NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous closure of patent foramen ovale for recurrent migraine

The foramen ovale is a hole in the wall that divides the two upper chambers of the heart. The hole is present in the heart of a developing fetus, but normally closes up soon after the baby is born. If it fails to close it is known as a patent foramen ovale (PFO). In most people, this doesn't cause any problems but some studies have suggested that there could be a link between having a PFO and recurrent migraines. This procedure involves passing a device through a large vessel in the groin up into the heart and closing/blocking the hole in the wall of the heart.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in May 2010.

Procedure name

- Percutaneous closure of patent foramen ovale for recurrent migraine

Specialty societies

- British Cardiovascular Intervention Society (BCIS)
- Society for Cardiothoracic Surgery in Great Britain and Ireland
- British Association for the Study of Headache

Description

Indications and current treatment

Migraine is a severe headache, often accompanied by sensitivity to light, sleep disruption and depression. It may also include aura which is characterised by a perception of an unusual light, an unpleasant smell or occasionally confusing thoughts or experiences.

The optimal treatment modality for patients with migraine is medical therapy, either to prevent or abort episodes. In patients for whom medical therapy has failed, invasive treatments such as nerve blocks or physical therapies such as acupuncture are sometimes used. Closure of a patent foramen ovale (PFO) has been used to treat migraine based on observations described below.

A PFO is the persistence of an opening (the foramen ovale) in the septum between the right atrium and left atrium of the heart. Before birth the fetal heart has a structural opening between the two atria called the foramen ovale. This normal passage allows blood from the placenta to bypass the lungs and be directed straight to the left side of the circulation, supplying blood to the brain and body before it returns to the placenta. The foramen ovale usually closes spontaneously after birth; however in as many as 1 out of 4 people the foramen ovale remains fully or partially patent into adulthood.

What the procedure involves

Several studies evaluating the outcome of PFO closure to prevent paradoxical thromboembolism noted a change in the incidence of migraine amongst patients and as a result, percutaneous closure of the PFO has been introduced as an option for patients with a PFO and recurrent migraine after medical therapy has failed. Any physiological effect of PFO closure in migraine treatment is not understood.

Percutaneous closure is performed using local anaesthesia and intravenous sedation, or general anaesthesia. A guidewire and delivery sheath are introduced through a small incision in the groin into the femoral vein and passed into the heart, across the PFO, with image guidance such as transoesophageal or transthoracic echocardiography, or transcranial Doppler ultrasound.

A closure device is introduced through the opening via the delivery sheath and released, closing the PFO. A range of devices of differing design and mechanism is available.

Instruments used to assess efficacy

Migraine Disability Assessment questionnaire (MIDAS) is a patient-completed 7-item questionnaire (with 5 scored items) which is often used to measure disability related to migraine. Questions cover the frequency and severity of migraine, and days lost from everyday activity. Scores of 21+ indicate severe

disability (grade 4), 11–20 moderate disability (grade 3), 6–10 mild disability (grade 2), and 0–5 little or no disability (grade 1).

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous closure of patent foramen ovale for recurrent migraine. Searches were conducted of the following databases, covering the period from their commencement to 26 August 2010: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with recurrent migraine.
Intervention/test	Percutaneous closure of patent foramen ovale.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 2337 patients from a randomised-controlled trial (RCT), 2 non-randomised comparative studies, 2 case series, 1 RCT of different devices, results from a registry, and 7 case reports.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on percutaneous closure of patent foramen ovale for recurrent migraine

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details

Dowson A (2008)[1]

RCT (double-blind)

UK

Recruitment period: not reported

Study population: migraine with aura (with frequent refractory attacks) and moderate to large PFO detected by TTE

n = **147 (74 percutaneous closure vs 73 sham)**

Mean age: 44.3 vs 44.6 years
Sex: 84% vs 85% female

Patient selection criteria: 18 to 60 years of age with history of migraine with aura as defined by the criteria of the International Headache Society starting before 50 years of age, ≥ 5 incidences per month but at least 7 headache-free days, failure of at least 2 other treatments (beta blockers, anticonvulsants, calcium channel blockers, tricyclics and serotonin antagonists)

Exclusion criteria: other cardiovascular defects, intracardiac thrombi, active endocarditis, other medical

Key efficacy findings

Number of patients analysed: **147 (74 percutaneous closure vs 73 sham)**

Closure of PFO (on TTE)

Not clear if this was tested immediately after implantation (5 patients [7%] of those randomised to closure were unable to have closure because no PFO was found or crossed so did not have the procedure)

Presence of residual shunt on TTE at final follow-up

All patients were tested with TTE and residual moderate or large atrial shunts were reported in 4 patients at 6 months (no differences in treatment effect in those closed versus those with residual shunt).

Presence of migraine and migraine-related disability (per protocol, n = 136)

	Percutaneous closure (n = 64*)		Sham (n = 71)		p value between groups
	Baseline	~6 months	Baseline	~6 months	
Patients without migraine (from daily patient diary)	0	3	1**	3	1.0
Mean frequency of attacks per month (No. of patients)	4.82 (64)	3.23 (64)	4.51 (71)	3.53 (71)	0.13
Median MIDAS score (migraine disability) (No. of patients)	36 (3-108) (57)	17 (0-270) (64)	34 (2-189) (67)	18 (0-240) (71)	0.89
Mean HIT-6	67	60	66	59	0.79

Key safety findings

Complications

Event in intervention group	Rate (No.)
Device embolisation into right atrium [a, b]	1.4% (1/74)
Device prolapse into right atrium [a, b]	1.4% (1/74)
Failure of device to deploy [b]	1.4% (1/74)
Cardiac tamponade before device deployment [c]	1.4% (1/74)
Chest pain [c]	1.4% (1/74)
Chest infection and asthma	1.4% (1/74)
Arrhythmia [c]	1.4% (1/74)
Retroperitoneal bleeding managed conservatively	1.4% (1/74)
Pericardial effusion	2.7% (2/74)

(rate calculated by analyst)

[a] these both occurred shortly after they were released; they were successfully retrieved with snares
[b] another device was successfully implanted
[c] patient withdrew from the study

Event in sham group	Rate (No.)
Incision site bleed	1.4%

Comments

Follow-up issues:

- Patients attending the clinic for 6 visits at intervals of around 30 days.
- 2 in sham group withdrew (stroke – 1, menorrhagia – 1), 9 withdrew in intervention group (5 unable to have closure because of no PFO, 3 because of safety events, 1 lost to follow-up)

Study design issues:

- Known as the MIST trial.
- 432 patients recruited from participating headache centres or by self-referral from website were screened for inclusion. 16 patients withdrew before randomisation (6 for personal reasons or loss

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments

Study details

condition or contraindication to the procedures and treatments, portal hypertension or pulmonary arteriovenous malformation, contraindication to aspirin or clopidogrel, other medical condition or contraindication to the procedures and treatments, pregnancy (or planning pregnancy), nursing during duration of study, PFO closure for other reasons (stroke or decompression illness)

Technique: all patients had aspirin and clopidogrel for 24 hours before procedure, randomization after general anaesthetic and TOE assessment: <u>percutaneous procedure</u>: STARFlex septal repair implant (NMT Medical Inc) with intravenous heparin periprocedurally or <u>sham</u>: skin incisions in groin; all patients continued existing migraine prophylaxis

Follow-up: **~ 6 months**

Conflict of interest/source of funding: funded and partly designed by manufacturer

Key efficacy findings

score (migraine disability) (No. of patients)	(57)	(64)	(67)	(71)	
Headache days over 3 months (range) (No. of patients)	26 (0-70) (57)	19 (0-90) (64)	30 (5-80) (67)	21 (0-80) (70)	0.85
Median migraine headache days per month (range)** (No. of patients)	6.0 (1-17.0) (62)	3.8 (0-13.3) (62)	5.0 (0-20.0) (70)	3.7 (0-16.7) (71)	0.027

*one patient was missing diary cards
**not clear why one patient had no migraine at baseline since the inclusion criteria requires patients with migraine. It is possible that this patient was not having a migraine episode at the time of the procedure
***results when 2 patients who accounted for 20% of all days were removed from the analysis of migraine headache days

Key safety findings

	(1/73)
Nosebleed	1.4% (1/73)
Anaemia from menorrhagia	1.4% (1/73)

Most patients in both groups reported ≥ 1 minor adverse event usually attributed to the antiplatelet medication.

Comments

to follow-up, 6 for medical reasons such as pregnancy, dental treatment, hysterectomy, 4 after TOE).

