Annals of Internal Medicine REVIEW

Percutaneous Closure Versus Medical Treatment in Stroke Patients With Patent Foramen Ovale

A Systematic Review and Meta-analysis

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Background: New evidence emerged recently regarding the percutaneous closure of patent foramen ovale (PFO) to prevent recurrent stroke in patients with cryptogenic stroke.

Purpose: To compare risks for recurrent cerebrovascular events in adults with PFO and cryptogenic stroke who underwent PFO closure versus those who received medical therapy alone.

Data Sources: PubMed, Scopus, and Google Scholar from 1 December 2004 through 14 September 2017; references of eligible studies; relevant scientific session abstracts; and cardiology Web sites.

Study Selection: Randomized controlled trials, published in English, that compared PFO closure using a currently available device with medical treatment alone and that reported, at minimum, the rates of stroke or transient ischemic attack (TIA) or of new-onset atrial fibrillation (AF) or atrial flutter (AFL).

Data Extraction: 2 investigators independently extracted study data and assessed study quality.

Data Synthesis: 4 of 5 trials comparing PFO closure with medical therapy used commercially available devices. These 4 trials, involving 2531 patients, found that PFO closure reduced the risk for the main outcome of stroke or TIA (risk difference [RD], −0.029 [95% CI, −0.050 to −0.007]) and increased the risk for new-onset AF or AFL (RD, 0.033 [CI, 0.012 to 0.054]). The beneficial effect of PFO closure was associated with larger interatrial shunts ($P = 0.034$).

Limitation: Trials were not double-blind, and inclusion criteria were heterogeneous.

Conclusion: Compared with medical treatment, PFO closure prevents recurrent stroke and TIA but increases the incidence of AF or AFL in PFO carriers with cryptogenic stroke.

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Patent foramen ovale (PFO) is a common finding that has been reported in 10% to 35% of persons (1, 2). The presence of PFO increases the risk for cardioembolic cerebrovascular accidents, such as stroke transient ischemic attacks (TIA), but most persons with PFOs remain asymptomatic and do not develop serious complications (2). Among young persons with a cryptogenic stroke, the prevalence of PFO is high (3), and approximately half have no apparent underlying causes (4).

Because PFO may be a nest of thrombus formation or the conduit for paradoxical embolism (1, 5, 6), percutaneous closure was introduced to prevent recurrent stroke in high-risk persons (7). Until 2017, evidence and guideline recommendations did not support the routine use of PFO closure (8–12): Individual randomized controlled trials suggested no benefit of closure over medical therapy alone (11–13), and meta-analyses of the trials showed no statistically significant reductions in recurrent stroke but possible increased risks for adverse effects (14–17). In late 2017, the results of 2 new randomized trials—CLOSE (Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence) and REDUCE (Gore Helex Septal Occluder/Gore Cardioform Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients)—as well as a long-term analysis of the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial changed the landscape of evidence (18–20). We undertook this systematic review to summarize the new evidence and compare risks for recurrent cerebrovascular events and adverse events in adults with PFO and cryptogenic stroke who received treatment with PFO closure versus those who received medical therapy alone.

Methods

We developed a protocol for the review on 5 June 2017 and registered it at PROSPERO (www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017074686) on 8 August 2017.

Data Sources and Searches

We searched PubMed, Scopus, and Google Scholar electronic databases from 1 December 2004 through 14 September 2017 using the following keywords and corresponding MeSH (Medical Subject Headings) terms: *PFO closure*, *cryptogenic stroke*, *patent foramen ovale*, and *randomized controlled trial*. We also checked the reference lists of eligible studies and screened scientific abstracts and relevant Web sites (www.clinicaltrialresults.org, www.escardio.org, www.tctmd.com, https://accscientificsession.acc.org, and

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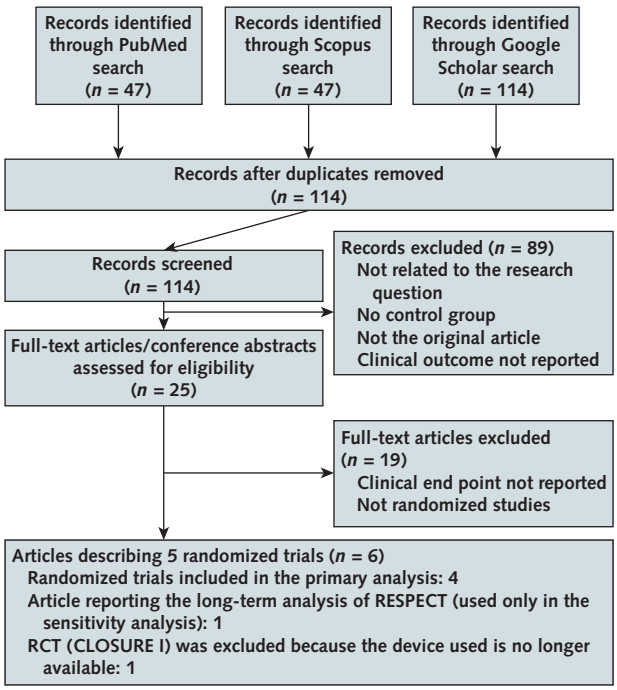
Figure 1. Evidence search and selection.



