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REVIEW TOPIC OF THE WEEK

Cryptogenic Stroke and Patent Foramen Ovale

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ABSTRACT

Nearly one-half of patients with cryptogenic stroke have a patent foramen ovale (PFO). The dilemma of whether to close these PFOs percutaneously, in an effort to reduce the risk of recurrent paradoxical embolism, has been a matter of ongoing debate for more than a decade. Early randomized clinical trials failed to demonstrate a significant benefit of percutaneous PFO closure for secondary prevention of cryptogenic stroke in an intention-to-treat analysis. The long-term follow-up data from the RESPECT trial and 2 new randomized trials (CLOSE and REDUCE) have clarified these findings. They showed that with good patient selection, transcatheter PFO closure significantly reduces the risk of recurrent stroke compared with medical therapy in patients with cryptogenic stroke, with no increased risk of serious adverse events or influence on major bleeding. (J Am Coll Cardiol 2018;71:1035–43). © 2018 by the American College of

The prevalence of patent foramen ovale (PFO) is 20% to 25% in the adult population. In people who suffer a cryptogenic stroke, 40% to 50% of patients have a PFO (1–3). A hypermobile septum primum, referred to as an atrial septal aneurysm, associated with a PFO has been found to increase the risk of an initial stroke (meta-analysis of 4 studies: odds ratio [OR]: 4.96; 95% confidence interval [CI]: 2.37 to 10.39) and recurrent stroke (OR: 23.93; 95% CI: 3.09 to 185.42). Changes in volume and pressure of the right atrium lead to moments of patency of the foramen ovale. An atrial septal aneurysm may open the PFO with every heartbeat, thereby increasing the potential for passage of thrombus from the venous to arterial system (3–5). A similar effect is exerted by a Eustachian valve (6) (or a Chiari network), which

directs blood flow from the inferior vena cava to the foramen ovale, as depicted in Figure 1.

Previous trials have shown that in patients with cryptogenic stroke, the risk of recurrent stroke is high, with no clear-cut difference in efficacy between antiplatelet and oral anticoagulation therapy with warfarin or novel oral anticoagulants, in the absence of atrial fibrillation (7–9). A meta-analysis of 48 observational comparative studies (n = 410,327) demonstrated that patients with cryptogenic stroke or transient ischemic attack (TIA) who received medical therapy had a 6.3-fold increased rate of recurrent neurological events compared with patients who underwent percutaneous PFO closure (10). Randomized clinical trials were performed to determine unequivocally if percutaneous PFO closure is superior

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ABBREVIATIONS AND ACRONYMS

FDA= Food and Drug
Administration

PFO= patent foramen ovale

TEE= transesophageal
echocardiography

TIA= transient ischemic
attack

to medical therapy for secondary
prevention of cryptogenic stroke
(Table 1).

DIAGNOSIS AND QUANTIFICATION OF PFO

Right heart catheterization,
with demonstration of
aguidewire
crossing the septum, is the most accurate
method for confirming the presence of a PFO.
Transesophageal

echocardiography (TEE) with bubble study is the accepted noninvasive standard for diagnosing a PFO, allowing quantification of shunt size, documentation of anatomic PFO characteristics, and differentiation among PFO, atrial septal defect, and pulmonary shunt (11,12). Transcranial Doppler is more sensitive but less specific because of its inability to differentiate between cardiac and pulmonary shunting; it carries a sensitivity of 97% and specificity of 93% when compared with TEE bubble study (13). Transthoracic echocardiography has a sensitivity of 46%, with improvement in sensitivity of up to 90% when performed with harmonic imaging (14–16). If a PFO is suspected, some centers prefer an initial screening with transcranial Doppler, followed by TEE (17,18). Angiographic documentation or exclusion of a PFO can be performed in case a cardiac catheterization is mandated for another reason (19).

