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Influence of procedural timing on the preventive yield of percutaneous patent foramen ovale closure

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ABSTRACT

Background The benefit of patent foramen ovale closure (PFOC) ≤9 months after a cryptogenic stroke has been demonstrated in several randomised clinical trials. There is, however, insufficient data to support PFOC in non-recent cryptogenic strokes.

Aims The objective of the study was to evaluate the effectiveness of PFOC in relation to the time since the patient's most recent cryptogenic cerebrovascular event (CVE) or systemic embolism (SE).

Methods We conducted a multicentre, retrospective cohort study with international participation, to assess the results of an early closure (EC, <9 months) for secondary prevention versus a delayed closure (DC, ≥9 months). Recurrence of CVE/SE following PFOC was evaluated as the primary endpoint.

Results 496 patients were included (65% in the EC and 35% in the DC group). With the exception of a larger defect size in the DC group (tunnel width 6 (4–14) vs 12 (6–16) mm, p=0.005), similar clinical and echocardiographic baseline features were observed between the groups. No differences were observed regarding the type of devices used for PFOC, procedural success rate (99.4 in EC vs 98.8% DC group) and periprocedural complications (2.1% vs 0.8%). Median follow-up was 2.0 (1.2–4.2) years in the whole study population. Recurrence of CVE/SE (3.9% vs 2.6%, p=0.443), death (1.4% vs 1.0%, p=0.697), residual shunt 12 months after PFOC, or antithrombotic treatment strategy were comparable in both groups during follow-up. A subanalysis comparing very delayed PFOC (≥24 months) also showed no differences in recurrence (4.2% in the <24-month vs 3.4% in the ≥24-month group, p=0.770).

Conclusion Patients undergoing PFOC before and after 9 months after the index event had a comparable recurrence rate of CVE/SE. These findings suggest that PFOC might be recommended in cryptogenic CVE/SE which are more remote than 9 months.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pivotal randomised clinical trials and meta-analysis which demonstrated the benefit of patent foramen ovale closure (PFOC) over medical therapy alone included with patients after a cryptogenic stroke occurring ≤9 months before. Evidence supporting PFOC in more remote cryptogenic strokes is lacking.

WHAT THIS STUDY ADDS

⇒ The yield of PFOC for secondary prevention did not change significantly between patients receiving PFOC before and after 9 months following the index event, according to this investigation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings may change daily clinical practice by widening the indication of PFOC regardless of the time elapsed since the index event. Moreover, the application of an arbitrary timing criterion which was developed from pivotal studies may also lead to patients receiving suboptimal treatment and being at a higher risk of recurrence if they are not treated.

INTRODUCTION

Percutaneous closure of patent foramen ovale (PFOC) has been available since the 1990s, being a safe technique intended to prevent paradoxical embolisms as a sort of mechanical vaccination.[1] Evidence supporting PFOC followed by antithrombotic treatment over medical therapy alone as secondary prevention after a cryptogenic stroke is based on several randomised controlled trials (RCT). CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischaemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen

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Table 1 Baseline characteristics at PFOC

	EC, <9 months (N=325)	DC, ≥9 months (N=171)	P value
Age	49 (40–57)	54 (43–62)	0.001
Female sex	130 (40.1)	75 (43.9)	0.422
Hypertension	69 (21.3)	46 (26.9)	0.160
Dyslipidaemia	80 (24.7)	60 (35.1)	0.015
Diabetes	12 (3.7)	10 (5.9)	0.271
Insulin-dependent	4 (1.2)	2 (1.2)	0.950
Tobacco use			0.090
Active	56 (17.3)	29 (9.0)	
Former	41 (24.0)	20 (11.7)	
BMI	25.7 (23.2–28.3)	25.1 (22.7–28.1)	0.408
Previous myocardial infarction	4 (1.2)	4 (2.3)	0.456
Previous PCI	4 (1.2)	2 (1.2)	0.950
Peripheral arteriopathy	5 (1.5)	6 (3.5)	0.158
Chronic renal disease	3 (0.9)	2 (1.2)	0.799
Atrial fibrillation	6 (1.9)	6 (3.5)	0.252
LVEF (%)	60 (60–65)	60 (60–62)	0.040
Type of event indicating PFO closure			0.622
Ischaemic stroke	252 (77.8)	135 (79.0)	
TIA	63 (19.4)	32 (18.7)	
SE	6 (1.9)	4 (2.3)	
Multiple embolism	3 (0.9)	0 (0)	
Concomitant PE to index event	11 (3.4)	4 (2.3)	0.518
Previous episodes of CVE/SE*			0.147
One episode	30 (9.2)	25 (14.6)	
Two episodes	24 (7.4)	9 (5.3)	
Thrombophilia tests performed	60 (18.5)	29 (17.0)	0.367
Identified cases of thrombophilia			0.087
Factor V Leiden	4 (6.7)	1 (3.4)	
Prothrombin gene mutation	3 5.0)	0 (0)	
Protein C deficiency	0 (0)	2 (6.9)	
Protein S deficiency	0 (0)	2 (6.9)	
MTHFR gene mutation	4 (6.7)	0 (0)	
Lupus anticoagulant	7 (11.7)	2 (6.9)	

