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Patent foramen ovale closure versus medical therapy after cryptogenic stroke: An updated meta-analysis of all randomized clinical trials

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Abstract

Background: *Cryptogenic strokes can be attributed to paradoxical emboli through patent foramen ovale (PFO). However, the effectiveness of PFO closure in preventing recurrent stroke is uncertain and the results of previous randomized clinical trials (RCTs) have been inconclusive. Hence, this study provides an updated meta-analysis of all RCTs comparing PFO closure with medical therapy for secondary prevention of cryptogenic stroke.*

Methods: *All RCTs were identified by a comprehensive literature search of PubMed, Embase, the Cochrane Collaboration Central Register of Controlled Trials, Scopus, and Clinicaltrials.gov. The primary outcome was recurrent ischemic stroke and secondary outcomes were transient ischemic attack (TIA), all-cause mortality, new-onset atrial fibrillation (AF), serious adverse events, and major bleeding.*

Results: *Five RCTs with 3440 participants were included in the present study (1829 patients underwent PFO closure and 1611 were treated medically). Pooled analysis showed a statistically significant reduction in the rate of recurrent stroke with PFO closure in comparison to medical therapy (OR 0.41; 95% CI 0.19–0.90; $p = 0.03$). However, there were no statistically significant reductions of recurrent TIAs (OR 0.77; 95% CI 0.51–1.14; $p = 0.19$) or all-cause mortality (OR 0.76; 95% CI 0.35–1.65; $p = 0.48$). The risk of developing new-onset AF was increased significantly with PFO closure (OR 4.74; 95% CI 2.33–9.61; $p < 0.0001$), but no significant differences in terms of serious adverse events or major bleeding between both groups.*

Conclusions: *Patent foramen ovale closure in adults with recent cryptogenic stroke was associated with a lower rate of recurrent strokes in comparison with medical therapy alone.* (Cardiol J 2019; 26, 1: 47–55)

Key words: patent foramen ovale, transcutaneous closure, septal occlude device, atrial tachyarrhythmia

Introduction

Cryptogenic strokes are defined as any ischemic stroke that is not attributable to an identifiable cause despite an extensive work-up [1]. They represent 10% to 40% of all ischemic strokes [2, 3]. Although approximately 25% of the general population has a benign patent foramen ovale (PFO), a fetal remnant of intraarterial septum [4], it can be found in up to 50% of adults younger than 55 years of age with cryptogenic strokes [5]. Studies have shown a strong association between

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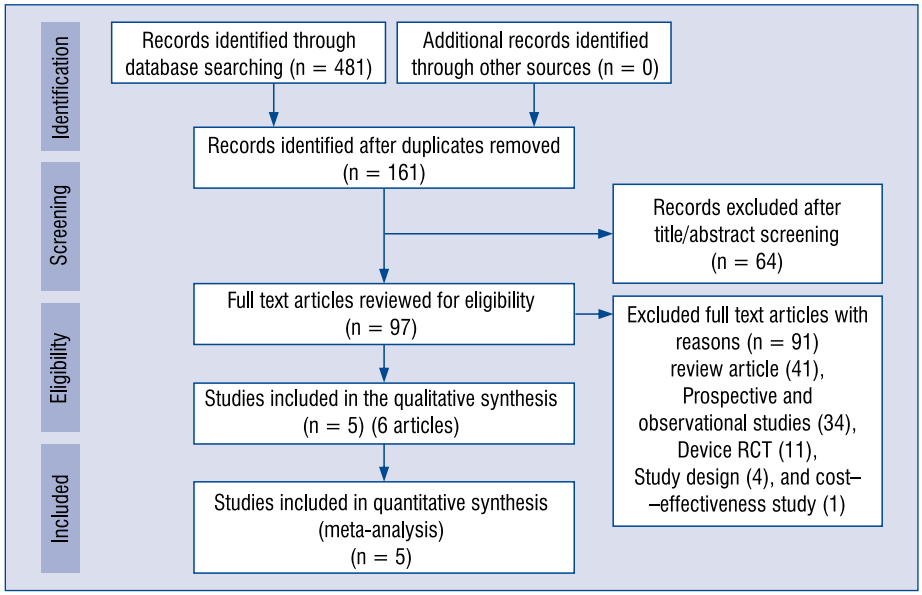

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram; RCT — randomized clinical trial.

the presence of PFO and the development of cryptogenic strokes, which suggests paradoxical embolism, through a right-to-left shunt, as a potential mechanism [6, 7]. Therefore, an index was developed to differentiate incidental PFO from stroke-related PFO [8].

