

Transcatheter Closure versus Medical Therapy of Patent Foramen Ovale and Presumed Paradoxical Thromboemboli

A Systematic Review

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Background: The optimal strategy to prevent recurrent presumed paradoxical emboli in patients with patent foramen ovale is unknown.

Purpose: To synthesize the current knowledge about and qualitatively assess the relative benefits of transcatheter closure versus medical therapy for patent foramen ovale.

Data Sources: English-language and foreign-language journals listed in the MEDLINE database from January 1985 to July 2003 were systematically searched. Secondary sources were also used.

Study Selection: Secondary prevention studies of transcatheter closure or medical therapy for patent foramen ovale were required to include at least 10 patients followed for more than 1 year and to report recurrent neurologic events.

Data Extraction: Data from published studies were manually extracted and summarized.

Data Synthesis: Ten studies of transcatheter closure (1355 patients) and 6 studies of medical therapy (895 patients) for patent

foramen ovale were included. Overall, the 1-year rate of recurrent neurologic thromboembolism with transcatheter intervention was 0% to 4.9%, and the incidence of major and minor complications was 1.5% and 7.9%, respectively. Medical management was associated with a 1-year recurrence rate of 3.8% to 12.0%. However, limitations resulting from uncontrolled data, nonstandardized definitions, vigilance of follow-up, and baseline imbalances preclude definitive conclusions about the superiority of a particular approach. General differences in study samples included older age, greater proportion of men, and higher prevalence of diabetes and smoking among medically treated patients. Patients undergoing treatment with a transcatheter device were more likely to have had multiple thromboembolic events at baseline.

Conclusion: Transcatheter closure of patent foramen ovale may prevent a substantial proportion of cryptogenic strokes. Randomized clinical trials are needed.

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Despite extensive evaluation, the cause of ischemic stroke remains undefined in approximately 40% of patients (1–4). Passage of thromboemboli from the right to left atrium across a patent foramen ovale, a remnant of the fetal circulation, has been postulated as a mechanism responsible for some of these cryptogenic strokes. Thrombus straddling a patent foramen ovale has been imaged on rare occasions (5–8). The association between patent foramen ovale and cryptogenic embolic stroke has been strengthened by epidemiologic studies that found a prevalence of patent foramen ovale of 44% to 66% in patients with cryptogenic stroke compared with 27% in autopsy series of all-cause death (2, 9–13).

The most appropriate therapy to prevent recurrent events in survivors of cryptogenic stroke or transient ischemic attack with documented patent foramen ovale is unknown and controversial. Traditionally, a conservative strategy of long-term medical therapy with antiplatelet agents or oral anticoagulants has been used. However, much debate exists over which agent provides the most favorable risk–benefit ratio. Surgical closure of patent foramen ovale has been proposed, but outcomes have varied (14–16). In the past decade, closure by implantation of a transcatheter device has emerged as a feasible low-risk alternative therapeutic option, but comparative studies are lacking. We therefore performed a systematic review to synthesize the current state of knowledge on transcatheter

closure of patent foramen ovale compared with medical therapy.