- Sample size estimated at 150; calculation anticipated cessation of migraine in 40% compared to 15% in sham for 80% power allowing for 10% drop-out rate and 4% loss of blinding (but less than 150 patients were recruited and 12% in intervention group dropped out). Powered for resolution of migraine (1st outcome), so may not give adequate representation of reduction of severity or frequency of migraines.
- Randomisation by telephoned

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
			central computerized service; blocks of 4 in 1:1 ratio • Only staff in cardiac catheterization laboratory knew treatment allocation (not patient or headache specialist); revealed at last visit. • Experienced interventional cardiology centres. • ITT analysis of randomised patients was performed but gave similar results. • MIDAS and HIT-6 scores taken retrospectively (for 3 and 1 months, respectively). • HIT-6 measures pain, social functioning, role functioning, vitality, cognitive functioning and psychological

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
			distress on a scale from 36 to 78 with higher numbers indicating greater impact. **Study population issues**: • The patients included in this study were taking very few prophylactics at baseline so they may have had failure of these treatments in the past. **Other issues**: • It is not clear how many patients had a successfully closed PFO.

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Rigatelli G (2010)[2]

Non-randomised comparative study
Italy and USA
Recruitment period: not reported
Study population: patients referred to centre with migraine with or without aura and PFO confirmed on TTE and TOE
n = 86 (40 percutaneous closure vs 46 medical therapy)
Mean age: 40 years
Sex: 79% female
Presence of aura: 80% (32/40) vs 21.7% (10/46)

Patient selection criteria: see above but for treatment allocation see ‘study design issues’
Technique: <u>percutaneous closure</u> – use of Premere (ST. Jude Medical) or an Amplatzer device (AGA Medical: PFO, Cribriform or ASD Occluder); <u>medical therapy</u> – continued on existing medical therapy
Mean follow-up: 29.2 months
Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 86 (40 percutaneous closure vs 46 medical therapy)

Presence of migraine and migraine-related disability

<table>
<tr><th></th><th colspan="2">Mean MIDAS score ± standard deviation</th><th>p value</th></tr>
<tr><th></th><th>Baseline</th><th>Mean follow-up 29.2 months</th><th></th></tr>
<tr><td>Percutaneous closure (n = 40)</td><td>35.8 ± 4.7</td><td>8.3 ± 7.8</td><td>p < 0.003</td></tr>
<tr><td>Medical therapy (n = 46)</td><td>22.6 ± 7.1</td><td>19.1 ± 8.2</td><td>p = 0.059</td></tr>
</table>

Aura disappeared in all 32 patients who had pre-procedural aura.

Closure of PFO (on TOE and TCD)
Closure was successful in all cases.
After mean follow-up of 29.2 months, 95% had complete PFO closure.

Presence of residual shunt
5% (2) had persistent small shunt on TOE</td>
<td>Complications
No periprocedural or in-hospital complications.

2 developed AF in early post-procedural period. These were successfully treated with post-procedural antiarrhythmic drugs.</td>
<td>Follow-up issues:
• TOE at 1 month and, if residual shunt, at 6 months; TTE and clinical visit at 1, 6 and 12 months; Holter monitoring at 1 month. MIDAS evaluation at 6 and 12 months.

Study design issues:
• Refractory disabling migraine defined as MIDAS score >25 and refractory to drug therapy.

Study population issues:
• Because of the treatment allocation criteria, those treated with the procedure were more likely to have basal shunt and shower/curtain pattern on TCD and echocardiograp</td>
</tr>
</table>

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
			hy, interatrial septal aneurysm and Eustachian valve, higher MIDAS score (class 3-4), higher grade of right-to-left shunt, coagulation abnormalities, refractory disabling migraine with or without aura

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Vigna C (2009)[3]
Non-randomised comparative study
Italy
Recruitment period: 2004 – 2006
Study population: moderate/severe migraine and PFO (confirmed with TCD and TOE) with large right-to-left shunt
n = 82 (53 percutaneous closure vs 29 control)
Mean age: 43 years
Sex: 90% female
Presence of aura: 43% vs 45%
Patient selection criteria: moderate/severe migraine (≥4 monthly attacks) with or without aura, PFO with significant right-to-left shunt on TCD, single or multiple brain lesions (on MRI)
Exclusion criteria: previous symptomatic episodes of cerebral ischaemia (stroke or TIA), neurodegenerative, psychiatric, inflammatory or infective diseases, pregnancy, contraindication to antiplatelets, chronic use of preventive medication
Technique: <u>percutaneous closure</u> – under local anaesthetic and ultrasound guidance, placement of Amplatzer (35 patients),</td>
<td>Number of patients analysed: 82 (53 percutaneous closure vs 29 control)

Recurrence of migraine/aura
Assessed in a patient-completed questionnaire including duration of attacks, intensity of pain (on 4 point scale, with 0 = no pain and 3 = severe pain), occurrence of aura or accompanying symptoms and response to symptomatic therapy. Disabling attacks lasted > 6 hours, were associated with severe pain, did not allow any activity and had multiple accompanying symptoms and a poor response to symptomatic pharmacological therapy.
<table>
<tr><th></th><th>PFO closure (n = 53)</th><th>Control group (n = 29)</th><th>p value</th></tr>
<tr><td>Aura:
- first 6 months before procedure
- 6 months after procedure</td><td>
43% (23)

19% (10)</td><td>
45% (13)

31% (9)</td><td>
not significant for either</td></tr>
<tr><td>Migraine attacks:
- difference*
- disappearance
> 50% reduction</td><td>
25 ± 13**
34% (18)
87% (46)</td><td>
6 ± 13**
7% (2)
21% (6)</td><td>
< 0.001
0.007
< 0.001</td></tr>
<tr><td>Disabling attacks:
- difference*
- disappearance
> 50% reduction</td><td>
18 ± 13***
53% (28)
89% (47)</td><td>
2 ± 7***
7% (2)
17% (5)</td><td>
< 0.001
< 0.001
< 0.001</td></tr>
</table>
*between 6 months before procedure to 6 months after
**decrease from baseline to follow-up was significant in both groups (p < 0.001 and p = 0.038)
***decrease from baseline to follow-up only significant in PFO closure group (p < 0.001).

Odds ratios for patients with PFO closure for:
- migraine disappearance: OR 6.9, 95% CI 1.5 to 32.5, p = 0.014
- disappearance of disabling attacks: OR 15, 95% CI 3.2 to 70, p < 0.001
- improvement of frequency: OR 25.2, 95% CI 7.6 to 83.6, p < 0.001</td>
<td>Complications
Not reported</td>
<td>Follow-up issues:
• TTE after 1 day in closure group and TCD at 3, 6, and 12 months and then annually. TOE at 6 months. Occurrence of migraine started at 6 months after procedure

Study design issues:
• 156 consecutive patients, less than 60 with migraine and PFO but without cardiac, aortic or cerebrovascular causes for cerebral ischaemia were selected
• Patients who did not agree to PFO closure formed the control group.
• Migraine was evaluated by experienced neurologist blinded to what procedure the</td>
</tr>
</table>

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
Cardio (10 patients), Cardioseal/STARFlex (8 patients) followed by double aspirin therapy (100 mg/day) and 75 mg/day clopidogrel for 3 months and then aspirin alone for 3 months; control – current therapy was evaluated by neurologist and 31% (9) received preventative therapy after evaluation period Follow-up: **16 months** Conflict of interest/source of funding: not reported	- severity of migraine attacks: OR 37.6, 95% CI 10.4 to 135.8, p < 0.001 ***Presence of residual shunt*** Residual grade 2 right-to-left shunt in 1 patient and grade 1 in 2 patients at 3 and 6 month follow-up with TCD and this persisted at 12-month follow-up. The first patient had a small decrease in total and disabling attacks after the procedure. Of the 2 with a residual grade of 1, 1 had a minor decrease in total attacks but not disabling attacks and the other had a clinically significant symptomatic benefit. There were no cardiovascular events during a mean of 16 months follow-up.		patient had. **Study population issues**: • No significant difference in baseline characteristics, including thrombogenic factors, between the groups. • Medical therapy in the control group was not standardised.

