



Original Article

Patent foramen ovale closure versus medical therapy for cryptogenic stroke: An updated systematic review and meta-analysis



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ABSTRACT

Objectives: The objective of this study was to compare safety and efficacy of patent foramen ovale (PFO) closure compared with medical therapy in patients with cryptogenic stroke (CS).

Background: The role of PFO closure in preventing recurrent stroke in patients with prior CS has been controversial.

Methods: We searched PubMed, EMBASE, the Cochrane Central Register of Controlled trials, and the clinical trial registry maintained at clinicaltrials.gov for randomized control trials that compared device closure with medical management and reported on subsequent stroke and adverse events. Event rates were compared using a forest plot of relative risk using a random-effects model assuming interstudy heterogeneity.

Results: A total of 6 studies ($n = 3747$) were included in the final analysis. Mean follow-up ranged from 2 to 5.9 years. Pooled analysis revealed that device closure compared to medical management was associated with a significant reduction in stroke (risk ratio [RR] = 0.41, 95% CI = 0.20–0.83, $I^2 = 51%$, $P = 0.01$). There was, however, a significant increase in atrial fibrillation with device therapy (RR = 5.29, 95% CI = 2.32–12.06, $I^2 = 38%$, $P < 0.0001$). No effect was observed on major bleeding ($P = 0.50$) or mortality ($P = 0.42$) with device therapy. Subgroup analyses showed that device closure significantly reduced the incidence of the composite primary end point among patients who had large shunt sizes (RR = 0.35, 95% CI = 0.18–0.68, $I^2 = 27%$, $P = 0.002$). The presence/absence of atrial septal aneurysm ($P = 0.52$) had no effect on the outcome.

Conclusion: PFO closure is associated with a significant reduction in the risk of stroke compared to medical management. However, it causes an increased risk of atrial fibrillation.

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1. Introduction

Stroke is one of the leading causes of disability worldwide and it is the fifth major cause of death in the United States.¹ Approximately one-third of all ischemic strokes is classified as cryptogenic stroke (CS), in which no clearly defined cause could be found, despite extensive diagnostic evaluation. CS accounts for approximately 200,000 strokes annually in the United States and is a major health burden.^{2–4} PFO is estimated to be present in approximately 40%–50% of patients with CS and has been postulated to be a

potential cause of cerebral infarct via paradoxical embolism, especially in the younger population who present with stroke of unknown etiology.⁵ The guidelines regarding the optimal therapy for secondary prevention of stroke in these patients are quite variable. The American guidelines recommend use of antiplatelet therapy, unless oral anticoagulation is indicated for other reasons.⁷ Conversely, the European Stroke Organization suggests percutaneous PFO closure in patients with CS and PFO that is likely to be stroke related.⁸ Considering the difference in treatment approaches, multiple observational studies and randomized clinical trials (RCTs) have been performed in the past decade to evaluate transcatheter PFO closure as compared to medical therapy. However, the results from these studies were limited by very low event rates, lack of appropriate patient selection, and large dropout rates at follow-up.^{9–11} Although PFO device closure had failed to show

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benefit in earlier studies, recently published RCTs showed a significant reduction in stroke recurrence in patients who underwent PFO closure combined with antiplatelet therapy.^{12–15} We performed an updated systematic review and meta-analysis of all published trials, including the recently published DEFENSE-PFO trial, to compare transcatheter PFO closure with antithrombotic therapy for the secondary prevention of cryptogenic stroke.

2. Materials and methods

2.1. Study design

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁶

2.2. Data sources and search strategy

We systematically searched PubMed, CINAHL, Cochrane Central, Scopus, and Web of Science databases for all studies that compared PFO closure with a percutaneous device versus medical therapy. All relevant combinations of the following keywords related to PFO closure were searched: Patent foramen ovale, PFO, PFO closure, catheter-based closure, atrial septal defect, inter-atrial shunt, stroke, cryptogenic stroke, cerebrovascular accident, brain infarction, brain ischemia, cerebrovascular disease, cerebrovascular disorder, transient ischemic attack, TIA, paradoxical embolism. The search was conducted from the inception of these databases to July 31, 2017. No language or age restrictions were applied. Pertinent trials were also searched in <http://www.clinicaltrials.gov> and in the proceedings of major international cardiology meetings (American College of Cardiology, American Heart Association, European Society of Cardiology, and Heart Rhythm Society). Included studies were required to be RCTs, which shared the outcome of the risk of cerebrovascular accident recurrence and included a minimum of 50 subjects, with at least 30 days of follow-up. Individual case reports, case series, editorials, review articles, retrospective studies, and case–control studies were excluded.

2.3. Study selection

Studies were included in the meta-analysis if they met the following criteria: (1) a study on human subjects with participants of any age undergoing PFO closure with a percutaneous device and (2) studies reporting the incidence of recurrent stroke comparing PFO closure versus antithrombotic therapy in patients with CS and PFO.

Studies that did not provide rates of recurrent strokes and studies that did not have direct comparison between closure device and medical therapy were excluded.

2.4. Data extraction

Two independent reviewers (SG and SP) screened the titles and abstracts for relevance. Discrepancies between reviewers were discussed until consensus was reached. The manuscripts of selected titles/abstracts were reviewed for inclusion and authors were contacted if additional data were needed. Using the aforementioned selection criteria, these two reviewers independently determined which articles were to be included and excluded, and the data from the relevant articles were extracted using predefined extraction forms. Any disagreements in data extraction were discussed until consensus was reached. Bibliographies of relevant publications were hand-searched to attempt complete inclusion of all possible studies of interest.

