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EDITORIAL

Patent Foramen Ovale Closure: The Debate Goes On

Nick Mezilis, MD, FESC

St. Luke's Hospital, Thessaloniki, Greece

ABSTRACT

Meta-analyses of retrospective and case-control studies support an association between a patent foramen ovale (PFO) and "cryptogenic stroke" (stroke without an identifiable cause), especially in young patients (age <55 years). Several reports have also suggested an increased risk of recurrent strokes in patients with PFO. Comparison of the two main strategies to reduce the risk of recurrent stroke in patients with cryptogenic stroke and PFO, antithrombotic therapy vs transcatheter closure of the PFO with a device, has shown PFO closure to confer a lower risk in non-randomized studies, which though has not been confirmed in randomized trials, although a tendency for a lower risk has been indicated, particularly in on-treatment or per-protocol analyses (compared with the intention-to-treat analysis), and appears to be device specific. Thus, PFO closure cannot be presented as the recommended treatment, but it may be offered as an alternative option in select patients, e.g. those with large shunts or with atrial septal aneurysms.

KEY WORDS: *patent foramen ovale; cryptogenic stroke; paradoxical embolism; PFO closure*

INTRODUCTION

Patent foramen ovale (PFO) is a persistent fetal communication between the right and left atrium due to incomplete closure of the atrial septum. PFO is common in the general population. In many autopsy-based studies it shows a prevalence of approximately 27%.[1] In most people the interatrial communication seals completely after birth. In around a quarter of the population, however, incomplete closure of the foramen results in a PFO that could provide a potential route for blood borne material from the venous to the systemic circulation (paradoxical embolism). Case reports of thrombus straddling a PFO (Fig. 1) confirm that material from the venous circulation can pass through the interatrial communication and cause systemic embolism to the brain and other organs,[2] but the frequency and clinical relevance of this phenomenon are controversial. Case-control studies to assess whether PFO is more common in people with stroke are confounded by selection bias and have provided conflicting results. However, meta-analyses of these studies support an association between a PFO and stroke without an identifiable cause ("cryptogenic stroke"), especially in young patients (age <55 years).[3,4] There are limited prospective data on the risk of stroke in otherwise healthy people with PFO. In one population-based study,[5] the incidence rate of ischemic stroke was 1.22 and 0.89 per 100 person years in subjects

Abbreviations
PFO = patent foramen ovale
TIA = transient ischemic attack

Correspondence to:
Nick Mezilis, MD, St. Luke's Hospital, Thessaloniki, Greece;
E-mail: mezilis@otenet.gr

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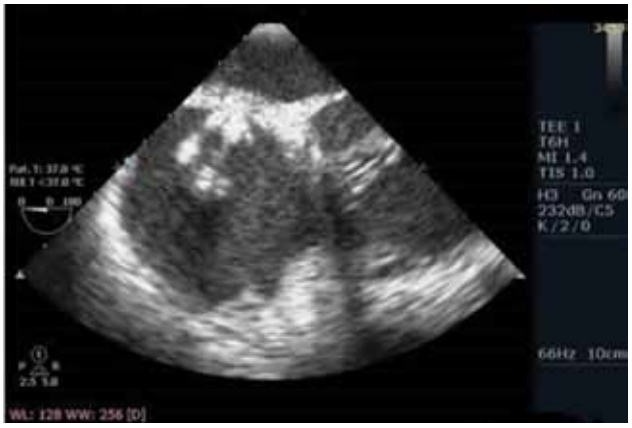

FIGURE 1. Thrombus straddling a PFO "caught in action".

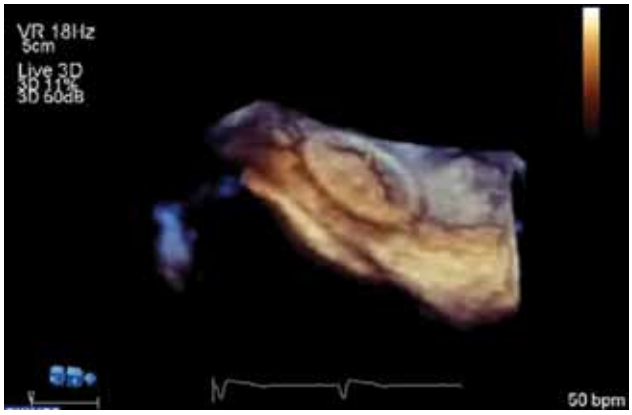

FIGURE 2. An Amplatzer PFO occluder visualized by 3D transesophageal ultrasound.

