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, I² = 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, I² = 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, I² = 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.6 Conversely, the European Stroke Organization suggests percutaneous PFO closure in patients with CS and PFO that is likely to be stroke related.7 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.8–11 Although PFO device closure had failed to show...
benefit in earlier studies, recently published RCTs showed a significant reduction in stroke recurrence in patients who underwent PFO closure combined with antiplatelet therapy.\textsuperscript{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.\textsuperscript{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 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.

2.4. 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 (BiosstatXL). 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 I² 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 $\geq 4$ mm, small to medium shunt with $<25$ microbubbles crossing from right to left as seen on echocardiogram or 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, Core 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 antplatelet 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 as shown in Fig. 2A. The patients randomized to PFO
| 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 | 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 + 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 | Helex septal occluder (cribriform septal occluder) + aspirin 100 mg AND 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**

| Age | 447 | 462 | 204 | 210 | 499 | 481 | 238 | 235 |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Male | 233 (52.1) | 238 (51.5) | 92 (45.1) | 92 (45.1) | 288 (53.7) | 268 (55.7) | 55 (11.4) | 55 (11.4) |
| BMI ≥ 30 | N/A | N/A | 26.6±5.6 | 26.6±5.6 | N/A | N/A | 19 (3.8) | 19 (3.8) |
| Current smoker | 96 (21.5) | 104 (22.6) | 52 (25.5) | 52 (25.5) | 75 (15) | 75 (15) | 9 (1.9) | 9 (1.9) |
| Coronary artery disease | 6 (1.3) | 4 (0.9) | N/A | N/A | 137 (28.6) | 137 (28.6) | 68 (28.6) | 68 (28.6) |
| Diabetes mellitus | N/A | N/A | 5 (2.5) | 5 (2.5) | 33 (6.6) | 33 (6.6) | 3 (1.3) | 3 (1.3) |
| Hyperlipidemia | 212 (47.4) | 189 (40.9) | 50 (24.5) | 50 (24.5) | 139 (28.9) | 139 (28.9) | 3 (0.6) | 3 (0.6) |
| Peripheral vascular disease | 5 (1.1) | 7 (1.5) | 3 (1.5) | 3 (1.5) | 5 (1) | 5 (1) | 0 (0) | 0 (0) |
| Hypertension | 151 (33.8) | 131 (28.4) | 49 (24.0) | 49 (24.0) | 158 (31.7) | 158 (31.7) | 2 (0.4) | 2 (0.4) |
| Myocardial infarction | 17 (3.6) | 15 (3.1) | 1 (0.5) | 1 (0.5) | 5 (1.0) | 5 (1.0) | 0 (0) | 0 (0) |
| Cryptogenic stroke | 324 (72.6) | 329 (71.4) | 165 (80.9) | 165 (80.9) | 53 (498) (10.6) | 53 (498) (10.6) | 10 (4.2) | 10 (4.2) |
| Transient ischemic attack | 122 (27.4) | 132 (28.6) | N/A | N/A | 51 (10.6) | 51 (10.6) | 4 (0.9) | 4 (0.9) |
| Migraine | N/A | N/A | 47 (23.0) | 47 (23.0) | 195 (39.1) | 195 (39.1) | 67 (28.2) | 67 (28.2) |

**Echocardiographic variables**

| Shunt size | Small | Medium | Large | Presence of atrial septal aneurysm |
|------------|-------|--------|-------|----------------------------------|
| N/A | N/A | 47 (23.0) | 195 (39.1) | 72 (38.5) | 67 (28.2) | 78 (33.2) |

**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; Helex; Premere; PFO occluder OCCLUTECH; PFO occluder GORE (GSO). N/A = not available.
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 (I² = 51%). In comparison, only 5 studies9,11–13,15 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 mortality9–15 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 studies9–14 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
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. Although earlier observational studies reported no benefit of device closure, newly published randomized prospective studies, and the long-term follow-up of previously conducted studies, have showed superiority of device closure. 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. 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. Similarly, RESPECT trial found no significant benefit in PFO closure in the primary intention-to-treat analysis. 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. 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 ($p = 0.046$). 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. 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. 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.

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. 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.
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. 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. 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. 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 antplatelet or anticoagulation but only antplatelet in Gore-REDUCE and CLOSE trials, which further authenticate the benefits of PFO closure.

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. 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
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
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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