2.5. Data analysis

To analyze the data, the authors used MIX 2.0 Pro software (BiostatXL). A random-effects model was used to calculate the pooled mean difference between the PFO device closure and the medical therapy arm. Analysis was performed on an intention-to-treat basis. Data were summarized across treatment arms using the Mantel–Haenszel risk ratio (RR). Heterogeneity between studies was assessed using the Cochrane Q test and I^2 statistics, which denotes the percentage of total variation across studies that is a result of heterogeneity rather than chance. Heterogeneity was considered significant if the *P* value was <0.05. The influence of individual studies was examined by removing each study one at a time to assess the degree to which the meta-analysis estimate depends on a particular study (exclusion sensitivity analysis).

2.6. Study end points

The primary end point for the study was the rate of recurrent ischemic stroke and TIA. Secondary outcomes included all-cause mortality, major bleeding, and incidence of atrial fibrillation. Furthermore, subgroup analysis was performed to delineate the impact of AMPLATZER PFO occluder device alone, to evaluate the impact of shunt size (large shunt defined as ≥ 25 microbubbles crossing from right to left as seen on echocardiogram or size ≥ 4 mm, small to medium shut with <25 microbubbles and size < 4 mm), as well as the presence or absence of atrial septal aneurysm, on the outcomes. All events that occurred during follow-up were analyzed using an intention-to-treat principle.

2.7. Study outline and characteristics

A total of 6 studies were included in the final analysis (Table 1 showing salient features of the studies).

3. Results

Fig. 1 shows PRISMA flow diagram describing the search strategy. A total of 693 studies were identified, out of which 492 studies were duplicated and were hence removed. Of the remaining articles, 466 were excluded after screening titles and abstracts and including only relevant ones. After full-text reading, we finally narrowed down to 6 individual full-text articles, including a total of 3747 patients, 1889 in the device closure arm and 1858 in the medical therapy arm. The pooled data were sourced from following six trials: CLOSURE I, PC trial, Gore REDUCE, CLOSE, RESPECT, and DEFENSE-PFO (Table 1). All studies were published between years 2011 and 2018, and all of them were multicenter studies. Most of the included patients had a previous history of stroke and TIA, with no obvious source of thromboembolism, and all patients had PFO or ASD. The mean age of the patients was 46 years and 55% were men. None of the patients had atrial fibrillation or atrial flutter at baseline, which was an exclusion criterion in all studies. In all the included studies, the presence of PFO was diagnosed using transesophageal echocardiography (TEE). The mean duration of follow-up ranged from 2 to 5.9 years. Patients who underwent PFO closure were treated with 1–6 months of dual anti-platelet therapy, as recommended. The patients included in the medical therapy cohort were treated with at least one antiplatelet or anticoagulant agent, selected at the discretion of the treating physician.

3.1. Primary outcome (recurrent ischemic stroke and TIA)

All the 6 studies reported outcomes on the rate of recurrent stroke^{9–15} as shown in Fig. 2A. The patients randomized to PFO

Table 1
Salient features of the studies included in the meta-analysis.