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; RCT = randomized controlled trial; RESPECT = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

https://exhibitatsessions.org). Further details on search sources are reported in Appendix Table 1 (available at Annals.org).

Study Selection

Two investigators (J.S and S.D.R.) independently screened search records to identify eligible trials. No disagreements occurred. Inclusion criteria were randomized controlled trials of patients with PFO and cryptogenic stroke that compared an intervention with a percutaneous PFO closure device versus medical therapy alone and reported at least 1 of the following outcomes: stroke or TIA (main outcome) or new-onset atrial fibrillation (AF) or atrial flutter (AFL). Exclusion criteria were duplicate publications, trials published in a language other than English, and studies in which the end point measure was not specified (at least stroke or TIA, or AF or AFL).

Data Extraction and Quality Assessment

Two reviewers (J.S. and S.D.R.) independently extracted data about study characteristics and event rates from full articles. Two investigators (S.D.R. and A.P.) independently assessed study quality for each trial by using the Cochrane Risk of Bias Tool (http://methods.cochrane.org/bias/assessing-risk-bias-included-studies). The following domains were evaluated: randomization method; allocation concealment; blinding of patient, investigator, and outcome adjudication committee; reporting bias; attrition bias; and any other potential sources of bias, such as those related to trial designs, or the risk for contamination or crossover between the groups. The assessment was done at the study level and focused on the main study outcome (stroke or TIA). Disagreements were resolved by consensus.

Data Synthesis and Analysis

We focused our primary summary of data on trials evaluating closure devices that are currently available commercially and used data extracted from the original primary publications (11, 12, 18, 19) because the longer-term follow-up data for 1 trial were deemed less complete because of poor retention (20). We based our primary analyses on the composite end point of stroke or TIA. We analyzed ischemic stroke and death as secondary end points and the new onset of AF or AFL, major bleeding, and serious adverse events as safety end points. We used the risk difference (RD) with 95% CI as the summary measure. The random-effects model with the Hartung–Knapp–Sidik–Jonkman method to estimate tau was used to compute estimates for the summary effect (21, 22). We used the treatment group correction for continuity described by Sweeting and colleagues (23) when one of the study groups had zero events. We used the double arcsine transformation when both treatment groups of a study reported zero events (24). Heterogeneity was assessed by using the Cochran Q test by means of a chi-square function. P values below 0.10 were considered indicative of heterogeneity. I^2 values were calculated to estimate variation among studies attributable to heterogeneity. Meta-analysis results were displayed with forest plots in which the measure of effect (RD) for each study is represented by a square and the area of each square is proportional to study weight.

A metaregression analysis was performed to examine the potential effect of interatrial shunt (IAS) size on ischemic stroke. Subgroup and sensitivity analyses were conducted using recently published long-term follow-up data (rather than the original shorter-term follow-up data) for 1 trial (20) and fixed-effects (Mantel–Haenszel) and random-effects (Hedges–Olkin and Sidik–Jonkman) models (22, 25, 26). Analyses were performed by using Open Meta-Analyst and R (The R Foundation).

Role of the Funding Source

The funding bodies had no role in the study's design, conduct, review, or reporting or the decision to submit the manuscript for publication.

RESULTS

Of 114 screened records, we identified 5 trials that compared PFO closure with medical therapy (Figure 1) (11–13, 18–20). We excluded 1 of these studies from our primary synthesis because it evaluated a device that was removed from the market because of low procedural success and a high risk for complications (13). Another trial (12) recently reported long-term results (20), which we used only in our sensitivity analyses.

Characteristics of the trials are presented in Tables 1 and 2 and Appendix Tables 2 and 3 (available at Annals.org). All trials were multicenter, open-label superiority studies, and all except CLOSE were funded by industry. The RESPECT trial (funded by St. Jude Medical) randomly assigned 980 patients to receive either PFO closure with the Amplatzer PFO Occluder (St. Jude Medical) plus antiplatelet therapy or medical treatment alone (12). Mean follow-up was 2.6 years for the initial publication; recently, results of a prolonged follow-up (median, 5.9 years) were published (20). Between 2000 and 2009, the PC-Trial (Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of PFO With Medical Treatment in Patients With Cryptogenic Embolism), funded by St. Jude Medical, randomly assigned 414 patients to undergo PFO closure with the Amplatzer PFO Occluder plus antiplatelet therapy or receive medical treatment at the physician's discretion. Mean follow-up was 4.0 years (11). The CLOSE study, funded by the French Ministry of Health, was a multicenter, open-label, 3-group superiority trial with blinded event adjudication. The trial was designed to enroll 900 patients with a 1:1:1 randomization to receive transcatheter PFO closure with any approved implantable medical device plus long-term antiplatelet therapy, long-term oral anticoagulation, or long-term antiplatelet therapy (18). Mean follow-up was 5.3 ± 2.0 years. The open-label REDUCE study (funded by W.L. Gore and Associates) assessed the efficacy and safety of PFO closure using a Gore septal occluder device (Helex or Cardioform) in 664 patients with a history of cryptogenic stroke randomly assigned in a 2:1 proportion (19). Mean follow-up was 3.2 years.

