NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous closure of patent foramen ovale for the secondary prevention of recurrent paradoxical embolism in divers

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) and in most people causes no problems. However, some studies have shown that having a PFO can increase the chance of substances (e.g. gas bubbles or blood clots) crossing from the right side into the left side of the heart, and from there into the arterial circulation where they may block blood vessels and cause serious problems such as a stroke. In divers resurfacing too quickly from a dive, bubbles of gas can form in the veins and cross into the arterial circulation causing permanent damage with stroke-like symptoms.

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. The aim is to lower the chances of substances crossing the heart and causing serious problems.

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 the secondary prevention of recurrent paradoxical embolism in divers

Specialty societies

- British Cardiovascular Intervention Society (BCIS)
- Association of British Neurologists (ABN)
- Institute of Naval Medicine

Description

Indications and current treatment

A patent foramen ovale (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.

In most people the persistence of this opening does not cause any complications. However, in divers it may cause problems during the decompression accompanying ascent to the surface following a deep dive.

During a dive inert gas (nitrogen when the diver is breathing air, but may be helium when the diver uses more exotic gas mixtures), accumulates within blood and tissues; the quantity dissolved being proportional to depth (pressure) and time. On ascent this excess gas is excreted via the lungs and, providing the diver ascends (decompresses) in accordance with appropriate decompression schedules, usually causes no ill effect. However, even when decompression is within appropriate decompression regimes, during some dives, in particular deep (greater than 20–30 msw) and long duration dives, venous gas emboli (VGE) often form. In the absence of a right to left shunt, such as a PFO, these VGE are ‘filtered’ by the lungs and appear to cause no harm. In the presence of a right to left shunt the VGE generated during a ‘normal’ dive may become arterialised and result in neurological dysfunction/damage, the symptoms of which may resemble a stroke and are termed ‘neurological decompression illness’.

There is currently no consensus on the optimal management of divers with a PFO who have a history of neurological decompression sickness.

What the procedure involves

Percutaneous closure of the PFO has been introduced as an option for divers who have had neurological decompression sickness and in whom paradoxical gas embolism through a PFO is considered to be the cause.

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.

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 the secondary prevention of recurrent paradoxical embolism in divers. Searches were conducted of the following databases, covering the period from their commencement to 27 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	Divers with patent foramen ovale at risk of recurrent paradoxical embolism.
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 2016 patients (136 with neurological decompression sickness) from 4 case series, 1 RCT of different devices, results from a registry, and 8 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 the secondary prevention of recurrent paradoxical embolism in divers

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; 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>Egred M (2007)[1]

Case series
Canada, UK
Recruitment period: 2003 – 2005
Study population: divers with intracardiac shunt through a PFO who have suffered from decompression illness treated at a tertiary centre
n = 44 of 109 patients with PFO closure for a number of indications
Of the 109 patients, the mean age was 43.5 years and 64% were male.

Patient selection criteria: not reported

Technique: Amplatzer PFO occluder (AGA Medical; some patients with larger PFOs had ASD occluder) until March 2005, then STARFlex (NMT Medical) in some patients (n = 13); all under general anaesthetic with TOE guidance and X-</td>
<td>Number of patients analysed: 185 patients with PFO or ASD closure for a number of indications (outcomes not separated by indication)

Occurrence of thromboembolic events
No deaths or stroke occurred over a mean follow-up of 16.9 months (range: 4 to 36 months).
No patients were readmitted and none had neurological symptoms. Two had palpitations within 4 weeks of the procedure; 1 resolved with no intervention and in the other a 24-hour ECG holter monitor showed only atrial ectopics and the symptoms resolved with no medication.

Closure of PFO (confirmed with TOE)
96.8% (179/185) of patients treated with ASD or PFO closure had a successful procedure
(In 6, it was incomplete: in 2 the ASD was too large, 2 had pericardial effusion and 2 had a PFO that was too small to cross – it is not clear if any of these were the divers)

