Archives of Cardiovascular Disease (2019) 112, 532—542

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EXPERT CONSENSUS

Transcatheter closure of patent foramen ovale to prevent stroke recurrence in patients with otherwise unexplained ischaemic stroke: Expert consensus of the French Neurovascular Society and the French Society of Cardiology

Fermeture percutanée du foramen ovale perméable chez les patients ayant infarctus cérébral par ailleurs inexpliqué. Consensus d'experts de la Société Française Neuro-Vasculaire et de la Société Française de Cardiologie

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Abbreviations: AF, atrial fibrillation; ASA, atrial septal aneurysm; CI, confidence interval; HR, hazard ratio; PFO, patent foramen ovale; RCT, randomized clinical trial; RR, risk ratio.

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https://doi.org/10.1016/j.acvd.2019.06.002

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Received 6 June 2019; accepted 12 June 2019
Available online 1 August 2019

KEYWORDS
Ischaemic stroke;
Patent foramen ovale;
Atrial septal aneurysm ;Prevention;
Randomized clinical trial

Summary
Background. — Unlike previous randomized clinical trials (RCTs), recent trials and meta-analyses have shown that transcatheter closure of patent foramen ovale (PFO) reduces stroke recurrence risk in young and middle-aged adults with an otherwise unexplained PFO-associated ischaemic stroke.
Aim. — To produce an expert consensus on the role of transcatheter PFO closure and antithrombotic drugs for secondary stroke prevention in patients with PFO-associated ischaemic stroke.
Methods. — Five neurologists and five cardiologists with extensive experience in the relevant field were nominated by the French Neurovascular Society and the French Society of Cardiology to make recommendations based on evidence from RCTs and meta-analyses.
Results. — The experts recommend that any decision concerning treatment of patients with PFO-associated ischaemic stroke should be taken after neurological and cardiological evaluation, bringing together the necessary neurovascular, echocardiography and interventional cardiology expertise. Transcatheter PFO closure is recommended in patients fulfilling all the following criteria: age 16—60 years; recent ($\leq$ 6 months) ischaemic stroke; PFO associated with atrial septal aneurysm (> 10 mm) or with a right-to-left shunt > 20 microbubbles or with a diameter $\geq$ 2 mm; PFO felt to be the most likely cause of stroke after thorough aetiological evaluation by a stroke specialist. Long-term oral anticoagulation may be considered in the event of contraindication to or patient refusal of PFO closure, in the absence of a high bleeding risk. After PFO closure, dual anti-platelet therapy with aspirin (75 mg/day) and clopidogrel (75 mg/day) is recommended for 3 months, followed by monotherapy with aspirin or clopidogrel for $\geq$ 5 years.
Conclusions. — Although a big step forward that will benefit many patients has been taken with recent trials, many questions remain unanswered. Pending results from further studies, decision-making regarding management of patients with PFO-associated ischaemic stroke should be based on a close coordination between neurologists/stroke specialists and cardiologists.

MOTS CLÉS
Infarctus cérébral ;
Foramen ovale perméable ;
Anévrisme du septum inter-auriculaire ;
Prévention ;
Essai contrôlé randomisé

Résumé
Contexte. — Contrastant avec les premiers essais randomisés, des essais récents et leurs méta-analyses ont montré que la fermeture d'un FOP par voie endovasculaire réduit le risque de récidive d'infarctus cérébral chez les adultes jeunes ou d'âge moyen ayant un infarctus cérébral par ailleurs inexpliqué.
Objectif. — Élaborer un consensus d'experts sur le rôle de la fermeture percutanée du FOP et des medicaments antithrombotiques en prévention des récidives d'AVC chez les patients ayant un infartcus cérébral associé à un FOP.
Methods. — Cinq neurologues et 5 cardiologues expérimentés ont été nommés par la Société Française NeuroVasculaire et la Société Française de Cardiologie pour faire des recommandations basées sur les résultats des essais cliniques randomisés et de leurs méta-analyses.
Résultats. — Toute décision concernant le traitement des patients ayant un infarctus cérébral associé à un FOP doit être prise après une évaluation neurologique et cardiologique, réunissant les compétences nécessaires: neurovasculaire, échocardiographie et cardiologie interventionnelle. La fermeture du FOP par voie endovasculaire est recommandée chez les patients

répondant à tous les critères suivants: âge entre 16 et 60 ans; infarctus cérébral récent (≤ 6 mois); FOP associé à un anévrysme du septum interauriculaire (> 10 mm) ou à un FOP avec shunt droit-gauche > 20 microbulles ou diamètre > 2 mm; le FOP est la cause la plus probable de l'infarctus cérébral après un bilan étiologique par un spécialiste neurovasculaire. Une anticoagulation orale au long cours peut être envisagée en cas de contre-indication à, ou de refus de fermeture du FOP par le patient, en l'absence de risque hémorragique élevé. Après la fermeture du FOP, une bithérapie par aspirine (75 mg/jour) et clopidogrel (75 mg/jour) est recommandée pendant 3 mois, suivie d'une monothérapie par aspirine ou clopidogrel pendant au moins 5 ans.
Conclusions. — Bien que les essais thérapeutiques récents soient une avancée thérapeutique pour de nombreux patients, de nombreuses questions restent à résoudre. En attendant les résultats de nouvelles études, les décisions concernant le traitement des patients ayant un infarctus cérébral associé à un FOP doit être le fruit d'une collaboration étroite entre neurologues et cardiologues.