*Apart from the index event.
BMI, body mass index; CVE/SE, cerebrovascular event or systemic embolism; DC, delayed closure; EC, early closure; LVEF, left ventricle ejection fraction; MTHFR, methylenetetrahydrofolate reductase; NA, not applicable (descriptive purposes only); PCI, percutaneous coronary intervention; PE, pulmonary embolism; PFOC, patent foramen ovale closure; SE, systemic embolism.

Ovale),[2 3] REDUCE (Gore Septal Occluder Device for Patent Foramen Ovale Closure in Stroke Patients),[4] CLOSE (Patent Foramen Ovale Closure or Anticoagulants vs Antiplatelet Therapy to Prevent Stroke Recurrence)[5 6] and DEFENSE-PFO (Device Closure vs Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale)[7] trials included patients with a cryptogenic stroke within the 6 months before randomisation. On the other hand, RESPECT (Randomised Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment)[8] trial established a temporal threshold for enrolment in 9 months.

A meta-analysis gathering this evidence showed that PFOC was more effective than medical therapy alone in preventing stroke recurrence,[9] particularly at extended follow-up periods,[10] leading to consensus documents supporting PFOC,[11] and a stronger recommendation for intervention by the American Academy of Neurology among those patients younger than 60 years old when no

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Table 2 Neurological and neuroimaging information at index CVE/SE

	EC, <9 months (N=267)	DC, ≥9 months (N=151)	P value
Clinical syndrome at presentation*			0.082
TACI	40 (17.5)	13 (10.6)	
PACI	115 (50.2)	65 (52.8)	
POCI	50 (21.8)	31 (25.2)	
Lacunar	24 (10.5)	14 (11.4)	
Neuroimaging localisation of ischaemic lesions*			0.151
Superficial	167 (66.5)	82 (60.3)	
Deep	39 (15.5)	24 (17.6)	
Both	8 (3.2)	1 (0.7)	
No imaging findings	37 (14.7)	29 (21.3)	
Anatomic localisation of ischaemic lesions*			0.991
MCA	103 (49.3)	57 (46.7)	
ACA	13 (6.2)	6 (4.9)	
PCA	26 (12.4)	16 (13.1)	
Vertebrobasilar – cerebellum	30 (14.4)	20 (16.4)	
Vertebrobasilar – brain stem	6 (2.9)	4 (3.3)	
Undetermined	5 (2.4)	4 (3.3)	
Contrast transcranial Doppler patterns			0.234
Micro-bubbles	23 (17.4)	10 (23.8)	
Shower	56 (42.4)	19 (45.2)	
Curtain	53 (40.2)	13 (31.0)	
Median NIHSS at admission*	2 (1–4)	1 (0–5)	0.049
Median mRS at discharge*	0 (0–1)	0 (0–1)	0.020
Active neoplasia*	7 (2.2)	3 (1.8)	0.768
RoPE score	7 (5–8)	6 (5–7)	0.077
Anatomic localisation of previous episodes of stroke/TIA†			0.452
Cortical	30 (11.2)	21 (14.8)	
Lacunar	26 (9.7)	19 (13.4)	

