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PFO closure - resurrected?

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Introduction

Patent foramen ovale (PFO) is a congenital lesion with an estimated prevalence of 10% in the general population. However, it can be observed in 54% of patients with cryptogenic stroke and no risk factors (1). Despite a strong association between PFO and cryptogenic stroke (2–4), previous randomised trials have failed to demonstrate any benefit from PFO closure over standard medical therapy (5–7). As such, the currently used American Heart Association/American Stroke Association (AHA/ASA) guidelines published in 2014 do not recommend PFO closure in patients with cryptogenic stroke or transient ischaemic attack (8).

Take Home Messages

- PFO is highly prevalent in patients with crytogenic stroke
- Previous RCTs failed to show benefit from PFO closure in patients with crytogenic stroke
- 3 recent simultaneously reported RCTs have demonstrated superiority of PFO device closure over medical therapy in young patients (<60 years) following cryptogenic stroke
- The evidence suggests that PFO device closure has an advantage in reducing recurrent stroke compared to antiplatelet therapy in carefully selected patients with cryptogenic stroke

However, 3 recent simultaneously published trials in New England Journal of Medicine (CLOSE (9), Gore REDUCE (10) and RESPECT (11)) each demonstrated superiority of PFO device closure over medical therapy.

Discussion

All the trials were multicentre, randomised and open-label. Patients were assigned to either PFO device closure (with subsequent antiplatelet therapy) or medical therapy alone. In general, eligible patients were <60 years old with previous cryptogenic stroke.

The trials were overwhelmingly in favour of PFO device closure over medical therapy to reduce the risk of recurrent stroke. In the CLOSE trial, no recurrent stroke occurred in the PFO closure group (n=238), whereas stroke occurred in 14 patients in the antiplatelet-only group (n=235), (hazard ratio (HR) 0.03; 95% confidence interval, 0 to 0.26, p<0.001). In the Gore REDUCE trial, recurrent ischaemic stroke occurred in 6 patients in the PFO closure group (n=441) and 12 patients in the antiplatelet-only group (n=223), (HR 0.23; 95% confidence interval, 0.09 to 0.62, p=0.002). In the RESPECT trial, recurrent ischaemic stroke occurred in 18 patients in the PFO closure group (n=499) and 28 patients in the medical therapy group (n=481), (HR 0.55; 95% confidence interval, 0.31 to 0.999, p=0.046).

There are important differences in these trials compared to previous ones, which may explain their differing results. Each trial had separate, strict inclusion and exclusion criteria in an attempt to select patients with the highest probability of paradoxical embolism due to PFO. The CLOSE and Gore REDUCE trials used a standardised evaluation to define cryptogenic stroke which were likely to have resulted in a low likelihood of alternative causes for the condition. Furthermore, both these trials had a reference treatment group of patients who received antiplatelet therapy alone. In contrast, the RESPECT trial had a reference medical therapy group that included those on antiplatelet (n=360) and anticoagulant (n=121) therapies, thereby potentially underestimating the benefits of PFO device closure versus antiplatelet therapy alone. In fact, the authors reported subgroup analysis showing similar outcomes with anticoagulant therapy alone compared to PFO device closure followed by anticoagulant therapy, and that the benefit seen with PFO device closure was driven solely by comparison with the antiplatelet-only patients. In a separate publication (12), authors of the CLOSE trial reported that further analysis of their data (9) had showed a possible trend towards less recurrent stroke with PFO device

closure compared to anticoagulant therapy, although this did not reach statistical significance (HR 0.14; 95% confidence interval, 0.00 to 1.45, p=0.08 by log-rank test). Interestingly during their systematic review of 3 randomised controlled trials, the authors also found no difference between anticoagulation and antiplatelet therapy (12). To my knowledge, no other randomised controlled trial has made direct head-to-head comparison between PFO device closure and anticoagulant therapy alone.