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Papa M (2009)[11]
Comparative case series
Italy
Recruitment period: 2006 – 2007
Study population: migraine with PFO and moderate to large right-to-left shunt (on TOE)
n = 76 (28 migraine associated with cerebral ischaemic lesions [on MRI] only vs 16 with previous stroke and migraine vs 32 with previous TIA and migraine)
Mean age: 39 vs 47 vs 44 years
Sex: 75% vs 56% vs 69% female
Patient selection criteria: ≥ 1 year history of migraine, age < 50 years at onset, ≥ 3 migraine attacks per month in previous 6 months, lack of a reduction (or partial reduction) in response to ≥ 3 types of preventive medications with no contraindications to antiplatelet therapy.
Exclusion criteria: carotid artery disease, TTE or TOE evidence of left-sided cardiac or aortic potential source of peripheral embolism and evidence of supraventricular/ventricular</td>
<td>Number of patients analysed: 76 (28 migraine associated with cerebral ischaemic lesions [on MRI] only vs 16 with previous stroke and migraine vs 32 with previous TIA and migraine)

Migraine severity scores
<table>
<tr><th></th><th>Migraine only (n = 28)</th><th>Previous stroke and migraine (n = 16)</th><th>Previous TIA and migraine (n = 32)</th></tr>
<tr><td>Intensity:
- baseline
- 12 months</td><td>
2.4
1.5</td><td>
2.3
1.6</td><td>
2.3
1.4</td></tr>
<tr><td>Duration:
- baseline
- 12 months</td><td>
2.1
0.9</td><td>
2.2
0.9</td><td>
2.1
0.9</td></tr>
<tr><td>Frequency:
- baseline
- 12 months</td><td>
1.8
1.0</td><td>
1.6
0.9</td><td>
1.8
1.0</td></tr>
<tr><td>Aura:
- baseline
- 12 months</td><td>
0.6
0.2</td><td>
0.7
0</td><td>
0.5
0.1</td></tr>
<tr><td>Total:
- baseline
- 12 months</td><td>
6.9
3.6</td><td>
6.8
3.4</td><td>
6.7
3.4</td></tr>
</table>
(Scoring of migraine severity not described)
Total severity scores were significantly improved from baseline to 12 months for each group ($p < 0.001$)

Migraine was abolished in 46% (35), improved in 36% (27) and unchanged in 18% (14) (this was similar in each group).
An increase in migraine intensity was seen in 3 patients (2 without immediate residual shunt and 1 with minimal immediate residual shunt) in the first 2 months after closure. At 12 months, there were no patients with worsening migraines.
At 12 months, 14% (11) were still taking anti-migraine therapy (acutely or stably).
(In those with a preoperative cerebrovascular event, none had recurrence in a mean 13.7 months of follow-up)</td>
<td>Periprocedural complications
Groin haematoma in 7% (5/76) resolving spontaneously in 1 month (percentage calculated by analyst).

Post-procedural complications
7% (5/76) had a decrease of > 1 g/dl in baseline haemoglobin levels because of blood loss.
11% (8/76) had palpitations in the 4 weeks after closure.
7% (5/76) reported sensations of continuous heaviness in the chest.
(there appeared to be a minor error in the calculation of the percentage [the above were reported to be 6%, 10%, and 6%, respectively] so this has been corrected by the analyst)
1 patient had sporadic supraventricular ectopic beats and a brief episode of AF shown on follow-up ECG monitoring</td>
<td>Follow-up issues:
• Clinical evaluation at 1, 3, 6, 12 months. Holter ECG and TTE at 1 month to check device positioning< TOE at 12 months with bubble test.
• None lost to follow-up.
Study design issues:
• 2 centres
• 182 with migraine and or cerebrovascular event were screened, resulting in 76 with migraine defined by International Headache Society
• Usual antimigraine preparation was allowed as continuous therapy

Study population issues:
• No differences in preoperative shunt severity.</td>
</tr>
</table>

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
rhythm disturbances Technique: implantation of Amplatzer device (AGA Medical; 45 patients), STARFlex (NMT Medical; 22 patients) or PFO-STAR (Applied Biometrics; 9 patients) with fluoroscopy plus intraoperative ultrasound or intracardiac echocardiography (when TOE used, light sedation used; when intracardiac echocardiographic monitoring, local anaesthetic); all had heparin at start of procedure; on discharge, 5 or 10 mg/kg aspirin for 6 months and clopidogrel for 3 months Mean follow-up: **13.7 months** Conflict of interest/source of funding: not reported	***Closure of PFO*** Devices successfully deployed in all patients. At 12 months, closure rate was 97% ***Presence of residual shunt*** Immediately after the procedure, microbubble test showed 8% (6) had residual shunt. This was minimal in 4 patients and moderate in 2. At 12 months, TOE showed that a minimal to moderate shunt persisted in 2 of these patients. However, migraine had been completely abolished in these patients.		Those with migraine alone were significantly younger than those with previous stroke and has significantly less prevalence of cardiovascular risk factors than those in the other groups. **Other issues**: • On admission all had brain MRI, anticoagulation screening, Holter ECG monitoring, supra-aortic vessel Doppler ultrasonography, TTE and TOE.

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
Rigatelli G (2009)[4] **Case series** Italy Recruitment period: not reported Study population: severe disabling migraine with aura refractory to anti-headache therapy and PFO diagnosed by echocardiography n = **20** Mean age: 40 years Sex: 60% female Patient selection criteria: right-to-left shunt on normal respiration, curtain pattern of shunt on TCD, ASA on TOE, symptomatic significant aura, coagulation abnormalities, refractory migraine with MIDAS class 3 or 4. Technique: implantation with Amplatzer PFO Occluder with no confirmed ASA and Amplatzer ASD cribriform for patients with FPO associated with ASA (anaesthetic not described) Mean follow-up: **10 months** Conflict of interest/source of	Number of patients analysed: **20** ***Recurrence of migraines*** All patients' migraine symptoms improved at mean follow-up of 10 months (range 7 to 14) (mean MIDAS score decreased from 38.9 ± 5.8 to 3.0 ± 2.1, p < 0.003). As a result: - 11 patients stopped previous anti-headache medication within 1 month. - 7 decreased the number of medications from 3 (anti-inflammatory, beta-blocker and triptan) to 1 (anti-inflammatory in 1, beta-blockers in 2). However, 2 patients reported very little change in migraine attacks (mean duration of episodes decreased from 6 to 2.5 hours) so they continued to take all previous medications. ***Closure of PFO*** Complete closure was shown in all patients on TOE and TCD.	***Complications*** 2 developed atrial fibrillation (on Holter ECG monitoring) so were treated with antiarrhythmic drugs to restore the sinus rhythm.	**Follow-up issues**: • TOE, TCT and ECG Holter monitoring at 1 month (and 6 months if small residual shunt detected), TTE and combined cardiologic and neurologic visit at 1, 6 and 12 months with MIDAS scoring. **Study design issues**: • 75 patients were referred to this study and screened using inclusion criteria resulting in 20 with procedure • Refractory disabling migraine was defined as MIDAS score > 25 refractory to conventional drugs such as beta blockers, anti-depressive drugs, triptan and anti-inflammatory medications.

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
funding: not reported			

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details

Taaffe M (2008)[5]

Cases from an RCT of different devices

USA

Recruitment period: not reported

Study population: history of stroke or TIA and a PFO shown on TOE

n = **50** with migraine of 660 patients treated for a number of indications randomised to different types of occluders Of the 660 patients, the mean age was 49.3 years and 55% were male

Technique: use of Amplatzer (n = 17), Helex Occluder (n = 15), or CardioSEAL-STARflex (n = 18) under local anaesthesia after fluoroscopy and TOE to measure size of the PFO. Valsalva maneuver after procedure to detect residual shunt and TTE within 24 hours after the procedure or before discharge. Aspirin and clopidogrel for first 6 months.

Follow-up: **30 days**

Conflict of interest/source of funding: not reported

Key efficacy findings

Number of patients analysed: **660 with PFO closure for a number of indications (outcomes not separated by indication)**

Efficacy not related to migraine outcomes (study included for safety data)

All closures were technically successful (not defined).

Post-procedural presence of residual shunt (on TOE)

	Amplatzer PFO (n = 220)	Helex (n = 220)	CardioSEAL-STARflex (n = 220)	Total*
Closed	52.3% (115)	41.8% (92)	44.1% (97)	46.1% (304)
Minimal	14.1% (31)	15.5% (34)	13.2% (29)	14.2% (94)
Moderate	11.4% (25)	19.5% (43)	15% (33)	15.3% (101)
Severe	15.5% (34)	21.4% (47)	24.5% (54)	20.5% (135)
TOE not possible	6.8% (15)	1.8% (4)	2.7% (6)	3.8% (25)

*calculated by the analyst

Residual shunt at 30 days (on TOE)

	Amplatzer PFO (n = 220)	Helex (n = 220)	CardioSEAL-STARflex (n = 220)	Total*
Closed	65.0% (143)	52.7% (116)	62.3% (137)	60.0% (396)
Minimal	4.5% (10)	8.2% (18)	2.3% (5)	5.0% (33)
Moderate	2.3% (5)	6.8% (15)	1.4% (3)	3.5% (23)

Key safety findings

Complications

The following events were reported to have occurred among all 660 patients with PFO closure. It is not clear if any of these patients were the patients who presented with decompression illness.

