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Authors
Mojadidi, Mohammad K
Zaman, Muhammad O
Elgendy, Islam Y
et al.

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REVIEW TOPIC OF THE WEEK

Cryptogenic Stroke and Patent Foramen Ovale

Mohammad K. Mojadidi, MD,[a] Muhammad O. Zaman, MD,[a] Islam Y. Elgendy, MD,[a] Ahmed N. Mahmoud, MD,[a] Nimesh K. Patel, MD,[b] Nayan Agarwal, MD,[c] Jonathan M. Tobis, MD,[d] Bernhard Meier, MD[e]

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 peo-ple who suffer a cryptogenic stroke, 40% to 50% of patients have a PFO (1–3). A hypermobile septum primum, referred to as a atrial septal aneu-rysm, 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 fo-ramen ovale. A atrial septal aneurysm may open the PFO with every heartbeat, thereby increasing the po-tential 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 fo- ramen 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 (n¼10,327) 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). Ran-domized clinical trials were performed to determine unequivocally if percutaneous PFO closure is superior

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From [a]Division of Cardiology, Department of Medicine, University of Florida College of Medicine, Gainesville, Florida; [b]Division of Cardiology, Department of Medicine, Virginia Commonwealth University, Richmond, Virginia; [c]Interventional Cardiology, Cardiovascular Institute of the South, Houma, Louisiana; [d]Program in Interventional Cardiology, Division of Cardiology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California; and the [e]Department of Cardiology, University Hospital of Bern, Bern, Switzerland. Dr. Tobis has served as a consultant for St. Jude Medical and W.L. Gore; as a coinvestigator of the RESPECT trial; and as a proctor for Cardiac Dimensions. Dr. Meier has served on the Speakers Bureau for Abbott; has received speaker fees from Abbott; and has served as a co-primary investigator of the PC trial. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

FDA = Food and Drug Administration

PFO = patent foramen ovale

TEE = transesophageal echocardiography

TIA = transient ischemic attack

tomedical therapy for secondary prevention of cryptogenic stroke (Table1).

DIAGNOSIS AND QUANTIFICATION OF PFO

A right heart catheterization, with demonstration of a guidewire 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 be- tween 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 per- formed 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 random-ized, multicenter, open-label trial (with blinded adju- dication of outcome events) to evaluate the 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 fibril- lation (5.7% vs. 0.7%) at 2 years (p < 0.001 for both) (20). Inconsistencies between CLOSURE I and previous

(NMT Medical, Boston, Massachusetts) itself. The device was associated with a higher than expected rate of atrial fibrillation. A total of 26 patients devel- oped 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-

observational studies have been attributedtoprob- lems with the STARFlex septal closuredevice

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

PCTRIAL.PC(Randomized Clinical TrialComparing the EfficacyofPercutaneous ClosureofPatentFora-menOvale [PFO] With Medical TreatmentinPatientsWith Cryptogenic Embolism;NCT00166257)wasarandomized, multicenter, open-label (withblinded adjudicationofoutcomeevents), trialincluding414 patients (age<60years) with cryptogenic stroke,TIA with pathological cerebral imaging,oraperipheral thromboembolic event,who had PFO(23). Patients were randomizedtotranscatheter PFO closurewiththeAmplatzerPFOOccluder(Abbott,Chicago,Illinois) versus medical therapy with antiplateletororal anti-coagulant treatment.Thetrialdemonstratednosignificantadvantageof PFOclosureovermedicaltherapyintheprimary endpointofdeath,nonfatalstroke, TIA,orperipheral embolism (3.4% vs. 5.2%;p ¼0.34)at4-year follow-up. Separately, therewasnostatistical superiorityofclosure when comparing ratesofnonfatal stroke (0.5% vs. 2.4%;p¼0.14) andTIA(2.5% vs. 3.3%;p¼0.56, respectively).Theincidenceofatrialfibrillation was not significantly increased after closure (2.9% vs. 1.0%;p¼0.16).Noadverse eventsorthromboses occurred that couldbeattrib-utedtothedevice.

