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SCIENTIFIC EDITORIAL

Closure of patent foramen ovale and ‘cryptogenic’ stroke: What’s new, what’s next?

Fermeture du foramen ovale perméable et infarctus cérébral « cryptogénique » : quoi de neuf ? Et ensuite ?

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Abbreviations

AF atrial fibrillation
ASA atrial septal aneurysm
PFO patent foramen ovale

Background

Patent foramen ovale (PFO) is a remnant of the foetal circulation that 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 1980s, several case-control studies have consistently shown that a PFO is significantly more frequent in patients with an otherwise unexplained ischaemic stroke (so-called ‘cryptogenic’) than in patients with a known cause of stroke or in controls. This association was found to be stronger in young and middle-aged patients, those with a low burden of traditional risk factors, and those with a PFO-associated with an atrial septal aneurysm (ASA) or a large PFO (i.e. with a substantial right-to-left shunt or a large PFO opening); both anatomical features are often referred to as ‘high-risk’ PFO [1–4].

MOTS CLÉS

Infarctus cérébral ;
Foramen ovale perméable ;
Anévrisme du septum inter-auriculaire ;
Prévention ;
Essai contrôle randomisé

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These findings have suggested that PFO 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 efficacy in the prevention of stroke recurrence was highly controversial until the recent publication of a series of new trials that strongly support the benefit of this procedure, and provide the first firm evidence to guide treatment.

Evidence for PFO closure

The evidence for PFO closure is based on six randomized clinical trials [5–11] (Table 1) that mainly involved adult patients aged up to 60 years, with a recent (<6 months in most trials) otherwise unexplained PFO-associated ischaemic stroke. One trial [6] also enrolled patients with transient ischaemic attack. In four trials [5,6,9–11], patients with any type of PFO were eligible, while in two trials [7,8], only patients with both a PFO and an ASA or a large PFO (without an ASA) could be enrolled. The reason for this is that PFO is common in the general population, and may coexist by chance alone in about 30% of young or middle-aged adults with cryptogenic stroke [4]. Selecting

patients with PFO characteristics more strongly associated with stroke increases the probability that PFO is causally related to the index stroke (and not an incidental finding). In four trials [5–7,9,10], 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 [8,11], PFO closure followed by antiplatelet therapy was compared with antiplatelet therapy only.

In contrast to the first negative trials [5,6,9], three new trials [7,8,11] and the extended follow-up of an initially negative trial [10] clearly showed that PFO closure reduces the risk of recurrent stroke in young or middle-aged adults with an otherwise unexplained ischaemic stroke (Fig. 1). A meta-analysis [12] of these trials (Fig. 1) showed that PFO closure was associated with a 62% lower risk of stroke recurrence compared with antithrombotic treatment alone (hazard ratio 0.38, 95% confidence interval 0.19–0.76; $P=0.007$). 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, because the annual rate of stroke recurrence on antithrombotic treatment is relatively low to start with, at 1.3 per 100 person-years. However,

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	<i>n</i>	Age range; mean (years)	PFO characteristics	Comparison	Mean follow-up (years)
CLOSURE 1 (2012)	909	18 to 60; 46.0	Unselected PFO: small (1–10 mb), 47.1%; moderate (10–25 mb) or large (>25 mb), 52.9%	PFO closure vs. antithrombotic treatment	2
PC Trial (2013)	414	<60; 44.5	Unselected PFO: small (1–5 mb), 34.4%; moderate (6–20 mb), 43.9%; large (>20 mb), 21.7%	PFO closure vs. antithrombotic treatment	4.1
RESPECT (2013/2017)	980	18 to 60; 45.9	Unselected PFO: small (1–9 mb), 22.7%; moderate (10–20 mb), 26.4%; large (>20 mb), 48.8%	PFO closure vs. antithrombotic treatment	2.1/5.9
CLOSE (2017)	663	16 to 60; 43.4	PFO + ASA (>10 mm) or PFO > 30 mb	PFO closure vs. antiplatelet treatment	5.3
Gore REDUCE (2017)	664	18 to <60; 45.2	Unselected PFO: small (1–5 mb), 19%; moderate (6–25 mb), 40%; large (>25 mb), 41%	PFO closure vs. antiplatelet treatment	3.4
DEFENSE-PFO (2018)	120	18 to 80; 51.8	PFO + ASA (≥ 10 mm) or PFO ≥ 2 mm	PFO closure vs. antithrombotic treatment	2.8

