

CLINICAL PRACTICE

Patent Foramen Ovale in Young Adults with Unexplained Stroke

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 38-year-old man notes abrupt loss of vision in his right visual field while reading. He has no significant medical history and reports that he neither smokes nor uses alcohol or illicit drugs. Physical examination reveals right homonymous hemianopia but no other abnormalities. Magnetic resonance imaging reveals acute left occipital infarction and normal head and neck vessels. Transesophageal echocardiography shows a patent foramen ovale without atrial septal aneurysm. What are the implications of this finding, and what therapy should be recommended?

THE CLINICAL PROBLEM

Stroke is a leading cause of death and long-term disability worldwide. Eighty-five percent of strokes are ischemic, and most ischemic strokes occur in persons older than 65 years of age in tandem with the development of atherosclerosis. Although a minority of ischemic strokes in the community affect younger adults,¹ as many as half the patients referred to tertiary care centers are younger than 65 years of age, and up to 12 percent are younger than 45 years.² Young patients with ischemic stroke often have few, if any, risk factors for atherosclerosis.³ Initial evaluation of the cerebral arteries is essential but frequently unrevealing, and thus in many cases the focus must shift to the detection of potential cardiac sources of embolism that are commonly associated with, and that may cause, unexplained stroke in young persons.⁴

In as many as 43 percent of affected young adults, strokes are cryptogenic (i.e., they do not have a definite cause despite extensive evaluation).¹ The most prevalent potential source of cardioembolism in young adults with cryptogenic stroke is patent foramen ovale, which is detected in more than half of such persons undergoing evaluation.⁵ This discussion focuses principally on patent foramen ovale occurring in young patients (those younger than 45 years old) or middle-aged patients (those 45 to 64 years old) who have minimal risk factors for atherosclerosis and in whom evaluations for vascular disease or systemic illnesses are negative. Other potential sources of cardioembolism in these patients are described in Table 1.

PATENT FORAMEN OVALE AND THE RISK OF STROKE

Patent foramen ovale, which is present in 27 percent of unselected adults,¹⁶ is a vestige of the fetal circulation and results from failure of the primum and secundum septa to fuse postnatally.¹⁷ Persistence of the one-way flap valve overlying the fossa ovalis allows right-to-left blood flow when right atrial pressure exceeds left atrial pressure (Fig. 1).¹⁷

In support of the proposition that patent foramen ovale can serve as a gateway to the arterial circulation for venous thromboemboli, various studies have documented thrombus straddling the foramen in patients with deep-vein thrombosis and systemic em-

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Table 1. Overview of Potential Cardiac Sources of Embolism Other Than Patent Foramen Ovale.*

Potential Source	Description	Associated Conditions and Risk Factors	Prevalence	Estimated Risk of Stroke	Possible Interventions and Evidence for Reduction in Risk of Stroke	References
Benign cardiac tumors			Patients with Cryptogenic Stroke			
Myxoma	Neoplasm arising from endocardium, typically in left atrium (70%), where it is attached to fossa ovalis; usually polypoid and attached by pedicle, but may be papillary with gelatinous, fragile extensions	May be sporadic or familial, as part of the Carney complex	<2%	High, but not quantifiable; one third of persons with myxoma present with systemic embolism; increased risk of papillary myxomas [†]	Surgical resection; anticoagulant or antiplatelet therapy of questionable benefit (no controlled data, but resection is required to eliminate risk of tumor-related embolism; tumor recurrence can occur, however, particularly in the Carney complex)	Reynen ^{6,7}
Papillary fibroelastoma (giant Lambli's excrescence)	Process of unclear cause (neoplastic, hamartomatous, or reparative); arises from valvular surfaces, typically left-sided valves (more often aortic than mitral); frondlike vs. circumscribed appearance; often a stalklike attachment	Unknown	Very low [‡]	Not quantifiable, but appears to be directly proportional to size and mobility [†]	Surgical resection vs. antiplatelet or anticoagulant therapy (no controlled data, but consensus is that larger [≥ 1 cm], mobile lesions warrant surgical resection)	Reynen, ⁷ McAllister and Fenoglio ⁸
Valvular strands (Lambli's excrescences)	Small filiform projections (width ≤ 1 mm, length ≤ 10 mm); arise near closure line of valves (mitral more often than aortic); result from traumatic abrasions of valve surface with fibrin deposition and endothelialization	Possibly age; intrinsic valvular disease; first described as a feature of rheumatic valve disease	38.8%	HR for recurrent stroke or death, 0.59; 95% CI, 0.08–4.43 (in older population with cryptogenic stroke) [‡]	Antiplatelet therapy (no evidence that anticoagulation is superior to antiplatelet therapy in reducing recurrent stroke or death)	Homma et al., ⁹ Meissner et al. ¹⁰