In addition, patients with established stroke in the setting of both PFO and atrial septal aneurysm have a significant increased risk for recurrent stroke and, therefore, other secondary preventive strategies than anti-thrombotic agents were suggested [9]. Previous randomized controlled trials (RCTs) didn't show a benefit of PFO closure over medical therapy [10, 11]. However, the results of recent RCTs showed promising evidence of a lower stroke recurrence rate among patients with recent cryptogenic stroke attributed to PFO [12–14].

In light of these new trials, it was undertaken to conduct an updated meta-analysis of all RCTs comparing transcutaneous device PFO closure with medical therapy for secondary prevention of cryptogenic strokes. In addition, adverse events and complications associated with PFO closure were investigated.

Methods

Literature search and studies selection

Meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015 (Fig. 1) [15] were performed. Two authors (B.K. and A.A.), along with a third author (M.O.) for any discrepancies, independently conducted a comprehensive database search of PubMed, Embase, the Cochrane Collaboration Central Register of Controlled Trials, Scopus, Clinicaltrials.gov and conference proceedings from inception to September 2017. We used Boolean operators for connections of the following headings: "patent foramen ovale", "PFO", "percutaneous closure", "humans" and "randomized clinical trials". Only the longest follow-ups that compared device PFO closure with medical therapy were included. Meta-analysis was restricted only to RCTs as they carry less confounding biases in comparison to observational studies. Studies that fulfill the following criteria were included: 1) The study is an RCT; 2) The trial has PFO closure in one arm; 3) The duration of follow-up is at least 30 days; 4) The trial reported at least one of the following clinical outcomes: stroke or transient ischemic attack (TIA).

Data extraction

Two authors extracted the data (B.K., A.A.) and any discrepancies were resolved by a third author (M.O.). From each RCT, the following were extracted: baseline characteristics, adverse events, procedural and clinical outcomes (Tables 1, 2). The primary outcome of this meta-analysis was recurrent ischemic stroke. Secondary outcomes were TIA, all-cause mortality, new onset atrial

Table 1. Details of the randomized clinical trials.

Characteristics	CLOSURE 1	PC	RESPECT	CLOSE	Gore REDUCE
Place (sites)	USA and Canada (87)	Europe, Canada, Brazil, and Australia (29)	USA and Canada (69)	France (32) and Germany (2)	Canada, Denmark, Finland, Norway, Sweden, the UK, and USA (63)
Publication year	2012	2013	2017	2017	2017
Registration	NCT00201461	NCT00166257	NCT00465270	NCT00562289	NCT00738894
Sponsors	NMT Medical	St. Jude Medical	St. Jude Medical	Assistance Publique — Hôpitaux de Paris	W.L. Gore and Associates
Randomization	Closure vs. medical — 1:1	Closure vs. medical	Closure vs. medical — 1:1	Closure vs. antiplatelet vs. anticoagulation — 1:1:1	Closure vs. medical — 2:1
Total number	909	414	980	663	664
Follow-up [years]	2	Mean 4.1	Median 5.9	Mean 5.3 ± 2	Median 3.2
Primary endpoint	Incidence of TIA, stroke, or mortality (all-cause mortality through the first 30 days all-cause then neurological mortality up to 2 years)	Composite of death, nonfatal stroke, TIA, or peripheral embolism	Composite of recurrent ischemic stroke or early death (within 30 days after implantation of the device or 45 days after randomization)	Occurrence of fatal or nonfatal stroke	1. Freedom from clinical evidence of an ischemic stroke at least 2 years 2. Incidence of new brain infarction (composite of clinical ischemic stroke or silent brain infarction)
Events rate, closure	5.5%	3.4	1.8% (0.66 per 100 patient-years)	0	1: 1.4% 2: 5.7%
Events rate, medical therapy	6.8%	5.2	3.3% (1.38 per 100 patient-years)	6	1: 5.4% 2: 11.3%
P-value	0.37	0.34	0.157 (0.08)	< 0.001	1: 0.002 2: 0.04

CLOSE — Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; CLOSURE 1 — Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale; Gore REDUCE — GORE® HELEX® Septal Occluder/GORE® CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients With Patent Foramen Ovale; PC — Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale (PFO) Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; RESPECT — Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; UK — United Kingdom; USA — United States; TIA — transient ischemic attack

Table 2. Baseline characteristics in the randomized control trials.

