NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events

Preventing recurrent stroke or transient ischaemic attack by closing patent foramen ovale using a device inserted via the groin

The foramen ovale is a hole between the 2 upper chambers of the heart, which should close at birth. If it fails to close it is known as patent foramen ovale (PFO) and there is a small risk that blood clots from the veins might pass through the PFO to the brain and cause a stroke or transient ischaemic attack.

This procedure involves passing a closure device through veins from the groin up into the heart to close off the PFO.

Introduction

The National Institute for Health and Care 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 March 2013 and updated in October 2013.

Procedure name

- Percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events

Specialist societies

- British Cardiovascular Intervention Society
- Society for Cardiothoracic Surgery in Great Britain and Ireland
- British Association of Stroke Physicians

Description

Indications and current treatment

Before birth the fetal heart has an opening called the foramen ovale between the right and left atrium. This allows blood 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 1in 4 people the foramen ovale remains fully or partially open into adulthood. This is then known as patent foramen ovale (PFO).

Most people with PFO suffer no ill effects. However, PFO increases the risk of particles (specifically thrombus or blood clot, for example from deep vein thrombosis in the legs) crossing from the right side into the left side of the heart, and from there into the arterial system where they may block blood vessels and cause serious events such as a stroke or a transient ischaemic attack (TIA). This passage of material from the right of the circulation to the left is called paradoxical embolism.

The optimal treatment for patients with PFO who have had a thromboembolic event remains undefined. Medical management with antiplatelet (for example aspirin) or anticoagulation therapy (usually warfarin) is commonly used to reduce the risk of further paradoxical thrombus emboli. Closure of the PFO is sometimes performed for people in whom medical management fails or those in whom anticoagulants are contraindicated (for example because of haemorrhagic complications). Surgical closure of PFO is sometimes performed as an adjunct to other open-heart surgery, but is rarely done on its own because of associated morbidity.

What the procedure involves

Percutaneous closure of PFO has been introduced as an option for patients who have had an embolic event (such as stroke or TIA) and in whom paradoxical embolism through PFO is considered to be the cause. It enables closure of the PFO without major surgery.

Percutaneous closure is performed using local anaesthesia and intravenous sedation, or general anaesthesia. A guide wire 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.

A closure device is introduced through the PFO via the delivery sheath and released, so closing the defect. 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. Searches were conducted of the following databases, covering the period from their commencement to 30 July 2013: 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 PFO at risk of a recurrent neurological event where no other likely cause has been demonstrated.
Intervention/test	Percutaneous closure of PFO.
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 18,560 patients from 1 meta-analysis of 58 observational studies (including 10 comparative studies), 3 randomised controlled trials, 1 non-randomised comparative study, results from a registry, and 7 case reports[1–12].

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 prevention of recurrent cerebral embolic events