Mitral-valve prolapse	Myxomatous degeneration of valve leaflets with billowing >2 mm past the annular plane in systole; malcoaptation results in mitral regurgitation	Connective-tissue disorders (Marfan's and Ehlers-Danlos syndromes); genetic; volume depletion; mitral regurgitation leading to left atrial and ventricular enlargement; atrial fibrillation, and need for mitral-valve surgery; relation to interatrial septal abnormalities	2.8% (<45 yr with stroke or TIA)	2.4% (2.7% in women and 2.1% in men; mean age, 56 yr)	Younger age: OR for stroke or TIA, 1.06 (95% CI, 0.11–5.73) in patients <45 yr; 0.4% risk of TIA (0 strokes) at 10 yr and RR, 1.7 (95% CI, 0.4–9.5) in patients <50 yr vs. community-based rates. Older age: 16% risk of stroke or TIA and RR, 2.3 (95% CI, 1.5–3.3) in patients ≥50 yr vs. community-based rates. Risk related to leaflet thickness and severity of mitral regurgitation, with incident atrial fibrillation and mitral-valve surgery responsible in large measure for incident cerebral ischemia¶	Antiplatelet therapy, with anticoagulant therapy as an alternative (no controlled data to support added benefit of anticoagulation therapy); valve repair or replacement in setting of severe regurgitation, as indicated	Gilon et al., ¹¹ Freed et al., ¹² Avierinos et al. ¹³
Intrapulmonary shunt	PAVM	HHT; liver disease	Very low‡	Not quantified (70% in patients with HHT; conversely, 25% of patients with HHT have PAVM)	Not quantifiable, but appears substantial for PAVM ≥3 mm‡	Percutaneous coil embolization for PAVM ≥3 mm in diameter; anticoagulation is alternative option for large PAVM (no controlled data)	Moussouttas et al. ¹⁴
Aortic-arch thrombosis	Thrombus attached to simple atheroma in the aortic arch, which otherwise exhibits no or minimal evidence of atherosclerotic disease	Risk factors for atherosclerosis; possibly hypercoagulable states	Very low‡	Not quantified	High, but not quantifiable¶	Anticoagulant therapy; surgical embolectomy with patch repair and percutaneous balloon embolectomy are alternatives (no controlled data)	Laperche et al. ¹⁵

* The information shown is limited to cardioembolic sources in patients with normal sinus rhythm and no or minimal atherosclerosis; without ischemic, valvular, or congenital heart disease; and without systemic inflammatory states, cancer, or infection. HR denotes hazard ratio, CI confidence interval, TIA transient ischemic attack, OR odds ratio, RR relative risk, HHT hereditary hemorrhagic telangiectasia, and PAVM pulmonary arteriovenous malformation.

† The available data are based on case series and case reports.

‡ Prevalence is well below 1 percent, but precise estimation was not possible.

§ The available data are based on case-control studies. These data showed an association, which was not reproduced in longitudinal studies or in a substudy of a randomized trial of aspirin as compared with warfarin for noncardioembolic stroke, although the latter studies had limited power.

¶ Early reports of an association in persons younger than 45 years of age used an older, less specific, definition of mitral-valve prolapse; the data have not been confirmed according to an updated definition, but studies are underpowered.

|| The available data are based on a single case series.

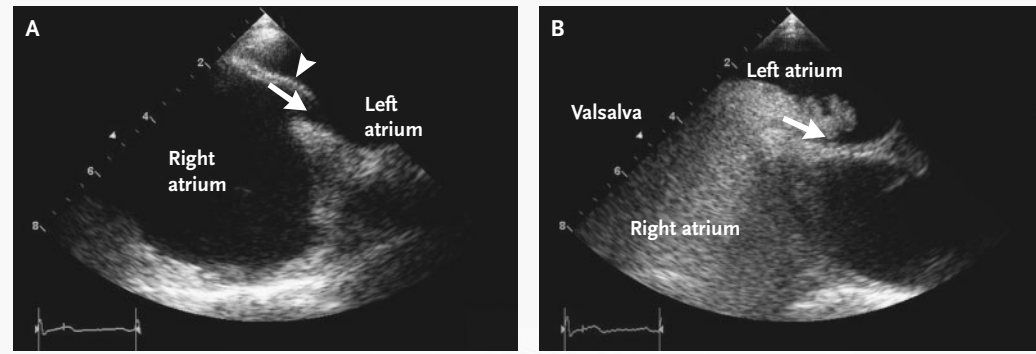


Figure 1. Transesophageal Echocardiograms of a Patent Foramen Ovale.

In Panel A, a transesophageal echocardiogram in the longitudinal plane shows a separation (arrow) between the primum septum (arrowhead) and the secundum septum — a finding consistent with the presence of patent foramen ovale. Panel B shows a transesophageal echocardiogram, also in the longitudinal plane, obtained during the injection of agitated-saline contrast material through an antecubital vein with use of the Valsalva maneuver. There is complete opacification of the right atrium, and passage of a cloud of bubbles (arrow) between the primum and secundum septa into the left atrium is visible.

bolism.¹⁷ Such “thrombus-in-transit,” however, is rarely detected in patients with stroke and patent foramen ovale, and the clinical diagnosis of paradoxical embolism instead depends on the concurrence of arterial embolism, venous thrombosis, interatrial communication, and a gradient favoring right-to-left shunting.¹⁸

An important role for patent foramen ovale in the pathogenesis of ischemic stroke was first suggested by a case-control study that showed a markedly higher frequency of patent foramen ovale (detected by transthoracic echocardiography) in patients with cryptogenic stroke who were younger than 55 years of age than in controls (54 percent vs. 10 percent).⁵ A meta-analysis of case-control studies subsequently confirmed an increased prevalence of patent foramen ovale among patients 55 years of age or younger with cryptogenic stroke as compared with stroke-free controls (odds ratio, 5.01; 95 percent confidence interval, 3.24 to 7.75)¹⁹ but not among persons 55 years of age or older (odds ratio, 1.20; 95 percent confidence interval, 0.56 to 2.56).¹⁹

Many of these studies, however, lacked blinded interpretation of echocardiograms — a limitation that may have led to ascertainment bias. Furthermore, the studies compared patients and controls who had been referred for echocardiography for

different indications and hence were susceptible to biases related to varying thoroughness in the assessment of patent foramen ovale or associated anatomical features. Nevertheless, a significant association between patent foramen ovale and cryptogenic stroke has since been documented in a prospective clinical trial in which ascertainment of patent foramen ovale was made without knowledge of the participants’ clinical history.²⁰