Patent foramen ovale (PFO), a remnant of the foetal circulation, is found in about 25% of the adult population; it maintains an interatrial channel through which blood may shunt from the right atrium to the left atrium. Starting in the late 20th century, several case-control studies have consistently reported that PFO is significantly associated with cryptogenic stroke, particularly in young and middle-aged patients, in those with a low burden of traditional risk factors, and in those who have an atrial septal aneurysm (ASA) in addition to a PFO or a PFO with a substantial right-to-left shunt or diameter. The association between PFO and cryptogenic stroke suggested that septal defect might account for a significant proportion of cryptogenic ischaemic strokes, which represent up to 40% of all ischaemic strokes, and that closure of the PFO could prevent stroke recurrence in these patients. Transcatheter PFO closure was introduced in the 1990s, but its effectiveness in the prevention of stroke recurrence was a very controversial issue until the recent publication of new randomized trials showing the benefit of this procedure and providing the first firm evidence to guide treatment.

Methods

The boards of the French Neurovascular Society and the French Society of Cardiology nominated five neurologists and five cardiologists with extensive experience in the relevant field to produce an expert consensus on the role of transcatheter PFO closure and antithrombotic drugs for secondary stroke prevention in patients with PFO-associated ischaemic stroke. Recommendations were based on the evidence from randomized clinical trials (RCTs) and their meta-analyses. Groups of authors wrote the text sections and the recommendations. The document was reviewed and corrected until approval by all experts (five iterations). The document was approved by the boards of the French Neurovascular Society and the French Society of Cardiology.

What is the evidence for PFO closure

Six RCTs [1—7] have compared transcatheter PFO closure with antithrombotic therapy to prevent stroke recurrence in adult patients aged up to 60 years (mean age of about 45 years) with a PFO and a recent (< 6 months in most trials) otherwise unexplained ischaemic stroke (Table 1). One trial [3] enrolled patients aged up to 80 years, but a minority of patients were older than 60 years, and the mean age was 51.8 years. One trial [2] also enrolled patients with transient ischaemic attack. In four trials [1,2,5—7] patients with any type of PFO were eligible, while in two trials [3,4] only patients with both a PFO and an ASA or a large PFO (without ASA) could be enrolled. In four trials [1—3,5,6], PFO closure followed by antithrombotic (mainly antiplatelet) therapy was compared with a control group of patients treated with antiplatelet or anticoagulant agents according to physician preference, whereas in two trials [4,7] PFO closure followed by antiplatelet therapy was compared with antiplatelet therapy only.

Benefit of PFO closure

In contrast to the first negative RCTs (CLOSURE1 [2], PC [5] and RESPECT [1]) published in 2012 and 2013, three new trials (CLOSE [4], REDUCE [7] and DEFENSE-PFO [3]) and the extended follow-up of RESPECT [6] clearly showed that PFO closure reduces the risk of recurrent stroke in young or middle-aged adults with an otherwise unexplained ischaemic stroke (Table 1). Several reasons may explain the differences in results between trials. First, stricter definitions of cryptogenic stroke were used in recent trials. In addition, CLOSE [4] and DEFENSE-PFO [3] only involved patients who had a PFO with an associated ASA or a PFO with large shunt. These features have been shown to be associated with an increased likelihood that a cryptogenic stroke is related to a PFO. Second, CLOSE [4] and REDUCE [7] compared PFO closure followed by long-term antiplatelet therapy with antiplatelet therapy alone. In contrast, the

Table 1 Summary of the design and results of randomized clinical trials comparing transcatheter patent foramen ovale closure with antithrombotic treatment in patients with an otherwise unexplained ischaemic stroke.

RCT	*n*	Age range; mean (years)	Stroke characteristics; Rankin score; time from stroke to inclusion; PFO characteristics	Comparison	Mean FU (years)	Recurrent stroke (*n*); HR (95% CI); *P*
CLOSURE 1 (2012)	909	18—60; 46.0	IS or TIA; Rankin < 3; < 6 months; unselected PFO (small [1—10 mb], 47.1%; moderate [10—25 mb] or large [> 25 mb], 52.9%)	PFO closure[a] versus antithrombic treatment[b]	2	12 vs 13; 0.90 (0.41—1.98); *P* = 0.79
PC trial (2013)	414	< 60; 44.5	IS; Rankin < 3; median 4.4 months; unselected PFO (small [1—5 mb], 34.4%; moderate [6—20 mb], 43.9%; large [> 20 mb], 21.7%)	PFO closure[a] versus antithrombic treatment[b]	4.1	1 vs 5; 0.20 (0.02—1.72); *P* = 0.14
RESPECT (2013, 2017)	980	18—60; 45.9	IS; Rankin < 3; < 9 months; unselected PFO (small [1—9 mb], 22.7%; moderate [10—20 mb], 26.4%; large [> 20 mb], 48.8%)	PFO closure[a] versus antithrombic treatment[b]	2.1/5.9	9 vs 16; 0.49 (0.22—1.11); *P* = 0.08 18 vs 28; 0.55 (0.31—0.999); *P* = 0.046
CLOSE (2017)	663	16—60; 43.4	IS; Rankin ≤ 3; < 6 months; PFO + ASA (> 10 mm) or PFO > 30 mb	PFO closure[a] versus antiplatelet treatment[c]	5.3	0 vs 14; 0.03 (0.00—0.26); *P* < 0.001
REDUCE (2017)	664	18—60; 45.2	IS; Rankin < 3; < 6 months; unselected PFO (small [1—5 mb], 19%; moderate [6—25 mb)], 40%; large [> 25 mb], 41%)	PFO closure[a] versus antiplatelet treatment[c]	3.2	6 vs 12; 0.23 (0.09—0.62); *P* = 0.002
DEFENSE-PFO (2018)	120	18—80; 51.8	IS; Rankin ≤ 3; < 6 months; PFO + ASA (≥ 10 mm) or PFO ≥ 2 mm	PFO closure[a] versus antithrombotic treatment[b]	2.8	0 vs 6; log-rank *P* = 0.013

