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Review Article

Management of patent foramen ovale in patients with cryptogenic stroke: Is device closure superior to medical treatment? A brief review

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Abstract

Background: Recent randomized controlled trial (RCTs) comparing percutaneous closure with antithrombotic treatment in patients with patent foramen ovale (PFO) and cryptogenic stroke revealed inconsistent results. Indeed, there is still no consensus on the management of these patients, namely closure or medical therapy treatment.

Methods: To take stock of the PFO management after cryptogenic stroke, we conducted a literature review that included 16 articles dealing with different therapeutic strategies and long-term outcomes of these results.

Results: The reviewed studies showed great methodological diversity rendering an exhaustive and balanced comparison between studies difficult. Low recurrence rates under prevention regimens, crossovers, procedure- and device-related complications, as well as inappropriate patient selection might explain the inconsistency of trials. However, despite the methodological heterogeneity certain patterns could be detected. It appears that device closure as secondary prevention measure is an effective and safe procedure reducing the recurrence of neurological events in cryptogenic stroke patients <60 years with large PFOs. Standardization of procedures and larger trials are needed to arrive to definitive conclusions.

Conclusion: In cryptogenic stroke patients <60 years with large PFOs, PFO closure seems to be safe and more effective compared to medical treatment alone. For all other patients group, for example, patients >60 years further trials are needed to clarify the role of PFO closure.

Key Words: Closure device, cryptogenic stroke, management, patent foramen ovale

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INTRODUCTION

The prevalence of stroke remains a global scourge (approximately 12 million strokes worldwide in 2010), despite considerable therapeutic advances in recent years.[9] Previous studies have demonstrated the relationship between a patent foramen ovale (PFO) and cryptogenic stroke, especially in patients aged >55 years who also had an atrial septal aneurysm (ASA) or an important right-to-left shunt.[2,3,6,10,11,18]

However, not all of these PFOs are pathogenic, in 30% of these patients the PFO is an incidental finding.[2] In September 1995,[13] the Amplatzer septal occluder was introduced as the first human percutaneous closure of PFO. Since then, numerous trials have been conducted, including five recent randomized trials comparing percutaneous closure with antithrombotic treatment that revealed inconsistent results – some of them were in favor of closure, whereas others showing no difference.[4,5,14]

Our objective was to carry out a literature review to evaluate the role of PFO closure in different patients group.

MATERIALS AND METHODS

We conducted a PubMed research that included all papers concerning PFO associated with stroke. We selected only articles written in English language by using the following key words: "stroke," "patent foramen ovale," "atrial septal defect," and "device closure PFO." Key words were used in different combinations: "patent foramen ovale" and "stroke." We chose only original studies including five randomized-controlled trials (RCT) and case series on management of PFO after cryptogenic stroke. We included 12 articles for the purpose of this review. To provide better overview we extracted the data and tabulated the data for demographics, results, and complications [Tables 1 and 2]. In a separate section we provide summaries of each study.

RESULTS

Studies diverted greatly for size and methodology. Despite this, certain patterns could be identified through a systematic analysis of the selected studies. There were five RCTs,[4,12,14,17,19] two meta-analysis,[1,8] and prospective case series,[15,21] including one propensity score-matched analysis.[20] The total number of patients based on our included studies were 25179 subjects (2393 female and 3543 male) with a mean age of 48.1 years (standard deviation (SD) 4.6). Mean study size was 2098.25 subjects (SD 3538.1) with a mean follow up of 51.4 months (SD 30.08). In summary, observational studies showed a significant superiority of device closure compared to medical therapy alone.[1,8,20] However, they are prone to selection bias and do not provide the quality of RCTs. The first three RCTs did not find any difference between device closure and medical treatment,[4,5,14] whereas long-time data of the RESPECT trial, the CLOSE, and the REDUCE trial were finally in favor of device closure.[12,17,19]