Despite this association, the etiologic role of patent foramen ovale in cryptogenic stroke has been questioned.²¹ Paradoxical embolism, the presumptive mechanism, requires a favorable pressure gradient for right-to-left shunting, but such a gradient normally occurs only transiently, in early systole.²² Moreover, conditions that promote right-to-left shunting, such as pulmonary hypertension or Valsalva-inducing activities, are rarely documented in patients with stroke who have patent foramen ovale.²¹

In addition, evaluation of patients with cryptogenic stroke and patent foramen ovale rarely reveals a venous source of thrombus.²¹ The reportedly low rate of detection of deep-vein thrombosis, however, may reflect delays in imaging, which often was performed after the initiation of anticoagulation.²³ Furthermore, the absence of a detectable venous thrombus is not unique to patients with

stroke and patent foramen ovale. In 20 to 30 percent of patients with pulmonary embolism, deep-vein thrombi are not identified.²⁴ Failure to detect a thrombus in such patients may be attributable to complete thrombus migration, inability to detect residual thrombus, or undetected thrombosis in a calf or pelvic vein. In a venographic study involving 42 patients with arterial embolism and patent foramen ovale, deep-vein thrombosis was documented in 24 of the patients; in 13, thrombosis was identified only in calf veins.²³ This finding raises the possibility that calf-vein thrombi, which must generally extend proximally before causing clinically important pulmonary embolism,²⁴ may be able to discharge small embolic fragments (1 mm in diameter) that are sufficient to cause a clinical stroke should they gain access to the arterial circulation.²⁵ In another study, pelvic-vein thrombi were documented by magnetic resonance venography in 20 percent of patients with cryptogenic stroke who had patent foramen ovale.²⁶

Nevertheless, the difficulty of confirming the occurrence of paradoxical embolism has led to the consideration of alternative explanations, such as in situ thrombosis or atrial tachyarrhythmia. The former, however, is very rarely found by transesophageal echocardiography or at autopsy.²⁷ Moreover, although patients with interatrial septal abnormalities and stroke have lower thresholds for the induction of atrial fibrillation,²⁸ this arrhythmia is almost never documented in patients with cryptogenic stroke and patent foramen ovale.²¹

Adding to the mechanistic uncertainty, population-wide figures suggest that the yearly risk of cryptogenic stroke in healthy persons with patent foramen ovale may be as low as 0.1 percent.²⁹ This observation suggests that additional factors may be necessary to increase the associated risk of stroke. Features of the patent foramen ovale may be important. A large anatomical separation (4 mm or more) between the primum and secundum septa,³⁰ increased right-to-left shunting³¹ or shunting at rest,³² increased septal mobility,³² and the presence of an atrial septal aneurysm³³ have been linked to an increased risk of stroke, but ascertainment bias remains possible. Moreover, the clinical relevance of patent foramen ovale is influenced by concurrent risk factors for venous thromboembolism, such as trauma, recent surgery, use of oral contraceptives, and hypercoagulable states.¹⁸

ATRIAL SEPTAL ANEURYSM

The prevalence at autopsy of atrial septal aneurysm, caused by redundancy of the interatrial septum (Fig. 2), is 1 percent.³⁴ A relation between atrial septal aneurysm and stroke has been documented,¹⁹ with one study reporting a greater prevalence among persons with stroke (7.9 percent) than among population-based controls (2.2 percent) on transesophageal echocardiography.³⁵ Detection of thrombi in situ on the interatrial septum led to the notion that the redundant membrane promotes thrombogenesis,³⁶ but in situ thrombosis is seen only rarely.³⁷ Alternative explanations for the increased risk of stroke in patients with atrial septal aneurysms are the high prevalence (50 to 90 percent) of coexisting patent foramen ovale, especially larger foramina, or of an atrial septal defect³⁵⁻³⁷ (as shown in Video Clip 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). Moreover, atrial septal aneurysms are associated with prominent eustachian valves or Chiari networks, right atrial membranes that facilitate right-to-left shunting by directing flow from the inferior vena cava toward the fossa ovalis,³⁸ and with tachyarrhythmias predisposing to thromboembolism.²⁸

STRATEGIES AND EVIDENCE

EVALUATION

Transesophageal echocardiography is superior to transthoracic echocardiography for the detection of potential sources of cardioembolism.⁴ Although transthoracic echocardiography identifies such sources in about 25 percent of patients with clinically apparent cardiac disease, its yield in patients without cardiac signs or symptoms is less than 10 percent.³⁹ By contrast, transesophageal echocardiography detects potential sources of cardioembolism in as many as 57 percent of patients with unexplained stroke.³⁹ Intravenous injection of saline mixed with air greatly enhances the diagnosis of right-to-left shunts by transthoracic or transesophageal echocardiography by permitting visualization of microbubbles in the chambers of the left side of the heart that would otherwise be filtered by the lung capillaries.¹⁷ The sensitivities of traditional transthoracic echocardiography with agitated-saline contrast agent for right-to-left shunts⁴⁰ and atrial septal aneurysm are at