Events	Amplatzer PFO (n = 220)	Helex (n = 220)	CardioSEAL-STARflex (n = 220)
During procedure:			
Atrial fibrillation episodes	0	0	1
Device embolisation[a]	0	2	0
Haemopericardium[b]	0	1	0
Before discharge:			
Tamponade[c]	1	0	0
TIA[d]	0	1	0
Device embolisation[a]	0	1	0
In 30 day follow-up:			
Thrombus on device[e]	0	0	8
Atrial fibrillation episodes	3	2	1
Paroxysmal supraventricular tachycardia	0	0	1
Development of fever	2	0	1
Thrombosis of peripheral vein	1	0	0
Complications from anticoagulants	10	10	0

[a] retrieved with snare catheter with no further complications (2 with embolisation during procedure had ASA), [b] punctured without affecting the device (probably because of multiple attempts to cross the PFO with a catheter), [c] requiring surgical explantation and subsequent surgical PFO closure, [d] recovered without treatment, [e] resolved with anticoagulation (patients remained asymptomatic)

Comments

Follow-up issues:

- TOE, fluoroscopy and chest X-ray after 4 weeks.

Study design issues:

- These patients were part of an RCT of 660 patients with 220 patients each randomised to Amplatzer, CardioSEAL-STARFlex or Helex Occluder.
- **Efficacy and safety outcomes were not split by indication**

Other:

- No data beyond 30 days.

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
	Severe | 1.8% (4) | 4.5% (10) | 4.1% (9) | 3.5% (23) *calculated by the analyst		

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details

Cunningham D (2010)[12]

Registry (Central Cardiac Audit Database)

UK

Recruitment period: 2000 – 2008

Study population: patients treated with percutaneous PFO closure

n = **1869 (1110 percutaneous PFO closure vs 753 surgical PFO closure)**

Mean age: 41.7 yrs
Sex: 49.4% male

Patient selection criteria: all patients with procedure code including "PFO closure" and procedure type = "Catheter"

Technique: PFO closure (type of device not reported)

Mean follow-up: **3.7 years**

Conflict of interest/source of funding: not reported

Key efficacy findings

Number of patients analysed: **1869**

Year	**Total percutaneous PFO closures by catheter**	**Percutaneous PFO closure as part of multiple procedure**	**Isolated percutaneous PFO closures by catheter**
2000	8	7	1
2001	18	14	4
2002	33	20	13
2003	51	28	23
2004	132	61	71
2005	238	70	168
2006	400	101	299
2007	540	162	378
2008	449	132	317
Total	**1869**	**595**	**1274**

Survival

	All PFO closures	**Surgical PFO closure as part of multiple procedure**	**Percutaneous PFO closures**
Survival	98.6% alive	97.6% alive	99% alive
Median FU (yrs)	3.7	3.9	3.6

In patients treated with percutaneous PFO closure alone, the incidence of surgical re-intervention was 2 cases (0.2%) and catheter re-intervention was 25 (2.2%) (no more details provided).

In patients treated with isolated percutaneous PFO closure, 15 required a new catheter re-intervention with a new transluminal prosthesis (no more details provided).

Key safety findings

Comments

Follow-up issues:

- Not reported

Study design issues:

- Registry data does not separate PFO closure by indication for which it was closed.
- Technical success, presence of residual shunt and recurrence of thromboembolic events were not reported.

Other issues:

- Results were not separated by indication

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
Youssef GS (2006) [7], Goldstein JA (2002)[8] **Case reports of safety (infectious endocarditis)** Australia, USA n = **2**	Case 1[7]: 20-year old male who had the procedure (Amplatzer PFO occluder) following a CVA, presented 4 months later with pain and discharge from bilateral in-grown toe nails. After 2 weeks of antibiotic treatment, he presented with malaise, fever, night sweats, and tachycardia and blood cultures grew ***Staphylococcus aureus.*** TTE and TOE revealed a large mass attached to both the right and left atrial surface of the device extending to the aortic root. A fistula between the aortic root and right atrium was evident after removal of the device which had not completely endothelialised. The patient had an uncomplicated post-operative course and 6 weeks intravenous flucloxacillin. Case 2[8]: 42-year old male presented with DVT, central retinal artery occlusion and PFO. The PFO was closed with a CardioSEAL device after 3 months of anticoagulation. 1 month before device closure he presented with streptococcal pharyngitis which was successfully treated with 2-weeks of Augmentin. 6 weeks after PFO closure, he presented with fever, sore throat and body aches and again treated with 2-weeks of Augmentin. One month later (10 weeks after closure), he presented for routine follow-up with complaints of fatigue and was shown on TOE to have a mass in the left atrium. This was explored surgically with removal of the device and excision of the interatrial septum (reconstruction with autologous pericardium). At routine follow-up, 19 days later, blood cultures were positive for ***Bacillus pumilus*** but no vegetation on TOE. He had a 6-week course of intravenous Vancomycin.		These case reports of safety events are reports from patients treated with percutaneous PFO closure for stroke or TIA. They have been included here because the safety profile of the use of the procedures is similar.
Raffa GM (2008)[6] **Case report of safety** USA, Germany, Italy n = **1**	6 months after implantation with the Cardia Star device in a 35-year old female, TTE and TOE demonstrated an incomplete PFO obliteration with residual shunting in both directions and **a fistula between the aortic root and right atrium**. Medical treatment was not successful (the patient presented with dyspnea and palpitations) so the device was removed surgically and the fistula closed. The postoperative care was uneventful with discharge on the 5th day. In the 18 months following, there were no more complications.		
Onorato E (2002)[9] **Case report of safety** Italy n = **1**	28-year old male with PFO, prominent Eustachian valve and history of TIA had Amplatzer device. As the device was being deployed, some **prominent valve tissue became trapped in the delivery cable which resulted in a piece of the valve being extracted**. TOE showed a correctly placed device with no residual leak and some flapping of the Eustachian valve against the device but it was not interfering with the device. The patient was given 100 mg/day aspirin for 6 months and endocarditis prophylaxis. At 3 and 12 month follow-up, TTE confirmed correct positioning with no interference by the Eustachian valve and no residual shunt during Valsalva maneuver.		
Coceani M (2007) [10] **Case report of safety** Italy n = **1**	61-year old female with PFO and history of transient cerebral ischaemic attack was treated with a 35-mm Amplatzer cribriform septal occluder. During the procedure the device was replaced with 24-mm Amplatzer septal occluder because of residual shunting. The patient was asymptomatic when they returned to the ward but did have reduced blood oxygen saturation (92%). 12-lead ECG showed normal sinus rhythm initially but after continuous monitoring was shown to have repetitive brief runs of polymorphic unsustained **ventricular tachycardia.** Intravenous lidocaine was started but the arrhythmic storm persisted and eventually an **intermittent left branch bundle block** occurred. TTE showed that the Amplatzer had migrated through the mitral valve and was obstructing the left ventricular outflow tract which required emergency surgery. After cardiopulmonary bypass and cardioplegic arrest, the device was manually retrieved after a right atriotomy using a transseptal approach. The patient was discharged after 7 days with an uneventful postoperative course.		

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECG, electrocardiogram; HIT-6, Headache Impact test; INR, international normalised ratio; ITT, intention to treat; MIDAS, Migraine Disability Assessment questionnaire; MRI, magnetic resonance imaging; PFO, patent foramen ovale; RR, risk ratio; SF-36v2, Short-Form 36 (version 2); TCD, transcranial Doppler; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
Gori T (2010)[13] **Case report of safety** Germany n = **1**	At 1 month follow-up, a long, mobile structure appeared on the right atrium attached to the device. It was thought to be a **thrombosis and/or endocarditis** and required hospital admission, anticoagulant therapy with heparin and then oral anticoagulation. After 6 weeks, the structure attached to the disc had disappeared but the right atrial disc was broadly mobile and off-axis – the **articulation between the discs had ruptured**. The device was removed percutaneously.		Comments for above case reports apply also to these case reports.
Murphy JC (2010)[14] **Case report of safety** Ireland n = **1**	Patient was found collapsed at home 223 days after the procedure. In hospital, **pericardial effusion with cardiac tamponade** requiring pericardiocentesis but no aortic perforation was shown on TTE and TOE. A **late perforation of the aortic root by the Atriasept device** was diagnosed requiring the patient to be transferred to a cardiothoracic surgical centre for emergency surgery. The device was removed, the PFO closed with surrounding pericardium and the aortic laceration repaired. No further sequelae except that the patient required prolonged renal replacement therapy.		