*Regarding the index event.
†Apart from the index event.
ACA, anterior cerebral artery; BMI, body mass index; CVE/SE, cerebrovascular event or systemic embolism; DC, delayed closure; EC, early closure ; LACI, lacunar cerebral infarct; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Score; PACI, partial anterior circulation infarct; PCA, posterior cerebral artery; POCI, posterior circulation infarction; NT proBNP, N-terminal pro-brain natriuretic peptide; RoPE, Risk of Paradoxical Embolism; TACI, total anterior circulation infarct; TIA, transient ischaemic attack; ULN, upper limit of normality.

other additional stroke mechanism was found. However, it remained unclear whether PFOC provides a similar benefit in patients who fit the pivotal studies' inclusion criteria but have had a more ancient stroke.[12] Moreover, limiting PFOC to a time frame of 9 months after the index event could expose those patients with more remote episodes to a higher risk of recurrence.[13]

The aim of our study was to compare the effectiveness of PFOC for secondary prevention, according to the time elapsed from patients' last cerebrovascular event or systemic embolism (CVE/SE).

Our study compared the effectiveness of PFOC for secondary prevention, based on the duration since patients' last SE or CVE.

METHODS

Study population

From October 2004 to April 2022, all consecutive adult patients referred to percutaneous closure of PFO or atrial septal defect (ASD) for secondary prevention after a CVE/SE were recruited. A total of eight different hospitals from Spain and Italy participated in this registry. Exclusion criteria included: (1) PFOC performed in the context of decompression sickness, desaturation syndromes, migraine or other clinical settings; (2) index CVE/SE not considered to be from unknown origin; (3) insufficient data regarding index event or follow-up shorter than 1 year after PFOC.

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Patients were classified according to the time elapsed from index CVE/SE to PFOC in an early closure (EC) group (PFOC within the first 9 months after the index CVE/SE) and a delayed closure (DC) group (PFOC performed after 9 months following the index event). Additionally, a subanalysis was performed including those patients with a highly delayed procedure (≥24 months after the index CVE/SE).

Index event definition

The causative role of PFO in every CVE/SE was assessed in each centre by a multidisciplinary 'PFO team', including neurologists, radiologists, cardiac imaging experts and interventional cardiologists, taking into consideration patients' characteristics and comorbidities, imaging stroke patterns and PFO features. In each case, a comprehensive diagnostic work-up was conducted, including anamnesis and physical examination, a neuroimaging study (brain CT and/or magnetic resonance (MR)), a blood study, an ECG, an assessment of the supra-aortic trunks and the circle of Willis by ultrasonography and/or CT/MR angiography, a transthoracic (TTE) and transoesophageal echocardiography (TOE). Contrast-enhanced transcranial Doppler and a coagulation disorders study were implemented at physicians' discretion.

PFO diagnosis

PFO diagnosis was established by demonstrating a right to left shunt on a cardiac echocardiogram or transcranial Doppler with agitated saline contrast test at rest and during the Valsalva manoeuvre. The anatomy of PFO was further studied by TOE, and other intracardiac shunts or sources of embolism were excluded.

Epidemiological data, information regarding neurological syndromes and neuroimaging at index CVE/SE, anatomic PFO parameters, procedural details and early outcomes were prospectively gathered, while patients were being enrolled, and retrospectively analysed. After PFOC, standard antiplatelet therapy comprised aspirin (100 mg daily) and clopidogrel (75 mg daily) for 3–6 months, followed by aspirin ever since, according to physician's discretion. Clinical long-term follow-up was performed by monitoring any recurrences of CVE/SE and other clinical events, such as death, a new diagnosis of atrial fibrillation (AF), deep vein thrombosis (DVT) or pulmonary embolism (PE). Also, the antithrombotic treatment regimen was reported during follow-up, and the presence of residual shunt was systematically investigated by TTE or TOE.