FIRST 3 RANDOMIZED TRIALS

CLOSURE I TRIAL. CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale; NCT00201461) was the first randomized, multicenter, open-label trial (with blinded adjudication of outcome events) to evaluate the

(NMT Medical, Boston, Massachusetts) itself. The device was associated with a higher than expected rate of atrial fibrillation. A total of 26 patients developed atrial fibrillation; 23 occurred in the device arm, and 3 of these 26 patients had recurrent stroke. In addition, of patients randomized to the device arm, 14% had relevant residual right-to-left shunting on 6-month follow-up echocardiography. However, an as-

efficacy and safety of percutaneous PFO closure plus medical therapy (aspirin, warfarin, or both) compared with medical therapy alone for secondary prevention of stroke or TIA. A total of 909 patients, 18 to 60 years of age, with cryptogenic stroke or TIA who had a TEE-confirmed PFO were included. At a 2-year follow-up, the primary composite endpoint of stroke, TIA, and death occurred in 5.5% of patients in the device arm and 6.8% in the medical therapy arm ($p=0.37$). In addition, PFO closure did not significantly reduce the incidence of recurrent stroke (2.9% vs. 3.1%; $p=0.79$) or TIA (3.1% vs. 4.1%; $p=0.44$). Device closure demonstrated a significantly higher rate of major vascular complications (3.2% vs. 0%) and atrial fibrillation (5.7% vs. 0.7%) at 2 years ($p<0.001$ for both) (20). Inconsistencies between CLOSURE I and previous

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observational studies have been attributed to problems with the STARFlex septal closure device

sociation between residual shunting and recurrent stroke has not been documented in randomized trials and some previous observational studies(21,22).

PC TRIAL. PC (Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of Patent Foramen Ovale [PFO] With Medical Treatment in Patients With Cryptogenic Embolism; [NCT00166257](#)) was a randomized, multicenter, open-label (with blinded adjudication of outcome events), trial including 414

patients (age < 60 years) with cryptogenic stroke, TIA

with pathological cerebral imaging, or a peripheral thromboembolic event, who had PFO(23). Patients were randomized to transcatheter PFO closure with the Amplatzer PFO Occluder (Abbott, Chicago, Illinois) versus medical therapy with antiplatelet or oral anti-coagulant treatment. The trial demonstrated no significant advantage of PFO closure over medical therapy in the primary endpoint of death, nonfatal stroke, TIA, or peripheral embolism (3.4% vs. 5.2%; $p = 0.34$) at 4-year follow-up. Separately, there was no statistical superiority of closure when comparing rates of nonfatal stroke (0.5% vs. 2.4%; $p = 0.14$) and TIA (2.5% vs. 3.3%; $p = 0.56$, respectively). The incidence of atrial fibrillation was not significantly increased after closure (2.9% vs. 1.0%; $p = 0.16$). No adverse events or thromboses occurred that could be attributed to the device.

A major

limitation of the PC trial was that it was statistically underpowered and prone to type II error. Also, inclusion of patients with noncerebral systemic embolisms made the study group different from those in most observational studies.

Moreover, the clinical presentation of TIA can be similar to transient neurological deficits experienced in migraine aura; addition of these patients may have resulted in inclusion of patients with symptoms unrelated to the PFO, although pathological cerebral imaging had to be present. Finally, lack of blinding and regular on-site audits may have resulted in undocumented off-label use of PFO occluding devices in the medical therapy arm(24,25).

RESPECT TRIAL. RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; [NCT00465270](#)) was a randomized, multicenter, open-label trial (with blinded adjudication of outcome

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events). It was event-driven and included patients 18 to 60 years of age with cryptogenic stroke who had a TEE-proven PFO. A total of 980 patients were randomized to closure with a PFO occluder of the type used in PC or medical therapy with aspirin, warfarin, clopidogrel, or aspirin plus dipyridamole. Selection of the appropriate medical therapy was left to the discretion of the neurologist.

Although initial results of the RESPECT trial at 2.6 ± 2.0 years of follow-up

(26) only showed a nonsignificant difference in recurrent stroke in the intention-to-treat analysis (0.7% vs. 1.4%; $p = 0.08$) (26), the long-term (median 5.9 years) follow-up data demonstrated that PFO closure significantly reduced the incidence of recurrent stroke compared with medical therapy (3.6% vs. 5.8%; hazard ratio [HR]: 0.55; 95% CI: 0.31 to 0.99; $p = 0.046$) (27). In addition, the extended follow-

up results of RESPECT showed a highly significant 62% relative risk reduction for recurrent stroke of unknown etiology in favor of closure. Reduction of stroke was enhanced in those with an atrial septal aneurysm (1.7% vs. 7.6%; HR: 0.20; 95% CI: 0.06 to 0.70; $p = 0.005$, interaction $p = 0.04$) and large shunt (2.0% vs. 6.9%; HR: 0.26; 95% CI: 0.10 to 0.71; $p = 0.005$, interaction $p = 0.04$). There was no significant difference in rate of serious adverse events, atrial fibrillation, or major bleeding between the 2 groups ($p > 0.10$ for all).

