Annals of Internal Medicine REVIEW

Device Closure Versus Medical Therapy Alone for Patent Foramen Ovale in Patients With Cryptogenic Stroke

A Systematic Review and Meta-analysis

Rahman Shah, MD; Mannu Nayyar, MD; Ion S. Jovin, MD, ScD; Abdul Rashid, MD; Beatrix R. Bondy, MD; Tai-Hwang M. Fan, MD, PhD; Michael P. Flaherty, MD, PhD; and Sunil V. Rao, MD

Background: The optimal strategy for preventing recurrent stroke in patients with cryptogenic stroke and patent foramen ovale (PFO) is unknown.

Purpose: To compare transcatheter PFO closure with medical therapy alone for prevention of recurrent stroke in patients with PFO and cryptogenic stroke.

Data Sources: PubMed and the Cochrane Library (without language restrictions) from inception to October 2017, reference lists, and abstracts from cardiology meetings.

Study Selection: Randomized trials enrolling adults with PFO and cryptogenic stroke that compared stroke outcomes (main outcome) and potential harms in those receiving transcatheter device closure versus medical therapy alone.

Data Extraction: Two investigators independently extracted study data and rated risk of bias.

Data Synthesis: Of 5 trials, 1 was excluded because it used a device that is no longer available due to high rates of complications and failure. Four high-quality trials enrolling 2892 patients showed that PFO closure decreased the absolute risk for recurrent stroke by 3.2% (risk difference, −0.032 [95% CI, −0.050 to −0.014]) compared with medical therapy. The treatment strategies did not differ in rates of transient ischemic attack or major bleeding. Closure of PFOs was associated with higher rates of new-onset atrial fibrillation (AF) than medical therapy alone in all trials, but this outcome had marked between-trial heterogeneity (I^2 = 82.5%), and high event rates in some groups resulted in extreme values for CIs.

Limitation: Heterogeneity of device type and antithrombotic therapy across trials, small numbers for some outcomes, and heterogeneous and inconclusive AF results.

Conclusion: In patients with PFO and cryptogenic stroke, transcatheter device closure decreases risk for recurrent stroke compared with medical therapy alone. Because recurrent stroke rates are low even with medical therapy alone and PFO closure might affect AF risk, shared decision making is crucial for this treatment.

Primary Funding Source: None.

Ann Intern Med. 2018;168:335-342. doi:10.7326/M17-2679 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 9 January 2018.

Stroke is a leading cause of death and long-term disability worldwide (1). Approximately one third of ischemic strokes have no identifiable cause and are classified as cryptogenic (1, 2). Many studies show that patent foramen ovale (PFO) is associated with cryptogenic stroke, particularly in young patients (3). Thus, transcatheter device closure of the defect may reduce the risk for recurrent stroke, and observational studies have suggested its efficacy (4, 5). However, the first 3 randomized clinical trials in this field failed individually to prove that PFO closure was superior to medical therapy alone (6–8). The primary criticisms of those trials have been small numbers of events and relatively short follow-up, raising the probability of a type II error (9). In recent months, 2 new randomized trials and a long-term follow-up study of 1 of the early trials have suggested that PFO closure is superior to medical therapy alone to prevent recurrent stroke in patients with cryptogenic stroke and PFO (10–12). Therefore, we did an updated meta-analysis of trials comparing transcatheter PFO closure with medical therapy alone for prevention of recurrent stroke in such patients.

Methods

We developed and followed a protocol that is not registered but is available online (Part 1 of the Supplement, available at Annals.org) and followed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (13).

Data Sources and Searches

We did computerized literature searches of the PubMed and Cochrane databases from their respective inceptions to October 2017 (without language restrictions). Searches were done using various combinations of the following terms: *patent foramen ovale*, *PFO*, *device*, *closure*, *medical therapy*, *stroke*, *transient ischemic attack*, *TIA*, and *clinical trial*. We also reviewed abstracts from major international cardiology meetings and cross-referenced relevant articles found in the searches. We searched Google Scholar and PubMed from January 2012 to October 2017 to identify relevant meta-analyses and reviewed their reference lists (Part 2 of the Supplement). Finally, we searched

See also:

