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**Percutaneous Device Closure of Patent Foramen Ovale for Secondary Stroke Prevention: A Call for Completion of Randomized Clinical Trials: A Science Advisory From the American Heart Association/American Stroke Association and the American College of Cardiology Foundation The American Academy of Neurology affirms the value of this science advisory.**

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## Percutaneous Device Closure of Patent Foramen Ovale for Secondary Stroke Prevention

### A Call for Completion of Randomized Clinical Trials

### A Science Advisory From the American Heart Association/American Stroke Association and the American College of Cardiology Foundation

*The American Academy of Neurology affirms the value of this science advisory.*

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**Abstract**—The optimal therapy for prevention of recurrent stroke or transient ischemic attack in patients with cryptogenic stroke and patent foramen ovale has not been defined. Although numerous observational studies have suggested a strong association between patent foramen ovale and cryptogenic stroke, a causal relationship has not been convincingly established for the majority of affected patients. Treatment choices include medical therapy with antiplatelet agents or vitamin K antagonists, percutaneous device closure, or open surgical repair. Whereas suture closure of an incidental patent foramen ovale is performed routinely during the course of an operation undertaken for another indication, primary surgical repair is rarely advocated in the current era. The choice between medical therapy and percutaneous device closure has been the subject of intense debate over the past several years, albeit one that has not been adequately informed by randomized, prospective clinical trial data to permit an objective comparison of the relative safety and efficacy of these respective approaches. Enrollment in clinical trials has lagged considerably despite frequent calls for participation from the US Food and Drug Administration and major professional societies. Completion and peer review of ongoing trials are critical steps to establish an evidence base from which clinicians can make informed decisions regarding the best therapy for individual patients. The present advisory strongly encourages all clinicians involved in the care of appropriate patients with cryptogenic stroke and patent foramen ovale—cardiologists, neurologists, internists, radiologists, and surgeons—to consider referral for enrollment in these landmark trials to expedite their completion and help resolve the uncertainty regarding optimal care for this condition. (*Circulation*. 2009;119:2743-2747.)

**Key Words:** AHA Scientific Statements ■ stroke ■ patent foramen ovale ■ aneurysm ■ antiplatelet agents  
■ anticoagulation ■ surgery

Stroke is the third-leading cause of death among adults in the United States and a major contributor to long-term functional impairment and disability.<sup>1</sup> Despite recent advances in diagnosis and treatment, approximately one fifth of

stroke survivors require institutional care 3 months after the index event, and 15% to 30% are permanently disabled.<sup>1</sup> Aggressive measures of primary prevention for at-risk patients are critical, because the majority of strokes are first

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events.<sup>2</sup> Nevertheless, of the estimated 780 000 strokes that occur in the United States each year, 180 000 are recurrent events.<sup>1</sup> Secondary prevention is equally important for survivors of stroke or transient ischemic attack.<sup>3</sup> The 90-day risk of stroke after transient ischemic attack has been estimated at 3% to 17% and is highest within the first 30 days.<sup>1</sup> The incidence of stroke appears to be increasing, and the associated economic costs are staggering. The 2008 estimated direct and indirect cost of stroke is \$65.5 billion, with a mean per capita lifetime cost of \$140 048.<sup>1</sup> The majority of strokes are ischemic; of these, approximately 25% to 40% have no identifiable cause despite a thorough evaluation and are designated as cryptogenic stroke (CS).<sup>4–7</sup> Other causes of ischemic stroke include large-artery atherosclerotic infarction, cardiac embolism, small-vessel disease, or a defined abnormality such as arterial dissection, hypercoagulable state, or sickle cell disease.