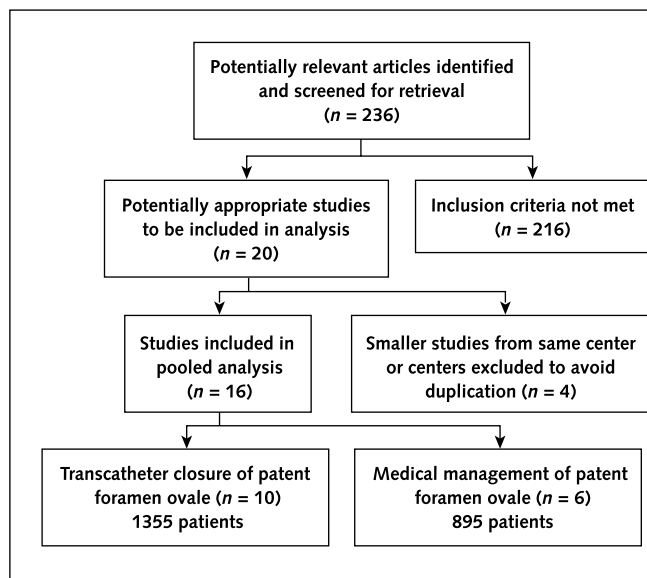
METHODS

Literature Search and Study Selection

Relevant articles published between January 1985 through July 2003 were identified through an electronic search of the MEDLINE database by using the following query terms: *patent foramen ovale* or *persistent foramen ovale* combined with *stroke*, *embolism*, *embolus*, *embolization*, *cerebral*, *cerebrovascular*, and *closure*. This strategy was supplemented by a manual search of secondary sources, including selected references from primary articles. Both English-language and foreign-language journals were examined. Unpublished data were not sought.

In the absence of controlled trials, identified articles were systematically screened for the following inclusion criteria: a study cohort that had secondary prevention of neurologic thromboembolic events by medical management of patent foramen ovale or transcatheter device implantation; minimum of 10 patients per cohort; assessment and report of neurologic thromboembolic events; mean duration of follow-up of at least 12 months (because the primary outcome of interest was the 1-year rate of recurrent events); and actuarial freedom from recurrent neurologic thromboembolic events at 1 year, as recorded or calculated from sufficient data. When more than 1 article originating from

Figure 1. Study identification.



the same center met the above criteria, the study that reported on the most patients was included and those with fewer patients were excluded to avoid duplication.

DATA SYNTHESIS

Study Identification

We identified 236 articles, of which 20 met the pre-specified inclusion criteria (Figure 1). Four studies with

potentially overlapping samples were excluded. Thus, 16 articles including 2250 patients were reviewed: 10 studies (1355 patients) on transcatheter closure and 6 studies (895 patients) on medical management. Table 1 shows the details of individual studies.

Definitions

All patients were treated for presumed paradoxical emboli associated with patent foramen ovale. When defined, patent foramen ovale was described as spontaneous or provokable right-to-left interatrial shunting on contrast echocardiography. The maximum number of cardiac cycles allowed after right atrial opacification when assessing contrast in the left atrium was 3 (17–20) or 5 (21). The threshold for the number of left atrial microbubbles that were considered significant was 1 (17, 20, 22, 23), 3 (18, 19, 24, 25), or 4 (21).

The most common definition of an aneurysmal or hypermobile atrial septum was septal movement into the right or left atrium exceeding 10 mm (20, 22, 23, 25–27). Other definitions included membrane mobility of 6.5 mm or greater (18), 11 mm (19), or 15 mm (21, 28) or diameter of the mobile portion of septum primum greater than 13 mm (27) or 15 mm (21).

The outcomes and means of their assessment were not uniform among studies. When defined, transient ischemic attack was characterized as a transient reversible neurologic defect confirmed by a neurologist that resolved completely within 12 hours (25) or 24 hours (18, 22–24, 28, 29). Stroke was defined as a clinically and neuroradiologically