Risk-of-bias assessments are reported in Appendix Figure 1 (available at Annals.org). All trials used an adequate method of randomization and allocation concealment. Blinding of patients and caregivers was not possible because no sham procedure was performed in the medical treatment group in any of the trials. End point adjudication committees were blinded to the treatment strategy in all trials. Risk of selection, detection, attrition, and reporting bias was judged as low. Risk of performance bias was present.

Measures of Efficacy

Findings related to potential benefits included the following: Stroke or TIA occurred in 3.6% of patients who received treatment with a PFO closure device, compared with 6.3% who received medical therapy (RD, −0.029 [95% CI, −0.050 to −0.007]; $P = 0.008$; $I^2 = 34\%$) (Figure 2, *A*). Stroke occurred in 1.2% of patients who received treatment with a PFO closure device, compared with 4.1% who received medical therapy (RD, −0.031 [CI, −0.051 to −0.010]; $P = 0.003$; $I^2 = 61\%$) (Figure 2, *B*). No statistically significant difference in death rate was found between groups in any study (Figure 2, *C*).

Measures of Safety

Findings related to adverse events or harms included the following: New-onset AF or AFL occurred in 4.1% of patients who received treatment with a PFO closure device, compared with 1.0% who received medical therapy (RD, 0.033 [CI, 0.012 to 0.054]; $P = 0.002$; $I^2 = 66\%$) (Figure 3, *A*). During follow-up, 0.9% of patients who received treatment with a PFO closure device and 1.2% of those who received medical therapy had a major bleeding event (RD, −0.002 [CI, −0.012 to 0.007]; $P = 0.605$; $I^2 = 28\%$) (Figure 3, *B*). Also during follow-up, 25.0% of patients who received treatment with a PFO closure device and 24.0% who received medical therapy had a serious adverse event (RD, −0.006 [CI, −0.036 to −0.048]; $P = 0.781$; $I^2 = 31\%$) (Figure 3, *C*).

Metaregression and Subgroup and Sensitivity Analyses

Across single studies, metaregression analysis showed a progressively greater beneficial effect on ischemic stroke prevention with increasing IAS size in patients with a moderate to large shunt ($P = 0.034$) (Appendix Figure 2, available at Annals.org).

Table 1. Characteristics of Trials of PFO Closure in Adults With PFO and Cryptogenic Stroke

Trial Name	Year of Publication	Follow-up, *y*	Patients Included, *n*	Medical Treatment	Primary Outcome	Study Design
PC-Trial	2013	4.1	909	antiPLT or OAC	Composite of death, stroke, TIA, or peripheral embolism	Prospective, randomized (1:1), controlled, multicenter, open-label
RESPECT	2013	2.1*	980	antiPLT or OAC	Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization	Prospective, randomized (1:1), controlled, multicenter, open-label
REDUCE	2017	3.2	664	antiPLT	Ischemic stroke and new brain infarction on imaging	Prospective, randomized (2:1), controlled, multicenter, open-label
CLOSE	2017	5.3	663	antiPLT in the main analysis, OAC	Stroke	Prospective, randomized (1:1:1), controlled, multicenter, open-label, investigator-initiated; 3 randomization groups

antiPLT = antiplatelet therapy; CLOSE = Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; OAC = oral anticoagulation; PC-Trial = Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of PFO 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.
* Longer-term results of the RESPECT trial were published in a different article (20).

Table 2. Characteristics of Patients in PFO Closure Trials

Characteristic	PC-Trial (n = 414)	RESPECT (n = 980)	REDUCE (n = 664)	CLOSE (n = 473)*
Clinical variables				
Mean age (SD), *y*	44.5 (10.2)	45.4 (9.8)	45.2 (9.6)	43.3 (10.5)
Male, %	49.8	54.7	60.1	59.0
Current smoker, %	23.9	13.3	13.3	28.9
Mean body mass index (SD), kg/m^2	26.5 (5.2)	29.4 (5.6)	NA	NA
Medical history, %				
Diabetes	2.66	7.45	4.2	2.6
Hypercholesterolemia	27.1	39.5	NA	14.0
Hypertension	25.8	31.4	26.0	10.7
Migraine	20.5	38.8	NA	30.7
Prior stroke/TIA	37.4	18.6	13.8	3.6
Echocardiographic variables, %				
Atrial septal aneurysm	23.7	35.6	13.0	25.6
Large PFO	19.3	48.8	40.7	92.8

CLOSE = Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; NA = not available; PC-Trial = Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of PFO 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.
* This trial comprised 663 patients in 3 different randomization groups. However, the main analysis based on results within groups 2 and 3 (n = 473) and group 1 included patients with a contraindication to PFO closure.

