

Patent foramen ovale transcatheter closure vs. medical therapy on recurrent vascular events: a systematic review and meta-analysis of randomized controlled trials

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Received 8 May 2013; revised 18 June 2013; accepted 27 June 2013; online publish-ahead-of-print 11 July 2013

See page 3336 for the editorial comment on this article (doi:10.1093/eurheartj/ehs340)

Background

In patients with cryptogenic stroke, transcatheter (TC) closure of a patent foramen ovale (PFO) has not been shown to better prevent recurrent vascular events than medical therapy. However, randomized controlled trials (RCT) to date have included few vascular events, and lack of power has been raised as an important concern.

Objective

To conduct a systematic review and meta-analysis of existing RCT published studies assessing the recurrence of vascular events after TC PFO closure when compared to medical therapy.

Methods

Using the search terms “patent foramen ovale”, “PFO”, “stroke”, “percutaneous closure” and “transcatheter closure”, Medline, Pubmed, Embase, and Cochrane databases were reviewed from inception through April 2013, with no language restrictions. Only studies in adult humans were considered. Additional references were obtained from the bibliographies of studies reviewed. The following criteria were used for study selection: 1) randomized controlled trial, 2) subjects were adult patients with cryptogenic stroke who were randomized to TC PFO closure or medical treatment (antiplatelet therapy and/or anticoagulation), and 3) reported outcomes included cardiac death, all death, stroke, transient ischemic attack, and peripheral embolism. Methodological and descriptive data, adverse events (including raw data and risk estimates), as well as procedural success and complications were abstracted in duplicate from each study independently, and agreement was tested. We followed rigorously the recommended guidelines for reporting and conducting and assessing quality of meta-analysis of RCT. The primary endpoints pre-specified in advance were recurrent vascular events, and composite endpoint of death, and recurrent vascular events.

Results

Three studies were identified as meeting selection criteria. These included a total of 2,303 patients, with 1,150 patients randomized to TC PFO closure and 1,153 patients randomized to medical therapy. Mean follow-up was 3.5 years. Baseline characteristics (age, sex, and cardiovascular risk factors) were similar across studies. Intention-to-treat analyses showed a statistically significant risk reduction in stroke and/or transient ischemic attack in the TC PFO closure group when compared to medical treatment, pooled HR = 0.59, 95%CI (0.36–0.97), $P = 0.04$. The combined outcome of death, and vascular events, showed a borderline statistically significant benefit for TC PFO closure when compared to medical treatment, pooled HR = 0.67, 95%CI (0.44–1.00), $P = 0.05$. Subjects with a substantial PFO shunt seem to benefit the most with TC PFO closure, pooled HR = 0.35, 95%CI (0.12–1.03), $P = 0.06$, however, it did not reach statistical significance.

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Conclusion

These results suggest that in patients with cryptogenic stroke, TC PFO closure may be beneficial in reducing the risk of recurrent vascular events when compared to medical treatment. The benefit of TC PFO closure may be greater in patients with a substantial shunt.

Keywords

PFO • Stroke • Transcatheter closure

Introduction

Patent foramen ovale (PFO) is a common finding in healthy adults.¹ In patients with cryptogenic stroke, its prevalence has been found to be higher (up to 66%) when compared with patients with stroke from known causes.¹

This difference in prevalence led to investigation of transcatheter (TC) PFO closure as a possible means of secondary prevention of neurological events. A recent comparative meta-analysis of observational studies showed that TC PFO closure was associated with an 84% reduction in the rate of recurrent neurological events when compared with medical management.² However, results from three recently published randomized controlled trials (RCTs), failed to show a significant benefit of TC PFO closure over medical therapy.^{3–5}

One of the main limitations of all three RCTs^{3–5} was the small number of events during the follow-up, raising the possibility of a 'type 2 error' (failure to detect a true difference between treatments due to lack of Power). With this in mind, we performed a systematic review and meta-analysis of the available RCT to evaluate possible benefits of TC PFO closure when compared with medical therapy for the prevention of recurrent neurological events.

Methods**Search strategy and selection criteria**

We searched, for studies reporting death, transient ischaemic attack (TIA), and stroke in adult patients with previous TIA and/or stroke and the diagnosis of PFO. Medline, Pubmed, Embase, and Cochrane electronic databases were reviewed using the search terms 'patent foramen ovale', 'PFO', 'stroke', 'percutaneous closure' and 'transcatheter closure', with no language restrictions, from their inception to April 2013. Eligible studies were limited to RCT with at least 30 days follow-up. We supplemented the search with references from selected articles, and correspondence with other investigators.

Two investigators (P.R.M. and J.P.) independently assessed the studies for eligibility and their agreement was tested. Inclusion criteria were: (i) studies including adult patients (> 18 years of age) with a history of TIA and/or stroke with a diagnosis of PFO; (ii) RCT of TC PFO closure compared with medical treatment (antiplatelet and/or anticoagulation); (iii) reported risk estimates and/or number of events for death from any cause, neurological event, TIA and/or stroke (fatal and non-fatal), and peripheral embolization; (iv) follow-up of at least 30 days following randomization. Standardized data collection sheets were used to gather data on age, sex, cardiovascular risk factors, use of antiplatelet or anticoagulation therapy, success rate for TC PFO closure, complications related to TC PFO closure (minor and major complications), presence or absence of atrial septal aneurysm, and shunt magnitude if reported in the studies. Agreement was also calculated for data extraction.

Two investigators (P.R.M. and J.P.) independently assessed the quality of the manuscripts and their agreement was tested. We used the Jadad score to assess the quality of trials that accounts for randomization

(0, 1, or 2 points), blinding (single, double, or triple = 0, 1, 2 points) and lost to follow-up (0, 1 points). A score of ≥ 3 is deemed to be very good.^{6–9} When disagreement between investigators was present, a third investigator (A.R.C.) abstracted that specific data, and a meeting between the three investigators was taken place to reach agreement.