ASA: atrial septal aneurysm; CI: confidence interval; HR: hazard ratio; PFO: patent foramen ovale; RCT: randomized controlled trial; RR: risk ratio.

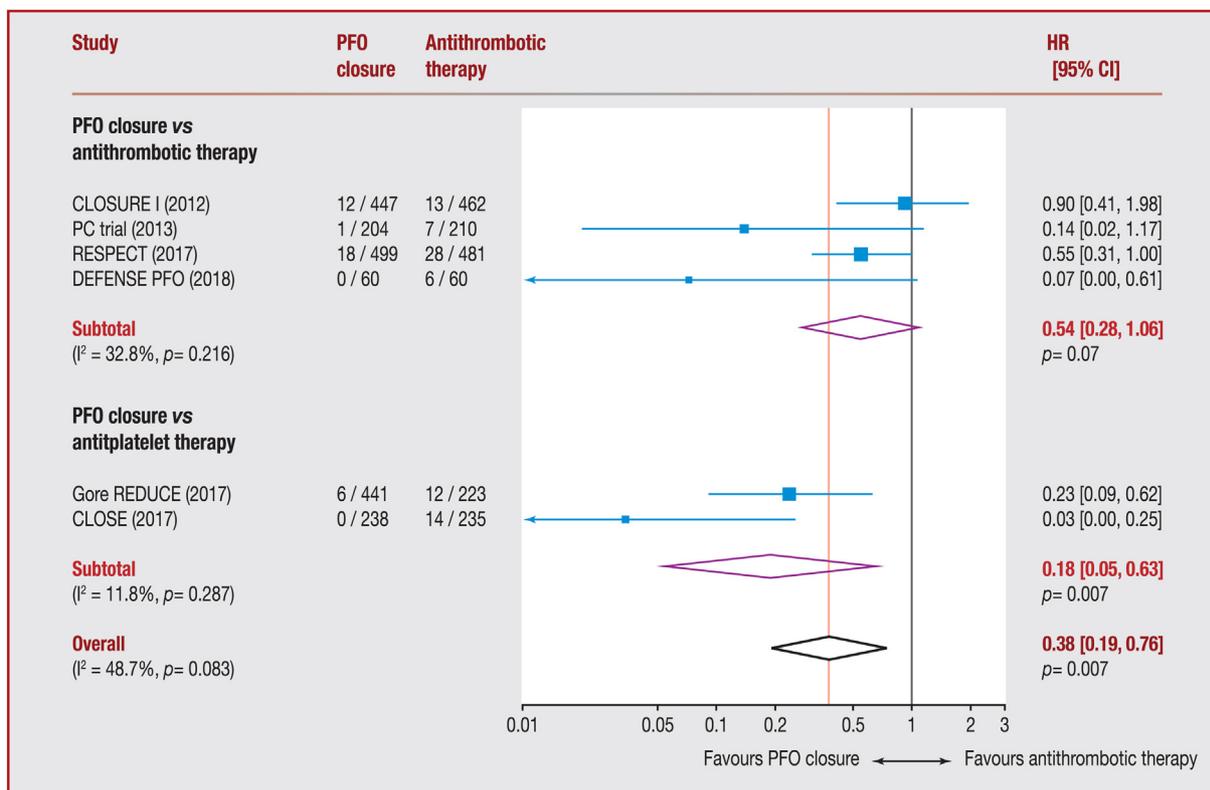


Figure 1. Pooled hazard ratio (HR) of recurrent stroke in patients randomized to patent foramen ovale (PFO) closure vs. antithrombotic therapy (random-effects meta-analysis). CI: confidence interval.