Amajor limitationofthePCtrialwasthatitwasstatistically underpoweredandpronetotypeIIerror.Also, inclusionofpatients with noncerebralsystemicembolisms madethestudy group different from thoseinmostobservationalstudies. Moreover,theclinicalpresentationofTIAcan besimilartotransient neurologicaldeficits experiencedinmigraineaura;additionofthese patientsmayhave resultedinin-clusionofpatients with symptoms unrelatedtothePFO,although pathological cerebralimaging hadtobepresent. Finally, lackofblinding and regularon-site auditsmayhave resultedinundocumentedoff-label useofPFOoccluding devicesinthemedicaltherapy arm(24,25).

RESPECT TRIAL.RESPECT (RandomizedEvaluation ofRecurrent Stroke ComparingPFOClosuretoEstablished Current StandardofCareTreatment;NCT00465270)wasar andomized, multicenter,open-label trial (with blindedadjudicationofoutcome

events).Itwasevent-drivenandincludedpatients18to 60yearsofage with cryptogenic stroke who hadaTEE-proven PFO.Atotalof980 patients were randomizedtoclosure withaPFOoccluderofthe type usedinPCormedicaltherapywithaspirin,warfarin,clopidogrel,oraspirinplusdipyridamole.Selection of theappropriate medical therapywaslefttothediscretionoftheneurologist. Although initialresultsoftheRESPECTtrialat2.6±2.0years offollow-up (26)onlyshowedanonsignificant differenceinrecurrent strokeintheintention-to-treat analysis (0.7% vs.1.4%;p¼0.08)(26), the long-term(median 5.9years) follow-up data demonstrated that PFO closure significantly reducedtheincidenceofrecur-rent stroke compared with medical therapy (3.6%vs.5.8%; hazard ratio [HR]: 0.55;95%CI: 0.31to0.999;p¼0.046)(27).Inaddition, the extendedfollow-upresultsofRESPECTshowedahighly significant 62% relative risk reduction for recurrent strokeofun- knownetiologyinfavorofclosure. Reductionofstroke was enhancedinthose withanatrialseptalaneurysm (1.7% vs. 7.6%; HR: 0.20;95% CI:0.06to0.70;p¼0.005, interactionp¼0.04)andlargeshunt(2.0% vs. 6.9%;HR:0.26: 95% CI: 0.10to0.71;p¼0.005; interactionp¼0.04). Therewasnosig-nificant differenceinrateofserious adverse events, atrialfibrillation,ormajor bleeding betweenthe2 groups (p>0.10 for all).

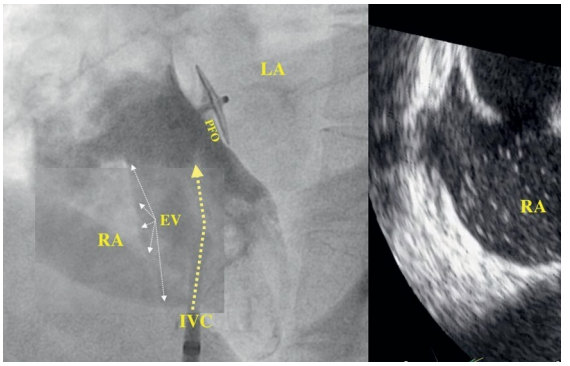
Despitethepresenceof 3patients randomizedtotheclosurearm who hadrecurrent strokesbuthadnotreceived devices,thelong-termintention-to-treat follow-updata fromRESPECTshowed that percuta- neous PFO closures reducetheincidenceofrecurrentstroke compared with medical therapyinpatientswith cryptogenic stroke.Inaddition, the trial identi-fiedplausible subsetsofpatientswhobenefit the most fromPFOclosure (i.e., patients with atrial septalaneurysmorlargeshunts).

All theearlier trials were limitedbyslowpatientrecruitment, whichmayatleast partlybeexplainedbypatient reluctancetoundergorandomizationbecauseofpersonal preferenceforeither closureormedicaltherapy. This also may havepotentiatedtheuseofoff-label PFO occluding devicesinthose pa- tients randomizedtothemedical therapy arm,andmayhave resultedinpredominantly low-riskpatientsinthetrials.

