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Foramen Ovale Closure devices for the treatment of migraine

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PRIORITISING SUMMARY

REGISTER ID: **000219**

NAME OF TECHNOLOGY: **FORAMEN OVALE CLOSURE DEVICES**

PURPOSE AND TARGET GROUP: **FOR MIGRAINE SUFFERERS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☐ Yes — ARTG number
- ☒ No
- ☐ Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States	✓		
Italy	✓		

IMPACT SUMMARY:

A number of manufacturers provide patent foramen ovale closure devices for the treatment of migraine headaches. Three devices are currently in clinical trials and have United States Food and Drug Administration (FDA) approval: the STARFlex™ septal occlusion system manufactured by NMT Medical, Premere™ PFO closure system produced by St Jude Medical and AGA Medical Corporation's AMPLATZER® PFO occluder. None of these devices have approval from the TGA.

BACKGROUND

Migraine is a chronic, debilitating neurovascular disorder characterised by unilateral throbbing headache which may last from four hours to three days. Migraine is more common in females than males and is a major cause of disability in the work place. Migraines are classified as either with or without aura. Migraines *without* aura are associated with symptoms including nausea, vomiting and sensitivity to light, sound and head movements. Migraines *with* aura are associated

with transient focal neurotic symptoms which may include loss of vision, pins and needles, flickering of lights, spots or lines on vision (Arulmozhi et al 2005).

A cause-and-effect relationship has yet to be established between migraine headache and patent foramen ovale (PFO), however it has been estimated to be present in 40-60 per cent of patients suffering migraine with aura, and in 20-30 per cent of migraine patients without aura, when compared to the general population (Schwedt and Dodick 2006). PFO is a residue of fetal circulation and results from the failure of the primum and secundum septa to fuse postnatally. The consequence of this is a one-way flap valve which overlays the fossa ovalis and results in the incomplete closure of the atrial septum (Kizer and Devereux 2005). PFO results in inter-arterial right-to-left shunting, however the effect is transient and is only present when the right arterial pressure exceeds the pressure in the left atrium (Ferrarini et al 2005). PFO is a common cardiac defect usually found in young cryptogenic stroke patients, where the excess pressure results in paradoxical embolism ie the atrial septum allows blood to flow backwards from the right atrium to the left atrium, potentially carrying venous thromboemboli to the brain, resulting in stroke (Kizer and Devereux 2005).

PFO closure devices are introduced into the right atrium via a catheter introduced from the right femoral vein under local anaesthesia. The catheter is advanced across the foramen into the left atrium where the closure device, a small umbrella-like implant is opened, closing the defect. The same steps are followed to close the right side of the defect. The closure device is released from the catheter and over time, tissue grows in and around the framework of the device, securing it in place (Figure 1). Patients are prescribed antiplatelet drugs and antibiotics for at least three months to prevent clot formation, and to continue aspirin for a further three months. Complete closure is reported in 80-95 per cent of patients (Kizer and Devereux 2005).

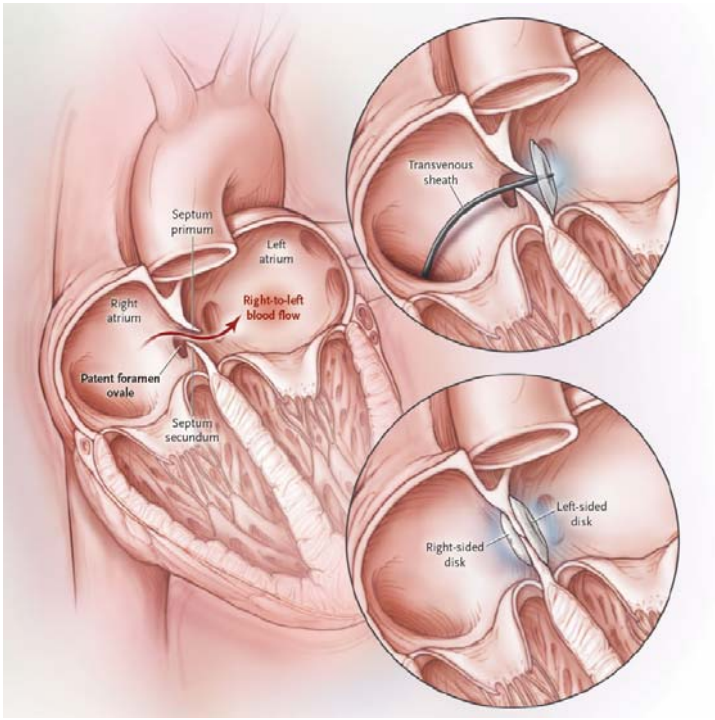

Figure 1 Closure of a patent foramen ovale (Printed with permission: Kizer and Devereux 2005)