Different devices were evaluated in the trials with overall reported success of: CLOSE - 11 different devices (top 3 were Amplatzer PFO Occluder, Intrasept PFO Occluder and Premere) with 99.6% implantation success rate; Gore REDUCE - Helex Septal Occluder or Cardioform Septal Occluder) with 98.8% successful device retention; RESPECT - Amplatzer PFO Occluder with 99.6% implantation success rate. The rates of immediate successful PFO closure however were lower: CLOSE - 88.6%; Gore REDUCE - 73.2%; RESPECT - not reported. It is unclear whether patients with recurrent stroke observed in the Gore REDUCE and RESPECT trials could be attributable to the presence of residual shunt. Furthermore, the authors failed to include methods to assess medication compliance which may have impacted on the outcomes observed. This is particularly relevant in the CLOSE and RESPECT trials where patients in the PFO device closure group received different antiplatelet regimes compared to the medical therapy group. In the Gore REDUCE trial, antiplatelet therapy was mandated to be the same between the two study groups for each participating site.

Although none of the trials found a difference in overall adverse events, the CLOSE and Gore REDUCE trials showed increased rates of atrial fibrillation or flutter with PFO device closure. There were 2 deaths with PFO device closure in the Gore REDUCE trial, while none were reported in the CLOSE or RESPECT trials.

	CLOSE trial (n=663)	Gore REDUCE trial (n=664)	RESPECT trial (n=980)
Study design	1:1:1 randomisation Device + APT vs APT alone vs OAC	2:1 randomisation Device + APT vs APT alone	1:1 randomisation Device + APT vs medical therapy (APT or OAC)
Eligibility	16-60 years CS within 180 days Septum primum excursion >10mm on TOE OR large PFO with >30 microbubbles in LA within 3 cardiac cycles after opacification of RA	18-59 years CS within 180 days PFO with ≥1 microbubbles in LA in any single frame during first 3 cardiac cycles after opacification of RA on TOE	18-60 years CS within 270 days PFO confirmed on TOE
Follow-up	5.3 ± 2.0 years	3.2 years (IQR 2.2 - 4.8)	5.9 years (IQR 4.2 - 8.0)
Primary endpoint	Fatal or nonfatal stroke	Stroke 24-month incidence of new brain infarction	Fatal or nonfatal stroke, or early death
Outcome	PFO closure superior to APT alone with HR 0.03 (0 - 0.26, p<0.001)	Less stroke with PFO closure, HR 0.23 (0.09 - 0.62, p=0.002) Less brain infarction with PFO closure, RR 0.51 (0.29 - 0.91, p=0.04)	PFO closure superior to medical therapy with HR 0.55 (0.31 - 0.999, p=0.046)

Table 1. Summary of Trials :APT: antiplatelet therapy, OAC: oral anticoagulant, CS: cryptogenic stroke, TOE: transoesophageal echocardiogram, LA: left atrium, RA: right atrium, PFO: patent foramen ovale, HR: hazard ratio, IQR: interquartile range, RR: relative risk

When interpreting these trials into clinical practice, it is important to have several considerations in mind. The benefit of PFO device closure over medical therapy has been demonstrated only in a highly selected, young population after careful evaluation for cryptogenic stroke. Furthermore, there appears to be an increased risk of atrial fibrillation or flutter with PFO device closure. In addition, only certain devices were evaluated and patients in the PFO device closure groups were commenced on antiplatelet therapies with differing regimes between trials.

The role for anticoagulant therapy in young patients with cryptogenic stroke needs further evaluation as analyses from the CLOSE and RESPECT trials suggest that outcome with anticoagulant therapy is comparable to PFO device closure. A subsequent trial (NAVIGATE ESUS) found that treatment with rivaroxaban compared to aspirin in patients with crytogenic stroke who have a PFO may reduce the risk of recurrent stroke by about half (13).

Conclusion

Among patients who have had a cryptogenic stroke, patent foramen ovale closure resulted in lower rates of recurrent stroke but is associated with increased risk of atrial fibrillation or flutter. The role of anticoagulant therapy alone for this condition warrants further investigation.

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