Statistical analysis

We abstracted risk estimates (relative risks, odds ratios, and hazard ratios with 95% confidence intervals) and total numbers of adverse events, comparing TC PFO closure to medical therapy. Agreement for inclusion of the studies, data extraction, and quality assessment was tested by calculating Cohen's kappa statistic.

Data for the main outcomes were pooled with the generic inverse variance method (logarithm of the risk estimate and its standard error) using fixed and random effect models (that accounts for the heterogeneity of the treatment effect across studies), yielding similar parameter estimates. We performed a meta-analysis and obtained pooled risk estimates for the development of TIA and/or stroke, and stroke alone for the TC PFO closure group when compared with medical treatment. For the combined outcome (death, TIA and/or stroke, peripheral embolism) pooled risk estimates for intention-to-treat (all three studies), and per-protocol (two studies) analyses were estimated, as these data were available.

Combining the three trials, we obtained an average for successful TC PFO closure and minor and major complications related to the procedure. Estimates for the development of new-onset atrial fibrillation between TC PFO closure vs. medical therapy were obtained by estimating odds ratios with 95% CI based on raw data reported in the trials.

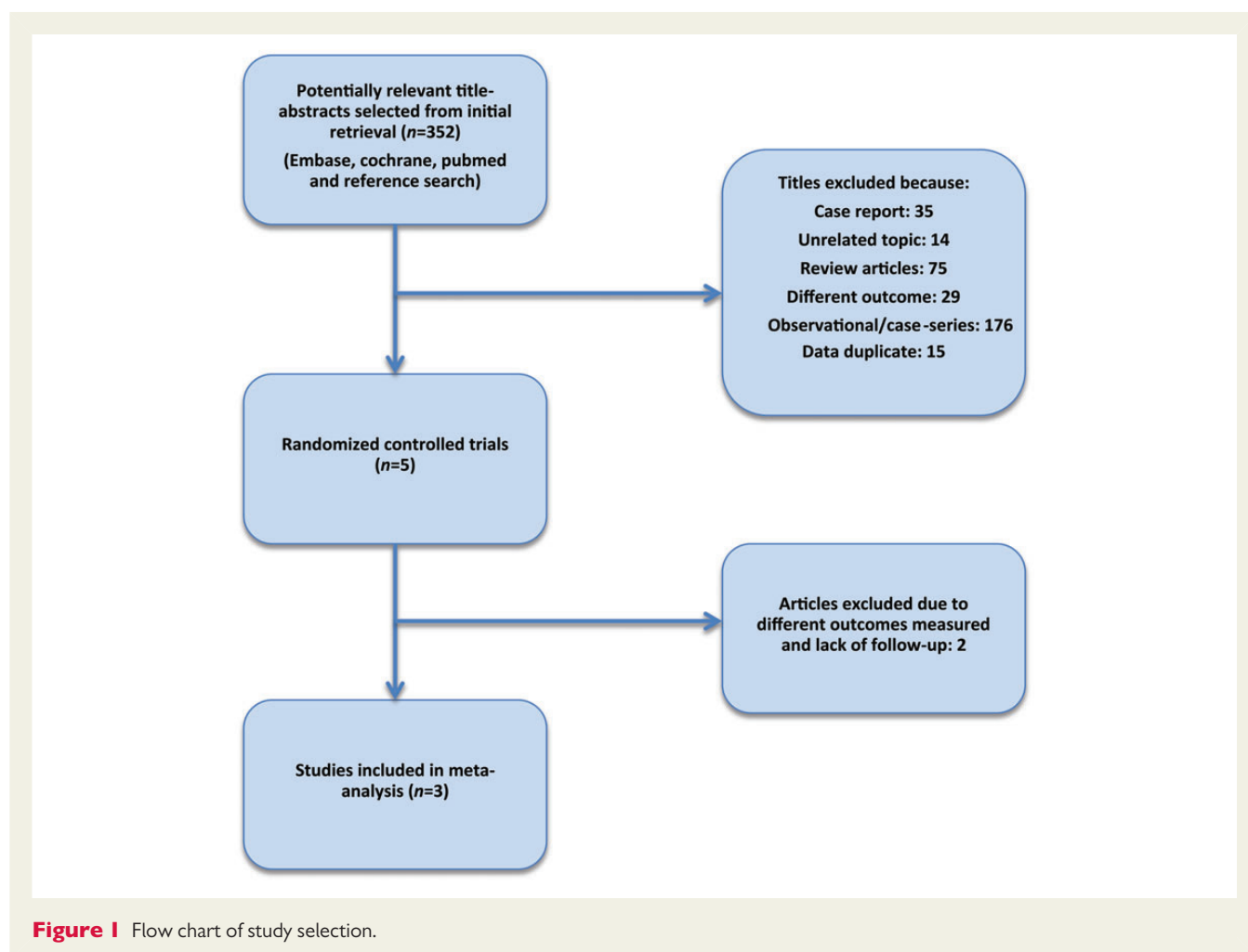
Subgroup analyses were defined in advance to assess features that have been suggested as 'high-risk PFO' on the development of vascular outcomes,^{10–12} such as: age (younger vs. older group), presence or absence of atrial septal aneurysm, and a substantial shunt. All studies reported risk estimates as hazard ratios and 95% confidence intervals (which accounts for time-to-event). We tested for risk-subgroup interactions when risk estimates differed significantly between studies and interventions, including type of device (STARFlex vs. Amplatzer). Heterogeneity was tested with the χ^2 test and inconsistency was quantified with the I^2 statistic. The RevMan 4.2.8 software was used for analyses.¹³

Results

Of the 352 articles initially identified, three studies met the inclusion criteria.^{3–5} The agreement for inclusion of the studies was excellent ($\kappa = 1.0$). Figure 1 shows details of the study selection.

The three studies included, collected data between 2000 and 2009 in populations from North America, Canada, Europe, Brazil, and Australia (Table 1). Combining the three studies, a total of 2303 patients were randomized to TC PFO closure ($n = 1150$) or medical therapy ($n = 1153$). Exclusion criteria for each study can be found in the Supplementary material online, Appendix.