Related article 343
Editorial comment 367

Web-Only
Supplement
CME/MOC activity

Table 1. Characteristics of Included Trials

Characteristic	PC, 2013 (7)	RESPECT Extended, 2017 (12)	CLOSE, 2017 (10)	REDUCE, 2017 (11)
Total participants, *n*				
Device group	204	499	238	441
MTA group	210	481	596*	223
Mean age (SD), *y*				
Device group	44.3 (10.2)	45.7 (9.7)	42.9 (10.1)	45.4 (9.3)
MTA group	44.6 (10.1)	46.2 (10.0)	43.8 (10.5)	44.8 (9.6)
Diabetes, %				
Device group	2.5	6.6	1.3	4.1
MTA group	2.9	8.5	3.8	4.5
Hypertension, %				
Device group	24.0	32.1	11.3	25.4
MTA group	27.6	31.8	10.2	26
Severe/substantial shunt, %				
Device group	23.2	49.5	90.7	42.8
MTA group	20.1	48.0	94.3	36.6
Atrial septal aneurysm, %				
Device group	23.0	36.1	34.0	20.4
MTA group	24.3	35.3	33.2	Not reported†
Funding	Industry (St. Jude Medical)	Industry (St. Jude Medical)	French Ministry of Health	Industry (W.L. Gore & Associates)
Follow-up, *y*				
Device group	4.1‡	Median: 5.9 (IQR, 4.2–8.0)	Mean: 5.4 (SD, 1.9)	Median: 3.2 (IQR, 2.2–4.8)
MTA group	4.0‡	Median: 5.9 (IQR, 4.2–8.0)	Mean: 5.2 (SD, 2.1)	Median: 3.2 (IQR, 2.2–4.8)
Study design	Prospective, multicenter, randomized, open-label, superiority trial	Prospective, multicenter, randomized, open-label, superiority trial	Investigator-initiated, multicenter, randomized, open-label, superiority trial	Prospective, multicenter, randomized, open-label, superiority trial
Study setting	29 centers in Europe, Canada, Brazil, and Australia	69 sites in the United States and Canada	32 sites in France and 2 sites in Germany	63 sites in Canada, Denmark, Finland, Norway, Sweden, United Kingdom, and the United States
Study dates	24 February 2000–19 February 2009	23 August 2003–28 December 2011; extended follow-up database was locked on 31 May 2016	December 2007–December 2016	December 2008–February 2015
Missing data (withdrawn or lost to follow-up), %				
Device group	15.2	20.8	8.8	8.8
MTA group	20.0	33.3	11.0	14.8

CLOSE = Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; IQR = interquartile range; MTA = medical therapy alone; PC = Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; REDUCE = GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients; RESPECT = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.
* Further stratified into the antiplatelet group (n = 409) and the anticoagulant group (n = 187).
† Presence of an atrial septal aneurysm was determined at the time of patent foramen ovale closure and therefore was not recorded before trial entry or among patients in the antiplatelet-only group.
‡ Mean (SD) was not reported by the investigators.

ClinicalTrials.gov (October 2017) to identify ongoing trials and evaluate the possibility of publication bias.

Study Selection

Randomized controlled trials (RCTs) were included if they enrolled patients with PFO and cryptogenic stroke and randomly assigned them to either transcatheter device closure or medical therapy alone. We excluded duplicate reports and studies not reporting on recurrent stroke. No restrictions based on study design (other than RCT), follow-up duration, or publication language were applied. Two reviewers independently screened the studies' titles and abstracts and then reviewed the full text of selected articles to confirm eligibility.

Data Extraction and Study Quality

Using prespecified forms, 2 investigators independently extracted data on study characteristics, design, outcomes, and funding sources. Disagreements were resolved by consensus. We contacted corresponding authors for additional information on trials that did not report various types of antithrombotic therapy.

Our main outcome of interest was risk for recurrent stroke. Secondary outcomes of interest were rates of transient ischemic attack (TIA), major bleeding, and new-onset atrial fibrillation (AF) or flutter. We abstracted the most up-to-date data (that is, from the longest follow-up) for each outcome in each study. Study definitions were used for outcome data (Appendix Table 1, available at Annals.org). Independent clinical event committees, whose members were unaware of study group assignments, adjudicated the end points. Potential risk of bias was appraised by using the Cochrane Collaboration guidelines (random sequence generation and random allocation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; and selective outcome reporting bias) (14). We assessed risk of bias for the main outcome of recurrent stroke.

Data Synthesis and Analysis

We summarized results for outcomes reported in studies that used commercially available PFO closure devices and combined data when we saw little or no statistical heterogeneity in outcome findings between those studies. A standard pairwise meta-analysis was done using Comprehensive Meta-Analysis software, version 3 (Biostat). Pooled effect sizes were calculated using the Knapp–Hartung random-effects estimator and were expressed as risk differences (RDs) and 95% CIs (15). We chose the Knapp–Hartung method because it captures the uncertainty associated with statistical heterogeneity better than the traditional DerSimonian–Laird method (16). When a treatment group had 0 events, continuity correction was done by adding a factor of the reciprocal of the size of the opposite treatment group to the cells (17). All analyses were based on the intention-to-treat approach. In the CLOSE (Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence) trial, medical therapy was further stratified into antiplatelet and anticoagulant groups (10). Heterogeneity across trials was evaluated using the Cochran Q test and the Higgins I^2 test (18). The measure of I^2 can be interpreted as the percentage of variability resulting from heterogeneity between studies rather than from sampling error (18). When statistical heterogeneity was discovered, a sensitivity analysis was done by excluding 1 study at a time and evaluating the effect on summary results (19). Publication bias was not assessed because the number of trials (<10) was inadequate to properly examine a funnel plot or to use more advanced regression-based assessments (20).

Role of the Funding Source

This review received no external funding or other support (such as supply of data).

RESULTS

Study Selection and Patient Populations

Of 621 articles initially identified, 5 RCTs trials met inclusion criteria (Appendix Figure 1, available at Annals.org). One 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), used the STARFlex device (NMT Medical) for PFO closure. This device is no longer commercially available because of its high complication rate and low procedural success rate (6, 21). To enhance generalizability of findings, we excluded CLOSURE I from further analysis and focused on 4 trials, including 2892 patients, that evaluated available devices (7, 10–12).

Table 1 presents the characteristics of the trials, and Part 3 of the Supplement shows each trial's inclusion and exclusion criteria. All were multicenter, randomized, open-label, superiority trials and were industry-sponsored, with the exception of the CLOSE trial, which was supported by a grant from the French Ministry of Health. Characteristics of enrolled patients, such as age, history of diabetes, and hypertension, were similar across all studies. The mean age of patients was less than 50 years. We classified all studies as high-quality (Appendix Figure 2, available at Annals.org).