A patent foramen ovale (PFO) is a remnant of the fetal circulation and has been identified at autopsy in 27% of patients with normal hearts.<sup>8</sup> In that postmortem series, its prevalence appeared to decline with age. Using contrast transthoracic echocardiography, Di Tullio and colleagues<sup>9</sup> detected a PFO in 14.9% of 1100 stroke-free subjects older than 39 years of age. An atrial septal aneurysm was present in 2.5% of the total patient cohort, most often in association with PFO. Meissner et al,<sup>10</sup> using transesophageal echocardiography, reported a higher 24.3% prevalence rate among 585 randomly sampled Olmsted County, Minnesota, residents 45 years of age or older participating in the Stroke Prevention Assessment of Risk in a Community (SPARC) study. An atrial septal aneurysm was present in 1.9% of subjects, including 4.3% of those with PFOs. The diagnosis of PFO is established by demonstration of an interatrial communication with right-to-left transit of contrast microbubbles within 3 to 4 cardiac cycles of right atrial opacification.<sup>11</sup> An atrial septal aneurysm is defined as a redundant and hypermobile portion of the interatrial septum that demonstrates more than 10-mm excursion from the centerline during the cardiac cycle.<sup>12</sup> A PFO provides an anatomic substrate for paradoxical embolization of thrombus with CS, as convincingly demonstrated in isolated echocardiographic case reports.<sup>13</sup> In most case series, deep venous thrombosis and/or thrombus-in-transit has been identified in only a small minority of patients with PFO and CS, although thrombosis prevalence rates may vary as a function of the screening methods used for detection.<sup>14–16</sup> Other potential mechanisms of CS among patients with PFO include paroxysmal atrial fibrillation (which may not bear any relation to the PFO itself), formation and release of thrombus from the rim of the defect or the left atrial aspect of an associated atrial septal aneurysm, the passage of unmeasured vasoactive humoral substances that escape pulmonary degradation, and causes not related to the defect.<sup>17</sup>

Most but not all observational studies have reported a higher prevalence of PFO among patients with CS than among normal control subjects and/or among patients for whom a cause of stroke could be identified. The association

between PFO and CS has been more convincingly demonstrated for younger (less than 55 years of age) versus older (55 years of age or older) patients. For example, Lamy et al<sup>18</sup> detected a PFO with transesophageal echocardiography in 45.9% of 581 young CS patients. In the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), a PFO was present by transesophageal echocardiography criteria in 33.8% of patients 30 to 85 years of age.<sup>19</sup> PFO was found in 39.2% of CS patients versus 29.9% of patients with a known cause of stroke ( $P<0.02$ ). Handke and colleagues<sup>20</sup> have recently reported a statistical association between PFO and CS for both younger and older (greater than 55 years of age) patients. In their study, the prevalence of PFO was 43.9% among younger CS patients compared with 14.3% among younger patients with stroke of known cause (odds ratio 4.70, 95% confidence interval [CI] 1.89 to 11.68,  $P<0.001$ ) and 28.3% among older CS patients compared with 11.9% among older patients with stroke of known cause (odds ratio 2.92, 95% CI 1.70 to 5.01,  $P<0.001$ ).<sup>20</sup> Prevalence rates of PFO among patients with CS do not equate with the longitudinal risk of stroke among asymptomatic subjects with PFO. In the Northern Manhattan Study (NOMAS), PFO was not associated with increased stroke risk in a multiethnic cohort of both men and women or in patients younger or older than 60 years.<sup>9</sup> PFO was also not a significant, independent predictor of stroke among normal subjects older than 45 years of age in the Olmsted County SPARC study.<sup>10</sup> Although many studies have implicated an increased risk of stroke related to the anatomic size of the PFO, the magnitude of the right-to-left shunt, and the coexistence of an atrial septal aneurysm, these associations have not been observed consistently.<sup>3,16,21,22</sup>

A PFO is usually detected as part of an evaluation for a cardioembolic source of stroke. Estimates of annual rates of recurrent stroke among patients with PFO range from 1.5% to 12% and depend on the characteristics of the population studied, including age.<sup>3,23</sup> In the Lausanne study,<sup>24</sup> in which patients were treated with aspirin, anticoagulation, or PFO closure, the annual stroke rate was 1.9%. In PICSS, which included patients older than those in the Lausanne study, all subjects were treated with aspirin (325 mg daily) or warfarin anticoagulation (international normalized ratio 1.4 to 2.8, mean  $2.04\pm 0.99$ ). The 2-year primary event rate for all-cause death or recurrent ischemic stroke was 15.9%.<sup>19</sup> There was no significant difference in primary event rates between patients with versus those without PFO. Whereas Cujec et al<sup>25</sup> reported that warfarin may be more effective than antiplatelet therapy for secondary stroke prevention, in PICSS, the primary event rates for CS patients with PFO treated with warfarin ( $n=42$ ) were not significantly different from those of patients treated with aspirin ( $n=56$ ; 9.5% versus 17.9%, hazard ratio 0.52, 95% CI 0.16 to 1.67,  $P=0.28$ ), although the study was not adequately powered for this specific comparison and the mean international normalized ratio achieved was 2.04.<sup>19</sup> In addition, event rates were similar for CS patients without PFO treated with warfarin ( $n=72$ , 8.3%) or aspirin ( $n=80$ , 16.3%; hazard ratio 0.50, 95% CI 0.19 to 1.31,  $P=0.16$ ).<sup>19</sup> A systematic review of nonrandomized studies of transcatheter closure ( $n=10$ ) or medical therapy ( $n=6$ ) for