Characteristic	CLOSURE 1		PC		RESPECT		CLOSE		Gore REDUCE	
	Closure (n = 447)	Medical (n = 462)	Closure (n = 204)	Medical (n = 210)	Closure (n = 499)	Medical (n = 481)	Closure (n = 238)	APT (n = 235)	Closure (n = 441)	Medical (n = 223)
Age [years]	46.3 ± 9.6	45.7 ± 9.1	44.3 ± 10.2	44.6 ± 10.1	45.7 ± 9.7	46.2 ± 10.0	42.9 ± 10.1	43.8 ± 10.5	45.4 ± 9.3	44.8 ± 9.6
Male sex	233 (52.1%)	238 (51.5%)	92 (45.1%)	114 (54.3%)	268 (53.7%)	268 (55.7%)	137 (57.6%)	142 (60.4%)	261 (59.2%)	138 (61.9%)
Body mass index	–	–	26.6 ± 5.6	26.3 ± 4.8	–	–	32 (13.4%)	27 (11.5%)	–	–
Cigarette smoking — no. of patients/total no.	96/447 (21.5%)	104/460 (22.6%)	52 (25.5%)	47 (22.4%)	75 (15.0%)	55 (11.4%)	68 (28.6%)	69 (29.4%)	63 (14.3%)	25 (11.2%)
Hypertension	151 (33.8%)	131 (28.4%)	49 (24.0%)	58 (27.6%)	160 (32.1%)	153 (31.8%)	27 (11.3%)	24 (10.2%)	112 (25.4%)	58 (26.0%)
Diabetes mellitus	–	–	5 (2.5%)	6 (2.9%)	33 (6.6%)	41 (8.5%)	3 (1.3%)	9 (3.8%)	18 (4.1%)	10 (4.5%)
Hyperlipidemia	212 (47.4%)	189 (40.9%)	50 (24.5%)	62 (29.5%)	196 (39.3%)	195 (40.5%)	30 (12.6%)	36 (15.3%)	–	–
Myocardial infarction	7 (1.6%)	5 (1.1%)	3 (1.5%)	1 (0.5%)	5 (1.0%)	2 (0.4%)	0	0	–	–
Peripheral vascular disease	5 (1.1%)	7 (1.5%)	3 (1.5%)	2 (1.0%)	5 (1.0%)	1 (0.2%)	–	–	–	–
Migraine	–	–	47 (23.0%)	38 (18.1%)	195 (39.1%)	186 (38.7%)	67 (28.2%)	78 (33.2%)	–	–
Cryptogenic stroke — no./total no.	324/446 (72.6%)	329/461 (71.4%)	165 (80.9%)	163 (77.6%)	53/498 (10.6%)	51 (10.6%)	10 (4.2%)	7 (3.0%)	42 (9.5%)	13 (5.8%)
TIA — no. of patients/ /total no.	122/446 (27.4%)	132/461 (28.6%)	33 (16.2%)	42 (20.0%)	58 (11.6%)	61 (12.7%)	–	–	26 (5.9%)	11 (4.9%)
TEE — no./total:										
Large			43/185 (23.2%)	37/184 (20.1%)						79/216 (36.6%)
Moderate/substantial shunt	250 (55.9%)	231 (50.0%)			247 (49.5%)	231 (48.0%)				
Large/no aneurysm							157 (66%)	161 (68.5%)	182/425 (42.8%)	
Large/aneurysm							59 (24.8%)	62 (26.4%)	86/422 (20.4%)	
Atrial septal aneurysm ≥ 10 mm	168 (37.6%)	165 (35.7%)	47 (23.0%)	51 (24.3%)	180 (36.1%)	170 (35.3%)				NA

Plus–minus values are means ± standard deviation.
APT — antiplatelet; CLOSE — Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence; CLOSURE 1 — Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale; Gore REDUCE — GORE® HELEX® Septal Occluder/GORE® CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients With Patent Foramen Ovale; PC — Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale (PFO) Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; RESPECT — Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; TEE — transesophageal echocardiography; TIA — transient ischemic attack; NA — not available; no. — number

tachyarrhythmia (atrial fibrillation [AF]), serious adverse events, and major bleeding.