Medical Therapy and Device Interventions

The antithrombotic therapies used at discharge and at last follow-up (Table 2) and the type of device used for PFO closure (Appendix Table 2, available at Annals.org) varied across trials. In the PC (Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism) and RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trials, an Amplatzer PFO Occluder (St. Jude Medical) was used (7, 12). Patients in the device group of the PC trial received aspirin (100 to 325 mg/d) for at least 5 months as well as ticlopidine (50 to 500 mg/d) or clopidogrel (75 to 150 mg/d) for 1 to 6 months. In the medical therapy–alone group, the decision to continue antithrombotic therapy was left to the discretion of the treating physician and could have included antiplatelet therapy or oral anticoagulation, provided that patients received at least 1 antithrombotic drug.

Patients in the device group of the RESPECT trial received 81 to 325 mg of aspirin and clopidogrel for 1 month, followed by aspirin monotherapy for 5 months. After 5 months, antithrombotic therapy was continued at the discretion of the site investigator. Patients in the medical therapy–alone group received aspirin, warfarin, clopidogrel, or aspirin combined with extended-

Table 2. Antithrombotic Therapies in the Included RCTs

Variable	PC, 2013 (7)	RESPECT Extended, 2017 (12)	CLOSE, 2017 (10)	REDUCE, 2017 (11)
Protocol for antithrombotic therapy				
Device group	Aspirin (5 or 6 mo) and ticlopidine or clopidogrel (1–6 mo).	Aspirin (6 mo) and clopidogrel (1 mo); after 6 mo, antithrombotic therapy was at the discretion of the site investigator	Aspirin (3 mo) and clopidogrel (3 mo); after 3 mo, single antiplatelet therapy was at the discretion of the site investigator	Clopidogrel (3 d). After 3 d, use of antiplatelet therapy was at the discretion of the site investigator
MTA group	Antiplatelet therapy or oral anticoagulation at the discretion of the site investigator, provided ≥1 antithrombotic therapy was used	Aspirin or warfarin or clopidogrel or aspirin and dipyridamole at the discretion of the site investigator	Antiplatelet group: Aspirin or clopidogrel or aspirin and dipyridamole* Anticoagulant group: Vitamin K antagonists or direct oral anticoagulants*	Aspirin or clopidogrel or aspirin and dipyridamole at the discretion of the site investigator
Antithrombotic therapies, %				
At discharge				
Aspirin				
Device group	89.2	–	–†	–
MTA group	57.1	60.9	–	–
Thienopyridine‡				
Device group	51.0	–	–	–
MTA group	16.7	20.2	–	–
Dipyridamole				
Device group	–	–	–	–
MTA group	–	8.1	–	–
Oral anticoagulant				
Device group	2.9	–	–	–
MTA group	30.5	25.2	–	–
None				
Device group	2.4	–	–	–
MTA group	3.9	–	–	–
At last follow-up				
Aspirin				
Device group	41.9	87.0	–	69.8
MTA group	63.3	65.0	–	65.4
Thienopyridine‡				
Device group	3.9	16.0	–	26.7
MTA group	8.6	15.0	–	33.1
Dipyridamole				
Device group	–	1.0	–	6.1
MTA group	–	8.0	–	8.1
Oral anticoagulant				
Device group	3.1	2.0	–	–
MTA group	17.7	19.0	–	–
None				
Device group	12.8	6.0	–	–
MTA group	51.2	2.0	–	–

CLOSE = Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; MTA = medical therapy alone; PC = Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; RCT = randomized controlled trial; REDUCE = GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients; RESPECT = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

* The MTA group was further stratified into the antiplatelet therapy group and the anticoagulant therapy group.

† Discharge and last follow-up medications in the CLOSE trial were not reported.

‡ In the PC trial, either clopidogrel or ticlopidine was used at the discretion of the prescribing physician. All other trials used clopidogrel as the thienopyridine of choice.

release dipyridamole at the discretion of the site investigator.

In the CLOSE trial, 1 of 11 devices was used (**Appendix Table 2**) (10). The device-closure groups received dual antiplatelet therapy (75 mg of aspirin plus 75 mg of clopidogrel daily) for 3 months, followed by single antiplatelet therapy for the remainder of the trial. The medical therapy–alone groups were further stratified into anticoagulant and antiplatelet groups. Patients assigned to oral anticoagulants received vitamin K antagonists or direct oral anticoagulants. Patients assigned to the antiplatelet group received aspirin, clopidogrel, or aspirin combined with extended-release dipyridamole at the discretion of the treating physician. The trial investigators did not report the exact proportion of patients who received various antithrombotic therapies at discharge or at last follow-up.

In the REDUCE (GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients) trial, the HELEX Septal Occluder (W.L. Gore & Associates) was implanted in 158 patients and the CARDIOFORM Septal Occluder (W.L. Gore & Associates) in 250 patients (11). Those in the device group were treated with a 300-mg loading dose of clopidogrel followed by 75 mg per day for 3 days. After 3 days, the decision to continue antiplatelet therapy was left to the discretion to the local investigator; the type of antiplatelet agent used in the medical therapy–alone group was also determined by the local investigator. However, the type of antiplatelet therapy had to be the same in both groups at a given site.