ASA: atrial septal aneurysm; CI: confidence interval; FU: follow-up; HR: hazard ratio; IS: ischaemic stroke; mb: microbubbles; *n*: number of patients; PFO: patent foramen ovale; RCT: randomized controlled trial; TIA: transient ischaemic attack.

[a] The following antithrombotic treatments were recommended in patients treated with PFO closure: CLOSURE 1: clopidogrel (75 mg) for 6 months and aspirin (81—325 mg) for 2 years; PC trial: aspirin (100—325 mg) for at least 5—6 months and ticlopidine (250—500 mg) or clopidogrel (75—100 mg) for 1—6 months; RESPECT: clopidogrel for 1 month and aspirin for 6 months, then antiplatelet therapy at the discretion of the investigator; REDUCE: clopidogrel 300 mg before or after the intervention, then clopidogrel 75 mg for 3 days, then antiplatelet therapy up to the end of the study; CLOSE: clopidogrel and aspirin for 3 months, then antiplatelet therapy up to the end of the study; DEFENSE-PFO: clopidogrel and aspirin for at least 6 months, then antiplatelet therapy or anticoagulant therapy at the discretion of the investigator.

[b] Patients randomized into the medical group were treated with antiplatelet drugs or oral anticoagulants at the discretion of the investigator in charge of the patient up to the end of the study.

[c] Patients randomized into the antiplatelet group were treated with antiplatelet drugs up to the end of the study.

reference treatment group used in previous trials included patients who received either antiplatelet drugs or oral anticoagulants according to physician preference. This may have confounded trial results if oral anticoagulants and antiplatelet drugs have different impacts on the risk of stroke recurrence.

A meta-analysis [8] of these trials (3560 patients from six RCTs) showed that PFO closure was associated with a 64% lower risk of recurrent stroke (risk ratio [RR] 0.36, 95% confidence interval [CI] 0.17—0.79) compared with antithrombotic therapy (antiplatelet therapy or anticoagulation) (Fig. 1). The benefit was greater when PFO closure was compared with antiplatelet therapy than with antithrombotic therapy, suggesting that anticoagulants may be superior to antiplatelet therapy in reducing stroke recurrence. The magnitude of the benefit conferred by PFO closure was moderate overall, at 1% per year, from 1.27 per 100 person-years (95% CI 0.84—1.78) on antithrombotic treatment to 0.29 per 100 person-years (95% CI 0.02—0.76) after PFO closure. However, even a modest reduction in annual stroke recurrence rate is clinically meaningful in young adults who otherwise would be at risk of stroke recurrence for a long period of time. In the two trials with the longest follow-up [4,6], the Kaplan-Meier curve for the antithrombotic therapy group did not suggest a decline in the rate of recurrent stroke over time, at least for the first 5—10 years, and there is no reason to believe that this benefit will not persist.