META-ANALYSISOFFIRST3RANDOMIZEDTRIALS

Anumberofmeta-analysesofthe earlier PFOandstroke trials(CLOSUREI,PC, and RESPECT)wereconductedinanefforttoincreasethe sample size and reduce the riskoftypeIIerror(28,29).Onestudy

FIGURE 1PFO 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*fl*uoroscopy (small solid white arrows) and by echocardiography. Thelarge dotted yellow arrowsindicate the blood directed from the IVC onto the patent foramen ovale by the EV. LA atrium; PFO¼patent foramen ovale; RA¼right atrium; TEE¼transesophageal echocardiography.

showed that regardlessofthetypeofdevice used,PFOclosurewasmore efficacious than medicalther- apy forpreventionofrecurrent neurological events(HR: 0.67; 95% CI: 0.44to1.00), with stronger benefit when onlyPCandRESPECT were pooled (HR:0.54;95% CI:0.29to1.01)inanintention-to-treatanalysis(28). Both thePCand RESPECT trials used the samePFOoccluder,which justifiedpoolingthe data from thesetrials.

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; p¼0.043), with a more robust benefit when the PFO occluder of PC and RESPECT was used (HR: 0.39; p¼0.013). A network meta-analysis including a trial randomizing between devices(31)confirmed that use of this PFO occluder was the pref- erable technique for PFO closure at that time(32).

CHANGE IN NORTH AMERICAN AND EUROPEAN STANCE

Followingthepositive resultsofthe meta-analysesofthefirst3trials andthelong-term follow-upoftheRESPECT trial, the U.S. Food and Drug Adminis- tration (FDA) approved thePFOoccluderusedinPCand RESPECTonOctober 28, 2016. This approvalwasfor percutaneousPFOclosureinpatients

TABLE 1Clinical 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	PrimaryOutcome	Results
CLOSURE I (20)	Cryptogenic stroke or TIAþ PFO; age 18–60 yrs(909)	PFO closureþaspirin and warfarin for 1 month, then aspirin for 2 yrs	Aspirin, warfarin or both	2yrs	Compositeofstroke,TIA, early deathfromany etiologyandlate neurologicaldeath	PFOclosuredidnot signi*fi*cantlyreduce recurrent stroke orTIA compared withmedical therapy
PC(23)	Cryptogenic stroke, TIA or peripheral embolismþPFO; age<60 yrs (414)	PFO closureþaspirin for 5–6 monthsþclopidogrelor antithromboticticlopidine for1–6months	Antiplatelet or therapy	Mean4yrs	Compositeofdeath, nonfatalstroke,TIA, signi*fi*cantlyreduceorperipheral recurrentembolic embolism	PFO closure didn ot events ordeath compared with medical therapy
RESPECT(27) (extended follow-up)	Cryptogenic strokeþPFO; age 18–60 yrs (980)	PFO closureþaspirin and clopidogrel for 1 month, then aspirin for 5 months	Aspirin, warfarin, clopidogrel or aspirinþextended release dipyridamole	Median 5.9 yrs	Compositeofrecurrent nonfatalandfatal strokeeventsstroke and withmedical	PFO closurereduced recurrent deathcompared therapy
CLOSE(40)	Cryptogenic strokeþPFO with large shunt or atrial septal aneurysm; age 16–60 yrs (663)	PFO closureþaspirin and clopidogrel for 3 months, then single antiplatelet therapy	Aspirin, clopidogrel, or aspirinþ extended-release dipyridamole or vitamin K	Mean5.3± 2.0yrs	Fatal or nonfatal stroke	PFO closurereduced recurrent strokeevents compared with medical therapy

			antagonist or direct oral anticoagulant			
Gore REDUCE (41)	Cryptogenic strokeþPFO; age 18–59 yrs (664)	PFO closureþaspirin, aspirin and dipyridamole, or clopidogrel	Aspirin, dipyridamole, or clopidogrel	Median 3.2 yrs	Freedomfromstroke; PFO closurereduced incidence ofnewbrain infarctonMRI	recurrent strokeevents and new braininfarcts on MRI compared with medical therapy