Clinical outcomes

Recurrence of CVE/SE following PFOC was the primary endpoint. Secondary endpoints included periprocedural complications, absence of residual shunt on echocardiographic follow-up, all-cause death, new-onset AF, PE or DVT during follow-up. Definition of central nervous system infarction included brain, spinal cord or retinal cell death imputable to ischaemia, based on imaging or clinical evidence for focal symptoms lasting ≥24 hours or until death, once other aetiologies had been excluded. Ischaemic stroke was defined as an episode of neurological dysfunction due to a central nervous system infarction. A transitory episode of neurological impairment brought on by focal brain, spinal cord or retinal ischaemia without evidence of acute infarction on imaging was defined as a transient

Table 3 PFO echocardiographic information and procedure details

	EC, <9 months (N=325)	DC, ≥9 months (N=171)	P value
Defect width (mm)	6 (4–14)	12 (6–16)	0.005
Tunnel length (mm)	12 (9–15)	14 (9–18)	0.259
Interatrial septal aneurysm	108 (47.6)	58 (51.3)	0.645
Access			0.037
Right femoral vein	268 (83.0)	156 (91.2)	
Left femoral vein	55 (17.0)	15 (8.8)	
TOE guidance	203 (83.2)	107 (87.0)	0.343
ICE guidance	54 (16.7)	19 (11.1)	0.095
Use of sizing balloon	3 (1.1)	5 (3.2)	0.122
PFOC device			0.250
Amplatzer	244 (75.1)	117 (68.4)	
Gore Cardioform	58 (17.9)	40 (23.4)	
MemoPart	16 (4.9)	10 (5.9)	
Hyperion	3 (0.9)	0 (0)	
Occlutech	1 (0.3)	2 (1.2)	
NobleStitch	1 (0.3)	2 (1.2)	
CeraFlex	1 (0.3)	0 (0)	
Figulla Flex II	1 (0.3)	0 (0)	
PFOC device size (mm)	25.1 (3.7)	24.8 (4.5)	0.378
Sheath diameter (Fr)	9 (8–11)	10 (8–11)	0.114
Procedure success	323 (99.4)	169 (98.8)	0.512
Haemostasia			0.069
Manual compression	195 (60.2)	106 (62.0)	
Figure of eight suture	117 (36.1)	50 (29.2)	
Closure device	12 (3.7)	15 (8.9)	
Periprocedural complications			0.678
Vascular access	1 (0.43)	0 (0)	
Device embolisation	2 (0.85)	1 (0.82)	
Death	0 (0)	0 (0)	
Other	2* (0.85)	0 (0)	

*One case of air embolism and another case of periprocedural transient ischaemic attack.
DC, delayed closure; EC, early closure; Fr, French; ICE, intracardiac echocardiography; PFOC, patent foramen ovale closure; TOE, transoesophageal echocardiography.

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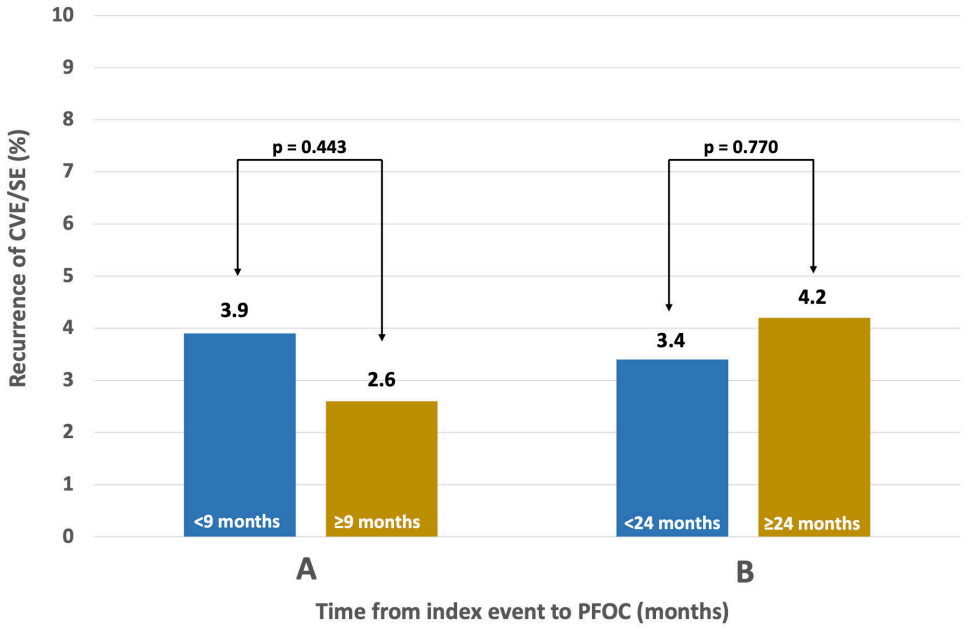