Statistical analysis

Aggregate odds ratios (ORs) were calculated and 95% confidence intervals (CIs) using a random--effects model. The heterogeneity was measured using Cochran's Q statistic ($p < 0.05$) and I^2 statistics. A random-effects model was used to account for between-study variation. P-value < 0.05 was considered statistically significant result. Data was analyzed with the intention-to-treat principle using RevMan, version 5.3 Windows (Cochrane Collaboration, Oxford, UK).

Results

Five RCTs with 3440 patients were included (54.97% male) with a mean age of 45.3 ± 9.7. 1829 patients underwent PFO closure and 1611 were treated medically. Pooled analysis showed a statistically significant reduction at the rate of recurrent ischemic stroke with device PFO closure in comparison with medical therapy (OR 0.41; 95% CI 0.19–0.90; $p = 0.03$). However, there were no statistically significant reductions of recurrent TIA (OR 0.77; 95% CI 0.51–1.14; $p = 0.19$) or all-cause mortality (OR 0.76; 95% CI 0.35–1.65; $p = 0.48$). The risk for new-onset AF in PFO closure was statistically significant (OR 4.74; 95% CI 2.33–9.61; $p < 0.0001$). In contrast, there were no significant differences in terms of serious adverse events (OR 1.07; 95% CI 0.91–1.25; $p = 0.40$) or major bleeding (OR 0.96; 95% CI 0.42–2.22; $p = 0.93$) (Fig. 2). The results of procedure outcomes can be found in Table 3.

In subgroup analyses an evaluation of potential heterogeneity of the treatment effect in relation to baseline covariates (Table 4), there may have been greater benefit of PFO closure versus medical therapy in younger (< 45 years of age), male patients and patients with substantial shunt. However, there was no evidence of significant interaction of the treatment effect (all $p \geq 1.2$ for interaction). In addition, new-onset AF was significantly increased in all PFO devices, including Amplatzer PFO Occluder ($p \leq 0.01$) (Table 5).

Discussion

Cryptogenic strokes constitute about one-third of all strokes, and approximately 60% are associated with PFO, which suggests paradoxical emboli via PFO shunt and/or in-situ thromboembolism [16]. The present meta-analysis indicates that PFO closure is superior to medical therapy in patients < 60 years of age with recent PFO--related cryptogenic stroke. In addition, these results support prior meta-analyses of both pooled individual-patient and network analysis [17, 18], which demonstrated the benefit of device PFO closure over medical therapy for recurrent ischemic stroke events.

Inconsistent results have been shown in the previous RCTs. The first RCT (CLOSURE 1) [10, 19] failed to demonstrate the benefit of PFO closure with the STARFlex device in preventing cryptogenic stroke over medical therapy alone. A similar result was obtained in the PC trial [11, 20]. Although the rate of nonfatal ischemic stroke recurrence in the intention-to-treat analysis of the original RESPECT trial showed a statistically insignificant result (9 events in the closure group vs. 16 events in the medical therapy group; hazard ratio [HR] with closure, 0.49; 95% CI 0.22–1.11; $p = 0.08$), the between-group difference in the prespecified per-protocol cohort (6 events vs. 14 events in the medical-therapy group; HR 0.37; 95% CI 0.14–0.96; $p = 0.03$) and in the as-treated cohort (5 events vs. 16 events; HR 0.27; 95% CI 0.10–0.75; $p = 0.007$) were significant [21]. The extended follow-up of the same trial (median 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 (HR with PFO closure vs. medical therapy, 0.55; 95% CI 0.31–0.999; $p = 0.046$ by the log rank test) [13]. However, it should be noted that treatment exposure in both groups was unequal due to a higher dropout rate in the medical therapy arm (3141 patient-years in the closure group and 2669 patient-years in the medical therapy group). Two other recent trials (CLOSE and Gore REDUCE) showed the superiority of PFO closure over medical therapy in lowering the rate of stroke recurrence [12, 14, 22]. In Gore REDUCE, there were different dropout rates, which could have biased the trial in relation to lower retention and thus attrition bias (8.8% discontinued the trial in the PFO closure vs. 14.8% in the antiplatelet group) [14]. Although previous reviews have suggested the benefits of oral anticoagulation over antiplatelet therapy for secondary prevention of PFO-related cryptogenic stroke [23], current guidelines voted for the use of antiplatelets only [24, 25]. Within this context, some trials have allowed the use of anticoagulants in the medical therapy group at the discretion of the