Efficacy

Presence of migraine and migraine-related disability

A double-blind RCT of patients comparing 74 patients randomised to percutaneous PFO closure with 73 patients randomised to sham reported that 3 patients in each group no longer had migraine at 6-month follow-up. The study reported no significant difference in the reduction in median MIDAS score, frequency of migraine attacks per month or mean migraine headache days over 3 months between the groups over the same time period (MIDAS score: 36 to 17 vs 34 to 18, frequency per month: 4.82 to 3.23 vs 4.51 to 3.53, mean migraine headache days over 6 months: 26 to 19 vs 30 to 21 days). However, when 2 patients who constituted 20% of the total migraine headache days were removed from the analysis, the difference in mean migraine headache days per month was significant (from 6.0 to 3.8 vs 5.0 to 3.7; $p = 0.027$)[1].

A non-randomised comparative study of 86 patients reported a decrease in MIDAS score in the 40 patients treated with percutaneous PFO closure and the 46 patients treated with medical therapy at a mean follow-up of 29.2 months (35.8 to 8.3, $p < 0.003$ vs 22.6 to 19.1, $p = 0.059$; significance of between-group difference not reported). In the 32 patients with aura before the procedure, aura had disappeared in all during the same follow-up period[2].

A non-randomised comparative study of 82 patients reported that the odds of a number of outcomes were significantly greater in 53 patients treated with the procedure compared to 29 treated with medical therapy from the period 6 months before the procedure to 6 months after. These outcomes included migraine disappearance (OR 6.9, 95% CI 1.5 to 32.5, $p = 0.014$), disabling migraine attack disappearance (OR 15, 95% CI 3.2 to 70, $p < 0.001$; disabling attack defined as having a duration greater than 6 hours, associated severe pain, a prohibiting effect on activity, multiple symptoms and a poor response to medical therapy), a reduction in the frequency of attacks (OR 25.2, 95% CI 7.6 to 83.6, $p < 0.001$) or a reduction in severity of migraine attacks (OR 37.6, 95% CI 10.4 to 135.8, $p < 0.001$)[3].

A case series of 76 patients which included 28 patients treated for migraine alone and 48 treated for previous stroke or TIA and migraine, reported that migraine was abolished in 46% (35/76), improved in 36% (27/76) and unchanged in 18% (14/76) during a 12-month follow-up (this trend was similar in patients with different indications). In a composite migraine severity score of intensity, duration, frequency and presence of aura, patients in each group significantly improved from baseline to 12-month follow-up (migraine only: 6.9 to 3.6, previous stroke and migraine: 6.8 to 3.4, previous TIA and migraine: 6.7 to 3.4; scale and scoring system not well-defined) [11].

A case series of 20 patients reported that all patients had symptom improvement at a mean follow-up of 10 months (MIDAS score 38.9 to 3.0, $p < 0.003$).

Subsequently, 11 patients stopped their medications and 7 decreased their medications within 1 month[4].

Residual shunt

The double-blind RCT reported that residual moderate or large atrial shunts were present in 4 patients at 6-month follow-up[1].

The non-randomised comparative study of 86 patients reported that 2 of the 40 patients treated with the procedure still had a persistent small shunt during the study (exact time of follow-up not reported)[2].

The non-randomised comparative study of 82 patients reported a residual right to left shunt in 3 patients at 3- and 6-month follow-up which persisted 12 months after the procedure. However, of the 2 with a mild shunt, 1 had a small decrease in total attacks but not disabling attacks and the other had a clinically significant symptomatic benefit. The patient with moderate shunt had a small decrease in total and disabling attacks after the procedure[3].

The case series of 76 patients reported that a microbubble test immediately after the procedure showed that 8% (6/76) had a residual shunt (minimal in 4 and moderate in 2). At 12 months, this had only persisted in 2 of these patients, however, migraine had disappeared in both these patients[11].

Survival and re-intervention

Data from a registry of 1869 patients reported that 99% of the 1110 patients treated with percutaneous PFO closure for unspecified indications were alive at a median follow-up of 3.7 years (exact numerator not reported). In the 1274 patients treated with percutaneous PFO closure alone, surgical re-intervention was required in 2 cases (0.2%) and catheter re-intervention was required in 25 (2.2%) (no more details provided). In the 595 patients treated with percutaneous PFO closure along with other procedures, 15 required a new catheter re-intervention with a new transluminal prosthesis (no more details provided)[12].

Safety

Cardiac tamponade and pericardial effusion

A case report described a patient who presented with pericardial effusion and cardiac tamponade 223 days after the procedure requiring pericardiocentesis. The device was then discovered to have perforated the aortic root and the patient required emergency cardiothoracic surgery. Apart from requiring prolonged renal replacement therapy, there were no further sequelae [14].

The double-blind RCT reported that 3 patients treated with the procedure withdrew from the study because of adverse events: 1 patient due to cardiac

tamponade before device deployment, 1 due to chest pain and 1 due to arrhythmia (subsequent management of these not reported)[1].

The study also reported pericardial effusion in 2 patients and retroperitoneal bleeding managed successfully with conservative treatment in 1 patient (subsequent treatment for pericardial effusion not reported).

The RCT of different devices used to close PFO for a variety of indications (including 50 with migraine) reported that cardiac tamponade requiring surgical explantation and surgical PFO closure occurred in 1 patient before they were discharged[5].

Device issues

The double-blind RCT reported that 3 patients undergoing the procedure had adverse events which required a new device to be deployed. Shortly after the initial device deployment, 1 patient each had device embolisation into the right atrium and device prolapse into the right atrium. The devices in both patients were successfully retrieved with snares without subsequent sequelae. In the third patient, the device failed to deploy[1].

The RCT of different devices reported device embolisation in 3 of the 660 patients treated with PFO closure; the embolisation occurred in 2 patients during the procedure and in 1 patient before discharge. The devices were retrieved with a snare catheter with no further complications[5].

There was a case report of a Eustachian valve becoming trapped in the delivery cable in a patient treated with PFO closure for a previous TIA who had a prominent Eustachian valve. A piece of the valve was consequently extracted and the part of the valve that remained was flapping slightly. However, this did not interfere with the device and there were no problems 12 months later[9].

Another case report described a patient who required hospital admission and medical therapy because of a long, mobile structure which had attached to the device, suspected to be thrombosis or endocarditis. After 6 weeks, the structure attached to the device had disappeared but the articulation between the discs of the device had ruptured requiring percutaneous removal [13].

Arrhythmia/atrial fibrillation

Episodes of atrial fibrillation developed in 2 patients in the non-randomised comparative study of 86 patients, 2 patients in the case series of 20 patients and 7 patients in the RCT that compared different devices. Most episodes developed in the early postoperative period except in 1 patient in the RCT where this occurred during the procedure. The 4 patients in the first 2 studies were reported to have been successfully treated with antiarrhythmic drugs (the RCT did not report subsequent treatment)[2,4,5]. The case series of 76 patients also reported sporadic supraventricular ectopic beats and a brief episode of atrial fibrillation

shown on follow-up electrocardiographic monitoring in 1 patient[11]. One patient in the double-blind RCT which compared the procedure with sham was reported to have withdrawn from the study because of arrhythmia (no other details provided)[1].

Ventricular tachycardia

The RCT of different devices reported that 1 patient developed paroxysmal supraventricular tachycardia during the 30-day follow-up (no more details provided)[5].

There was a case report of a patient who developed ventricular tachycardia and eventually an intermittent left branch bundle block after being treated for PFO closure after a transient cerebral ischaemic attack. The device had migrated through the mitral valve and was blocking the left ventricular outflow tract. Emergency surgery was required to manually remove the device, and the patient was discharged after 7 days with an uneventful postoperative course[10].

Other

The RCT of different devices reported a thrombus on the device in 8 asymptomatic patients of the 660 patients treated with PFO closure. All resolved with anticoagulation[5].

The RCT of different devices which treated patients for previous stroke or TIA (including 50 with migraine) reported that haemopericardium developed during the procedure in a patient who required multiple attempts to cross the PFO, and thrombosis of the peripheral vein occurred in another patient during the 30-day follow-up[5]. The haemopericardium resolved after puncture but there were no more details about the thrombosis.

The case series of 76 patients reported periprocedural groin haematoma resolving spontaneously within 1 month in 7% (5/76) of patients. Post-procedural complications included a decrease of greater than 1 g/100 ml in baseline haemoglobin levels because of blood loss in 7% (5/76) patients, palpitations in the 4 weeks after closure in 11% (8/76) of patients and sensations of continuous heaviness in the chest in 7% (5/76) of patients[11].

There were 2 case reports of infective endocarditis requiring removal of the device in patients treated with percutaneous PFO closure for thromboembolic events: *Staphylococcus aureus* was detected in a 20-year old male 4 ½ months after the procedure and *Bacillus pumilus* was detected in a 42-year old male 2 weeks after removal of the device following complications 10 weeks after the procedure[7,8].