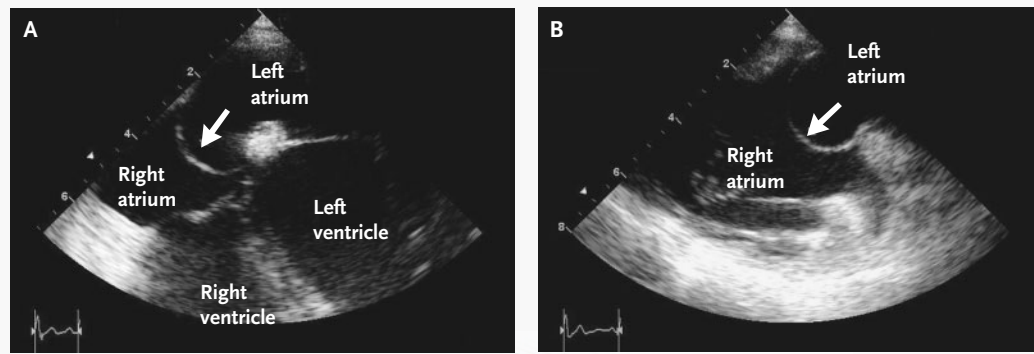


Figure 2. Transesophageal Echocardiograms of an Atrial Septal Aneurysm.

In Panel A, a transesophageal echocardiogram (in the horizontal plane) shows an atrial septal aneurysm protruding into the right atrium (arrow). Atrial septal aneurysm is defined as either sustained bowing of a 15-mm segment of interatrial septal membrane in the fossa ovalis of at least 11 mm (or at least 15 mm by a more conservative definition) beyond the plane of the interatrial septum or as phasic excursion to either side totaling the same distance. Panel B shows a transesophageal echocardiogram showing the same atrial septal aneurysm (arrow) viewed in the longitudinal plane.

most half those of contrast-based transesophageal echocardiography,³⁷ but recent refinements (for example, a contrast-based transmitral Doppler technique) have improved its diagnostic accuracy.¹⁷ Another alternative, contrast transcranial Doppler sonography, in which imaging of the middle cerebral arteries is used to detect right-to-left shunting of microbubbles, offers accuracy similar to that of transesophageal echocardiography.¹⁷ Its utility, however, is limited by its inability to assess interatrial septal morphologic features or other cardiac structures. Although transesophageal echocardiography is semi-invasive, it is associated with a low risk of serious complications (0.2 percent), which may include bronchospasm, hypoxia, arrhythmias, upper gastrointestinal trauma, or bleeding.⁴¹

Formal analyses of the optimal use of echocardiography in young patients with cryptogenic stroke are lacking. Nevertheless, the increased diagnostic yield of transesophageal echocardiography as compared with that of transthoracic echocardiography or transcranial Doppler sonography supports the use of the transesophageal technique in this population, pending further evidence regarding the benefits of treating specific lesions found on echocardiography.

TREATMENT

The available evidence on pharmacologic approaches (involving the use of antiplatelet or anticoagulant

agents) and mechanical approaches to secondary prevention in patients with cryptogenic stroke who have patent foramen ovale is inadequate for assessment of their relative merits. To date, no study has randomly assigned patients with cryptogenic stroke and patent foramen ovale to different therapies. Studies thus far have been observational, with disparate definitions of the qualifying or recurrent cerebrovascular event, nonuniform criteria for interatrial septal abnormalities, absence of blinding during examination of echocardiograms or ascertainment of end points, and incomplete accounting of associated risk factors or the use of adjunctive therapies.

The risk of stroke recurrence in patients 60 years of age or younger who have unexplained cerebral ischemia and patent foramen ovale appears to be low, regardless of the therapy used. In a prospective study of 140 such patients treated medically or surgically at their physicians' discretion, the annual rate of stroke recurrence was 1.9 percent, and the type of treatment had no detectable influence.⁴² Similarly, a longitudinal study of 581 persons 55 years of age or younger who had cryptogenic stroke treated with aspirin found similarly low rates of recurrence at four years among those who had a patent foramen ovale (2.3 percent) and those who did not (4.2 percent).³³ Patients who had both patent foramen ovale and atrial septal aneurysm, however, had a 15.2 percent rate of recurrence despite the use of aspirin therapy — a rate nearly fourfold that

among patients who did not have either abnormality. Unlike prior investigations, this study found that a greater shunt magnitude was not associated with increased risk, but the study had limited power to assess the relative effects of foraminal size and atrial septal aneurysm.³³

By contrast, in a randomized trial in which aspirin therapy and warfarin therapy were compared in older patients with stroke, the two-year rate of recurrent stroke or death in the subgroup with cryptogenic stroke was not significantly higher among those who had a patent foramen ovale and atrial septal aneurysm than among those with neither abnormality.³⁸ However, the study was underpowered for this comparison, and patients without interatrial septal abnormalities had more risk factors²⁰ for subclinical atherosclerotic disease than did those with those abnormalities. Post hoc analyses⁴³ of data from this study indicated that there was no significant association between patent foramen ovale and the risk of recurrent stroke or death among patients younger than 65 years of age but an association was observed in older patients. These findings, however, are limited by the small numbers of events in each subgroup and by the performance of multiple comparisons that were not prespecified.