Observational studies

Kitsios *et al.*[8] conducted a systematic review of observational and randomized evidence of secondary stroke prevention by percutaneous closure of PFO or medical therapy. They included in their review 52 single arm studies, 7 comparative non-randomized trials, and the CLOSURE I trial (the first RCT on device closure). They found 0.36 recurrent cerebrovascular events (stroke and transient ischemic attack (TIA)) per 100 person–years (95% confidence interval (CI), 0.24–0.56) for closure patients versus 2.53 events (95% CI, 1.91–3.35) for medical therapy patients. Percutaneous closure was superior to medical treatment in comparative observational studies (IR ratio = 0.19, 95% CI, 0.07–0.54), which was not the case in the CLOSURE I trial. In the CLOSURE I study, the rate of recurrence was higher in the closure arm than the summary of recurrent event from observational studies.

Agarwal *et al.*[1] performed a meta-analysis of transcatheter closure versus medical therapy for secondary prevention of recurrent cerebrovascular event after paradoxical embolism. They included 48 observational studies of 10.327 patients who had a cryptogenic stroke or a TIA. The primary outcome of the study reported was a recurrent stroke or TIA. Procedural failure, device-related complications, and residual shunting post procedure were the secondary outcomes. The results showed that the risk of recurrent cerebral events was significantly lower in the closure group compared to medical therapy (RR 0.25, 95% CI, 0.11–0.58, I^2 =66%, 10 studies). The incidence of recurrent cerebral events was 0.76 per 100 patients per year (95% CI, 0.48–1.05) for transcatheter closure and 4.39 per 100 patient years (95% CI, 3.20–5.59) for medical therapy.

Wahl *et al.*[20] conducted a propensity score-matched comparison between PFO closure and medical treatment in 308 patients with cryptogenic stroke or TIA. One-hundred and fifty patients underwent PFO closure and 108 received a medical treatment with a median follow up of 10 years. A composite of stroke, TIA, or peripheral embolism was defined as the primary outcome. It occurred in 11% of patients of PFO closure group and 21% in patients of medical therapy group (P = 0.033). The low event rate in favor of closure PFO was due to a low rate of TIA, 5% versus 14% in the medical therapy group (P = 0.039). The risk of all-cause mortality and cardiovascular mortality was similar in both groups.

Randomized studies

Furlan *et al.*[5] reported data of the CLOSURE I a multicenter, randomized, open-label trial of closure with