Baseline characteristics, such as age, sex, and cardiovascular risk factors, were similar between treatment groups in all the studies (Table 2). Agreement for data inclusion was very good ($\kappa = 0.80$).



The mean of follow-up was 3.45 years, and varied across studies (4.1 years for the PC trial, 2 years for the CLOSURE I trial, and 2.6 years for the RESPECT trial). However, risk estimates in all the studies were presented as hazard ratios, which accounts for time-to-event. The average lost to follow-up was 12%. The agreement for all variables of quality by the Jadad score (randomization, blinding, and lost to follow-up) was good ($\kappa = 0.63$), and there was excellent agreement ($\kappa = 1.0$) that all studies were of very good quality (≥ 3 on the Jadad score).

The primary outcome for the three studies was different (Table 3). Overall there were 95 vascular events in the three studies combined, 39 (3.39%) in the TC PFO closure group, and 56 (4.85%) in the medical treatment group. When focusing on TIA or stroke outcomes, a total of 98 events occurred in the three studies combined, 40 (3.47%) in the TC PFO closure group vs. 58 (5.03%) in the medical treatment group. For the primary outcome of our study, recurrent neurological events—stroke and/or TIA, there was a statistically significant benefit of TC PFO closure when compared with medical therapy, pooled HR = 0.59, 95% CI (0.36–0.97), P -value = 0.04 (Figure 2A). When assessing stroke alone, there was no benefit from the TC PFO closure when compared with medical therapy, pooled HR = 0.62, 95% CI (0.36–1.07), P -value = 0.09 (Figure 2B).

All three studies presented a composite outcome (death, recurrent neurological events, and peripheral embolism) based on intention-to-treat analyses (Figure 3), showing a possible benefit of the TC PFO closure that was borderline statistically significant when compared with medical treatment, pooled HR = 0.67, 95% CI (0.44–1.00), P -value = 0.05. Two studies presented their analyses on a per-protocol basis (Figure 4), which again showed a possible benefit of the TC PFO closure that was borderline statistically significant when compared with medical therapy, pooled HR = 0.62, 95% CI (0.38–1.00), P -value = 0.05.

We performed subgroup analyses to assess which 'high-risk PFO' characteristics were associated with vascular events, namely—the presence of an atrial septal aneurysm (all three studies), shunt magnitude at baseline (two studies), and age < 45 vs. > 45 years (two studies). Figure 5A and B shows that subjects with a significant shunt (substantial vs. trace, none, or moderate) had a tendency towards decreased vascular events in patients when randomized to the TC PFO closure when compared with medical therapy, pooled HR = 0.35, 95% CI (0.12–1.03), P -value = 0.06. However, when testing for interaction between risk estimates by type of intervention regarding shunt magnitude, the P -value was non-significant ($P = 0.15$). Both, the presence or

Table 1 Trials baseline characteristics

Author	Study acronym	Enrolment	Country	Number of patients	Mean follow-up (months)	Lost to F/U	Intervention group	Medical therapy group	Study conclusions
Carroll et al.	RESPECT	2003–11 multicentre, 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	2000–09 multicentre randomization by web-based system	29 Centres in Europe, Canada, Brazil, and Australia	414	49	Medical group 15% 31/210 Device group 12% 24/204	Amplatzer PFO occluder + aspirin (5–6 months) and ticlopidine OR clopidogrel	Antiplatelet OR, AND coumadin (left 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 the medical therapy group
Furlan et al.	CLOSURE I	2003–08 multicentre, 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 (left at the discretion of treating physician)	No significant difference between closure with a percutaneous device plus antiplatelet therapy and medical therapy alone with respect to the prevention of recurrent stroke or TIA

PFO, patent foramen ovale.

Table 2 Baseline characteristics and risk factors

Trial		Number of patients	Age (years) means \pm SD	Men (%)	ASA (%)	Hypertension (%)	Hyperlipidaemia (%)	Smoking (%)	Diabetes (%)
RESPECT, n = 980	Device group	499	45.7 \pm 9.7	268 (53.7)	180 (36.1)	158 (31.7)	194 (38.9)	75 (15)	33 (6.6)
	Medical therapy	481	46.2 \pm 10.0	268 (55.7)	169 (35.1)	150 (31.2)	193 (40.1)	55 (11.4)	40 (8.3)
PC, n = 414	Device group	204	44.3 \pm 10.2	92 (45.1)	47 (23.0)	49 (24.0)	50 (24.5)	52 (25.5)	5 (2.5)
	Medical therapy	210	44.6 \pm 10.1	114 (54.3)	51 (24.3)	58 (27.6)	62 (29.5)	47 (22.4)	6 (2.9)
CLOSURE I, n = 909	Device group	447	46.3 \pm 9.6	233 (52.1)	168 (37.6)	151 (33.8)	212 (47.4)	96 (21.5)	NR
	Medical therapy	462	45.7 \pm 9.1	238 (51.5)	165 (35.7)	131 (28.4)	189 (40.9)	104 (22.6)	NR

ASA, atrial septal aneurysm.