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; HR, hazard ratio; INR, international normalised ratio; MRI, magnetic resonance imaging; OR, odds ratio; PFO, patent foramen ovale; RR, risk ratio; TCD, contrast transcranial doppler sonography; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
Agarwal S (2012)[1] **Meta-analysis** USA Search date: not reported Study population: observational studies reporting outcomes after transcatheter PFO closure or medical management **n=10,327** (58 studies including 10 comparative studies) Mean age range (years): 38–57 Sex: 39%–74% male Exclusion criteria: case series with fewer than 100 patients, studies that reported composite outcomes for atrial septal defects along with PFO, unless it was possible to clearly determine the outcomes of PFO closure. Technique: the most common devices used were: Amplatzer (AGA Medical Corporation, USA), CardioSEAL (NMT Medical, USA), PFOstar, Starflex (NMT Medical, USA), Helex (Gore Medical, USA). **Mean follow-up: 0.1–6.7 years** Conflict of interest/source of funding: not reported	Number of patients analysed: **10,327 (8185 percutaneous closure, 2142 medical management)** ***Pooled incidence of recurrent neurological events (per 100 patient-years)*** • Percutaneous closure=0.76 (95% CI 0.48 to 1.05) • Medical therapy=4.39 (95% CI 3.20 to 5.59) With comparative studies, there was a significantly reduced number of recurrent neurological events among patients treated by percutaneous closure compared to those managed medically (RR 0.25, 95% CI 0.11 to 0.58). After adjusting for mean age, proportion of men in the study and proportion of patients with atrial septal aneurysm, there was a significant reduction of recurrent neurological events in patients treated by percutaneous closure compared to those managed medically (3.5 events/100 person years [95% CI 2.1 to 5.0], p<0.001). ***Procedural failures***: n=6288 (0.01%, 95% CI 0 to 0.2) ***Residual shunt after the procedure (not further defined)***=25.4% (95% CI 17.4 to 33.5) ***Residual shunt for 12 months or less***=12.5% (95% CI 9.6 to 15.5) ***Residual shunt for more than 12 months***=6.3% (95% CI 0.1 to 18.2) In the medical management arm, the risk of recurrent neurological events was significantly lower with anticoagulation therapy compared to antiplatelet therapy (2.2 [95% CI 1.1 to 3.4] events/100 person years versus 4.2 [95% CI 2.9 to 5.4]). The rate of recurrent neurological events was similar between the older and younger age groups undergoing percutaneous closure but the rate was significantly higher in older patients managed medically. In the percutaneous closure group, there was no difference in rate of recurrent neurological events between patients with atrial septal aneurysm and those without.	***Device-related complications*** • Pericardial effusion or tamponade=0.3% (95% CI 0 to 0.6) • Perforation=0.1% (95% CI 0 to 0.3) • Embolisation or malposition=0.4% (95% CI 0.2 to 0.7) • Infection=0.1% (95% CI 0 to 0.8) • Thrombus=0.6% (95% CI 0.3 to 0.9) • Atrial arrhythmia=3.9% (95% CI 2.7 to 6.1) • Air embolism=0.6% (95% CI 0.2 to 1.0) • Any bleeding complication=1.7% (95% CI 1.1 to 2.4) • Reintervention=0.9% (95% CI 0.2 to 1.6) • Surgical intervention=0.3% (95% CI 0.1 to 0.5) • Death=0.4% (95% CI 0.1 to 0.8) • Related death=0.1% (95% CI 0 to 0.3) (not further defined) • Unrelated death=0.3% (95% CI 0 to 0.6) • Any above complication excluding unrelated death=4.1/100 person years (95% CI 3.2 to 5.0) **Medical therapy** • Any bleeding complication=1.1% (95% CI 0 to 2.5) • Death=1.1% (95% CI 0.1 to 2.0) • Any above complication excluding unrelated death=0.4/100 person years (95% CI 0 to 0.9)	**Study design issues:** • Primary outcome was defined as recurrent stroke or TIA in the follow-up period. • 10 studies (n=1886) were included for pooled comparative analysis. • Several studies included in the meta-analysis have small numbers or have short follow-up periods. **Population issues:** • There were inherent differences in patient selection and baseline characteristics between studies. • Antiplatelet and/or anticoagulant therapy varies considerably across the studies with regard to regimen and dosage. **Other issues:** • Significant differences in baseline characteristics of the included studies limit the interpretation of the pooled effect estimates. • The authors noted that there was no significant publication bias in the meta-analysis of recurrent neurological events after percutaneous closure but there was significant publication bias for medical therapy.

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; HR, hazard ratio; INR, international normalised ratio; MRI, magnetic resonance imaging; OR, odds ratio; PFO, patent foramen ovale; RR, risk ratio; TCD, contrast transcranial doppler sonography; 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>Furlan AJ (2012)[2]

Randomised controlled trial (CLOSURE 1)

USA and Canada
Recruitment period: 2003–8
Study population: patients with cryptogenic stroke or TIA and PFO

n=909 (447 percutaneous PFO closure vs 462 medical therapy)
Mean age: 46 years
Sex: 52% male

Patient selection criteria: aged between 18 and 60 years, ischaemic stroke or TIA within the previous 6 months, PFO documented by TOE. Exclusion criteria were any identified potential cause of ischaemic stroke or TIA other than the PFO.

Technique: percutaneous closure – STARflex device (NMT Medical) followed by standard antiplatelet regimen; medical therapy – warfarin, aspirin, or both.

Follow-up: 2 years
Conflict of interest/source of funding: supported by NMT Medical, Boston.</td>
<td>Number of patients analysed: 909 (447 percutaneous PFO closure vs 462 medical therapy)

Procedural success (successful implantation of device at closure site during the index procedure)=89.4% (362/405)

Closure of PFO at 6 months (confirmed with TOE)=86.1% (315/366)
Closure of PFO at 2 years=86.7% (320/369)

