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Percutaneous Closure of Patent Foramen Ovale in Patients with Cryptogenic Stroke — An Updated Comprehensive Meta-Analysis☆

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ABSTRACT

Background: The ideal treatment strategy for patients with cryptogenic stroke and patent foramen ovale (PFO) is not yet clear. Previous randomized controlled trials (RCTs) comparing transcatheter PFO closure with medical therapy in patients with cryptogenic stroke to prevent recurrent ischemic stroke showed mixed results. This meta-analysis aims to compare rates of recurrent stroke, transient ischemic attack (TIA) and all-cause mortality with PFO closure and medical therapy vs. medical therapy alone.

Methods: PubMed and the Cochrane Center Register of Controlled Trials were searched for studies published through June 2018, comparing PFO closure plus medical therapy versus medical therapy alone. Six RCTs (n = 3750) comparing PFO closure with medical therapy were included in the analysis. End points were recurrent stroke, TIA and all-cause mortality. The odds ratios (OR) with 95% confidence interval (CI) were computed and $p < 0.05$ was considered as a level of significance.

Results: A total of 1889 patients were assigned to PFO closure plus medical therapy and 1861 patients were assigned to medical therapy only. Risk of recurrent stroke was significantly lower in the PFO closure plus medical therapy group compared to medical therapy alone. (OR 0.47, 95% CI 0.33–0.67, $p < 0.0001$). Rate of TIA was similar between the two groups (OR 0.76, 95% CI 0.52–1.14), $p = 0.18$). There was no difference in all-cause mortality between two groups (OR 0.73, CI 0.33–1.58, $p = 0.42$). Patients undergoing PFO closure were more likely to develop transient atrial fibrillation than medical therapy alone (OR: 5.85; CI: 3.06–11.18, $p \leq 0.0001$) whereas the risk of bleeding was similar between the groups (OR: 0.93; CI: 0.55–1.57, $p = 0.78$).

Conclusions: The results of this meta-analysis suggest that transcatheter closure of PFO plus medical therapy is superior to medical therapy alone for the prevention of recurrent cryptogenic stroke. However, PFO closure in these patients has not been shown to reduce the risk of recurrent TIA or all-cause mortality. There is a higher rate of transient atrial fibrillation post PFO closure device placement, the long-term effects of which have yet to be studied.

1. Introduction

Approximately 30–40% of ischemic strokes do not have a defined cause and are thus referred to as cryptogenic strokes [1–3]. Even after adjusting for risk factors, patients with cryptogenic stroke have a higher prevalence of PFO than patients with stroke of known etiology in all age groups [4]. Smaller PFOs tend to close with advanced age and hence the prevalence and size of PFO decrease with age. The risk of stroke in patients with PFO is determined by the size of PFO, length of defect, presence of atrial septal aneurysm (ASA) and degree of shunting [5].

Three previously conducted randomized controlled trials (RCT), namely, CLOSURE I, RESPECT and PC, failed to show benefit of PFO closure over medical therapy in preventing recurrent stroke, TIA or death [6–8]. However, recently published RCTs and extended follow-up of RESPECT trial have shown that PFO closure reduces risk of recurrent stroke compared with medical therapy alone. We aim to present new

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comparison outcomes through an updated comprehensive review and meta-analysis including all published RCTs thus far.

2. Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, [9] and, Meta-Analysis of Observational Studies in Epidemiology [10] statements for reporting systematic reviews. General guidelines from the Cochrane Handbook for Systematic Reviews of Interventions, version 5.0.2 were used in developing methods, and the meta-analysis was conducted in adherence to these guidelines. We searched the National Library of Medicine PubMed, National Institutes of Health clinical trials registry (ClinicalTrials.gov), the Cochrane Central Register of Controlled Trials, google scholar, OVID, Medline, WHO international clinical trials and EMBASE to include clinical studies published through June 2018 which compared the risk of recurrent stroke, TIA and/or mortality in patient with a history of cryptogenic stroke and PFO who underwent closure of PFO in addition to standard medical therapy versus patients treated with medical therapy alone. The key words used for searching studies were "PFO closure", "Transcatheter PFO closure", "Cryptogenic stroke", "Percutaneous PFO closure" "Cryptogenic embolism", "TIA", and "Transient ischemic attack". In addition to our computerized search, we manually reviewed the reference lists and related links of all retrieved reports to complete our search. Two independent investigators (PS and MK) reviewed all titles from the search results, and reports were selected for final data extraction.