Study	Closure 1		PC trial		Respect		Close		Gore REDUCE		DEFENSE PFO	
	Device closure	Medical management	Device closure	Medical management	Device closure	Medical management	Device closure	Medical management	Device closure	Medical management	Device closure	Medical management
Intervention	STARFlex septal closure (umbrella occluder) + clopidogrel, 75 mg for 6 m AND aspirin (81 or 325 mg) for 2 y	Warfarin, aspirin, or both	Amplatzer PFO occluder (disc occluder) + aspirin 100–325 mg for at least 5–6 m AND ticlopidine 250–500 mg OR clopidogrel 75–150 mg for 1–6 m	Antiplatelet therapy or anticoagulation	Amplatzer PFO occluder (disc occluder) + aspirin 81–325 mg AND clopidogrel daily for 1 m, followed by aspirin monotherapy for 5 m	Aspirin or warfarin or clopidogrel or/and aspirin plus dipyridamole	Different types of closure devices ^a + aspirin 75 mg AND clopidogrel 75 mg for 3 m, followed by single antiplatelet therapy for the rest of the trial	Aspirin OR aspirin plus dipyridamole OR clopidogrel	Helix septal occluder orcardioform septal Occluder + clopidogrel 75 mg for 3 d (max 300 mg dose if necessary) and then same antiplatelet therapy as in the other study arm for the rest of the trial	Aspirin OR clopidogrel OR aspirin plus dipyridamole	Amplatzer PFO occluder (disc occluder) + aspirin 100 mg AND clopidogrel 75 mg for at least 6 m after the procedure	Single or dual antiplatelet therapy or anticoagulation (warfarin)
Number of patients in each group	447	462	204	210	499	481	238	235	425	216	60	60
Age	46.3 ± 9.6	45.7 ± 9.1	44.3 ± 10.2	44.6 ± 10.1	45.7 ± 9.7	46.2 ± 10.0	42.9 ± 10.1	43.8 ± 10.5	45.4 ± 9.3	44.8 ± 9.6	49 ± 15	54 ± 12
Male	233 (52.1)	238 (51.5)	92 (45.1)	114 (54.3)	268 (53.7)	268 (55.7)	137 (57.6)	142 (60.4)	261 (59.2)	138 (61.9)	33 (55.0)	34 (56.7)
BMI ≥ 30	N/A	N/A	26.6 ± 5.6	26.3 ± 4.8	N/A	N/A	32 (13.4)	27 (11.5)	N/A	N/A	N/A	N/A
Current smoker	96 (21.5)	104 (22.6)	52 (25.5)	47 (22.4)	75 (15)	55 (11.4)	68 (28.6)	69 (29.4)	63 (14.3)	25 (11.2)	10 (16.7)	16 (26.7)
Coronary artery disease	6 (1.3)	4 (0.9)	N/A	N/A	19 (3.8)	9 (1.9)	N/A	N/A	N/A	N/A	N/A	N/A
Diabetes mellitus	N/A	N/A	5 (2.5)	6 (2.9)	33 (6.6)	40 (8.3)	3 (1.3)	9 (3.8)	18 (4.1)	10 (4.5)	6 (10.0)	8 (13.3)
Hyperlipidemia	212 (47.4)	189 (40.9)	50 (24.5)	62 (29.5)	194 (38.9)	193 (40.1)	30 (12.6)	36 (15.3)	N/A	N/A	18 (30.0)	25 (41.7)
Peripheral vascular disease	5 (1.1)	7 (1.5)	3 (1.5)	2 (1.0)	5 (1.)	1 (0.2)	N/A	N/A	N/A	N/A	N/A	N/A
Hypertension	151 (33.8)	131 (28.4)	49 (24.0)	58 (27.6)	158 (31.7)	150 (31.2)	27 (11.3)	24 (10.2)	112 (25.4)	58 (26.0)	12 (20.0)	17 (28.3)
Myocardial infarction	7 (1.6)	5 (1.1)	3 (1.5)	1 (0.5)	5 (1.0)	2 (0.4)	N/A	N/A	N/A	N/A	N/A	N/A
Cryptogenic stroke	324 (72.6)	329 (71.4)	165 (80.9)	163 (77.6)	53/498 (10.6)	51 (10.6)	10 (4.2)	7 (3.0)	42 (9.5)	13 (5.8)	28 (46.7)	36 (60.0)
Transient ischemic attack	122 (27.4)	132 (28.6)	N/A	N/A	58 (11.6)	61 (12.7)	*	*	26 (5.9)	11 (4.9)	N/A	N/A
Migraine	N/A	N/A	47 (23.0)	38 (18.1)	195 (39.1)	185 (38.5)	67 (28.2)	78 (33.2)	N/A	N/A	N/A	N/A
Echocardiographic variables^b												
Shunt size												
Small	N/A	N/A	55/185 (29.7)	72/184 (39.1)	108 (21.6)	114 (23.7)	N/A	N/A	77 (18.11)	43 (19.9)	N/A	N/A
Medium	N/A	N/A	87/185 (47.0)	75/184 (40.8)	138 (27.7)	121 (25.2)	N/A	N/A	166 (39.05)	94 (43.5)	N/A	N/A
Large	N/A	N/A	43/185 (23.2)	37/184 (20.1)	247 (49.5)	231 (48.0)	157 (65.8)	161 (68.5)	182 (42.8)	79 (36.5)	N/A	N/A
Presence of atrial septal aneurysm	168 (37.6)	165 (35.7)	47 (23.0)	51 (24.3)	180 (36.1)	169 (35.1)	81 (34.03)	74 (31.4)	86/422	N/A	5 (8.3)	8 (13.3)

Values are mean ± SD or N (%) or N/n (%) of patients with available data, unless otherwise indicated.

^a Findings on transesophageal echocardiography.

^b Amplatzer PFO occluder or cribriform; Starflex; CardioSEAL; Intrasept PFO; PFOStar; Helix; Premere; PFO occluder OCCLUTECH; PFO occluder GORE (GSO). N/A = not available.

