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on behalf of the Council  
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## Patent foramen ovale and migraine: no reason to intervene

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Cardiac embolism is the most frequent cause of ischaemic stroke in hospital-based and population-based registers. Patent foramen ovale (PFO) with and without atrial septal aneurysm (ASA) has been recognised as a potential risk factor for ischaemic stroke. Besides paradoxical embolism from small thrombi that arise in the venous system and cardiac thrombus formation secondary to PFO/ASA-related cardiac arrhythmia, another likely ischaemic stroke cause is thrombus formation in the PFO.

Several studies have investigated a possible link between PFO and migraine. Del Sette et al. compared 44 patients with migraine with aura, 73 patients less than 50 years of age with focal cerebral ischaemia, with 50 control individuals without cerebrovascular disease or migraine using transcranial Doppler [1]. The prevalence of right-to-left shunt was significantly higher in patients with migraine with aura (41%) and cerebral ischaemia (35%) than in controls (8%). Anzola and colleagues performed a case-control study of 113 consecutive patients with migraine with aura, 53 patients with migraine without aura and 25 age-matched nonmigraine individuals [2]. The prevalence of PFO was significantly higher in patients with migraine with aura (48%) compared with patients with migraine without aura (23%) and controls (20%). A

number of other studies confirmed by different methods (transcranial Doppler, transoesophageal echocardiography) the relationship between PFO and migraine with aura [3, 4]. There seems to be a much weaker association with migraine without aura and other headaches. A possible explanation might be that both conditions, migraine with aura and PFO, could be dominantly inherited and share a common genetic background [5].

A coincidence of two conditions, however, does not necessarily imply a causal relationship. Moreover, it is difficult to imagine how PFO could lead to a migraine attack with aura – a neural event in the occipital cortex caused by spreading depression. Even if small emboli arise from a PFO, these would travel preferentially into the anterior circulation rather than into the posterior cerebral artery.

Should PFOs be closed in patients with migraine? Even if we assume there is a causal relationship between PFO and migraine, closure of PFO should then result in migraine improvement. To date, only one randomised and controlled prospective trial has been performed in the UK. The MIST trial is not yet published, but the results were reported at an international meeting. This trial recruited patients with frequent migraine with aura refractory to preventive treatment (although topira-

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mate and lamotrigine were not used [6, 7]). The trial randomised 147 patients to either transcutaneous PFO closure with the STARFlex device or a sham procedure. One hundred and thirty-five patients completed the trial after 6 months. The primary endpoint, cure of migraine, was not significantly different between the 2 treatment groups. There was a trend for a reduction of migraine frequency in the operated group, which is not significant if one corrects for the imbalance in migraine frequency at baseline. The procedure was associated with some serious adverse events e.g., pericardial tamponade, pericardial effusion, retroperitoneal bleed, atrial fibrillation and chest pain. AEs in the sham group included incision site bleed, anaemia, nose bleed and a brainstem stroke.

In a retrospective study, 215 stroke patients with PFO were examined and underwent closure of PFO as a secondary prevention measure [8]. A year later, patients were asked about their migraine frequency before and after PFO closure to determine whether this intervention affected migraine attacks. Patients with a PFO and a history of stroke had higher migraine prevalence (22%) than the general population (10%). In patients with migraine with aura, percutaneous PFO closure reduced the frequency of migraine attacks by 54% ( $1.2 \pm 0.8$  vs.  $0.6 \pm 0.8$  per month;  $p=0.001$ ) and in patients with migraine without aura by 62% ( $1.2 \pm 0.7$  vs.  $0.4 \pm 0.4$  per month;  $p=0.006$ ). PFO closure did not have a statistically significant effect on headache frequency in patients with nonmigraine headaches. Several other retrospective studies found a similar relationship between PFO closure and migraine improvement [9–14]. However, with one exception, all these studies had major limitations. First, despite migraine improving spontaneously with age, no study had a control group. Second, the high placebo response can reduce the frequency of migraine by up to 70%.

Third, after PFO closure, most patients received aspirin, which has a modest migraine prophylactic activity, at least in men [15, 16]. Clopidogrel, given as an aspirin alternative, might also reduce migraine frequency [17, 18]. Fourth, retrospective collection of headache data is highly unreliable; recall bias has a major influence on the results. Furthermore, the most recent study observed that as many patients improve from migraine as develop new onset migraine after PFO closure [11].

Thus, to date there is insufficient evidence on the hypothesis that migraine frequency is improved by PFO closure. Additional properly conducted, prospective studies in migraine patients including control groups with other or no headaches are needed. These are underway in Europe and the USA. Until then PFO closure should not be used for the prophylaxis of migraine.

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## References

1. Del Sette M, Angeli S, Leandri M et al (1998) Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. *Cerebrovasc Dis* 8:327–330
2. Anzola GP, Magoni M, Guindani M et al (1999) Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. *Neurology* 52:1622–1625
3. Schwerzmann M, Nedeltchev K, Lager F et al (2005) Prevalence and size of directly detected patent foramen ovale in migraine with aura. *Neurology* 65:1415–1418
4. Carod-Artal FJ, da Silveira Ribeiro L, Braga H et al (2006) Prevalence of patent foramen ovale in migraine patients with and without aura compared with stroke patients. A transcranial Doppler study. *Cephalalgia* 26:934–939
5. Wilmshurst PT, Pearson MJ, Nightingale S et al (2004) Inheritance of persistent foramen ovale and atrial septal defects and the relationship to familial migraine with aura. *Heart* 90:1245–1247
6. Lampl C, Bonelli S, Ransmayr G (2004) Efficacy of topiramate in migraine aura prophylaxis: preliminary results of 12 patients. *Headache* 44:174–177
7. Lampl C, Katsarava Z, Diener HC, Limmroth V (2005) Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. *J Neurol Neurosurg Psychiatry* 76:1730–1732
8. Schwerzmann M, Wiher S, Nedeltchev K et al (2004) Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. *Neurology* 62:1399–1401
9. Post M, Thijs V, Herroelen L, Budts W (2004) Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine. *Neurology* 62:1439–1440
10. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL (2000) Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. *Lancet* 356:1648–1651
11. Mortelmans K, Post M, Thijs V et al (2005) The influence of percutaneous atrial septal defect closure on the occurrence of migraine. *Eur Heart J* 26:1533–1537
12. Reisman M, Christofferson RD, Jesurum J et al (2005) Migraine headache relief after transcatheter closure of patent foramen ovale. *J Am Coll Cardiol* 45:493–495

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13. Azarbal B, Tobis J, Suh W et al (2005) Association of interatrial shunts and migraine headaches: impact of transcatheter closure. *J Am Coll Cardiol* 45:489–492
  14. Anzola GP, Frisoni GB, Morandi E et al (2006) Shunt-associated migraine responds favorably to atrial septal repair: a case-control study. *Stroke* 37:430–434
  15. Buring JE, Peto R, Hennekens CH (1990) Low-dose aspirin for migraine prophylaxis. *JAMA* 264:1711–1713
  16. Diener HC, Hartung E, Chrubasik J et al (2001) A comparative study of acetylsalicylic acid and metoprolol for the prophylactic treatment of migraine. A randomised, controlled, double-blind, parallel group phase III study. *Cephalalgia* 21:140–144
  17. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL (2005) Clopidogrel reduces migraine with aura after transcatheter closure of persistent foramen ovale and atrial septal defects. *Heart* 91:1173–1175
  18. Sharifi M, Burks J (2004) Efficacy of clopidogrel in the treatment of post-ASD closure migraines. *Catheter Cardiovasc Interv* 63:255