Studies were included in analysis if they met all inclusion criteria: (1) the study must compare outcomes of PFO closure in addition to medical therapy versus medical therapy alone in patients with a PFO who suffered from cryptogenic stroke and (2) the study must report one or more of the following outcomes; recurrent stroke, TIA and/or all-cause mortality. After applying selection criteria, a total of six RCTs (total n = 3750) were included in the analysis. The search and selection process is outlined in Fig. 1. Data was extracted from each study by two independent reviewers, including years performed, study design, sample size, follow-up duration, types of closure devices used, types of medical therapy used in each arm and baseline clinical characteristics of the patient population. End points included recurrent stroke, TIA and/or all-cause mortality. Inter-rater agreement was 90%, and disagreements were resolved by consensus.

The quality of the included studies was assessed using the Newcastle-Ottawa Scale for quality assessment of cohort studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). Briefly, studies were quoted using prespecified items on patient selection (representativeness and selection of patients, ascertainment of exposure), comparability of cohorts, and assessment of outcomes (recording, adequacy of follow-up). Ratings for each item were added to provide a study quality score (maximal score of 9) by two independent reviewers using Newcastle- Ottawa Scale grading. Discrepancies in rating were solved by consensus.

The eleven devices investigated in the six included trials were Amplatzer PFO occluder (AGA Medical, St. Jude Medical), Intrasept PFO occluder (Cardia), Premere (St. Jude Medical), STARFlex septal occluder system (NMT Medical), Amplatzer cribriform occluder (AGA Medical), Figulla Flex II PFO occluder (Occlutech, Inc), Atriasept II occluder (Cardia), Amplatzer ASD occluder (AGA Medical), Figulla Flex II UNI occluder (Occlutech), Gore septal occluder (Helex/Cardioform) (Gore Medical) and Figulla Flex II ASD occluder (Occlutech).

3. Results

Study overview and baseline characteristics are listed in Table 1. This meta-analysis included a total of 3750 patients with 15,133 patient-years follow-up. The mean age of the population was 46.05 ± 10.4 years and 55.26% of the population were males.

There were 1889 patients who underwent PFO closure combined with medical therapy and 1861 patients were assigned to medical therapy alone. Risk of recurrent stroke was significantly lower in the PFO closure group compared to medical therapy only group (OR 0.47, 95% confidence interval (CI) 0.33–0.67, $p < 0.0001$) (Fig. 2). The risk of TIA was similar between the two groups (OR 0.76, CI 0.52–1.14, $p = 0.18$) (Fig. 3) although TIA was not a primary end point in four of six trials included in the meta-analysis. There was no difference in all-cause mortality between two groups (OR 0.73, CI 0.33–1.58, $p = 0.42$) (Fig. 4). Patients who underwent PFO closure were more likely to develop transient atrial fibrillation as compared with patients in medical therapy only group (OR: 5.85; CI: 3.06–11.18, $p \leq 0.0001$) (Fig. 5) but the risk

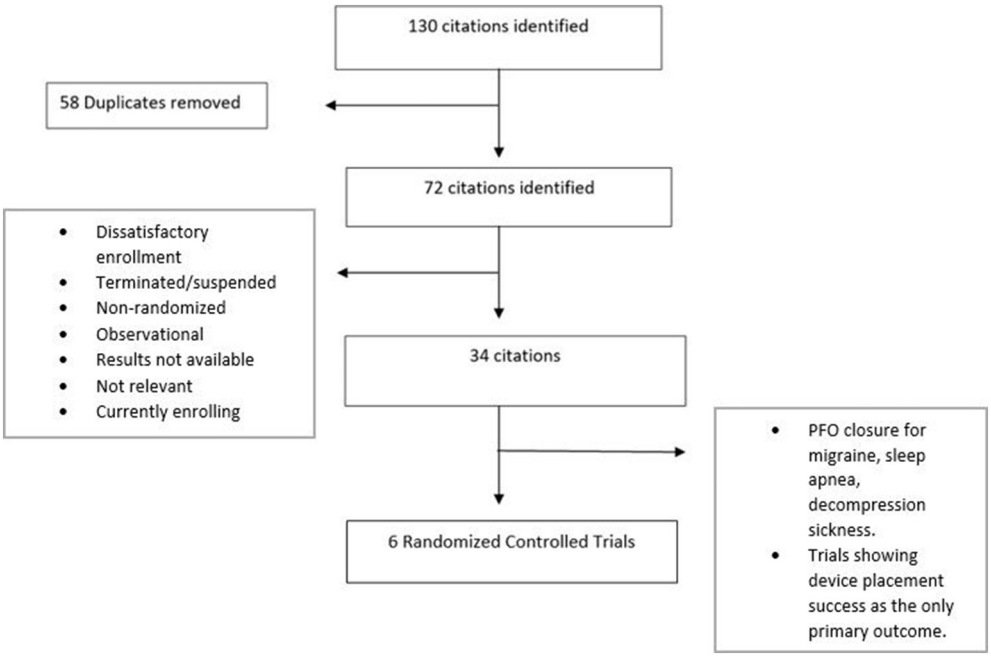

Fig. 1. Study selection process.

of bleeding was similar between the two groups (OR: 0.93; CI: 0.55–1.57, $p = 0.78$) (Fig. 6).

