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Updated meta-analysis of closure of patent foramen ovale versus medical therapy after cryptogenic stroke☆

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ABSTRACT

Background: Among patients with cryptogenic stroke, PFO closure has remained controversial. We hypothesized that with the cumulative number of subjects in randomized controlled trials (RCTs), there is now sufficient power to ascertain whether PFO closure in patients with cryptogenic stroke improves the risk of stroke.
Methods: We performed an updated meta-analysis by including newer RCTs that examined the benefit of PFO closure compared with medical therapy for improvement in risk of stroke. We utilized random effects models to compute the association and performed subgroup analyses by medical therapy, shunt size and presence/absence of atrial septal aneurysm.
Results: Overall, 6 RCTS were included with 1839 patients that underwent PFO closure and 1671 patients that received medical therapy and were followed for a period of 2–6 years. The incidence of recurrent stroke was 1.52% among PFO closure group and 3.94% among medical therapy group. There was decreased risk of stroke in PFO closure group (OR 0.34, 95% CI 0.15–0.79, $p = 0.012$). Patients with larger shunt size derived more benefit from PFO closure than smaller or moderate sized shunts. There was no difference in outcomes by presence or absence of atrial septal aneurysm or type of medical therapy used i.e. antiplatelet therapy only vs. antiplatelet + anticoagulant therapy.
Conclusion: This meta-analysis of 6 RCTs demonstrated benefits of PFO closure for secondary prevention of stroke among patients with cryptogenic stroke and small increase in risk of new onset atrial fibrillation.

1. Introduction

Current estimates suggest that a patent foramen ovale (PFO) may exist in up to 25% of the general population [1, 2]. This prevalence is much higher among patients with cryptogenic stroke and is quoted to be in range of 35–40% [3–6]. Stroke is the second most common cause of death and the most common cause of disability worldwide [7]. An estimated 200,000 strokes occur each year in United States without evidence of cardiac or cerebrovascular disease [8]. This number suggests that up to 90,000 of these patients would have PFO. Transcatheter closure of PFO was first reported in 1992 [9]. Since then, 9 different transcatheter devices have been tested in various studies [10]. Clinicians have used clinical judgment to treat PFOs even before the first randomized controlled trial (CLOSURE I) results in 2012 [11]. However, this clinical trial using a first generation device (CardioSEAL/STARFlex occluder) failed to demonstrate a statistically significant impact of closing PFO on the outcomes. On the other hand, subsequent randomized and non-randomized studies showed consistent reduction of recurrent neurological event rate up to 6 times lower in patients with PFO closed compared to medical therapy alone [12]. Yet, 3 meta-analyses of clinical trials and observational studies failed to establish a true benefit of PFO closure for patients with cryptogenic stroke. This led to the 2014 American College of Cardiology/American Heart Association guidelines in favor of treating cryptogenic stroke PFO patients with medical therapy for secondary prevention of stroke with addition of anticoagulation in patients who had history of deep venous thrombosis [13]. Whether PFO closure is superior medical therapy remains a matter of debate given the consistent signal of benefit in virtually all RCTs. The aim of the present meta-analysis is to incorporate data from three new RCTs, the CLOSE trial, GORE REDUCE trial and the DEFENSE-PRO trial that have since become available [14–16]. The findings of these trials have been largely in favor of PFO closure. Moreover, Saver et al. has recently published 10-year outcomes for RESPECT trial which again has shown potential long-term benefits of

Abbreviations: PFO, Patent foramen ovale; RCT, Randomized controlled Trials.
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PFO closure over medical therapy [17]. In addition, data regarding the anatomical features of PFO and types of medical therapy is also inconclusive. This meta-analysis was performed to analyze the risks and benefits of PFO closure in patients with cryptogenic strokes.

2. Methods

Our study model was based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines including the overall design, implementation, and data presentation. We searched for studies that reported on recurrence of stroke in adults with history of cryptogenic stroke and diagnosed PFO. Multiple databases including Medline, Pubmed, EMBASE, Google Scholar and Cochrane were reviewed for studies from inception till December 2017 using the search terms “patent foramen ovale”, “PFO”, “stroke”, “cryptogenic stroke”, “percutaneous closure” and “transcatheter closure”. Search was limited to randomized controlled trials (RCTs) only. No language barriers were used. Additional studies were searched from the references and supplementary material of the included studies.