Table 1. Baseline Characteristics

Study, Year (Reference)	Patients	Mean Age ± SD	Men	Atherosclerosis Risk Factor				Atrial Septal Aneurysm	Type of Cerebrovascular Accident		≥2 Cerebrovascular Accidents
				Hypertension	Diabetes Mellitus	Smoking	Dyslipidemia		Stroke	Transient Ischemic Attack	
	n	y	←	%				→			
Transcatheter closure											
Ende et al., 1996 (30)	10	40 ± 12	30	–	–	–	–	20.0	70.0	30.0	40.0
Hung et al., 2000 (31)	63	46 ± 18	57	9.5	–	14.3	–	–	87.3	7.9	42.9
Sievert et al., 2001 (26)	281	47 ± 13	–	17.4	3.6	–	–	22.8	65.5	39.9	42.0
Butera et al., 2001 (29)	35	48 ± 14	66	–	–	–	–	17.1	34.3	65.7	17.1
Wahl et al., 2001 (22)	152	50 ± 12	53	28.3	5.3	34.9	–	27.0	63.8	30.9	43.4
Beitzke et al., 2001 (27)	162	40 ± 12	59	35.2	–	–	–	21.6	60.5	37.0	24.7
Martin et al., 2002 (24)	110	47 ± 14	53	16.4	0	20.0	26.4	14.5	98.2*	–	24.5
Du et al., 2002 (32)	18	43 ± 17	44	–	–	–	–	–	77.8	33.3	27.8
Braun et al., 2002 (25)	276	45 ± 14	34	14.9	6.9	35.9	11.2	23.9	72.8	98.9	75.0
Onorato et al., 2003 (28)	248	48 ± 15	41	–	–	–	–	33.6	40.7	58.1	10.1
Medical therapy											
Bogousslavsky et al., 1996 (21)	140	36 ± 14	59	14.3	4.3	31.4	14.3	25.0	84.3	15.7	–
Cujec et al., 1999 (17)	52	43 ± 27	60	23	11.5	50.0	28.8	11.5	50.0	50.0	–
De Castro et al., 2000 (18)	74	53 ± 14	–	–	–	–	–	36.5	100*	–	–
Mas et al., 2001 (19)	267	40.3†	53	9.0	3.0	41.9	11.6	19.1	100	–	2.2
Homma et al., 2002 (20)	203	58 ± 13	59	53.2	83.7	84.7	–	21.7	100	–	13.3
Nedeltchev et al., 2002 (23)	159	51 ± 14	58	32.7	9.4	32.7	30.2	22.0	74.8	23.9	27.7

* Values span columns because the proportion of patients with each individual condition was not provided.

† Median value.

Table 2. Complications of Transcatheter Closure of Patent Foramen Ovale

Study, Year (Reference)	Patients	Complications		Device Implanted*
		Minor	Major	
		← n →		
Ende et al., 1996 (30)	10	1	1	Sideris buttoned device
Hung et al., 2000 (31)	63	15	2	Clamshell, CardioSEAL, Sideris buttoned device
Sievert et al., 2001 (26)	281	41	1	Sideris buttoned device, ASDOS, Angel wings, PFO-Star, CardioSEAL, STARflex, Amplatzer ASD occluder, Helex septal occluder
Butera et al., 2001 (29)	35	0	0	Amplatzer ASD occluder, CardioSEAL, STARflex, PFO-Star
Wahl et al., 2001 (22)	152	9	1	Sideris buttoned device, Angel wings, Amplatzer ASD occluder, CardioSEAL, CardioSEAL, STARflex, PFO-Star, Amplatzer PFO occluder
Beitzke et al., 2001 (27)	162	8	5	Rashkind 17-mm PDA occluder, Amplatzer ASD occluder, Amplatzer PFO occluder, CardioSEAL
Martin et al., 2002 (24)	110	2	6	Sideris buttoned device, CardioSEAL
Du et al., 2002 (32)	18	0	0	Angel wings, Amplatzer ASD occluder, Amplatzer PFO occluder
Braun et al., 2002 (25)	276	9	2	PFO-Star
Onorato et al., 2003 (28)	248	22	3	Amplatzer PFO occluder, Helex septal occluder, PFO-Star
All studies	1355	7.9†	1.5†	

* Manufacturer information on closure devices is as follows. Sideris buttoned device, Custom Medical Devices, Amarillo, Texas; Clamshell, Bard Clamshell Septal Umbrella, USCI Division, CR Bard, Billerica, Massachusetts; CardioSEAL, Nitinol Medical Technologies, Boston, Massachusetts; ASDOS, Osypka Corp., Grenzach-Wyhlen, Germany; Angel wings, Microvena Corp., White Bear Lake, Minnesota; PFO-Star, Cardia, Burnsville, Minnesota; STARflex, Nitinol Medical Technologies; Amplatzer ASD occluder, AGA Medical, Golden Valley, Minnesota; Helex septal occluder, W.L. Gore and Associates, Flagstaff, Arizona; Amplatzer PFO occluder, AGA Medical; Rashkind 17-mm PDA occluder, USCI Angiographics, CR Bard.

† Summary data are the percentage of complications.

confirmed focal deficit persisting for more than 24 hours (18–20, 22–25, 28, 29). Rigor of follow-up and surveillance for end points differed among the reports and was often liberally described as standard neurologic care.