Medical Therapy

In a retrospective study of 90 patients younger than 60 years of age with cerebral ischemia, 52 of whom had patent foramen ovale, those receiving aspirin or no therapy had a rate of recurrence almost threefold that of patients treated with warfarin.⁴⁴ (The numbers were too small to allow comparison between the group that received aspirin and the group that did not receive therapy.) The results are inconclusive, however, for several reasons: treatment assignments were at the discretion of the consulting neurologist; treatment crossover was frequent; and ascertainment of end points, which included multiple events, was not blinded. For similar reasons, it is impossible to draw firm conclusions from a meta-analysis that found that warfarin (as compared with antiplatelet therapy) lowered the risk of recurrence (odds ratio, 0.37; 95 percent confidence interval, 0.23 to 0.60) among patients with cerebral ischemia and patent foramen ovale.⁴⁵ In a randomized trial, subgroup analysis of 98 patients with cryptogenic stroke and patent foramen ovale revealed a nonsignificant reduction in the two-year incidence of recurrent stroke or death with warfarin

therapy as compared with aspirin therapy (9.5 percent vs. 17.9 percent; hazard ratio, 0.52; 95 percent confidence interval, 0.16 to 1.67), but the power of the analysis was limited.²⁰ Although the incidence of major hemorrhage did not differ between warfarin and aspirin (1.78 vs. 1.91 events per 100 patient-years, $P=1.0$), warfarin did increase the rate of minor hemorrhage (22.9 vs. 8.66 events per 100 patient-years, $P<0.001$).²⁰

Mechanical Closure

The traditional approach to foraminal closure involves open thoracotomy. Reported case series are small, but the rate of postoperative stroke ranges from 0 to 3.5 percent⁴⁶⁻⁴⁸ at two years. The mortality associated with closure of an uncomplicated atrial septal defect is less than 1.5 percent.⁴⁹ Perioperative risks also include atrial fibrillation, pericardial sequelae, and the need for reexploration because of bleeding.⁴⁶⁻⁴⁸ Minimally invasive surgery⁵⁰ is an alternative approach, but percutaneous-closure techniques hold greater appeal (Fig. 3). A systematic review found that among 1355 patients undergoing percutaneous closure, the rate of recurrent stroke or transient ischemic attack was 0 to 4.9 percent at one year.⁵¹ Although these values appeared favorable next to one-year recurrence rates among 895 patients receiving medical therapy (3.8 to 12.0 percent),⁵¹ several considerations — the nonrandomized treatment assignment, differences in the clinical characteristics of the patients treated by the various techniques, and inconsistent criteria for ascertainment of outcomes — preclude meaningful comparison. Serious complications of percutaneous closure (major hemorrhage, cardiac tamponade, the need for surgery, pulmonary embolism, and death) were reported in 1.5 percent of the patients, and minor complications (arrhythmia, device fracture or embolization, air embolism, femoral hematoma, and fistula) in 7.9 percent.⁵¹

In one follow-up study of young patients with cryptogenic stroke and patent foramen ovale, surgical closure was performed if at least two of four purported “high-risk” features for paradoxical embolism (major shunt [>50 bubbles], atrial septal aneurysm, infarcts in multiple territories, and Valsalva-provoking activity preceding the onset of stroke⁴²) were present. There were no recurrences after 23 months, but the study did not include a control group.⁴⁶ A decision analysis modeling different therapeutic approaches in a 55-year-old