**Table. Current Ongoing Clinical Trials on PFO Closure to Prevent Recurrent Cryptogenic Stroke**

Trial Name	Device Utilized	Sponsor	Start Date	Projected Completion Date	Estimated Enrollment	For More Information
RESPECT: Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment	Amplatzer PFO occluder	AGA Medical	2003	Study ongoing; completion date not available	500	<a href="http://www.strokecenter.org/trials">http://www.strokecenter.org/trials</a>
CLOSURE-1: Evaluation of the STARFlex Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale (PFO)	STARFlex septal closure system	NMT Medical	2003	Study ongoing; no longer recruiting participants	900	<a href="http://www.clinicaltrials.gov">http://www.clinicaltrials.gov</a> Identifier # NCT00201461
PC-Trial: Patent Foramen Ovale and Cryptogenic Embolism	Amplatzer PFO occluder	AGA Medical	2000	Study ongoing; projected to complete in December 2007 but has been extended	500	<a href="http://www.clinicaltrials.gov">http://www.clinicaltrials.gov</a> Identifier # NCT00166257
Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE)	Any device can be used provided it has been approved by the ad hoc committee of the study	Assistance Publique–Hôpitaux de Paris	2007	December 2012	900	<a href="http://www.clinicaltrials.gov">http://www.clinicaltrials.gov</a> Identifier # NCT00562289
GORE HELEX Septal Occluder for Patent Foramen Ovale (PFO) Closure in Stroke Patients (Gore REDUCE)	GORE HELEX septal occluder	WL Gore and Associates	2008	2014	664	<a href="http://www.clinicaltrials.gov">http://www.clinicaltrials.gov</a> Identifier # NCT00738894

PFO reported a 1-year rate of recurrent neurological thromboembolism of 0% to 4.9% with transcatheter intervention and 3.8% to 12.0% with medical therapy.<sup>26</sup> Rates of major and minor complications with device closure were 1.5% and 7.9%, respectively. Wöhrle’s more recent review of nonrandomized trials has also suggested a lower rate of recurrent stroke after device closure of PFO, especially among patients with coexistent atrial septal aneurysm.<sup>22</sup> The mean frequency of major complications was 2.3% among patients undergoing PFO closure.

Both the American Heart Association/American Stroke Association (AHA/ASA)<sup>3</sup> and American College of Chest Physicians (ACCP)<sup>27</sup> guidelines recommend antiplatelet therapy for patients with ischemic stroke or transient ischemic attack and PFO (AHA/ASA Class IIa, Level of Evidence: B; ACCP grade 1A), unless other indications exist for vitamin K antagonist therapy (eg, atrial fibrillation, hypercoagulable state; AHA/ASA Class IIa, Level of Evidence: C; ACCP grade 1C). The AHA/ASA guidelines for secondary stroke prevention state that “insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent CS despite optimal medical therapy (Class IIb, Level of Evidence: C).”<sup>3</sup>