Patient Characteristics

Among patients undergoing transcatheter closure of patent foramen ovale, the mean age per study ranged from 40 ± 12 years to 50 ± 12 years. In contrast, medically treated patients had a mean age older than 50 years in 3 of 6 studies. Overall, one third to two thirds of patients in studies of transcatheter device closure were male, whereas all studies of medically managed patients that reported sex included more men than women.

A tendency toward a higher prevalence of risk factors for atherosclerosis was noted in medically managed patients. In studies of transcatheter device closure that reported such risk factors, hypertension was documented in 10% to 28% of patients, diabetes in 0% to 7%, and smoking in 14% to 36%. In contrast, medically managed patients had prevalences of hypertension, diabetes, and smoking of 9% to 53%, 3% to 84%, and 31% to 85%, respectively. No major differences were noted in the prevalence of hypercholesterolemia among patients having transcatheter closure (11% to 26%) and those receiving medical therapy (12% to 30%). Data were insufficient to analyze body mass index or the prevalence of previous recognized symptomatic atherosclerotic heart or peripheral vascular disease.

Atrial septal aneurysms were present in a similar proportion of patients undergoing transcatheter closure (15% to 34%) or medical therapy (12% to 37%). The type of cerebrovascular accident, classified as stroke or transient ischemic attack, varied among patients who had transcath-

eter closure. However, all studies of medically treated patients that subclassified type of cerebrovascular accident reported a prevalence of previous stroke of at least 50% (100% of patients in the 2 largest studies). Multiple cerebrovascular events were, however, more common in patients undergoing transcatheter closure (10% to 75%, compared with 2% to 28% in 3 studies of medically treated patients that reported this information).

Medical Therapy

Medical treatment varied among the patients in this review. Antiplatelet therapy consisted of a daily prescribed aspirin dosage of 250 mg (21), 300 mg (19), or 325 mg (17, 20) or a mean (\pm SD) dose of 233 ± 83 mg (23). A minority of patients received clopidogrel or ticlopidine (17, 23). In anticoagulated patients, target international normalized ratios were 1.4 to 2.8 (20), 2.0 to 3.0 (23), 3.0 to 4.0 (21), or undefined (17, 18). Although therapy was randomly allocated in 1 study (20), in most patients, medical management decisions were individualized according to the discretion of the treating physician. Adherence to therapy was assessed monthly (20) or at 6-month intervals (19), or was not stated (17, 18, 21, 23).

Transcatheter Device Closure

Table 2 shows reported complications of closure of patent foramen ovale by using a transcatheter device. Technical procedural success, imaging techniques to assess complete closure, and device-related complications were not uniformly defined. Individual characteristics of patients who had complete closure after device implantation were not recorded, thereby limiting analysis.

Major complications were death (26), hemorrhage requiring blood transfusion (27), cardiac tamponade (22, 24,

Table 3. Follow-up and Recurrent Events in Patients with Transcatheter Closure or Medical Therapy for Patent Foramen Ovale*