Meta-analyses for most outcomes showed no substantial statistical heterogeneity. Subgroup analysis showed that the heterogeneity found for the end point of ischemic stroke (I^2 = 61%) (**Appendix Figure 3**, *A*, available at Annals.org) decreased to below 50% (I^2 = 49%) after the results of the original RESPECT trial (12) were substituted with those assessed at the prolonged follow-up analysis (20) (**Appendix Figure 3**, *B*). Meta-analysis results were similar when compared using the fixed-effects (Mantel–Haenszel) or random-effects (Hedges-Olkin, Sidik − Jonkman) models (22, 25, 26). Detailed results of sensitivity analyses for the primary efficacy end point of stroke or TIA and the main safety end point of new-onset AF or AFL are reported in **Appendix Tables 4** and **5** (available at Annals.org), respectively. All devices were associated with an increased risk for AF or AFL compared with medical treatment (3.0% vs. 1.3% with the Amplatzer device and 6.6% vs. 0.4% with the Gore devices).

DISCUSSION

The results of this meta-analysis demonstrate that PFO closure prevents cardioembolic cerebrovascular events in patients with cryptogenic stroke and PFO. This finding represents a positive change in evidence, because 3 recent randomized trials failed to demonstrate superiority of PFO closure over medical therapy alone (11–13). Undersizing or inadequate sample sizes initially were blamed for the failure of these trials to demonstrate benefit, but the reasons are probably multifactorial. Specific anatomical features are associated with a higher stroke risk in persons with PFO. These include the diameter of the defect (27, 28), the length of the tunnel (29), the degree of interatrial shunting (28), the presence of atrial septal aneurysm (18, 30, 31), and a prominent Eustachian valve or Chiari networks (32, 33). Findings of the recent CLOSE and REDUCE trials indirectly confirm these concepts, supporting the hypothesis that patient selection is key. The CLOSE study included patients at high risk for PFO-related stroke, because they had either a large IAS or an atrial septal aneurysm (18). Similarly, 80% of the patients included in the REDUCE trial had a moderate to large shunt (19). In line with these results, our meta-regression analysis found that the efficacy of percutaneous PFO closure was progressively greater for the studies that enrolled a larger proportion of patients with a moderate to large IAS. This finding should be interpreted with caution given the limited number of studies included in the analysis. Conversely, both the PC-Trial and RESPECT enrolled a lower-risk population. The proportion of participants with a large IAS in these studies was 16.7% and 19.3%, respectively, whereas the proportion of those with a moderate to large IAS was 58.4% and 75.2, respectively. Although a greater number, it was still smaller than in the subsequent REDUCE (>80% of patients with a moderate to large IAS) and CLOSE (all patients with at least a moderate IAS) trials (18, 19).

Our meta-analysis showed that percutaneous PFO closure was associated with an increased incidence of AF and AFL. Postprocedural AF often is transient (34). The long-term results of RESPECT showed that the effect of PFO closure on stroke prevention was maintained over time, despite the increase in AF incidence (20). More than 80% of episodes of AF or AFL in the REDUCE trial were registered within 45 days from randomization and resolved within 2 weeks (19). In the CLOSE trial, more than 90% of AF episodes in the PFO closure group were recognized during the first month and did not recur (18). In the PC-Trial, new-onset AF