Table 1: Demographics of studies included in the review

Author (first)	Reference	Year	Trial	Study size	Female/ Male	Mean age	Co-morbidities	Follow-up (in months)
Carroll	4	2013	Prospective, randomized, multicenter trial	980	444/536	46	1) diabetes mellitus 2) systemic hypertension 3) current smoker (13,3%) and former somker (28,3%) 4) hypercholesterolemia 5) coronary artery disease 6) previous myocardial infarction 7) peripheral vascular disease 8) previous transient ischemic attack 9) previous stroke 10) family history of stoke 11) migraine 12) deep vein thrombosis 13) congestive heart failure 14) COPD 14) hormone replacement therapy	30
Furlan	5	2012	Prospective study	909	438/471	46	1) hypertension 31% 2) hypercholesterolemia 44% 3) family history of cardiovascular disease 55% 4) congestive heart disease 0,2% 5) coronary artery disease 1% 6) previous myocardial infarction 1,3% 7) valvular dysfunction 10,3% 8) arrythmia 5% 9) catherization 4,4% 10) PTCA 0,9% 11) peripheral vascular disease 1,3% 12) Stokes Adams syndrome 0,8% 13) pulmonary embolus 0,4% 14) pericarditis 0,6% 14) cardiomyopathy 0,1% 15) smoking during the previous year 22%	24
Meier	14	2013	Prospective, randomized, multicenter study	414	208/206	44	1) family history of cerebrovascular event 22,4% 2) current smoker 23,9% 3) hypertension 25,8% 4) diabetes mellitus 2,6% 5) hypecholesterolemia 27% 6) valvular heart disease 3,1% 7) peripheral vascular disease 3,1% 8) coronary artery disease 1,9% 9) history of myocardial infarction 1% 10) migraine 20,5%	48
Windecker	21	2000	Prospective study	80	30/50	52	NM	60
Saver	17	2017	Multicenter, randomized prospective trial	980	444/536	46	1) diabetes mellitus 7,6% 2) arterial hypertension 31,9% 3) current smoker 13,3%/former smoker 28,3% 4) hypercholesterolemia 39,9% 5) peripheral vascular disease 0,6% 6) coronary artery disease 2,9% 7) family history of stroke 25,1% 8) myocardial infarction 0,7% 9) previous stroke 10,6% 10) previous TIA 12,1% 11) migraine 38,9% 12) deep vein thrombosis 3,6% 13) congestive heart failure 0,3% 14) COPD 1,1%	70
Mas	12	2017	multicenter, randomized, open-label, prospective study	663	178/485	43	1) diabetes mellitus (3%) 2) arterial hypertension (13%) 3) current smoker (36%) 4) hypercholesterolemia (17%) 5) migraine (37%) 6) stroke (4%) 7) deep vein thrombosis or pulmonary embolism (2%) 8) myocardial infarction (0,01%) 9) obesity (15%)	63
Mono	15	2004	Retrospective study	308	44/264	51	1) arterial hypertension (46%) 2) diabetes mellitus (11%) 3) smoking (49%) 4) hypercholesterolemia	48
Kitsios	8	2012	Meta analysis, 52 single-arm studies, 7 comparative nonrandomized studies, CLOSURE I trial reviewed	8916	NM	47	1) arterial hypertension 2) diabetes mellitus 3) current smoking 4) hypercholesterolemia	NM
Argawal	1	2012	Meta analysis, 48 observationnal studies	10327	NM	NM	1) hypertension 6 to 51,6% 2) hypercholesterolemia 3) diabetes 4) ASA 4,5 to 62%	NM
Wahl	20	2012	Prospective, Propensity score-matched analysis	308	44/264	51	1) arterial hypertension (46%) 2) diabetes mellitus (11%) 3) smoking (49%) 4) hypercholesterolemia	120

Contd...

Table 1: Contd...

Author (first)	Reference	Year	Trial	Study size	Female/ Male	Mean age	Co-morbidities	Follow-up (in months)
Homma	6	2017	Prospective, randomized study	630	298/332	59	1) arterial hypertension (60,%) 2) diabetes mellitus (28%) 3) current smoking (29%) 4) obesity (49%) 5) sendatary (35%) 6) heart disease (15%) 7) prior stroke (14,7%) 8) heavy alcohol consumption (40%)	13
Sondergaard	19	2017	Multinational, randomized, prospective, controlled trial	664	265/399	45	1) arterial hypertension (25%) 2) diabetes mellitus (4%) 3) current smoking (13%)	38

percutaneous device compared with medical therapy alone in a total of 909 patients who presented with a cryptogenic stroke or TIA and had a PFO. Four-hundred and five patients had attempted implantation of the STARFlex device with 89.4% success rate. Primary end point was defined as a composite of stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years. The primary end point was achieved in 5.5% in the closure group (447 patients) compared to 6.8% in the medical therapy group (462 patients, $P = 0.37$). No death was reported in 30 days in either group, and there were no deaths from neurologic causes during the 2 year follow-up period. Effective closure was documented in 86.1% patients at 6 months. In 20 patients in the closure group and 22 patients in the medical group an alternative cause more likely than paradoxical embolism for the recurrent cerebrovascular found.