Outcomes

Transcatheter device closure of PFO compared with medical therapy alone decreased absolute risk for recurrent stroke by 3.2% (RD, −0.032 [95% CI, −0.050 to −0.014]; $P = 0.011$) (Figure 1). The summary result did not change when we used data only from the antiplatelet subgroup (RD, −0.033 [CI, −0.063 to −0.004]; $P = 0.037$) or anticoagulant subgroup (RD, −0.021 [CI, −0.040 to −0.002]; $P = 0.037$) from the medical therapy–alone group of the CLOSE trial.

Device closure did not decrease risk for TIA (RD, −0.004 [CI, −0.017 to 0.010]; $P = 0.46$) compared with medical therapy alone (Figure 2, *top*). Major bleeding risk did not differ between the 2 groups (RD, −0.021 [CI, −0.051 to 0.009]; $P = 0.093$) (Figure 2, *middle*).

Transcatheter device closure of PFO was associated with higher rates of new-onset AF than medical therapy alone in all trials (Figure 2, *bottom*). Because between-trial heterogeneity was evident for this outcome ($Q = 17.14$; $P < 0.001$; $I^2 = 82.5\%$) and high event rates in some groups heavily influenced CIs, a pooled estimate was considered inappropriate (22). Removing any 1 of the studies during sensitivity analyses did not eliminate heterogeneity. Heterogeneity most likely resulted from use of different types of devices across the trials.

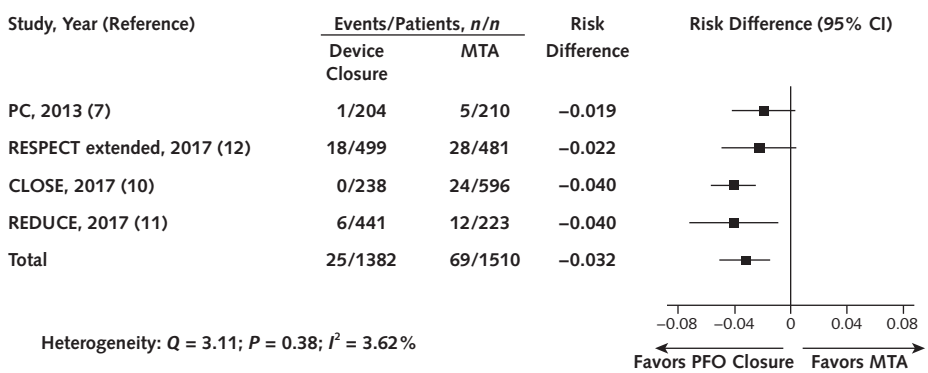
DISCUSSION

In this analysis of 2892 patients enrolled in 4 RCTs, we found that transcatheter device closure of PFO decreased the absolute risk for recurrent stroke by 3.2% compared with medical therapy alone in patients with PFO and cryptogenic stroke. Rates of major bleeding and TIA did not differ between the 2 therapies. We considered the association of device therapy with new-onset AF to be inconclusive because of marked heterogeneity between trials and extreme values for CIs in some cases.

Stroke is a leading cause of morbidity and mortality worldwide (1). It is a clinically heterogeneous event, and about 87% of strokes are ischemic (23). An estimated 25% to 40% of ischemic strokes are cryptogenic, defined as involving a brain infarction not clearly attributable to a definite cause (such as cardioembolism, large artery atherosclerosis, or small artery disease) despite extensive vascular, cardiac, and serologic evaluations (2). Thus, without clear cause, managing cryptogenic stroke is a major clinical conundrum and is mostly based on educated guesses. Several case–control studies have shown that PFO is associated with cryptogenic stroke (3). It is one of the most common congenital abnormalities, is present in about 25% of the population, and is not associated with increased risk for stroke in the general population (24, 25). The prevalence of PFO might be as high as 66% in patients younger than 55 years who are affected by cryptogenic stroke (5). A paradoxical embolism is the mechanism by which PFO might cause stroke, and transcatheter device closure of the defect might reduce the risk for recurrent stroke. A meta-analysis of 48 observational studies showed that PFO closure is associated with an 84% lower risk for recurrent stroke than medical therapy alone (4).

Surprisingly, the first 3 RCTs (CLOSURE I, PC, and RESPECT) in this field failed individually to show that PFO closure was superior to medical therapy alone (6–8). The primary limitations of these trials were small numbers of events and relatively short follow-up. In ad-

Figure 1. Forest plot for recurrent stroke.



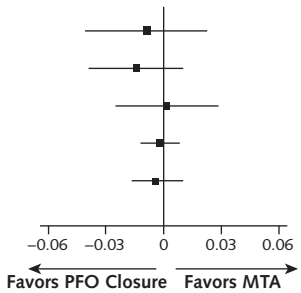
Individual and pooled risk ratios are shown for recurrent stroke. CLOSE = Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; MTA = medical therapy alone; PC = Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; PFO = patent foramen ovale; REDUCE = GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients; RESPECT = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

Figure 2. Forest plots for TIA, major bleeding, and atrial fibrillation.