Table 3 Outcomes for included trials

	Events	Intervention group (%)	Medical therapy (%)	Hazard ratio	Confidence interval	P-value
RESPECT intention-to-treat	Non-fatal ischaemic stroke	9/499	16/481	0.49	0.22–1.11	0.08
RESPECT per protocol		6/471	14/473	0.37	0.14–0.96	0.03
RESPECT as-treated		5/474	16/484	0.27	0.1–0.75	0.007
PC	Composite: death, stroke, TIA or peripheral embolism	7 (3.4)	11 (5.2)	0.63	0.24–1.62	0.34
	Death	2 (1.0)	0	5.2	0.25–107.61	0.24
	Stroke	1 (0.5)	5 (2.4)	0.2	0.02–1.72	0.14
	TIA	5 (2.5)	7 (3.3)	0.71	0.23–2.24	0.56
	Composite stroke, TIA, peripheral embolism	5 (2.5)	11 (5.2)	0.45	0.16–1.29	0.14
CLOSURE I intention-to-treat	Composite: death from any cause during first 30 days, death from neurological causes between 31 days and 2 years, stroke, and TIA	23 (5.5)	29 (6.8)	0.78	0.45–1.35	0.37
	Stroke	12 (2.9)	13 (3.1)	0.9	0.41–1.98	0.79
	TIA	13 (3.1)	17 (4.1)	0.75	0.36–1.55	0.44
CLOSURE I modified intention-to-treat	Composite: death from any cause during first 30 days, death from neurological causes between 31 days and 2 years, stroke, and TIA	22/400 (5.6)	29/451 (6.9)	0.78	0.44–1.35	0.37
	Stroke	12/400 (3.1)	13/451 (3.1)	0.94	0.43–2.07	0.88
	TIA	12/400 (3.0)	17/451 (4.2)	0.72	0.34–1.51	0.38
CLOSURE I per protocol	Composite: death from any cause during first 30 days, death from neurological causes between 31 days and 2 years, stroke, and TIA	22/378	29/375	0.74	0.42–1.29	0.28
	Stroke	12/378	13/375	0.91	0.41–1.99	0.8
	TIA	12/378	17/375	0.68	0.33–1.43	0.31

TIA, transient ischaemic attack.

absence of atrial septal aneurysm (Figure 6A and B), and age (≥ 45 vs. < 45 years, Figure 7A and B) were not associated with an increased incidence of vascular events.

Device implantation was successful in 93.8% on average (Table 1), being lowest with the STARFlex device in the CLOSURE I trial (89.4%). On average, there were 13 (1.13%) vascular complications, and there were two cases (0.17%) of cardiac perforation. There were

no fatal events related to the TC PFO closure (Table 4). New-onset atrial fibrillation was significantly higher in the TC PFO group (Figure 8A) when compared with medical therapy 31 (2.7) vs. 6 (0.5%), respectively, pooled OR = 5.77, 95% CI (2.4–13.83), $P < 0.001$. When stratifying by type of device (excluding STARFlex device), the Amplatzer device (Figure 8B) had a non-significant increased risk for developing new-onset atrial fibrillation: 8 (1.1) vs.

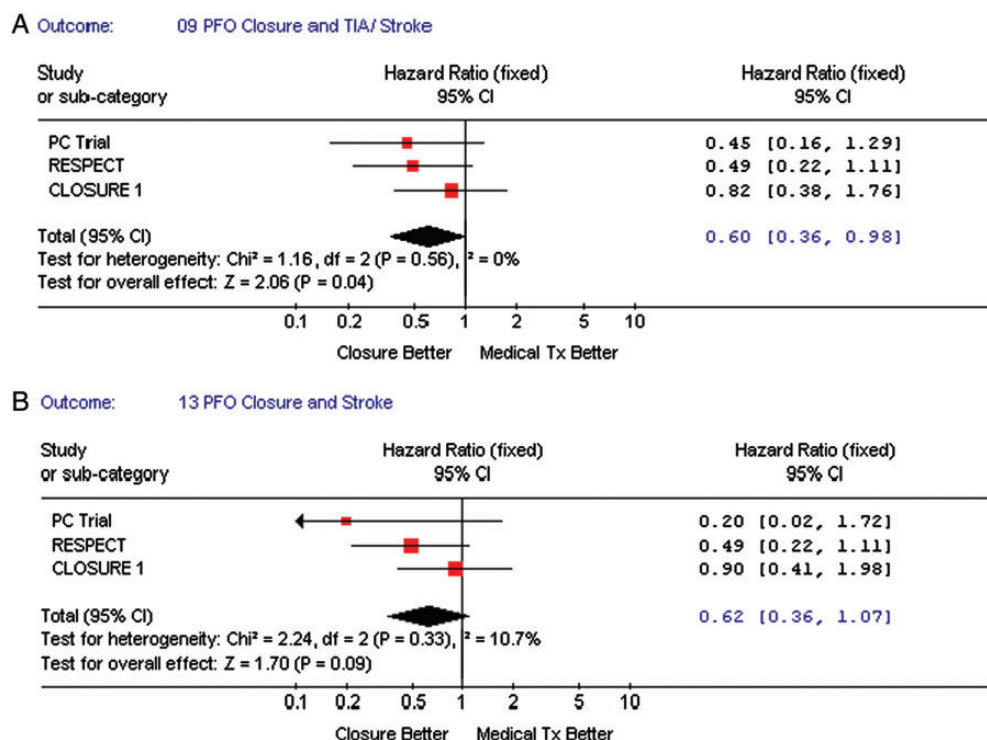


Figure 2 (A) The forest plot of randomized controlled trial comparing vascular outcomes (stroke/transient ischaemic attack) between transcatheter patent foramen ovale closure vs. medical treatment (intention-to-treat). (B) The forest plot of the randomized controlled trial comparing vascular outcomes (stroke) between transcatheter patent foramen ovale closure vs. medical treatment (intention-to-treat).

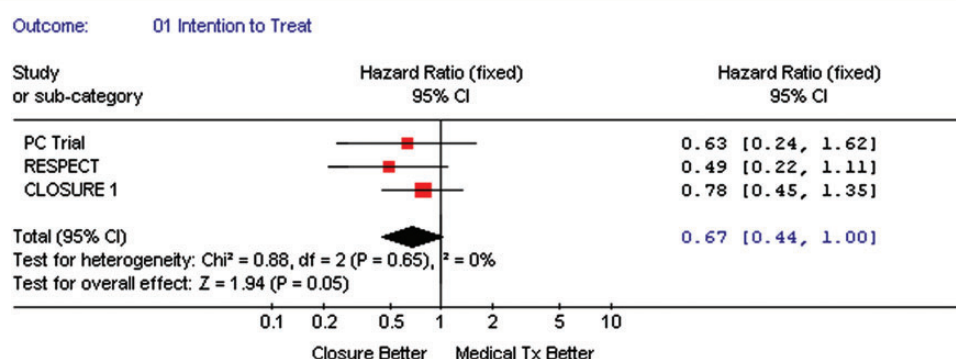


Figure 3 The forest plot of randomized controlled trial comparing composite outcome (death/vascular events) between transcatheter patent foramen ovale closure vs. medical treatment (intention-to-treat).