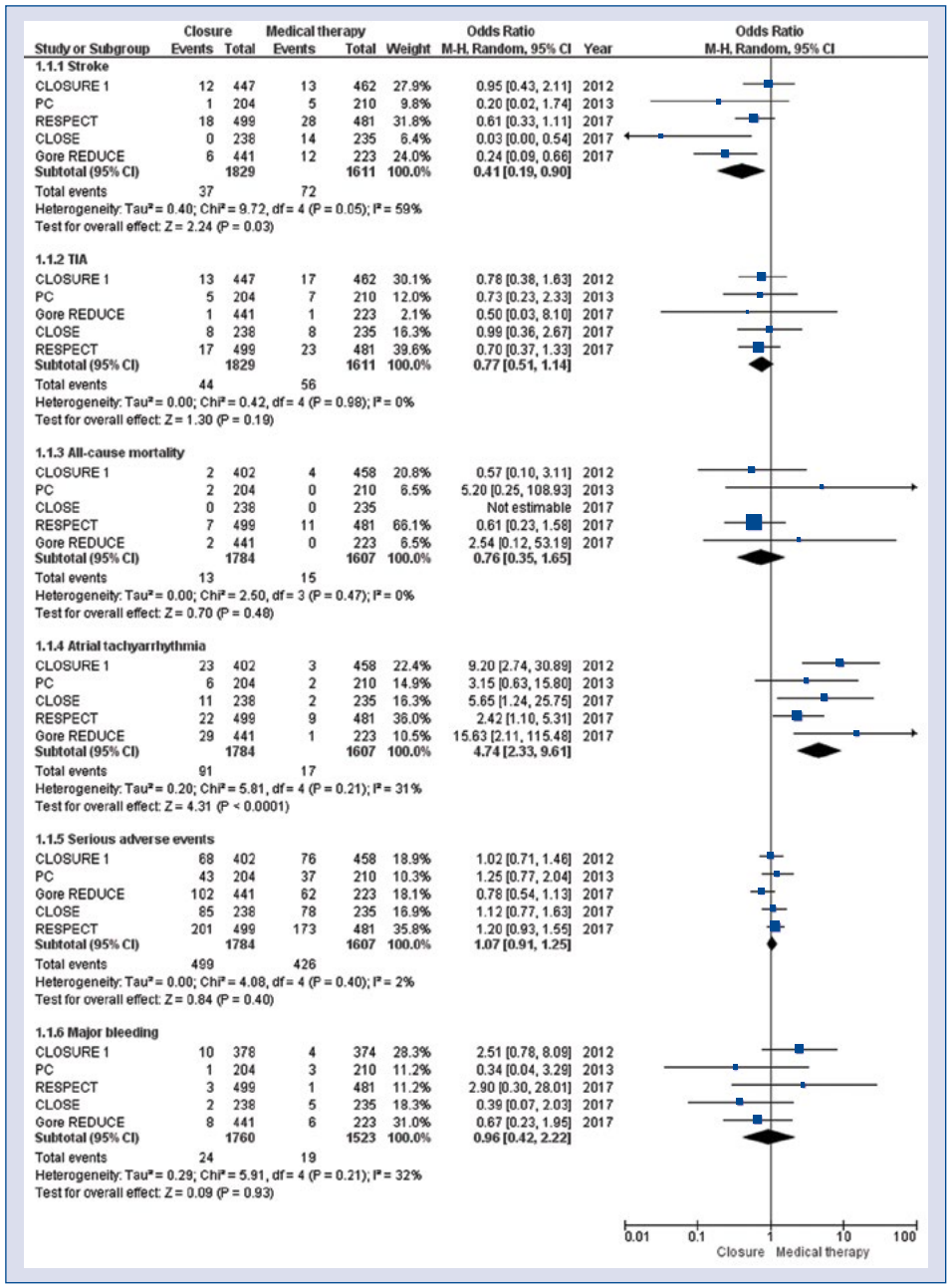

Figure 2. Forest plot of clinical outcomes; CI — confidence interval; TIA — transient ischemic attack.

physicians which might have reduced the overall risk of cerebrovascular accident (CVA) in patients with undiagnosed thrombotic tendencies, a situation that could lead to a bias within the control group.

Previous studies have shown that recurrent CVA/TIA in patients with PFO may be related to mechanisms unrelated to paradoxical embolism and thus, PFO closure protects against PFO related mechanisms only [23]. In contrast, medical therapy can have a protective effect on recurrent CVA for both PFO related and unrelated events. Therefore, the reported recurrent CVA/TIA events in this meta-analysis could have included non-embolic events unrelated to PFO.

A common limitation among previous trials is the absence of prolonged cardiac monitoring for subclinical AF detection in patients with cryptogenic stroke. Although occult AF is uncommon among patients < 60 years of age with cryptogenic stroke [26], the American Heart Association/American Stroke Association guidelines for stroke prevention recommends at least 30 days of cardiac monitoring in patients with no apparent cause of stroke/TIA to detect occult AF based on observational studies

Table 3. Procedural outcomes in the randomized clinical trials.

Study	Device used	Index technical success*	Index procedural success**	Complete/effective closure (TEE grade 0/1)
CLOSURE 1	STARFlex (NMT Medical)	—	89.4%	86.1% at 6 months 86.7% at 24 months
PC	Amplatzer PFO Occluder	—	95.9%	95.9% at 6 months
RESPECT	Amplatzer PFO Occluder	99.1%	96.1%	93.50% at 6 months 72.70% at 6 months (complete)