TIA

Study, Year (Reference)	Events/Patients, *n*/*n*		Risk Difference
	Device Closure	MTA	
PC, 2013 (7)	5/204	7/210	−0.009
RESPECT extended, 2017 (12)	17/499	23/481	−0.014
CLOSE, 2017 (10)	8/238	19/596	0.002
REDUCE, 2017 (11)	1/441	1/223	−0.002
Total	31/1382	50/1510	−0.004

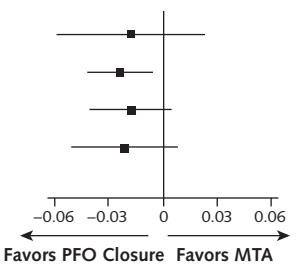
Heterogeneity: $Q = 0.97$; $P = 0.81$; $I^2 = 0.00\%$



Major Bleeding

Study, Year (Reference)	Events/Patients, *n*/*n*		Risk Difference
	Device Closure	MTA	
PC, 2013 (7)	8/204	12/210	−0.018
CLOSE, 2017 (10)	2/238	19/596	−0.023
REDUCE, 2017 (11)	4/441	6/223	−0.018
Total	14/883	37/1029	−0.021

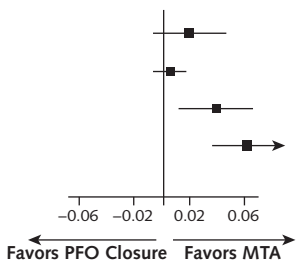
Heterogeneity: $Q = 0.16$; $P = 0.92$; $I^2 = 0.00\%$



Atrial Fibrillation

Study, Year (Reference)	Events/Patients, *n*/*n*		Risk Difference
	Device Closure	MTA	
PC, 2013 (7)	6/204	2/210	0.020
RESPECT extended, 2017 (12)	7/499	4/481	0.006
CLOSE, 2017 (10)	11/238	4/596	0.040
REDUCE, 2017 (11)	29/441	1/223	0.061

Heterogeneity: $Q = 17.14$; $P < 0.001$; $I^2 = 82.5\%$



Individual and pooled risk ratios are shown for TIA and major bleeding. For risk for atrial fibrillation, only risk ratios for individual trials are shown. CLOSE = Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; MTA = medical therapy alone; PC = Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; PFO = patent foramen ovale; REDUCE = GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients; RESPECT = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; TIA = transient ischemic attack.

dition, CLOSURE I used a device (the STARFlex occluder) that is now considered inferior because of its high complication rate and low procedural success rate (6, 21, 26). Nevertheless, a meta-analysis of the first 3 trials suggested that device closure of PFO was superior to medical therapy alone for prevention of recurrent stroke (9, 27–29). This led the U.S. Food and Drug Administration (FDA) to approve the Amplatzer PFO Occluder for percutaneous closure of PFO in October 2016. However, the FDA mandated that the device should be used only after a patient had been evaluated carefully by a neurologist and a cardiologist and after other known causes of stroke had been ruled out. The importance of the meticulous work-up to exclude other causes of stroke was highlighted by the CLOSURE I study, in which investigators found other causes of re-

current stroke or TIA in one fourth of patients initially believed to have cryptogenic stroke (6). Despite FDA approval, the American Academy of Neurology recommends that clinicians avoid routinely offering PFO closure to patients with cryptogenic stroke outside of a research setting (30); however, these recommendations were made before the positive reports from recent trials.

Extended follow-up (median, 5.9 years) results for the RESPECT trial were recently reported. It is the largest trial on PFO closure to date and now has the longest follow-up (12). It showed that the Amplatzer PFO Occluder decreased the risk for recurrent stroke by 45%, yet the absolute benefit was small (0.49 fewer events per 100 patient-years with PFO closure). Similarly, in the other 2 recently reported trials (CLOSE and REDUCE), PFO closure reduced recurrent stroke compared with medical therapy alone (10, 11). The positive results in these 2 trials may be due to better patient selection using a thorough evaluation to identify true cryptogenic stroke. Although our searches identified several previous meta-analyses (9, 27, 29, 31, 32), none included these recent trials with positive results. Our updated meta-analysis clearly showed that PFO closure decreased risk for recurrent stroke. Absolute benefits were small; however, the absolute cumulative benefit could have clinical relevance because most patients with PFO and cryptogenic stroke are relatively young and have long risk periods for recurrent stroke.

Current literature is mixed on the increased risk for new-onset AF with transcatheter device closure of PFO. However, the absolute risk seems low: Many AFs are paroxysmal, and some are transient, occurring only during the procedure. The type of device might play a role in the risk for postprocedural AF. The risk seems to be lower with the FDA-approved Amplatzer PFO Occluder (27). In CLOSURE I, the STARFlex device was associated with a statistically significantly higher risk for AF than medical therapy alone (6). Similarly, in the recently reported REDUCE trial (in which the HELEX and CARDIOFORM septal occluders were used), the risk for AF with device therapy was higher than with medical therapy alone (11). On the other hand, in PC and RESPECT (in which only the Amplatzer PFO Occluder was used), risk for AF did not statistically significantly differ between device therapy and medical therapy alone (7, 12). In CLOSE, in which the Amplatzer PFO Occluder was used in half of the cases, risk for AF did not statistically significantly differ between the 2 treatment strategies (10). Even in these 3 trials, the risk for AF with device therapy was 2 to 3 times higher than with medical therapy alone. Thus, a type II error cannot be excluded. Regardless, we found marked heterogeneity between trials and extreme values for CIs in some instances, so we consider current evidence about the magnitude of risk for AF with PFO closure to be inconclusive.

Nevertheless, risk for AF is a critical safety issue because patients having PFO closure could ultimately require anticoagulation for AF, another cause of stroke. Patients should be informed about this potential risk during shared decision making (24). Continued, longer-term follow-up for current trials is needed to evaluate risk, and additional studies are needed to assess whether device or technique improvement can abate the risk. One ongoing study, PFO PAS (Amplatzer PFO Occluder Post Approval Study; ClinicalTrials.gov: NCT03309332), will provide additional insights about the safety and efficacy of PFO closure for patients with cryptogenic stroke by using real-world patient data. The investigators will follow 1214 adult patients across 100 centers in the United States and Canada for 5 years after implanting the Amplatzer PFO Occluder. Another ongoing study, the DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale; ClinicalTrials.gov: NCT01550588) trial, will evaluate the safety and efficacy of PFO closure in Asian patients with cryptogenic stroke.