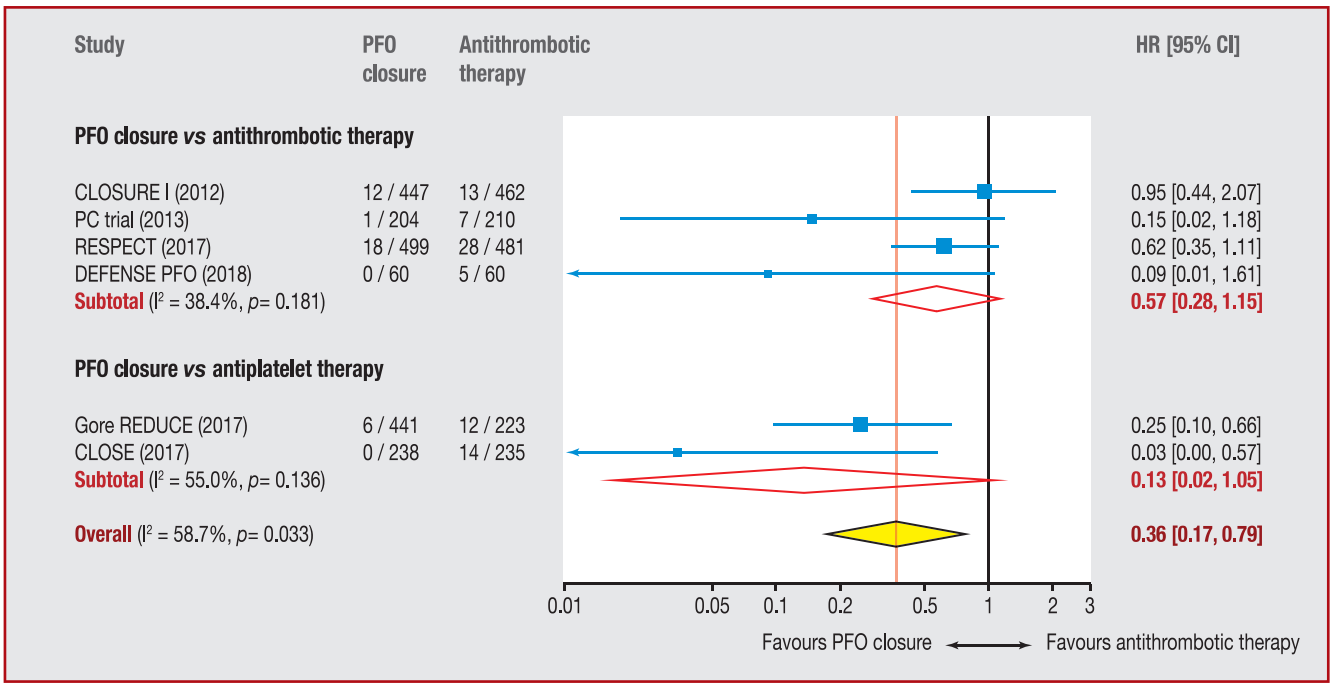

Figure 1. Pooled risk ratio (RR) of recurrent stroke in patients randomized to patent foramen ovale (PFO) closure versus antithrombotic therapy (random-effects meta-analysis) [8]. CI: confidence interval.

Risks associated with PFO closure

New-onset atrial fibrillation (AF) (irrespective of its duration) was present in 93 of 1844 patients randomized to PFO closure versus 17 of 1667 patients randomized to antithrombotic therapy (RR 4.33, 95% CI 2.37—7.89; $P < 0.001$). The pooled incidence of new-onset AF per 100 patients treated was 4.56 (95% CI 3.58—5.63) [8]. Most cases of AF occurred within 1 month of the procedure, were reported to be transient and did not seem to recur during follow-up. AF was reported to be persistent in about one-third of cases. Some cases of AF may be related to paroxysmal AF undiagnosed before the qualifying stroke, as new-onset AF also occurred in about 1% of patients allocated to medical therapy alone. Altogether, of the 93 patients who had new-onset AF after PFO closure, five had a recurrent stroke. The pooled incidence of new-onset AF per 100 patients treated with nitinol double disk devices was 3.65 (95% CI 2.48—5.01), compared with 5.61 (95% CI 4.11—7.29) for patients treated with other devices ($P = 0.02$) [8]. Although most cases of AF occurring after PFO closure have been without major consequences, their determinants and prognosis need to be clarified by further studies.

Other device- or procedure-related serious adverse events were reported in about 3% of patients, including vascular access site complications, thrombus formation on the device, pericardial effusion with tamponade, cardiac perforation, device dislocation, infective endocarditis and air embolism [1—7]. Although these complications may have serious consequences, none resulted in death or reportedly permanent disability. Mortality did not differ between groups: 13 deaths among 1844 patients randomized to PFO closure versus 15 among 1667 patients randomized to antithrombotic therapy (RR 0.79, 95% CI 0.39—1.60; $P = 0.51$). Major bleeding occurred in 34 of 1820 patients randomized to PFO closure versus 28 of 1583 patients randomized to antithrombotic therapy (RR 0.97, 95% CI 0.43—2.20; $P = 0.94$) [8]. All trials reported no difference between groups in serious adverse events.

Which patients benefit most from PFO closure?

''High-risk'' PFO

Because PFO is a common finding in the general population, it may coexist by chance alone in about 30% of patients with cryptogenic stroke [9]. Therefore, selecting patients with clinical characteristics that increase the probability that PFO is causally related to the index stroke could enhance the benefits of PFO closure. In this respect, several studies have shown that PFOs with a large shunt or large diameter and those associated with an ASA (so-called ''high-risk'' PFO) are more strongly associated with cryptogenic stroke than PFOs without these features, and are therefore more likely to be causally related to the index stroke than an incidental finding [4]. In the RESPECT trial [1], subgroup analyses suggested a much greater effect of PFO closure in patients with an ASA or a substantial shunt size than in those with neither a large shunt nor an ASA. In line with RESPECT [6], our meta-analysis of RCTs [8] suggests that patients who have a PFO with an ASA or a large PFO (without an ASA) benefit more from PFO closure (RR 0.27, 95% CI 0.11—0.70) than patients without those features (RR 0.80, 95% CI 0.43—1.47) (Fig. 2) [8,10]. It is interesting to note that no recurrent stroke was observed after PFO closure in CLOSE [4] and DEFENSE-PFO [3], which enrolled only patients with ''high-risk'' PFOs, whereas recurrent strokes were common despite PFO closure, although at a lower rate,