No device specific for PFO closure after CS has been approved by the US Food and Drug Administration (FDA).<sup>28–30</sup> Three FDA advisory committee meetings (1997, 2002, and 2007) over the past 10 years have affirmed the need for completion of appropriately powered randomized, controlled clinical trials to compare medical therapy with percutaneous device closure. Enrollment in

trials has been insufficient to allow completion and has lagged considerably for several reasons, including the strongly held opinions of individual clinicians, investigators, and patients regarding optimal therapy for recurrent stroke prevention in a predominantly younger population, concerns regarding the limitations and pitfalls of medical therapy, the reluctance of patients and physicians to participate in randomized treatment trials, and the widespread off-label use of closure devices. Indeed, Opatowsky et al<sup>31</sup> reported a 50-fold increase in the weighted national estimate of the annual number of percutaneous PFO/atrial septal defect closures over the time period of 1998 to 2004. After FDA review, the human device exemptions for 2 percutaneous closure devices granted in 2000 and 2002 were withdrawn in 2006, because the patient population described by the approved indication (patients with recurrent CS due to presumed paradoxical embolism through a PFO for whom conventional drug therapy has failed) was significantly in excess of 4000 patients per year in the United States.<sup>32</sup> This finding meant that these devices were no longer eligible for humanitarian use device designation and therefore could not be marketed under a human device exemption. Investigational device exemption studies are available to permit eligible patients access to these devices. Three such trials are ongoing in the United States (RESPECT [Randomized Evaluation of recurrent Stroke comparing PFO closure to Established Current standard of care Treatment],<sup>33</sup> CLOSURE I [Evaluation of the STARFlex Septal Closure System in Patients With a Stroke or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a PFO],<sup>34</sup> and REDUCE [GORE HELEX

Septal Occluder for Patent Foramen Ovale (PFO) Closure in Stroke Patients (Gore REDUCE)<sup>35</sup>, 1 in France (Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence [CLOSE]<sup>36</sup>), and 1 in Europe and Australia (PC-Trial<sup>37</sup>). The current status of these ongoing trials is summarized in the Table. At its most recent meeting, the FDA's Circulatory System Devices Panel asked for the support of provider and voluntary health organizations to increase awareness regarding the need to complete these trials.<sup>38</sup> The importance of patient and provider education was emphasized. Recommendations were issued to facilitate statistically appropriate pooling of data across trials when possible and to curtail the off-label use of closure devices.

The magnitude of the problem posed by recurrent stroke in patients with CS and PFO, coupled with the continued uncertainty regarding the optimal approach to secondary

prevention, underscores the critical need for completion of these pivotal trials. Randomized, controlled trials offer the best means for assessing the safety and efficacy of percutaneous device closure relative to antithrombotic therapy. Despite the potential benefit of alternative, statistically valid methods of pooling data across trials, the need for traditional randomized, controlled trials is reaffirmed. This advisory is a call to action for clinicians to support referral of patients with CS and PFO to 1 of these ongoing studies. Practitioners are encouraged to refer patients across the spectrum of perceived risk for recurrent stroke, so as to minimize biased enrollment of relatively healthier patients. Failure to achieve the projected sample sizes in a timely fashion could result in withdrawal of funding, premature study termination, and continued lack of clarity around this vexing management problem. An informed answer is required.

## Disclosures

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\*Modest.

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NIH-NINDS indicates National Institutes of Health–National Institute of Neurological Disorders and Stroke; DSMB, Data Safety and Monitoring Board.

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\*Modest.

†Significant.