3 (0.4%), respectively, pooled OR = 2.73, 95% CI (0.72–10.33), $P = 0.14$, though, the test for interaction between risk estimates by closure device was not significant ($P = 0.18$).

Heterogeneity in the analyses performed was low (0% in the intention-to-treat analyses for TIA and/or stroke and combined outcomes), except for analyses for the presence of atrial septal aneurysm ($I^2 = 54.4\%$), and age >45 years ($I^2 = 45\%$) groups.

Discussion

In this meta-analysis of RCT, we report a possible benefit from the TC PFO closure, when compared with medical therapy, for prevention of recurrent vascular events. In pooled analyses, there was a statistically significant 41% risk reduction in recurrent TIA or stroke. In addition, there was a 33% risk reduction in the risk

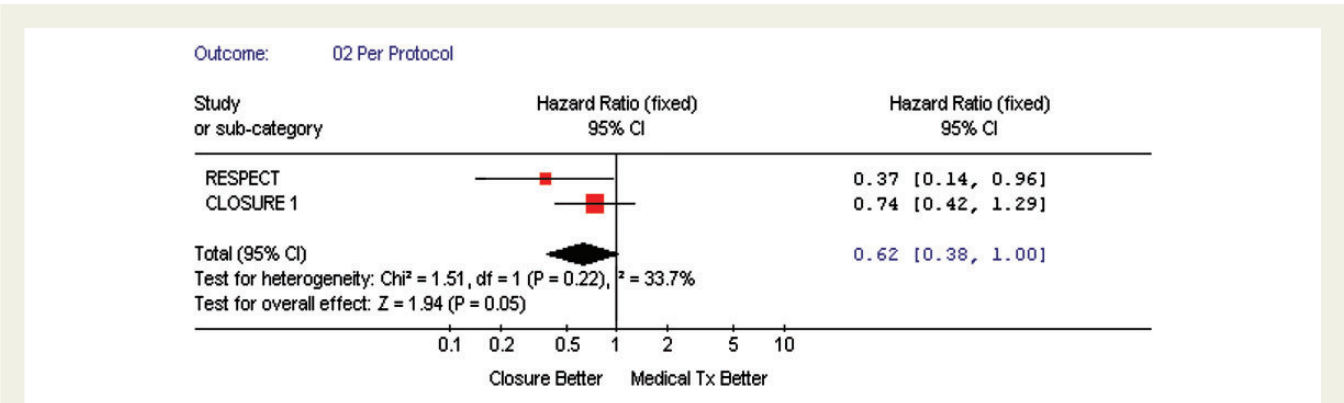


Figure 4 The forest plot of randomized controlled trial comparing composite outcome (death/vascular events) between transcatheter patent foramen ovale closure vs. medical treatment (per protocol).

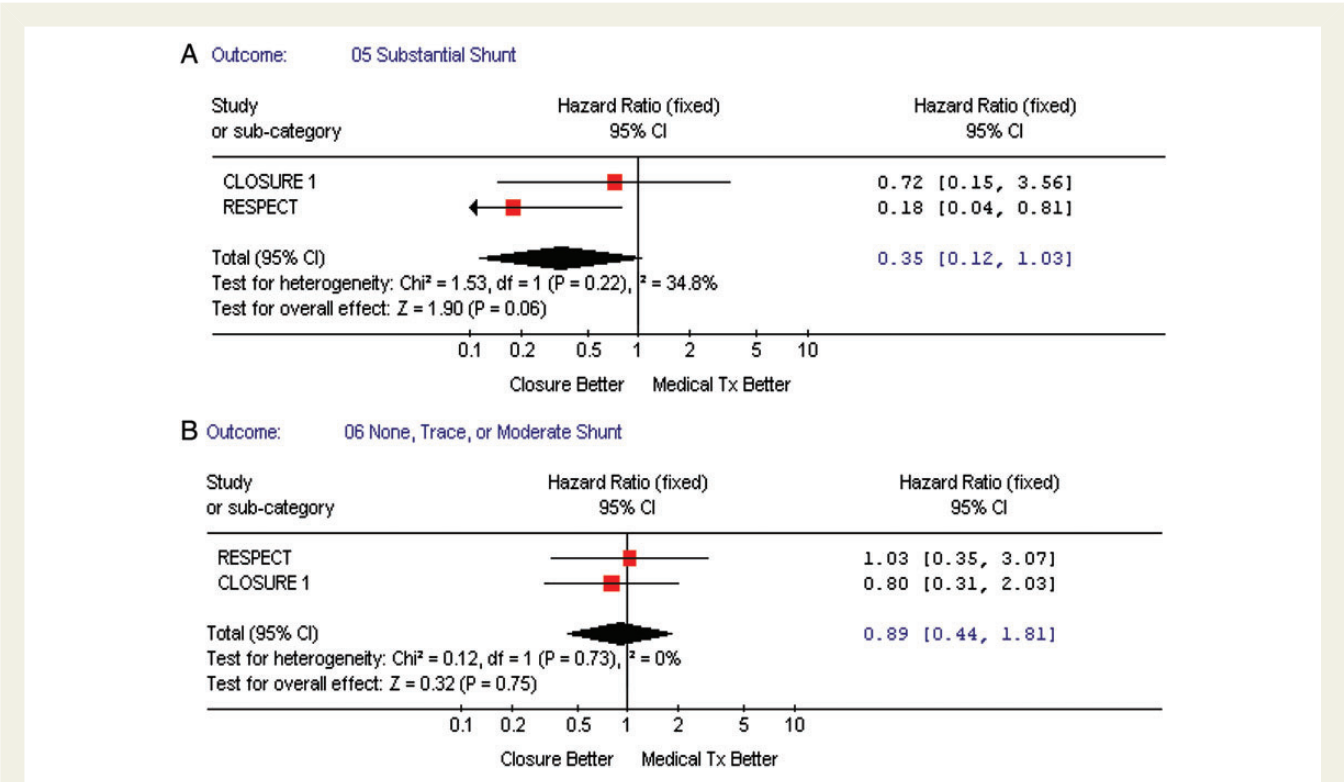


Figure 5 (A) The forest plot of randomized controlled trial comparing composite outcome (death/vascular events) between transcatheter patent foramen ovale closure vs. medical treatment by shunt magnitude (substantial). (B) The forest plot of randomized controlled trial comparing composite outcome (death/vascular events) between transcatheter patent foramen ovale closure vs. medical treatment by shunt magnitude (trace, none, or moderate).