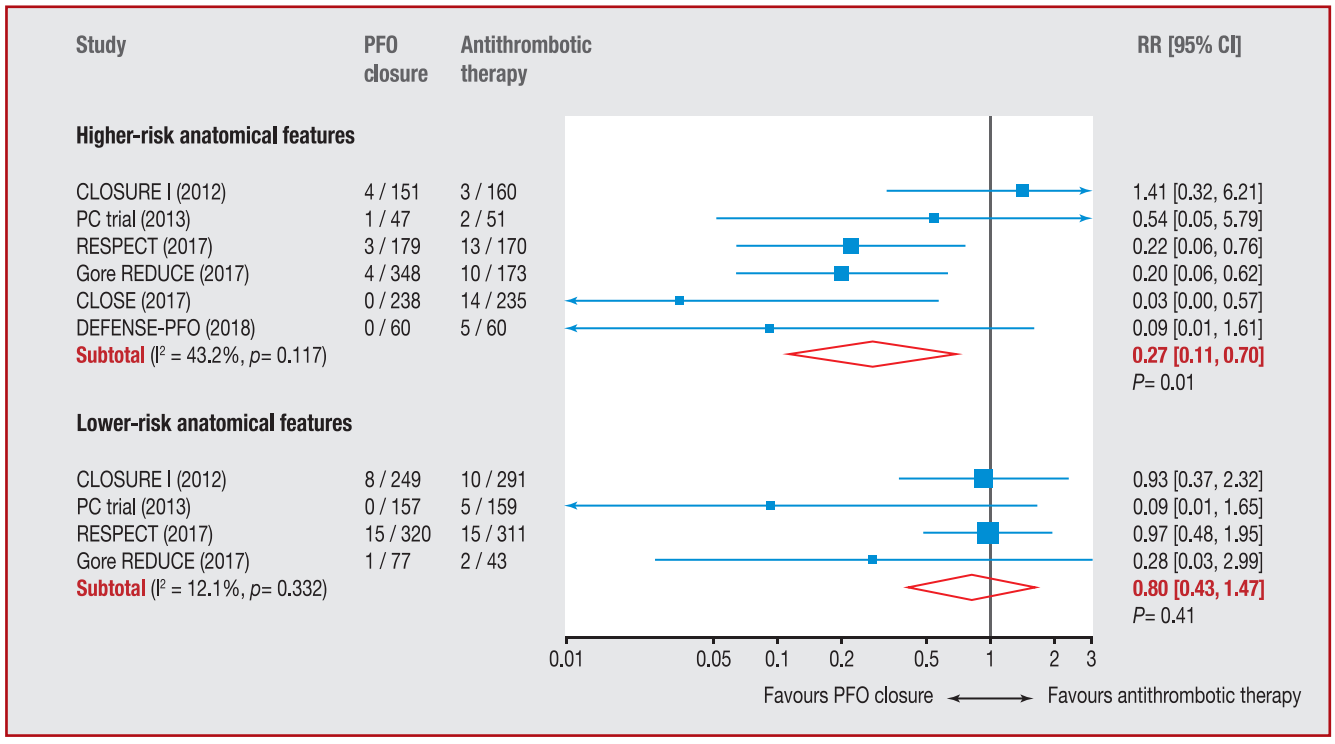

Figure 2. Pooled risk ratio (RR) of recurrent stroke in patients randomized to patent foramen ovale (PFO) closure versus antithrombotic therapy, according to PFO anatomical features (random-effects meta-analysis) [8]. For the present meta-analysis, we defined higher-risk anatomical features as follows: for CLOSURE I, PC trial and RESPECT: presence of an atrial septal aneurysm (ASA), regardless of shunt size; for CLOSE and DEFENSE-PFO: presence of an ASA and/or a large shunt (i.e. all included patients); for Gore REDUCE: moderate or large shunt (note that the presence or absence of ASA could not be analysed because it was not recorded in patients randomized to the antiplatelet group). The numbers of recurrent strokes in each group were extracted from the original publications of the randomized trials or calculated using published data by Kent et al. [10]. CI: confidence interval.

in trials that enrolled patients with unselected PFOs, suggesting that these anatomical features may be helpful in selecting those patients with PFO-associated stroke who are more likely to benefit from closure.

Data from the CLOSE trial [4] suggests that patients with both a PFO and an ASA might benefit more from PFO closure than patients with a large shunt only. Indeed, in this trial, the absolute rate of recurrent stroke in the antiplatelet-only group was about four times higher in patients with both a PFO and an ASA than in those with a PFO with a large shunt (but no ASA). Interestingly, in the DEFENSE-PFO trial [3], four of the five recurrent strokes occurred in patients with both a PFO and an ASA. These findings are consistent with the PFO-ASA study [11], a large prospective observational study of 581 patients with cryptogenic stroke, in which patients with both PFO and ASA had a 4-times higher risk of stroke recurrence on aspirin than patients with PFO alone, whatever the degree of shunting.

RoPE score

The RoPE score [12] was developed to assess the probability that a PFO discovered in the setting of a cryptogenic stroke is related to stroke (versus incidental), based on clinical characteristics. In brief, the younger the patient and the smaller the number of traditional risk factors, the higher the score and the probability that the PFO is related to stroke. However, this study showed that the higher the score the lower the risk of stroke recurrence. Therefore, the RoPE score alone may not be appropriate to select the patients that benefit most from PFO closure.