Two investigators (UBN and WTQ) independently evaluated the studies for eligibility and finalized inclusion was based on mutual decision. Inclusion criteria was limited to RCT of adults with age > 18 years of age, with a history of transient ischemic attack (TIA) or stroke and underlying diagnosed PFO who underwent either percutaneous PFO closure of were treated medically with antiplatelet and/or anticoagulation therapy. We excluded non randomized controlled trial studies and trials including participants with other indications for PFO closure (e.g., hemodynamic significance). We did not restrict our outcome to any specific follow-up period.

In this analysis, recurrence of stroke was considered as the primary outcome measure. Secondary outcome was based on recurrence of stroke in antiplatelet therapy alone (no anticoagulants) versus PFO closure. Subgroup analyses were performed based on the presence of atrial septal aneurysm (defined as septum primum excursion of >10 mm) and the size of the shunt. The shunt size was defined as small to moderate or large (>30 microbubbles in the left atrium after 3 cardiac cycles).

Baseline characteristics of all studies were expressed a mean ± standard deviation for continuous variables and percentages for categorical

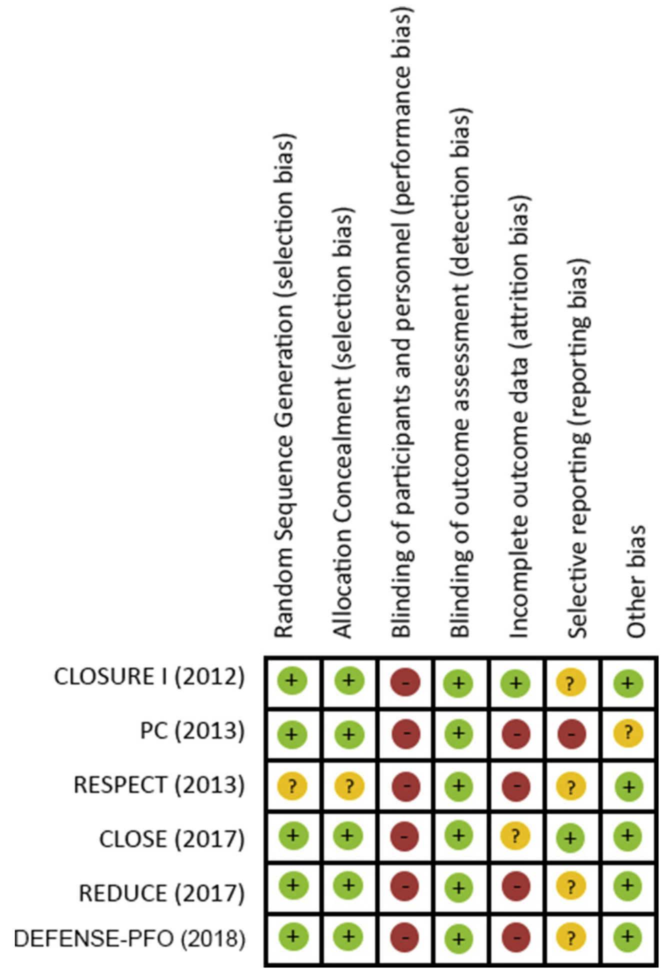

Fig. 2. Newcastle-Ottawa scale assessment of pooled studies.