Primary end point at 2 years (Kaplan-Meier event rates) – intention-to-treat population
<table>
<tr><th>End point</th><th>Closure</th><th>Medical therapy</th><th>Hazard ratio (95% CI)</th><th>p value</th></tr>
<tr><td>Composite end point</td><td>23 (5.5%)</td><td>29 (6.8%)</td><td>0.78 (0.45–1.35)</td><td>0.37</td></tr>
<tr><td>Stroke</td><td>12 (2.9%)</td><td>13 (3.1%)</td><td>0.90 (0.41–1.98)</td><td>0.79</td></tr>
<tr><td>TIA</td><td>13 (3.1%)</td><td>17 (4.1%)</td><td>0.75 (0.36–1.55)</td><td>0.44</td></tr>
</table>
Primary end point at 2 years (Kaplan-Meier event rates) –per-protocol population
<table>
<tr><th>End point</th><th>Closure</th><th>Medical therapy</th><th>Hazard ratio (95% CI)</th><th>p value</th></tr>
<tr><td>Composite end point</td><td>22/378 (5.8%)</td><td>29/375 (7.7%)</td><td>0.74 (0.42–1.29)</td><td>0.28</td></tr>
<tr><td>Stroke</td><td>12/378 (3.2%)</td><td>13/375 (3.5%)</td><td>0.91 (0.41–1.99)</td><td>0.80</td></tr>
<tr><td>TIA</td><td>12/378 (3.2%)</td><td>17/375 (4.6%)</td><td>0.68 (0.33–1.43)</td><td>0.31</td></tr>
</table>
There were no deaths within 30 days in either group and no deaths due to neurological causes (defined as death related to acute ischaemic or haemorrhagic stroke either directly from increased intracranial pressure or indirectly from complications including pneumonia/sepsis, pulmonary embolism, heart failure, cardiac arrhythmia and myocardial infarction) during the 2-year follow-up.

Possible alternative explanations for recurrent TIA or stroke were apparent in 87.0% (20/23) of patients in the closure group and 75.9%</td>
<td>‘Serious adverse events’
Major vascular procedural complications=3.2% (13/402)
(4 haematomas >5 cm at access site, 3 transfusions, 3 retroperitoneal haemorrhage, 1 perforation of left atrium, 1 vascular surgical repair, 1 peripheral nerve injury)
Atrial fibrillation
• Closure=5.7% (23/402) (17 transient, 6 persistent; 14 periprocedural)
• Medical therapy=0.7% (3/458), p<0.001
Major bleeding episode
• Closure=2.6% (10/378)
• Medical therapy=1.1% (4/374), p=0.11
Death other than end point
• Closure=0.5% (2/402) (cardiac arrest on day 232, cardiac arrhythmia on day 242)
• Medical therapy=0.9% (4/458), p=0.51
(septic shock on day 269, suicide on day 489, amyotrophic lateral sclerosis on day 557 and metastatic cancer on day 569)
Nervous system disorder
• Closure=1.5% (6/402)
• Medical therapy=3.5% (16/458), p=0.15
Any serious adverse event
• Closure=16.9% (68/402)
• Medical therapy=16.6% (76/458), p=0.90</td>
<td>Follow-up issues:
• 8 patients in the closure group and 3 in the medical therapy group either withdrew consent or were lost to follow-up.
Study design issues:
• Multicentre, open label trial.
• Primary endpoint was a composite of stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days, or death from neurological causes (defined in efficacy column) between 31 days and 2 years.
• Trial was designed to detect a two-thirds reduction in the risk of recurrent events in the closure group and was underpowered to detect a smaller reduction.
• Three TIAs occurred in the closure group after randomisation but before device insertion, and these were included in the intention-to-treat analysis.
Study population issues:
• There were no significant differences between the two groups with respect to medical history, prior events, or risk factors for stroke.</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; HR, hazard ratio; INR, international normalised ratio; MRI, magnetic resonance imaging; OR, odds ratio; PFO, patent foramen ovale; RR, risk ratio; TCD, contrast transcranial doppler sonography; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
	(22/29) of patients in the medical therapy group (including new-onset atrial fibrillation, a clot in the left atrium, subcortical lacunar infarction with risk factors, aortic-arch atheroma, complex migraine, vasculitis, and conversion disorder).		