with and without PFO respectively, but this difference did not reach statistical significance. Several reports have also studied the risk of recurrent strokes in patients with PFO. The results of these studies are heterogeneous, but in a meta-analysis the pooled rate of recurrent stroke for patients on medical treatment was 1.6 events per 100 person years.[6] Some studies also suggest that the risk of stroke is influenced by PFO size, the presence of an atrial septal aneurysm, or risk factors for thromboembolism, but the predictive value of these markers has not been confirmed.[7,8]

MANAGEMENT OF PATIENTS WITH PFO AND CRYPTOGENIC STROKE

There are 2 main strategies to reduce the risk of recurrent stroke in patients with cryptogenic stroke and PFO: medical management which includes antiplatelet therapy and anticoagulation, and transcatheter closure of the PFO with a device (Fig 2).

The efficacy of acetylsalicylic acid was suggested by a multicenter trial, which found that the incidence of recurrent stroke after 4 years of follow-up of 216 patients with cryptogenic stroke and PFO was greater than in stroke patients without an intracardiac shunt.[9] Both groups were given acetylsalicylic acid (300 mg daily) as secondary prophylaxis. The incidence of recurrent stroke during the same period was four times as high in 51 of the patients with co-existing atrial septal aneurysm. The conclusion of the study was that warfarin should be considered for this subgroup.

Percutaneous closure has been used widely to prevent episodes of embolism through the interatrial communication, and observational studies suggest that this procedure lowers the risk of recurrent cerebrovascular events in patients with PFO when compared with medical management.[10,11] The PFO in cryptogenic stroke study (PICSS), on the other hand, evaluated acute stroke patients with and without PFO assigned to acetylsalicylic acid (325 mg daily) or warfarin,[12] There was no significant difference with respect to two-year risk of recurrent stroke or death between the groups, or for patients with co-existing atrial septal aneurysm. A systematic literature review of 20 studies to examine the efficacy of transcatheter closure compared to antithrombotic therapy showed that the annual risk of recurrent transient ischemic attack (TIA) or stroke was lower in the group with closure than in patients who received antithrombotic therapy.[13] This applied in particular to patients with co-existing atrial septal aneurysm. Many clinicians therefore consider that closure is justified in patients with cryptogenic stroke and PFO to prevent stroke recurrence, but these non-randomized data may be confounded by imbalances in the underlying risk of recurrent events between the two treatment groups. Moreover, PFO closure is associated with procedural and long term risks, and randomized clinical trials[14] are required to fully evaluate the balance of risks and benefits of closure versus medical treatment.

RANDOMIZED STUDIES AND MEETA-ANALYSES

To date, three randomized controlled trials of PFO closure with antiplatelet therapy versus medical therapy alone have reported results. The *CLOSURE-I trial* randomized 909 patients with PFO and cryptogenic stroke or TIA to closure with the Starflex device combined with medical therapy (aspirin) versus medical therapy (aspirin or warfarin, or both). Successful implantation of a device was achieved in 81% of patients in the closure arm. At two years' follow-up there was no significant difference in the rate of the primary endpoint (stroke, TIA, or death) between the 2 treatment groups (5.5%

in the closure group versus 6.8% in the medical therapy group). In most cases the recurrent neurological events were attributed to causes unrelated to the PFO, but left atrial thrombus was detected in four (1.1%) of the 366 closure patients who underwent transesophageal echocardiography within 6 months of the procedure, two of whom had a stroke. Moreover, protocol-defined major vascular complications occurred in 3.2% of the closure group but none of the medical therapy group, and atrial fibrillation was significantly more common in the closure group than in the medical therapy group (5.7% *vs* 0.7%).[15]

The *PC trial* randomized 414 patients with PFO and ischemic stroke, TIA, or extracranial thromboembolism to closure using the Amplatzer PFO occluder (St Jude Medical) or to standard medical care (antiplatelet therapy or anticoagulation). A device was successfully implanted in 93.6% of the closure group. At a mean follow-up of around 4 years, the primary composite endpoint (death, non-fatal stroke, TIA, and peripheral embolism) had occurred in 3.4% of the closure group and 5.2% of the medical care group. As with CLOSURE-I, there was a slightly higher rate of atrial fibrillation of new onset in the closure group (2.9% *vs* 1.0%), but there was no evidence of thrombus associated with the device.[16]