Presence of residual shunt
TTE after the procedure and before discharge showed residual shunt on colour flow in 20% (37/185)
On 6-month follow-up echocardiogram (not stated if TTE or TOE), there were only 5.4% (10/185) with a residual shunt remaining. These patients were readmitted for a redo procedure which was successful in all.</td>
<td>Complications
The following events were reported to have occurred among all 185 patients treated with PFO or ASD closure. It is not clear if any of these patients were the patients who presented with decompression illness.
<table>
<tr><th></th><th>Rate (No.)</th></tr>
<tr><td>Major complications</td><td></td></tr>
<tr><td>Retroperitoneal haematoma requiring transfusion</td><td>0.5% (1)</td></tr>
<tr><td>Pericardial effusions after transseptal puncture requiring aspiration</td><td>1% (2)</td></tr>
<tr><td>Minor complications</td><td></td></tr>
<tr><td>Minor venous access bleeding</td><td>2.2% (4)</td></tr>
<tr><td>Transient AF (1 during and 1 after the procedure)</td><td>1.1% (2)</td></tr>
<tr><td>Retroperitoneal haematoma</td><td>0.5% (1)</td></tr>
<tr><td>Transient inferior ST elevation during procedure</td><td>0.5% (1)</td></tr>
<tr><td>Chest pain after the procedure</td><td>0.5% (1)</td></tr>
<tr><td>Septicaemia 3 weeks after the procedure*</td><td>0.5% (1)</td></tr>
</table>
* treated successfully with no lasting effects (not clear if related to</td>
<td>Follow-up issues:
At 6 months and then annually. All divers have a follow-up TTE and bubble study to ensure complete closure before diving.
Study design issues:
Retrospective
185 consecutive patients who received a PFO or ASD occluder for a number of indications (109 for PFO closure: cerebrovascular incident – 46, dilated right ventricle – 2, decompression illness – 44, migraine – 12)
The centre was a tertiary referral centre which accepts referrals from a local centre with specialist in diving medicine.
Efficacy and safety outcomes were not split by indication.
Patients received different devices.</td>
</tr>
</table>

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram: TTE, transthoracic echocardiograph			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
ray fluoroscopy Mean follow-up: **16.9 months** Conflict of interest/source of funding: not reported		procedure) All 3 with major complications recovered and were discharged with no long-term problems. No death or device embolisation occurred.	**Study population issues**: • In 5.4% (10/185) of patients, the procedure was performed for a residual shunt (in the others it was the first time the procedure was done) **Other issues**: • The presence of a PFO was confirmed by TTE before the procedure before TOE to assess the size of the defect and determine its suitability for closure.

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; 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>Wahl A (2008)[2]

Case series
Switzerland
Recruitment period: 1994 – 2006
Study population: divers with PFO (confirmed on TTE) and neurological decompression illness
n = 51 of 825 patients with PFO closure for a number of indications
Of the 825 patients, the mean age was 51 years and 58% were male.

Patient selection criteria: not reported

Technique: implantation of PFO occluder (usually Amplatzer PFO Occluder, AGA Medical, but also Sideris Buttoned Device, Angle-Wings Occluder, Amplatzer ASD Occluder, CardioSEAL/STARFlex Septal Occluder, Helex Septal Occluder, Premere) under local anaesthetic guided by fluoroscopy only; patient returned to full physical activity after a few</td>
<td>Number of patients analysed: 825 with PFO closure for a number of indications (outcomes not separated by indication)

Closure of PFO (confirmed with TTE)
Device success in patients ≥ 55 years (n = 348) was 100% compared to 99.6% in patients < 55 years (n = 477).
(The procedure failed in 2 patients during the early experience because of laceration of the femoral artery when the venous sheath was inserted requiring surgical intervention in 1 patient and because of embolisation of the device as reported in the safety section)

Presence of residual shunt (on TTE)
When tested within 24 hours, residual shunt was reported in 15% of patients.
Complete PFO closure at ≥ 6 months in 88% without residual shunt (exact numbers for these outcomes was not reported).
At ≥ 6 months, minimal, moderate or large residual shunts persisted in 7%, 3% and 2% of patients respectively (exact numbers not reported). This occurred more in patients with larger devices (≥30 mm, p < 0.001) and an associated ASA (p = 0.02).
23 patients were treated with a second device because of a significant residual shunt in the region of the PFO (despite TTE showing correct placement). This new device implantation resulted in complete closure in 91% (21/23). One had a minor residual shunt at 6 months but this was no longer present 4 years later. One had residual shunt at 6 months and this persisted even 2 years later. One had a moderate</td>
<td>The following events were reported to have occurred among all 825 patients with PFO closure. It is not clear if any of these patients were the patients who presented with decompression illness.
Periprocedural complications
<table>
<tr><th></th><th>No. of patients</th></tr>
<tr><td>Retroperitoneal haematoma after laceration of femoral artery by venous sheath requiring surgery (and surgical closure)</td><td>1</td></tr>
<tr><td>Embolisation of the device (or parts of the device)*</td><td>5</td></tr>
<tr><td>Air embolism with transient symptoms</td><td>4</td></tr>
<tr><td>TIA with visual symptoms (occlusion of branch of central retinal artery after implantation)</td><td>1</td></tr>
<tr><td>Pericardial tamponade requiring pericardiocentesis</td><td>1</td></tr>
<tr><td>Vascular access site problems**</td><td>7</td></tr>
<tr><td>Thrombus detected on device in asymptomatic patient at 6 months***</td><td>5</td></tr>
</table>
*all removed percutaneously
**5 of these had undergone simultaneous coronary angiography
***all treated with oral anticoagulation: 3 resolved after 3 months, 1 remained unchanged after 4 months and 1 resolved after 6 months. The last patient had a recurrence 10 months later, which was successfully treated, and had normal TOE at 7 years.
There were no in-hospital deaths and no long-term sequelae from any of the complications.
Patients with occluder devices categorised as small (<30 mm, n = 701) had less procedural complications than those with larger devices (n = 121).</td>
<td>Follow-up issues:
Contrast TTE at 6 months and then annually if significant residual shunt (repeat device implantation if it persisted at 1 year).
Study design issues:
A number of devices were used in the study period and efficacy varied between the devices.
825 consecutive patients who received a PFO occluder for a number of indications (presumed paradoxical embolism – 698, embolic event – 47, migraine – 13, miscellaneous –16, diving – 51)
Efficacy and safety outcomes were not split by indication
Patients received different devices.
Other issues:
Difference in results between the type of device used and the size of the device.</td>
</tr>
</table>