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; HR, hazard ratio; INR, international normalised ratio; MRI, magnetic resonance imaging; OR, odds ratio; PFO, patent foramen ovale; RR, risk ratio; TCD, contrast transcranial doppler sonography; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
Carroll JD (2013)[3] **Randomised controlled trial (RESPECT)** USA and Canada Recruitment period: 2003–11 Study population: patients with cryptogenic stroke and PFO **n=980 (499 percutaneous PFO closure vs 481 medical therapy)** Mean age: 46 years; Sex: 55% male Patient selection criteria: aged 18–60 years, ischaemic stroke within previous 270 days, PFO documented by TOE. Exclusion criteria: mechanism for index stroke other than paradoxical embolism, such as large-vessel disease, any cardioembolic source, a lacunar infarct that was probably due to intrinsic small-vessel disease, or arterial hypercoagulable state. Technique: percutaneous closure – Amplatzer PFO occluder (St Jude Medical); medical therapy – warfarin, aspirin, clopidogrel, or aspirin combined with extended-release dipyridamole. **Follow-up: mean 2.6 years** Conflict of interest/source of funding: supported by St Jude Medical.	Number of patients analysed: **980 (499 percutaneous PFO closure vs 481 medical therapy)** ***Technical success (delivery and release of device)=99.1%*** ***Complete closure of PFO at 6 months (confirmed with TOE)***=72.7% ***Primary composite end point at follow-up (rate per 100 patient years)*** **Population** / **Closure** / **Medical therapy** / **Hazard ratio (95% CI)** / **p value** Intention-to-treat (n=499 vs 481) / 0.66 / 1.38 / 0.49 (0.22–1.11) / 0.08 Per-protocol (n=471 vs 473) / 0.46 / 1.30 / 0.37 (0.14–0.96) / 0.03 As-treated (n=474 vs 484) / 0.39 / 1.45 / 0.27 (0.10–0.75) / 0.007 A total of 25 primary end-point events occurred, all of which were non-fatal ischaemic strokes ***Recurrent ischaemic stroke (event rate point estimates, intention-to-treat population)*** **Follow-up** / **Closure** / **Medical therapy** / **p value** 1 year / 1.3% / 1.7% / Not stated 2 years / 1.6% / 3.0% / Not stated 5 years / 2.2% / 6.4% / Not stated	**'Serious adverse events'** • Closure=23.0% • Medical therapy=21.6%, p=0.65 There were 22 serious adverse events in the closure group that were adjudicated as device-related or procedure-related: • Pericardial tamponade=0.4% (2/499) (treated during the course of the procedure) • Pericardial effusion=0.2% (1/499) (treatment not described) • Cardiac thrombus=0.4% (2/499) (a procedure-related cardiac thrombus in the right atrium developed in 1 patient and the procedure was abandoned with no device implanted; the other thrombus was detected 4 months after the procedure, together with a pulmonary embolism and a deep vein thrombosis). • Cardiac perforation=0.2% (1/499) (not further described) • Ischaemic stroke(timing not stated)=0.4% (2/499) • Major bleeding=0.4% (2/499) • Major haematoma=0.2% (1/499) • Infective or bacterial endocarditis=0.2% (1/499) (not further defined) None of the study-related serious adverse events resulted in death or permanent disability. Other events that each occurred in 1 patient: allergic drug reaction, atrial fibrillation, atrial flutter, chest tightness, deep vein thrombosis, pulmonary embolism, residual shunt needing closure, sepsis, nonsustained	**Follow-up issues**: • The dropout rate was 17% in the medical therapy group and 9% in the closure group, resulting in a significant between-group difference in follow-up observation (1375 years in the closure group versus 1184 years in the medical therapy group, p=0.009). **Study design issues**: • Multicentre, open label trial with blinded adjudication of end-point events. • Randomisation was stratified according to site, recommended medical treatment before randomisation, and presence or absence of an atrial septal aneurysm. • Primary end-point was a composite of recurrent nonfatal ischaemic stroke, fatal ischaemic stroke, or early death after randomisation (within 30 days of device implantation or 45 days after randomisation). **Study population issues**: • Baseline characteristics were well balanced between the 2 groups.

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; HR, hazard ratio; INR, international normalised ratio; MRI, magnetic resonance imaging; OR, odds ratio; PFO, patent foramen ovale; RR, risk ratio; TCD, contrast transcranial doppler sonography; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
		ventricular tachycardia, vasovagal reaction. 3 deaths in the closure group and 6 in the medical therapy group occurred after the early post-randomisation period and were adjudicated as not study-related.	

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; HR, hazard ratio; INR, international normalised ratio; MRI, magnetic resonance imaging; OR, odds ratio; PFO, patent foramen ovale; RR, risk ratio; TCD, contrast transcranial doppler sonography; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph

Study details	Key efficacy findings	Key safety findings	Comments
Meier B (2013)[4] **Randomised controlled trial (PC Trial)** Switzerland, UK, Poland, Denmark, Germany, Canada, Brazil, Australia. Recruitment period: 2000–9 Study population: patients with cryptogenic stroke or TIA and PFO **n=414 (204 percutaneous PFO closure vs 210 medical therapy)** Mean age: 44 years; Sex: 50% male Patient selection criteria: aged <60 years, clinically and neuroradiologically verified ischaemic stroke, TIA with a neuroradiologically cerebral ischaemic lesion, or a clinically and radiologically verified extracranial peripheral thromboembolic event, PFO documented by TOE and no other identifiable cause of stroke or peripheral thromboembolism Technique: <u>percutaneous closure</u> – Amplatzer PFO occluder (St Jude Medical); <u>medical therapy</u> – antithrombotic treatment was left to the discretion of the treating physician. **Follow-up: mean 4 years** Conflict of interest/source of funding: supported by St Jude Medical.	Number of patients analysed: **414 (204 percutaneous PFO closure vs 210 medical therapy)** ***Technical success (delivery and release of device)=95.9% (188/196)*** ***Effective closure of PFO at 6 months (no or minimal shunting, confirmed with TOE)***=95.9% (142/148) ***Clinical outcomes at follow-up (intention-to-treat population)*** **Outcome** / **Closure** / **Medical therapy** / **Hazard ratio (95% CI)** / **p value** Primary composite outcome of death, non-fatal stroke, TIA or peripheral embolism: 3.4% (7/204) / 5.2% (11/210) / 0.63 (0.24–1.62) / 0.34 Stroke (major): 0.5% (1/204) / 2.4% (5/210) / 0.20 (0.02–1.72) / 0.14 TIA: 2.5% (5/204) / 3.3% (7/210) / 0.71 (0.23–2.24) / 0.56 There were 2 deaths in the closure group and none in the medical therapy group (1 patient died of respiratory failure because of chronic obstructive pulmonary disease; the other died from a glioma).	**Serious adverse events** • Closure=21.1% (43/204) • Medical therapy=17.6% (37/210), p=0.37 Procedural complication=1.5% (3/204) (2 episodes of minor bleeding at access site, 1 periprocedural episode of atrial fibrillation that resolved within 6 hours) **PFO-related hospital admission (not further defined)** • Closure=6.4% (13/204) • Medical therapy=6.2% (13/210), p=0.95 **Myocardial infarction** • Closure=1.0% (2/204) • Medical therapy=0.5% (1/210), p=0.62 **Serious atrial fibrillation (not further defined)** • Closure=1.0% (2/204) • Medical therapy=1.0% (2/210), p=1.00 **Minor atrial fibrillation** • Closure=3.4% (7/204) • Medical therapy=4.3% (9/210), p=0.65 **Serious bleeding** • Closure=0.5% (1/204) • Medical therapy=1.4% (3/210), p=0.62	**Follow-up issues**: • 7 patients in the closure group and 11 in the medical therapy group withdrew from study; 24 and 31 others, respectively, were lost to follow-up. **Study design issues**: • Primary end-point was a composite of death, nonfatal stroke, TIA, or peripheral embolism. • Blinded adjudication of end-point events. **Study population issues**: • Baseline characteristics were similar in the 2 groups. • The authors noted that the patients were younger (p=0.006), had a lower rate of diabetes (p<0.001), and were less likely to be men (p=0.08) than the cohorts in a published meta-analysis (Agarwal S, 2012). **Other issues:** • The authors noted that they had difficulty recruiting patients, which led to a selected patient population that may limit generalisability of the study. • Patient retention was lower than expected.

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; HR, hazard ratio; INR, international normalised ratio; MRI, magnetic resonance imaging; OR, odds ratio; PFO, patent foramen ovale; RR, risk ratio; TCD, contrast transcranial doppler sonography; 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 (2012)[5]

Non-randomised comparative study
Switzerland
Recruitment period: 1994–2000

Study population: patients with cerebrovascular events presumably related to PFO

n=308 (150 percutaneous PFO closure vs 158 medical therapy)

Mean age: 50 years (closure)
Sex: 54% male (closure) vs 58% male (medical therapy)

Exclusion criteria: patients with permanent or paroxysmal atrial fibrillation or major aortic plaques.

Technique: <u>percutaneous closure</u> – under local anaesthetic and fluoroscopic guidance, insertion of various devices (Amplatzer PFO Occluder, PFO Star, Sideris buttoned device, Angel Wing device, Amplatzer ASD Occluder, CardioSEAL); followed by aspirin for 6 months until endothelialisation; <u>medical therapy</u> – coumarin or antiplatelet therapy.

Median follow-up: 9 years (range 8–14)
Conflict of interest/source of funding: there was no external funding.</td>
<td>Number of patients analysed: 308 (150 percutaneous PFO closure vs 158 medical therapy)

Closure of PFO (confirmed with TOE)
99% (148/150) had successful closure (2 were considered failures).

Presence of residual shunt
At 6 months, 82% (123/150) had complete closure but 10%, 3% and 5% of patients had small, moderate or large shunts.