CLOSE	11 different devices (Amplatzer PFO occluder n = 121/235)	99.6%	88.6%	93% at 10.8 months
Gore REDUCE	1. Helex Septal Occluder (HELEX; W.L. Gore and Associates) 2. Cardioform Septal Occluder (GSO; W.L. Gore and Associates)	98.8%	73.2%	94.50% at 12 months 75.6% at 12 months (complete)

*Technical success: delivery and release of the device. **Procedural success: implantation with no in-hospital complications. Abbreviations — see Tables 1 and 2

Table 4. Subgroups analyses to evaluate heterogeneity in relation to baseline covariates.

Subgroups	PFO closure (events/total)	Medical therapy (events/total)	Odds ratio (95% CI)	P	P for interaction
Age:					0.58
16–45 years	10/649	27/533	0.34 (0.16–0.71)	0.004	
46–60 years	21/726	38/611	0.47 (0.18–1.24)	0.13	
Gender:					0.23
Male	20/874	52/780	0.35 (0.15–0.81)	0.01	
Female	26/704	20/478	0.75 (0.30–1.85)	0.53	
Shunt size:					0.12
Substantial	12/839	34/630	0.27 (0.14–0.54)	0.0002	
None, trace or moderate	29/667	45/679	0.65 (0.27–1.52)	0.31	
Atrial septal aneurysm:					0.99
Present	7/226	15/221	0.63 (0.06–6.67)	0.70	
Absent	18/477	24/470	0.65 (0.23–1.83)	0.41	
Entry event:					
Stroke	20/465	23/487	0.91 (0.49–1.69)	0.77	0.50
Transient ischemic attack	9/139	17/173	0.64 (0.27–1.48)	0.30	
Cardiovascular disease history:					
Present	2/98	8/102	0.29 (0.07–1.24)	0.09	0.92
Absent	5/344	17/343	0.24 (0.01–9.15)	0.44	
Medical therapy:					0.55
Antiplatelet	25/653	39/252	0.82 (0.40–1.69)	0.58	
Anticoagulation	9/157	13/232	1.19 (0.43–3.26)	0.74	

CI — confidence interval; PFO — patent foramen ovale

Table 5. Subgroup analysis to evaluate the type of device occluder on the development of atrial tachyarrhythmia.