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram: TTE, transthoracic echocardiograph			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
hours Follow-up: **≥ 6 months (not otherwise described)** Conflict of interest/source of funding: 3 authors hold research grants or are part of the speaker bureau for AGA Medical	shunt 9 months later.	***Other complications*** In 1 patient, TOE after 2 years showed a new, tiny ASD near the lower rim of the device, which was thought to be resulting from erosion of the device. In 1 patient, TOE at 6 months showed complete occlusion but a new ASD was seen on the lower rim of the device. Both defects were successfully closed with another occluder. There were no further device related complications.	

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram: TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
Wilmshurst PT (2000)[3] **Case series** UK Recruitment period: not reported Study population: divers with right-to-left shunts on TTE n = **32** (31 PFO and 1 ASD) 55% (16/29) of those available for follow-up had migraine before closure (9 of these were present before diving and 7 developed migraine around the time they started diving; 11 of these [38% of divers] also had aura and fortification spectra); Of the 37 patients with PFO or ASD closure for a number of indications: Mean age: 32.8 years in those with migraine and 40.1 years in those without Sex: 62% male Patient selection criteria: not reported Technique: closure with Amplatzer PFO device (16),	Number of patients analysed: **37 (including 29 divers) with transcatheter closure of PFO (32) or ASD (5) (outcomes not separated by indication)** ***Presence of residual shunt*** 6 weeks after the procedure, 57% (21/37, 20 with PFO) of patients had no residual shunt. - 5 had a small shunt at rest, not affected by the Valsalva manoeuvre so thought to be very small - 10 (7 PFO, 3 ASD; 2 with no history of migraine) had a residual shunt only with the Valsalva manoeuvre (large in 6 and small in 4; likely to be due to residual shunt across atrial septum). These shunts were said to be smaller than before closure and closer to the size of those found in a quarter of the normal population. All residual shunts decreased in size or disappeared during long-term follow-up every 3 to 6 months (exact length of follow-up not reported). ***Return to diving*** 79% (23/29) had resumed diving (this included 7 professional divers) 3 had only had closure recently so had not yet resumed diving and another 3 had not resumed diving because of unrelated illness, social or employment reasons. Of the 23 who have resumed diving, none have reported recurrences of decompression illness and none of the 9 who had fortification spectra before diving (all who have returned to diving) have had recurrences (mean follow-up not reported). 18 have dived deeper than 30 metres, 13 deeper than 40	The following events were reported to have occurred among all 37 patients with PFO or ASD closure. It is not clear if any of these patients were the patients who presented with decompression illness. ***Post-procedural complications*** One patient who was also a medical practitioner noticed splinter haemorrhages (up to 5 per day) on her fingers. Since there was no fever or other symptoms, no action was taken. 30% (11/37) of patients treated with transcatheter closure of PFO or ASD reported new or unusually frequent or severe fortification spectra immediately after closure. Symptoms were greater in the first few days but tailed off over the next few weeks. ***Longer-term follow-up*** No patients without migraine before shunt closure developed migraine during long-term follow-up.	**Follow-up issues**: • 3 divers with PFO closure (and no history of migraine) were lost to follow-up because they had moved to work abroad (2 as professional divers and the other continued diving). These patients were excluded from the analysis. • TTE 6 weeks after closure. **Study design issues**: • Retrospective. • 37 consecutive patients who received a PFO or ASD occluder for a number of indications (32 PFO closure: decompression illness – 28, stroke – 4; 5 with haemodynamic ASD closure [which included 1 who also had decompression illness]). • The purpose of the study was to elucidate relationship between right-to-left shunt and

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram: TTE, transthoracic echocardiograph			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Amplatzer septal occluder (17), 2 Amplatzer septal occluders (2), Sideris buttoned device (2), Cardioseal (1), ASDOS (1) followed by 150 mg of aspirin for 6 months (use of anaesthetic not reported). Follow-up: **not reported** Conflict of interest/source of funding: not reported	metres, and 8 deeper than 50 metres.		migraine. • Patients received different devices. **Study population issues**: • One patient with decompression illness also had a history of stroke (this patient did not have migraine).