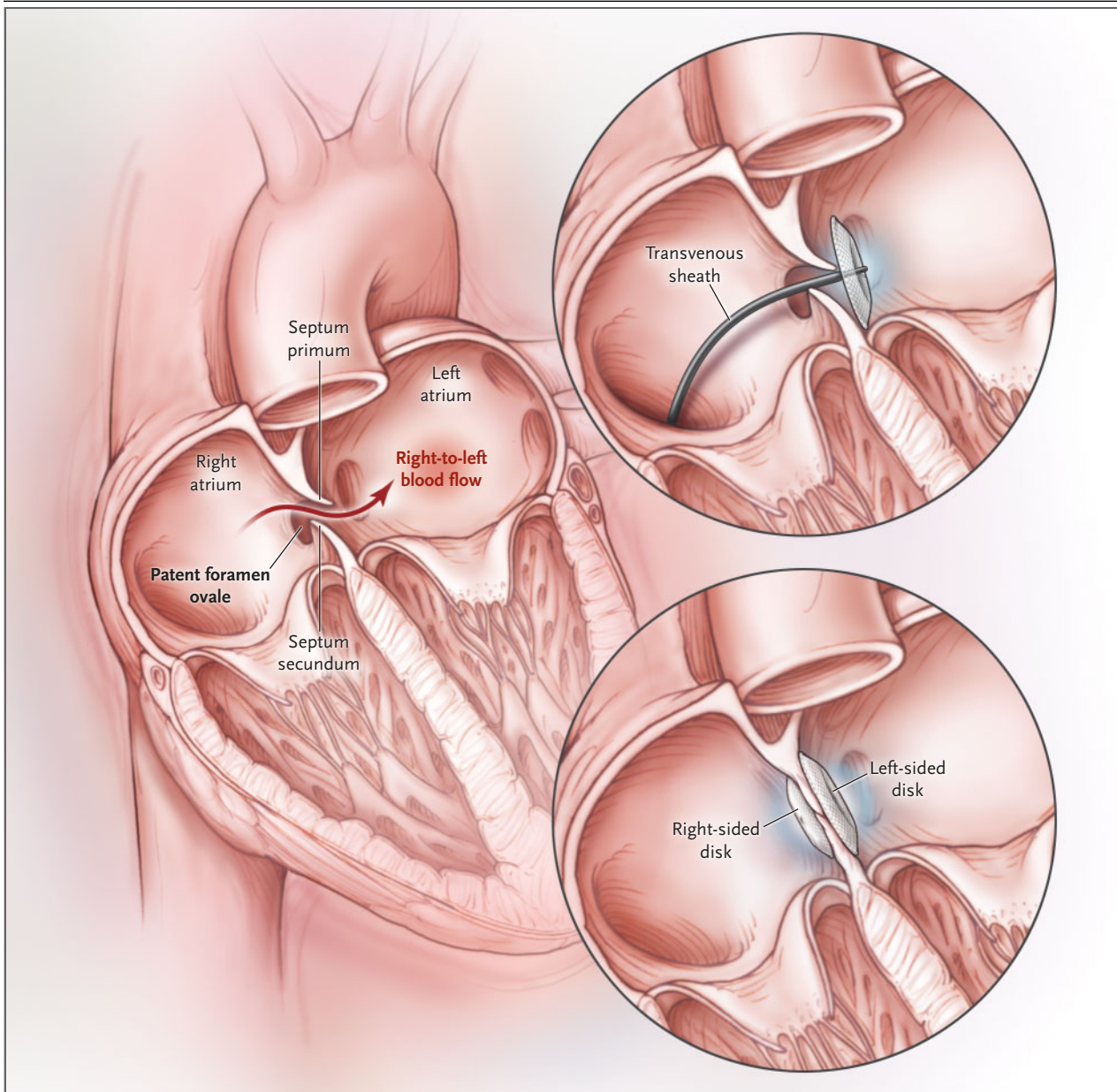


Figure 3. Percutaneous Closure of a Patent Foramen Ovale.

With use of a femoral approach, a transvenous sheath is advanced across the foramen into the left atrium, where a folded disk is expanded and pulled back, apposing the primum and secundum septa closed. This step is followed by deployment of a right-sided disk, at which time the two-disk device is released. Clopidogrel and aspirin are recommended for a period of three months to prevent thrombus formation on the device, with aspirin therapy continued for an additional three months, when endothelialization is complete. Antibiotic prophylaxis for six months is recommended. Complete late closure of the foramen has been reported in 80 to 95 percent of patients.

patient with patent foramen ovale concluded that, for a yearly risk of stroke recurrence of 0.8 percent, surgical closure or warfarin were the best options.⁴⁹ (Percutaneous closure was not considered.) Surgery became preferable when the annual risk of

recurrence reached 1.4 percent. These conclusions, however, rest on the questionable assumptions that paradoxical embolism underlies the risk of stroke and that anticoagulation lowers the risk of recurrence to the same degree as it does in persons with

Table 2. Guidelines from Professional Societies.*

Purpose and Technique	American College of Cardiology/ American Heart Association/ American Society of Echocardiography ⁵³	American Academy of Neurology ⁵⁴	American College of Chest Physicians ⁵⁵
Diagnosis			
Echocardiography (TTE or TEE)	Class I: younger patients (typically <45 yr) with cerebrovascular events; older patients (typically >45 yr) with neurologic events without evidence of cerebrovascular disease or other obvious cause; patients for whom a clinical therapeutic decision (e.g., anticoagulation) will depend on results of echocardiography†	Combination of patent foramen ovale and atrial septal aneurysm may confer increased risk of subsequent stroke in medically treated patients <55 yr; thus, in younger patients with stroke, studies that can identify patent foramen ovale or atrial septal aneurysm may be considered for prognostic purposes (level C)‡	—
TTE vs. TEE	No specific recommendations. When positive, TTE considered sufficient for diagnosis of mitral stenosis, dilated cardiomyopathy, left ventricular aneurysm, left ventricular thrombus, mitral-valve prolapse, vegetation, or atrial septal defect. But TEE may be additive when TTE is negative. TEE required primarily or alone for diagnosis of left atrial thrombus, left atrial spontaneous contrast, atrial septal aneurysm, patent foramen ovale, or aortic atheroma	—	No specific recommendations. TEE more sensitive than TTE for detecting cardioembolic sources, particularly when searching for left atrial sources, atrial septal defects, and aortic atheroma
Management			
Patent foramen ovale	—	Evidence insufficient to determine whether warfarin or aspirin is superior in preventing recurrent stroke or death (level U),§ but minor bleeding is more frequent with warfarin (level C)‡; there is insufficient evidence to evaluate the efficacy of surgical or endovascular closure (level U)§	—
Patent foramen ovale alone	—	—	Antiplatelet therapy recommended over no therapy (grade 1C+) and antiplatelet therapy suggested over warfarin (grade 2A)¶
Patent foramen ovale in combination with other risk factors (e.g., hypercoagulability or atrial septal aneurysm)	—	—	Inadequate data available to allow recommendation of optimal medical therapy (anticoagulation or antiplatelet therapy) vs. endovascular or surgical closure
Patent foramen ovale with concomitant deep-vein thrombosis or pulmonary embolism	—	At least 3 mo of anticoagulation	Anticoagulation recommended

* Dashes indicate that no recommendations are provided. TTE denotes transthoracic echocardiography, and TEE transesophageal echocardiography.

† Class I indicates that there is evidence, general agreement, or both that a given procedure or treatment is useful or effective.

‡ Level C indicates that the recommendation or statement is qualified as possible.

§ Level U indicates that the data are inadequate or conflicting. Given current knowledge, the treatment is unproven.

¶ Grade 1C+ indicates a strong recommendation; experts are very certain that the benefits of therapy do outweigh the risks, burdens, and costs on the basis of overwhelming evidence from observational studies. Grade 2A is a weaker recommendation, qualified as a suggestion, and is based on consistent results from randomized clinical trials.

venous thromboembolism or atrial fibrillation. Currently, the Food and Drug Administration allows the use of transcatheter-closure devices under a humanitarian device exemption only in cases of recurrence of stroke during therapeutic oral anticoagulation.⁵²

AREAS OF UNCERTAINTY

The pathogenesis of cryptogenic stroke in patients with interatrial septal abnormalities is not well understood. Features of the interatrial septum that best predict the risk of thromboembolism and the role of hypercoagulable disorders in determining risk also remain unclear. Data from ongoing randomized trials that evaluate warfarin, aspirin, or both as compared with transcatheter closure are needed. Pending completion of such studies, which have been hampered by slow recruitment,⁵² the relative safety and efficacy of these approaches remain uncertain.