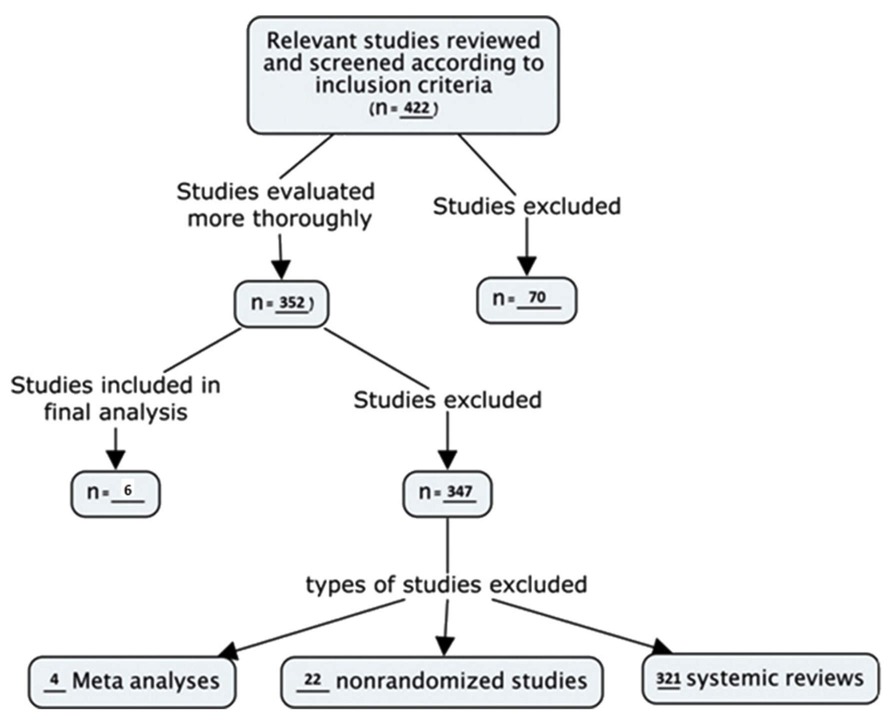

Fig. 1. Flow diagram of study selection.

Table 1
Baseline characteristics.

Study	CLOSE		GORE REDUCE		PC		CLOSURE I		RESPECT		DEFENSE-PFO	
	PFO Closure	Medical Therapy	PFO Closure	Medical Therapy	PFO Closure	Medical Therapy	PFO Closure	Medical Therapy	PFO Closure	Medical Therapy	PFO Closure	Medical Therapy
N	238	235	441	223	204	210	447	462	499	481	60	60
Mean age ± SD	42.9 ± 10.1	43.8 ± 10.5	45.4 ± 9.3	44.8 ± 9.6	44.3 ± 10.2	44.6 ± 10.1	46.3 ± 9.6	45.7 ± 9.1	45.7 ± 9.7	46.2 ± 10.0	49 ± 15	54 ± 12
Male (%)	137 (57.6)	142 (60.4)	261 (59.2)	138 (61.9)	92 (45.1)	114 (54.3)	233 (52.1)	238 (51.5)	268 (53.7)	268 (55.7)	33 (55.0)	34 (56.7)
Smoker (%)	68 (28.6)	69 (29.4)	63 (14.3)	25 (11.2)	52 (25.5)	47 (22.4)	96 (21.5)	104 (22.6)	75 (15)	55 (11.4)	10 (16.7)	16 (26.7)
Medical history - no. (%)												
Diabetes	3 (1.3)	9 (3.8)	18 (4.1)	10 (4.5)	5 (2.5)	6 (2.9)	NA	NA	33 (6.6)	40 (8.3)	6 (10.0)	8 (13.3)
Hypertension	27 (11.3)	24 (10.2)	112 (25.4)	58 (26.0)	49 (24.0)	58 (27.6)	151 (33.8)	131 (28.4)	158 (31.7)	150(31.2)	12 (20.0)	17 (28.3)
Hyperlipidemia	30 (12.6)	36 (15.3)			50 (24.5)	62 (29.5)	212 (47.4)	189 (40.9)	194 (38.9)	193 (40.1)	18 (30.0)	25 (41.7)
Ischemic heart disease					4 (2.0)	4 (1.9)	6 (1.3)	4 (0.9)	19(3.8)	9 (1.9)		
Myocardial infarction	0	0			3 (1.5)	1 (0.5)	7 (1.6)	5 (1.1)	5 (1.0)	2 (0.4)		
Valvular dysfunction					8 (3.9)	5 (2.4)	49 (11.0)	45 (9.7)				
Peripheral vascular disease					3 (1.5)	2 (1.0)	5 (1.1)	7 (1.5)	5 (1.0)	1 (0.2)		
DVT/pulmonary embolism	5 (2.1)	4 (1.7)					0	4 (0.9)	20 (4.0)	15 (3.1)		
Previous stroke	10 (4.2)	7 (3.0)	62 (14.1)	23 (10.3)	165 (80.9)	163 (77.6)			53 (10.6)	51 (10.6)		
Migraine	67 (28.2)	78 (33.2)							195 (39.1)	185 (38.5)		
PFO characteristics- N (%)												
Moderate or higher shunt	179 (75.2)	173 (73.6)	348 (81.8)	173 (80)	130 (70)	112 (61)	250 (55.9)	231 (50.0)	385 (78)	352 (72)	31 (51.7)	34 (56.7)
Atrial septal aneurysm			86 (20.4)	NA	47 (23.0)	51 (24.3)	168 (37.6)	165 (35.7)	180 (36.1)	169 (35.1)	5 (8.3)	8 (13.3)