Despite the presence of 3 patients randomized to the closure arm who had recurrent strokes but had not received devices, the long-term intention-to-treat follow-up data from RESPECT showed that percutaneous PFO closures reduce the incidence of recurrent stroke compared with medical therapy in patients with cryptogenic stroke. In addition, the trial identified a plausible subset of patients who benefit the most from PFO closure (i.e., patients with atrial septal aneurysm or large shunts).

All the earlier trials were limited by slow patient recruitment, which may at least partly be explained by patient reluctance to undergo randomization because of personal preference for either closure or medical therapy. This also may have potentiated the use of off-label PFO occluding devices in those patients randomized to the medical therapy

arm, and may have resulted in predominantly low-risk patients in the trials.

META-ANALYSIS OF FIRST 3 RANDOMIZED TRIALS

A number of meta-analyses of the earlier PFO and stroke trials (CLOSURE I, PC, and RESPECT) were conducted in an effort to increase the sample size and reduce the risk of type II error (28,29). One study

FIGURE 1 PFO by Fluoroscopy and TEE

A PFO is shown angiographically after device closure (left) and by transesophageal echocardiography in the same projection before device closure (right). A contrast medium injection (left) from the inferior vena cava (IVC) shows no more passage through the channel still visible between the septum primum (SP) to the right and the septum secundum (SS) to the left on the image. The Eustachian valve (EV) is visible both by fluoroscopy (small solid white arrows) and by echocardiography. The large dotted yellow arrows indicate the blood directed from the IVC onto the patent foramen ovale by the EV. LA, atrium; PFO, patent foramen ovale; RA, right atrium; TEE, transesophageal echocardiography.

95% CI: 0.44 to 1.00), with stronger benefit when only PC and RESPECT were pooled (HR: 0.54; 95% CI: 0.29 to 1.01) in an intention-to-treat analysis (28). Both the PC and RESPECT trials used the same PFO occluder, which justified pooling the data from these trials.

Subsequently, a patient-level meta-analysis of CLOSURE I, PC, and RESPECT was published (30). The study confirmed that among 2,303 patients with a cryptogenic cerebrovascular event, PFO closure was superior to medical therapy for secondary prevention of stroke (HR: 0.58; $p = 0.043$), with a more robust benefit when the PFO occluder of PC and RESPECT was used (HR: 0.39; $p = 0.013$). A network meta-analysis including a trial randomizing between devices (31) confirmed that use of this PFO occluder was the preferable technique for PFO closure at that time (32).

CHANGE IN NORTH AMERICAN AND EUROPEAN STANCE

Following the positive results of the meta-analyses of the first 3 trials and the long-term follow-up of the RESPECT trial, the U.S. Food and Drug Administration (FDA) approved the PFO occluder used in PC and RESPECT on October 28, 2016. This approval was for percutaneous PFO closure in patients

showed that regardless of the type of device used, PFO closure was more efficacious than medical therapy for prevention of recurrent neurological events (HR: 0.67;

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TABLE 1 Clinical Trials Randomizing Cryptogenic Stroke Patients to Percutaneous PFO Closure or Medical Therapy

Randomized Clinical Trial (Ref. #)	Cohort (Number of Patients)	Device Arm	Medical Arm	Follow-Up	Primary Outcome	Results
CLOSURE I (20) yrs (909)	Cryptogenic stroke or TIA; PFO; age 18–60	PFO closure; aspirin and warfarin for 1 month, then aspirin for 2 yrs	Aspirin, warfarin or both	2 yrs	Composite of stroke, TIA, PFO closure did not early death from any etiology and late neurological death	significantly reduce recurrent stroke or TIA compared with medical therapy
PC (23)	Cryptogenic stroke, TIA or peripheral embolism; PFO; age < 60 yrs (414)	PFO closure; aspirin for 5–6 months; clopidogrel or antithrombotic ticlopidine for 1–6 months	Antiplatelet or aspirin; extended release dipyridamole	Mean 4 yrs	Composite of death, nonfatal stroke, TIA, significantly reduce or peripheral recurrent embolic events or death compared with medical therapy	PFO closure did not
RESPECT (27) (extended follow-up)	Cryptogenic stroke; PFO; age 18–60 yrs (980)	PFO closure; aspirin and clopidogrel for 1 month, then aspirin for 5 months	Aspirin, warfarin, clopidogrel or aspirin; extended release dipyridamole	Median 5.9 yrs; closure reduced	Composite of recurrent nonfatal and fatal stroke events; stroke and early death compared with medical therapy	recurrent PFO
CLOSE (40)	Cryptogenic stroke; PFO with large shunt or atrial septal aneurysm; age 16–60 yrs (663)	PFO closure; aspirin and clopidogrel for 3 months, then single antiplatelet therapy	Aspirin, clopidogrel, or aspirin; extended-release dipyridamole or vitamin K	Mean 5.3 ± 2.0 yrs	Fatal or nonfatal stroke; PFO closure reduced recurrent stroke events compared with medical therapy	PFO closure reduced