4. Discussion

Stroke is the second leading cause of death worldwide after ischemic heart disease [11]. Majority of strokes are ischemic in nature. Etiology of ischemic stroke varies and includes large artery atherosclerosis, cardiac thromboembolism, small vessel occlusion (lacune), and other determined etiology such as vasculitis or arterial dissection. In up to 40% of cases, an etiology cannot be established after an adequate and extensive evaluation for a possible cause. The prevalence of PFO in patients with cryptogenic stroke is as high as 40%, and thus higher than the 25% prevalence in the general population. While up to half of the PFOs in patients with cryptogenic stroke may be incidental, some may be pathogenic and responsible for stroke via paradoxical embolism from a lower extremity thrombus. The presence of an atrial septal aneurysm further increases risk of stroke in patients with a PFO [12–14]. Several studies have demonstrated a positive association between PFO size, right to left shunt size and cryptogenic stroke [15–17]. The exact definition of a large shunt varied in each study; anywhere between 20 and 40 microbubbles shunted into the left atrium within 3 cardiac cycles was considered large. However, the exact relation between PFO shunt size and infarct size on brain Magnetic Resonance Imaging has been controversial. [18,19]

Transcatheter closure of a PFO can theoretically lower the risk of recurrent stroke compared with medical therapy alone but the evidence for this is conflicting. A meta-analysis of 48 observational studies including 10,327 patients by Agarwal et al. with a follow-up of 6.7 years demonstrated that transcatheter PFO closure was associated with a significantly lower risk of recurrent neurological events 0.8 (95% CI: 0.5–1.1) compared to medical therapy group 5.0 (95% CI: 3.6–6.9) events per 100 persons-years [20]. However, three subsequently conducted RCTs utilizing two different closure devices, failed to show a benefit of PFO closure for prevention of recurrent stroke, TIA or death [6–8]. The primary outcomes and adverse effects of these trials, CLOSURE I [6] (Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale using the STARFLEX device), RESPECT [7] (Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke) and PC [8] (Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism) are shown in Table 2 and Table 3 respectively.

In CLOSURE I trial, the use of the STARFLEX device showed no benefit over medical therapy for prevention of recurrent strokes. The inclusion of TIA and lacunar strokes, incomplete closure and an older generation device with a high incidence of device thrombus and atrial fibrillation were major drawbacks of this trial. The RESPECT and PC trials which used the Amplatzer PFO Occluder device did not show superiority of PFO closure over medical therapy in intention to treat analysis of primary end points.

These RCTs were criticized due to several limitations which included under powering with low sample size and likely overestimation of recurrent events during follow-up, slow enrollment and short duration of follow-up. The trials also limited by the lack of standardization of medical therapy or type of closure device used, for instance the CLOSURE I trial used STARFlex device while the other two trials used the Amplatzer devices. Moreover, there were several instances of off label use of PFO closure device in the medical therapy group. To increase statistical power, several meta-analyses combining the three RCTs were published. Pickett et al. showed a reduction in the combined risk of recurrent stroke, TIAs and death in PFO plus medical therapy arm compared to medical therapy only [21]. Another study showed that PFO closure compared to medical therapy was beneficial in prevention of recurrent neurological events [22]. Stortecky et al. performed a network meta-analysis investigating the Amplatzer, STARFlex and Helex devices and concluded that PFO closure was advantageous compared to medical therapy when an Amplatzer device was used [23]. These affirmative results led to the Food and Drug Administration's approval of the Amplatzer PFO Occluder device in 2016 in selected patients. Results of a meta-analysis by Kent et al. [24] reported a statistically significant reduction of recurrent stroke and composite endpoint of stroke, TIA and death in patients with PFO closure. An RCT [25] compared the three different closure devices in terms of procedural complication and long-term effects shown decrease rate of neurological events with Amplatzer device compared to STARFLEX and Helex devices. Similarly, a recent meta-analysis of PFO closure versus medical therapy by Ahmad et al. [26] has shown that PFO closure is superior to medical therapy for prevention of recurrent strokes especially in patients with moderate to large shunts. Kim et al. [27] also reported superiority of PFO closure over medical therapy for prevention of recurrent strokes in patients with cryptogenic stroke and moderate grade PFO shunts.