CLINICAL NEED AND BURDEN OF DISEASE

The 2001 National Health Survey reported that over 1.4 million Australians had a self-reported nervous system disease, and that more than three-quarters (1.2 million) of these individuals suffered from migraine. The reported rate for migraine was 3.6% and 8.7% for males and females, respectively, with an overall population rate of 6.2% (AIHW 2004).

In 2002, Waldie and Poulton reported on the results of the Dunedin Multidisciplinary Health and Development Study, a birth cohort born in Dunedin, New Zealand between 1972 and 1973. This cohort (n=980) was investigated at 26 years of age for the prevalence of headache and migraine. The 1-year prevalence for migraine was 7.4% and for combined migraine with tension-type headache was 4.3%.

A large population-based study reported that of individuals suffering from migraine, 64% had migraine without aura, 18% had migraine with aura and 13% had both types of migraine (5% had aura without headache) (Arulmozhi et al 2005).

Dalla Volta et al (2005) examined a large case series of patients who suffered from migraines (n=372) (level IV aetiology evidence). All patients were screened for PFO by contrast-enhanced transcranial Doppler. Of the 260 patients who suffered migraine with aura, 161 had a PFO (62%). By contrast only 12/74 (16%) pf patients who suffered migraine without aura had a PFO. The remaining 38 patients suffered from cluster headaches and of these, 14 (36.8%) had a PFO.

It has been estimated that a patent foramen ovale is present in 27 per cent of unselected adults (Kizer and Devereux 2005).

DIFFUSION

PFO closure devices are not used in Australia or New Zealand for the treatment of migraine. NMT Medical intends to distribute the STARFlex® closure device in New Zealand and Australia in the near future (personal communication, NMT Medical May 2006).

COMPARATORS

Modifications of lifestyle, including avoidance of stress, lack of sleep, certain foods and the oral contraceptive, may alleviate migraine in some patients. Pharmaceutical treatments for migraine aim to either prevent migraine from occurring or to abolish the acute pain of the headache once it has occurred. Current treatments include calcium channel blockers, 5-HT receptor agonists (serotonin agonists or triptans), beta adrenoceptor blockers and γ-amino butyric acid (GABA) agonists. Ergotamine and the triptans are two of the most "popular" classes of drugs used for the treatment of migraine. Ergotamine is a vasoconstrictor and an alpha-1 selective adrenergic agonist. The exact mode of action of triptans is unknown, however it has been suggested that they either act via vasoconstriction of meningial, dural, cerebral or pial vessels; or inhibit dural neurogenic inflammation; or inhibit pain transmission. Sumatriptan was the first 5-HT agonist to be developed but many more have been developed since (Arulmozhi et al 2005).

EFFECTIVENESS AND SAFETY ISSUES

A large double blind, sham-controlled, randomised controlled trial of the STARFlex® device (MIST 1 trial) has been completed and preliminary results were presented to the American College of Cardiology conference, in 2006 (level II Intervention evidence). Patients suffering from migraine with aura were recruited (n=432) and screened for PFO using transthoracic echocardiography. Of these, 163 (37.7%) had a large PFO of whom 147 were randomised to either the treatment arm (n=74) or the sham arm (n=73), with 16 patients being excluded. A six

month follow-up was completed by 135 patients. Initial results indicate that the primary aim of the study was not fulfilled in that patients in the treatment group did not experience the full abolition of migraine headache. However, 42 per cent of patients in the treatment group experienced a 50 per cent reduction in the number of headache days, compared to 23 per cent in the sham-operated group (p=0.038). This study also reported a significant reduction in the headache burden (frequency x duration) of 50 hours per months in the treatment group (37% reduction) compared to the sham-control group (17% reduction), (p=0.033). However, it should be noted that the baseline values for the treatment group were much higher than for the sham-control group (Wilmhurst 2006).