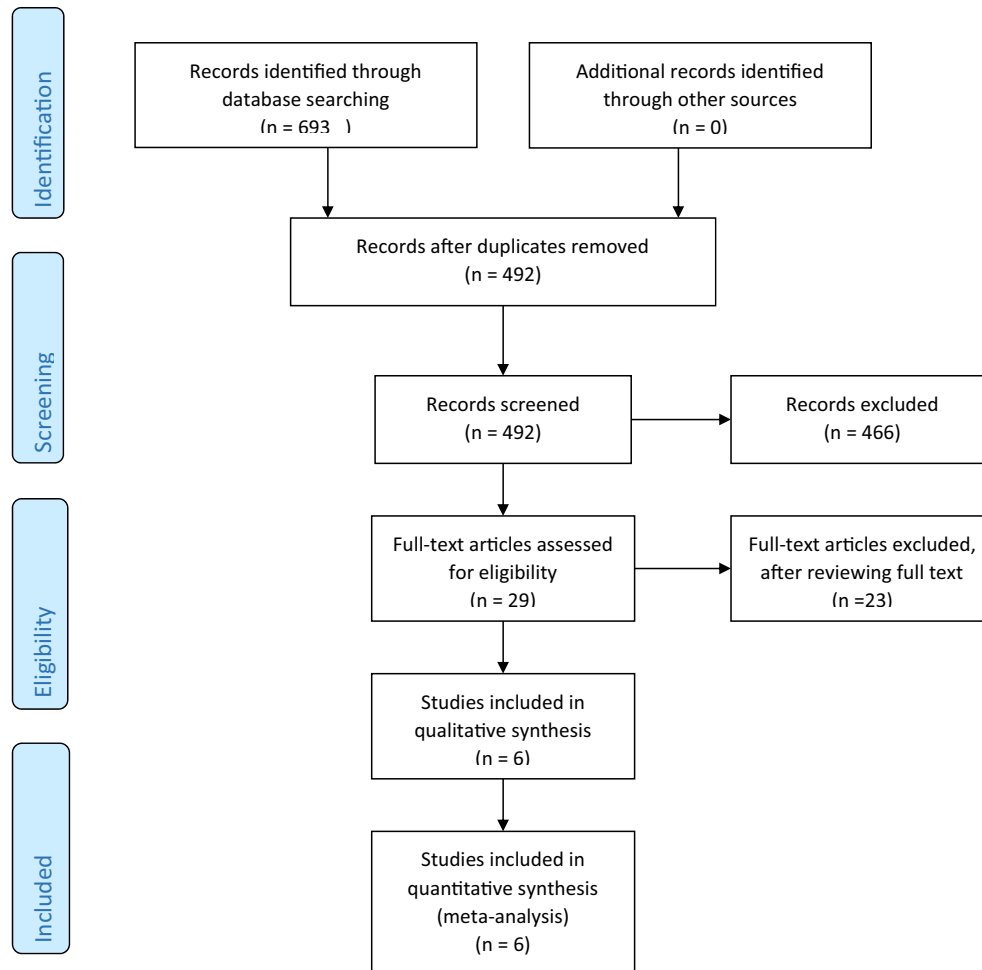


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

closure had lower recurrence of recurrent stroke as compared to patients in the medical therapy group (37/1889 versus 80/1858; RR 0.41, 95% CI 0.20–0.83; $p = 0.01$). There was a moderate evidence of heterogeneity between the studies ($I^2 = 51\%$). In comparison, only 5 studies^{9,11–13,15} reported outcomes on TIA between the treatment arms (Fig. 2B). PFO closure was numerically associated with lower TIA events as compared to patients in medical therapy arm (43/1448 versus 61/1635; RR 0.79, 95% CI 0.54–1.16; $p = 0.23$); however, it was not statistically significant.

3.2. Secondary outcome (all-cause mortality, major bleeding, and atrial fibrillation)

All the 6 studies reported outcomes on all-cause mortality^{9–15} and major bleeding events as shown in Fig. 3. There was no observed difference in all-cause mortality (13/1889 in PFO group versus 16/1858 in medical therapy; RR 0.73, 95% CI 0.35–1.55; $p = 0.42$) and major bleeding (24/1820 in PFO group versus 32/1770 in medical therapy; RR 0.73, 95% CI 0.29–1.84; $p = 0.50$) between the two groups.

In comparison, only 5 studies^{9–14} reported outcomes on atrial fibrillation. Pooled analysis showed an increased rate of atrial fibrillation with PFO device closure compared to medical therapy (76/1784 versus 12/1794; RR 5.29, 95% CI 2.32–12.06; $p < 0.0001$). However, it should be acknowledged that a vast majority of these fibrillation occurred in the periprocedural or early post procedure

period, that is, within a month after the procedure and also most of these episodes were transient or paroxysmal in nature. Owing to heterogeneity in the device type and small numbers of individual device type utilized, the independent risk of atrial fibrillation events with each device type could not be assessed individually.

3.3. Subgroup analysis (shunt size and presence of aneurysm)

We performed a subgroup analysis evaluating the presence of aneurysm and the shunt size between the two groups. The effect of PFO closure on stroke prevention was more substantial in patients with large sized PFOs (RR = 0.35, 95% CI 0.18–0.68; $p = 0.002$). However, there was no significant difference in recurrent stroke risk on subgroup analysis based on the presence of atrial septal aneurysm (RR = 0.68, 95% CI 0.21–2.21; $p = 0.52$) as seen in Fig. 4 (see Fig. 5).

We also analyzed the impact of AMPLATZER PFO occluder device alone on all the outcomes and found that there were no significant differences in all the primary and secondary outcomes between the aforementioned device and the medical therapy groups (Supplemental Material).

4. Discussion

The findings from our meta-analysis showed that (1) PFO closure significantly reduced the risk of recurrent stroke compared

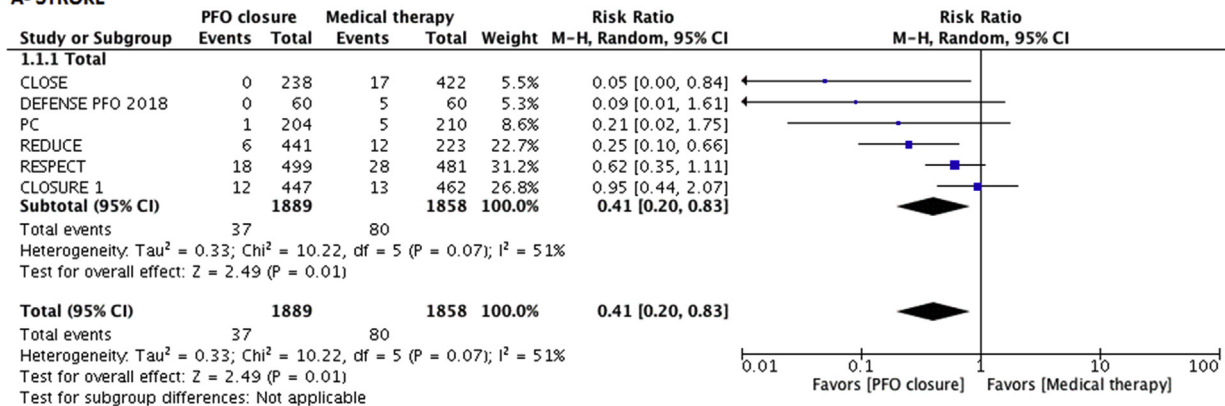
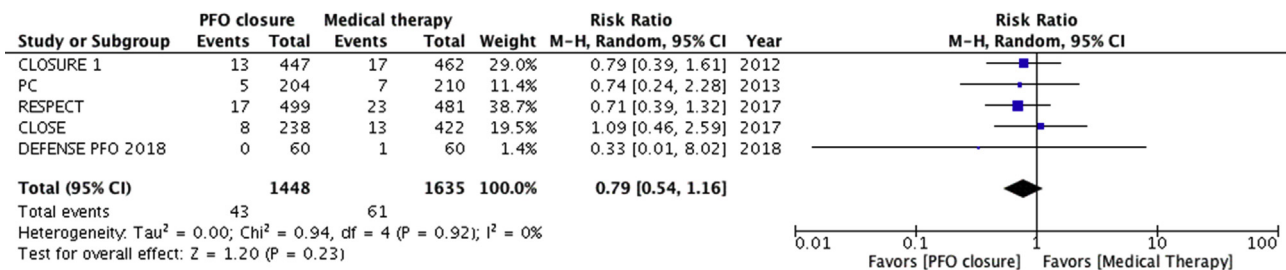
A- STROKE**B- TIA**