What is the evidence for oral anticoagulants?

CLOSE [4] was the only trial in which patients were randomized to PFO closure, oral anticoagulation or antiplatelet therapy. Among 187 patients allocated to oral anticoagulants, three had a recurrent stroke versus seven among 174 allocated to antiplatelet therapy, a non-significant 56% (95% CI 0.11—1.48) reduction in the risk of recurrent stroke (hazard ratio [HR] 0.44, 95% CI 0.11—1.48) in patients allocated to oral anticoagulants. However, as many patients (n = 129) had contraindications to anticoagulants, the comparison was underpowered. In a small single-centre study [13], five among 21 patients allocated to warfarin had a recurrent stroke or transient ischaemic attack versus two among 23 patients allocated to aspirin (HR 0.33, 95% CI 0.06—1.7). Information on stroke alone was not provided.

A pooled analysis of patients included in CLOSE and patients with a PFO included in three trials comparing oral anticoagulants with antiplatelets (including two recent trials testing non-vitamin K antagonist oral anticoagulants) in patients with cryptogenic stroke [14—16], showed a non-significant trend favouring anticoagulation over antiplatelet

therapy for prevention of recurrent ischaemic stroke (3.8% vs 5.8%; odds ratio 0.68, 95% CI 0.42—1.11; $P = 0.12$), with no evidence of heterogeneity ($I^2 = 0\%$).

No conclusion can be drawn from the comparison of oral anticoagulants with PFO closure in CLOSE (not planned in the statistical analysis); three of the 180 patients allocated to oral anticoagulants had a recurrent stroke versus none of the 173 patients allocated to PFO closure (HR 0.14, 95% CI 0.00—1.45).

Expert consensus

Brain and heart team

The working group recommends that any decision concerning the treatment of patients with PFO-associated ischaemic stroke should be taken after a neurological and cardiological evaluation, bringing together the necessary expertise: neurovascular, echocardiography and interventional cardiology.

The neurologist is responsible for confirming the diagnosis of ischaemic stroke most likely attributable to a PFO, making sure that the diagnostic and aetiological workup has been in conformity with the standards in force. The neurologist will specify whether the characteristics of the infarct are compatible with an embolic mechanism, and if the patient has a history of recurrent ischaemic stroke.

The echocardiographer is responsible for confirming: (1) the diagnosis of PFO and ASA according to the recommendations in this document; and (2) the absence of another potential cardiac or aortic source of cerebral embolism.

The interventional cardiologist judges the feasibility and risks of the intervention, and ensures that the intervention will be carried out according to the recommendations in this document.

The patient is informed precisely of the risks and benefits (in terms of absolute risk and relative risk of recurrence) incurred according to different therapeutic strategies, and is engaged in shared decision making.

This multidisciplinary meeting gives rise to a report validated by all the participants, and distributed to the patient's referring doctors.

PFO closure

Transcatheter PFO closure is recommended in patients fulfilling all the following criteria:

- age 16—60 years
- recent ($\leq$ 6 months) ischaemic stroke (although this delay can be extended if prolonged detection of AF is necessary);
- PFO associated with an ASA (> 10 mm) or with a right-to-left shunt > 20 microbubbles (a large shunt was defined in RCTs by the passage of > 20, 25 or 30 microbubbles) or a diameter $\geq$ 2 mm;
- PFO felt to be the most likely cause of the stroke after a thorough aetiological evaluation by a stroke specialist (see Tables A1, A2 and A3).

The closure of the PFO must be performed in a centre with expertise in structural interventional cardiology (Table A4), as soon as the patient's neurological state allows it.

Patients not fulfilling all of the above criteria

The therapeutic decision must be made in a patient clearly informed of the uncertainties or lack of scientific evidence regarding the benefit of PFO closure in their case, and of the existence of other therapeutic options. This concerns patients with one of more of the following characteristics or conditions: age > 60 years; transient ischaemic attack; ischaemic stroke dating back > 6 months; asymptomatic cerebral infarct on neuroimaging; disabling stroke (Rankin $\geq$ 3); alternative cause of ischaemic stroke; PFO $\leq$ 20 microbubbles (without an ASA); patient requiring long-term anticoagulant therapy for another reason; pregnant woman.

The therapeutic decision must take into account the following arguments to assess the probability of a causal relationship between PFO and the patient's cerebral ischaemic event:

- PFO characteristics: PFO with ASA, PFO > 20 microbubbles or $\geq$ 2 mm, Chiari's network, Eustachian valve;
- patient's characteristics: age, burden of traditional stroke risk factors (e.g. hypertension, diabetes, smoking), RoPE score;
- stroke characteristics: brain imaging consistent with an embolic infarct; transient ischaemic attack confirmed by a stroke neurologist, after consultation with another stroke neurologist if in doubt, absence of an alternative cause of ischaemic stroke associated with high risk of stroke, recurrent ischaemic stroke on antithrombotic therapy; and
- features suggesting paradoxical embolism: concurrent venous thrombotic event (within 48—72 hours of stroke onset), circumstances promoting venous thrombotic event (recent immobility [prolonged travel, etc.], history of venous thrombotic event, venous hypercoagulable state), stroke onset coincident with a Valsalva manoeuvre (heavy lifting, straining at stool, etc.) or permanently increased right-to-left pressure gradient (chronic arterial pulmonary hypertension).