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram: TTE, transthoracic echocardiograph			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Walsh KP (1999)[4] **Case series** UK Recruitment period: not reported Study population: divers who had experienced symptoms and signs of shunt-related decompression illness (large right to left shunt was seen during normal quiet respiration without provocative manoeuvres) n = **7** Age: 18 to 60 years Sex: 6 males, 1 female Brief description of divers: 3 professional, 4 amateur; 6 had 1 episode of decompression illness (3 spinal, 3 cerebral) and 1 had 2 episodes (both cerebral); all dive profiles followed decompression algorithms used in Britain at the time; 1 also had cutaneous decompression; one also had history of small cerebrovascular accident not related to diving with compete recovery within 4 days; all	Number of patients analysed: **7** All were treated with a single occluder except 1 patient – a professional diver – who required 2 separate devices to close 3 separate defects in his ASA (the third defect had closed by 1-month TOE). The others had flap-valve PFOs. ***Closure of PFO*** Device placement was successful in all patients with complete occlusion in all but 1 patient shown on right atrial angiography. It appeared that the patient with 3 separate defects had 1 that remained open but this was shown to be closed at 1-month TOE. ***Presence of residual shunt (on TOE)*** At discharge, 3 patients had some left- to-right shunting, while the others had complete PFO occlusion. After 1 month, only 1 patient who was treated with the largest occluder (14 mm) did not have complete PFO occlusion with TOE showing a trivial right-to-left shunt (between 1 and 10 bubbles were seen in the left heart when contrast injection was supplemented with the Valsalva manoeuvre on 3 occasions but not on another 3 occasions). ***Presence of decompression illness*** All patients were allowed to return to diving 6 weeks after the implant. Over a follow-up ranging from 3 to 12 months, no divers experienced neurological decompression illness.	***Complications*** There were no acute complications	**Follow-up issues**: • Echocardiography performed 1 month after implantation. **Study design issues**: • Patients were referred to this centre. • Patients were not given formal anticoagulation (even the patient with a history of stroke) because of the lack of evidence of the effectiveness of any post device closure anticoagulation protocol. **Study population issues**: • While most PFOs are said to have a larger right- to-left sizing than the left-to-right, these patients had similar diameters which may indicate that this group of patients had larger non-adherent flap valves than usual. • One patient also had an ASA with 3

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram: TTE, transthoracic echocardiograph			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
divers had normal lung function tests and chest radiographs Patient selection criteria: not reported Technique: implantation of Amplatzer septal occluder under general anaesthetic with TOE guidance (TOE also used to check position of occluder before release); prophylactic antibiotics were given for 6 months after implantation and aspirin for 3 months. Follow-up: **3 to 12 months** Conflict of interest/source of funding: not reported			separate defects and was treated with 2 devices.

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; 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: divers with a history of decompression illness and a PFO shown on TOE

n = **3** of 660 patients 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 = 2) or Helex Occluder (n = 1) 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**

Key efficacy findings

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

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% (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% (143)	52.7% (116)	62.3% (137)	60% (396)
Minimal	4.5% (10)	8.2% (18)	2.3% (5)	5% (33)

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 anticoagulates	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, [d] recovered without treatment, [e] resolved with anticoagulation

Comments

Follow-up issues:

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

Study design issues:

- These 3 patients were part of an RCT of 660 patients with 220 patients each randomised to Amplatzer, CardioSEAL-STARFlex or Helex Occluder (no patients treated for decompression illness were treated with the CardioSEAL-STARFlex device).
- **Efficacy and safety outcomes were not split by indication.**

Other:

- No data beyond 30 days.

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram: TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
Conflict of interest/source of funding: not reported	Moderate 2.3% (5) 6.8% (15) 1.4% (3) 3.5% (23) Severe 1.8% (4) 4.5% (10) 4.1% (9) 3.5% (23) *calculated by the analyst	(patient remained asymptomatic)	

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram: TTE, transthoracic echocardiograph			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Chessa M (2005)[6] **Case report** Italy Recruitment period: not reported Study population: divers with decompression illness (one with TIA) and a PFO shown on TOE n = **2** Age: 39 and 48 years Sex: both male Technique: use of STARFlex (NMT Medical) or Cardia Intrasept device (Cardia Inc), TOE after procedure and after Valsalva maneuver to detect residual shunt, discharge 24 hours after procedure with spring (3 months in 1 patient and 6 in the other) and clopidogrel for 6 months (in 1 patient following specific indications for Cardia) . Follow-up: **24 and 6 months** Conflict of interest/source of funding: not reported	Number of patients analysed: **2** ***Case 1:*** Patient had 2 episodes of musculocutaneous decompression illness 15 minutes after surfacing from a dive of a maximum 75 metres in 20 minutes. ***Case 2:*** Patient had no remarkable medical or surgical history. He developed a TIA after surfacing from a dive of a maximum 35 metres in 40 minutes. He had no vertigo, tinnitus or nausea but had multiple intracranial ischaemic lesions identified on MRI. ***Closure of PFO/presence of residual shunt*** No residual shunt was detected after implantation on TOE in either patient. ***Recurrence of decompression illness or TIA*** One patient (with no TIA) was reported to have returned to diving 6 months after the procedure. This patient had not had any further episodes of decompression illness in the 24 months after the procedure. The patient with TIA was reported to have had no recurrence during the 6 months of follow-up.	***Complications*** There was no thrombus detected on the device in either patient during follow-up (24 months and 6 months, respectively).	**Follow-up issues**: • TOE and clinical exam at 1, 6, 12 and 24 months in 1 patient and 1 and 6 months in the other. **Study design issues**: • Patients received different devices (STARFlex or Cardia Intrasept).