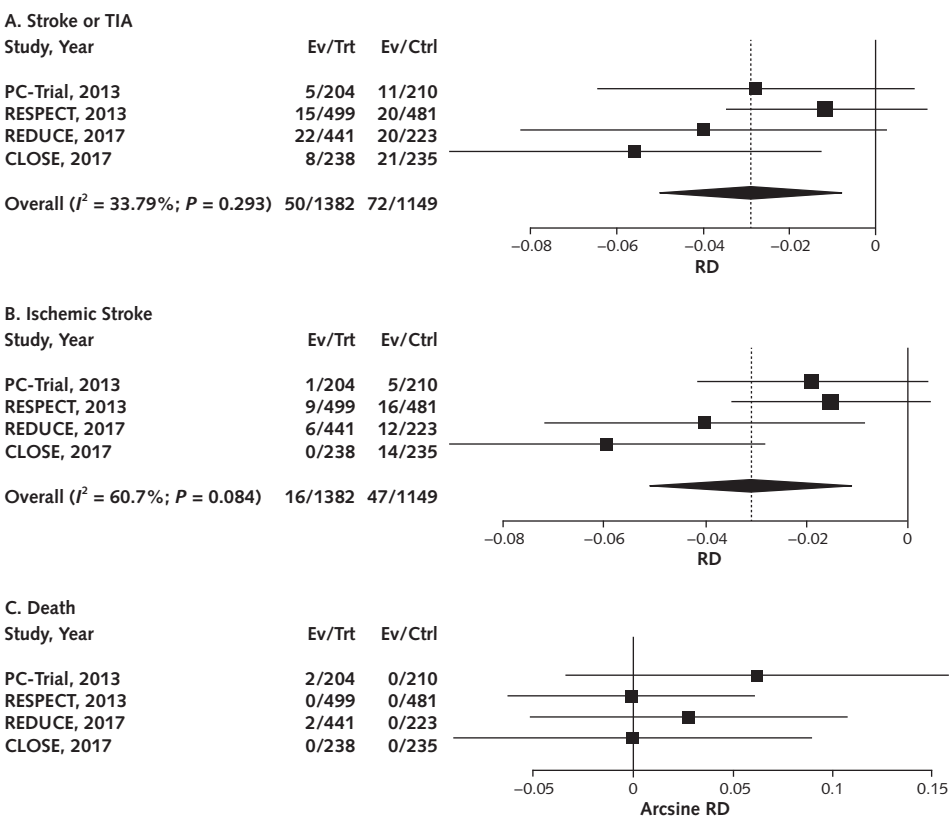
was reported in 6 patients (2.9%) in the PFO closure group and was transient in 5 of these cases (11). A meta-analysis of nonrandomized studies (2570 patients enrolled in 6 studies) found a reduced incidence of new-onset AF after PFO closure (35).

Given the high prevalence of PFO in the general population (1), future management strategies must include effective risk stratification based on anatomical and functional PFO features as well as patient-related variables. The ideal candidate would have a medium to large IAS. However, the importance of atrial septal aneurysm is still being debated.

We believe that the new evidence warrants a revision of current practice guidelines. In addition, we think this finding of efficacy of PFO closure for patients with cryptogenic stroke might ignite further discussion regarding extending this treatment to primary prevention. The identification of an efficient tool to stratify stroke risk will be of key importance, especially in PFO carriers without previous cryptogenic stroke. In all cases, a comprehensive clinical assessment should be strongly recommended before PFO closure to exclude potential underlying causes of the "cryptogenic" stroke. The ideal work-up should be adapted to the clinical profile of individual patients, including brain imaging to exlude small-vessel disease (such as lacunar stroke) or cerebral lesions not related to stroke, transesophageal echocardiography to rule out potential intracardiac embolic sources unrelated to PFO and to screen for large atheromas of the aortic arch, prolonged monitoring to detect occult or subclinical AF, vascular imaging to exclude potential vascular causes, and screening for a hypercoagulable state. Once direct potential causes of stroke have been excluded, further stratification of stroke risk is possible by using the Risk of Paradoxical Embolism score (36). In a recent validation study, a score above 7 points indicated a PFO-attributable stroke fraction of 71.1% (37).

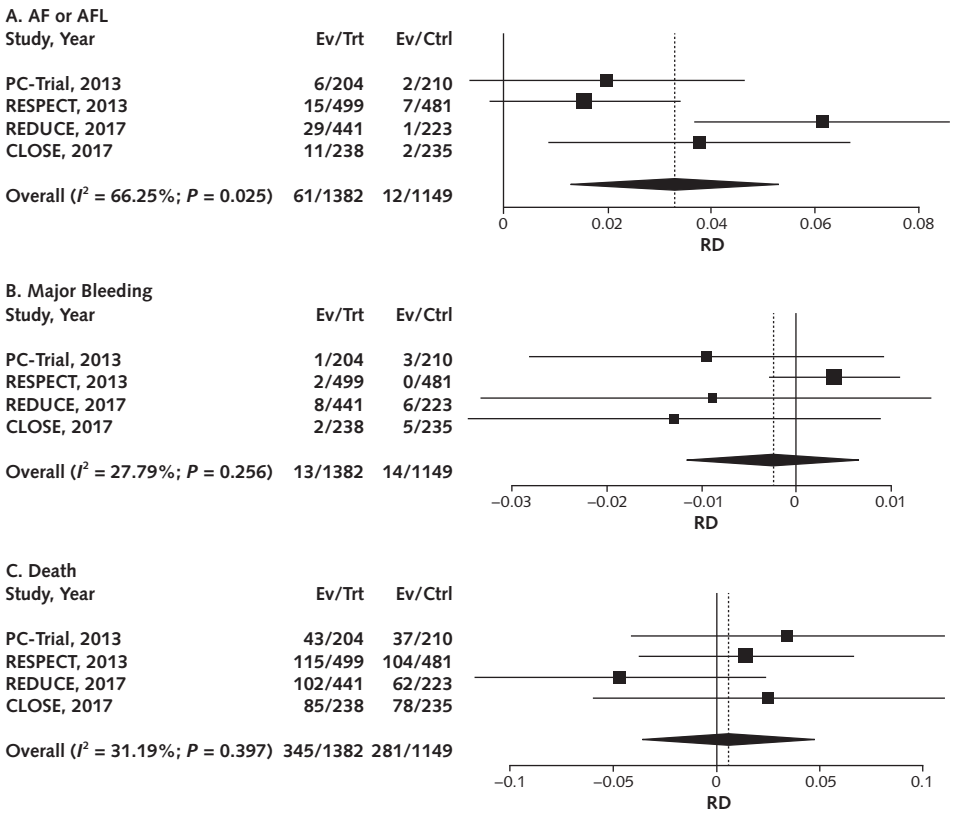
We searched PubMed through 17 November 2017 for other systematic reviews on this topic and found a