One case report described a fistula between the aortic root and right atrium in a 35-year old woman, 6 months after the procedure. This patient did not respond to medical therapy so the device was removed[6].

Validity and generalisability of the studies

- The inclusion and exclusion criteria for the included studies varied with the more recent papers setting complex selection criteria designed to identify patients most likely to respond to the procedure. For example, patients with coagulation abnormalities were excluded from the RCT[1] but included in some of the case series[2,4]. White matter lesions were a mandatory inclusion criterion for at least one study[3] but not for another[2].
- There are a number of published studies which report on the prevalence of migraine before and after percutaneous PFO closure in patients with previous thromboembolic events. However, since these were considered to be a different group of patients than those presenting with migraine alone, these studies have been included in appendix A. (There is also a potential confounding affect of antiplatelet therapy on migraine)
- A number of case reports on the procedure for stroke or transient ischaemic events were included in table 2 because the safety profile for the different indications is similar.
- Different imaging studies were used to confirm the preoperative presence of the PFO and right-to-left shunt. One used transoesophageal echocardiography[5], one used transthoracic echocardiography[1], one used both transoesophageal and transthoracic echocardiography[2], and another two used contrast transcranial Doppler and transoesophageal echocardiography[3,4].

Existing assessments of this procedure

In 2006, the Haute Autorité de Santé (France) were unfavourable on the use of PFO closure for migraine.

The FDA have only approved use of this procedure in patients with recurrent stroke despite anticoagulant. They have requested double-blind RCTs to investigate the percutaneous PFO closure for migraine (these are listed below in 'Issues for consideration by IPAC').

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Percutaneous closure of patent foramen ovale for the prevention of cerebral embolic stroke. NICE interventional procedures guidance 109 (2005). Available from www.nice.org.uk/guidance/IPG109
- Endovascular closure of atrial septal defect. NICE interventional procedures guidance 96 (2004). Available from www.nice.org.uk/guidance/IPG96
- Transcatheter endovascular closure of perimembranous ventricular septal defect. NICE interventional procedures guidance 336 (2010). Available from www.nice.org.uk/guidance/IPG336

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Dr Richard Peatfield, British Association for the Study of Headache, Dr Stephen Brecker, Dr Alun Harcombe, British Cardiovascular Intervention Society.

- Two Advisers have performed the procedure at least once and one has not performed the procedure but takes part in patient selection for the procedure.
- Two Advisers considered the procedure established (though one stated that the indication is of uncertain status) and the other Adviser stated that it is a minor variation of an existing procedure.
- One Adviser commented that many doubt the causal link between PFO and migraine
- The comparator is regular prophylactic medication (such as beta blockers, valproate, topiramate, methysergide).
- The greatest concern and controversy about the procedure is its efficacy. The Advisers pointed out that there is significant controversy about the MIST trial and discussion about this trial is ongoing.
- Key efficacy outcomes are evidence of complete closure and frequency and severity of migraine.
- The safety of the procedure for migraine is similar to the use of the procedure for other indications. Anecdotal events include device embolisation, pericardial effusion and worsening migraine.

- Double-blind trials are required. These should help identify which patients will benefit from this procedure. Some trials have closed because of problems recruiting.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent 50 questionnaires to 1 trust for distribution to patients who had the procedure (or their carers). NICE received 17 completed questionnaires.

Issues for consideration by IPAC

- There are a number of trials currently underway. The trials underway include:
  - PREMIUM trial: an FDA-approved double-blind RCT comparing Amplatzer PFO Occluder with sham is currently recruiting patients (NCT00355056; US-based; funded by AGA Medical; estimated enrollment 230; estimated study completion date January 2013).
  - PRIMA trial: an international, double-blind RCT comparing Amplatzer PFO Occluder with medical management (funded by AGA Medical; at least 144 randomised to PFO closure).
  - MIST III: follow-up of patients in the MIST trial[1].
- Two FDA-approved RCTs and an RCT in Belgium closed because of problems recruiting patients: ESCAPE (Premere Occluder, St. James Medical vs sham), MIST II (STARFlex, NMT Medical vs control), and FORMAT (Intrasept, Cardia).

References

1. Dowson A, Mullen MJ, Peatfield R et al. (2008) Migraine intervention with STARFlex technology (MIST) trial: a prospective, multicentre, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 117:1397–1404.

2. Rigatelli G, Dell'Avvocata F, Ronco F et al. (2010) Primary transcatheter patent foramen ovale closure is effective in improving migraine in patients with high-risk anatomic and functional characteristics for paradoxical embolism. Journal of the American College of Cardiology: Cardiovascular Interventions 3:282–7.

3. Vigna C, Marchese N, Inchingolo V et al. (2009) Improvement of migraine after patent foramen ovale percutaneous closure in patients with subclinical brain lesions: a case-control study. Journal of the American College of Cardiology: Cardiovascular Interventions 2:107–13.

4. Rigatelli G, Cardaioli P, Giordan M et al. (2009) Transcatheter interatrial shunt closure as a cure for migraine: can it be justified by paradoxical embolism-risk-driven criteria? American Journal of Medical Science 337:179–81.

5. Taaffe M, Fischer E, Baranowski A et al. (2008) Comparison of three patent foramen ovale closure devices in a randomised trial (Amplatzer versus CardioSEAL-STARFlex versus Helex Occluder). The American Journal of Cardiology 101:1353–8.

6. Raffa GM, Pellegrini C, Lentini S et al. (2008) Minimally invasive video-assisted surgery for iatrogenic aortic root-to-right atrium fistula after incomplete percutaneous occlusion of patent foramen ovale: case report and review of the literature. Journal of Cardiac Surgery 23:63–78.

7. Youssef GS, Allan RM, Manganas C et al. (2006) Case report: a tale of two toes. Heart, Lung and Circulation 15:267–8.

8. Goldstein JA, Beardsle MA, Zu H et al. (2002) Infective endocarditis resulting from CardioSEAL closure of a patent foramen ovale. Catheterization and Cardiovascular Interventions 55:217–220.

9. Onorato E, Pera IG, Melzi G et al. (2002) Persistent redundant eustachian valve interfering with Amplatzer PFO Occluder placement: anatomico-clinical and technical implications. Catheterization and Cardiovascular Interventions 55:521–4.

10. Coceani M, Zucchelli G, Bongiorni MG et al. (2007) An arrhythmic storm: a potential complication on opening the umbrella for percutaneous closure of interatrial communications. American Journal of Cardiology 100:1181–3.

11. Papa M, Gaspardone A, Fracasso G et al. (2009) Usefulness of transcatheter patent foramen ovale closure in migraineurs with moderate to large right-to-left shunt and instrumental evidence of cerebrovascular damage. American Journal of Cardiology 104:434–9.

12. Personal communication. Unpublished data provided by David Cunningham on behalf of the Central Cardiac Audit Database. April 2010.

13. Gori T, Schrader R, and Genth-Zotz S (2010) Thrombosis, fracture, and percutaneous removal of a patent foramen ovale closure device 1 month after successful deployment. Catheterization and Cardiovascular Interventions VOL 75; NUMBER 5 778–81.

14. Murphy JC, Walsh SJ, and Spence MS. (2010) Late aortic perforation with an atriasept device resulting in life-threatening tamponade. Catheterization and Cardiovascular Interventions 76:132–4.

Appendix A: Additional papers on percutaneous closure of patent foramen ovale for recurrent migraine

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Anzola GP, Frisoni GB, Morandi E et al. (2006) Shunt-associated migraine responds favorably to atrial septal repair: a case-control study. Stroke 37:430–4.	Comparative case series n = 23 with previous stroke, 27 without previous stroke, 27 with medical treatment Follow-up = 1 year	Overall migraine significantly improved by 3.7 and 2.8 points, respectively, in the first 2 groups ($p < 0.001$) but decreased by 0.1 points in those treated with medical treatment.	Patients with presumed paradoxical embolism may be a different patient group than those who present with migraine alone.
Brighina F, Gurgone G, Gaglio RM et al. (2009) A case of atypical sporadic hemiplegic migraine associated with PFO and hypoplasia of vertebra-basilar system. Journal of Headache and Pain 10:303–6.	Case report n = 1	Patient with hemiplegic migraine treated with PFO closure to have remission of headache for greater than 4 years. After 5 years, the migraine attacks returned and a mild opening of the PFO was found. Anticoagulation therapy was prescribed.	Larger studies in table 2
Butera G, Biondi-Zoccai GGL, Carminati M et al. (2010) Systematic review and meta-analysis of currently available clinical evidence on migraine and patent foramen ovale percutaneous closure: Much ado about nothing? Catheterization and Cardiovascular Interventions 75:494–504.	Systematic review and meta-analysis n = 1306 patients (11 studies)	Complete cure for migraine in 46% (95% CI 25 to 67%) Resolution or significant improvement of migraine occurred in 83% (95% CI 78 to 88%)	Patients with presumed paradoxical embolism may be a different patient group than those who present with migraine alone.
Chessa M, Colombo C, Butera G et al. (2009) Is it too early to recommend patent foramen ovale closure for all patients who suffer from migraine? A single-centre study. Journal of Cardiovascular Medicine 10:401–5.	Case series n = 42 patients with migraine (28 with aura; 21 also had history of a TIA)	Complete closure in 73% with residual shunt in TCT in 10 patients at 6 months. Overall migraine scores improved significantly in global score, intensity, duration, frequency and the presence of aura ($p < 0.0001$ for all). 26% (11) had resolution of migraine, 52% (22) had reduction in frequency of attacks.	Difficult to separate the outcomes in patients with previous TIA who are a different patient group than those who present with migraine alone.

