

New and Emerging Technology Briefing

*National
Horizon
Scanning
Centre*

Patent foramen ovale closure for migraine

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Horizon Scanning Review

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**UNIVERSITY OF
BIRMINGHAM**

Patent foramen ovale closure for migraine

Summary

There is evidence that the prevalence of patent foramen ovale (PFO) is increased in people with migraine, and retrospective observational trial data from patients with stroke and divers with decompression illness suggesting that percutaneous closure of PFO reduces the frequency of migraine attacks. One company has completed enrolment into a clinical trial in patients with refractory migraine with aura. A second device has just started a phase II clinical trial.

Developer – There are several PFO closure devices, but only 2 in clinical trials in migraine: NMT Medical's STARFlex septal repair implant, and St Jude Medical's Premere PFO closure device.

Regulatory status – Both devices are CE marked.

Unit cost – PFO closure devices cost just over £4,000. Procedure costs are additional.

NHS or Government priority - None identified.

Relevant existing UK guidance – Interventional Procedures Programme guidance on PFO closure in stroke prevention.

Burden of disease - Migraine is common with an estimated one-year prevalence of 10% (5M people in England and Wales). 10-15% of those with migraine have migraine with aura (500,000–750,000 people in the England Wales). About 10% of people having weekly attacks (50,000–75,000 people in England Wales).

Potential clinical benefit – If PFO closure can reduce the frequency and impact of migraine attacks without significant adverse effects, then this technology may be welcomed by patients and health staff alike. Selection of the most appropriate patients to benefit is likely to be important.

NHS or societal resource impact - Although the prevalence of PFO in patients with migraine is higher than in people without migraine, until results from intervention trials are presented, a cause and effect relationship cannot be assumed. The first intervention trial to report is relatively small, and any positive results may need confirming. Although there is increasing interest from patients and health staff, diffusion may be limited by the number of neurologists and interventional cardiologists available to screen patients with migraine for subsequent PFO closure.

Background

A patent foramen ovale (PFO) is the persistence of a hole in the wall between the right and left atria of the heart. The foramen ovale usually closes spontaneously after birth, however in as many as 1 in 4 people it does not close completely and remains patent throughout life. In most people the persistence of a PFO does not cause any complications. However there have

been a number of studies reporting an increased prevalence of PFO (and other atrial shunts) in people with migraine, particularly migraine with aura (47% in one study¹). Studies of PFO closure in divers with decompression illness and for the prevention of recurrent strokes have suggested that closure improves migraine.

For patients with a PFO as an isolated finding no special treatment is indicated. In patients with stroke or transient ischaemic attacks (TIAs), treatment is aimed at preventing recurrent events, and can include anticoagulant therapy, open surgical closure, and percutaneous closure. Percutaneous closure of PFO involves placing an umbrella-like closure device across the PFO to seal the hole. Echocardiography and fluoroscopic guidance are used to determine the size and position of the defect and to check the placement of the closure device.

379 PFO closures were undertaken in 28 centres in Britain in 2004, and 195 closures in 22 centres in 2003.²

The technology

There are several different devices available for PFO closure, although only two, the STARFlex device (NMT Medical) and the Premere device (St Jude Medical), are in clinical trials in migraine.

STARFlex – NMT Medical

STARFlex is a septal repair implant that is CE marked and used in the UK for PFO closure to reduce the risk of recurrent stroke and TIAs, and for decompression illness. Implantation uses similar facilities and takes a similar time as angiography, requires access to transoesophageal echocardiography, a light general anaesthetic, and may involve an overnight hospital stay. A newer imaging technique, intracardiac echocardiography (ICE), eliminates the need for transoesophageal echocardiography and the general anaesthetic.

The next-generation NMT Medical PFO closure device, BioSTAR, is in early clinical trials, and is a bioresorbable, drug eluting implant with tissue engineered collagen matrix discs.

Premere device – St Jude Medical

The Premere device is CE marked and has just started in clinical trials for migraine.

PFX radiofrequency closure system – Cierra

A new technique for PFO closure is in clinical trials within Europe. This technique uses radiofrequency energy delivered percutaneously to seal the PFO. Patients are not left with a cardiac implant *in situ* as with current closure devices. The company anticipate receiving a CE mark by mid-2006, and plan to launch the technique for PFO closure in patients with migraine in the USA during 2006.

Burden of disease and patient group

Migraine is a primary headache disorder manifesting as recurrent attacks usually lasting 4-72 hours and involving pain of moderate to severe intensity, often with nausea, sometimes vomiting, and/or sensitivity to light, sound and other sensory stimuli.³ About 15% of people have migraine with aura and experience visual or other neurological disturbance.

Migraine is common with a female to male predominance and an estimated one-year prevalence of 10% (5M people in England and Wales); 15% in women and 6% in men.⁴ Between age 10 and 19 there is a sharp rise in the one-year prevalence with a peak around ages 14-16. For women this is followed by a second rise until age 40 (with a peak prevalence of around 24%). 10-15% of those with migraine have migraine with aura (500,000–750,000 people in the England Wales). The average number of migraine attacks reported per year is 13, with at least 10% of people having weekly attacks (50,000–75,000 people in England Wales). The Migraine Trust estimate that one third of people with migraine will experience significant disability as a result of their migraines at some or all stages of their lives.⁵

Current treatment and alternatives

The tendency to migraine headaches cannot be cured, but can be modified and controlled by lifestyle adjustments and the use of medicines. Lifestyle modification may include avoidance of: stress, lack of sleep, particular foods, and oral contraceptives. Pharmacological therapy can be divided into drugs intended to alleviate the acute headache (simple analgesics, anti-emetics, 5-HT₁ agonists – the ‘triptans’) and those designed to prevent future attacks (pizotifen, beta-blockers, amitriptylline, sodium valproate, topiramate – some as unlicensed indications). Preventive treatment is usually considered for patients who have at least 2 attacks a month, have an increasing frequency of headaches, and/or have significant disability despite suitable treatment or cannot take suitable treatment. Other beneficial therapies include relaxation therapy and acupuncture.