Figure 2. Efficacy end points.



Forest plots illustrating the results of a meta-analysis of the composite end point of stroke or TIA (*A*), ischemic stroke (*B*), or death (*C*). The calculated summary effect demonstrates the superiority of PFO closure compared with medical treatment alone in reducing the composite end point of stroke or TIA as well as preventing recurrent stroke. Horizontal lines represent the 95% CI of the effect size; solid squares indicate the mean effect size in single studies; diamond shapes depict the summary effect size (diamond center) and the relative 95% CI (lateral edges); the dotted vertical lines indicate the identity line, where no difference between the treatment groups exists; the black vertical lines represent the reference "0" line. CLOSE = Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; Ctrl = number of patients who received standard medical treatment; Ev = number of events; PC-Trial = Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of PFO With Medical Treatment in Patients With Cryptogenic Embolism; PFO = patent foramen ovale; RD = risk difference; 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; Trt = number of patients who received treatment with PFO closure.

Figure 3. Safety end points.



Forest plots illustrating the results of a meta-analysis of the rate of AF or AFL (*A*), major bleeding (*B*), and any serious adverse event (*C*). Horizontal lines represent the 95% CI of the effect size; solid squares indicate the mean effect size in single studies; diamond shapes depict the summary effect size (diamond center) and the relative 95% CI (lateral edges); the dotted vertical lines indicate the identity line, where no difference between the treatment groups exists; the black vertical lines represent the reference "0" line. AF = atrial fibrillation; AFL = atrial flutter; CLOSE = Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; Ctrl = number of patients who received standard medical treatment; Ev = number of events; PC-Trial = Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of PFO With Medical Treatment in Patients With Cryptogenic Embolism; PFO = patent foramen ovale; RD = risk difference; 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; Trt = number of patients who received treatment with PFO closure.

research letter by Mojadidi and colleagues (38) updating a previous meta-analysis. Their results point in the same direction as ours, but some differences are worth mentioning. First, we provide a more comprehensive analysis, including results of 6 different end points, sensitivity analysis, subgroup analysis, and metaregression. Second, they included the results of the 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) trial, which we excluded because the STARFlex closure device (NMT Medical) is no longer commercially available (13). Third, the authors selected the long-term data for RESPECT (20). However, retention was low for that study; only 716 patients (73.1%) remained in active follow-up. In addition, the authors indicated the publication year as 2013, whereas the long-term RESPECT data were published only recently, in 2017, which might be confusing for readers. Fourth, we noticed several inconsistencies in the Mojadidi group's analysis: An error appears in the number of events reported in the control group of the CLOSE trial; we are not sure where the number of events reported for the CLOSURE I trial comes from, because it does not reflect the results of the intention-to-treat or the per-protocol analysis; and the results for different end points are mixed up, with recurrent stroke reported for some trials (12, 18, 19) and the composite end point for others (11, 13). Fifth, the authors used the DerSimonian–Laird estimator for tau. This method performs poorly when the number of studies included in the analysis is small, as in our case (39–41). For this reason, we used the Sidik–Jonkman estimator with the Knapp–Hartung small-sample adjustment, which is more accurate in such instances (21, 22). These methodological differences led to a smaller effect size in the analysis by Mojadidi and colleagues compared with our results. Finally, the authors used risk ratios, whereas we preferred to use RD, because we believe that reporting the absolute effect is more clinically meaningful.