Carroll *et al.*[4] investigated in a prospective, multicenter, randomized trial (RESPECT) on 980 patients (mean age of 45.9 years) with cryptogenic stroke whether device closure is superior to medical therapy alone in preventing recurrent ischemic stroke or early death by using the Amplatzer PFO occluder. Patients medically treated received one or more antiplatelet medications (74.8%) or were anticoagulated with warfarin (25.2%). Recurrent non-fatal ischemic stroke, fatal ischemic stroke, or early death after randomization were defined as primary efficacy end point. In the intention-to-treat cohort, 93% of the 499 patients assigned to the closure group underwent the procedure. A total of 25 primary end-point events occurred (non-fatal ischemic strokes). Nine events occurred in patients in the closure group and 16 in patients in the medical therapy group ($P = 0.08$). In the closure group, there were 23.0% device-related or procedural-related serious adverse events and 21.6% in the medical therapy group ($P = 0.65$). Incidence of atrial fibrillation was not significantly different between the closure group and the medical therapy group (3.0% and 1.5%, $P = 0.13$, respectively).

In the per-protocol cohort, primary end point in the closure group was at 0.46 events per 100 patient–years versus 1.30 events in the medical group ($P = 0.03$). In the as-treated cohort, the rate of primary end point was significantly different between the closure group (0.39 events per 100 patient–years) and the medical therapy group (1.45 events per 100 patients–years) ($P = 0.007$).

Concerning secondary end point, complete PFO closure at 6 months was reached in 72.7% of patients and 93.5% met criteria for effective closure (defined as a shunt grade of 0 or 1).

Saver *et al.*[17] reported the long-term outcomes of the RESPECT trial patients. The mean follow up was 6 years. The primary efficacy end point included non-fatal and fatal ischemic stroke and early death after randomization. Eighteen patients (3.6%) in the closure group had a recurrent ischemic stroke versus 28 (5.8%) in the medically treated group ($P = 0.046$).

Meier *et al.*[14] investigated the best therapeutic option in secondary prevention of a cryptogenic embolism in a randomized, multicenter, prospective study. The PC trial included 414 patients divided into two groups: 204 in the closure group with an average age of 44 years and 210 patients in the medical therapy group with a mean age of 45 years. The mean follow up was 4 years. The primary end point was defined by a composite of death, a non-fatal stroke, TIA, or peripheral embolism. Patients of the closure group were also medically treated with acetylsalicylic acid at 100–325 mg daily for at least 5–6 months in combination with ticlopidine at 250–500 mg daily or clopidogrel at 75–150 mg daily for 1–6 months. Patients in the second group were treated with antiplatelet therapy or oral anticoagulation with at least one antithrombotic drug. About 3.4% of patients in the closure group presented one of the primary end point versus 5.2% in the medical therapy group ($P = 0.34$). One patient (0.5%) of the closure group presented a non-fatal stroke versus five patients (2.4%) in the second group ($P = 0.14$) and respectively five patients (2.5%), and seven patients (3.3%) presented at TIA ($P = 0.56$). Two patients (1.0%) died from a non-cardiovascular death in the closure group versus no patient in the medical therapy group ($P = 0.24$).

Mas *et al.*[12] investigated in the CLOSE trial (randomized and prospective) the best therapeutic option for patients