Morandi et al (2005) conducted a small cohort study (level III-2 intervention evidence) which compared 12 consecutive women treated with conventional anti-migraine medication (NSAIDS and 5-HT agonists) to 12 consecutive women treated with a PFO closure device (device not stated). In both groups, 10 women suffered from migraine with aura and two suffered from migraine without aura. All had a large right-to-left shunt and follow-up was 12 months. A migraine severity score was obtained before and after treatment (ranging from 0-10, see appendix). Table 1 summarises these results. Differences in total score were significantly reduced in the PFO closure device group (p<0.0001). Migraine was reported in 10/12 (83%) of the medically treated group compared to 1/11 (9%) of the PFO implant group (OR= 55, 95% CI 4.3, 703, Fisher's Exact Test p=0.0006).

Table 1 Migraine severity score of medically treated patients vs PFO closure (Morandi et al 2005)

Medical group	Intensity score	Duration score	Frequency score	Total score
Baseline	1.9	2.2	1.9	6.8
1-year	2.2	2.1	2.2	7.2
PFO closure group				
Baseline	2.3	2.0	1.3	6.3
1-year	1.0	1.1	0.6	3.6

Reisman et al (2005) performed PFO closure on 162 consecutive patients with cryptogenic stroke (level IV intervention evidence). Fifty seven patients (35%) suffered from migraine and of these, 39/57 (68%) suffered from migraine with aura. At a mean follow-up time of 37 ± 23 weeks, patients (n=50) reported significantly fewer migraine episodes per month after PFO closure (1.4 ± 3.4 episodes) compared to before closure (6.8 ± 9.6 episodes) (p<0.001). Migraine resolution results are described in Table 2.

Table 2 Migraine resolution (Reisman et al 2005)

	Complete relief	Significant relief	No relief
MA^+ and MA^- (n=50)	28/50 (56%)	7/50 (14%)	15/50 (30%)
MA^+ (n=38)	54.1%	13.5%	32.4%
MA^- (n=12)	61.5%	15.4%	23.1%

MA^+ = migraine with aura, MA^- = migraine without aura

Giardini et al (2006a) performed PFO closure on 38 consecutive patients for the treatment of cryptogenic stroke (level IV intervention evidence). Three types of closure devices were used: the AMPLATZER® PFO occluder, the CardioSEAL or the Helex device. Of the 38 patients, 13 (34%) suffered from migraine with aura. The PFO closure device was implanted successfully in all 38 patients. One patient underwent the removal of the PFO closure device and had it replaced with a larger closure device. Residual right-to-left shunting was detected in 16/38 (42%) patients immediately after implantation, however at 6 months a residual shunt was detected in only 6/38 (16%) of patients, and of these two were migraine sufferers. Immediately after the PFO closure procedure, 12/13 (92%, 95%CI 65, 99) had complete resolution of migraine headache. After a mean follow-up of 4.9 ± 1.4 years, migraine was completely resolved in 11/13 patients (85%, 95% CI 57, 97). The number of migraine episodes before treatment were 16.4 ± 18.2, which were reduced at follow-up to 1.8 ± 2.6 (time span not stated) (p<0.0001). A MIDAS (migraine disability assessment questionnaire) score was calculated by adding up the number of functional days lost due to migraine. The MIDAS score before treatment was 38.6 ± 26.3, which was reduced at follow-up to 4.4 ± 5.1 (p<0.0001). Migraine was not resolved in 1/13 (7.7%) but an improvement in the severity of symptoms was noted. One patient reported a severe relapse of migraine symptoms one year after the procedure.

The FDA MAUDE database for the registration of adverse events associated with medical devices lists 17 adverse events associated with PFO closure devices, used for the management of stroke, during the period 2004-2006. The majority of these adverse events were associated with operator error, due to a lack of training in the insertion of such devices. There were three deaths recorded on the database: one was not device related and two were as a result of device embolisation. There were three adverse events involving embolisation of the device, which was subsequently surgically removed (FDA 2006).