Study, Year (Reference)	Study Design	Mean Duration of Follow-up ± SD	Recurrent Event			Events at 1 Year	Patients Lost to Follow-up	Outcome Assessment
			Transient Ischemic Attack	Stroke	Noncerebrovascular Systemic Embolism			
		mo	← n →			%	n	
Transcatheter closure								
Ende et al., 1996 (30)	Retrospective	32 ± 17	0	0	0	0	Not reported	Chart review, TTE at 1, 3 mo; TEE at 6 mo
Hung et al., 2000 (31)	Retrospective	31 ± 29	1	3	0	3.2	Not reported	Chart review; TTE at 1, 6, and 12 mo, then annually
Sievert et al., 2001 (26)	Retrospective	12 ± 6	7	2	0	4.3	Not reported	TEE at 6 mo; questionnaire every 6–12 mo
Butera et al., 2001 (29)	Retrospective	12 ± 8	0	0	0	0	Not reported	Chart review; TTE at 1, 6, and 12 mo
Wahl et al., 2001 (22)	Prospective	20 ± 19	6	1	2	4.9	3	TEE at 6 mo, clinic visits, telephone follow-up
Beitzke et al., 2001 (27)	Retrospective	19 ± 6	3	0	0	1.7	44†	Chart review, TEE at 3–6 mo
Martin et al., 2002 (24)	Prospective	47 ± 14	1	1	0	0.9	Not reported	TTE and clinic visit at 1, 6, and 12 mo, then annually
Du et al., 2002 (32)	Retrospective	26 ± 22	0	0	0	0	Not reported	Chart review; TTE or TEE at 1, 6, and 12 mo, then annually
Braun et al., 2002 (25)	Prospective	15 ± 6	6	0	0	1.7	0	TEE and clinic visit at 1, 6, and 12 mo, then annually
Onorato et al., 2003 (28)								
Ende et al., 1996 (30)	Prospective	19	0	0	0	0	Not reported	TTE and clinic visit at 1, 3, and 6 mo; TEE at 1 y
Medical therapy								
Bogousslavsky et al., 1996 (21)	Retrospective	36 ± 14	8	8	–	3.8	0	Chart review, clinic visits every 6–12 mo
Cujec et al., 1999 (17)	Retrospective	43 ± 27	12	7	–	12.0	Not reported	Chart review, telephone interview
De Castro et al., 2000 (18)	Prospective	31	3	5	–	5.9	0	Biannual neurologic evaluation
Mas et al., 2001 (19)	Prospective	38 ± 10	9	12	0	4.1	2 (0.3)‡	Neurologic evaluation every 6 mo, validation committee
Homma et al., 2002 (20)	Prospective	13 ± 11	11	29	–	10.4	10 (1.6)‡	Visit or phone every month, regulation of international normalized ratio
Nedeltchev et al., 2002 (23)	Retrospective	29 ± 23	14	7	–	5.5	2	Chart review, telephone questionnaire

* TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.
 † Complete follow-up available on 116 patients; 2 deaths were reported.
 ‡ Unknown whether patients lost to follow-up were part of the subgroup with patent foramen ovale.

27, 28), need for surgical intervention (30), and massive fatal pulmonary emboli (24, 25, 27, 28, 31). Minor complications were defined differently in each study and included bleeding not requiring transfusion (27), periprocedural atrial arrhythmias (24–26, 30), transient atrioventricular node block (25), device arm fractures (25, 31), device embolization with successful catheter retrieval (22, 25–27), asymptomatic device thrombosis (25, 26), need for recatheterization (22, 26), symptomatic air embolism (22, 25, 28), transient ST-segment elevation (25, 27), arteriovenous fistula formation (22), and femoral hematoma (28). According to this classification scheme, the reported incidence of major and minor complications was 1.5% and 7.9%, respectively.

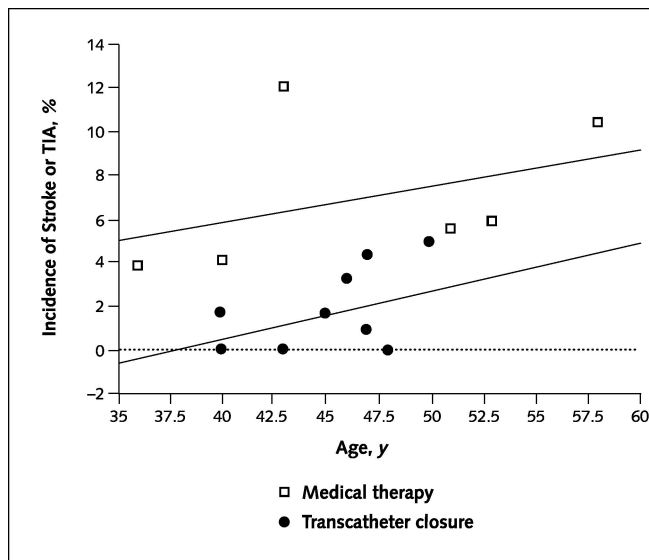
Antiplatelet or anticoagulant regimens after transcatheter closure of patent foramen ovale differed in the clarity

of definition, duration of therapy, and assessment of compliance. Regimens consisted of daily aspirin, 3 to 5 mg/kg of body weight (27), 5 to 10 mg/kg (29, 30), 81 mg (32), 100 mg (22, 25), or 325 mg (24), with or without clopidogrel, 75 mg/d (24–26), or ticlopidine, 250 mg twice daily (24). Aspirin therapy was continued for 6 to 12 weeks (30), 6 months (22, 26–29, 31), or 12 months (25). Most patients receiving warfarin did so for indications other than transcatheter closure of patent foramen ovale.