This meta-analysis has several limitations. We did not have individual participant data. Our statistical analysis was done at the study level, and each study had its own protocol, definitions, and follow-up duration. The types of antithrombotic therapies varied across studies. Because cryptogenic stroke has no clear known cause, a universally accepted medical therapy does not exist. Thus, in these trials, PFO closure was compared with the local standard of care at the discretion of each site's principal investigator. We found few studies, and in some instances few events occurred. The type of device used for PFO closure varied across studies, and some are believed to be more effective or safe than others. A previous RCT comparing 3 devices (Amplatzer, HELEX, and STARFlex) and a network meta-analysis have suggested that the Amplatzer device might be the most efficacious and safe (26, 32).

In patients with PFO and cryptogenic stroke, transcatheter device closure of PFO decreases the risk for recurrent stroke. Because rates of recurrent stroke are low even with medical therapy, patients and clinicians should share the decision about PFO closure, keeping in mind patient expectations and the potential risks and benefits of the procedure.

From University of Tennessee and Veterans Affairs Medical Center, Memphis, Tennessee; Virginia Commonwealth University, Richmond, Virginia; Jackson Clinic and University of Tennessee, Jackson, Tennessee; University of Louisville, Louisville, Kentucky; and Duke Clinical Research Institute, Durham, North Carolina.

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-2679.

Reproducible Research Statement: *Study protocol:* See Part 1 of the **Supplement** (available at Annals.org). *Statistical code:* See Methods. *Data set*: See tables, figures, and appendices.

Requests for Single Reprints: Rahman Shah, MD, University of Tennessee, School of Medicine, Division of Cardiovascular Diseases, Coleman College of Medicine Building, 956 Court Avenue, Suite A312, Memphis, TN 38163; e-mail, Shahcardiology@yahoo.com.

Current author addresses and author contributions are available at Annals.org.