Table 2: Specific of trials

Author	Reference	Inclusion criteria	Exclusion criteria	Size of ASD/VSD	Complications (%)
Carroll	4	1) aged between 18 and 60 years 2) cryptogenic ischemic stroke 3) patent foramen ovale identified by TEO	mechanism for stroke identified	>10 mm	1) atrial fibrillation 0,2% 2) atrial flutter 0,2% 3) cardiac perforation 0,2% 4) cardiac thrombus 0,2% 5) chest tightness 0,2% 6) deep vein thrombosis 0,2% 7) infective or bacterial endocarditis 0,2% 8) ischemic stroke 0,4% 9) pericardial effusion 0,2% 10) pericardial tamponnade 0,4% 11) pulmonary embolism 0,2% 12) residual shunt requiring closure 0,2% 13) sepsis 0,2% 14) nonsustained ventricular tachycardia 0,2% 15) bleeding 0,4% 16) hematoma 0,2%
Furlan	5	1) aged between 18 and 60 years 2) ischemic stroke or TIA within the previous 6 months 3) patent foramen ovale identified by TEO with bubble study with a right-to-left shunt at the atrial level during a Valsalva maneuver	1) patients with other probable causes for a cardioembolic stroke such as clinically significant carotid artery stenosis >50%, complex aortic arch artheroma, clinically significant left ventricular dysfunction or left ventricular aneuvrysm, or atrial fibrillation 2) congenital cardiac defects not repaired prior to enrollment 3) previously implanted atrial septal device	>10 mm	1) atrial fibrillation 2,9% 2) strokes 1,5% 3) TIA 1,9%
Meier	14	1) age <60 years 2) presence of PFO by TEO 3) no other identifiable cause of stroke or peripheral thromboembolism 4) presence clinically or neurodadiogically of ischemic stroke or TIA or extracranial peripheral thrombolic event	NM	NM	1) myocardial infarction 0,7% 2) atrial fibrillation 1,9% 3) bleeding 4,8%
Windecker	21	1) Presence of PFO with spontaneous or provocable right to left shunt confirmed by TEO with or without ASA 2) TIA or stroke confirmed clinically or neuroradiologically 3) exclusion of any identifiable cause for the thromboembolic event	Any identifiable cause for the thromboembolic event	>10 mm	1) device embolization 3,9% 2) cardiac tamponade 1,3% 3) retroperitoneal hematoma 1,3% 4) embolization of air with transient symptoms 2,6% 5) cerebrovascular accident<48h 1,3%
Saver	17	1) aged between 18 to 60 years 2) presence of PFO confirmed by TEO 3) presence of cryptogenic ischemic stroke	Any identifiable cause for the stroke (largevessel arteriopathy, cardiac source of embolism, intrinsec small-vessel disease, or an arterial hypercoagulable state	NM	1) Allergic drug reaction 0,2% 2) Atrial fibrillation 0,4% 3) Atrial flutter 0,2% 3) Cardiac perforation 0,2% 4) Cardiac thrombus 0,4% 5) Chest tightness 0,2% 6) Deep-vein thrombosis 0,2% 7) Infective endocarditis 0,2% 8) Ischemic stroke 0,4% 9) Pericardial effusion 0,2% 10) Pericardial tamponade 0,4% 11) Pulmonary embolism 0,4% 12) Residual shunt requiring closure 0,4% 13) Sepsis 0,2%

Contd...

Table 2: Contd...

Author	Reference	Inclusion criteria	Exclusion criteria	Size of ASD/VSD	Complications (%)
Mas	12	1) aged between 16 to 60 years 2) ischemic stroke within the previous 6 months without any cause other than PFO 3) presence of an ASA or large interatrial shunt	NM	NM	1) procedural complications 5,9% 2) atrial fibrillation or flutter (4,6% in the closure group)
Mono	15	1) Presence of PFO with spontaneous or provocable right to left shunt confirmed by TEO with or without ASA 2) TIA or stroke confirmed clinically or neuroradiologically	Any identifiable cause for the thromboembolic event	>10 mm	1) major bleeding (1.3%) in patients with anticoagulants 2) major bleeding (0,6%) in patients on antiplatelets
Kitsios	8	NM	NM	NM	NM
Argawal	1	1) presence of patent foramen ovale 2) stroke or TIA of unknown cause	NM	NM	NM
Wahl	20	1) Presence of PFO with spontaneous or provocable right to left shunt confirmed by TEO with or without ASA 2) TIA or stroke confirmed clinically or neuroradiologically	Any identifiable cause for the thromboembolic event	>10 mm	1) major bleeding (1.3%) in patients with anticoagulants 2) major bleeding (0,6%) in patients on antiplatelets
Homma	6	1) aged between 30 and 85 2) presence of ischemic stroke within the previous 30 days 3) patients rated 3 on the Glasgow Outcome Scale	1) patients with a baseline INR above 1,4 2) stroke related to a procedure or a cardioembolic source 3) patients planned to undergo surgery for high grade carotid stenosis 4) patients with a contraindication to TEE	>2 mm	NM
Sondergaard	19	1) aged between 18 to 59 2) cryptogenic ischemic stroke within 180 days before randomization 3) presence of a PFO with a right to left shunt	1) stroke with a small, deep infarction (<1.5 cm in diameter) 2) presence of a typical clinical lacunar syndrome 2) uncontrolled diabetes mellitus or hypertension or autoimmune disease 3) recent history of alcohol or drug abuse 4) presence of a specific indication for anticoagulation	NM	1) atrial fibrillation or flutter (2%) 2) procedure complications (5,9%) 3) major or fatal bleeding complication (2%)

