

## Papers that could change practice in cardiovascular research:

### 4 April 2013 – PFO closure and Cryptogenic Stroke

Around 25% of us have a patent foramen ovale, the residual connection between right and left atria, which can allow blood and thrombus to shunt from the right to the left atrium and which has the potential for the rare but disastrous cerebrovascular consequence of paradoxical embolism and stroke. This connection is identified twice as often in those who have stroke at a young age and have no other identifiable cause (cryptogenic stroke).

Two important papers published in the New England Journal of Medicine report on studies that have attempted to define whether closure of a PFO with a trans-catheter device can reduce the chance of further strokes in this group. Both trials (the PC Trial<sup>1</sup> and RESPECT<sup>2</sup>) compared the deployment of the Amplatzer PFO Occluder (St Jude Medical) and antiplatelet drugs for at least five months, with standard medical therapy, which included at least one anti thrombotic drug. A previous trial (CLOSURE 13) had compared the STARflex device (NMT Medical) with medical therapy.

None of the three studies to date have rejected the null hypothesis, with the primary end points being a composite of death, fatal or non-fatal stroke (and systemic embolism also included in the PC trial). There was no difference in the occurrence of the primary composite end point between device and medical therapy. These three trials took a long time to recruit adequately because of off label use of the closure devices without evidence that this is a worthwhile endeavour. However, unlike the earlier CLOSURE<sup>1</sup> trial, the recent trials hinted that with device implantation there may be a reduction in non-fatal strokes, though with wide confidence intervals and a failure to achieve accepted statistical significance threshold of P value of 0.05, (2.4% after medical therapy vs 0.5% for closure in PC trial, and 6.4% for medical vs 2.2% with closure after five years in RESPECT). The rate of recurrent stroke, even in those with a PFO and cryptogenic stroke is relatively low when appropriate anti-thrombotic therapies are instigated. Studies with low and modest statistical powers may fail to demonstrate significance, but are also prone to bias and spurious results while single end points may fail to assess complications and adverse effects of the procedure. These trials should not be seen as evidence to support the use of devices for PFO closure to prevent stroke. More evidence from larger trials is needed to answer this and show which type of patients are most likely to gain benefit.

1. Meier B, Kalesan B, Mattle HP et al. Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism. *N Engl J Med* 2013; 368:1083-1091
2. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013;368:1092-1100
3. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012;366:991-999

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