Oral anticoagulants

Vitamin K antagonists seem to be more effective than antiplatelet agents in preventing stroke recurrence in patients with PFO, although their superiority has not been formally established by therapeutic trials; their effectiveness compared with PFO closure is not known. Current data suggest that the difference in efficacy between the two treatments might be small.

Anticoagulant therapy is recommended in case of concomitant venous thromboembolism. The duration of this treatment depends on the context of occurrence and the factors favouring recurrence (see recommendations on the duration of anticoagulant treatment after venous thrombosis or pulmonary embolism).

Long-term oral anticoagulation with vitamin K antagonists may be considered in the event of a contraindication to or patient refusal of PFO closure, in the absence of a high risk of bleeding. There are no data on non-vitamin K antagonist oral anticoagulants in this indication.

Oral anticoagulant therapy may also be considered to prevent early recurrences while awaiting PFO closure, especially in patients with both PFO and ASA, but the superiority of anticoagulants over antiplatelet agents is not known.

Antiplatelet therapy

Dual antiplatelet therapy with aspirin (75 mg/day) and clopidogrel (75 mg/day) is recommended for 3 months, followed by long-term single therapy with one of these drugs. The duration of this treatment is not known. Pending further data, we recommend a duration of at least 5 years.

Antiplatelet therapy is recommended if there is no indication for PFO closure or anticoagulant therapy.

Conclusions

Although a big step forward that will benefit many patients has been taken with recent trials, the story has not come to an end, and many new and old questions remain unanswered, including—but not restricted to—those summarized in Table A5 [17]. Pending results from further studies, decision-making regarding management of patients with PFO-associated ischaemic stroke should be based on close coordination between neurologists/stroke specialists and cardiologists.

Sources of funding

None.

Appendix A

Table A1 Aetiological work-up in young and middle-aged adults (aged ≤ 60 years); to be performed by clinicians with stroke and cardiovascular expertise.

Standard evaluation
Brain MRI (DWI, FLAIR, T2* gradient echo sequences) or brain CT scan if MRI not possible
Extracranial and intracranial arterial imaging: cervical ultrasound and transcranial Doppler AND magnetic resonance angiography of cervical and Willis circle arteries (including axial cervical slices on T1 fat-suppression sequences) OR CT angiography assessing extracranial and intracranial arteries
Biological tests: complete blood count, glycaemia, blood electrolytes, creatinine clearance, CRP, lipids, proteinuria, prothrombin time, activated thromboplastin time, fibrinogen, troponin, ASAT, ALAT, gamma GT
ECG, ECG monitoring during stroke unit stay, Holter ECG (see also Table A2)
TTE with contrast, TOE with contrast (if no major cardiac embolic source has been detected)
Transcranial Doppler (with bubble study) may be used as a screening tool for detection and quantification of right-left shunts
Other tests to be performed on a case-by-case basis[a]
Search for toxic abuse (cannabis, cocaine, amphetamine, etc.)
Antiphospholipid syndrome: anticardiolipin antibodies, lupus anticoagulant and anti β2-GP1 antibodies (with sequential assessment)
Homocysteinaemia
Haemopathies (e.g. sickle cell disease): haemoglobin electrophoresis, etc.
If a neoplasm is suspected: thoracic and abdominal CT scans, etc.
Infectious vasculitis (viral, bacterial or fungal infections), inflammatory vasculitis (e.g. central nervous system primary vasculitis, systemic disease vasculitis, Susac's syndrome) or non-inflammatory angiopathies (e.g. Moya-Moya disease): CSF examination, conventional cerebral angiography, ophthalmological examination, leptomeningeal/cerebral biopsy, temporal artery biopsy, etc.
Genetic diseases (e.g. Fabry disease, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy [CADASIL], etc.): enzymatic diagnosis, search for genetic mutation, etc.
Paradoxical embolism: search for deep vein thrombosis, pulmonary fistula, deficit of coagulation factors (protein C, protein S, antithrombin, factor V Leiden mutation, factor II mutation)

ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase; CRP: C-reactive protein; CSF: cerebrospinal fluid; CT: computed tomography; DWI: diffusion-weighted imaging; ECG: electrocardiogram; FLAIR: fluid-attenuated inversion recovery; GP: glycoprotein; GT: glutamyltransferase; MRI: magnetic resonance imaging; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography.

[a] Depending on anamnestic information and results of the initial work-up.

Table A2 Detection of paroxysmal atrial fibrillation in patients aged ≤ 60 years with ischaemic stroke.

Definition of AF
AF is defined as irregular RR intervals without any well individualized P-wave on a surface ECG or an implantable loop recorder (duration > 30 seconds)
Both continuous (conventional Holter ECG, currently with a duration of up to 21 days) or sequential (implantable or external) recording may be helpful to identify AF
The longer the duration of monitoring, the higher its diagnostic yield
Recommendations
12-lead ECG and telemetric monitoring in a neurovascular intensive care unit in the acute phase of ischaemic stroke and Holter ECG should be performed systematically performed
Implantation of an event recorder should be proposed for at least 6 months to patients aged < 60 years who have at least two risk factors for developing AF (see below), before deciding whether to close a PFO
This subcutaneous monitoring system (able to identify AF episodes ≥ 2 minutes) should be implanted without delay after discharge from neurology
Risk factors for developing AF
Congestive heart failure, underlying heart disease
Documented atrial hyperexcitability
Uncontrolled hypertension, uncontrolled diabetes, obesity
Chronic respiratory failure
Thyroid gland disease

AF: atrial fibrillation; ECG: electrocardiogram; PFO: patent foramen ovale.