variables stratified by treatment arm. We used the Mantel-Haenszel method to obtain pooled risk ratios (RRs) using the random-effects model regardless of the level of heterogeneity. We pooled data for the primary outcome measure with the generic inverse variance method using the random-effects model, yielding risk estimates as pooled hazard ratio (HR), which accounts for time-to-event outcomes.

3. Results

3.1. Study selection and quality

Of the 422 articles initially identified, 352 were thoroughly reviewed. Non-randomized studies and review articles were excluded. 6 studies met the inclusion criteria. Fig. 1 shows details of the study selection. The 6 studies included, collected data between 2000 and 2016 in populations from North America, Canada, Europe, Brazil, Japan and Australia. The quality of studies was assessed by using Newcastle-Ottawa scale (Fig. 2).

3.2. Baseline characteristics

Overall, 3510 patients were included in these studies; 1839 (53%) of these patients underwent PFO closure and 1671 (47%) received medical therapy. Baseline characteristics, such as age, sex, and cardiovascular risk factors, were similar between treatment arms in all the studies (Table 1). The Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT), cryptogenic stroke in high-risk PFO patients (DEFENSE-PFO) and the patent foramen ovale and cryptogenic embolism (PC) trial employed the use of Amplatzer PFO occluder device (St. Jude Medical) while the Evaluation of the STARFlex® Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale (CLOSURE I) trial used STARFlex device. The Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients With Patent Foramen Ovale (REDUCE) trial used GORE® HELEX® Septal Occluder/GORE® CARDIOFORM Septal Occluder while the Patent foramen ovale closure or anticoagulants versus antiplatelet therapy to prevent stroke recurrence (CLOSE) trial used multiple approved devices. Study characteristics are given in Table 2.

3.3. Risk of stroke/TIA

Out of 1889 patients who underwent PFO closure, 28 (1.52%) suffered from recurrence of stroke in comparison to 66 (3.94%) of 1671 medically treated (antiplatelet ± anticoagulation) patients. The odds of having recurrence of stroke were significantly lower among patients who were treated with PFO closure (OR 0.34, 95% CI 0.15–0.79, $p = 0.012$) versus medical therapy in random effects model. (Fig. 3).

3.4. Antiplatelet therapy

Three studies RESPECT, REDUCE and CLOSE examined antiplatelet use without including anticoagulation and compared it with PFO closure for the recurrence of stroke. There was significant reduced risk of recurrent stroke among the PFO closure group compared with antiplatelet group (OR 0.24; 95% CI 0.09–0.59, $p = 0.002$). (Fig. 4).

3.5. Atrial septal aneurysm

The presence or absence of atrial septal aneurysm was evaluated in 3 trials namely; CLOSURE, PC Trial and RESPECT. However, there was no particular difference in the outcomes between the PFO closure group and medical therapy group when stratified by atrial septal aneurysm (Fig. 5).

3.6. Shunt size

The shunt size was evaluated in 4 trials namely; CLOSE, CLOSURE, REDUCE and RESPECT. The benefit of PFO closure was stronger among patients with large shunts (OR 0.27; 95% CI 0.14–0.54, $p = 0.0002$) (Fig. 6).