Following the approval of Amplatzer device, several RCTs were conducted to further investigate the benefit of PFO closure. The CLOSE trial [28] (Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelet after Stroke) randomized patients with cryptogenic stroke and an associated atrial septal aneurysm or large interatrial shunt into 3 groups (PFO closure plus long-term antiplatelet therapy, antiplatelet only and anticoagulation only). Eleven different closure devices were used in the PFO closure group. The primary end point of recurrent stroke was lower in the PFO closure group compared to the medical therapy group receiving antiplatelet therapy only. Although the rate of atrial fibrillation was higher in the PFO closure group, the number of overall serious adverse events were similar. Most cases of atrial fibrillation occurred early after the procedure with no recurrence during follow up. The REDUCE trial [29] comparing PFO closure and antiplatelet therapy in cryptogenic stroke refined the selection of patients by defining cryptogenic stroke. Stroke was defined as cryptogenic after other identifiable mechanisms of stroke were ruled out, such as large-artery atherosclerotic disease, established cardioembolic source, small-vessel occlusive disease (lacunar stroke), hypercoagulable disorder requiring anticoagulation or arterial dissection. An ischemic stroke was defined as an acute focal neurologic deficit, resulting in clinical symptoms lasting 24 h or more or was associated with evidence of relevant infarction on magnetic resonance imaging or computed tomography of the brain [29]. The rate of recurrent stroke and new brain infarction was significantly lower in the PFO closure group, while the incidence of silent brain infarction was almost equal in both study arms. Serious adverse events occurred more frequently in the medical therapy group. Atrial fibrillation following PFO closure occurred mostly within 45 days and resolved within 2 weeks after it was diagnosed. The DEFENSE-PFO trial [30] is the most recent RCT which evaluated the benefit of PFO closure in patients with certain high risks features on transesophageal echocardiography. High risk PFO features included atrial septal aneurysm or hypermobility and large PFO. The results of this trial showed that PFO closure in selected patients with high-risk features lowered the rate of the composite endpoint of stroke, vascular death, or Thrombolysis in Myocardial Infarction - major bleeding during 2 years of follow-up, as well as recurrence of stroke.

Several factors may explain the benefit of PFO closure over medical therapy noted in the newer trials. The population studied in some of the older trials had a greater number of patients with vascular risk factors, such as hypertension and hypercholesterolemia, compared to the patients included in the recent trials. Newer trials such as DEFENSE [30] and CLOSE [28] only included patients with high-risk PFO features, which may explain the effectiveness of PFO closure in the population studied. The patients in REDUCE [29] and DEFENSE [30] were screened with imaging modalities to exclude patients with >50% stenosis in a major vessel which is independently associated with a higher incidence of adverse vascular outcomes. These trials also excluded patients with uncontrolled hypertension, uncontrolled diabetes, and unstable angina to include a more favorable population with lower risk of vascular events and this may have increased the success of PFO closure. Of note, TIA was only a primary endpoint in two of the clinical trials (PC

Table 1
Baseline study characteristics.