MRI¼magnetic resonance imaging; PFO¼patent foramen ovale; TIA¼transient ischemic attack.

aged18 to 60yearswho hadstrokes from presumedparadoxicalembolism when another cause could notbedetermined after extensive clinical evaluationby aneurologist and cardiologist(33). The FDA concluded that the device demonstratedareassuring levelofefficacy and safety. Applicable specialtyorganiza- tionsintheUnited States haveyet toreacttothesedata regarding their recommendations(34,35).Incontrast,as ofNovember 2017, the Canadian guide- lines were updatedtorecommend PFO closurepluslong-term antiplatelet therapy overlong-term antithrombotictherapy alone,inpatients age18to 60years with recent cryptogenic strokesorTIAs(36).ThestanceinEurope had been more liberal and pro- active regarding PFO closure for more thanadecadeinmost countries(37), except for the UnitedKingdom(38).Itwasthought that therewasnoneed for adaptationofguidelinesinmost countriesor bytheEuropean Stroke Organization(39).

NEWERRANDOMIZEDTRIALS

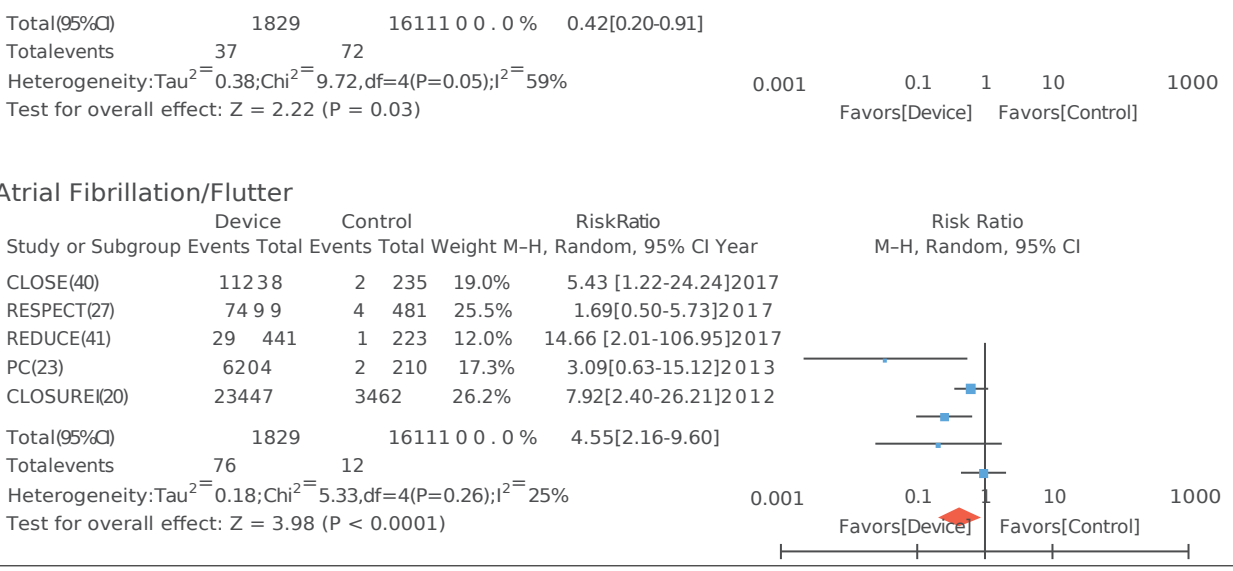
THECLOSE TRIAL.CLOSE (Patent Foramen Ovale ClosureorAnticoagulantsversus AntiplateletTher-apytoPrevent Stroke Recurrence;NCT00562289)wasarandomized, multicenter, open-label trial(with blinded adjudicationofoutcome events)enrolling663patients aged16 to 60yearswho hadrecentstrokes attributedtoPFO. Only patients withassoci-ated large interatrial shuntsoratrial septal aneu- rysms were included. Patients eligible for all3armswere randomizedin a1:1:1 ratiototranscatheterPFO closure plusantiplatelettherapy,antiplatelettherapy alone,ororalanticoagulation.Closureusingavariet yof 11deviceswasdirectly compared withantiplatelet therapyand oralanticoagulation,andantiplatelettherapy was alsocomparedwithoral anticoagulation(40).