Prodigy published revised guidance on migraine in July 2005.⁶

The Interventional Procedures Programme at NICE reviewed percutaneous closure of PFO for the prevention of cerebral embolic stroke in January 2005. They reported that evidence at that time suggested that there were no major safety concerns and that percutaneous closure was efficacious in closing the hole; however its efficacy in preventing future strokes was not clearly shown.

Cost

The STARFlex and Premere devices cost just over £4,000 (£3,500 + VAT). Procedure costs are additional.

Current research evidence

Effectiveness

STARFlex – NMT Medical

Preliminary findings from the Migraine Intervention with STARFlex Technology 1 (MIST1) trial, a prospective, double-blind, placebo-controlled randomised trial of PFO closure in adults aged 18 to 60 with frequent migraines with aura not controlled by 2 or more classes of prophylactic medical therapy have been reported in abstract. Patients underwent contrast

transthoracic echocardiography to identify those with a shunt, followed by a transoesophageal echocardiography under general anaesthetic to confirm the presence of a PFO. Patients with PFO were randomised to immediate closure with the STARFlex device or no further intervention. The primary outcome is the incidence of headache during the first 6 months. Secondary outcomes include incidence of migraine in the first 3 months, change in frequency, characteristics and severity of migraine attacks based on MIDAS (migraine disability assessment) and HIT-6 (headache impact test) scores, and change in quality of life (SF36-v2). Other endpoints include safety of the procedure and fitting of the device, and the incidence of adverse events. Follow up is for 6 months. At 6 months patients who did not have PFO closure can opt to have closure. Of the 432 people with refractory migraine with aura screened, 16.7% had a small atrial or pulmonary shunt, 5.1% had a large pulmonary shunt, 0.7% had an atrial septal defect, and 37.7% had a large PFO.⁷ This is about 6 times what you would expect in the normal population. Of the 163 people with a large PFO 16 were withdrawn before randomisation, 73 were randomised to the control group, and 74 to PFO closure.

Cost-effectiveness

No economic evaluations have been identified.

Adverse effects

The Interventional Procedures Programme guidance reported major and minor complication rates of 1.5% and 7.9% respectively.^a Major complications included death, haemorrhage requiring blood transfusion, cardiac tamponade, the need for surgical intervention and pulmonary embolus. Minor complications included bleeding, arrhythmia, device fracture, device embolisation, air embolisation and arteriovenous fistula formation. The Specialist Advisors noted that serious adverse events were uncommon, and that other minor side effects include migraine, minor arrhythmias and local bruising.

Ongoing or related research

STARFlex – NMT Medical

MIST II, a USA-based trial with a planned patient recruitment of approximately 600 people with refractory migraine with aura, started recruiting in January 2006. Enrolment is scheduled to be complete by the end of 2006, with a follow up period of 1 year.

Premere - St Jude Medical

A USA-based randomised, double-blind, placebo-controlled phase II trial (ESCAPE trial) comparing PFO closure with medical therapy in patients with refractory migraine and a PFO has just started recruitment. Outcomes include frequency and characteristics of migraine attacks, procedure success, adverse events, and long-term device performance.

PFX radiofrequency closure system – Cierra

A European non-randomised, active control, open label study of the PFX system in patients with stroke, TIA, refractory migraine and decompression illness is planned. Recruitment of the planned 60 patients has not yet started. Outcomes include successful PFO closure, adverse

^a A difficulty in assessing the incidence of adverse events from published case series is that different closure devices were used in different studies. Patients with previous stroke or TIA will, in general, be older than any patients with migraine considered for PFO closure.

events, conduction abnormalities, and migraine severity and frequency at 6 and 12 months post procedure for those enrolled with migraine.

Cost impact and projected diffusion

Although the prevalence of PFO in patients with migraine, particularly migraine with aura, is higher than in people without migraine, until results from intervention trials are presented, a cause and effect relationship cannot be assumed. The first intervention trial to report is relatively small, and any positive results may need confirming before invasive PFO closure with its associated adverse events can be recommended unreservedly to patients with refractory migraine with aura. Although there is increasing interest from patients and health staff, diffusion may be limited by the number of neurologists and interventional cardiologists available to screen patients with migraine and for subsequent PFO closure. Access to transthoracic or intracardiac echocardiography and percutaneous intervention facilities is required and may impact on access to the same facilities by patients with coronary artery disease. If trials prove positive and given the size of the potential patient group (possibly in the region of 50,000-75,000 people in England and Wales), this development, could have a significant impact on NHS services, costs and patient quality of life.

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The National Horizon Scanning Centre,
Department of Public Health and Epidemiology
University of Birmingham, Edgbaston, Birmingham, B15 2TT, England
Tel: +44 (0)121 414 7831 Fax +44 (0)121 414 2269
www.pcpoh.bham.ac.uk/publichealth/horizon