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				antagonist or direct oral anticoagulant		
Gore REDUCE (41)	Cryptogenic strokePFO; age 18–59 yrs (664)	PFO closureaspirin, aspirin and dipyridamole, or clopidogrel	Aspirin, dipyridamole, or clopidogrel	Median 3.2 yrs closure	Freedomfromstroke; incidence ofnewbrain infarctionMRI	PFO recurrent strokeevents and new braininfarcts on MRI compared with medical therapy
MRI¼magnetic resonance imaging; PFO¼patent foramen ovale; TIA¼transient ischemic attack.						

aged 18 to 60 years who had strokes from presumed paradoxical embolism when another cause could not be determined after extensive clinical evaluation by a neurologist and cardiologist (33). The FDA concluded that the device demonstrated reassuring levels of efficacy and safety. Applicable specialty organizations in the United States have yet to react to these data regarding their recommendations (34,35). In contrast, as of November 2017, the Canadian guidelines were updated to recommend PFO closure plus long-term antiplatelet therapy over long-term antithrombotic therapy alone, in patients age 18 to 60 years with recent cryptogenic strokes or TIAs (36). The stance in Europe had been more liberal and proactive regarding PFO closure for more than a decade in most countries (37), except for the United Kingdom (38). It was thought that there was no need for adaptation of guidelines in most countries or by the European Stroke Organization (39).

NEW ERRANDOMIZED TRIALS

THE CLOSE TRIAL. CLOSE (Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; NCT00562289) was a randomized, multicenter, open-label trial (with

blinded adjudication of outcome events) enrolling 663 patients aged 16 to 60 years who had recent strokes attributed to PFO. Only patients with associated large interatrial shunts or atrial septal aneurysms were included. Patients eligible for all 3 arms were randomized in a 1:1:1 ratio to transcatheter PFO closure plus antiplatelet therapy, antiplatelet therapy alone, or oral anticoagulation. Closure using a variety of 11 devices was directly compared with antiplatelet therapy and oral anticoagulation, and antiplatelet therapy was also compared with oral anticoagulation (40).

At a mean follow-up of 5.3 ± 2.0 years, PFO closure was superior, with a lower rate of recurrent stroke (in fact no stroke at all) compared with medical therapy (0% vs. 6.0%; HR: 0.03; 95% CI: 0 to 0.26; $p < 0.001$). Successful closure was documented in 93% of patients on follow-up echocardiography. The rate of procedural complications from PFO closure was 5.9%. There was no significant difference in serious adverse events including major bleeding comparing closure with antiplatelet therapy alone ($p > 0.10$) but atrial fibrillation occurred at a higher rate in the device arm (4.6% vs. 0.9%; $p = 0.02$). Of 11 cases of atrial fibrillation after implantation of devices, 10 (91%) occurred within 1 month after the procedure with no recurrence during

FIGURE 2 Recurrent Stroke and Atrial Fibrillation/Flutter Outcomes in Cryptogenic Stroke Patients Randomized to PFO Closure or Medical Therapy

A Recurrent Stroke

Study or Subgroup	Device Events Total	Control Events Total	Weight	Risk Ratio M–H, Random, 95% CI	Risk Ratio M–H, Random, 95% CI
CLOSE (40)	02 38	14 235	6.1%	0.03 [0.00–0.57]	2017
RESPECT (27)	184 99	28 481	32.2%	0.62 [0.35–1.11]	2017
REDUCE (41)	6 441	12 223	24.1%	0.25 [0.10–0.66]	2017
PC (23)	12 04	5 210	9.5%	0.21 [0.02–1.75]	2013
CLOSURE (20)	124 47	134 62	28.0%	0.95 [0.44–2.07]	2012