Chessa M, Citro R, Butera G et al. (2009) Implantation of second Amplatzer device to eliminate residual shunt after transcatheter patent foramen ovale closure. Journal of Cardiovascular Medicine 10:736–7.	Case report n = 1 treated for migraine	Recurrent migraine at 6 months, TOE showed residual shunt hypothesized to be due to erosion of the device (due to lateness of occurrence), second device implanted, no more recurrence of migraine.	Larger studies in table 2
Dubiel M, Bruch L, Schmehl et al. (2007) Migraine headache relief after percutaneous transcatheter closure of interatrial communications. Journal of Interventional Cardiology 21:32–7.	Case series n = 191 with presumed paradoxical embolism Mean follow-up = 38 months	24% (46) had migraine with aura; in 24% (11/46), this had disappeared completely at follow-up and 63% (29/46) had improved.	Patients with presumed paradoxical embolism may be a different patient group than those who present with migraine alone.
Giardini A, Donti A, Formigari R et al. (2006) Long-term efficacy of transcatheter patent foramen ovale closure on migraine headache with aura and recurrent stroke. Catheterization and Cardiovascular Interventions 67:625–9.	Case series n = 38 for cryptogenic stroke Mean follow-up = 4.8 years	34% (13) had migraine with aura. 92% (12/13) had complete resolution at 4.9 years. Midas score decreased significantly (38.6 to 4.4, $p < 0.0001$)	Patients with presumed paradoxical embolism are a different patient group than those who present with migraine alone.
Girdauskas E, Diab M, Secknus MA et al (2010) Late Cardiac Perforation After Transcatheter Closure of Patent Foramen Ovale Mimicking Acute Type A Aortic Dissection. Annals of Thoracic Surgery VOL 89; NUMBER 5 1649–51	Case report n = 1 Time of occurence = not clear how much time had elapsed since PFO closure	**Near fatal late cardiac perforation which presented as an acute pericardial tamponade**. CT scan showed one superior 'strut' of the Cardia Star device passing through the roof of the left atrium and impinging on the noncoronary sinus of the aortic root. The device was completely removed, area repaired with a bovine patch and the patient recovered uneventfully but required a pacemaker.	Event reported in table 2.
Jesurum JT, Fuller CJ, Kim CJ et al. (2008) Frequency of migraine headache relief following patent foramen ovale 'closure' despite residual right-to-left shunt. American Journal of Cardiology 102:916–20.	Case series n = 77 treated for presumed paradoxical embolism and migraine to prevent secondary stroke (55 also had aura)	Data on 67 patients was available. 23 had incomplete PFO closure Migraine relief was independent of closure status. Migraineurs with aura were 4.5 times more likely to have migraine relief.	Patients with presumed paradoxical embolism are a different patient group than those who present with migraine alone.

Kimmelstiel C, Gange C, Thaler D. (2007) Is patent foramen ovale closure effective in reducing migraine symptoms? A controlled study. Catheterization and Cardiovascular Interventions 69: 740–6.	Retrospective comparative case series n = 41 PFO with percutaneous closure vs 63 with PFO and no intervention vs no PFO	Migraine was more prevalent in both PFO groups (particularly with aura; $p < 0.05$). Frequency was reduced by 83% in closed PFO compared to 0% of open PFO group. MIDAS scores were significantly reduced in closure group when compared to other groups ($p < 0.0001$ and $p = 0.035$).	Retrospective and not clear about indication for PFO closure.
Morandi E, Anzola GP, Casilli F et al. (2005) Migraine: traditional or 'innovative' treatment? A preliminary case-control study. Paediatric Cardiology 26:231–3.	Case-control n = 24 (12 occlusion vs 12 medical therapy) with previous TIA or stroke and migraine Follow-up = 12 months	Decrease in migraine in those treated with the procedure from score (composed of intensity, duration, frequency and presence of aura with higher scores worse) from 6.3 to 3.6.	Patients with presumed paradoxical embolism are a different patient group than those who present with migraine alone.
Morandi E, Anzola GP, Angeli S et al. (2003) Transcatheter closure of patent foramen ovale: a new migraine treatment? Journal of Interventional Cardiology 16:39–42.	Case series n = 17 of 62 patients referred for closure after stroke or TIA (the 17 were migraineurs; 8 with aura) Follow-up = 6 months	Composite scores of frequency, duration and intensity of attacks and occurrence of aura (0 to 10 with 10 worst migraine) dropped from 6.5 to 2.5 in those with aura and from 6 to 4.2 in those without aura. 5 no longer had migraine and 10 were substantially improved	Patients with presumed paradoxical embolism are a different patient group than those who present with migraine alone.
Onorato E, Melzi G, Casilli F et al. (2003) Patent foramen ovale with paradoxical embolism: mid-term results of transcatheter closure in 256 patients. Journal of Interventional Cardiology 16:43–51.	Case series n = 27 for migraine with aura (of 265 treated for a variety of indications) Mean follow-up = 19 months	Substantial relief of symptoms with statistically significant decline in migraine total scores at 1, 3 and 6 months postoperatively. Total occlusion rate on TTE or TOE: 98%	Larger studies in table 2.
Prasad S, Meredith I, and Harper RW. (2010) Novel approach to successful removal of right atrial thrombus during percutaneous patent foramen ovale closure. International Journal of Cardiology 142:e8–10.	Case report n = 1 Time of occurrence = during procedure	A **highly mobile mass** was noted on the TOE images before the device was advanced. The operators noted that heparin had not been administered after venous puncture. The clot was aspirated with the delivery catheter. This was successful and the procedure was completed.	Event reported in table 2.

Reisman M, Christofferson RD, Jesurum J et al. (2005) Migraine headache relief after transcatheter closure of patent foramen ovale. Journal of the American College of Cardiology 45:493–5.	Retrospective case series n = 165 patients treated for paradoxical cerebral embolism to prevent further events Follow-up = 1 year	35% (57/162) of those treated had active migraine and 68% (39/57) of these also had aura. At 1 year, complete resolution of migraine occurred in 56% (28/50) and 14% (7/50) had significant (≥50% reduction). 80% reduction of mean number of migraine episodes per month (6.8 to 1.4, $p < 0.001$)	Patients with presumed paradoxical embolism are a different patient group than those who present with migraine alone.
Rigatelli G, Cardaioli P, Dell'Avvocata F et al. (2010) Transcatheter patent foramen ovale closure is effective in reducing migraine independently from specific interatrial septum anatomy and closure devices design. Cardiovascular Revascularization Medicine 11:29–33.	Case series n = 34 with previous paradoxical embolism and migraine with aura Mean follow-up = 9 months	All patients had improved their migraine symptoms (30 to 6 mean MIDAS score, $p < 0.03$).	Patients with presumed paradoxical embolism are a different patient group than those who present with migraine alone.
Rigatelli G, Cardaioli P, Braggion G et al. (2007) Resolution of migraine by transcatheter patent foramen ovale closure with Premere occlusion system in a preliminary series of patients with previous cerebral ischaemia. Catheterization and Cardiovascular Interventions 70:429–33.	Case series n = 10 with previous stroke and severe disabling migraine Mean follow-up = 10.9 months	All patients free from migraine symptoms at follow-up (mean MIDAS score from 38.9 to 2.9).	Patients with presumed paradoxical embolism are a different patient group than those who present with migraine alone.
Schwedt TJ, Demarschalk BM, Dodick DW. (2008) Patent foramen ovale and migraine: a quantitative systematic review. Cephalalgia 28:531–40.	Systematic review of both retrospective and prospective studies (n = 6 studies) Follow-up = up to 1 year	Association between migraine and PFO was OR 2.54 (95% CI 2.01, 3.08). PFO closure seemed to affect migraines favorably but it was of low-to-moderate grade evidence.	Included studies with patients treated for presumed paradoxical embolism. These are a different patient group than those who present with migraine alone.
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.	Case series n = 216 treated for presumed paradoxical embolism	22% (48) had migraine frequency of attacks decreased by 54% (1.2 to 0.6, $p = 0.001$) in those with migraine and aura, and 62% (1.2 to 0.4; $p = 0.006$) in those without aura.	Patients with presumed paradoxical embolism are a different patient group than those who present with migraine alone.