Atameanfollow-upof5.3±2.0years,PFOclosurewassuperior,wit halowerrateofrecurrentstroke(infactnostrokea tall) compared with medicaltherapy (0% vs. 6.0%; HR: 0.03;95% CI:0 to0.26;p<0.001). Successful closurewasdocumentedin93%ofpatientsonfollow -up echocardiography. The rateofproce- duralcomplicationsfromPFOclosurewas5.9%.The rewasnosignificant differenceinserious adverse events includingmajorbleedingcomparingclosurewithan - tiplatelettherapyalone(p>0.10)butatrialfibrillation occurredatahigher rateinthedevicearm(4.6%vs.0.9%;p¼0.02).Of11 casesofatrialfibrillationafterimplantationofdevic es,10(91%) occurredwithin1month aftertheprocedure withnorecurrenceduring

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

ARecurrent Stroke

Study or Subgroup	Device Events	Total	Control Events	Total	Weight	RiskRatio M–H, Random, 95% CI	Year	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	
CLOSUREI(20)	124	47	134	62	28.0%	0.95[0.44-2.07]	2012	



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 ¼ confidence interval; CLOSE ¼ Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; CLOSURE I ¼ 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 ¼ Mantel-Haenszel; PC ¼ Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of Patent Foramen Ovale (PFO) With Medical Treatment in Patients With Cryptogenic Embolism; PFO ¼ patent foramen ovale; REDUCE ¼ 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 ¼ 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 percu-taneous 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, Ari-zona) 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 computer tomography or magnetic resonance angi-ography, 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,

FIGURE 3 PFO Occluders Used in Randomized Clinical Trials*

(A)TheSTARFlexPFOdevicewasusedinthedevicearmoftheCLOSUREItrial.
(B)TheAmplatzerPFOOccluderwasusedinthedevicearmof thePCandRESPECTtrials.
(C)TheGoreCardioformSeptalOccluderwas1of2devicesusedinthedevicearmoftheGoreREDUCEtrial.*The CLOSEtrialused11differentPFOoccludingdevices.AbbreviationsasinFigure2.

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

At amedian follow-upof3.2years, recurrent ischemic stroke occurred less frequentlyintheclosuregroup compared with the medical therapy group(1.4%vs. 5.4%; HR: 0.23; 95% CI: 0.09to0.62;p¼0.002). Also,therateofnewinfarctionsconfirmedbybrain imagingwaslowerinthePFOclosurearmcompared with the antiplatelet-only arm (5.7% vs. 11.3%; risk ratio [RR]: 0.51; 95% CI: 0.29 to 0.91; p¼0.04).

Therewasnostatisticaldifferenceinserious adverse events—including major bleeding, between closure and antiplatelettherapyalone(p>0.10).Yet,atrialfibrillation occurred at a significantly higher rate with PFO closure (6.6% vs. 0.4%; p<0.001). Most cases of post-device implant atrialfibrillation (83%) occurred within 45d a y s afterclosure,and59%resolvedwithin2weeks.Of29patientswithatrialfibrillationorflutterintheclosurearm,1 had a recurrentstroke.

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

Astudy levelmeta-analysisofall5randomizedclinicaltrials(n¼3,440) confirmedthatpercutaneousPFOclosure reducestheriskofrecurrent stroke compared with medical therapy (2.0%vs.4.5%;RR:0.42;95%CI: 0.20to0.91;p¼0.027). However, the meta-analysis also foundasignificantly increasedriskofatrialfibrillationinpatients with devices(4.0% vs. 0.7%;RR:4.55;95% CI:2.16to9.60;p<0.01) (Figure2).Theriskofatrialfibrillationwasfoundtobe device dependent. The increase was nonsignificant with the PFO occluder of PC and RESPECT (RR: 2.10; p¼0.13), but significant with the septal closure sys- tems used in CLOSURE I (RR: 7.92; p<0.01), CLOSE (RR: 5.43; p¼0.027), and Gore REDUCE (RR: 14.66; p<0.01) devices(42).