with cryptogenic stroke and large PFO for coinciding ASA in preventing a recurrent stroke comparing percutaneous closure with anticoagulation and with antiplatelet agents. Five-hundred and twenty-four patients were randomized into three groups: 238 patients in the closure group, 187 patients in the anticoagulation treatment (coumadin) group, and 238 patients were included in the antiplatelet group. All patients of the closure group received 75 mg of aspirin plus 75 mg of clopidogrel per day during 3 months and then a single antiplatelet agent. Different closure device were used: Amplatzer PFO occluder, Intrasept PFO occluder, Premere device, Starflex septal occluder system, Amplatzer cribriform occluder, Figulla Flex II PFO occluder, Atriasept II occluder, Amplatzer ASD occluder, Figulla Flex II UNI occluder, Gore septal occluder, and Figulla Flex II ASD occluder. The primary outcome was defined as ischemic stroke. Mean follow up was 5.3 years. The results showed that among the 238 patients in the closure group none had a stroke, whereas 14 patients of the antiplatelet group suffered a stroke ($P < 0.001$). Patients with device closure developed more often atrial fibrillation than patients

within the antiplatelet group (4.6% vs. 0.9%, $P = 0.02$). There was no significant difference between the groups in terms of serious adverse events defined as major bleeding and atrial fibrillation (35.7% of the patients in the PFO closure group and 33.2% of the patients in the antiplatelet-only group, $P = 0.56$).

The REDUCE trial conducted by Søndergard *et al.*[19] enrolled 664 patients (of whom 81% had moderate or large interatrial shunts) with a mean age of 45.2 years and a mean follow up of 3.2 years. Patients who had presented a cryptogenic stroke in the previous 180 days were randomized into two groups, one with PFO closure (using the Gore Helex septal occluder or the Gore Cardioform septal occluder) plus antiplatelet therapy versus antiplatelet therapy alone. The antiplatelets agent used was aspirin alone or aspirin plus dipyridamole or clopidogrel alone. There were two primary end points, the first was the absence of ischemic stroke for at least 24 months after randomization and the second was the incidence of cerebral infarction (clinical or imaging) at 2 years of follow up. Recurrent clinical ischemic stroke occurred in 1.4% of patients who underwent PFO closure and in 5.4% of patients with antiplatelet only ($P = 0.002$). The second composite end point was lower in the closure PFO group than in the second group (5.7% vs. 11.3%, $P = 0.04$). There was no significant difference between the two groups concerning the incidence of silent brain infarction ($P = 0.97$). After PFO closure, atrial fibrillation occurred in 6.6% of patients.

Safety and efficacy of PFO closure

The rate of effective closure of the PFO in the CLOSURE I trial was 86.7%. Regarding serious adverse events there were no significant differences between the two groups (16.9% in the closure group vs. 16.6% in the medical therapy group, $P = 0.90$). About 1.1% of the closure group patients had a thrombus in the left atrium within 6 months of whom two had a stroke. Another general complication in the closure group was atrial fibrillation. In this trial, 5.7% of closure group patients had atrial fibrillation versus 0.7% of the patients in the medical group ($P < 0.001$).