Recurrence of Neurologic Thromboembolic Events

Although the mean (± SD) duration of follow-up was similar in studies of transcatheter device closure (12 ± 6 months to 47 ± 14 months) and studies of medical management (13 ± 11 to 43 ± 27 months), pattern analysis suggests an overall longer duration of follow-up in medi-

Figure 2. Incidence of recurrent events by patient age per study for medical therapy and transcatheter closure of patent foramen ovale.



Solid lines are regression lines; the dotted line marks the zero level. TIA = transient ischemic attack.

cally managed patients (Table 3). The mean duration of follow-up was 1 or 2 years in 6 of 10 studies of transcatheter device closure compared with 1 of 6 studies of medical management. Follow-up exceeded an average of 3 years in 3 of 6 studies of medically managed patients compared with 1 of 10 studies of transcatheter device intervention.

Figure 2 shows a trend toward an increased incidence of recurrent events with increasing mean age per study for medical therapy and transcatheter closure. Analysis of medically managed patients revealed an incidence of stroke or transient ischemic attack after the first year of follow-up that ranged from 3.8% to 12.0%. In contrast, the incidence of recurrent transient ischemic attack or stroke after 1 year of follow-up in patients who underwent transcatheter closure of patent foramen ovale ranged from 0% to 4.9%, with 7 of 10 studies reporting an incidence of 1.7% or less. In the 2 largest studies of medical therapy and transcatheter closure, 1-year recurrence rates were 4.1% to 10.4% and 1.7% to 4.3%, respectively. In studies of transcatheter device intervention, no correlation was observed between 6-month rates of complete closure of patent foramen ovale and incidence of stroke or transient ischemic attack (Figure 3).

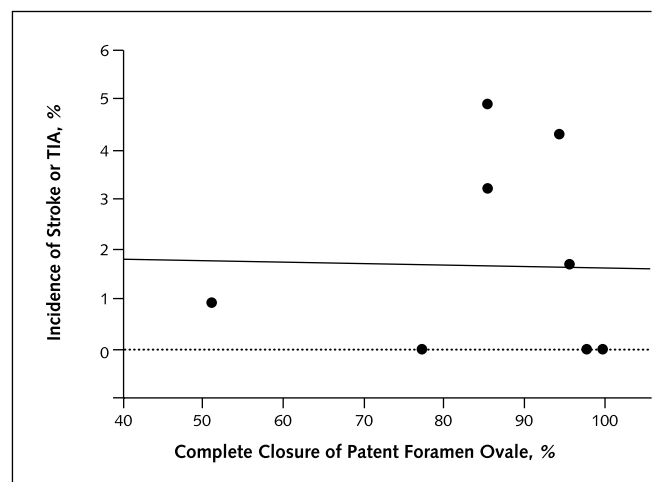
Given the higher prevalence of risk factors for atherosclerosis, particularly diabetes mellitus and smoking, in medically treated patients with patent foramen ovale, crude comparisons may overestimate benefits of transcatheter device implantation. Analyses should consider the population-attributable fraction of strokes that result from smoking, which is estimated to be 15% (33–35). Similarly, the population-attributable risk for stroke from diabetes is reported to be 18% in men and 22% in women (36–38).