Study name	CLOSE N = 663		REDUCE N = 664		RESPECT N = 980		CLOSURE 1 N = 909		PC N = 414		DEFENSE N = 120	
	PFO or Anticoagulation vs. Antiplatelet after stroke		PFO closure or Antiplatelet therapy for cryptogenic stroke		Long-term outcomes of PFO closure or medical therapy after stroke		Closure or medical therapy for cryptogenic stroke with PFO		Percutaneous closure of PFO in cryptogenic embolism		Cryptogenic stroke and high-risk PFO	
Type of study	RCT, multicenter, open label trial (with blinded adjudication of outcome events)		RCT, multicenter, open label trial (with blinded adjudication of outcome events)		RCT, multicenter, open label trial (with blinded adjudication of outcome events)		RCT, multicenter, open label trial (with blinded adjudication of outcome events)		RCT, multicenter, open label trial (with blinded adjudication of outcome events)		RCT multicenter, randomized, open label, superiority trial	
Intervention	PFO N = 238	MT N = 425	PFO N = 441	MT N = 223	PFO N = 499	MT N = 481	PFO N = 447	MT N = 462	PFO N = 204	MT N = 210	PFO N = 60	MT N = 60
Study years	2007–2016		2017		2017		2012		2013		2011–2017	
Age of patients (years)	16–60		18–59		18–60		18–60		<60		51.8	
Study sites and centers	34 sites (32 France and 2 Germany)		63 sites (Canada, Denmark, Finland, Norway, Sweden, the United Kingdom, and USA)		69 sites in USA and Canada		79 sites USA		29 centers (Europe, Canada, Brazil, Australia)		2 sites in South Korea	
Type of device	STARFlex septal closure		Helex septal occluder and Cardioform septal occluder		Amplatzer PFO occluder		STARFlex septal closure		Amplatzer PFO occluder		Amplatzer occluder	
Mean follow-up	5.3 ± 2.0 years		3.2 years		5.9 years		2 years		4.0–4.1 years		2 years	
Medical therapy used	DAPT for 3 m then ASA or clopidogrel for remainder of trial	ASA, plavix, or ASA + ER dipyridamole	One dose of clopidogrel 300 mg before or immediately after the procedure followed by ASA, clopidogrel or ASA + dipyridamole for remainder of trial	ASA alone, ASA + ER dipyridamole or clopidogrel alone	DAPT for 1 m, then ASA for 5 m then AP drug at discretion of site	ASA, clopidogrel, ASA + ER dipyridamole, DAPT or warfarin	DAPT for 6 m (ASA + clopidogrel) then aspirin 81 to 325 mg for 2 y	Warfarin, ASA or Both	DAPT for 1–6 m (aspirin 100–325, clopidogrel, ticlopidine)	AP or PO AC per physician discretion	DAPT for 6 m followed by single AP, DAPT or AC at investigators discretion (ASA, ASA + clopidogrel; ASA + cilostazol or warfarin	ASA, ASA and clopidogrel; ASA and cilostazol or warfarin
Medical history												
Age (years) Mean ± SD	42.9 ± 10.1	43.8 ± 10.5	45.4 ± 9.3	44.8 ± 9.6	45.7 ± 9.7	46.2 ± 10.0	46.3 ± 9.6	45.7 ± 9.1	44.3 ± 10.2	44.6 ± 10.1	49 ± 15	54 ± 12
Male sex N (%)	137(57.6)	142(60.4)	261(59.2)	138(61.9)	268(53.7)	268(55.7)	233(52.1)	238(51.5)	92(45.1)	114(54.3)	33(55.0)	34(56.7)

Hypertension N (%)	27(11.3)	24(10.2)	112(25.4)	58(26.0)	160/499(32.1)	153/481 (31.8)	151(33.8)	131(28.4)	49(24)	58(27.6)	12(20.0)	17(28.3)
Diabetes mellitus N (%)	3(1.3)	9(3.8)	18(4.1)	10(4.5)	33/499(6.6)	41/481(8.5)	NA	NA	5(2.5)	6(2.9)	6(10.0)	8(13.0)
Current or former smoker N (%)	68(28.6)	69(29.4)	63(14.3)	25(11.2)	209/499(41.8)	198/481 (41.1)	96/447 (21.5)	104/460 (22.6)	52(25.5)	47(22.4)	10(16.7)	16(26.7)
Hyperlipidemia N (%)	30(12.6)	36(15.3)	NA	NA	196/499(39.3)	195/481 (40.5)	212 (47.4)	189(40.9)	50(24.5)	62(29.5)	18(30.0)	25(41.7)
Coronary artery disease N (%)	NA	NA	NA	NA	19/499(3.8)	9/481(1.9)	6(1.3)	4(0.9)	4(2)	4(1.9)	NA	NA
Migraine N (%)	67(28.2)	78(33.2)	NA	NA	195/499(39.1)	186/481 (38.7)	NA	NA	47(23)	38(18.1)	NA	NA
Stroke N (%)	10(4.2)	7(3.0)	42(9.5)	13(5.8)	53/498(10.6)	51/481(10.6)	324/446 (72.6)	329/461 (71.4)	165(80.9)	163(77.6)	28(46.7)	36(60)
Previous TIA N (%)	NA	NA	26(5.9)	11(4.9)	58/499(11.6)	61/481(12.7)	122/446 (27.4)	132/461 (28.6)	33(16.2)	42(20)	NA	NA
DVT/PE N (%)	5(2.1)	4(1.7)	NA	NA	20/499(4.0)	15/481(3.1)	0	4(0.9)	6(2.9)	5(2.4)	NA	NA
Arrhythmia N (%)	NA	NA	NA	NA	NA	NA	26(5.8)	19(4.1)	NA	NA	NA	NA
Peripheral vascular disease N (%)	NA	NA	NA	NA	5/499(1.0)	1/481(0.2)	5(1.1)	7(1.5)	3(1.5)	2(1)	NA	NA
Large right to left shunt N (%)	216/238 (90.7)	223/235 (94.8)	348/425(81.8)	173/216 (80.0)	247/499(49.5)	231/481 (48.0)	250(55.9)	231(50.0)	130/185 (70.2)	112/184 (60.8)	35(58.4) (right to left; left to right and bidirectional)	34(56.7) (only left to right shunt)
Atrial septal aneurysm N (%)	Patients may have atrial septal aneurysm or a large right to left shunt		86/422(20.4)	NA	180/499(36.1)	170/481 (35.3)	168(37.6)	165(35.7)	47(23)	51(24.3)	33(55) (Aneurysm + Hypermobility)	35 (58.3) (Aneurysm +Hypermobility)