Table 2
Study characteristics.

	Study acronym	Enrollment	Country	Number of patients	Mean follow up (months)	Lost to follow up	Intervention group	Medical therapy group	Study conclusion
Carroll et al.	RESPECT	2003–2011; multicenter, randomized	USA and Canada	980	31	Medical group 17.2% (83/481); Device group 9.2% (46/499)	Amplatzer PFO occluder + aspirin and clopidogrel for 1 month followed by aspirin for at least 5 months	Aspirin 46.5%; coumadin 25.2%; clopidogrel 14%; Aspirin + dipyridamole 8.1%; Aspirin + clopidogrel 6.2%	No significant benefit of PFO closure for recurrent stroke prevention
Meier et al.	PC	2000–2009; multicenter, randomized by web based system	29 centers across Europe, Canada, Brazil, and Australia	414	49	Medical group 15% (31/210); Device group 12% (24/2014)	Amplatzer PFO occluder + aspirin (5–6 months) and ticlopidine OR clopidogrel	Antiplatelet OR, AND coumadin (at the discretion of treating physician)	No significant reduction in the risk of recurrent embolic events or death in the closure group, as compared with medical therapy group
Furlan et al.	CLOSURE I	2003–2008; multicenter, randomized	USA and Canada	909	44	Medical group 17% (77/462); Device group 5% (24/447)	STARFlex + aspirin (2 years) and clopidogrel (6 months)	Aspirin, coumadin OR aspirin, and coumadin (at discretion of treating physician)	No significant difference between closure with percutaneous device plus antiplatelet therapy and medical therapy alone with respect to prevention of recurrent stroke of TIA
Mas et al.	CLOSE	2008–2014; multicenter, randomized	32 centers in France, 2 in Germany	663	53	Medical group 5.1% (12/235); Device 8.8% 21/238	Any device approved Interventional Cardiology Committee (Amplatz PFO Occluder or Cribriform; Starflex; CardioSeal; Intrasept PFO; PFOStar; Helex; Premere; PFO occlude OCCLUTECH; PFO occluder GORE) + aspirin and clopidogrel (3 months), aspirin or clopidogrel for remainder	aspirin, clopidogrel, or aspirin and dipyridamole	PFO closure plus long-term antiplatelet therapy reduced the risk of stroke compared with antiplatelet therapy alone
Sondergaard et al.	REDUCE	2008–2015; multicenter, randomized	63 sites in Canada, Denmark, Finland, Norway, Sweden, the United Kingdom, and the United States	664	38	Medical group 14.8% (33/223) Device 8.8% (39/441)	HELEX or GSO device + aspirin, aspirin and dipyridamole, or clopidogrel	aspirin, aspirin and dipyridamole, or clopidogrel	The risk of recurrent stroke was significantly lower with PFO closure plus antiplatelet therapy than with antiplatelet therapy alone
H. Lee et al.	DEFENSE-PFO	2011–2017; multicenter, randomized, open label, superiority trial	2 sites in South Korea	60	24	Medical group 38.3% (23/60) Device 33.3% (20/60)	Amplatzer PFO occluder	Dual Antiplatelet OR, AND coumadin (at the discretion of treating physician)	The risk of recurrent stroke was significantly lower with PFO closure than with medical therapy alone

