Patent foramen ovale, is it more dangerous to close it than to leave it open?

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The answer to the question in the title is clearly no. The CLOSURE I [1] trial is the first randomised trial to confirm what has been known from countless observational studies and a propensity-matched long-term analysis [2].

The controversy is not about whether a foramen ovale should be shut or patent but about whether closing the patent foramen ovale (PFO) carries more risk than leaving it open. This has now been refuted by a randomised controlled study, so let us move on and close PFOs once they are recognised. We should at least close those that have already caused a problem or those that are associated with an aggravating factor such as an atrial septal aneurysm, a Eustachian valve or a Chiari network.

Apparently all questions have not been answered and the uninspired reader of the CLOSURE I trial may even turn away from PFO closure for all the wrong reasons. A common interpretation is that the trial may well have shown that it is as safe to close the PFO as to leave it open but that the design was to prove that closure is superior and because of that, the trial was negative.

CLOSURE I trial [1]

The CLOSURE I trial was designed in the early years of the millennium by one of the companies producing a device for PFO closure (NMT Medical, Boston, Massachusetts, USA producing the STARFlex occluder). The full name of the trial was: "Recurrent neurological events in patients with patent foramen ovale treated with percutaneous STARFLex closure versus best medical therapy". There is no claim of superiority in the title but the trial was indeed a 2-arm superiority trial involving 87 centres in North America and randomising qualifying patients open-label to either closure of their PFOs with a STARFlex device or medical treatment (warfarin, acetylsalicylic acid, clopidogrel, or a combination thereof were allowed) [3]. Inclusion criteria included age 18–60 years, and stroke or definite transient ischaemic attack (TIA) within six months and without an identifiable conventional cause (atherosclerosis proximal to the head, prior myocardial infarction, atrial fibrillation, or endocarditis). Treatment after device closure included clopidogrel for 6 months and acetylsalicylic acid for the entire follow-up duration of 2 years. A follow-up transoesophageal echocardiogram (TOE) at six months was followed by further TOEs in patients with incomplete closure. The primary endpoint was defined as death, stroke or TIA. The initial power calculation suggested enrolment of 1600 patients to achieve a significant reduction of the primary endpoint from 6% to 3% in two years. After only enrolling 611 patients in the first 4 years (2003–2006) the trial design was officially changed to include 800 patients based on a primary endpoint of 6% and 2% at 2 years in the conventional and closure patients, respectively. Trial enrolment was stopped on October 24, 2008 after 909 patients had been randomised. Analysis occurred after the last patient had accumulated two years of follow-up.

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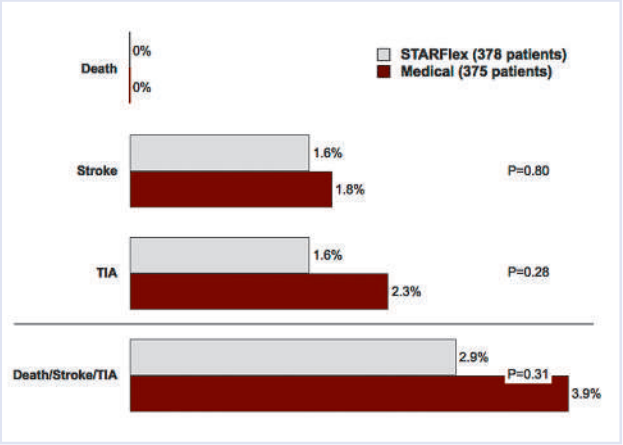
Figure 1
Primary endpoint (death, stroke or transient ischaemic attack) per year of follow-up in patients randomised to STARFlex closure of the PFO or medical treatment (per protocol analysis) [1].



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Device implantation was successful in 89% and no or minimal residual shunt was seen at the 6-month TOE in 86%. Both these figures are way below results achievable with the state-of-the-art device, the Amplatzer PFO occluder [4].

These facts may be the main reasons why the primary endpoint was missed. It was 7.7% in the conservatively treated patients and 5.8% in the device patients. The respective figures for cardiovascular death, stroke, or TIA were 0 and 0, 3.5% and 3.2%, or 4.6% and 3.2%, respectively (fig. 1 depicts the percentages per year). None of these differences were statistically significant. In addition, atrial fibrillation during follow-up occurred in 9 of the 362 patients with a device implanted (2.4%) compared to 3 of the 462 control patients (0.6%). These facts were brought forward to explain the lack of significant advantages of device closure. A thrombus was seen on the device in 1.1%, which was lower than the approximately 7% observed in a comparable trial [5] with the same device family but this may still have negatively impacted results.

The very short follow-up of the CLOSURE I trial (no patient longer than 2 years) was an even greater problem than the use of an inferior device which had been abandoned for poor quality at our centre almost 10 years ago and has now left the market completely.

Other compelling data

Figure 2 shows results of a comparable study [2]. It was not randomised but patients were arbitrarily selected for medical treatment or PFO closure by neurologists at the end of the last millennium when there were practically no criteria at hand that could have biased the allocations. The average follow-up was about 10 years. The yearly recurrent events were reduced by a significant margin (reduction of all-cause deaths, stroke, or TIA from 4.5% to 1.5% per year) that was even more marked than postulated, but not achieved, in the CLOSURE I trial (respective reduction projected from 3 to 1% per year, but observed to be only from 3.9 to 2.9%, fig. 1). It comes as no surprise that it takes a long follow-up or a large group of compared patients to show a mortality or stroke benefit with PFO closure. In addition, the best available technique should be used by operators with a significant case load to optimise the results.