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram: TTE, transthoracic echocardiograph

Study details

Cunningham D (2010)[13]

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: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram: TTE, transthoracic echocardiograph			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Scott P (2009)[7] **Case report of fractured device** UK n = **1**	A 43 year old male professional diving instructor who had neurological decompression sickness with vestibular symptoms after a dive had percutaneous PFO closure with the GORE HELEX septal occluder. After the procedure, the patient's PFO was confirmed to be closed with no residual shunt on TOE. Despite protruding into the atria, the device was well apposed to the septum. After 3 months, the patient returned to have percutaneous closure of a patent ductus arteriosus. During fluoroscopic screening, there appeared to be a fracture of the locking loop of the HELEX device. Subsequent TOE showed that there was some movement of the outermost portion of the left atrial disc during the cardiac cycle and a larger residual right-to-left shunt. The device appeared to be stable. Bubble contrast study performed at 6 months showed only a tiny residual shunt, and TOE showed that, while the right atrial and inner left atrial discs were adherent, the outer portion of the left atrial disc was still relatively mobile. The decision to recommence diving awaits further monitoring of the device and residual shunt. There were no thromoboembolic or other device-related complications at the 6-month review.		
Youssef GS (2006)[8], Goldstein JA (2002)[9] **Case reports of safety (infectious endocarditis)** Australia, USA n = **2**	Case 1[9]: 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[10]: 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 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)[10] **Case report of safety** USA, Germany, Italy n = **1**	6 months after implantation with the Cardia Starr 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 5th day. In the 18 months following, there were no more complications.		These case reports of

Abbreviations used: ASA, atrial septal aneurysm; ASD, atrial septal defect; ECG, electrocardiogram; MRI, magnetic resonance imaging; PFO, patent foramen ovale; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram: TTE, transthoracic echocardiograph			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Onorato E (2002)[11] **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.		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.
Coceani M (2007)[12] **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 echocardiogram 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 transeptal approach. The patient was discharged after 7 days with an uneventful postoperative course.		
Gori T (2010)[14] **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.		
Murphy JC (2010)[15] **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

Successful closure of patent foramen ovale and residual shunt

A case series which included 44 divers treated with PFO closure for neurological decompression sickness, reported that 97% (179/185) of patients treated with percutaneous closure of PFO or ASD for a number of indications had successful closure (confirmed on TOE). In the 6 patients without successful closure, 2 were because the ASD was too large, 2 were because the PFO was too small to cross, and 2 patients had pericardial effusion (not reported if the last 2 patients had PFO or ASD closure of if any of these patients included the 44 divers treated for neurological decompression sickness)[1].

The same case series reported residual shunt on colour flow in 20% of the 185 patients after being treated for either PFO or ASD (exact numbers not reported). On 6-month follow-up echo, there were only 5% (10/185) with a residual shunt remaining. These patients were readmitted for another procedure which was successful in all.

A case series which included 51 divers treated with percutaneous PFO closure for neurological decompression sickness reported successful device placement on TOE in all 825 patients treated for PFO closure: 100% of patients 55 years or older (n = 348) compared with 99.6% of patients younger than 55 years (n = 477)[2].

The same study reported that residual shunt was present in 15% of patients when it was tested by TTE within 24 hours after the procedure. When this was tested again at 6 months, complete PFO closure without residual shunt was reported in 88% of patients and minimal, moderate or large residual shunts persisted in 7%, 3%, and 2% of patients respectively (exact number of patients not reported). In this study, 23 patients were treated with a second device because of a significant residual shunt in the region of the PFO (despite TTE showing correct placement). This resulted in complete closure in 91% (21/23) – 1 had a minor residual shunt at 6 months but this was no longer present 4 years later, 1 had residual shunt at 6 months and this persisted even 2 years later and 1 had a moderate shunt 9 months later.