Abbreviations: TIA; transient ischemic attack, PFO; patent foramen ovale

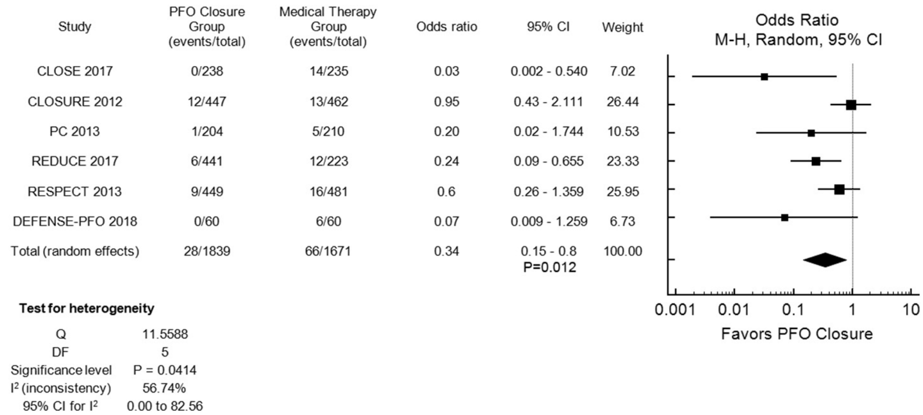

Fig. 3. Forrest plot showing comparison of stroke attacks between patent foramen ovale (PFO) closure and medical therapy groups.

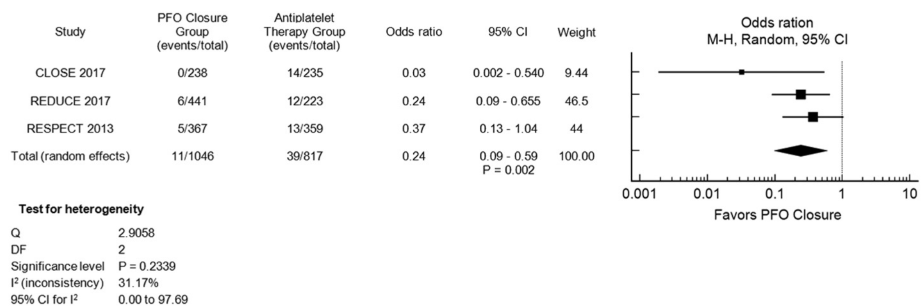

Fig. 4. Forrest plot showing comparison of stroke attacks between patent foramen ovale (PFO) group and antiplatelet therapy alone.

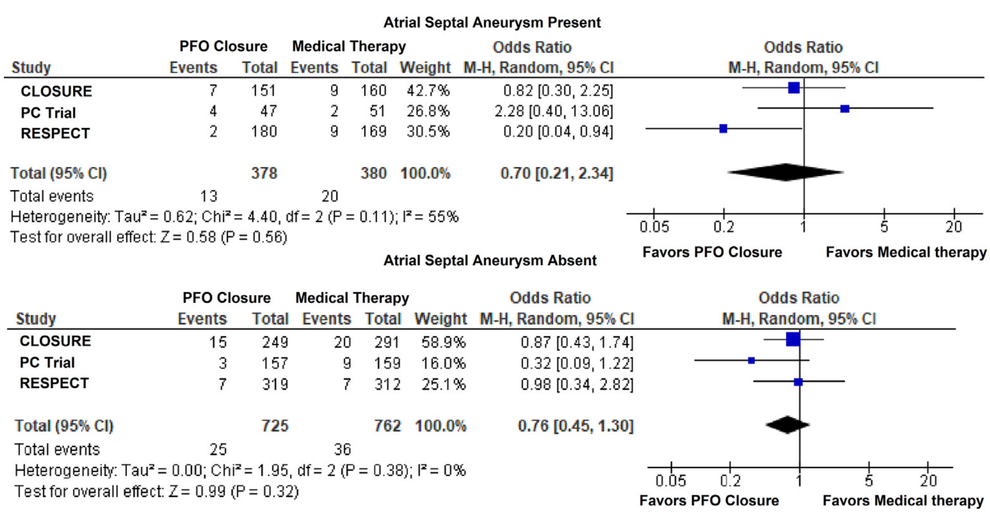

Fig. 5. Forrest plot showing comparison of stroke/transient ischemic attacks between patent foramen ovale (PFO) group and medical therapy among patients with and without atrial septal aneurysm.

3.7. Safety

Procedural success was reported by all 6 trials. The overall procedure success was 89.12%. The most common side effect reported was atrial fibrillation. Patients undergoing PFO closure had significantly increased incidence of new onset atrial fibrillation (OR 3.45 CI 95% 1.39–8.58, $p = 0.008$) (Fig. 7). Up to 60% of these episodes were periprocedural. The side effects were numerically higher for Amplatzer PFO occluder device. There were no periprocedural deaths.