In the RESPECT trial, the success rate of delivery and release device was 99.1%. The rate of procedure-related or device-related serious adverse events was 4.2% in the closure group. The atrial fibrillation rate was not significantly different between the groups (3% vs. 1.5%, $P = 0.13$).

In the long-term follow up of RESPECT trial, the rate of pulmonary embolism in the closure group was 0.41 per 100 patient–years and 0.11 per 100 patient–years in the medical group ($P = 0.04$).

In the PC trial, there was no device-related thrombus in any patient. The difference observed between the two groups about atrial fibrillation was not significant, 2.9% in the closure group versus 1% in the medical group, $P = 0.16$.

The REDUCE trial found a significant difference concerning atrial fibrillation or flutter between the PFO closure group and the antiplatelet group (6.6% vs. 0.4%, $P < 0.001$, respectively).

The CLOSE trial reported 5.9% of device-related procedure in the PFO closure group. Atrial fibrillation was more common in the PFO closure group than in the antiplatelet group (4.6% vs. 0.9%, $P = 0.02$, respectively). The rate of serious adverse events did not differ significantly between the two groups ($P = 0.56$).

Wahl *et al.* observed in their propensity score-matched study a complete PFO closure in 82% of patients at 6 months. However, there were cases of residual shunt, small in 10% of patients, moderate in 3%, and large in 5%. A device-related thrombus was observed in two patients, resolved under anticoagulation. Major bleeding occurred in 1% of patients in the PFO closure group and in 2.9% of patients in the medically treated group ($P = 0.34$).

The following study did not seek to compare the different current management of PFO, but evaluated the long-term outcomes of closure.

The study from Windecker *et al.*[21] was a prospective study with a follow up of 5 years in 80 patients with a mean age of 52 years. All patients had a PFO associated with a paradoxical embolic event (stroke, TIA, or peripheral embolism) and had undergone transcatheter closure with five different devices (Buttoned device for 28 patients, PFO-STAR for 19 patients, Amplatzer Occluder for 14 patients, Angel-wings Occluder for 10 patients, and CardioSEAL for 9 patients). Twenty patients had an associated ASA, the remaining had only a PFO. The closure procedure had a complete closure rate at 98%. There were eight procedure-related device complications. In one patient, the procedure was cancelled before device delivery because of laceration of the femoral artery during venous puncture. Device embolization occurred in another patient with PFO and a large ASA into the pulmonary artery 12 hours after the procedure. Cerebrovascular event occurred in a patient due to air embolism. Two patients presented embolization of the counter occluder in the pulmonary artery. Perforation of the right atrium occurred in one patient under oral anticoagulation, resulted in a pericardial effusion. Two patients presented cardiac and cerebral events due to embolization of air into the systemic circulation.

The role of anticoagulants

It is still an open question if anticoagulants are as effective as closure? In the PICSS trial, Homma *et al.*[7] have sought to evaluate the impact of antithrombotic therapies

by comparing them to oral anticoagulation in patients with cryptogenic stroke-associated PFO. They enrolled 630 patients with a cryptogenic stroke, 312 (49.5%) were randomized to warfarin and 318 (50.5%) to aspirin. The primary end points were recurrent ischemic stroke or death. In the end, there was no significant difference in the primary end point between patients treated with warfarin and those who received aspirin ($P = 0.49$).

Argawal *et al.*[1] also demonstrated that the risk of recurrent cerebrovascular events was lower with anticoagulants than with antiplatelets (RR 0.58, 95% CI, 0.41–0.82, 12 studies, $I^2 = 0\%$).

Data from Kitsios[8] meta-analysis showed a clear superiority of anticoagulants versus antiplateles in preventing recurrent events. (IR ratio = 0.42, 95% CI, 0.18–0.98).