Table A3 Echocardiographic assessment of cardiac sources of ischaemic stroke.

Technique
Both TTE and TOE, using cineloop, colour Doppler and contrast injection, should be performed in experienced centres to assess all potential cardiac sources of embolism
The interatrial septum and the amount of interatrial shunt should be assessed using multiple echocardiographic views, both at baseline and after provocative manoeuvres
Provocative manoeuvres (Valsalva and cough) should be explained to the patient before starting echocardiography
Numeric recording of the totality of the echocardiographic studies should be performed
Definitions
PFO is considered to be present when more than three bubbles are identified in the left atrium in the first 3—5 cardiac cycles following right atrial opacification
Shunt size: minimal (< 10 mb); moderate (10—20 mb); severe (> 20 mb)
Large PFO: height (maximum separation of the septum primum from the septum secundum) ≥ 2 mm on TOE
Atrial septal aneurysm is defined as an excursion > 10 mm of the dilated segment of the septum beyond the level surface of the atrial septum

PFO: patent foramen ovale; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography.

Table A4 Patent foramen ovale closure technique.

Environment
PFO closure should be performed in centres with expertise in structural heart interventions, a cardiac intensive care unit on-site and cardiac surgery in close proximity
Operators are considered autonomous for PFO closure after 20 procedures with at least 10 devices of the same type
Once trained, operators should perform a minimum of 10 procedures per year
Contraindications
Thrombosis of the inferior vena cava
Allergy to nickel or titanium
Procedure
The procedure may be performed under general anaesthesia with TOE or under local anaesthesia with intracardiac echocardiography; TTE alone is not optimal but can be used in experienced centres
Pretreatment with dual antiplatelet therapy by aspirin (81—325 mg) and clopidogrel (75 mg) or with a loading dose of 300 mg of clopidogrel the day before the procedure; discontinue anticoagulant therapy before the procedure
Implement endocarditis prophylaxis
Use the femoral venous approach followed by immediate heparin administration (70—100 IU/kg, ACT $\geq$ 250 seconds)
Perform implantation under fluoroscopic and echocardiographic guidance
Measure right pressures to ensure they are normal
Cross the defect either with the guidewire or, most often, with the aid of a multipurpose 5F catheter
Place a guidewire in the upper left pulmonary vein
Advance the delivery system
Slowly withdraw the dilator to avoid air suction (aspiration effect)
Carefully flush the catheter
Cross the septum
Insert the device into the catheter, taking care to avoid entry of any air or bubbles, and flush again carefully
Advance the device to implantation site and deploy
Verify stability of the device with carefully push and pull manoeuvres
Release the device after echocardiographic control of the device position, specifically with regard to surrounding structures
Patients can be discharged on the day after the procedure after control TTE to ensure correct device placement and absence of pericardial effusion or thrombosis of the device
Follow-up
Dual antiplatelet therapy for 3 months followed by aspirin alone for at least 5 years
Clinical examination, 12-lead ECG and contrast TTE should be performed at 1 and 12 months
TOE should be performed if displacement or thrombosis of the device is suspected on TTE, or if there is a suspicion of endocarditis, recurrent stroke or TIA

ACT: activated clotting time; PFO: patent foramen ovale; TIA: transient ischaemic attack; TOE: transoesophageal echocardiography; TTE: transthoracic echocardiography.

Table A5 Selected questions regarding patent foramen ovale closure that remain to be answered.

Which patients (aged < 60 years) with PFO-associated ischaemic stroke benefit a lot, just a little or not at all from PFO closure?
Do patients who were excluded from randomized clinical trials, particularly those aged > 60 years or with a competitive cause of stroke, benefit from PFO closure?
Could oral anticoagulants be an alternative to PFO closure?
What is the long-term clinical relevance of AF induced by PFO closure?
Will new PFO closure devices improve closure rates and decrease closure complications?
What is the optimal duration of antiplatelet therapy following PFO closure?
What are the mechanisms of PFO- and ASA-associated strokes?
What is the role of PFO closure in the primary prevention of stroke?

AF: atrial fibrillation; ASA: atrial septal aneurysm; PFO: patent foramen ovale.

Disclosure of interest

J.-L. M. Honoraria from/advisory board member for the companies Abbott, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb.

P. G. Honoraria from the company Abbott. Research funded by the companies Boston Scientific, Edwards Lifesciences and Medtronic.

E. Massardier Expenses from the companies Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Medtronic and Pfizer.

N. M. Consultancy/advisory board member for the companies Abbott, Alliance BMS/Pfizer, Bayer, Edwards Lifesciences and Terumo. Honoraria from the companies AstraZeneca, Sanofi Regeneron and Boehringer Ingelheim.

The other authors declare that they have no competing interest.

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