SAFETY OF PERCUTANEOUS PFO CLOSURE

Anumberofdifferent PFO occluding devices have been implantedinthe clinical trials: CLOSUREIusedanabandonedsystem;PCand RESPECTthemarket- leading PFOoccluder;GoreREDUCE2generationsof aproprietary septal occluder; and CLOSE11different devices (Figure3).

Observational studies have reported chest painasanoccasional complication associated withdeviceimplantation, thoughtto besecondaryto anenhancedinflammatory response,insome casesduetonickel allergy.ThePFOoccluderofPCandRESPECTcontains more nickel than other devicesand hasbeenhigh-lightedforthis complication(43);however,PCandRESPECThadno increased chest pain eventsinthedevicearmcompared withthemedical therapyarm(p¼NSforboth).Itshouldbenoted thatanobserva-tional surveyofcloseto14,000PFOdevice implants worldwide reportedanincidenceof1 in500implantsresultinginsurgical removal, most commonly dueto severe, persistentchest pain, thoughtto becausedbyallergy-induced formationofexcessive scar tissuein50%ofcases(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 incidenceofatrialfibrillationinthe device arm. Most casesofatrialfibrillationinthe trialsoccurredearly(<45days)afterimplantationa ndconsistedofasingleparoxysmal episodethatresolved spontaneously, medically, or with cardioversion. Only 3.8% of postclosure atrialfibrillation episodes report- edly progress to permanent atrialfibrillation(44).

Theno-longer-availabledeviceofCLOSUREIhadpreviously been associated withthehighest incidenceofsignificant devicethrombosis,with 3.6% versus0%with septal occludersofPC, RESPECT,orGoreREDUCE(45). Atrialfibrillationwasalso mostcommonwiththedevicesofGoreREDUCEwith 6.6%,whichwashigher than expectedfrompreviousobservational studies(44,45), followedby thedeviceofCLOSUREIwith 5.7%andthe deviceofPC andRESPECT with 1.8%(20,23,27,41,42).

CONCLUSIONS: FUTURE GUIDELINES

Basedonthe patient-level meta-analysisofthefirst3randomized trials(30), the CLOSE(40),RESPECT(extended follow-up) (26),andGore REDUCE(41)trials,andthe meta-analysisofall5randomizedtrials(42), PFO-occluding devices decreasetheriskofrecurrent stroke compared with medical therapyinpatients with cryptogenic stroke. Also, basedonsub-groupanalysesoftheRESPECTtrial(26,27),efficacy of PFOclosureforpreventionofstrokeisenhancedinth ose patients with certain echocardiographic fea- tures (i.e., atrial septal aneurysmorlargeshunt).

Reasons forthediscrepancy betweentheearlier numerically positivebutstatistically not significant randomized dataandmorerecent significantly positive trialsmustbemultifactorial.Weattribute this largelytoinclusionofpatients with index strokes more likely secondarytoparadoxicalembolismorhigher-risk PFOsin the3newlypub-lished trials. Gore REDUCEhadvery strict exclusion criteriatoomit patients with other causesofstroke,suchaslarge-artery atherosclerotic diseaseandsmall- vessel disease (lacunar infarcts), basedonextensivecerebrovascularimaging.Italso excludedpatientswith uncontrolled risk factors. CLOSE onlyincludedpatients withechocardiographicfeaturessuggestiveofgreater potential benefit with closure (atrial septal aneurysmorlarge shunt); this could explain the remarkable outcomeofzero recurrent strokesinthedevicearmduring5years. Although RESPECT also used strict inclusion criteriaforselecting patients with cryptogenic stroke, the early negative resultsmaybeexplainedby averylowfrequencyofrecurrentstroke(1% peryear). However,therateofrecurrentstrokewascontinuous over the10yearsobserved,