Clinical outcomes over median 9 years (propensity score-matched cohort)
<table>
<tr><th>Event</th><th>PFO closure n=103</th><th>Medical therapy, n=103</th><th>HR (95% CI)</th><th>p value</th></tr>
<tr><td>Death, overall</td><td>6 (6%)</td><td>6 (6%)</td><td>1.00 (0.32 to 3.10)</td><td>1.00</td></tr>
<tr><td>Cardiovascular death</td><td>3 (3%)</td><td>3 (3%)</td><td>1.00 (0.20 to 4.95)</td><td>1.00</td></tr>
<tr><td>Stroke</td><td>6 (6%)</td><td>8 (8%)</td><td>0.75 (0.26 to 2.16)</td><td>0.59</td></tr>
<tr><td>TIA</td><td>5 (5%)</td><td>14 (14%)</td><td>0.31 (0.10 to 0.94)</td><td>0.039</td></tr>
<tr><td>Peripheral embolism</td><td>0</td><td>0</td><td>-</td><td>-</td></tr>
<tr><td>Major bleeding</td><td>1 (1%)</td><td>3 (3%)</td><td>0.33 (0.03 to 3.20)</td><td>0.34</td></tr>
<tr><td colspan="5">Composite outcomes</td></tr>
<tr><td>Stroke or death</td><td>12 (12%)</td><td>12 (12%)</td><td>0.92 (0.40 to 2.08)</td><td>0.84</td></tr>
<tr><td>Stroke, TIA or peripheral embolism</td><td>11 (11%)</td><td>22 (21%)</td><td>0.43 (0.20 to 0.94)</td><td>0.033</td></tr>
<tr><td>Stroke, TIA, peripheral embolism, or death</td><td>16 (16%)</td><td>25 (24%)</td><td>0.57 (0.29 to 1.12)</td><td>0.10</td></tr>
</table>
In the medical treatment group, 32% (33/103) matched patients crossed over to subsequent percutaneous (n=29) or surgical (n=4) PFO closure.</td>
<td>Safety outcomes were not reported.</td>
<td>Follow-up issues:
• 98% (301/308) of patients were available for follow-up to a maximum of 15 years; 2 patients with PFO closure and 5 patients with medical treatment were lost to follow-up.
Study design issues:
• Treatment allocation based on both patient and physician preference.
• 103 propensity score-matched pairs of patients were analysed (matched on age, sex, cerebrovascular index event, >1 cardiovascular event and interatrial right to left shunt).
• Aspirin was continued beyond 6 months after closure in 57 patients (residual shunt in 26 and mild coronary artery disease in 31).
• The prespecified primary endpoint was the composite of stroke, TIA, or peripheral embolism.
Study population issues:
• Patients treated with percutaneous closure were more likely to have had >1 cerebrovascular event or a larger right-to-left shunt at baseline than patients in the medical therapy group. After matching, baseline characteristics were similar in the two groups.</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; HR, hazard ratio; INR, international normalised ratio; MRI, magnetic resonance imaging; OR, odds ratio; PFO, patent foramen ovale; RR, risk ratio; TCD, contrast transcranial doppler sonography; 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>Cunningham D (2010)[6]

Registry (Central Cardiac Audit Database)
UK
Recruitment period: 2000 – 2011
Study population: patients treated with percutaneous PFO closure
n=5616 (4625 percutaneous PFO closure vs 991 surgical PFO closure)
Mean age: 45.3 years (percutaneous closure)

Sex: not reported
Patient selection criteria: all patients with procedure code including “PFO closure” and procedure type = “Catheter”

Technique: PFO closure (type of device not reported)

Median follow-up: 3.8 years
Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 5616

<table>
<tr><th></th><th>Total percutaneous PFO closures by catheter</th><th>Percutaneous PFO closure as part of multiple procedure</th><th>Isolated percutaneous PFO closures by catheter</th></tr>
<tr><td>Total</td><td>4625</td><td>315</td><td>4310</td></tr>
</table>

Survival
Validated mortality data was available for 4202 cases (97.5%).
At a median follow up of 3.8 years, 4133 (98.4%) patients were alive and 69 (1.6%) were dead.
• Actuarial 5-year survival=98.1%
• Actuarial 10-year survival=97.2%
(7 deaths were due to stroke)

Redo PFO closure rate=7.7%
There were 21 other reinterventions: 14 catheter (2 duct closures, 2 ASD closures, 7 arrhythmia-related procedures, 1 embolectomy and 2 complications) and 7 surgical (6 ASD closures and 1 pulmonary valve replacement).</td>
<td>Not reported</td>
<td>Follow-up issues:
• Not reported

Other issues:
• Results were not separated by indication.
• PFO was the indication for the procedure in 89% (3837/4310) of patients. Other indications included non-cardiac abnormality associated with heart disease, interatrial communication, atrial septum abnormality, ASD within oval fossa, systemic hypertension, Ebstein’s malformation of tricuspid valve, myocardial infarction, and patent arterial duct.</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; HR, hazard ratio; INR, international normalised ratio; MRI, magnetic resonance imaging; OR, odds ratio; PFO, patent foramen ovale; RR, risk ratio; TCD, contrast transcranial doppler sonography; 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[5]: 20-year old male who had the procedure (Amplatzer PFO occluder) following a CVA, presented 4 months later with pain and discharge from bilateral ingrown 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[6]: 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. One month before device closure he presented with streptococcal pharyngitis, which was successfully treated with 2 weeks of Augmentin therapy. 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.		
Raffa GM (2008)[9] **Case report of safety** USA, Germany, Italy n=**1**	Cardia Starr device implanted in a 35-year-old female with a history of 2 acute neurological events likely to be on ischaemic grounds. 6 months later, 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 dyspnoea and palpitations) so the device was removed through a minithoracotomy and the fistula was closed. The post-operative care was uneventful with discharge on day 5. In the 18 months following, there were no more complications.		
Onorato E (2002)[10] **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 not interfering with it. 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 manoeuvre.		
Coceani M (2007)[11] **Case report of safety** Italy n=**1**	61-year-old female with PFO and history of TIA was treated with a 35-mm Amplatzer cribriform septal occluder. During the procedure the device was replaced with a 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 device 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 post-operative course.		