GUIDELINES

Current guidelines from professional societies (Table 2) do not include specific recommendations regarding the optimal diagnostic strategy for transthoracic and transesophageal echocardiography.⁵³ Moreover, they deem the available evidence insufficient to permit firm recommendations for the management of interatrial septal abnormalities.^{54,55}

CONCLUSIONS AND RECOMMENDATIONS

In patients with cryptogenic stroke, assessment for patent foramen ovale and other potential cardiac

sources of embolism is recommended; transesophageal echocardiography is more sensitive for detecting these abnormalities than is transthoracic echocardiography. Because the presumed pathophysiology of cryptogenic stroke in younger patients with patent foramen ovale is paradoxical embolism of fibrin-rich thrombus, and because observational data suggest a benefit with warfarin relative to aspirin, we would consider the use of warfarin anticoagulation for three to six months in patients such as the man described in the vignette. Available data are not sufficient for confirmation that this approach is preferable to aspirin therapy, however, and current guidelines do not specifically recommend one over the other.^{54,55} Appropriate investigation for deep-vein thrombosis and thrombophilia is essential. We recommend switching most patients' therapy to aspirin after they have received a course of warfarin. However, we favor long-term anticoagulation in patients with associated venous thromboembolism or selected hypercoagulable states and probably in patients with high-risk features (atrial septal aneurysm, major shunt, infarcts in multiple territories, or antecedent Valsalva-provoking activity).

Decisions must take into account coexisting conditions and the patients' preferences. Patients should be encouraged to participate in ongoing randomized trials comparing percutaneous closure and medical therapy. Otherwise, percutaneous closure is currently indicated in the United States only for patients with recurrence despite therapeutic anticoagulation. Surgical closure may be considered for high-risk patients when warfarin is contraindicated.

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REFERENCES

- Leys D, Bandu L, Henon H, et al. Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. *Neurology* 2002;59:26-33.
- Bogousslavsky J, Van Melle G, Regli F. The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. *Stroke* 1988;19:1083-92.
- Kristensen B, Malm J, Carlberg B, et al. Epidemiology and etiology of ischemic stroke in young adults aged 18 to 44 years in northern Sweden. *Stroke* 1997;28:1702-9.
- DeRook FA, Comess KA, Albers GW, Popp RL. Transesophageal echocardiography in the evaluation of stroke. *Ann Intern Med* 1992;117:922-32.
- Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988;318:1148-52.
- Reynen K. Cardiac myxomas. *N Engl J Med* 1995;333:1610-7.
- Idem*. Frequency of primary tumors of the heart. *Am J Cardiol* 1996;77:107.
- McAllister HA Jr, Fenoglio JJ Jr. Tumors of the cardiovascular system. *Atlas of tumor pathology*. 2nd series. Fascicle 15. Washington, D.C.: Armed Forces Institute of Pathology, 1978.
- Homma S, Di Tullio MR, Sciacca RR, Sacco RL, Mohr JP. Effect of aspirin and warfarin therapy in stroke patients with valvular strands. *Stroke* 2004;35:1436-42.
- Meissner I, Whisnant JP, Khandheria BK, et al. Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study. *Mayo Clin Proc* 1999;74:862-9.