Ussia GP, Cammalleri V, Mule, M et al. (2009) Percutaneous closure of patent foramen ovale with a bioabsorbable occluder device: single-centre experience. Catheterization and Cardiovascular Interventions 74: 607–14.	Case series n = 23 patients treated for migraine (8 with aura) and positive for silent ischaemia (9 had cardiovascular event) Mean follow-up = 7.8 months	Successful implantation in 96% (22) patients. 1 haemorrhagic stroke related to double antiplatelet therapy, 4 trivial microbubbles	Outcomes not related to the presence of migraine.
Wahl A, Praz F, Tai T, et al. (2010) Improvement of migraine headaches after percutaneous closure of patent foramen ovale for secondary prevention of paradoxical embolism. Heart 96:967–73.	Case series n = 150 patients with migraine treated for secondary prevention of paradoxical embolism (96 with aura) Mean follow-up = 5 years (up to 9 years)	Complete PFO closure in 91% (136/150) at 6 months; minimal, moderate or large shunts in 7% (11/150), 1% (1/150) and 1% (1/150), respectively. Migraines disappeared in 34% (51/150) and improved in 48% (72/150).	Patients with presumed paradoxical embolism are a different patient group than those who present with migraine alone.
Wahl A, Praz F, Findling O et al. (2009) Percutaneous closure of patent foramen ovale for migraine headaches refractory to medical treatment. Catheterization and Cardiovascular Interventions 74:124–9.	Case series n = 17 treated for migraine refractory to medical treatment (patients unwilling to participate in RCT; none with stroke, TIA, peripheral embolism or decompression illness) Mean follow-up = 2.7 years	All implantations successful. Residual shunt at 6 months in 1 patients Migraine headaches disappeared in 24% (4) and improved in 47% (8). Overall prevalence of migraine decreased from 82 to 24 % (p = 0.002) 18% (3) had 75% decrease in headaches, 18% (3) had 50% decrease and 12% (2) had 25% decrease. 29% (5) had no change and no patients had worsening headaches.	Larger studies in table 2.
Wilmshurst PT, Nightingale S, Walsh KP et al. (2000) Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. The Lancet 356: 1648–51.	Case series n = 37 (including 29 divers) with transcatheter closure of PFO (32) or ASD	21 had a history of migraine before the procedure (aura in 16 and without aura in 5). Immediately after the procedure, 11 had fortification spectra. Over the long-term, no migraine symptoms were reported in 7 with previous migraine and aura and 3 with previous migraine with no aura.	Most patients in this study were treated for decompression illness or cerebrovascular events so are a different patient group than those who present with migraine alone.

Zaidi AN, Cheatham JP, Galantowicz M et al. (2010) Late thrombus formation on the Helex septal occluder after double-lung transplant. Journal of Heart and Lung Transplantation VOL 29; NUMBER 7 814-816.2010.	Case report n = 1 Time of occurrence = 1 year	1 year after procedure following at the time of double-lung transplant, patient admitted with *Staphylococcus aureus*. After several days on antibiotics, she was re-admitted and a **large mobile echogenic mass was discovered on the left atrium, adherent to the device** requiring surgical removal with full recovery.	Thrombus on device and infection reported in table 2.

Appendix B: Related NICE guidance for percutaneous closure of patent foramen ovale for recurrent migraine

Guidance	Recommendations
Interventional procedures	**Percutaneous closure of the patent foramen ovale for the prevention of cerebral embolic stroke. NICE interventional procedures guidance 109 (2005)** 1.1 Current evidence suggests that there are no major safety concerns and that percutaneous closure of patent foramen ovale for the prevention of cerebral embolic stroke is efficacious in achieving closure of the foramen. However, its efficacy in preventing future strokes has not been clearly shown. 1.2 Clinicians wishing to undertake percutaneous closure of patent foramen ovale should take the following actions. • Ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information. Use of the Institute's Information for the public is recommended. • Audit and review clinical outcomes of all patients having percutaneous closure of patent foramen ovale. 1.3 The procedure should be performed in units where there are arrangements for cardiac surgical support in the event of complications. 1.4 The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients onto this database (www.ccad.org.uk). 1.5 Further research will be useful and clinicians are encouraged to collect longer-term follow-up data. The Institute may review the procedure upon publication of further evidence. **Endovascular closure of atrial septal defect. NICE interventional procedures guidance 96 (2004)** 1.1 Current evidence on the safety and efficacy of endovascular closure of atrial septal defect appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 The procedure should be performed in units where there are arrangements for cardiac surgical support in the event of complications. 1.3 The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients onto this database (www.ccad.org.uk). **Transcatheter endovascular closure of perimembranous ventricular septal defect. NICE interventional procedures guidance 336 (2010)** 1.1 Current evidence on the safety and efficacy of transcatheter endovascular closure of perimembranous ventricular septal defect (VSD) is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 Patient selection is important, especially in children and in

	asymptomatic patients and should be carried out by a multidisciplinary team including an interventional cardiologist and a cardiac surgeon with specific expertise in the management of congenital heart disease. 1.3 When carried out on children, this procedure should only be undertaken in specialist paediatric cardiology units. For patients of all ages, this procedure should only be undertaken by cardiologists trained in the technique, including the management of complications. There should be access to emergency cardiac surgery by a surgeon experienced in the treatment of congenital heart disease. 1.4 Clinicians should enter details about all patients undergoing transcatheter endovascular closure of perimembranous VSD onto the UK Central Cardiac Audit Database (www.ccad.org.uk). 1.5 NICE encourages publication of further long-term follow-up data, specifically on the occurrence of heart block compared with open surgery.

Appendix C: Literature search for percutaneous closure of patent foramen ovale for recurrent migraine

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	26/8/2010	Issue 8 of 12, Aug 2010
Database of Abstracts of Reviews of Effects – DARE (CRD website)	26/8/2010	N/A
HTA database (CRD website)	26/8/2010	N/A
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	26/8/2010	Issue 8 of 12, Aug 2010
MEDLINE (Ovid)	26/8/2010	1950 to August Week 3 2010
MEDLINE In-Process (Ovid)	26/8/2010	August 25, 2010
EMBASE (Ovid)	26/8/2010	1980 to 2010 Week 33
CINAHL (NHS Evidence)	26/8/2010	1981 to Present
ZETOC	26/8/2010	Aug 2010

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 ((Percutan* or transcath* or device*) adj3 (clos* or block* or shut* or plug*)).tw. (3852)
2 Heart catheterization/ (33519)
3 (Heart* adj3 catheter*).tw. (4178)
4 ((Solysafe or Helex or Cardio or Premere) adj3 Occluder).tw. (30)
5 Amplatzer.tw. (1060)
6 STARFlex.tw. (63)
7 cardioSEAL.tw. (100)
8 GORE HELEX.tw. (6)
9 Solysafe.tw. (2)
10 BioSTAR.tw. (51)
11 PFO STAR.tw. (15)
12 Coherex.tw. (1)
13 Occlutech.tw. (6)
14 or/1-13 (38549)
15 Foramen Ovale, Patent/ (570)

16	Foramen Ovale/ (29)
17	(Foramen* adj3 Oval*).tw. (3246)
18	PFO.tw. (1005)
19	exp Heart Septal Defects/ (21771)
20	(Heart* adj3 Septal* adj3 Defect*).tw. (253)
21	or/15-20 (23329)
22	14 and 21 (4378)
23	Embolism, Paradoxical/ (510)
24	Intracranial Embolism/ (2122)
25	((Paradox* or Peripheral* or Cross* or Intracranial* or Brain* or Cerebral*) adj3 Embol*).tw. (6327)
26	(TGA or TGAS).tw. (594)
27	(Transient* adj3 (Ischem* or Ischaem*) adj3 Attack*).tw. (217)
28	TIA.tw. (127)
29	((Myocardial* or Heart*) adj3 Infarct*).tw. (2677)
30	MI.tw. (939)
31	(Platypnoea* adj3 orthodeoxia*).tw. (0)
32	Migrain*.tw. (515)
33	(Decompress* adj3 Sickness*).tw. (17)
34	(Div* adj3 Decompress*).tw. (6)
35	(The adj3 Bend*).tw. (0)
36	(Amnio* adj3 Fluid* adj3 Pregnan*).tw. (15)
37	or/19-36 (8639)
38	18 and 37 (24)