Figure 1 Incidence of recurrent episodes of CVE/SE according to PFOC timing. (A) Recurrent episodes of CVE/SE in patients undergoing PFOC<9 months and ≥9 months after the index event. (B) Recurrent episodes of CVE/SE in patients undergoing PFOC<24 months and ≥24 months after the index event. CVE, cerebrovascular event; PFOC, patent foramen ovale closure; SE, systemic embolism.

ischaemic attack (TIA). Patients with index events consisting of silent infarctions, defined as imaging evidence of central nervous system infarction in the absence of a history of acute neurological dysfunction attributable to the lesion,[14] were excluded due to the impossibility of determining the time elapsed from the event. Procedural success was defined as the successful implantation of a PFO closure device without any major complications (death, pericardial effusion or periprocedural CVE/SE).

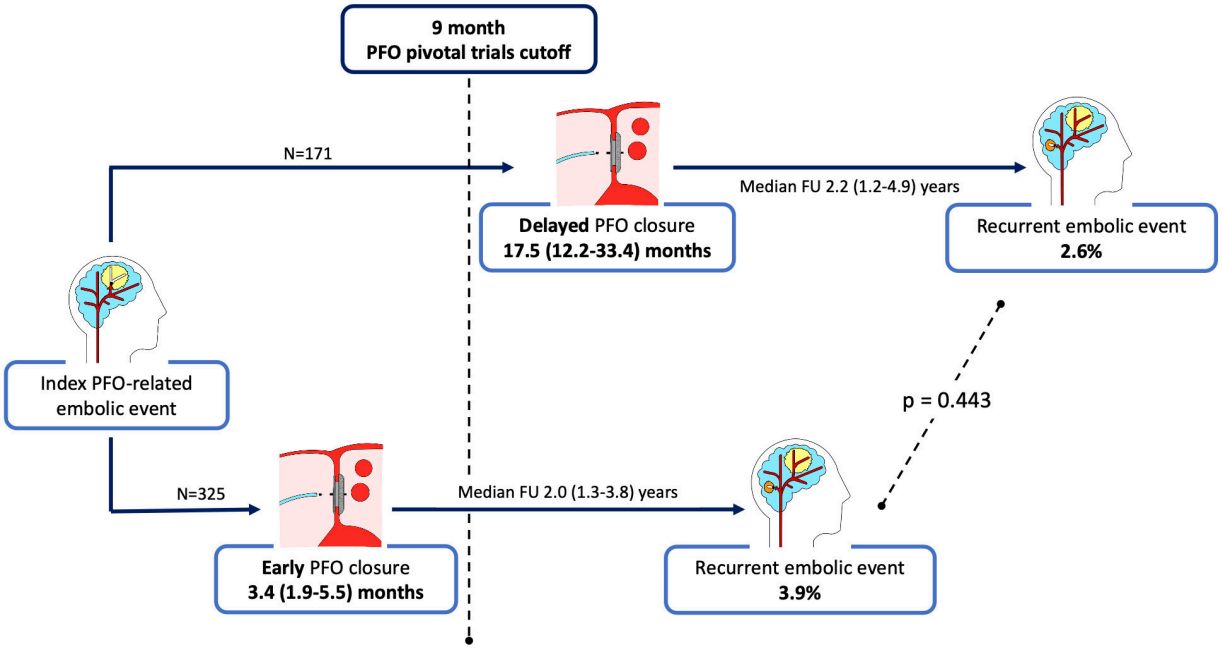

Figure 2 Visual overview of the study and primary endpoint results. A total of 496 patients were included. 325 (65.5%) were allocated to the EC group, with a median elapsed time from the index event to PFOC of 3.4 (1.9–5.5) months. 171 (34.5%) were assigned to the DC group, with a median delay time of 17.5 (12.2–33.4) months (p=0.001). Median follow-up after PFOC was 2.2 (1.2–4.9) years in the EC and 2.0 (1.3–3.8) years in the DC group (p=0.721). No differences were observed in cerebrovascular event/systemic embolism recurrence incidence, being 3.9% in the EC group and 2.6% in the DC group (p=0.443). DC, delayed closure; EC, early closure; FU: follow-up; PFOC, patent foramen ovale closure.