In a subgroup analysis of the RESPECT trial, there were no differences regarding risk of recurrence between the closure group and patients treated with anticoagulants (HR, 0.64; 95% CI, 0.34–1.20; $P = 0.16$). In the CLOSE trial, 524 were randomized into three groups: 173 patients in the closure group, 180 patients in the anticoagulation (coumadin) treatment group, and 171 patients were included in the antiplatelet group. In the intention-to-treat cohort, they observed three strokes in the anticoagulation group and seven strokes in the antiplatelet group. The authors did not proceed to a statistical significance because the study was not adequately powered to compare results in the two groups. However, other results are still expected in this study, which dates only from 2017.

Other etiologies for first-ever and recurrent stroke in patients with PFO

An intensive diagnostic work-up is needed in all patients with PFO and first-ever or recurrent stroke before evaluation a potential closure as closure can only prevent PFO-associated strokes.

In the CLOSURE I trial other etiologies could explain the recurrent cerebrovascular event (TIA or stroke) in 20 patients of the 23 in the closure group and in 22 patients of the 29 of the medical therapy group. The etiologies evoked were atrial fibrillation, a clot in the left atrium, subcortical lacunar infarction with risk factors, aortic arch atheroma, migraine complex, vasculitis, and conversion disorder. There were 12 strokes in the closure group. For three of these patients, the etiology found was atrial fibrillation and for two of them there was a thrombus device-related on the transesophageal echocardiogram (TEE). Regarding the medical therapy group, there were 13 strokes of which 1 was related to atrial fibrillation.

Mono *et al.*[15] investigated the etiology of a recurrent event in 308 cryptogenic stroke patients of whom 158 patients received medical therapy (aspirin for 48%, clopidogrel for 2%, and oral anticoagulation for 50%) and150 patients had undergone percutaneous PFO closure. The mean follow up was 8.7 years. During the follow up, they observed 13 strokes and 19 TIA in the medical therapy group and 8 strokes and 8 TIA occurred in the closure group. Other etiologies were selected for 38% of recurrent cerebrovascular events in the medical group: large artery disease (9%), small artery disease (6%), cardioembolism (13%), cerebral vasculitis (3%), and antiphospholipid antibody syndrome (6%). Forty-four percent of recurrent cerebrovascular events had an etiology other than PFO in the closure group: large artery disease (6%), small artery disease (19%), cardioembolism (13%), and thrombophilic disorder (6%). The frequency of concurrent etiologies between the two groups was not significantly different ($P = 0.68$).

CONCLUSION

A PFO closure can only be effective in PFO-related strokes, which means that an extensive diagnostic work-up is needed to identify patients with "real" cryptogenic stroke who might derive benefit from PFO closure. Patients selection (e.g., inclusion of patients with lacunar stroke probably due to microangiopathy), inclusion of TIA patients as in the CLOSURE I trial, inclusion of TIA as endpoint event, low recurrence rates under prevention regimens, crossovers, procedure- and device-related complications might explain the observed inconsistency of trials. Our findings are echoed by the recent study of Ntaios *et al.*[16] a meta-analysis based on five trials (PC, Respect, Closure-I, Reduce, Close) that found equally that PFO closure was superior to medical treatment in reducing ischemic stroke recurrence in patients with cryptogenic stroke or TIA. The analysis found further that the AMPLATZER PFO occluder and the more recent used Helex and Cardioform septal occluders were superior to medical treatment.

In summary, closure seems to be effective in patients >60 years with classical cryptogenic stroke, especially if there is a large shunt (Grade 2 and 3) or a coinciding ASA. However, we still do not know if closure is also effective in patients <60 years and if anticoagulants are as effective as closure or superior to antiplatelets, respectively. Atrial fibrillation is observed in up to 7% after closure and might be of clinical significance. Careful selection of clear cryptogenic stroke patients is the key to the success of the percutaneous closure procedure. In case of a recurrent event, an intensive workup is needed to rule out alternative causes of recurrence.

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Conflicts of interest

There are no conflicts of interest.

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