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Total(95%CI) 1829 16111 0 0 . 0 % 0.42[0.20-0.91]
 Totalevents 37 72
 Heterogeneity: $\tau^2 = 0.38$; $\chi^2 = 9.72$, $df = 4$ ($P = 0.05$); $I^2 = 59\%$ 0.001 0.1 1 10 1000
 Test for overall effect: $Z = 2.22$ ($P = 0.03$) Favors[Device] Favors[Control]

B Atrial Fibrillation/Flutter

Summary forest plot for the efficacy outcome of recurrent stroke and safety outcome of atrial fibrillation/flutter. The relative size of the data markers indicates the weight of the sample size from each study. Reprinted with permission from Mojadidi et al.

(42). CI: confidence interval; CLOSE: Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; CLOSURE: Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale; M-H: Mantel-Haenszel; PC: Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of Patent Foramen Ovale (PFO) With Medical Treatment in Patients With Cryptogenic Embolism; PFO: patent foramen ovale; REDUCE: Gore Helex Septal Occluder/Gore Cardioform Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed Transient Ischemic Attack in Patients With PFO; RESPECT: Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

a median follow-up of 4.4 years. Oral anticoagulation was discontinued in 70% (7 of 10) of these patients after a median of 6 months.

Results of the CLOSE trial confirmed the early and long-term follow-up data of RESPECT, where percutaneous PFO closure was associated with significantly fewer recurrent strokes in patients with cryptogenic stroke who have certain echocardiographic features (i.e., presence of large shunt or atrial septal aneurysm). THE GORE REDUCE TRIAL. Gore REDUCE (Gore Helex Septal Occluder/Gore Cardioform Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale [PFO]; NCT00738894) was a randomized, multicenter, open-label trial (with blinded adjudication of outcome events), enrolling 664 patients, 18 to 59 years of age, with recent cryptogenic strokes, and who had a PFO

documented by TEE bubble study. Patients were randomized in a 2:1 ratio to undergo percutaneous PFO closure with the Gore Helex or Cardioform septal occluders (W.L. Gore and Associates, Flagstaff, Arizona) plus antiplatelet therapy or antiplatelet therapy alone. The index ischemic stroke was labeled as cryptogenic after other recognizable causes of stroke were ruled out, including large-artery atherosclerosis, small-vessel disease (lacunar infarct), established cardioembolic cause such as atrial fibrillation, hypercoagulable disorder needing anticoagulation, or arterial dissection. Exclusion of these etiologies was done with extensive cerebrovascular imaging via computed tomography or magnetic resonance angiography, ultrasonography, or catheter angiography. In addition, patients were excluded if they had strong risk factors for other mechanisms of stroke, including uncontrolled hypertension, uncontrolled diabetes,

(A) The STARFlex PFO device was used in the device arm of the CLOSURE I trial.
(B) The Amplatzer PFO occluder was used in the device arm of the PC and RESPECT trials.
(C) The Gore Cardioform Septal Occluder was 1 of 2 devices used in the device arm of the Gore REDUCE trial. *The CLOSURE I trial used 11 different PFO occluding devices. Abbreviations as in Figure 2.

autoimmune disease, or recent history of drug or alcohol use⁽⁴¹⁾.

At a median follow-up of 3.2 years, recurrent ischemic stroke occurred less frequently in the closure group compared with the medical therapy group (1.4% vs. 5.4%; HR: 0.23; 95% CI: 0.09 to 0.62; $p=0.002$).

Also, the rate of new infarctions confirmed by brain imaging was lower in the PFO closure arm compared with the antiplatelet-only arm (5.7% vs. 11.3%; risk ratio [RR]: 0.51; 95% CI: 0.29 to 0.91; $p=0.04$).

There was no statistical difference in serious adverse events—including major bleeding, between closure and antiplatelet therapy alone ($p>0.10$). Yet, atrial fibrillation occurred at a significantly higher rate with PFO closure (6.6% vs. 0.4%; $p<0.001$). Most cases of post-device implant atrial fibrillation (83%) occurred within 45 days after closure, and 59% resolved within 2 weeks. Of 29 patients with atrial fibrillation or flutter in the closure arm, 1 had a recurrent stroke.