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Statistical analysis

The median and IQR or mean and SD were used to express quantitative variables. For continuous variables, the Shapiro-Wilk test and the Levene test were used to determine normality and equality of variances, respectively. The Mann-Whitney U test, Student's t-test or Fisher's exact test were then used, when applicable, to compare continuous variables. Categorical variables were reported using frequencies and percentages. All tests were two-sided, and p values<0.05 indicated statistical significance. The log-rank test was used to compare the incidence rate of recurrences following PFOC between groups. These data were presented as the number of incidents per 100 patient-years and percentages. Statistical analyses were performed using Stata/IC V.14.1 statistical software package (StataCorp, College Station, Texas, USA).

RESULTS

Baseline characteristics of the population

A total of 496 patients were included. 325 (65.5%) were allocated to the EC group, with a median elapsed time from the index event to PFOC of 3.4 (1.9–5.5) months. On the other hand, 171 (34.5%) were assigned to the DC group, with a median delay time of 17.5 (12.2–33.4) months (p=0.001). In both groups, ischaemic stroke was the most common type of event indicating PFOC, followed by TIA and SE. Patients from the DC group were significantly older at the moment of PFOC (54 (43–62) years vs 49 (40–57) years, p=0.001) and presented a higher prevalence of dyslipidaemia (35.1% vs 24.7%, p=0.015), with otherwise similar baseline characteristics. Roughly, one-fifth of the patients had a history of at least two or more episodes of CVE/SE in both groups (p=0.147) (online supplemental file 1). Baseline characteristics of both groups at the moment of PFOC are summarised in table 1.

Neurological presentation and neuroimaging data

Descriptive information on the neurological presentation and neuroimaging data is shown in table 2. No significant differences were observed concerning the debut clinical syndrome at the index event. However, a trend towards a higher prevalence of total anterior circulation infarction and a lower proportion of silent episodes was observed among the EC group. Likewise, shower and curtain patterns of transcranial Doppler were numerically more frequent in these patients (p=0.059), consistent with larger defects. Anatomic localisation of ischaemic lesions in neuroimaging was similar in both groups, as was the Risk of Paradoxical Embolism score (median 7 vs 6, p=0.077). National Institutes of Health Stroke Scale at admission was low overall but slightly higher in the EC closure (2 (1–2) vs 1 (0–5), p=0.042). Modified Rankin Scale (mRS) in both groups revealed that most index CVEs were non-disabling.

Table 4 Outcomes after PFOC and antithrombotic treatment regimen

	EC, <9 months (N=301)	DC, ≥9 months (N=162)	P value
Follow-up duration (years)	2.0 (1.3–3.8)	2.2 (1.2–4.9)	0.721
One-year post procedure follow-up			
Recurrence of CVE/SE	7 (2.5)	1 (0.6)	0.268
All-cause death	2* (0.75)	0 (0)	0.536
Antithrombotic treatment			0.454
None	14 (5.0)	7 (4.4)	
SAPT	222 (79.6)	128 (80.0)	
DAPT	17 (6.1)	6 (3.8)	
AC	25 (9.0)	16 (10.0)	
SAPT+AC	1 (0.4)	3 (1.9)	
Residual shunt	15 (5.9)	6 (4.1)	0.691
Longest follow-up available			
Recurrence of CVE/SE	11† (3.9)	4‡ (2.6)	0.443
Time from PFOC to recurrence (years)	0.9 (0.1–2.1)	6.1 (2.5–8.8)	0.090
New onset AF	6§ (2.4)	3§ (2.0)	0.418
PE/DVT	3 (1.5)	4 (3.8)	0.183
All-cause death	3 (1.5)	3 (1.9)	0.697
Antithrombotic treatment			0.116
None	21 (7.7)	9 (5.8)	
SAPT	214 (78.1)	124 (80.0)	
DAPT	17 (6.2)	4 (2.6)	
AC	19 (6.9)	18 (11.6)	
SAPT+AC	3 (1.1)	0 (0)	