Fig. 2. (A) Forest plot showing rate of recurrent stroke comparing PFO closure versus medical therapy. (B) Forest plot showing rate of transient ischemic attack comparing PFO closure versus medical therapy.

to medical therapy alone; (2) PFO closure did not reduce the rate of TIA recurrence; (3) percutaneous device closure of PFO is a relatively safe treatment option with no increased risk of major bleeding or mortality but is associated with an increased incidence of newly diagnosed atrial fibrillation; and 4. patients with large shunt size have comparatively larger benefit with device closure as compared to the medical therapy alone.

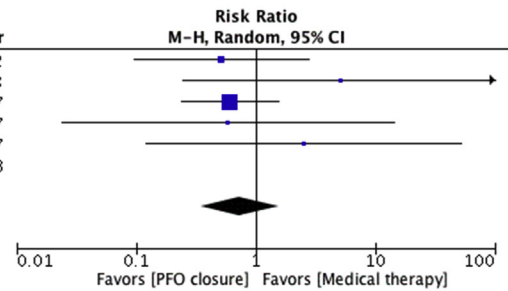
The role of PFO closure in preventing stroke in patients with prior CS has been controversial. Multiple prospective, multicenter, open-label, randomized trials have looked at the efficacy of PFO closure in reducing recurrent stroke and mortality relative to medical therapy alone with inconsistent results.^{9–15} Although earlier observational studies reported no benefit of device closure,^{17–19} newly published randomized prospective studies, and the long-term follow-up of previously conducted studies, have showed superiority of device closure.^{11–15} One of the very first RCTs, CLOSURE I, comparing PFO closure with medical therapy for CS patients, reported that PFO closure was not superior to medical therapy alone for the prevention of recurrent stroke.⁹ The study however was largely criticized for including a significant proportion of patients with multiple cardiovascular risk factors, which may have confounded the data. In addition, there was suboptimal PFO closure in 14% of patients undergoing PFO occlusion which could have contributed to increased recurrent stroke rate in the closure arm.⁹ Similarly, RESPECT trial found no significant benefit in PFO closure in the primary intention-to-treat analysis.¹⁰ However, PFO closure was superior to medical therapy alone in the per-protocol and as-treated analyses. This could be explained by the fact that some patients in the PFO closure arm experienced recurrent stroke even before the procedure was performed.¹⁰ On the other hand, recently published extended follow-up data of RESPECT trial with a median follow-up of 5.9 years showed statistically significant results in the intention-to-treat population with 0.58

events in the closure group per 100 patient years and 1.07 events in the medical therapy group per 100 patient-years ($p = 0.046$).¹¹ However, it should be taken into account that treatment exposure in both groups was not equal due to a higher dropout rate in the medical therapy arm. More recently, the CLOSE and Gore REDUCE trials demonstrated a lower rate of stroke recurrence with PFO closure combined with antiplatelet therapy versus antiplatelet therapy alone.^{14,15} Recently published DEFENSE PFO trial showed that in a selected group of high-risk PFO patients, the rate of recurrent ischemic stroke was significantly lower with the closure of the PFO plus medical therapy group than with the medical therapy alone group.¹⁶ Given the inconsistency of reported data from these RCTs and the low incidence of stroke during follow-up (even lower than expected), it may be difficult to reach definite conclusions based on the results of individual investigations, and only pooled analyses of data from multiple studies can help clarify such uncertainties. Therefore, we performed this meta-analysis to analyze all the RCTs that have been performed to date. The results of our meta-analysis are in concordance with the previously published reports.^{20–26}

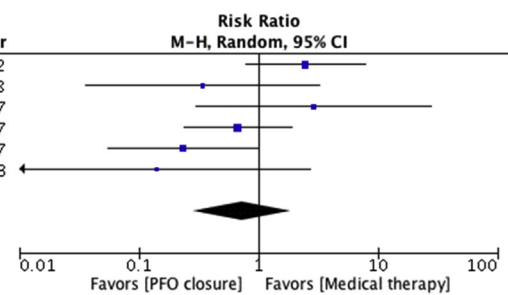
The difference in the results between the older trials and the recently published studies could be explained by the fact that newer trials with positive findings have a different study design in terms of medications, patient selection (large PFO size), and the follow-up duration.^{12–15} Although warfarin was included in all old trials with negative findings, only antiplatelet therapy was the comparator in the newer trials with positive findings. On the contrary, in DEFENSE PFO trial, warfarin was allowed to be included in the medication-only group, and 25% of patients in the medication-only group continued to receive warfarin up to 1 year after the randomization, thereby supporting the powerful beneficial effect of device closure of PFO in patients with cryptogenic stroke.¹⁶

