacy of warfarin compared with aspirin for the prevention of mortality.

The inherent complexity of potential stroke mechanisms in patients with developmental abnormalities of the interatrial septum is also germane. Paradoxical embolism of thrombus from a peripheral venous source is pathogenically analogous to cardiogenic embolism in patients with atrial fibrillation and is theoretically more likely to respond better to anticoagulation with warfarin than to administration of aspirin, a platelet inhibitor.19 In fact, the lack of superiority of warfarin over aspirin in the PICSS is indirect evidence that thromboembolism related to atrial arrhythmias or venous disease was perhaps not the predominant mechanism of stroke in patients with PFO. In contrast to a previous study that found a higher rate of recurrent stroke in patients with both PFO and ASA,9 Homma and colleagues found no such multiplicative effect on risk, nor was there a relationship between the size of the intracardiac shunt and risk of recurrent stroke. Furthermore, vascular mechanisms to explain the apparent association of stroke with PFO cannot be discounted. An example is the independent association of PFO with migraine (an association that is even stronger when ASA is also present), suggesting either a common genetic predisposition17,18 or, hypothetically, transmission across the atrial septum into the arterial circulation of vasoactive substances that would otherwise have been deactivated in the pulmonary circulation.19

With regard to the implication that medical therapy is protective against recurrent stroke and death, the antithrombotic approach was not compared to interventions directed at the protective approach was not compared to interventions directed at the antithrombotic strategy. Thus, although transcatheter closure of PFO by surgical and percutaneous catheter–based methods has been proposed as an alternative to anticoagulation in patients with suspected paradoxical embolism. In uncontrolled studies, low (but not negligible) rates of recurrent stroke have typically been reported.20,21 Comparisons between these observations are hampered by factors affecting case selection. Thus, although transcatheter closure of PFO represents an effective alternative therapy for prevention of presumed paradoxical embolism, further studies are needed to identify the patients most likely to benefit from this intervention with regard to surgery or long-term anticoagulation. Pending data from properly designed randomized trials, we recommend closure of PFO in younger stroke survivors with no other apparent source of embolism when either recurrent ischemia has occurred during anticoagulant therapy or a contraindication to anticoagulant therapy exists. Such intervention seems most appropriate for patients in whom brain imaging suggests multiple or recurrent small infarcts, where thrombus has been identified in the veins of the lower extremities, and when there was a temporal relationship between the onset of cerebral ischemic symptoms and elevation of right atrial pressure (eg, Valsalva strain).

Despite considerable progress, the clinician is left with a great deal of uncertainty in the management of patients with cryptogenic stroke in whom a PFO or ASA is identified by TEE or other imaging modalities. To the extent that abnormalities of the endocardial surface of the interatrial septum may be a nidus for activation of platelets, aspirin may be sensible. On the other hand, warfarin may be more useful for stasis-related thrombi originating in the cardiac chambers or the peripheral venous system. Mainly on the basis of its efficacy against thrombus formation and embolism across a wide range of thrombogenic mechanisms, we still favor warfarin anticoagulation as the main approach for secondary prevention when another cardiac or arterial source cannot be identified. A meta-analysis found warfarin superior to anti-platelet therapy in preventing recurrent ischemic events (OR 0.37, 95% CI 0.23 to 0.60) and surgical PFO closure comparable to anticoagulation (OR 1.19, 95% CI 0.62 to 2.27).22

As in all cases of suspected embolism in the cardiovascular system, it is still important to search not only for the conduit but also for a potential source. When paradoxical embolism is the presumed mechanism, a peripheral venous thrombus should be considered as the source, most commonly in the deep veins of the lower extremities or the pelvis. Because a relatively small embolus can completely occlude a major cerebral vessel, this requires use of the most sensitive test available for clot detection. The association of ischemic events with hypercoagulable states calls, in some cases, for detailed hematologic testing as well, including a search for markers of thrombogenicity, because failure to provide adequate systemic antithrombotic prophylaxis on a long-term basis predisposes patients to ongoing risk.23 In such cases, the finding of a PFO or other intracardiac structural anomaly may lead to mistaken conclusions about stroke mechanisms and treatment, which is akin to incriminating a suspect on the basis of the findings of a victim and a bullet hole without actually locating the weapon.

References


**KEY WORDS:** Editorials stroke anticoagulants embolism shunt
Patent Foramen Ovale and Recurrent Stroke: Another Paradoxical Twist
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Circulation. 2002;105:2580-2582
doi: 10.1161/01.CIR.0000020353.63751.2F
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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