The lack of double-blinding represents a limitation. Notwithstanding the practical challenges and ethical

concerns related to the use of a sham intervention, to what extent this determined a bias in the original studies and the present analysis remains unclear. The included studies did not adopt the same criteria to define atrial septal aneurysm, leaving an open question about the clinical effect of a hypermobile septum or atrial septal aneurysm. Most of the atrial arrhythmias registered were limited to the periprocedural period; hence, their prognostic importance may have been overweighted. The results of this meta-analysis cannot be extended to persons who have PFO without cryptogenic stroke, even if it is associated with another clinical condition that may raise the risk for stroke, such as thrombophilia, venous thromboembolic disease, or recurrent cerebrovascular events. The percentage of participants receiving anticoagulants was heterogeneous across the studies included. Therefore, the applicability of these results to real-life scenarios may be influenced by the degree of oral anticoagulant use. Because PFO closure is permanent but medical treatment efficacy depends on patient adherence, the efficacy of closure in daily practice also will depend on adherence to pharmacologic treatment. Finally, the small number of studies available does not allow further assessment of the effect of moderator variables.

Our ClinicalTrials.gov search (November 2017) identified 2 trials, 1 ongoing and 1 not completed. The ongoing DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foremen Ovale) trial (NCT01550588), designed to assess whether percutaneous PFO closure is superior to antithrombotic treatment in preventing stroke recurrence in patients with cryptogenic stroke and high-risk PFO, may provide further insight regarding risk-based patient stratification. The CryptoCard (Effect of Device Closure of Patent Foramen Ovale in Elderly Patients With Cryptogenic Stoke/TCI) study (NCT01018355) was terminated prematurely because of an extremely low recruitment rate. Other research is evaluating new closure devices, such as the FlatStent occluder (Coherex Medical), bioabsorbable PFO occluders, and the HeartStitch occluder (Sutura), that aim to reduce complications and improve the effectiveness of PFO occlusion.

In conclusion, our results demonstrate the superiority of percutaneous PFO closure compared with medical treatment alone in preventing recurrent stroke or TIA in PFO carriers with cryptogenic stroke. However, diverging results among single studies suggest that candidates for PFO closure should be selected carefully by using cardiac imaging to maximize clinical benefit and to avoid unnecessary risks for complications.

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Reproducible Research Statement: *Study protocol:* Available at PROSPERO (www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017074686). *Statistical code:* See Methods; additional information available from Dr. De Rosa (e-mail, saderosa@unicz.it). *Data set:* See **Appendix Tables** and **Figures**; additional information available from Dr. De Rosa (e-mail, saderosa@unicz.it).

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Appendix Table 1. Information on Search Sources

Database	Search Start	Search End	Terms	Limitations
PubMed	01/12/2004	14/09/2017	"PFO closure," "cryptogenic stroke," "patent foramen ovale," "randomized controlled trial."	Languages different from English; not human study; review; nonrandomized.
Scopus	01/12/2004	14/09/2017	"PFO closure," "cryptogenic stroke," "patent foramen ovale," "randomized controlled trial."	Languages different from English; not human study; review; nonrandomized.
Google Scholar	01/12/2004	14/09/2017	"PFO closure," "cryptogenic stroke," "patent foramen ovale," "randomized controlled trial."	Languages different from English; not human study; review; nonrandomized.

PFO = patent foramen ovale.

Appendix Table 2. Definition of Large IAS

Study Name	Definition of Large IAS
CLOSE	More than 30 microbubbles in the left atrium within 3 cardiac cycles after opacification of the right atrium
REDUCE	More than 25 microbubbles in the left atrium within 3 cardiac cycles after opacification of the right atrium
RESPECT	More than 20 microbubbles in the left atrium within 3 cardiac cycles after opacification of the right atrium
PC-Trial	More than 50% of the left atrium filled with contrast within 3 cardiac cycles after opacification of the right atrium

CLOSE = Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; IAS = interatrial shunt; PC-Trial = Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of PFO 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 3. Effective PFO Closure Across All Studies

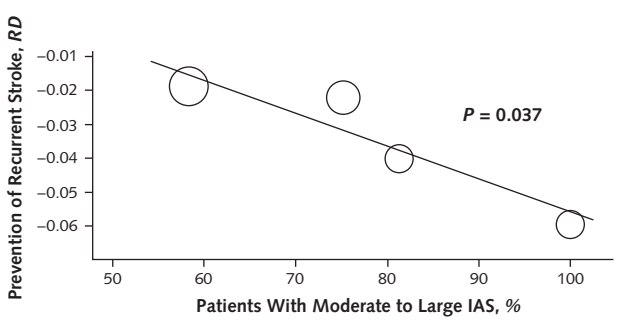
Study Name	Effective PFO Closure, %	Time of Evaluation, *mo*	Device Used
PC-Trial	95.9	6	Amplatzer PFO Occluder*
RESPECT	93.5	6	Amplatzer PFO Occluder*
REDUCE	94.5	12	Helex/Cardioform Septal Occluder†
CLOSE	93.0	11	All devices allowed (11 different used)

CLOSE = Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; PC-Trial = Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of PFO 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.
* St. Jude Medical.
† W.L. Gore and Associates.

Appendix Figure 1. Study quality assessment.