Abbreviations used: AF, atrial fibrillation; ASA, atrial septal aneurysm; ASD, atrial septal defect; CI, confidence interval; CVA, cerebrovascular accident; DVT, deep vein thrombosis; HR, hazard ratio; INR, international normalised ratio; MRI, magnetic resonance imaging; OR, odds ratio; PFO, patent foramen ovale; RR, risk ratio; TCD, contrast transcranial doppler sonography; TIA, transient ischaemic attack; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiograph			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Gori T (2010)[12] **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** requiring 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.		

Efficacy

Recurrence of thromboembolic events

A meta-analysis of 58 observational studies (8185 patients treated by percutaneous PFO closure and 2142 patients treated by medical therapy) reported a pooled incidence of recurrent neurological events of 0.8 (95% CI 0.5 to 1.1) per 100 person-years for percutaneous closure and 4.4 (95% CI 3.2 to 5.6) per 100 person-years for medical therapy[1].

A randomised controlled trial of 909 patients treated by percutaneous PFO closure or medical therapy reported the cumulative incidence of a composite end point of stroke or transient ischaemic attack (TIA) during 2 years of follow-up, death from any cause during the first 30 days, or death from neurological causes between 31 days and 2 years, was 6% and 7% respectively (p=0.37)[2].

A randomised controlled trial of 980 patients treated by percutaneous PFO closure or medical therapy reported rates of stroke of 0.7 and 1.4 per 100 patient-years respectively in the intention-to-treat population (p=0.08)[3].

A randomised controlled trial of 414 patients treated by percutaneous PFO closure or medical therapy reported a composite of death, non-fatal stroke, TIA or peripheral embolism in 3% (7/204) and 5% (11/210) of patients respectively with a mean follow-up of 4 years (p=0.34)[4].

A non-randomised comparative study of 308 patients reported recurrent stroke in 6% (6/103) patients treated by percutaneous PFO closure compared with 8% (8/103) of patients treated with medical therapy over a median follow-up of 9 years (p=0.59, propensity score-matched pairs of patients). Recurrent TIA occurred in 5% (5/103) and 14% (14/103) of these groups, respectively (p=0.04). There were 3 cardiovascular deaths in each group. The primary composite endpoint of stroke, TIA or peripheral embolism occurred in 11% (11/103) of patients treated by percutaneous PFO closure and 21% (22/103) of patients treated medically (p=0.03)[5].

Successful closure of PFO and residual shunt

The meta-analysis of 58 observational studies (8185 patients treated by percutaneous PFO closure and 2142 patients treated by medical therapy) reported a residual shunt after the procedure in 25% (95% CI 17 to 34) of patients; 6% (95% CI 0 to 18) of patients had a residual shunt for more than 12 months[1].

The randomised controlled trial of 909 patients treated by percutaneous PFO closure or medical therapy reported successful closure in 87% (320/369) of patients at 2 years follow-up[2].

The non-randomised comparative study of 308 patients treated by percutaneous PFO closure or medical therapy reported that 99% (148/150) of patients treated by percutaneous closure had successful closure (2 procedures were considered failures; not defined)[5].

The same study reported that 82% of patients had complete closure at 6 months, but that 10%, 3% and 5% of patients had small, moderate or large shunts, respectively.

Survival

Data from a registry of 4625 patients treated with percutaneous PFO closure for mixed indications reported that 98% (4133/4202) of patients were alive at a median follow-up of 3.8 years[6].

Safety

Death

Death related to the procedure was reported in 0.1% (95% CI 0 to 0.3) of patients in the meta-analysis of 58 studies[1].

Pericardial effusion, cardiac tamponade or perforation

Pericardial effusion or tamponade was reported in 0.3% (95% CI 0 to 0.6) of patients in the meta-analysis of 58 studies[1]. Perforation was reported in 0.1% (95% CI 0 to 0.3) of patients. Details of treatment and outcome were not provided.

Pericardial tamponade was reported in 0.4% (2/499) of patients treated by percutaneous closure in the randomised controlled trial of 980 patients. In the same study there was 1 report each of pericardial effusion and cardiac perforation.

Infection

Infection was reported in 0.1% (95% CI 0 to 0.8) of patients in the meta-analysis of 58 studies[1].

There were 2 case reports of infective endocarditis needing removal of the device in patients treated with percutaneous PFO closure for thromboembolic events: *Staphylococcus aureus* was detected in a 20-year-old man 4.5 months after the procedure and *Bacillus pumilus* was detected in a 42-year-old man 19 days after removal of the device following complications 10 weeks after the procedure[7,8].