for the composite outcome of death, neurological events, and peripheral embolism based on intention-to-treat analyses. However, when assessing for stroke prevention alone (excluding TIAs), TC PFO closure did not show a statistically significant benefit. These results support the notion that previous RCTs were underpowered.¹⁴

A recent meta-analysis of 48 observational studies showed an incidence of recurrent neurological events per year of 0.8% for the TC

PFO closure group vs. 5% for the medical therapy group, which translates to 2.8% neurological events in the TC PFO group and 17.5% in the medical therapy group at 3.5 years of follow-up (14.7% absolute risk reduction).² In contrast, our pooled results found an incidence of neurological events of 3.47% in the TC PFO vs. 5.03% in the medical group (1.56% absolute risk reduction) at a similar average follow-up (3.45 years). This important difference in absolute risk reduction raises the possibility of significant

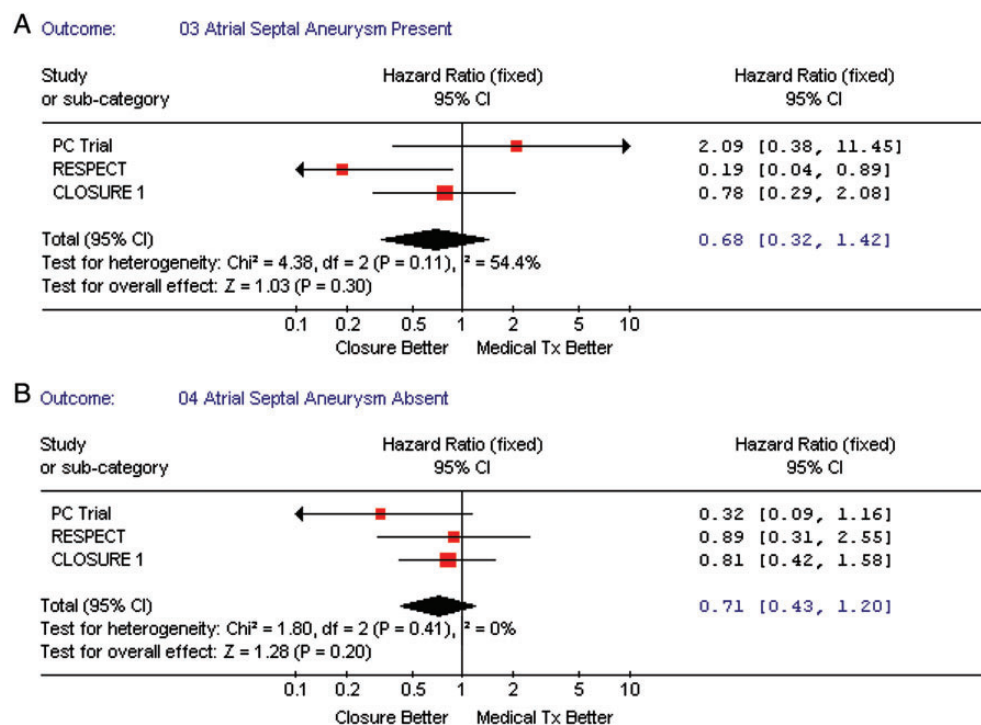


Figure 6 (A) The forest plot of randomized controlled trial comparing composite outcome (death/vascular events) between transcatheter patent foramen ovale closure vs. medical treatment by the presence of atrial septal aneurysm. (B) The forest plot of randomized controlled trial comparing composite outcome (death/vascular events) between transcatheter patent foramen ovale closure vs. medical treatment by the absence of atrial septal aneurysm.