*One case of PE and one case of cardiogenic shock after coronary artery bypass graft surgery.
†Five cases of stroke; five cases of TIA; one case of SE. Two of these patients had a second recurrence (one stroke and one TIA).
‡Two case of stroke; two cases of TIA.
§One case from the EC group and the three cases from DC permanently remained in AF after PFOC.
AC, anticoagulation; AF, atrial fibrillation; CVE/SE, cerebrovascular event or systemic embolism; DAPT, dual antiplatelet therapy; DC, delayed closure; DVT, deep vein thrombosis; EC, early closure ; PE, pulmonary embolism; PFOC, patent foramen ovale closure; SAPT, single antiplatelet therapy; SE, systemic embolism; TIA, transient ischaemic attack; TOE, transoesophageal echocardiography.

PFO imaging characteristics and procedural details

Patients from the DC group had a defect width significantly larger (12 (6–16) mm vs 6 (4–14) mm, p=0.005), but no differences were observed with respect to tunnel length nor the presence of an interatrial septal aneurysm. 4.5% of the patients within the EC group and 5.3% in the DC group presented ASD (p=0.749). All the procedures were performed through femoral venous access, and TOE guidance was used in over 80% of the cases. The most frequently used devices for PFOC were

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Table 5 PFOC outcomes for very remote CVE/SE

	<24 months (N=441)	≥24 months (N=55)	P value
Age	50 (41–58)	53 (42–63)	0.234
Female sex	180 (40.9)	25 (45.5)	0.416
Time from CVE/SE to PFOC (months)	4.7 (2.4–9.4)	55.0 (35.4–94.5)	0.001
RoPE score	2.0 (1.2–4.1)	2.6 (1.4–6.7)	0.235
One-year CVE/SE recurrence	8 (2.1)	0 (0)	0.300
Last available follow-up CVE/SE recurrence	13 (3.4)	2 (4.2)	0.770

CVE/SE, cerebrovascular event or systemic embolism; PFOC, patent foramen ovale closure; RoPE, Risk of Paradoxical Embolism.

Amplatzer (Abbott Vascular, USA) (75.1% vs 68.4%) and Gore Cardioform (Gore, USA) (17.9% vs 23.4%) in both groups. The procedure success rate was 99% in both groups, and very few periprocedural complications were reported, including device embolisation in two cases in the EC group and another in the DC group. More information regarding PFO anatomy and PFOC procedure is summarised in table 3.

Primary and secondary endpoints

Median follow-up after PFOC was 2.0 (1.2–4.2) years. No differences were observed in the primary endpoint, with a CVE/SE recurrence incidence of 3.9% in the EC group versus 2.6% in the DC group (p=0.443), resulting in rates of 1.2 versus 0.7 events per 100 patient-years (p=0.375) (figure 1A). At 1 year, there were also no differences, with recurrence rates of 2.5% EC group versus 0.6% DC group (p=0.268) (figure 2). Likewise, the presence of residual shunt at TOE performed 1 year after PFOC, the incidence of newly diagnosed AF and recurrences of DVT or PE during follow-up were similar. The antithrombotic treatment regimen was comparable in both groups (table 4).

Outcomes of PFOC in very remote CVE/SE

A subanalysis was performed to assess the yield of PFOC in secondary prevention for more remote episodes. 55 (11.1%) patients from the study population who underwent PFOC later than 24 months after their last event were identified (table 5). In comparison with PFOC in more recent episodes, no significant differences were observed in terms of CVE/SE recurrences during follow-up (4.2% vs 3.4%, p=0.770; 0.9 vs 1.1 events per 100 patients-years, p=0.952) (figure 1B).