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, 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.

Randomized trials have shown that, overall, PFO closure is a relatively safe procedure in young or middle-aged adults treated by experienced interventionists [12]. However, most trials have shown a 4.3 times increased risk of new-onset atrial fibrillation (AF) after PFO closure, with a pooled incidence of 5.6 per 100 patients treated [12]. In most cases, AF occurred early (<45 days) after implantation, was transient and did not seem to recur. Some episodes of AF in the device arm were probably not related to the procedure or device because they also occurred in 1% of patients in the control groups. Five patients with AF had a stroke (<0.3% of patients randomized to the device arm). Although the low stroke rates after PFO closure suggest that AF after closure is of limited clinical consequence, further research is needed to assess the long-term consequences of AF after device implantation.

Which patients benefit most from PFO closure?

Our meta-analysis [12] of the six randomized trials (Fig. 2) suggests that patients who have a PFO with an ASA or a large PFO (without an ASA) benefit more from PFO closure than patients without those features. It is interesting to note that no recurrent stroke was observed after PFO closure in the CLOSE [8] and DEFENSE-PFO [7] trials, which only enrolled patients with high-risk PFOs, whereas recurrent strokes were common despite PFO closure, although at a lower rate, 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 [8] 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 [7], 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

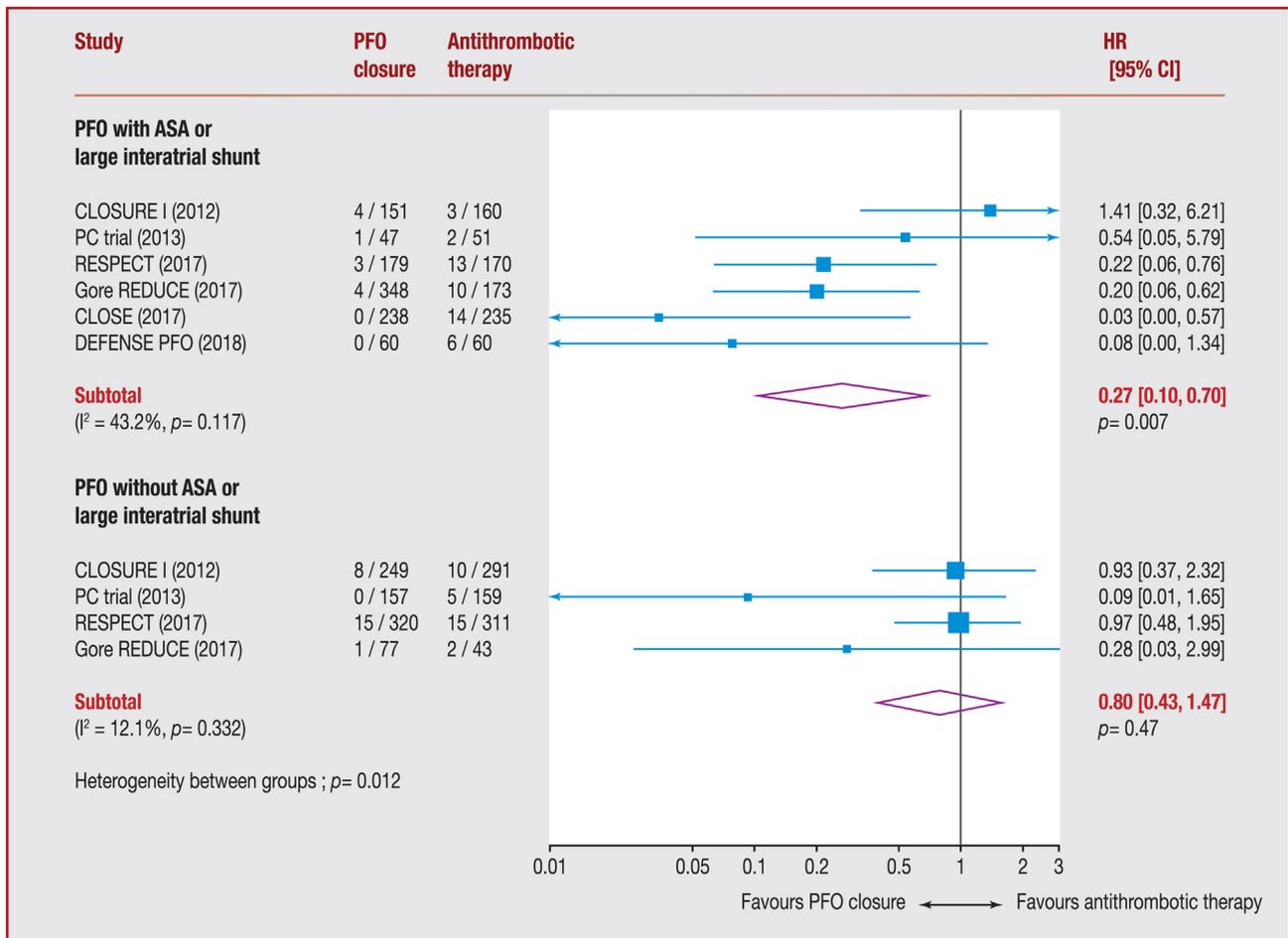


Figure 2. Pooled risk ratio (RR) of recurrent stroke in patients randomized to patent foramen ovale (PFO) closure vs. antithrombotic therapy, according to PFO anatomical features (random-effects meta-analysis). For the present meta-analysis, we defined higher-risk anatomical features as follows: for CLOSURE I, the PC Trial and RESPECT: the presence of an atrial septal aneurysm (ASA), regardless of shunt size; for CLOSE and DEFENSE-PFO: the presence of an ASA and/or a large shunt (i.e. all included patients); for Gore REDUCE: a 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 data published by Kent et al. [15]. CI: confidence interval.