RCT, randomized controlled trial, PFO, patent foramen ovale, MT, medical therapy, ASA, aspirin, AP, antiplatelet, AC, anticoagulation, INR, international normalized ratio, TIA, transient ischemic stroke, DVT, deep vein thromboembolism, PE, pulmonary embolism, m, months, y, years, DAPT, dual antiplatelet therapy, ER, extended release, PO, per os, NA, not applicable, SD, Standard deviation.

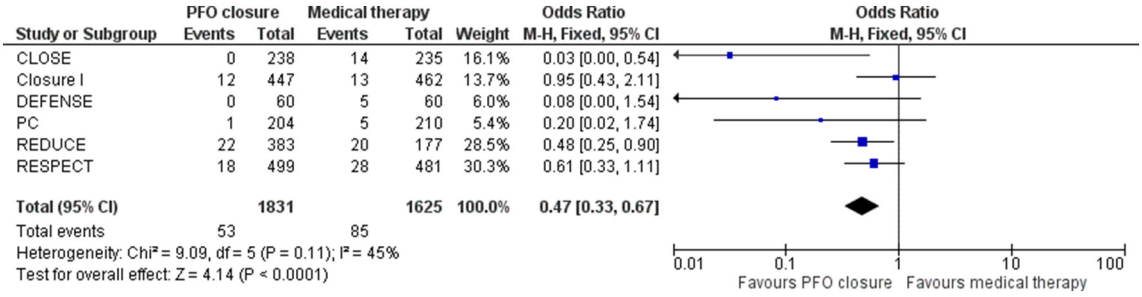

Fig. 2. Meta-analysis comparison of recurrent stroke between PFO closure plus medical therapy and medical therapy alone. PFO, patent foramen ovale.

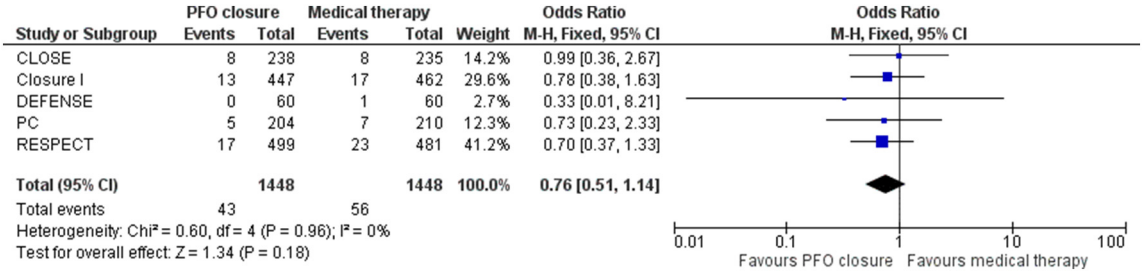

Fig. 3. Meta-analysis comparison of transient ischemic attacks between PFO closure plus medical therapy and medical therapy alone. PFO, patent foramen ovale.

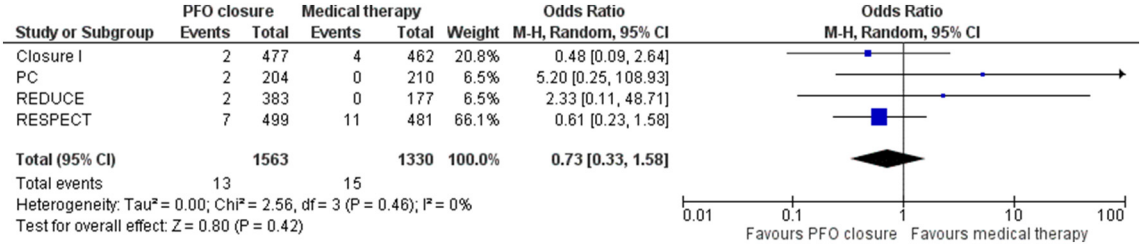

Fig. 4. Meta-analysis comparison of all-cause mortality between PFO closure plus medical therapy and medical therapy alone. PFO, patent foramen ovale.