Device type	PFO closure (events/total)	Medical therapy (events/total)	Odds ratio (95% CI)	P
Amplatzer PFO Occluder	28/703	11/691	2.54 (1.26–5.16)	≤ 0.01
Other PFO Occluders	52/843	4/681	10.61 (3.77–29.89)	≤ 0.01

CI — confidence interval; PFO — patent foramen ovale

[25, 27]. A previous RCT (CRYSTAL AF) has supported the prolonged cardiac monitoring and the results showed that AF was more frequently detected in patients with recent cryptogenic stroke (12.4% detection rate in the monitored group vs. 2% in the unmonitored group; HR 7.3; 95% CI 2.6–20.8; $p < 0.001$) [28]. In addition, a meta-analysis of RCTs showed improved detection of AF after cryptogenic stroke/TIA with prolonged cardiac monitoring [29]. Therefore, even in the presence of PFO, AF should be considered as a potential cause of some presumptive cryptogenic strokes.

In addition, lower than expected patient recruitment was predominant among prior trials, which could have resulted in an extended recruitment of very selected patients and, therefore, an unreliable population sample [11]. Additionally, on-treatment and per-protocol rates were not reported for adverse events in the previous trials and thus safety analyses were not possible [30]. Furthermore, not all trials have reported all adverse events in their supplementary materials, which could mask other significant potential risks.

In the meta-analysis, a high association of PFO closure with new onset AF was found. The timing of AF was related to the PFO closure in different trials. For example, 91% of AF occurred in first month of PFO closure in the CLOSE trial, 83% were detected within 45 days in the Gore REDUCE trial, and 61% were periprocedural in the CLOSURE trial. Such an association will need to be considered in treating PFO patients with percutaneous devices and their clinical relevance and overall CVA/TIA risk requires further investigation. It was assumed that an implanted PFO device may trigger a new focus for AF. Therefore, it may be suggested that a multidisciplinary and physician-patient clinical decision be made before proceeding with PFO closure when considering risks and benefits for such a procedure. In the RESPECT extended follow-up, a tendency for a higher venous thromboembolism rate was observed in the PFO closure group, which, in part, might suggest a tendency of higher long-term risks of venous thromboembolism in patients with recent cryptogenic stroke [13]. Whether such an association exists, it may be suggested that a large powered RCT be used to examine the high tendency of thrombophilic phenomena in PFO.

The strength of this study is that only RCTs were included. The pooled analysis included a large number of populations from different backgrounds, despite prolonged recruitment, which could reflect a representative sample. Risks of atrial tachyarrhythmia across all trials along with other adverse events were also measured. In contrast, there are several limitations of this study. First, 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. Second, these results should not be generalized to patients other than those with recent PFO-related cryptogenic stroke ≤ 60 years of age. Third, different types of PFO devices were used across all trials and the efficacy and safety of each device should be considered when interpreting these results. Fourth, other factors such as left atrial size to detect the actual effect of different PFO devices on AF induction were not provided in the clinical trials to ascertain a cause-effect relationship.

Conclusions

Meta-analysis of all RCTs showed that PFO closure was associated with a lower rate of recurrent ischemic strokes among adults who had had a recent cryptogenic stroke in comparison with medical therapy. However, PFO closure was associated with an increased risk of developing a new onset atrial tachyarrhythmia.

Clinical perspectives

Competency in medical knowledge: PFO can be associated with cryptogenic strokes. The rate of recurrent stroke is relatively low. However, pooled results of RCTs showed lower recurrent strokes with PFO closure with associated higher risk of AF.

Translation outlook: Comparative studies of various types of PFO closure devices including their safety and efficacy are warranted. In addition, studies of antiplatelet and anticoagulant treatment regimens are needed to closeknowledge gaps.

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