The benefit of closure has been depicted with the help of long-term follow-up in other studies from Austria [6], Belgium [7], and Korea [8].

In 1998 it had already been shown that a PFO is a harbinger of death in case of clinically significant pulmonary embolism (increase of mortality from 14 to 33% by the mere presence of a PFO) [9]. This had been corroborated by a study looking at brain infarction during clinically apparent pulmonary embolism [10] and (without acknowledging it, however) by a field study in Denmark proving a 3-fold incidence of stroke and myocardial infarction in the realm of deep venous thrombosis or pulmonary embolism [11]. And there is more compelling evidence that the PFO can have grave consequences [12–15].

It is quite likely that the next two randomised trials expected to be published within a year and performed with the Amplatzer occluder ultimately and unequivocally prove the benefit of PFO closure at least as pertaining to the Amplatzer technique. These are the PC trial (Randomised Clinical Trial Comparing the Efficacy of Percutaneous Closure of *P*atent Foramen Ovale (PFO) with Medical Treatment in Patients with *C*ryptogenic Embolism) [16] and the RESPECT trial (*R*andomised *E*valuation of Recurrent *S*troke Comparing *P*FO Closure to *E*stablish Current Standard of *C*are *T*reatment). A positive outcome of the latter is all but

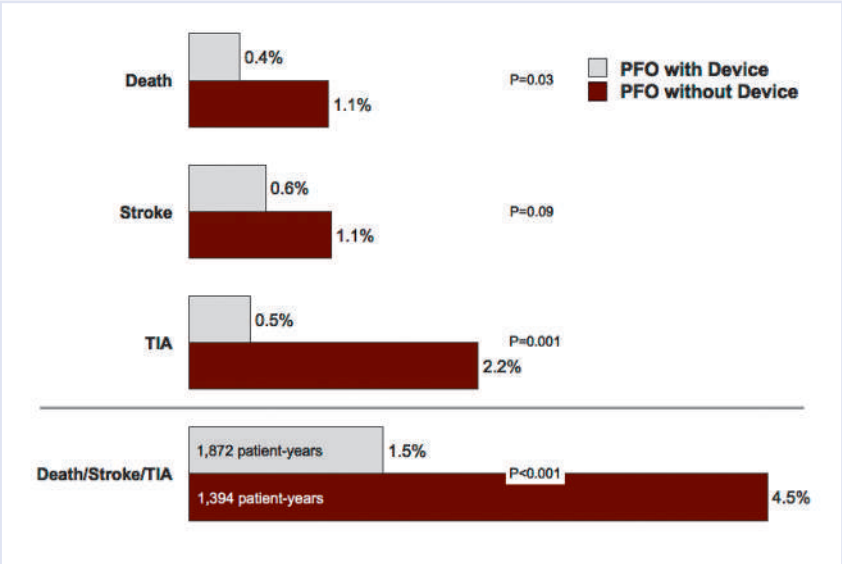

Figure 2
Non randomised retrospective analysis of patients arbitrarily selected by neurologists for PFO closure or medical treatment. The endpoints were collected and adjudicated by neurologists and in contrast to the CLOSURE trial, all-cause death rather than only cardiovascular death was counted [2].

guaranteed because it was stopped, according to its design, after a certain amount of all-cause deaths and strokes had occurred. As a fairly healthy cohort had been randomised (initial cryptogenic event, meaning that no other significant disease was found), it is highly likely that subsequent problems mainly occurred due to paradoxical embolism via the PFO left open.

Many colleagues, including representatives from the Food and Drug Administration in the United States, use the failure of the CLOSURE I trial to reach the predefined endpoints to caution against closing a PFO electively. While conceding not to give up the concept altogether, they advocate restricting PFO closure to randomised trials. Is that ethically acceptable? It means identifying a patient with a risk for paradoxical embolism (mainly because she or he had suffered a cerebral event that found no other reason than the PFO demonstrated) and then decide to randomise. One arm entails a 15-minute procedure with virtually no risk and discomfort for the patient allowing full physical activity as early as a few hours after the intervention. This procedure eliminates the potential for paradoxical embolism. The other arm does not eliminate that potential and entails life-long medical treatment with either oral anticoagulation or anti-platelet therapy implying an increased bleeding risk even with the most modern of drugs. Events will occur in this arm and will be acknowledged with some macabre glee as they will add to the still lacking evidence. What about the patient?

Let us look at the CLOSURE I trial in the way that it found the patients with PFO closure (albeit with poor technique and equipment) at no disadvantage at two years of follow-up. They should be much better equipped for the rest of their lives due to the fact that most of them are no longer PFO carriers. Late problems of the device are unlikely to be expected.

On top of that and for no additional cost or risk they might benefit from improvement of their migraine (not a bad deal) [17] or at least the soothing knowledge that the hole in the heart which they once had, is no longer a threat to them.

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