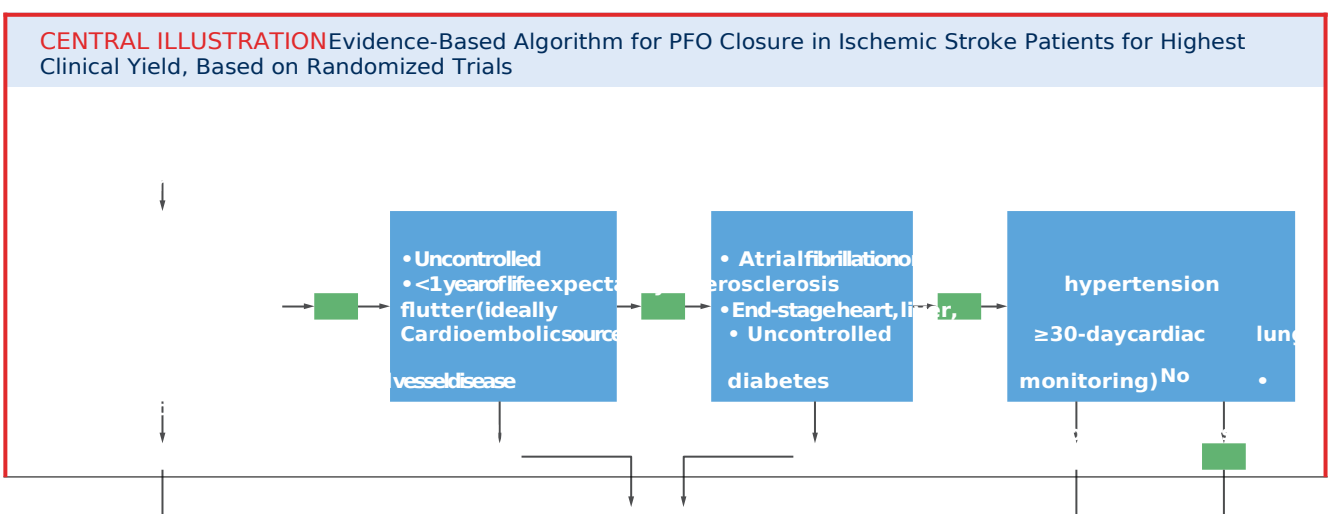
andthusthebenefit with device closure becamesig-nificant with longer follow-up. Although there areno randomizeddata beyond10years, thereisnoreasontobelieve that this protective benefit will not persist.Thelessons learned from all5trials have allowedtherecognitionofa“purer” patient populationatgreaterriskofrecurrent paradoxical embolism. Strictexclu-sionofotherdetectablecausesofstrokeaidsin therecognitionofpatientswhomost likely haveischemicstroke associated with PFO.Insuch patients,achangeinguidelinestorecommend percutaneousPFOclosureasfirst-line therapymay bewarranted.