11. Gilon D, Buonanno FS, Joffe MM, et al. Lack of evidence of an association between mitral-valve prolapse and stroke in young patients. *N Engl J Med* 1999;341:8-13.
12. Freed LA, Levy D, Levine RA, et al. Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med* 1999;341:1-7.
13. Avierinos JF, Brown RD, Foley DA, et al. Cerebral ischemic events after diagnosis of mitral valve prolapse: a community-based study of incidence and predictive factors. *Stroke* 2003;34:1339-44.
14. Moussouttas M, Fayad P, Rosenblatt M, et al. Pulmonary arteriovenous malformations: cerebral ischemia and neurologic manifestations. *Neurology* 2000;55:959-64.
15. Laperche T, Laurian C, Roudaut R, Steg PG. Mobile thromboses of the aortic arch without aortic debris: a transesophageal echocardiographic finding associated with unexplained arterial embolism. *Circulation* 1997;96:288-94.
16. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984;59:17-20.
17. Kerut EK, Norfleet WT, Plotnick GD, Giles TD. Patent foramen ovale: a review of associated conditions and the impact of physiological size. *J Am Coll Cardiol* 2001;38:613-23.
18. Meacham RR III, Headley AS, Bronze MS, Lewis JB, Rester MM. Impending paradoxical embolism. *Arch Intern Med* 1998;158:438-48.
19. Overell JR, Bone I, Less KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;55:1172-9.
20. Homma S, Sacco RL, Di Tullio MR, et al. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002;105:2625-31.
21. Falk RH. PFO or UFO? The role of a patent foramen ovale in cryptogenic stroke. *Am Heart J* 1991;121:1264-6.
22. Eggebrecht H, Naber CK, Plato C, Erbel R, Bartel T. Analysis of fossa ovalis membrane velocities by transesophageal Doppler tissue echocardiography: a novel approach to functional assessment of patent foramen ovale. *J Am Soc Echocardiogr* 2004;17:1161-6.
23. Stollberger C, Slany J, Schuster I, Leitner H, Winkler WB, Karnik R. The prevalence of deep venous thrombosis in patients with suspected paradoxical embolism. *Ann Intern Med* 1993;119:461-5. [Erratum, *Ann Intern Med* 1994;120:347.]
24. Hirsh J. Diagnosis of venous thrombosis and pulmonary embolism. *Am J Cardiol* 1990;65:45C-49C.
25. Mohr JP. Cryptogenic stroke. *N Engl J Med* 1988;318:1197-8.
26. Cramer SC, Rondorf G, Maki JH, et al. Increased pelvic vein thrombi in cryptogenic stroke: results of the Paradoxical Emboli from Large Veins in Ischemic Stroke (PELVIS) study. *Stroke* 2004;35:46-50.
27. Kasner SE, Chiu D, Grotta J. Stroke and pfo: a role for surgery? *Neurol Net Comm* 1997;1:127-31.
28. Berthet K, Lavergne T, Cohen A, et al. Significant association of atrial vulnerability with atrial septal abnormalities in young patients with ischemic stroke of unknown cause. *Stroke* 2000;31:398-403.
29. Lock JE. Patent foramen ovale is indicted, but the case hasn't gone to trial. *Circulation* 2000;101:838.
30. Schuchlenz HW, Weihs W, Horner S, Quehenberger F. The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. *Am J Med* 2000;109:456-62.
31. Serena J, Segura T, Perez-Ayuso MJ, Basaganyas J, Molins A, Davalos A. The need to quantify right-to-left shunt in acute ischemic stroke: a case-control study. *Stroke* 1998;29:1322-8.
32. De Castro S, Carboni D, Fiorelli M, et al. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke* 2000;31:2407-13.
33. Mas J-L, Arquizán C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med* 2001;345:1740-6.
34. Silver MD, Dorsey JS. Aneurysms of the septum primum in adults. *Arch Pathol Lab Med* 1978;102:62-5.
35. Agmon Y, Khandheria BK, Meissner I, et al. Frequency of atrial septal aneurysms in patients with cerebral ischemic events. *Circulation* 1999;99:1942-4.
36. Hanley PC, Tajik AJ, Hynes JK, et al. Diagnosis and classification of atrial septal aneurysm by two-dimensional echocardiography: report of 80 consecutive cases. *J Am Coll Cardiol* 1985;6:1370-82.
37. Mugge A, Daniel WG, Angermann C, et al. Atrial septal aneurysm in adult patients: a multicenter study using transthoracic and transesophageal echocardiography. *Circulation* 1995;91:2785-92.
38. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Atrial anatomy in non-cardioembolic stroke patients: effect of medical therapy. *J Am Coll Cardiol* 2003;42:1066-72.
39. Rahmatullah AF, Rahko PS, Stein JH. Transesophageal echocardiography for the evaluation and management of patients with cerebral ischemia. *Clin Cardiol* 1999;22:391-6.
40. Di Tullio MR, Sacco RL, Venketasubramanian N, Sherman D, Mohr JP, Homma S. Comparison of diagnostic techniques for the detection of a patent foramen ovale in stroke patients. *Stroke* 1993;24:1020-4.
41. Daniel WG, Erbel R, Kasper W, et al. Safety of transesophageal echocardiography: a multicenter survey of 10,419 examinations. *Circulation* 1991;83:817-21.
42. Bogousslavsky J, Garazi S, Jeanrenaud X, Aebischer N, Van Melle G. Stroke recurrence in patients with patent foramen ovale: the Lausanne Study. *Neurology* 1996;46:1301-5.
43. Homma S, Di Tullio MR, Sacco RL, Sciacca RR, Mohr JP. Age as a determinant of adverse events in medically treated cryptogenic stroke patients with patent foramen ovale. *Stroke* 2004;35:2145-9.
44. Cujec B, Mainra R, Johnson DH. Prevention of recurrent cerebral ischemic events in patients with patent foramen ovale and cryptogenic strokes or transient ischemic attacks. *Can J Cardiol* 1999;15:57-64.
45. Orgera MA, O'Malley PG, Taylor AJ. Secondary prevention of cerebral ischemia in patent foramen ovale: systematic review and meta-analysis. *South Med J* 2001;94:699-703.
46. Devuyst G, Bogousslavsky J, Ruchat P, et al. Prognosis after stroke followed by surgical closure of patent foramen ovale: a prospective follow-up study with brain MRI and simultaneous transesophageal and transcranial Doppler ultrasound. *Neurology* 1996;47:1162-6.
47. Homma S, Di Tullio MR, Sacco RL, Sciacca RR, Smith C, Mohr JP. Surgical closure of patent foramen ovale in cryptogenic stroke patients. *Stroke* 1997;28:2376-81.
48. Dearani JA, Ugurlu BS, Danielson GK, et al. Surgical patent foramen ovale closure for prevention of paradoxical embolism-related cerebrovascular ischemic events. *Circulation* 1999;100:Suppl II:II-171-II-175.
49. Nendaz MR, Sarasin FB, Junod AF, Bogousslavsky J. Preventing stroke recurrence in patients with patent foramen ovale: antithrombotic therapy, foramen closure, or therapeutic abstention? A decision analytic perspective. *Am Heart J* 1998;135:532-41.
50. Deek RK, Thomas RM, Sakiyalak P, Botkin S, Blakeman B, Bakhos M. Minimal access closure of patent foramen ovale: is it also recommended for patients with paradoxical emboli? *Ann Thorac Surg* 2002;74:S1326-S1329.
51. Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med* 2003;139:753-60.
52. Maisel WH, Laskey WK. Patent foramen ovale closure devices: moving beyond equipoise. *JAMA* 2005;294:366-9.
53. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of

the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *Circulation* 2003;108:1146-62.

54. Messe SR, Silverman IE, Kizer JR, et al.

Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2004;62:1042-50.

55. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and throm-

bolytic therapy for ischemic stroke: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:Suppl:483S-512S.

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