Quality assessment was performed at the trial level for the primary study outcome. The funding sources are listed on the right. CLOSE = Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; PC-Trial = Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of PFO 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.
* Risk of bias was assessed for the original results of the RESPECT trial (12) (follow-up, 2.1 y).

Appendix Figure 2. Progressively increased efficacy of PFO closure with larger IAS.

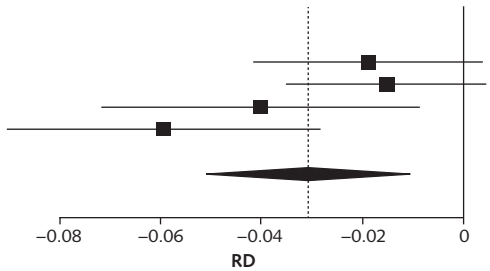


The metaregression plot shows a significant inverse interaction of the effect size with the proportion of patients with a medium to large IAS in single studies. Studies are represented by circles indicating the effect size. Circle size is proportional to the study's weight. IAS = interatrial shunt; PFO = patent foramen ovale; RD = risk difference.

Appendix Figure 3. Subgroup analysis according to follow-up length.

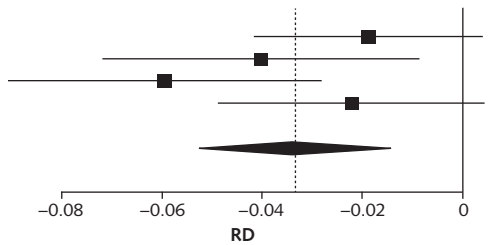
A. Results With Original RESPECT Publication

Study, Year	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
PC-Trial, 2013	−0.019 (−0.042 to 0.004)	1/204	5/210
RESPECT, 2013	−0.015 (−0.035 to 0.005)	9/499	16/481
REDUCE, 2017	−0.040 (−0.072 to −0.009)	6/441	12/223
CLOSE, 2017	−0.059 (−0.091 to −0.028)	0/238	14/235
Overall (I^2 = 60.7%; P = 0.084)	−0.031 (−0.051 to −0.010)	16/1382	47/1149



B. Results With Long-Term RESPECT Data

Study, Year	Estimate (95% CI)	Ev/Trt	Ev/Ctrl
PC-Trial, 2013	−0.019 (−0.042 to 0.004)	1/204	5/210
REDUCE, 2017	−0.040 (−0.072 to −0.009)	6/441	12/223
CLOSE, 2017	−0.059 (−0.091 to −0.028)	0/238	14/235
RESPECT Long-Term, 2017	−0.022 (−0.049 to 0.004)	18/499	28/481
Overall (I^2 = 49.26%; P = 0.171)	−0.033 (−0.053 to −0.014)	25/1382	59/1149



A. Results with the original RESPECT publication. B. Results with long-term RESPECT data. Horizontal lines represent the 95% CI of the effect size; solid squares indicate the mean effect size in single studies; diamond shapes depict the summary effect size (diamond center) and the relative 95% CI (lateral edges); the dotted vertical lines indicate the identity line, where no difference between the treatment groups exists; the black vertical lines represent the reference "0" line. *Estimate* is the effect size expressed as a risk ratio. CLOSE = Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; Ctrl = number of patients who received standard medical treatment; Ev = number of events; PC-Trial = Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of PFO With Medical Treatment in Patients With Cryptogenic Embolism; RD = risk difference; 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; Trt = number of patients who received treatment with PFO closure.

Appendix Table 4. Sensitivity Analysis for the End Point of Stroke or TIA

Study Removed	Study Weight, %	Risk Difference (95% CI)	*P* Value
All studies included	–	-0.029 (-0.050 to -0.007)	0.008
PC-Trial	23.2	-0.031 (-0.058 to -0.003)	0.030
RESPECT	39.4	-0.040 (-0.065 to -0.015)	0.002
REDUCE	18.8	-0.027 (-0.054 to -0.001)	0.043
CLOSE	18.6	-0.022 (-0.042 to -0.001)	0.040

CLOSE = Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; PC-Trial = Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of PFO 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; TIA = transient ischemic attack.

Appendix Table 5. Sensitivity Analysis for the End Point of AF or AFL

Study Removed	Study Weight, %	Risk Difference (95% CI)	*P* Value
All studies included	–	0.033 (0.012–0.054)	0.002
PC-Trial	23.6	0.037 (0.011–0.063)	0.006
RESPECT	29.5	0.040 (0.016–0.064)	0.001
REDUCE	24.9	0.022 (0.006–0.038)	0.006
CLOSE	22.0	0.032 (0.004–0.060)	0.027

AF = atrial fibrillation; AFL = atrial flutter; CLOSE = Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; PC-Trial = Randomized Clinical Trial Comparing the Efficacy of Percutaneous Closure of PFO 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.