A case series which reported on 29 divers treated with PFO closure (n = 28) or ASD closure (n = 1) for neurological decompression sickness reported that of 37 patients treated for a number of indications, 57% (21/37) had no residual shunt seen on TTE 6 weeks after the procedure. Five still had small shunts but these were not affected by the Valsalva manoeuvre so were thought to be small and 10 had residual shunt only with the Valsalva manoeuvre. However, these shunts were said to be smaller than before the procedure, were closer to the size of shunts found in the general population with shunts and decreased in size or disappeared over the long term (exact length of follow-up not reported)[3].

The case series of 7 divers treated for neurological decompression sickness reported that right atrial angiography and echocardiography showed that the device was completely occluded in all but 1 diver who required 2 devices to close 3 separated defects. However, the 1 defect which originally appeared to remain open was shown to be closed on TOE 1 month later[4].

The same study reported that 3 divers had some left-to-right shunting present on TOE at discharge. However, the diver who was treated with the largest occluder (14 mm) had a trivial right to left shunt on TOE after 1 month (between 1 and 10 bubbles were seen in the left heart when contrast injection was supplemented with the Valsalva manoeuvre on 3 occasions but not on another 3 occasions).

An RCT of different devices included 3 divers who were treated for neurological decompression sickness. All 660 patients had a technically successful procedure (not defined). Minimal, moderate and severe residual shunts were detected by TOE in 14% (94/660), 15% (101/660) and 20% (135/660) respectively after the procedure. These were still present in 5% (33/660), 3% (23/660) and 3% (23/660) respectively after 30 days[5].

A case report of 2 divers treated for PFO closure reported no residual shunt after implantation in either patient[6].

Presence of neurological decompression sickness

The case series which reported on 29 divers treated for neurological decompression sickness reported that 79% (23/29) had returned to diving (3 had only recently had closure and 3 had not returned to diving for other unrelated reasons). Of the 23 who had returned to diving, none had reported recurrences of neurological decompression sickness, and none of the 9 who had fortification spectra before diving had recurrences (follow-up not reported)[3].

The case series of 7 divers reported that all were allowed to return to diving 6 weeks after the implant. Over a follow-up ranging from 3 to 12 months, no divers experienced further neurological decompression illness[4].

The case report of 2 divers reported that 1 had returned to diving 6 months after the procedure without further episodes of neurological decompression sickness in the 24 months after the procedure. The other diver who had presented with a TIA was reported to have had no recurrence during the 6 months of follow-up[6].

Occurrence of thromboembolic events

The case series which included 44 divers with neurological decompression sickness reported that no deaths or stroke occurred in any of the 185 patients treated for closure of PFO or ASD over a mean follow-up of 16.9 months (range: 4 to 36 months). Two patients had palpitations within 4 weeks of the procedure. One resolved with no intervention and in the other a 24-hour ECG holter monitor

showed only atrial ectopics and the symptoms resolved with no medication (it is not clear if these patients were treated for ASD or PFO)[1].

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%) (no more details provided). Of 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)[13].

Safety

The case series which included 44 divers treated with PFO closure for neurological decompression sickness reported adverse events that occurred after percutaneous PFO or ASD closure in 185 patients treated for a number of indications. Retroperitoneal haematoma occurred in 2 patients but only required transfusion in 1 of these patients. Pericardial effusion occurred after transseptal puncture in 2 patients who required aspiration. Transient atrial fibrillation was reported in 1 patient during the procedure and 1 patient after the procedure. Transient inferior ST elevation during the procedure, chest pain after the procedure and septicaemia 3 weeks after the procedure each occurred in one patient (septicaemia was successfully treated with no lasting effects but it was not clear if it was related to the procedure)[1].

The case series which included 51 divers treated for PFO closure reported a number of adverse events which occurred after PFO closure in the 825 patients treated for a number of indications. Periprocedural events included TIA with visual symptoms after implantation in 1 patient, retroperitoneal haematoma after laceration of the femoral artery requiring surgery in 1 patient, pericardial tamponade requiring pericardiocentesis in 1 patient, and air embolism with transient symptoms was reported in 4 patients[2].

The same study reported that a new, tiny atrial septal defect had appeared in 2 patients on TOE (in 1 after 3 years and in 1 after 6 months). In 1 patient, this was thought to be related to erosion of the device. Both defects were successfully closed with another occluder.

The RCT of different devices which included 3 divers reported safety events in all patients treated for a variety of indications. Episodes of atrial fibrillation developed in 1 patient during the procedure and 6 patients in 30-day follow-up. Haemopericardium developed during the procedure in 1 patient who required multiple attempts to cross the PFO; this resolved after puncture. Cardiac tamponade requiring surgical explantation and TIA which resolved without

treatment occurred each in 1 patient before they were discharged. During the 30-day follow-up, paroxysmal supraventricular tachycardia and thrombosis of the peripheral vein developed in 1 patient each[5].

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[8.9].

There was a case report of a fistula discovered 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[10].

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 so required emergency surgery to manually remove the device. The patient was discharged after 7 days with an uneventful postoperative course[12].