An editorial by Shapiro (2006) stated that in a series of 272 patients treated for cerebral ischemia with a PFO closure device, a periprocedural complication rate of 6.6% was reported. However, five of these patients (1.8%) experienced a transient ischemic attack or a stroke, likely due to their pre-existing condition. Two patients (0.7%) required surgery to remove devices that had migrated and embolised. Other potential complications include thrombus formation on the implanted closure device or incomplete closure.

COST IMPACT

NMT Medical currently markets the STARFlex® in the United States for US$5,000, not including the cost of implantation. In addition, an economic analysis on the use of PFO closure devices for the treatment of migraine in Europe is currently being conducted (personal communication, NMT Medical May 2006).

Implantation of the PFO closure device is performed by the insertion of a catheter into the heart. Right heart catheterisation with left heart catheterisation, including fluoroscopy is listed on the Medicare Benefits Schedule (item number 38206) for a fee of $556.15.

The usage and cost of commonly prescribed pharmaceuticals for migraine that are available on the PBS are listed in Table 3. With the implantation of a PFO closure device, the overall cost of pharmaceuticals may be reduced. A study conducted in 1990, estimated that the *annual* cost of migraine to the community in Australia at that time, through loss of productivity and the cost of medical services, was $302-$721 million (Lance 1996).

Table 3 Usage and cost of common migraine drugs (July 2004 - June 2005)

Generic drug name	PBS code	Dispensed price ($)	Number of services July 2004 - June 2005	PBS benefit ($) July 2004 - June 2005
Sumatriptan	8341B	15.94	38,158	499,724
Dihydroergotamine mesylate	1323P	15.46	1,610	25,873
Naratriptan hydrochloride	8298R	26.94	54,962	1,087,629
Zolmitriptan	8266C	26.88	89,605	1,735,601
Total			184,335	3,348,827

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

The MIST01 double blinded randomised trial (n=150) comparing PFO closure with STARFlex® implant to control patients (sham procedure) was due to be completed by May 2005, however results from this trial have not been identified. A phase III trial of this device began recruitment of patients (expected enrolment n=610) in February 2006 and expects to complete follow-up in December 2007 (CCT 2006). AGA Medical Corporation are currently recruiting 120 patients to participate in a randomised, shame-controlled trial of their AMPLATZER® device. St Jude Medical are currently enrolling 500 patients in a randomised controlled trial comparing the Premere PFO closure device to sham-control patients (*Headache* 2006).

CONCLUSION:

Preliminary results from one high quality study indicate that closure of a patent foramen ovale may reduce the frequency and severity of migraine headaches, but not completely abolish them.

HEALTHPACT ACTION:

The cause and effect relationship of migraine and patent foramen ovale is yet to be established. It is therefore recommended that this technology be archived.

SOURCES OF FURTHER INFORMATION:

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Waldie, K. E. & Poulton, R. (2002). 'The burden of illness associated with headache disorders among young adults in a representative cohort study', *Headache,* 42 (7), 612-619.

Wilmhurst, P. (2006). 'A Prospective, Multicenter, Randomized, Double Blind, Placebo-Controlled Trial to Evaluate the Efficacy of Patent Foramen Ovale Closure with the STARFlex® Septal Repair Implant to Prevent Refractory Migraine Headaches: The MIST Trial', Conference Proceeding: American College of Cardiology, Atlanta, United States.

LIST OF STUDIES INCLUDED

Total number of studies	
Level II intervention evidence	1
Level III-2 intervention evidence	1
Level IV intervention evidence	2

SEARCH CRITERIA TO BE USED:

Heart Catheterization
Heart Septal Defects, Atrial
Migraine Disorders
*Prostheses and Implants
Headache Disorders, Primary
Migraine with Aura
Migraine without Aura

APPENDIX

Migraine severity score

Intensity

0= no pain, 1= mild (not interfering with daily activity), 2 = severe (interfering with daily activity), 3 = unbearable (confined to bed)

Duration

0 = no pain, 1= <6 hours, 2= 6-12 hours, 3= >12 hours

Frequency

0 = no pain, 1= 1-4/month, 2= 5-9/month, 3= >10/month

Aura
0= no aura, 1= aura