[13], a large prospective observational study of patients with “cryptogenic” stroke, in which patients with both a PFO and an ASA had a four times higher risk of stroke recurrence on aspirin than patients with a PFO alone, whatever the degree of shunting.

What about oral anticoagulants?

The three-arm CLOSE trial [8] was the only one in which patients were randomized to PFO closure, oral anticoagulation or antiplatelet therapy. However, as many patients had contraindications to anticoagulants, the comparisons were underpowered. This study showed a non-significant 56% (95% confidence interval 0.11–1.48) reduction in the risk of recurrent stroke in patients allocated to oral anticoagulants (3/187 vs. 7/174), compared with patients allocated to antiplatelet therapy. A pooled analysis [14] of CLOSE and subgroups of patients with a PFO in two trials comparing oral anticoagulants with antiplatelets in patients

with cryptogenic stroke, suggested that anticoagulants are superior to aspirin in this setting, with a 52% reduction in stroke recurrence (odds ratio 0.48, 95% confidence interval 0.24–0.96; $P = 0.04$; no heterogeneity). No conclusion can be drawn from the comparison of oral anticoagulants with PFO closure in CLOSE (not planned in the statistical analysis). Whether oral anticoagulants (particularly the new ones) are as effective as PFO closure is not known, and should be assessed in a randomized clinical trial.

What’s next?

Recent trials have shown that young and middle-aged adults (aged up to 60 years) with a recent ischaemic stroke most likely attributable to PFO benefit from transcatheter PFO closure. The benefit appears to be higher in patients who have an ASA in addition to a PFO or a large PFO (without an ASA).

Table 2 Some of the questions about PFO 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 RCTs, particularly those aged > over 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; RCT: randomized controlled trial.

Although a big step forward that will benefit many patients has been taken with recent trials, the story has not reached its conclusion, and many new and old questions remain to be answered, including, but not restricted to, those listed in [Table 2](#).

Pending results from further studies, decision-making regarding the management of patients with PFO-associated ischaemic stroke should be based on close coordination between neurologists/stroke specialists and cardiologists.

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Disclosure of interest

The author declares that he has no competing interest.

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