DISCUSSION

Although approximately 25% of strokes have no apparent cause and are termed “cryptogenic” (10, 20), this diagnosis of exclusion remains dependent on the thoroughness of clinical investigation. In such patients, diagnostic work-up reveals a patent foramen ovale in 44% to 66% (2, 9–13). Lechat and colleagues (10) reported a prevalence of 54% in patients with no risk factors or identifiable cause of stroke, 40% in those with no identifiable cause but atherosclerotic risk factors, 21% in those with an apparent cause of stroke, and 10% in controls. Autopsy series and transesophageal studies report an age-dependent prevalence of patent foramen ovale ranging from 9% to 34%, with a mean of approximately 27% (2, 9–13). It is therefore estimated that patients with cryptogenic stroke are roughly twice as likely as nonaffected persons to have a patent foramen ovale. Paradoxical embolism remains a presumed but unproven pathophysiologic mechanism in most of these patients.

Secondary prevention of stroke or transient ischemic attack in patients with patent foramen ovale is fraught with uncertainty. This systematic review was not intended to provide definitive evidence favoring a particular therapeutic strategy; the limited available data preclude such an analysis. Rather, the objective was to summarize existing literature on medical therapy versus transcatheter implantation of a closure device for patent foramen ovale in secondary prevention of cryptogenic stroke or transient ischemic attack, synthesize the data, identify limitations, and summarize trends regarding the relative benefit of these approaches. Nonetheless, the substantial reduction in the 1-year incidence of recurrent stroke or transient ischemic attack among patients undergoing transcatheter closure compared with medically treated patients provides evidence of the potential benefit of the former therapy.

Figure 3. Six-month rates of complete patent foramen ovale closure in studies of transcatheter device intervention.



The solid line is a regression line; the dotted line marks the zero level. TIA = transient ischemic attack.

Differing opinions on the preferred prophylactic medical regimen reflect inconsistencies in the literature. In patients with no significant carotid atherosclerosis and no identifiable cause of stroke, antiplatelet therapy has been reported to reduce the rate of recurrent stroke by 30% (39). Nonrandomized studies in patients with patent foramen ovale suggest that fewer recurrent thromboembolic events occur with oral anticoagulants than with aspirin (17, 40). A meta-analysis found therapy with warfarin to be superior to aspirin in preventing recurrent ischemic events, with an odds ratio of 0.37 (95% CI, 0.23 to 0.60) (40). However, the annual rate of bleeding complications during warfarin therapy is purported to be 1.8% to 4.8% (26, 41, 42). Moreover, primary event rates did not differ significantly in the only randomized trial of aspirin (325 mg/d) and warfarin (target international normalized ratio, 1.4 to 2.8) in patients with patent foramen ovale (20). However, the trial did not have a placebo-controlled arm, which limits the assessment of treatment efficacy, and was not powered to assess therapeutic equivalence (3). The nature of the data included in our systematic review did not permit comparisons between antiplatelet and anticoagulant therapy. Nevertheless, the absence of solid evidence favoring a particular regimen provides some clinical justification for pooling a heterogeneous group of medically treated patients with patent foramen ovale for comparison with transcatheter closure.

Catheter closure of patent foramen ovale was first reported in 1992 by Bridges and associates, who used Clamshell devices (Bard, USCI, Billerica, Massachusetts) in 36 patients with presumed paradoxical events (43). New devices specifically designed for closure of patent foramen ovale have since been developed, and the procedure has become more widely available. Transcatheter implantation of patent foramen ovale closure devices has been reported as safe and effective, with a high success rate, low incidence of periprocedural complications, and excellent results during long-term follow-up (22, 24–27, 29–32). No controlled trials have compared transcatheter closure of patent foramen ovale with medical therapy. The lower 1-year recurrence rates in patients treated with device implantation compared with those receiving medical therapy suggests that research should be directed toward identification of suitable candidates for transcatheter closure of patent foramen ovale.

Our results are consistent with those of a published Markov-based decision analysis for a hypothetical cohort of 55-year-old patients with presumed paradoxical embolism (44). Over a wide range of risk for stroke (0.8% to 7% per year), the gain provided by closing the patent foramen ovale exceeded that obtained by medical therapy.