A- MORTALITY

Study or Subgroup	PFO closure		Medical therapy		Weight	Risk Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
CLOSURE 1	2	447	4	462	19.4%	0.52 [0.10, 2.81]	2012
PC	2	204	0	210	6.1%	5.15 [0.25, 106.54]	2013
RESPECT	7	499	11	481	63.0%	0.61 [0.24, 1.57]	2017
CLOSE	0	238	1	422	5.4%	0.59 [0.02, 14.43]	2017
REDUCE	2	441	0	223	6.0%	2.53 [0.12, 52.56]	2017
DEFENSE PFO 2018	0	60	0	60		Not estimable	2018
Total (95% CI)		1889		1858	100.0%	0.73 [0.35, 1.55]	
Total events	13		16				
Heterogeneity: Tau ² = 0.00; Chi ² = 2.59, df = 4 (P = 0.63); I ² = 0%							
Test for overall effect: Z = 0.81 (P = 0.42)							

**B- MAJOR BLEEDING**

Study or Subgroup	PFO closure		Medical therapy		Weight	Risk Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
CLOSURE 1	10	378	4	374	23.8%	2.47 [0.78, 7.82]	2012
PC	1	204	3	210	11.7%	0.34 [0.04, 3.27]	2013
RESPECT	3	499	1	481	11.7%	2.89 [0.30, 27.70]	2017
REDUCE	8	441	6	223	25.4%	0.67 [0.24, 1.92]	2017
CLOSE	2	238	15	422	19.4%	0.24 [0.05, 1.02]	2017
DEFENSE PFO 2018	0	60	3	60	7.9%	0.14 [0.01, 2.71]	2018
Total (95% CI)		1820		1770	100.0%	0.73 [0.29, 1.84]	
Total events	24		32				
Heterogeneity: Tau ² = 0.60; Chi ² = 9.63, df = 5 (P = 0.09); I ² = 48%							
Test for overall effect: Z = 0.67 (P = 0.50)							

**C- ATRIAL ARRHYTHMIAS**

Study or Subgroup	PFO closure		Medical therapy		Weight	Risk Ratio M-H, Random, 95% CI	Year
	Events	Total	Events	Total			
CLOSURE 1	23	402	3	458	25.2%	8.73 [2.64, 28.87]	2012
PC	6	204	2	210	17.9%	3.09 [0.63, 15.12]	2013
RESPECT	7	499	4	481	24.6%	1.69 [0.50, 5.73]	2017
REDUCE	29	441	1	223	13.0%	14.66 [2.01, 106.95]	2017
CLOSE	11	238	2	422	19.3%	9.75 [2.18, 43.63]	2017
Total (95% CI)		1784		1794	100.0%	5.29 [2.32, 12.06]	
Total events	76		12				
Heterogeneity: Tau ² = 0.33; Chi ² = 6.43, df = 4 (P = 0.17); I ² = 38%							
Test for overall effect: Z = 3.96 (P < 0.0001)							

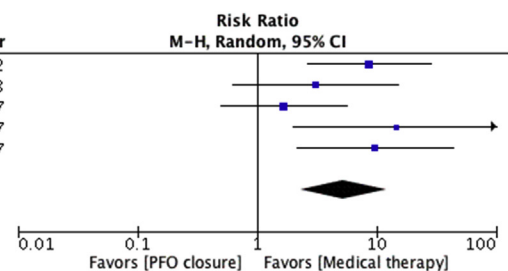


Fig. 3. (A) Forest plot showing all-cause mortality between PFO closure versus medical therapy. (B) Forest plot showing major bleeding between PFO closure versus medical therapy. (C) Forest plot showing incidence of atrial fibrillation between PFO closure versus medical therapy.

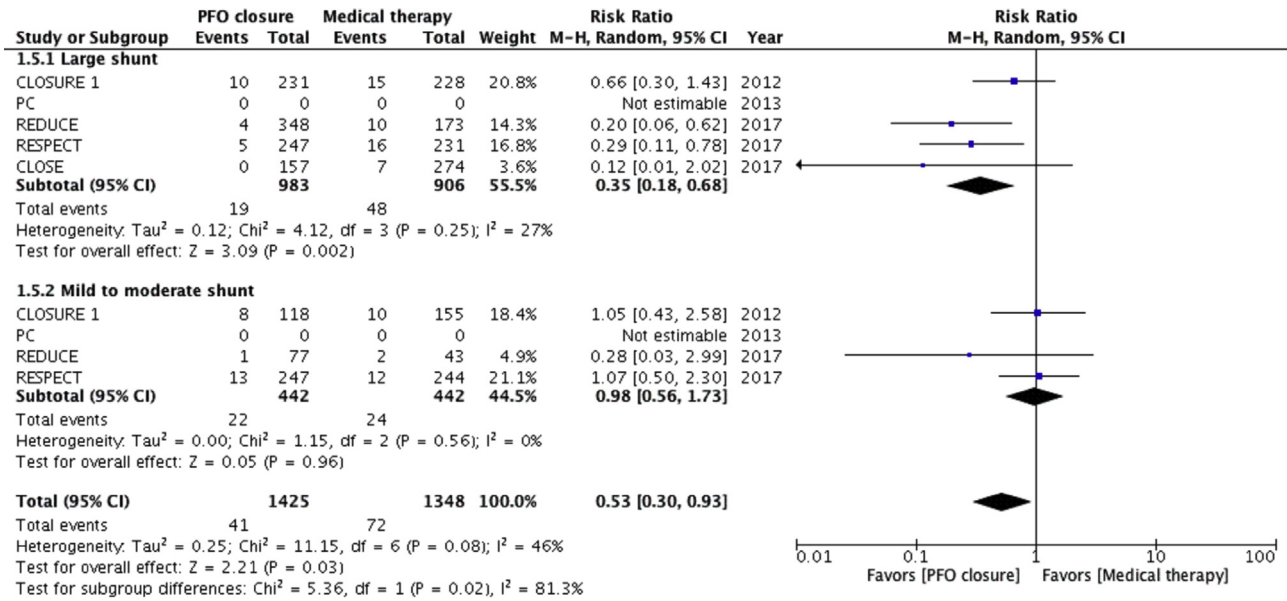
Although it is hypothesized that a larger PFO, with a larger right to left shunt, or the presence of an atrial septal aneurysm may result in an increased risk of stroke, it has never been confirmed.²⁷ To clarify this effect and measure the efficacy of device closure in such a patient population, we performed a subgroup analysis based on the shunt size, and whether an atrial septal aneurysm was present. All RCTs included in this meta-analysis, except for the PC and DEFENSE PFO trials, reported the size of the shunt and classified the size according to the amount of bubbles detected in the left atrium on TEE. The positive correlation between shunt size and stroke recurrence was confirmed in our analysis. Patients who had large shunt sizes showed more beneficial effect of device closure, and thus, a lower stroke rate as compared to the medical group. However, the presence or absence of aneurysms had no effect on stroke rate with device closure.