References

1. **Lozano R, Naghavi M, Foreman K, et al.** Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095-128. [PMID: 23245604] doi:10.1016/S0140-6736(12)61728-0
2. **Li L, Yiin GS, Geraghty OC, et al; Oxford Vascular Study.** Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. Lancet Neurol. 2015;14:903-13. [PMID: 26227434] doi:10.1016/S1474-4422(15)00132-5
3. **Overell JR, Bone I, Lees KR.** Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology. 2000;55:1172-9. [PMID: 11071496]
4. **Agarwal S, Bajaj NS, Kumbhani DJ, Tuzcu EM, Kapadia SR.** Meta-analysis of transcatheter closure versus medical therapy for patent foramen ovale in prevention of recurrent neurological events after presumed paradoxical embolism. JACC Cardiovasc Interv. 2012;5:777-89. [PMID: 22814784] doi:10.1016/j.jcin.2012.02.021
5. **Khairy P, O'Donnell CP, Landzberg MJ.** Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. Ann Intern Med. 2003;139:753-60. [PMID: 14597460]
6. **Furlan AJ, Reisman M, Massaro J, et al; CLOSURE I Investigators.** Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med. 2012;366:991-9. [PMID: 22417252] doi:10.1056/NEJMoa1009639
7. **Meier B, Kalesan B, Mattle HP, et al; PC Trial Investigators.** Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med. 2013;368:1083-91. [PMID: 23514285] doi:10.1056/NEJMoa1211716
8. **Carroll JD, Saver JL, Thaler DE, et al; RESPECT Investigators.** Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med. 2013;368:1092-100. [PMID: 23514286] doi:10.1056/NEJMoa1301440
9. **Rengifo-Moreno P, Palacios IF, Junpaparp P, Witzke CF, Morris DL, Romero-Corral A.** Patent foramen ovale transcatheter closure vs. medical therapy on recurrent vascular events: a systematic review and meta-analysis of randomized controlled trials. Eur Heart J. 2013;34:3342-52. [PMID: 23847132] doi:10.1093/eurheartj/eht285
10. **Mas JL, Derumeaux G, Guillon B, et al; CLOSE Investigators.** Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med. 2017;377:1011-21. [PMID: 28902593] doi:10.1056/NEJMoa1705915
11. **Søndergaard L, Kasner SE, Rhodes JF, et al; Gore REDUCE Clinical Study Investigators.** Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med. 2017;377:1033-42. [PMID: 28902580] doi:10.1056/NEJMoa1707404
12. **Saver JL, Carroll JD, Thaler DE, et al; RESPECT Investigators.** Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med. 2017;377:1022-32. [PMID: 28902590] doi:10.1056/NEJMoa1610057
13. **Moher D, Shamseer L, Clarke M, et al; PRISMA-P Group.** Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1. [PMID: 25554246] doi:10.1186/2046-4053-4-1
14. **Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group.** The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. [PMID: 22008217] doi:10.1136/bmj.d5928
15. **Knapp G, Hartung J.** Improved tests for a random effects meta-regression with a single covariate. Stat Med. 2003;22:2693-710. [PMID: 12939780]
16. **Cornell JE, Mulrow CD, Localio R, et al.** Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med. 2014;160:267-70. [PMID: 24727843]
17. **Sweeting MJ, Sutton AJ, Lambert PC.** What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23:1351-75. [PMID: 15116347]
18. **Higgins JP, Thompson SG, Deeks JJ, Altman DG.** Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60. [PMID: 12958120]
19. **Sutton A, Abrams K, Jones D, Sheldon T, Song F.** Methods for Meta-analysis in Medical Research. Chichester, United Kingdom: Wiley; 2000.
20. **Sterne JA, Sutton AJ, Ioannidis JP, et al.** Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002. [PMID: 21784880] doi:10.1136/bmj.d4002
21. **Thaler DE, Wahl A.** Critique of closure or medical therapy for cryptogenic stroke with patent foramen ovale: the hole truth? Stroke. 2012;43:3147-9. [PMID: 22989503] doi:10.1161/STROKEAHA.112.659599
22. **Rao G, Lopez-Jimenez F, Boyd J, et al; American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; and Stroke Council.** Methodological standards for meta-analyses and qualitative systematic reviews of cardiac prevention and treatment studies: a scientific statement from the American Heart Association. Circulation. 2017;136:e172-94. [PMID: 28784624] doi:10.1161/CIR.0000000000000523
23. **Mozaffarian D, Benjamin EJ, Go AS, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee.** Heart disease and stroke statistics–2015 update: a report from the American Heart Association. Circulation. 2015;131:e29-322. [PMID: 25520374] doi:10.1161/CIR.0000000000000152
24. **Farb A, Ibrahim NG, Zuckerman BD.** Patent foramen ovale after cryptogenic stroke–assessing the evidence for closure. N Engl J Med. 2017;377:1006-9. [PMID: 28902595] doi:10.1056/NEJMp1700218
25. **Di Tullio MR, Sacco RL, Sciacca RR, Jin Z, Homma S.** Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. J Am Coll Cardiol. 2007;49:797-802. [PMID: 17306710]
26. **Taaffe M, Fischer E, Baranowski A, et al.** Comparison of three patent foramen ovale closure devices in a randomized trial (Amplatzer versus CardioSEAL-STARflex versus Helex occluder). Am J Cardiol. 2008;101:1353-8. [PMID: 18435971] doi:10.1016/j.amjcard.2007.12.040
27. **Kent DM, Dahabreh IJ, Ruthazer R, et al.** Device closure of patent foramen ovale after stroke: pooled analysis of completed randomized trials. J Am Coll Cardiol. 2016;67:907-17. [PMID: 26916479] doi:10.1016/j.jacc.2015.12.023
28. **Pickett CA, Villines TC, Ferguson MA, Hulten EA.** Percutaneous closure versus medical therapy alone for cryptogenic stroke patients with a patent foramen ovale: meta-analysis of randomized controlled trials. Tex Heart Inst J. 2014;41:357-67. [PMID: 25120387] doi:10.14503/THIJ-13-3879
29. **Khan AR, Bin Abdulhak AA, Sheikh MA, et al.** Device closure of patent foramen ovale versus medical therapy in cryptogenic stroke: a systematic review and meta-analysis. JACC Cardiovasc Interv. 2013;6:1316-23. [PMID: 24139929] doi:10.1016/j.jcin.2013.08.001
30. **Messé SR, Gronseth G, Kent DM, et al.** Practice advisory: recurrent stroke with patent foramen ovale (update of practice parameter): report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2016;87:815-21. [PMID: 27466464] doi:10.1212/WNL.0000000000002961
31. **Kitsios GD, Thaler DE, Kent DM.** Potentially large yet uncertain benefits: a meta-analysis of patent foramen ovale closure trials. Stroke. 2013;44:2640-3. [PMID: 23868270] doi:10.1161/STROKEAHA.113.001773
32. **Stortecky S, da Costa BR, Mattle HP, et al.** Percutaneous closure of patent foramen ovale in patients with cryptogenic embolism: a network meta-analysis. Eur Heart J. 2015;36:120-8. [PMID: 25112661] doi:10.1093/eurheartj/ehu292

Current Author Addresses: Drs. Shah, Nayyar, Bondy, and Fan: University of Tennessee, Division of Cardiovascular Diseases, Coleman College of Medicine Building, 956 Court Avenue, Suite A312, Memphis, TN 38163.
Dr. Jovin: Virginia Commonwealth University, Department of Internal Medicine, PO Box 980509, Richmond, VA 23298.
Dr. Rashid: University of Tennessee, Jackson Clinic, 700 West Forest Avenue, Jackson, TN 38301.
Dr. Flaherty: University of Louisville, Rudd Heart & Lung Building, 201 Abraham Flexner Way, Suite 600, Louisville, KY 40292.
Dr. Rao: The Duke Clinical Research Institute, 2400 Pratt Street, Durham, NC 27705.