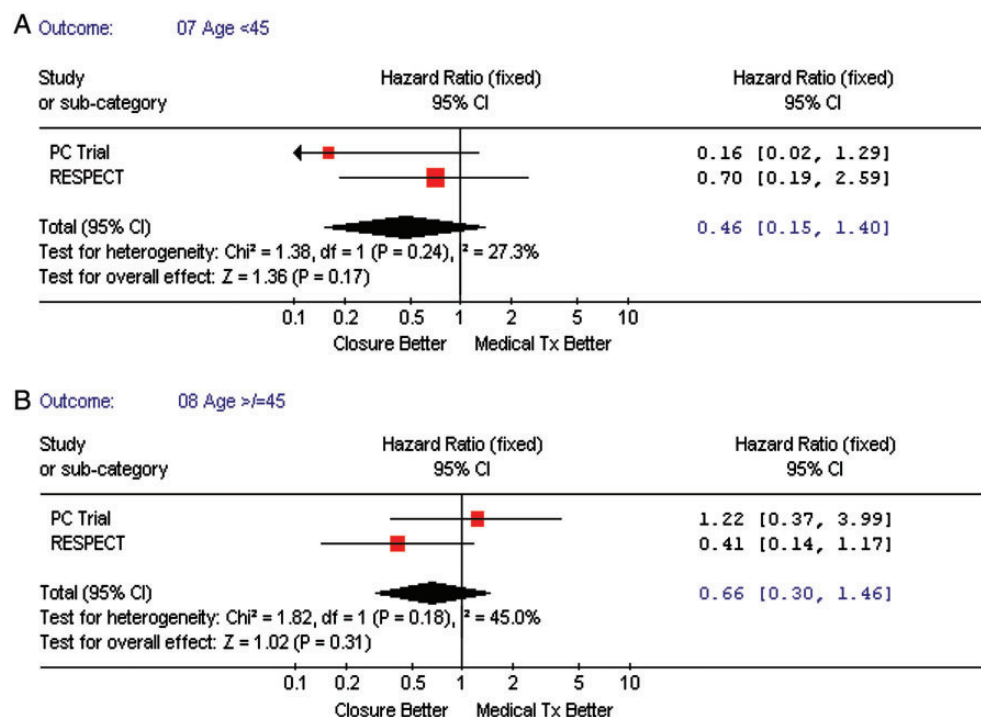


Figure 7 (A) The forest plot of randomized controlled trial comparing composite outcome (death/vascular events) between transcatheter patent foramen ovale closure vs. medical treatment in patients >45 years. (B) The forest plot of randomized controlled trial comparing composite outcome (death/vascular events) between transcatheter patent foramen ovale closure vs. medical treatment in patients <45 years.

Table 4 Adverse events for included trials

Trial	Events	Intervention group (%)	Medical therapy (%)	Hazard ratio	Confidence interval (95% CI)	P-value
PC trial	New-onset atrial fibrillation	6 (2.9) Two transient, 2 required pharmacological cardioversion, 1 required electrical cardioversion, and 1 sustained AF	2 (1)	3.15	0.64–15.6	0.16
	Myocardial infarction	2 (1)	1 (0.5)	2.04	0.19–22.5	0.62
	Hospital admission related to patent foramen ovale	13 (6.4)	13 (6.3)	1.02	0.48–2.21	0.95
	Bleeding	8 (3.9)	12 (5.7)	0.66	0.27–1.62	0.40
	Vascular procedural complication	2 (1)	N/A	N/A	N/A	N/A
CLOSURE 1	New-onset atrial fibrillation	23 (5.7) Only 14 during the initial 30 days of follow-up, it was transient in 17 patients and persistent in 6 patients	3 (0.7)	N/A	N/A	<0.001
	Major bleeding episode	10/378 (2.6)	4/374 (1.1)	N/A	N/A	0.11
	Death other than endpoint	2 (0.5)	4 (0.9)	N/A	N/A	0.51
	Nervous system disorder	6 (1.5)	16 (3.5)	N/A	N/A	0.15
	Vascular procedural complication	8 (1.7)	N/A	N/A	N/A	N/A
	Cardiac perforation	1 (0.2)	0	N/A		
RESPECT	New-onset atrial fibrillation	(3)	(1.5)	N/A	N/A	N/A
	Pulmonary embolism	6 (1.2)	1 (0.2)	N/A	N/A	0.12
	Major bleeding episode	8 (1.6)	9 (1.9)	N/A	N/A	0.81
	Vascular procedural complication	3 (0.6)	0	N/A	N/A	0.124
	Cardiac perforation	1 (0.2)	0	N/A	N/A	0.124

selection bias in these observational studies, in addition to all the potential biases inherent in non-randomized studies. Several possible reasons for fewer events among device-treated patients in the observational studies have been put forth.^{14,15} Among the most important are that type of treatment was based on physician preference, and the interventional therapy was being offered using off-label devices for septal defects, resulting on enrolment difficulties, and by unclear reasons, vascular events at follow-up have been lower than expected.^{14,15}

In our analyses, we also explored features that have been suggested as ‘high-risk PFO’ in patients with cryptogenic stroke, such as young age, presence of atrial septal aneurysm, and shunt magnitude.^{10–12} In our analyses, the rate of recurrent neurological events in younger patients compared with older patients (<45 vs. ≥45 years) was not significantly different in the TC PFO closure group when compared with the medical group. In addition, the presence of an atrial septal aneurysm was not identified as a high-risk feature of future vascular events neither in the TC PFO nor medical therapy groups, but it is important to mention that these results had the greatest heterogeneity (54.4%), suggesting important differences between studies that could not be accounted in our analyses.

An important finding in our analyses is that patients with a ‘substantial shunt’ appear to have better outcomes with device closure; however, the results did not reach statistical significance ($P =$

0.06). We could not explore this hypothesis further, as the PC trial did not report their findings stratified by shunt magnitude. Ideally, collaboration from the investigators conducting these trials can result in joining individual data to further explore this finding.

Currently, there are no studies proving benefit of a particular class of medications for secondary prevention of cryptogenic stroke, and both antiplatelets and/or anticoagulation are deemed reasonable options.^{16,17} It is important to mention that the use of antiplatelet and/or anticoagulation therapy in these studies was at discretion of the treating physician. Because of this, and low event rate, no meaningful comparisons based on type of medication vs. TC PFO were possible.

Since atrial fibrillation is a major risk factor for stroke, all three trials excluded patients with this condition. Interestingly, in our analysis we found a small, but statistically significant, increased risk of developing new-onset atrial fibrillation with the TC PFO closure group when compared with medical therapy (2.7 vs. 0.5%, OR = 5.7 $P < 0.0001$). Despite this increased risk of new-onset atrial fibrillation, the TC PFO closure was still significantly associated with lower risk of TIA and/or stroke in our analyses. Furthermore, excluding CLOSURE I population from the analyses, TC PFO closure using the Amplatzer device, failed to demonstrate a statistically significant increased risk for the development of new-onset atrial fibrillation when compared with the medical therapy group. These findings