Results from the Gore REDUCE trial confirmed the meta-analyses of earlier trials, long-term follow-up data from RESPECT and CLOSE, where transcatheter PFO closure was found to be superior to medical therapy alone in patients with cryptogenic stroke.

META-ANALYSIS OF ALL RANDOMIZED TRIALS

A study level meta-analysis of all 5 randomized clinical trials ($n=3,440$) confirmed that percutaneous PFO closure reduces the risk of recurrent stroke compared with medical therapy (2.0% vs. 4.5%; RR: 0.42; 95% CI: 0.20 to 0.91; $p=0.027$). However, the meta-analysis also found a significantly increased risk of atrial fibrillation in patients with devices (4.0% vs. 0.7%; RR: 4.55; 95% CI: 2.16 to 9.60; $p<0.01$) (Figure 2). The risk of atrial fibrillation was found to be

device dependent. The increase was nonsignificant with the PFO occluder of PC and RESPECT (RR: 2.10; $p=0.13$), but significant with the septal closure systems used in CLOSURE I (RR: 7.92; $p<0.01$), CLOSE (RR: 5.43; $p=0.027$), and Gore REDUCE (RR: 14.66; $p<0.01$) devices⁽⁴²⁾.

SAFETY OF PERCUTANEOUS PFO CLOSURE

A number of different PFO occluding devices have been implanted in the clinical trials: CLOSURE I used an abandoned system; PC and RESPECT the market-leading PFO occluder; Gore REDUCE 2 generation of a proprietary septal occluder; and CLOSE 11 different devices (Figure 3).

Observational studies have reported chest pain as an occasional complication associated with device implantation, thought to be secondary to an enhanced inflammatory response, in some cases due to nickel allergy. The PFO occluder of PC and RESPECT contains more nickel than other devices and has been high-lighted for this complication⁽⁴³⁾; however, PC and RESPECT had no increased chest pain events in the device arm compared with the medical therapy arm ($p=NS$ for both). It should be noted that an observational survey of close to 14,000 PFO device implants worldwide reported an incidence of 1 in 500 implants resulting in surgical removal, most commonly due to severe, persistent chest pain, thought to be caused by allergy-induced formation of excessive scar tissue in 50% of cases⁽⁴³⁾.

Safety results from the clinical trials showed no significant difference in all-cause serious adverse events (including major bleeding) when comparing percutaneous PFO closure with medical therapy. However, all trials, except for PC and RESPECT, had a

significantly higher incidence of atrial fibrillation in the device arm. Most cases of atrial fibrillation in the trials occurred early (<45 days) after implantation and consisted of a single paroxysmal episode that resolved spontaneously, medically, or with cardioversion. Only 3.8% of postclosure atrial fibrillation episodes reportedly progress to permanent atrial fibrillation (44).

The non-longer-available device of CLOSURE II had previously been associated with the highest incidence of significant device thrombosis, with 3.6% versus 0% with septal occluders of PC, RESPECT, or Gore REDUCE (45).

Atrial fibrillation was also most common with the devices of Gore REDUCE with 6.6%, which was higher than expected from previous observational studies (44,45), followed by the device of CLOSURE II with 5.7% and the device of PC and RESPECT with 1.8% (20,23,27,41,42).

CONCLUSIONS: FUTURE GUIDELINES

Based on the patient-level meta-analysis of the first 3 randomized trials (30), the CLOSE (40), RESPECT (extended follow-up) (26), and Gore REDUCE (41) trials, and the meta-analysis of all 5 randomized trials (42), PFO-occluding devices decrease the risk of recurrent stroke compared with medical therapy in patients with cryptogenic stroke. Also, based on subgroup analyses of the RESPECT trial (26,27), efficacy of PFO closure for prevention of stroke is enhanced in those patients with certain echocardiographic features (i.e., atrial septal aneurysm or large shunt).