4. Discussion

In this pooled analysis of 6 RCTs, PFO closure was associated with significant decrease in recurrent stroke compared with medical therapy alone. This association was consistent irrespective of the type of medical therapy i.e. antiplatelet use only or antiplatelet and anticoagulant use. Large sized PFO shunts appeared to derive more benefit from PFO closure compared with small to moderate sized PFOs, however the presence or absence of atrial septal aneurysm did not appear to affect this association. PFO closure can be attained with high rate of success

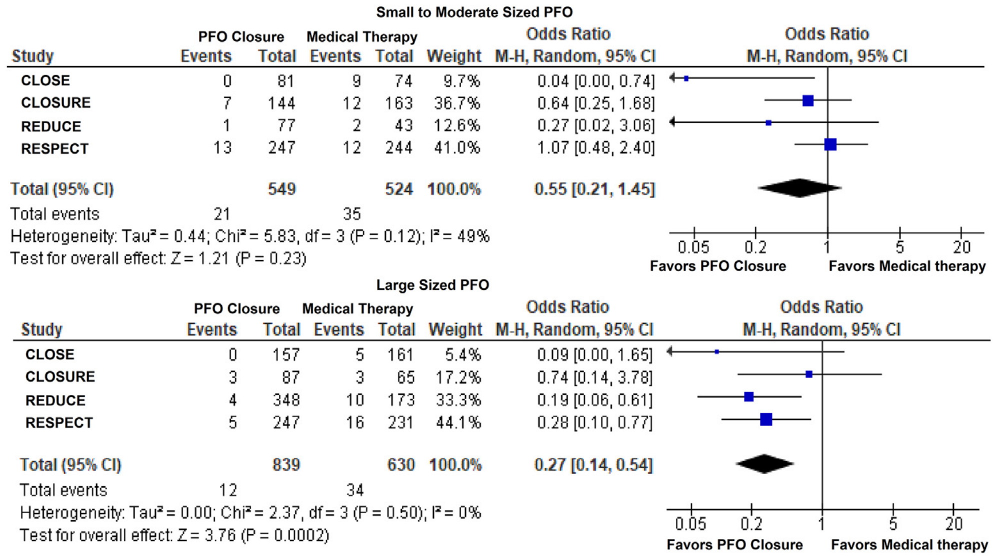

Fig. 6. Forrest plot showing comparison of stroke/transient ischemic attacks between patent foramen ovale (PFO) group and medical therapy among patients with and without large PFO shunt.

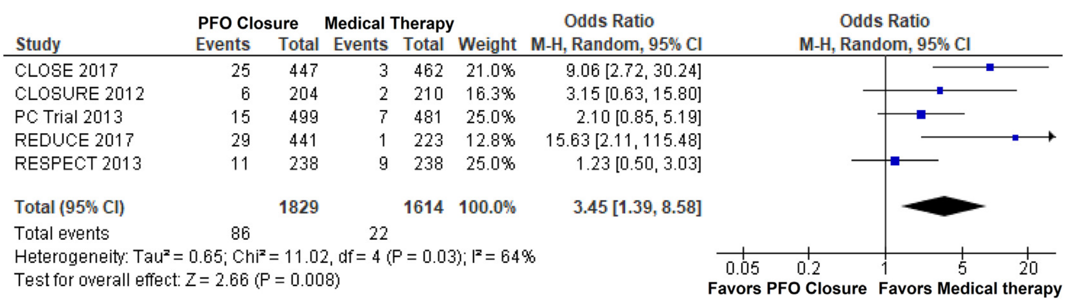

Fig. 7. Forrest plot showing comparison of post procedure atrial fibrillation between patent foramen ovale (PFO) closure and medical therapy groups.

(>85% for all studies). However, there appeared to be an increased incidence of new onset atrial fibrillation post procedure.