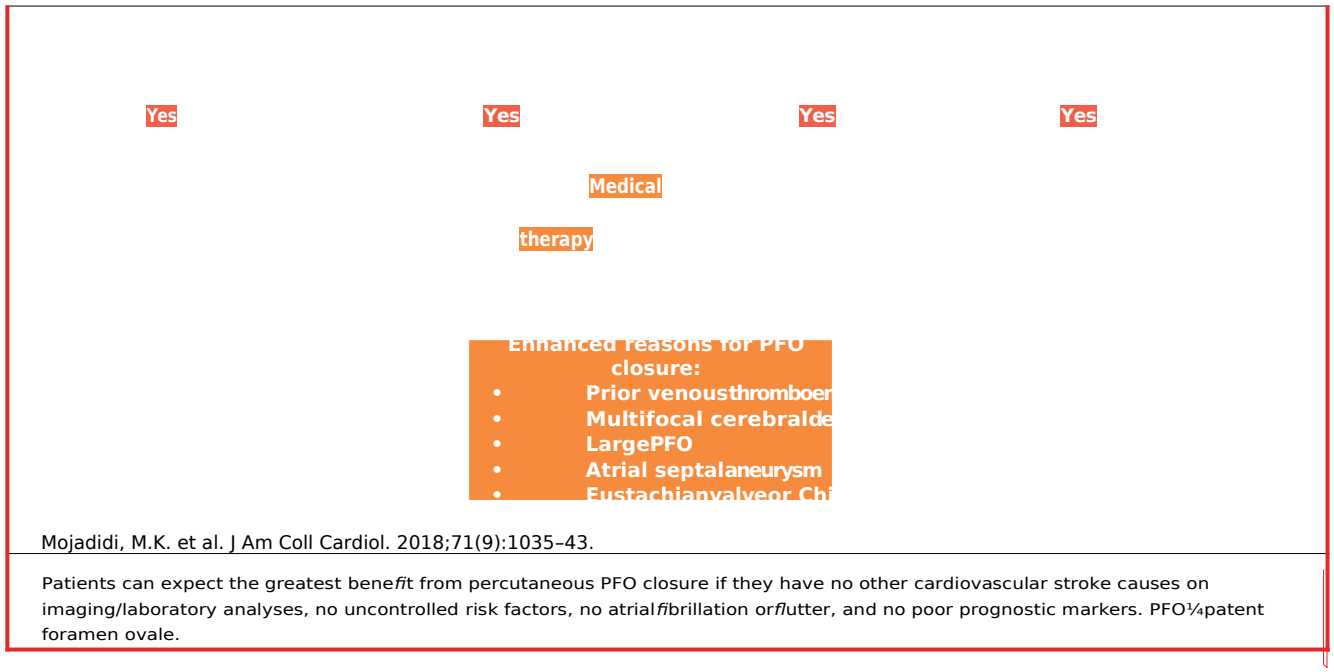
Although there is a pathophysiological rationale for the use of oral anticoagulants to prevent recurrent paradoxical embolism, there is a paucity of data showing superiority or comparativeness of anti-coagulation compared with PFO closure or anti- platelets(9). The CLOSE trial demonstrated a nonsignificant 56% lower risk of stroke when oral anticoagulation was used instead of antiplatelet ther- apy. 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 thattranscatheterPFOclosureissafe, withnodifferenceinseriousadverse events compared with medical therapy, exceptfor theriskofatrialfibrillation afterimplan-tationofthedevice. Giventhepotentialofearlyun-detected atrialfibrillationasanetiologyofstroke,and theadded riskofpost-closureatrialfibrillation,it isrecommendedtouse prolonged($30days)cardiacmonitoringtostringently avoid undiagnosedatrialfibrillation. Although extended cardiac monitoringissuperiorto24-h monitoringtodetect atrialfibrillationinpatients with stroke thatissuspectedto becryp-togenic(47,48), thiswas notaninclusion criterionin any of the5cryptogenic stroke trials.Furtherresearchisneededtobetter understand thelong-termprognostic outcomesofatrialfibrillationafterdeviceimplantation.Atpresent, these long-termprognosticoutcomesareunknown.

The pathwaytomanagingandlabelingapatient’s strokeasrelatedto aPFOshould involveamultidisciplinary team includinganeurologist, cardiologist,andother healthprofessionalstrainedin thecareofpatients with stroke. The initialdiagnosisofcryptogenic strokeismadeby aneurologist;car-diologistsshoulddocumentthePFOandensurethat

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





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 riskfactorshave been ruledoutwhen recommendingPFO closure. Counselingbeforeclosure should includediscussionofindividualized risksoftheprocedurebasedoncomorbiditiesanda discussionofthe atrial septal anatomy and degreeofright-to-leftshunting (Central Illustration).Weadvocateformultidisci-plinary cryptogenic stroke teamstofacilitate this pathway. This ensures that PFO closureisrecom-mendedfor allpatientswhohave stroke fromnoother likelysource.

Therelative safetyandsimplicityofpercutaneousPFOclosure andtheproven protection againststrokeopenanavenueoffurther indicationsforPFOclosure,suchas inthepresenceofotherpotentialcausesofstrokeor evenasprimary preventionofstrokeinhigh-riskpersons.

ADDRESS FOR CORRESPONDENCE:Prof. Bernhard Meier, Department of Cardiology, University Hospi- tal, Freiburgstrasse, 3010 Bern, Switzerland. E-mail:bernhard.meier@insel.ch.

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