DISCUSSION

The present study shows comparable recurrence rates of CVE/SE after PFOC, regardless the procedure was performed within the first 9 months from the index event or after. This finding suggests that a delayed indication of PFOC may not influence the expected outcomes in terms of secondary prevention. Additionally, no differences were found in the subanalysis comparing a longer delay (24 months) following the index event. As a unique aspect of the study, detailed information regarding neurological events before PFOC and during follow-up was included, showing that the clinical profile of the patients was roughly similar, with a trend towards larger defects in the delayed closure group.

PFO is found in up to 25% of the general population and might be associated with cryptogenic stroke due to paradoxical embolism.[15] Evidence for recommending PFOC followed by antithrombotic therapy over medical treatment alone in this clinical scenario is grounded on several RCT and meta-analysis enrolling patients who underwent the procedure within the first 6 or 9 months after the index CVE.[2–10] Thus, subsequent clinical practice guidelines and consensus documents on the matter emphasise that it is still unknown whether the preventive yield of PFOC is comparable in patients with a previous CVE more remote than the studies' temporal threshold.[11 12] Still, the Asian-Pacific expert statement remarks that PFOC later than 1 year after the index event may be considered in selected cases.[16]

Therefore, investigating whether the benefit of an early PFOC following a cryptogenic stroke may be extensible to more remote events becomes of capital relevance. Moreover, the use of arbitrary timing thresholds may have a role in the setting of an RCT but also might result in suboptimal treatment and exposure to an increased risk of recurrence, if literally translated to clinical practice.[13] In the absence of RCTs comparing delayed PFOC with medical therapy, a recent observational study by Guedeney *et al* assessed the outcomes of PFOC in over 1100 patients, according to the time elapsed from the index event.[17] After a median follow-up of 2.6 years, no differences were observed in terms of CVE recurrences (0.51 vs 0.29 events per 100 patients-years), in accordance with our results and those from the patients undergoing PFOC in the RESPECT study, with the longest temporal threshold for enrolment among pivotal trials (9 months).[10] In the study by Guedeney *et al*, the median closure timing of the DC group was 11.2 months (only 2 months later than the theoretical threshold of 9 months), and the difference in PFOC timing between both groups was only 8 months, differences which seem scarcely relevant from a clinical point of view. Conversely, the median delay in PFOC in our series differs in more than 14 months among groups, which may be more clinically meaningful. Moreover, we performed a subanalysis focusing on even more remote

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index events (≥24 months), which also did not find any differences in terms of recurrences of CVE/SE during follow-up.

Regarding baseline characteristics, some differences were observed. Patients were older in the DC group, possibly associated with a thorough AF screening that is recommended before indicating PFOC in older patients, resulting in a delay between the index event and the procedure. Besides, PFO size (tunnel width) was larger in the DC group (12 (6–16) vs 6 (4–14) mm, p=0.005). Regarding functional outcomes after the index event, the NIHHS score corresponded to minor strokes in both groups and median mRS revealed that most events were non-disabling, as previously reported in PFO-related CVE.[18 19] On the other hand, we cannot completely rule out the possibility that patients with poor functional outcomes after the index event might have been precluded from an interventional procedure and, therefore, would not be included in the study population. Finally, the higher proportion of partial anterior circulation infarct and posterior circulation infarction over total anterior circulation infarct found at index CVE was concordant with previously reported PFO-related stroke series.[19]

This study has some limitations inherent to observational studies. Regarding neurological information, the number of each specific neuroimaging test performed is not available. There was no core-laboratory evaluation of PFO anatomical features or neuroimaging. Loss of follow-up and under-reporting of events are possible in observational studies, although all selected hospitals have stroke clinics that keep follow-up of at least 1 year. Finally, our results should be considered hypothesis-generating due to their observational nature. However, a prospective RCT comparing delayed PFOC with medical therapy is unlikely to be performed, considering the recommendation of an early intervention following a cryptogenic stroke in the presence of PFO. Therefore, we believe this could impact clinical practice as complementary evidence to available clinical trials and other studies, supporting PFOC in more remote strokes.

To conclude, the recurrences of CVE/SE following PFOC for secondary prevention were similar, regardless of the time elapsed since the index event. In the absence of randomised evidence to confirm these findings, this study would support extending the recommendation of PFOC to patients with cryptogenic strokes more remote than 9 months.

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