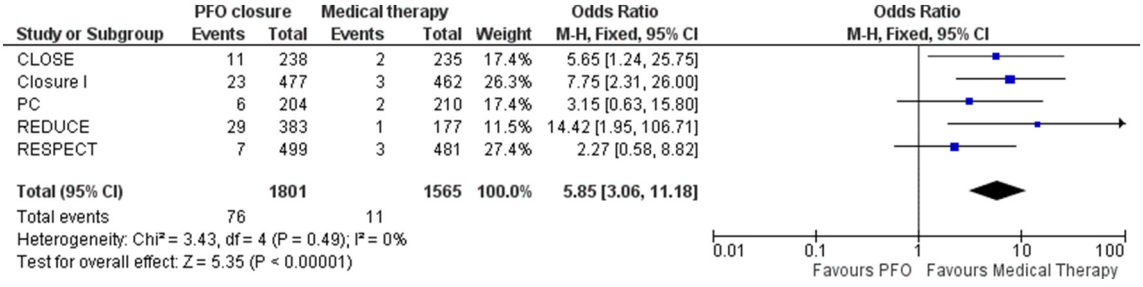

Fig. 5. Meta-analysis comparison of atrial fibrillation between PFO closure plus medical therapy and medical therapy alone. PFO, patent foramen ovale.

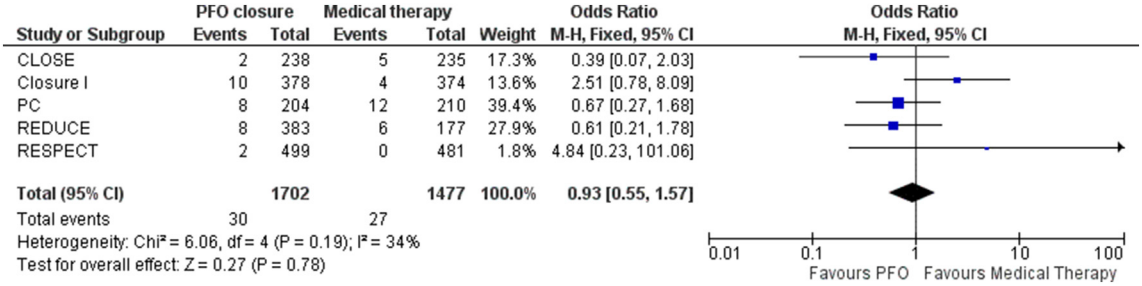

Fig. 6. Meta-analysis comparison of bleeding between PFO closure plus medical therapy and medical therapy alone. PFO, patent foramen ovale.

Table 2
Comparison of primary outcomes.

Study	Primary end points
CLOSURE I	Stroke or TIA at 2 years, all-cause mortality at 30 days, death from a neurological cause; Cumulative incidence: 5.5% vs 6.8% ($p = 0.37$), recurrent stroke: 2.9% vs 3.1% ($p = 0.79$) and TIA: 3.1% vs 4.1% ($p = 0.44$) in PFO closure + MT vs MT group.
PC	Composite end point of death, non-fatal stroke, TIA or peripheral embolism; Cumulative incidence: 3.4% vs 5.2% ($p = 0.34$), recurrent non-fatal stroke: 0.5% vs 2.4% ($p = 0.14$) and TIA: 2.5% vs 3.3% ($p = 0.56$) in PFO closure + MT vs MT group.
RESPECT	Composite of recurrent nonfatal ischemic stroke: 1.8% vs 2.2% ($p = 0.157$), fatal ischemic stroke: none, or early death: (none after randomization) TIA was not a primary endpoint.
CLOSE	Recurrent stroke: 0% vs 5.9%; ($p < 0.001$) in PFO closure + MT vs MT therapy. TIA was not a primary endpoint.
REDUCE	Two coprimary end points: Freedom from clinical evidence of ischemic stroke (% of patients who developed recurrent stroke) through at least 24 months after randomization and the 24 months incidence of new brain infarction, which included both clinical ischemic stroke and silent brain infarction detected on imaging. Recurrent stroke: 1.4% vs 5.4% (hazard ratio, 0.23; 95% CI, 0.09 to 0.62; $p = 0.002$) in PFO closure + MT vs MT New brain infarcts: 5.7% vs. 11.3% ($p = 0.04$) in PFO closure + MT vs MT Silent brain infarction: equal in both the study groups ($p = 0.97$) TIA was not a primary endpoint.
DEFENSE	Primary end points were stroke, vascular death or TIMI defined major bleeding during 2 years of follow-up. Cumulative incidence in MT group was 12.9% ($p = 0.013$), ischemic stroke 10.5% ($p = 0.023$) and major bleeding 2.4% No event of primary endpoint occurred in the PFO closure group. TIA was not a primary endpoint.