It is interesting that primary intervention for ST elevation MI was not accepted as standard of care as late as 2004, even after 23 RCTs [18]. This delayed adoption into practice guidelines likely deprived many patients of optimal outcomes. Similarly, PFO closure has been a matter of debate for the past two decades. The first trial, CLOSURE I trial was unable to demonstrate significant difference in stroke risk between 447 patients with PFO closure and 462 patients on warfarin and/or aspirin therapy. This was attributed to small number of events, short duration of follow up, inclusion of transient ischemic attacks that are difficult to adjudicate, and perhaps a relatively high rate of significant residual shunt (up to 14%) with a first-generation device [19]. The CardioSEAL/STARFlex occluder used in the CLOSURE I trial had about a 9–10% spontaneous external device thrombus formation rate. The observed thrombus was primarily formed on the outside of the device on the polyester fabric which have increased the stroke rates in the follow up period [12]. Additionally, this device had the lowest closure rate of all the different devices at 6 months and had a significant tendency towards frame wire fractures which brings in the possibility of inadequate mechanical closure [20].

The pathophysiology made sense to the clinicians for a long time however lack of rigorous design for a rare condition like this led to more clinical trials. Improvement in device design, much more restricted inclusion criteria and longer duration of follow-up in CLOSE, RESPECT and REDUCE trials led to significant positive results in favor of PFO closure. For example, REDUCE trial did extensive work up to exclude lacunar infarcts. Holter monitoring was used to rule out atrial fibrillation in CLOSE and RESPECT trials but not REDUCE. However, none of the studies excluded patients with thrombophilia.

We observed that the benefit of PFO closure was significant for large sized shunts. In CLOSURE I trial, recurrent strokes only occurred in patients with large PFOs or large PFOs with atrial aneurysm. A similar trend was observed in later trials. The DEFENSE-PFO trail which ended early due to significant results in favor of PFO closure involved only high-risk PFO patients. The high-risk PFO was defined as PFO with atrial septal aneurysm, hypermobility (phasic septal excursion into either atrium ≥10 mm), or PFO size (maximum separation of the septum primum from the secundum) ≥2 mm. There are several morphological variants of PFO. PFO may be smaller in size but may be in the form of tunnel that might open up with Valsalva maneuver. Lynch et al. [21] demonstrated 5% right to left shunting at physiologic baseline in patients with PFO that may increase to 18% with Valsalva maneuver, thus facilitating the migration of a thrombus into the arterial circulation.

Interestingly, we found consistent benefit of PFO closure irrespective of type of medical therapy used. It was presumed that CLOSE and REDUCE study might have shown positive results in favor of PFO closure because they chose to restrict medical therapy arm to antiplatelet use only which might not provide adequate protection especially because the mechanism of recurrent stroke is presumed to be paradoxical embolism. The usual treatment of venous thromboembolism is anticoagulant use and having an inadequately treated control arm would show benefit of PFO closure. The CLOSE trial had a separate sub group for patients who required antithrombotic medications. This contrasted with CLOSURE I and RESPECT trials where use of anticoagulants was concomitant with antiplatelet therapy and to the PC trial where use of anticoagulants was left to physician's discretion. It is notable that PFO closure was superior in the DEFENSE-PFO RCT despite warfarin use in almost a fourth of the medical therapy group.

Major side effects in both PFO closure and medical therapy group were comparable. No differences were noted in terms of mortality or adverse bleeding. However, new onset atrial fibrillation was found to be significantly associated with PFO closure which might be related to irritation of atrium during the procedure. Most of these episodes were periprocedural with minimal incidence of persistent or long-term episodes of AF. Moreover, while AF is an independent risk factor for embolic stroke and can lead to 5 fold stroke risk in historical trials, there has been no excess stroke after device closure in the long-term RCTs. This is validated by our findings that showed no difference in incidence of embolic stroke, likely due to the fact that these PAF episodes were periprocedural, short lived and self-limiting. On the other hand, there has been no protocolized long-term AF monitoring in all the studies we examined, and such studies are needed to comprehensively quantify subsequent AF burden. The major limitation of our analysis was the lack of individual data in terms of procedural benefit.

In conclusion, PFO closure has significant benefits in lower incidence of stroke and TIA when compared to medical therapy.

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