Reasons for the discrepancy between the earlier numerically positive but statistically not significant randomized data and more recent significantly positive trials must be multifactorial. We attribute this largely to inclusion of patients with index strokes more likely secondary to paradoxical embolism or higher-risk PFOs in the 3 newly published trials. Gore REDUCE had very strict exclusion criteria to omit patients with other causes of stroke, such as large-artery atherosclerotic disease and small-vessel disease (lacunar infarcts),

based on extensive cerebrovascular imaging. It also excluded patients with uncontrolled risk factors. CLOSE only included patients with echocardiographic features suggestive of greater potential benefit with closure (atrial septal aneurysm or large shunt); this could explain the remarkable outcome of zero recurrent strokes in the device arm during 5 years. Although RESPECT also used strict inclusion criteria for selecting patients with cryptogenic stroke, the early negative results may be explained by a very low frequency of recurrent stroke (1% per year). However, the rate of recurrent stroke was continuous over the 10 years observed,

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and thus the benefit with device closure becomes significant with longer follow-up. Although there are no randomized data beyond 10 years, there is no reason to believe that this protective benefit will not persist. The lessons learned from all 5 trials have allowed the recognition of a "purer" patient population at greater risk of recurrent paradoxical embolism. Strict exclusion of other detectable causes of stroke aids in the recognition of patients whom it is likely have ischemic stroke associated with PFO. In such patients, a change in guideline to recommend percutaneous PFO closure as first-line therapy may be warranted.

Although there is a pathophysiological rationale for the use of oral anticoagulants to prevent recurrent paradoxical embolism, there is a paucity of data showing superiority or comparative effectiveness of anticoagulation compared with PFO closure or antiplatelets (9). The CLOSE trial demonstrated a nonsignificant 56% lower risk of stroke when oral anticoagulation was used instead of antiplatelet therapy. As anticoagulation was contraindicated in numerous patients, the study was

underpowered in this respect (46). Until a randomized trial is performed comparing efficacy and safety of oral anticoagulation versus PFO closure in patients with PFO-associated cryptogenic stroke, percutaneous PFO closure is to be considered the most effective and safest option to reduce the risk of recurrent stroke, according to evidence-based randomized data.

The clinical trials demonstrated that transcatheter PFO closure is safe, with no difference in serious adverse events compared with medical therapy, except for the risk of atrial fibrillation after implantation of the device. Given the potential of early undetected atrial fibrillation as a netiology of stroke, and the added risk of post-closure atrial fibrillation, it is recommended to use prolonged (≥30 days) cardiac monitoring to stringently avoid undiagnosed atrial fibrillation. Although extended cardiac monitoring is superior to 24-h monitoring to detect atrial fibrillation in patients with stroke that is suspected to be cryptogenic (47,48), this was not an inclusion criterion in any of the 5 cryptogenic stroke trials. Further research is needed to better understand the long-term prognostic outcomes of atrial fibrillation after device implantation. At present, these long-term prognostic outcomes are unknown.

The pathway to managing and labeling a patient's stroke as related to a PFO should involve a multidisciplinary team including a neurologist, cardiologist, and other health professional trained in the care of patients with stroke. The initial diagnosis of cryptogenic stroke is made by a neurologist; cardiologists should document the PFO and ensure that

CENTRAL ILLUSTRATION Evidence-Based Algorithm for PFO Closure in Ischemic Stroke Patients for Highest Clinical Yield, Based on Randomized Trials

Yes

Yes

Yes

Yes

Medical

therapy

Enhanced Reasons for PFO closure:

- Prior venous thromboembolism
- Multifocal cerebral deep white matter lesions
- Large PFO
- Atrial septal aneurysm
- Eustachian valve or Chiari network

Mojadidi, M.K. et al. J Am Coll Cardiol. 2018;71(9):1035-43.

Patients can expect the greatest benefit from percutaneous PFO closure if they have no other cardiovascular stroke causes on imaging/laboratory analyses, no uncontrolled risk factors, no atrial fibrillation or flutter, and no poor prognostic markers. PFO¼patent foramen ovale.

cardiovascular culprits and uncontrolled risk factors have been ruled out when recommending PFO closure. Counseling before closure should include discussion of individualized risks of the procedure based on comorbidities and discussion of the atrial septal anatomy and degree of right-to-left shunting (Central Illustration). We advocate for multidisciplinary cryptogenic stroke team to facilitate this pathway. This ensures that PFO closure is recommended for all patients who have stroke from no other likely source.

The relative safety and simplicity of percutaneous PFO closure and the proven protection against stroke open an avenue of further indications for PFO closure, such as in the presence of other potential causes of stroke or even as primary prevention of stroke in high-risk persons.

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