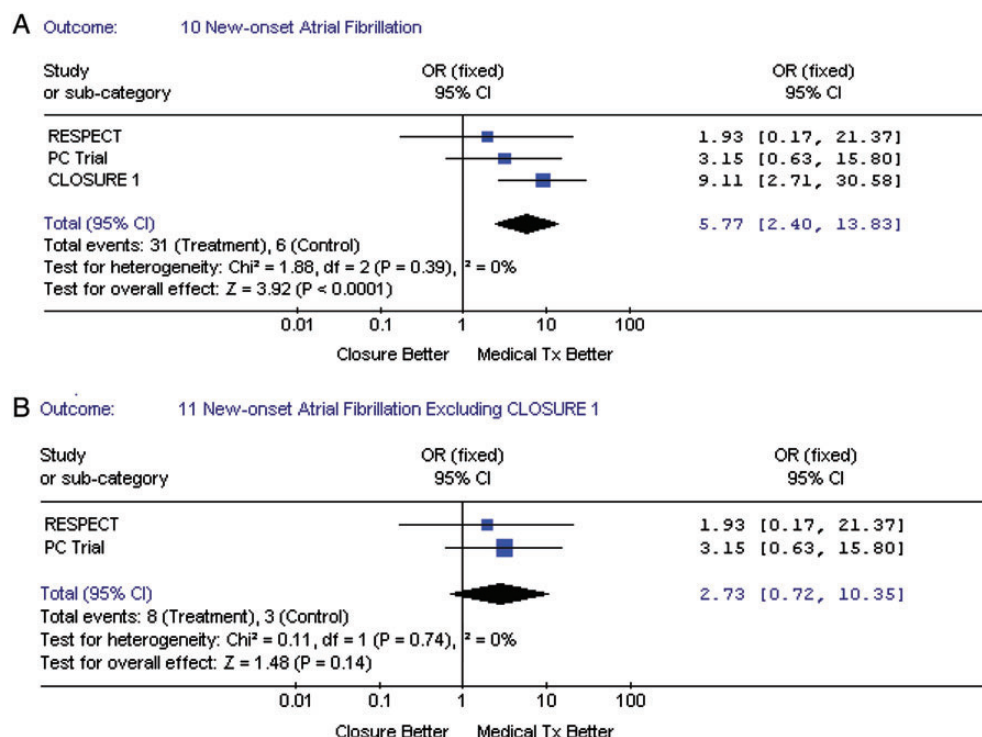


Figure 8 (A) The forest plot of randomized controlled trial comparing new-onset atrial fibrillation between transcatheter patent foramen ovale closure vs. medical treatment. (B) The forest plot of randomized controlled trial comparing new-onset atrial fibrillation between transcatheter patent foramen ovale closure vs. medical treatment excluding STARFLEX closure device.

are consistent with a recently reported meta-analysis of observational studies showing that STARFlex or CardiolSEAL, but not the Amplatzer device were associated with an increased risk of developing new-onset atrial fibrillation.¹⁸ Nonetheless, the impact of the potential increased risk for developing new-onset fibrillation in the TC PFO group, and its potential role in the development of neurological events should be further explored by future analyses, including individual data from these three trials where adjustment of this variable in their outcomes would be possible.

Regarding success of the TC PFO, the analyses show that it can be achieved at a high rate (~94%), with low complications rates, and with no reported deaths related to the procedure itself. This becomes highly relevant as the medical treatment for cryptogenic stroke associated with PFO may include dual antiplatelet therapy and/or warfarin with their known potential risks.^{16,17}

Strengths of our study include: (i) we followed rigorously the recommended guidelines for reporting and conducting meta-analysis of RCT,⁷⁻⁹ (ii) the use of proper quality assessment of the studies by a previously well-validated scale (Jadad),⁸ and (iii) all of our studies were of high quality with scores ≥ 3 points on the Jadad scale. In addition, all three populations had similar baseline characteristics, which make them suitable for meta-analysis (heterogeneity = 0% in the intention-to-treat and TIA/stroke analyses).

The major limitation of our study is that we lacked individual-level data for analyses. Given the similar populations studied, the similar study methodologies and the absence of heterogeneity in most of our analyses, we believe our results are robust. However, individual

data are needed, not only to support the current findings, but also to clarify the role of 'high-risk PFO features', in the development of vascular events. Such data might also shed light on, possible impact of device-related new-onset atrial fibrillation on future neurological events. Another limitation is that the medical therapy group in all three trials did not receive a standardized therapy (antiplatelet and/or anticoagulant), but rather was left upon the physicians discretion, furthermore, the antiplatelet therapy in the intervention group differ between the three trials, making the interpretation of the data difficult. In addition, whether the benefit of the TC PFO closure will persist at long term is unclear as none of the studies had follow-up longer than 5 years. Finally, publication bias is unlikely in our study, as all three RCTs included had negative results.

In summary, this meta-analysis of RCT is the first study to show a possible benefit from the TC PFO closure for prevention of recurrent neurological events in patients with cryptogenic stroke when compared with medical therapy. This finding has the potential to affect clinical practice. Until further analyses with individual-level data are available or currently undergoing RCT with similar outcomes and appropriate follow-up are published,^{19,20} these results might be the best evidence of significant benefit from the TC PFO closure.

Conclusions

In patients with cryptogenic stroke, when compared with medical treatment, the TC PFO closure may be beneficial in reducing the risk of recurrent vascular events. The benefit of the TC PFO closure may

be greater in patients with large degree of shunt, but these findings need to be confirmed in further studies. Finally, it appears that the TC PFO closure increases the risk of new-onset atrial fibrillation and might be associated with the type of device. Despite this increase in new-onset atrial fibrillation, the TC PFO closure showed a possible benefit in reducing the incidence of recurrent neurological events.

Acknowledgements

P.R.-M. contributed: design of the study, data extraction, and writing the manuscript. I.F.P. contributed: design of the study, and writing the manuscript. P.J. contributed: data extraction and writing the manuscript. C.F.W. contributed: writing the manuscript. L.D.M.: design of the study, and writing the manuscript. A.R.-C.: design of the study, data extraction, statistical analyses, and writing the manuscript. Special thanks to Dr Gregg Pressman (cardiologist) and Dr Ferdinando Buonanno (neurologist) for providing valuable insight during the preparation of the manuscript. We would like to thank all the investigators and personnel in charge of designing and completing the CLOSURE I, PC trial and RESPECT.

Conflicts of interest: none declared.

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