Percutaneous PFO closure, further data but many unanswered questions

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This editorial refers to ‘Patent foramen ovale closure in patients with cryptogenic thrombo-embolic events using the Cardia PFO occluder’ by C. Spies et al., on page 365.

The pace of technological development in interventional congenital cardiology over the last two decades has been fast and relentless. Successful and reliable closure of secundum atrial septal defects in the catheter laboratory translated to interest in the use of similar devices for the occlusion of the patent foramen ovale (PFO), a common remnant of the fetal circulation. The pathological potential of the PFO in the genesis of unexplained thrombotic stroke had long been suspected, with Lechat et al. in 1988 reporting a higher prevalence of PFO in patients with cryptogenic thrombotic stroke, an observation confirmed in a number of subsequent studies. With low risk and a simple technique for PFO closure as an alternative to surgery, many clinicians faced with patients affected by cryptogenic stroke have been quick to advance the cause of percutaneous therapy in this setting, despite the lack of a really robust evidence base. As a result, we have found ourselves in a scenario familiar to many involved with transcatheter intervention in congenital heart disease where technological advances and the ability to perform a procedure have to some degree outpaced our understanding of the procedural indications and efficacy.

At present, data relating to secondary prevention using transcatheter-delivered PFO closure devices in cryptogenic stroke are limited to non-randomized studies which suggest a trend to benefit in those patients undergoing closure compared with treatment with medical therapy. Randomized data upon which to really judge the efficacy of device closure and test the cause–effect hypothesis between PFO and cryptogenic stroke are still not available. A number of randomized trials are underway, but transcatheter PFO closure is now well established in the treatment armamentarium such that recruitment for these studies has been slow, due in some part to patient reluctance to take part for fear of recurrent neurological events or the complications of anticoagulation.

Spies et al. report the largest series of single device transcatheter PFO closures (403 patients) for secondary prevention of cryptogenic stroke published to date. Closures were performed in a single tertiary referral centre over a 6-year period using three generations of the Cardia occluder (formerly known as the PFOSstar). The arena of device closure for PFO is highly competitive, the standards by which devices are judged are exacting, and the authors should be congratulated as this well-constructed report goes a long way in helping us understand the strengths and weaknesses of this particular device. Given the uncertainties concerning the indications for PFO closure in patients with cryptogenic stroke, a prerequisite of transcatheter PFO closure is that the procedure itself must be low risk. The procedural complication rate of 2% (mainly minor complications but with two-device embolizations and two pericardial effusions) although not negligible is firmly within the range of complication rates reported for other devices and an improvement on previous reports of PFO closure using this device. Ultimately, all devices are not made equal and this study, along with others before it, strongly suggests that differences in the performance of these devices in situ translate to important differences in the longer term risk, particularly that of stroke recurrence. Clearly, there have been improvements in the design of the Cardia device such that with the current modification limb fractures (so far median follow-up 12.6 months) appear to have been eliminated. Residual shunts still appear to be a problem (10% of the generation-3 devices), and although they were not a statistical predictor of further stroke in this study, other authors have identified residual shunt as a risk factor which given the underpinning mechanistic hypothesis would seem to make sense. Previous studies have also shown this device to be at a disadvantage when compared with some of its peers in terms of the occurrence of device-related thrombus. In this series, Spies et al. report a small number of device-related thrombi (3.2% for the whole group). Interestingly, but perhaps not entirely surprisingly, prior device-related thrombus was a highly statistically significant predictor of a recurrent thrombotic event, despite the apparent resolution of the thrombus with treatment as evidenced by transoesophageal echocardiography (TEE). The authors...
attribute this to either missed thrombus on repeat TEE or recurrence of clot following the examination. However, there is another potential explanation. It was not part of the study protocol to rule out procoagulant states prior to PFO closure, and it is conceivable that a subgroup of patients were at greater risk of recurrent events after PFO closure with a potential nidus for thrombus formation in the atrial septum. One of the great dangers of our current lack of understanding of the indications for this procedure is that patient selection is inevitably crude and therefore we may be putting small subgroups of patients who we think we are helping at an even greater risk of another stroke.

What of the bigger picture? On the basis of this study are we any further with regard to our understanding of the relationship between the PFO and the cryptogenic stroke? Despite the suggestion of event reduction after device closure in this study, there are clearly methodological issues here (not least the differences in antiplatelet therapy before and after PFO closure) that counsel caution in the interpretation of this evidence. Like a number of previous studies, Spies et al. have given us tantalizing glimpses which suggest that with regard to PFO closure in cryptogenic stroke, we are probably on the right path. However, it is a sobering thought that the indications for PFO closure may be about to broaden to the treatment of migraine before we even have a robust evidence base to guide us in device closure of the PFO for cryptogenic stroke. If this occurs, then within a short period of time this procedure has the potential to rival coronary revascularization as the most common transcatheter cardiological intervention in adult patients. Without a clear understanding of the primary indications and the true efficacy of the procedure for PFO closure to occur in these sorts of numbers is unthinkable and more than ever we need data from those randomized trials.

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**References**