TIA, Transient ischemic attack, PFO, Patent foramen ovale, MT, Medical therapy, TIMI, Thrombolysis in Myocardial Infarction, CI, confidence interval.

and CLOSURE I trial). The effects of stroke risk reduction in these trials seem to be device independent as several different devices were used, although the most commonly used device was Amplatzer.

The placement of a PFO closure device increases the risk of post procedural atrial fibrillation which may increase the risk of recurrent stroke. Our meta-analysis confirms the finding of the recent clinical trials and supports the use of PFO closure to reduce the incidence of stroke. Although the rate of atrial fibrillation was higher in the PFO closure group, it did not lead to an increased risk of stroke. The exact mechanism causing the increased rate of atrial fibrillation is unclear at this point. These trials did not provide long-term data on incidence of atrial fibrillation following PFO closure. The long-term effects of the impact of post-procedural atrial fibrillation have yet to be studied.

Our meta-analysis has several limitations. The included studies were all open label and not double blinded, which may have led to bias. The type of PFO closure device used varied among the studies and it is uncertain if one type of device is superior to the other although a RCT [25] and a network meta-analysis [23] showed higher efficacy of Amplatzer as compared to Helex and STARFlex devices. There was also lack of standardization in the type of medical therapy used and continuation of medical therapy after the protocol mandated duration was left up to the discretion of the local investigator or physician. Moreover, this analysis used study level data and not patient level data. There was non-uniformity in the follow-up period, patient characteristics and inclusion criteria between the included studies. TIA as a primary end-point was included in only two trials. Despite these limitations, the pooled data indicates that PFO closure in selected patients may be superior to medical therapy alone in prevention of stroke.

5. Conclusion

This meta-analysis suggests that PFO closure in addition to standard medical therapy lowers the incidence of recurrent stroke in selected patients with a PFO presenting with cryptogenic stroke. However, PFO closure in these patients has not been shown to reduce the risk of recurrent TIA or all-cause mortality. There is a higher rate of transient atrial fibrillation post-PFO closure device placement, the long-term effects of which have yet to be studied.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2018.09.010.

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Table 3
Comparison of adverse events.

Study	Adverse events
CLOSURE I	Atrial fibrillation: 5.7% vs 0.7% and vascular complications: 3.2% vs 0% in PFO closure + MT vs MT group respectively at 2 years ($p < 0.0001$ for both)
PC	Atrial fibrillation: 2.9% vs 1.0% ($p = 0.16$) in PFO closure + MT vs MT group
RESPECT	Serious adverse events: 0.48 per 100 patient-years and 0.34 per 100 patient-years, ($p = 0.36$) in PFO closure + MT vs MT group Atrial fibrillation: 0.6% vs 0.8% in PFO closure + MT group vs MT only group respectively Pulmonary embolism: 0.41 per 100 patient-years in the PFO closure group and 0.11 per 100 patient-years in the MT group (hazard ratio, 3.48; 95% CI, 0.98 to 12.34; $p = 0.04$) Deep vein thrombosis: 0.16 per 100 patient-years and 0.04 per 100 patient-years, (hazard ratio, 4.44; 95% CI, 0.52 to 38.05; $p = 0.14$) in PFO closure + MT vs MT group
CLOSE	Atrial fibrillation: 4.6% vs 0.9% ($p = 0.02$), in PFO closure + MT vs MT group. Procedure related complications were 5.9%.
REDUCE	Serious adverse events occurred in 23.1% of the patients in the PFO closure group vs 27.8% of the patients in the antiplatelet-only group ($p = 0.22$). Serious device-related adverse events occurred in 6 patients (1.4%) in the PFO closure group. Atrial fibrillation occurred in 29 patients (6.6%) after PFO closure mostly within 45 days post procedure and resolved within 2 weeks vs 0.4% in MT only group.
DEFENSE	The events in the medication-only group included ischemic stroke (n = 5), cerebral hemorrhage (n = 1), TIMI-defined major bleeding (n = 2), and TIA (n = 1). In PFO closure + MT group, non-fatal procedural complications included development of atrial fibrillation (n = 2), pericardial effusion (n = 1) and pseudoaneurysm (n = 1).

PFO, Patent foramen ovale, MT, Medical therapy, TIMI, Thrombolysis in Myocardial Infarction, CI, confidence interval, TIA, Transient ischemic attack.

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