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 [15].

Problems with the device

The case series including 51 divers reported periprocedural embolisation of the device or parts of the device in 5 of the 825 patients treated for PFO closure (all were removed percutaneously)[2].

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

A case report of a diver reported that a fracture in the locking hoop of the device used to occlude the PFO was detected on fluoroscopy 3 months after implantation. The PFO had originally been confirmed to be closed with no residual shunt but a fracture was detected when the diver returned to have percutaneous closure of a patent ductus arteriosus. The device was monitored and there were no thromboembolic events at the 6-month review[7].

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[11].

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 [14].

Thrombus on the device

The case series including 51 divers reported a thrombus detected on the device in 5 asymptomatic patients out of 825 patients treated with PFO closure at 6 months. This was subsequently treated with anticoagulation and in 3 had resolved in 3 months, in 1 had remained unchanged 4 months later, and in a third patient whose thrombus had initially resolved there was a recurrence 10 months later which was successfully treated[2].

The RCT of different devices which included 3 divers reported thrombus on the device in 8 asymptomatic patients of the 660 patients treated with PFO closure. All resolved without anticoagulation[5].

The case report of 2 divers reported that no thrombus was detected on the device in either diver during follow-up (24 months and 6 months respectively)[6].

Validity and generalisability of the studies

- The published literature on the use of this procedure in divers is limited for outcomes focusing on the alleviation of decompression sickness, and also over the long-term.
- Two publications of letters in prominent journals which reported on transcatheter occlusion of the PFO for divers (7 of 53 patients treated for other indications in 1 publication; and a case report of 2 professional divers) were not included because they were not peer-reviewed publications.
- A number of the studies included patients treated by percutaneous PFO closure for decompression illness among other patients treated by PFO closure for other indications. Outcomes were not usually reported separately by indication.

Existing assessments of this procedure

In 2006, the Haute Autorité de Santé (France) considered the use of this procedure for a number of indications, including for the secondary prevention of decompression sickness. The website states that they appear to have given the procedure unfavourable recommendations for this indication, though in the document they appear to have given a favourable recommendation with multiple relapses of decompression sickness because the PFO appears to be the only risk factor of multiple instances of decompression illness (closing it eliminates this risk) and despite no data showing a decrease in the relapse of incidences, there are also no data showing more complications.

The UK Sports Diving Medical Committee medical standards for sport divers with intracardiac shunts recommend that divers with no other cardiac contraindication should be allowed to dive shallower than 15 metres. If they wish to go deeper than 15 metres they can use nitrox with an air decompression table or a table like the Defence and Civil Institute of Environmental Medicine (DCIEM) table, which may result in little or no bubble nucleation. They state that some individuals may return to unrestricted diving after transcatheter closure but, with more understanding of the mechanisms involved, hope to be able to adapt their advice at a later time.

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. 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 Peter Wilmshurst, Dr Azfar Zaman, British Cardiovascular Intervention Society.

- One Adviser does not perform the procedure but refers patients for the procedure regularly. The other Adviser performs the procedure regularly for this indication.
- The Advisers consider the procedure to be established practice and no longer new.
- One Adviser was concerned that some divers have the procedure without adequate pre-procedural assessment and this may be because the clinician involved does not have adequate knowledge of diving medicine.
- The comparator for a commercial diver is to give up both their job and diving. Amateur divers can stop diving, considerably modify their diving to decrease the risk or have surgical closure.
- Key efficacy outcomes include adequate closure of the PFO assessed with a suitable technique (such as bubble contrast echocardiography, transcranial Doppler and TOE) and reduction of paradoxical embolism.
- There is uncertainty about whether or not divers who have had closure after shunt-related decompression sickness are at normal risk of decompression illness.
- Anecdotal adverse events include device embolisation, transient increase in migraine, and anaphylactoid reaction to the muscle relaxant used by the anaesthetist before the procedure. Transient palpitations are also common but not serious.
- Additional theoretical events include vascular injury, risks from general anaesthetic, device erosion in the long-term resulting in tamponade (though this is more frequent with ASD closure and varies according to type and size of device used), and late thrombosis on the devices (but this varies with device type).
- One Adviser considered the procedure safe in expert hands in institutions experienced in the procedure.
- Training should include use of an animal model and mentoring in a tertiary centre. Clinicians should have knowledge of diving medicine.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to receive patient commentary for this procedure.

Issues for consideration by IPAC

- The Committee may wish to change the title to 'Percutaneous closure…for the prevention of paradoxical embolism, including decompression sickness, in divers'.

References

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2. Wahl A, Praz F, Stirnimann J et al. (2008) Safety and feasibility of percutaneous closure of patent foramen ovale without intra-procedural echocardiography in 825 patients. Swiss Medical Weekly 138:567–72.

3. 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.