The recently published *RESPECT trial* randomized 980 patients with PFO and cryptogenic stroke to closure with the Amplatzer PFO occluder (St Jude Medical) or to medical therapy alone (with anticoagulation or antiplatelet therapy).[17] The device was successfully implanted in 92.6% of the closure group. Over a mean 2.6 years of follow-up, the primary endpoint (recurrent fatal or non-fatal ischemic stroke or early death) occurred in 1.8% of the closure group and 3.3% of the medical therapy group. The investigators reported different durations of follow-up in the two arms of the trial because some patients in the medical arm withdrew from the study and underwent non-assigned PFO closure. Exploratory survival analyses by treatment received suggested that PFO closure might have reduced the risk of recurrent stroke. The rate of serious adverse events did not differ between the two groups, although the closure group showed slightly higher rate of new atrial fibrillation (3.0% *vs* 1.5%) and pulmonary embolism (1.2% *vs* 0.2%).[17]

The results of the RESPECT trial indicate that PFO closure with the Amplatzer PFO Occluder is not superior to medical management in reducing recurrent strokes in patients with cryptogenic stroke and evidence of a PFO. There were, however, trends toward benefit on per-protocol analysis and in patients with large shunts and those with atrial septal aneurysms. In general, the overall negative results are consistent with those noted in the CLOSURE I trial (with the STARFlex device) and the PC trial (also with the Amplatzer device). These data are hypothesis-generating, but do not support routine PFO closure in patients with cryptogenic stroke and PFO. It is possible that there might be a benefit in select subgroups.

Overall, these 3 randomized trials enrolled 2303 participants over 5 to 9 years, but it is likely that a much larger number of patients underwent PFO closure at the 162 participating sites during the recruitment period,[18] and it is unclear how the trial results relate to the wider population of patients with cryptogenic stroke and PFO. The individual trials have relatively small sample sizes and short follow-up times, and the hazard ratios are bounded by wide confidence intervals that encompass clinically relevant treatment effects. Furthermore, interpretation of the trial results is complicated by treatment crossovers and incomplete follow-up.

Several meta-analyses of these 3 randomized trials (CLOSURE I, PC, and RESPECT trials) have been performed.[19-25] The analyzed data concern 2,303 patients, of whom 1,150 were in the PFO closure group and 1,153 in the medical therapy group. In the intention-to-treat analysis, transcatheter device closure of PFO was not superior to standard medical therapy in the secondary prevention of cryptogenic stroke, but there was a trend in favor of the PFO closure, but also a trend for the more frequent occurrence of atrial fibrillation in the PFO closure group. In the as-treated or per-protocol analyses, the stroke and/or TIA risk was significantly less frequent in the PFO closure group. The conclusion has been that successful transcatheter closure of PFO might be more effective than medical therapy alone for the prevention of recurrent thromboembolic events. Subjects with a substantial PFO shunt tended to benefit the most with transcatheter PFO closure (HR=0.35, P=0.06).[24]

Recently, a pooled analysis was performed of the PC and RESPECT trials, in which a similar device was used, indicating beneficial effects of device closure: the effect-estimate hazard ratios being 0.54 (95% confidence intervals-CI: 0.29 to 1.01) in the intention-to-treat, 0.48 (95% CI: 0.24 to 0.94) in the per-protocol, and 0.42 (95% CI: 0.21 to 0.84) in the as-treated populations.[25]

Also recently, a randomized trial, comparing 3 different devices (Amplatzer, CardioSEAL-STARflex, and Helex occluder, n=220 per group) for percutaneous closure of a PFO in 660 patients with cryptogenic stroke, showed significant differences in the neurological event rate among devices.[26] The authors concluded that procedural complications and long-term neurological event rates are low regardless of device used; however, the recurrent neurological event rate was significantly lower after the Amplatzer device implantation.[26] Finally, further results from ongoing randomized trials, including REDUCE and CLOSE, are awaited in the near future.

CONCLUSION

In conclusion, based on current evidence, closure should not be presented as the recommended treatment, but it should be mentioned as an alternative option in selected patients (those with large shunts or with atrial septal aneurysms).

The patient then has the choice between a relatively simple and short procedure and life-long anticoagulants with their inherent risk over time. In older patients the risk of recurrent stroke attributable to PFO is likely to be small relative to the overall risk of stroke, especially in those with hypertension or other vascular risk factors. In most patients, a definite relation between the PFO and the index stroke cannot be established, and, regardless of whether device closure is recommended, other secondary prevention treatments, including antiplatelet therapy, blood pressure control and cholesterol lowering agents will also be appropriate.

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