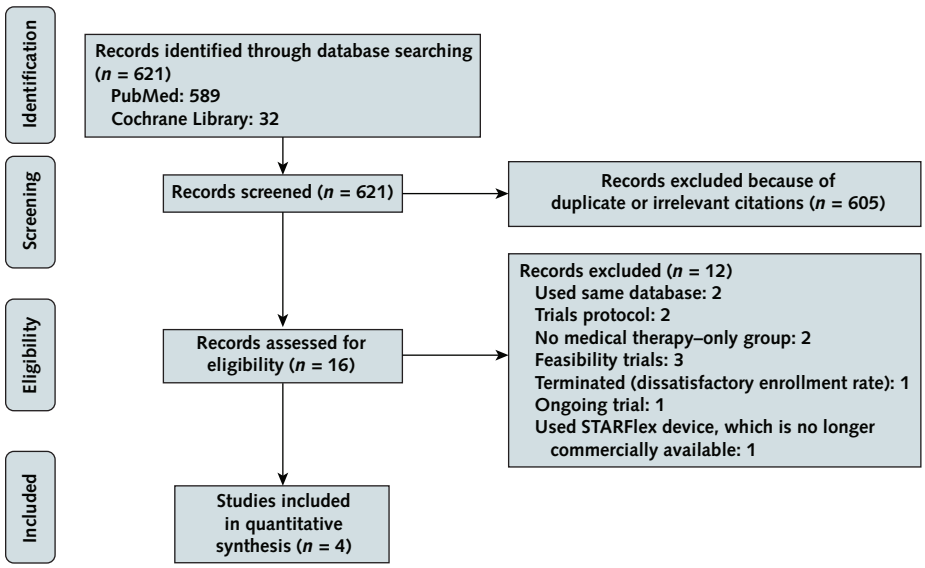
Author Contributions: Conception and design: R. Shah, M. Nayyar.
Analysis and interpretation of the data: R. Shah, M. Nayyar, I.S. Jovin, A. Rashid, B.R. Bondy, M.P. Flaherty, S.V. Rao.
Drafting of the article: R. Shah, M. Nayyar, A. Rashid.
Critical revision of the article for important intellectual content: R. Shah, M. Nayyar, I.S. Jovin, A. Rashid, B.R. Bondy, T.H.M. Fan, M.P. Flaherty, S.V. Rao.
Final approval of the article: R. Shah, M. Nayyar, I.S. Jovin, A. Rashid, B.R. Bondy, T.H.M. Fan, M.P. Flaherty, S.V. Rao.
Provision of study materials or patients: M. Nayyar.
Statistical expertise: R. Shah.
Administrative, technical, or logistic support: M. Nayyar.
Collection and assembly of data: R. Shah, M. Nayyar, A. Rashid, B.R. Bondy.

Appendix Table 1. Definition of Recurrent Stroke for Each Included RCT

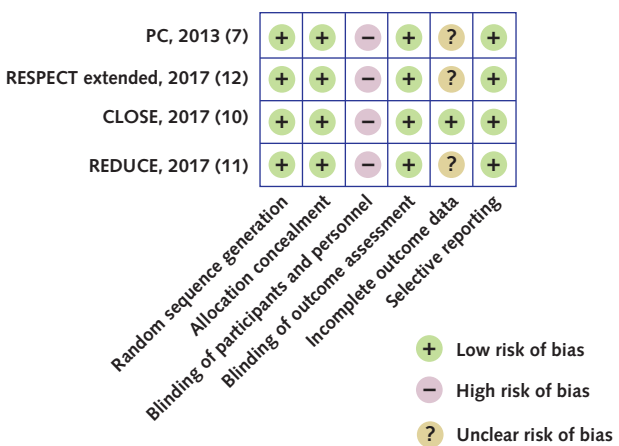
Study, Year (Reference)	Definition
PC (7)	Stroke deemed to have caused death or any neurologic deficit lasting >24 h, typically confirmed on MRI or CT.
RESPECT extended, 2017 (12)	Stroke deemed to have caused death or acute focal neurologic deficit, presumed to be due to focal ischemia, and either symptoms persisting ≥24 h, or symptoms persisting ≤24 h but associated with MRI or CT findings of a new, neuroanatomically relevant cerebral infarction.
CLOSE, 2017 (10)	Sudden onset of focal neurologic symptoms with the presence of cerebral infarction in the appropriate territory on brain imaging (MRI or CT) regardless of the duration of the symptoms (less than or more than 24 h).
REDUCE, 2017 (11)	A focal neurologic deficit, presumably due to ischemia, lasting >24 h or until death, or a deficit associated with MRI or CT evidence of a new brain infarction

CLOSE = Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; CT = computed tomography; MRI = magnetic resonance imaging; PC = Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; RCT = randomized controlled trial; REDUCE = GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients; RESPECT = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

Appendix Figure 1. Evidence search and selection.



Appendix Figure 2. Risk of bias of included randomized controlled trials, assessed at the outcome (recurrent stroke) level.



CLOSE = Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; PC = Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; REDUCE = GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients; RESPECT = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

Appendix Table 2. Device Types in the Included RCTs

PC, 2013 (7)	RESPECT Extended, 2017 (12)	CLOSE, 2017 (10)	REDUCE, 2017 (11)
Amplatzer PFO occluder	Amplatzer PFO occluder	Amplatzer PFO occluder (*n* = 121), Intrasept PFO occluder (*n* = 31), Premere (*n* = 22), STARFlex septal occluder (*n* = 21), Amplatzer cribriform occluder (*n* = 15), Figulla Flex II PFO occluder (*n* = 15), Atriasept II occluder (*n* = 3), Amplatzer ASD occluder (*n* = 2), Figulla Flex II UNI occluder (*n* = 2), Gore septal occluder (*n* = 2), or Figulla Flex II ASD occluder (*n* = 1)	CARDIOFORM septal occluder (*n* = 250) or HELEX septal occluder (*n* = 158)

ASD = atrial septal defect; CLOSE = Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; PC = Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; PFO = patent foramen ovale; RCT = randomized controlled trial; REDUCE = GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients; RESPECT = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.