In our analysis, we were unable to demonstrate the beneficial effect of PFO closure on reducing the incidence of TIA. This could be contributed to the fact that TIA is very hard to detect clinically and even harder to confirm on imaging. Also, the reported rates of TIA in studies were very low, which reduces the power to detect an effect during pooled analysis.

Although multiple meta-analyses on this topic have been published before, the previous analyses did not include the latest data from the DEFENSE-PFO trial.^{20–26} In DEFENSE-PFO trial, the

benefits of PFO closure were specifically evaluated on patients with cryptogenic stroke and high-risk PFO evaluated by transesophageal echocardiogram, which was not the case in other 3 favorable clinical trials.¹⁵ DEFENSE-PFO trial provided further insight into the role of morphologic characteristics of PFO to select optimal candidates who can benefit most from PFO closure. Furthermore, patients in DEFENSE-PFO trial received either antiplatelet or anticoagulation but only antiplatelet in Gore-REDUCE and CLOSE trials, which further authenticate the benefits of PFO closure.¹⁵

In our study, transcatheter PFO closure was shown to be a safe and effective method, without any significant increase in the rate of all-cause mortality or bleeding, when compared to the medical therapy only arm. By contrast, the PFO closure group demonstrated a higher incidence of atrial fibrillation as compared to medical therapy alone. Of note, postimplant atrial fibrillation mostly occurred early after PFO closure (within 45 days) and was transient, resolving spontaneously, or with electrical or pharmacological cardioversion. Only a small proportion of all atrial fibrillations (AFs) or atrial flutters after PFO closures were reported to progress to permanent AF.²⁷ Although there are several explanations for the higher incidence of fibrillation in the device closure group, one may attribute the likely etiology to be from device triggers. Also, given the difficulty in diagnosing paroxysmal AF, the possibility of having AF before device implantation cannot be ruled out or ignored. This



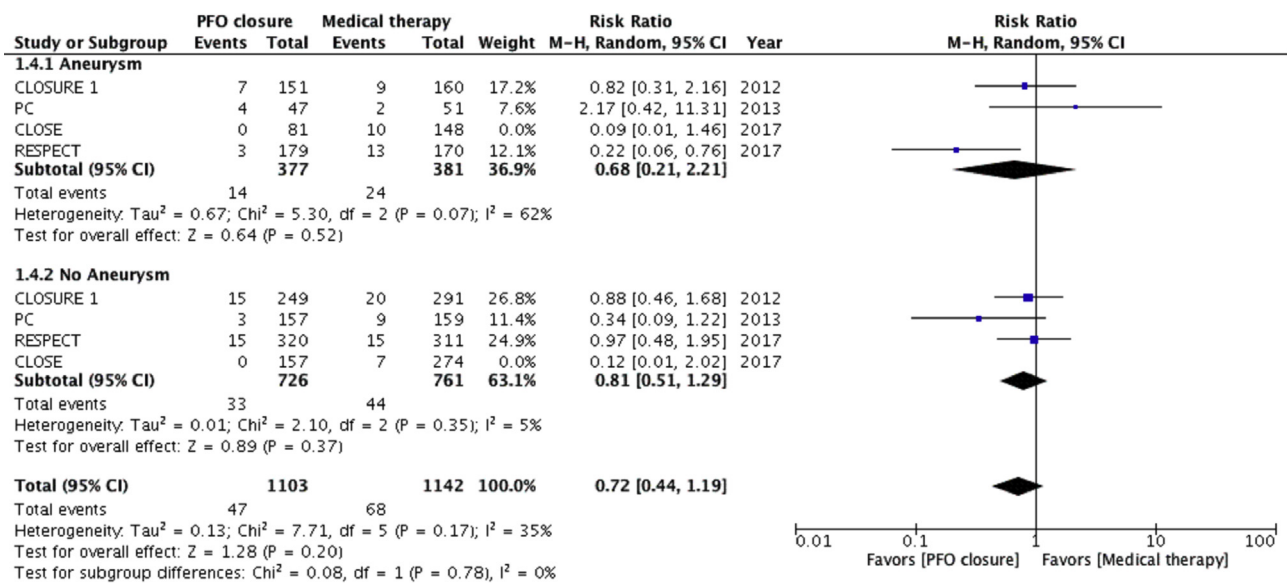
PFO SHUNT SIZE

Fig. 4. Forest plot showing the effect of shunt size on the PFO device closure versus medical therapy.

may explain the reason for the increased incidence of atrial fibrillation in the PFO closure group. This argument is supported by the RESPECT trial finding, which excluded paroxysmal AF and showed no difference in the rates of AF between the two groups (0.6% in both closure and medical therapy group).¹⁰

The strength of this meta-analysis is that only RCTs were included. The pooled analysis which included a large number of patients from different backgrounds reflects a representative sample despite prolonged recruitment period. Risks of atrial arrhythmia, other adverse events, and effect of PFO size on device closure were also measured.