4. Walsh KP, Wilmshurst PT, Morrison WL. (1999) Transcatheter closure of patent foramen ovale using the Amplatzer septal occluder to prevent recurrence of neurological decompression illness in divers. Heart 81:257–61.

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. Chessa M, Clai F, Vigna C et al. (2005) Patent foramen ovale in scuba divers. A report of two cases and a brief review of the literature. Italian Heart Journal 6:73–6.

7. Scott P, Wilson N, Veldtman G. (2009) Fracture of a GORE HELEX Septal Occluder following PFO closure in a diver. Catheterisation and Cardiovascular Interventions 73:828–31.

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

9. 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.

10. 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.

11. 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.

12. 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.

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

14. 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.

15. 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 the secondary prevention of recurrent paradoxical embolism in divers

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
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.
Greutmann M, Greutmann-Yantiri M, Kretschmar O et al. (2009) Percutaneous PFO closure with Amplatzer PFO occluder: predictors of residual shunts at 6 months follow-up. Congenital Heart Disease 4: 252–7.	Case series n = 5 (of 135 treated for a number of indications) Follow-up = 6 months	Residual interatrial shunt detected in 19.3% (26/135) of patients; this was considered significant in 38% (10/26) (>20 bubbles in left atrium spontaneously or after Valsalva) 2 patients in the whole group had recurrent ischaemic events during follow-up: 1 had a diving accident without permanent sequelae (not further described) and the other had a TIA without permanent sequelae	Outcomes reported in table 2.
Hildick-Smith D, Behan M, Haworth P et al. (2008) Patent foramen ovale closure without echocardiographic control: use of 'standby' intracardiac ultrasound. Journal of the American College of Cardiology: Cardiovascular Interventions 1:387–91.	Case series n = 2 with decompression illness (out of 70 treated for stroke, TIA or decompression illness) Follow-up not reported	All 70 had procedural success without significant complications (including device embolisation).	Studies with more patients treated for decompression illness in table 2.
Luermans JGLM, Post MC, Plokker HWM et al. (2008) Complications and mid-term outcome after percutaneous patent foramen ovale closure in patients with cryptogenic stroke. Netherlands Heart Journal 16:332–6.	Case series n = 1 with decompression illness (out of 83 treated for other indications including stroke, TIA, and peripheral embolism) Mean follow-up = 1.9	Stroke recurred in 1.2%, TIA in 3.6% and peripheral embolism during a mean follow-up of 1.9 years. One device did not open in a patient and needed to be removed surgically because it was lost in the subcutis. TIA	Studies with more patients treated for decompression illness in table 2. Outcomes of the patient who presented with decompression illness were not reported separately.

	years	occurred during follow-up in this patient. Other complications: inguinal haematoma which did not require blood transfusion (1), atrial arrhythmias within 2 months treated medically (mostly AF; 7)	
Lisignoli V, Lanzone A, Zavalloni D et al. (2007) Closure of patient foramen ovale: when and how? Current Vascular Pharmacology 5:322–7.	Case series n = 1 professional scuba diver (out of 98 treated for other indications including TIA, stroke, peripheral embolism, migraine, platypnea-orthodeoxia syndrome) Follow-up not reported	All patients had successful device delivery with no thromboembolic recurrences at follow-up (time not reported). 1 patient had heparin-induced thrombocytopenia and 1 had device dislodgement (minor complications: mild immediate shunt [2], atrial arrhythmia [1], femoral pseudoaneurysm [2], device tangled in Chiari network [1])	Studies with more patients treated for decompression illness in table 2. Outcomes of the patient who presented with decompression illness were not reported separately.
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.
Schwertzman M, Windecker S, Wahl A et al. (2004) Percutaneous closure of patent foramen ovale: impact of device design on safety and efficacy. Heart 90:186–90.	Non-RCT of 2 different devices n = 2 with 'diving accident' (out of 100 patients with paradoxical embolism) Follow-up = 6 months	More procedural complications in the STAR than the Amplatzer group (8/50 vs 1/50, p = 0.01). Residual shunt 6 months after the procedure occurred in more patients treated with STAR (17/50 vs 3/60, p = 0.004). Actuarial risk of recurrent thromboembolic events after 3.5 years was 16.8% with STAR and 2.7% after 3 years with Amplatzer (p = 0.08).	Studies with more patients treated for decompression illness in table 2.
Zaidi AN, Cheatham JP, Galantowicz M et al. (2010) Late thrombus	Case report n = 1	1 year after procedure following at the time of double-lung transplant,	Thrombus on device and infection reported in

formation on the Helex septal occluder after double-lung transplant. Journal of Heart and Lung Transplantation VOL 29; NUMBER 7 814-816.2010.	Time of occurrence = 1 year	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.	table 2.

Appendix B: Related NICE guidance for percutaneous closure of patent foramen ovale for the secondary prevention of recurrent paradoxical embolism in divers

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 the secondary prevention of recurrent paradoxical embolism in divers

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)