Overall, in our pooled analysis, the rate of major complications occurring with transcatheter closure of patent foramen ovale was less than 2%. Recent reports on transcatheter closure suggest that adverse events with older devices may in part reflect a learning curve and that newer

devices pose less risk of dislodgement and embolization and offer a higher rate of complete closure (22, 24, 26, 31). Although some investigators have reported a higher incidence of recurrent thromboembolic events in the presence of a residual shunt (relative risk, 4.2 [95% CI, 1.1 to 17.8]) (22, 45), we and others have not confirmed this finding (25, 26, 31).

An aneurysmal or hypermobile atrial septum has a prevalence of 0.3% to 7.9% in healthy persons (26, 27) and is present in conjunction with patent foramen ovale in 28% to 58% of patients with cryptogenic stroke (6, 46, 47). Although the significance of this association is not clear, atrial septal aneurysms have been identified as a source of cardiogenic emboli (6, 19). A meta-analysis reported that atrial septal aneurysms significantly increased the risk for recurrent stroke in patients with patent foramen ovale who are 55 years of age or younger (48). Mas and coworkers (19) found that the combination of both atrial abnormalities was a significant predictor of increased risk for recurrent stroke (hazard ratio, 4.17 [95% CI, 1.47 to 11.84]). Disparate findings have, however, been reported. In a recently reported substudy of patent foramen ovale and cryptogenic stroke, no significant differences in outcome were noted between patients with isolated patent foramen ovale and those with patent foramen ovale in association with atrial septal aneurysm (20). This pooled analysis could not assess the strength of association between atrial septal aneurysm and recurrent events. Of note, however, the similar prevalence of septal aneurysms in medically treated patients and those undergoing transcatheter closure guards against potential confounding by this proposed risk factor.

Systematic reviews of case series lack the experimental element of random allocation to a particular intervention. Thus, particular challenges arise as a result of inherent biases and differences in definitions, means of assessing outcome, and study designs (49). Nevertheless, systematic reviews may elucidate sources of variability, summarize trends, generate hypotheses, and identify areas for future research. Our intention was to summarize the current state of knowledge about transcatheter closure of patent foramen ovale versus medical therapy within the constraints of available noncontrolled data.

The diagnosis of cryptogenic stroke is one of exclusion and depends on the meticulousness of clinical investigation and follow-up, which was not uniform across studies. Definitions of such neurologic events as stroke or transient ischemic attack and such risk factors as atrial septal aneurysms, hypercholesterolemia, and diabetes varied or were not provided in some reports. Perhaps more important, the lack of controlled data with nonstandardized entry criteria exposes this type of analysis to possible selection bias. In addition, case series of transcatheter device closure of patent foramen ovale that had more favorable outcomes are more likely to be reported and published.

Several imbalances favoring transcatheter closure were

identified. Moreover, confounding by unmeasured factors that may arise from nonrandom treatment allocation could not be excluded. The preponderance of men among medically treated patients and higher prevalence of risk factors for atherosclerosis may have resulted in a higher rate of thromboembolic events, thereby overestimating benefits of transcatheter closure. In contrast, patients with patent foramen ovale closure were more likely to have had recurrent thromboembolic events before device intervention, suggesting a higher-risk group with potential bias toward the null hypothesis. The relative impact of these various factors and net effect on risk estimates are unknown and cannot be accurately estimated from available data.

In conclusion, our systematic review suggests that a substantial proportion of recurrent thromboembolic events may be prevented by implantation of a patent foramen ovale closure device compared with medical therapy. Moreover, transcatheter closure of patent foramen ovale is safe, with a rate of major complications of less than 2%. However, limitations ensuing from analysis of noncontrolled data and baseline imbalances between reported series of patients treated medically and by percutaneous device intervention preclude definitive conclusions about the superiority of a particular approach. Well-controlled randomized clinical trials must corroborate the benefits of transcatheter closure of patent foramen ovale, define the subgroups most likely to profit from this intervention, and assess the cost-effectiveness of this strategy in the modern management of cryptogenic stroke (50, 51).

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Potential Financial Conflicts of Interest: Dr. Landzberg has participated in research trials involving numerous transcatheter devices, as well as medical therapies. On occasion, expenses related to these trials have been covered by individual pharmaceutical or manufacturing companies.

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