There are several limitations to this meta-analysis: (1) the analysis is based on pooled data from different trials and it shares the possible limitations of the individual included trial; (2) most of the RCTs suffered from a slow enrollment process over decades and with variable follow-up periods, thereby the data from the initial phase are not comparable with the more current data due to device iterations, change in clinical practice, and operator's experience; (3) the absence of patient-level data precludes further stratified or adjusted analyses to account for possible confounders; (4) different types of PFO devices were used in the trials, and therefore the efficacy and safety of each device should be considered when



PRESENCE OR ABSENCE OF ANEURYSM

Fig. 5. Forest plot showing the effect of atrial septal aneurysm on the PFO device closure versus medical therapy.

interpreting these results; (5) each trial allowed for different medical therapy strategies within their study groups and therefore the differences within each study and across all RCTs may have affected the final results.

5. Conclusion

Based on the findings from our meta-analysis, it can be concluded that percutaneous PFO closure is a safe option for patients with CS who are found to have a large size PFO. It is associated with a significant reduction in the risk of recurrent stroke when compared to medical management alone, though it is associated with an increased risk of atrial fibrillation. Individualized risk-benefit analyses will provide patients with the knowledge to select a personalized treatment option. Multidisciplinary teams consisting of cardiologists, neurologists, and interventionalists can offer an innovative option for correct decision-making on a patient-by-patient basis, which will help avoid unnecessary procedures and provide patients with the highest level of available care.

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Conflict of interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

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References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990–2010: findings from the global burden of disease study 2010. *Lancet*. 2014 Jan 18;383(9913):245–254.
2. Grau AJ, Weimar C, Buggle F, et al. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. *Stroke*. 2001 Nov;32(11):2559–2566.
3. Petty GW, Brown Jr RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. *Stroke*. 1999 Dec;30(12):2513–2516.
4. Li L, Yiin GS, Geraghty OC, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol*. 2015 Sep;14(9):903–913.
5. Homma S, Sacco RL. Patent foramen ovale and stroke. *Circulation*. 2005 Aug 16;112(7):1063–1072.
7. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014 Jul;45(7):2160–2236.
8. Rengifo-Moreno P, Palacios IF, Junpapap 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 Nov;34(43):3342–3352.
9. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med*. 2012;366:991–999.
10. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med*. 2013;368:1083–1091.
11. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med*. 2013;368:1092–1100.
12. Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med*. 2017;377:1022–1032.
13. Søndergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med*. 2017;377:1033–1042.
14. Mas JL, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med*. 2017;377:1011–1021.
15. Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. *J Am Coll Cardiol*. 2018 May 22;71(20):2335–2342.
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009 Aug 18;151(4):W65–W69.
17. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation*. 2002;105:2625–2631.
18. Lechat P, Lascault G, Mas JL. Prevalence of patent foramen ovale in young patients with ischemic cerebral complications. *Arch Mal Coeur Vaiss*. 1989;82:847–852.
19. Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med*. 2001;345:1740–1746.
20. Hakeem A, Marmagkiolis K, Hacıoglu Y, et al. Safety and efficacy of device closure for patent foramen ovale for secondary prevention of neurological events: comprehensive systematic review and meta-analysis of randomized controlled trials. *Cardiovasc Revascularization Med*. 2013 Nov-Dec;14(6):349–355.
21. 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 Dec;6(12):1316–1323.
22. Kwong JSW, Lam Y-Y, Yu C-M. Percutaneous closure of patent foramen ovale for cryptogenic stroke: a meta-analysis of randomized controlled trials. *Int J Cardiol*. 2013;168:4132–4138.
23. Li J, Liu J, Liu M, et al. Closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and a history of cryptogenic stroke or transient ischemic attack. *Cochrane Database Syst Rev*. 2015 Sep 8;(9). CD009938.
24. Qiu B, Cai Y, Wang D, Lin J, Fan Y. Closure versus medical therapy for patent foramen ovale in patients with cryptogenic stroke: an updated meta-analysis of randomized controlled trials. *J Stroke Cerebrovasc Dis*. 2018 Dec;27(12):3463–3472.
25. Vukadinović D, Schirmer SH, Vukadinović AN, et al. Interventional closure vs. medical therapy of patent foramen ovale for secondary prevention of stroke: updated meta-analysis. *Clin Res Cardiol*. 2019 Feb;108(2):157–166.
26. Sá MPBO, Vieira EES, Cavalcanti LRP, et al. Updated meta-analysis on the closure of patent foramen ovale in reduction of stroke rates: the DEFENSE-PFO trial does not change the scenario. *Braz J Cardiovasc Surg*. 2018 Sep-Oct;33(5):511–521.
27. De Castro S, Cartoni D, Fiorelli M, et al. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke*. 2000;31:2407–2413.