## References

1. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;117:e25–e146.
2. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group [published correction appears in *Circulation*. 2006;114:e617]. *Circulation*. 2006;113:e873–e923.
3. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention. *Circulation*. 2006;113:e409–e49.
4. Sacco RL, Ellenberg JH, Mohr JP, et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann Neurol*. 1989;25:382–90.
5. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST, Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35–41.
6. Grau AJ, Weimar C, Buggle F, et al. Risk factors, outcome, and treatment subtypes of ischemic stroke: the German stroke data bank. *Stroke*. 2001;32:2559–66.
7. Lee BC, Hwang SH, Jung S, et al. The Hallym Stroke Registry: a web-based stroke data bank with an analysis of 1,654 consecutive patients with acute stroke. *Eur Neurol*. 2005;54:81–8.
8. 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.
9. Di Tullio MR, Sacco RL, Sciacca RR, et al. Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. *J Am Coll Cardiol*. 2007;49:797–802.
10. Meissner I, Khandheria BK, Heit JA, et al. Patent foramen ovale: innocent or guilty? Evidence from a prospective population-based study. *J Am Coll Cardiol*. 2006;47:440–5.
11. Attaran RR, Ata I, Kudithipudi V, et al. Protocol for optimal detection and exclusion of a patent foramen ovale using transthoracic echocardiography with agitated saline microbubbles. *Echocardiography*. 2006;23:616–22.
12. Mügge 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.
13. Srivastava TN, Payment MF. Images in clinical medicine: paradoxical embolism—thrombus in transit through a patent foramen ovale. *N Engl J Med*. 1997;337:681.
14. Lethen H, Flachskampf FA, Schneider R, et al. Frequency of deep vein thrombosis in patients with patent foramen ovale and ischemic stroke or transient ischemic attack. *Am J Cardiol*. 1997;80:1066–9.
15. Stöllberger C, Slany J, Schuster I, et al. The prevalence of deep venous thrombosis in patients with suspected paradoxical embolism [published correction appears in *Ann Intern Med*. 1994;120:347]. *Ann Intern Med*. 1993;119:461–5.
16. Homma S, Sacco RL. Contemporary reviews in cardiovascular medicine: patent foramen ovale and stroke. *Circulation*. 2005;112:1063–72.
17. Halperin JL, Fuster V. Patent foramen ovale and recurrent stroke: another paradoxical twist. *Circulation*. 2002;105:2580–2.
18. Lamy C, Giannesini C, Zuber M, et al. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. *Stroke*. 2002;33:706–11.
19. 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.
20. Handke M, Harloff A, Olschewski M, et al. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med*. 2007;357:2262–8.
21. Mas JL, Arquizan 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.
22. Wöhrle J. Closure of patent foramen ovale after cryptogenic stroke. *Lancet*. 2006;368:350–2.
23. Homma S, DiTullio MR, Sacco RL, et al. Age as a determinant of adverse events in medically treated cryptogenic stroke patients with patent foramen ovale. *Stroke*. 2004;35:2145–9.
24. Bogousslavsky J, Garazi S, Jeanrenaud X, et al. Stroke recurrence in patients with patent foramen ovale: the Lausanne Study: Lausanne Stroke with Paradoxical Embolism Study Group. *Neurology*. 1996;46:1301–5.
25. 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.
26. 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.
27. Salem DN, O'Gara PT, Madias C, et al. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(suppl):593S–629S.
28. Maisel WH, Laskey WK. Patent foramen ovale closure devices: moving beyond equipoise. *JAMA*. 2005;294:366–9.
29. Flachskampf FA, Daniel WG. Closure of patent foramen ovale: is the case really closed as well? *Heart*. 2005;91:449–50.
30. Dalen JE. Are patients with a patent foramen ovale at increased risk of stroke? A billion dollar question. *Am J Med*. 2007;120:472–4.
31. Opatowsky AR, Landzberg MJ, Kimmel SE, Webb GD. Trends in the use of percutaneous closure of patent foramen oval and atrial septal defect in adults, 1998–2004. *JAMA*. 2008;299:521–2.
32. Information for Physicians and Patients on the Withdrawal of Two Humanitarian Device Exemptions (HDEs) for Patent Foramen Ovale (PFO) Occluders. US Food and Drug Administration Web site. 2006. Available at: <http://www.fda.gov/cdrh/ode/h000007-h990011withdraw.html>. Accessed January 14, 2008.
33. RESPECT: Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment Web page. Available at: [http://www.strokecenter.org/trials/trialDetail.aspx?tid=482&search\\_string=PFO](http://www.strokecenter.org/trials/trialDetail.aspx?tid=482&search_string=PFO). Accessed January 6, 2009.
34. CLOSURE 1: Evaluation of the STARFlex Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale (PFO). Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00201461?term=PFO+AND+stroke&rank=5>. Accessed March 20, 2009.
35. GORE HELEX Septal Occluder for Patent Foramen Ovale (PFO) Closure in Stroke Patients (Gore REDUCE). Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00738894?term=NCT00738894&rank=1>. Accessed March 20, 2009.
36. Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE). Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00562289?term=PFO+AND+stroke&rank=4>. Accessed January 6, 2009.
37. PC-Trial: Patent Foramen Ovale and Cryptogenic Embolism. Available at: <http://www.clinicaltrials.gov/ct2/show/NCT00166257?term=PFO+AND+stroke&rank=8>. Accessed March 20, 2009.
38. Slottow TL, Steinberg DH, Waksman R. Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel meeting on patent foramen ovale closure devices. *Circulation*. 2007;116:677–82.