Device issues

Device embolisation or malposition was reported in 0.4% (95% CI 0.2 to 0.7) of patients in the meta-analysis of 58 studies[1].

There was a case report of a Eustachian valve becoming trapped in the delivery cable in a patient 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[10].

Another case report described a patient who needed hospital admission and medical therapy because of a long mobile structure that 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 and needed percutaneous removal[12].

Air embolism

Air embolism was reported in 0.6% (95% CI 0.2 to 1.0) of patients in the meta-analysis of 58 patients (not further described)[1].

Arrhythmias

Atrial arrhythmia was reported in 4% (95% CI 3 to 6) of patients in the meta-analysis of 58 studies (not further described)[1].

The randomised controlled trial of 909 patients treated by percutaneous PFO closure or medical therapy reported atrial fibrillation in 6% (23/402) and 0.7% (3/458) of patients respectively ($p<0.001$)[2]. In the closure group, 61% (14/23) of the patients with atrial fibrillation developed it within 30 days of the procedure; atrial fibrillation was transient in 17 patients and persistent in 6 patients. The randomised controlled trial of 414 patients reported serious atrial fibrillation in 1% (2/204 and 2/210) of patients in each group[4].

There was a case report of a patient who developed ventricular tachycardia and eventually an intermittent left branch bundle block. The device had migrated through the mitral valve and was blocking the left ventricular outflow tract so emergency surgery was needed to manually remove the device. The patient was discharged after 7 days with an uneventful post-operative course[11].

Thrombus

Thrombus was reported in 0.6% (95% CI 0.3 to 0.9) of patients in the meta-analysis of 58 studies (not further described)[1].

Fistulae

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. Medical therapy

was not successful so the device was removed and the fistula was closed through a minithoracotomy[9]. The postoperative course was uneventful.

Validity and generalisability of the studies

- The overview for Interventional Procedure Guidance 109 included 8 case series and 1 systematic review with a maximum follow-up of 2 years for efficacy outcomes (3 years for complication rates). This overview now includes a meta-analysis of 58 observational studies, 3 randomised controlled trials, 1 non-randomised comparative study, results from a registry and 7 case reports of adverse events, with a maximum follow-up of more than 9 years.
- Studies including fewer than 50 patients were excluded from this overview (the main extraction table and the appendix) unless they reported a serious safety event because there has been a significant amount of literature published since the previous overview, with a large proportion consisting of case series and case reports.
- Assessment of the efficacy of the procedure was difficult because of the variety of potential causes for the event. The original thromboembolic event may not have been caused by substances crossing the PFO and therefore a recurrent event may not be related to lack of efficacy of the device.
- Different devices were used in the studies and these may have different safety and efficacy profiles.
- There is heterogeneity in patient populations between studies. The enrolment criteria for the RESPECT trial were more stringent than those in the CLOSURE trial[2,3].
- One randomised controlled trial noted that problems with patient recruitment led to an unusually long recruitment period and a selected patient population that may limit the generalisability of the study's findings[4].
- There were a large number of case reports of serious safety events including cardiac tamponade, perforation and thrombosis on the device. Because of the space limitations in table 2, these reports were included only if they gave unique information that was not reported in the larger studies. The other case reports have been included in appendix A (with the event highlighted in bold).

- There are some reports of new-onset migraine after the procedure. It has been suggested that this may be related to nickel sensitivity.
- Other sources of paradoxical emboli could include arteriovenous shunts. Two case reports of pulmonary arteriovenous fistulae have been included in appendix A (Goldstein et al.;Youssef et al.).

Existing assessments of this procedure

In 2006, the Haute Autorité de Santé (France) was unable to make determinate recommendations on PFO closure for the secondary prevention of cerebral or transitory ischaemic events. It permitted the use of the procedure on patients with PFO and atrial septal aneurysm in the context of research.

Currently, the American Heart Association, the American Stroke Association and the American College of Chest Physicians recommend antiplatelet therapy for patients with ischaemic stroke or TIA and PFO. They have stated that there is insufficient data for PFO closure for secondary stroke prevention in patients with a PFO who have had a stroke (although patients with recurrent stroke may be considered for PFO closure; from 2006 report). In 2007, the Circulatory System Devices Panel of the US Food and Drug Administration (FDA) made recommendations about the use of PFO devices. It felt that randomised controlled trials (RCTs) were needed to assure the proof of concept for the rationale of using PFO closure devices to prevent recurrent stroke. It discussed viable alternative trial designs, endpoints and barriers to enrolment. The FDA has approved use of these devices only in patients with recurrent stroke despite anticoagulant therapy.

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 secondary prevention of recurrent paradoxical embolism in divers. NICE interventional procedures guidance 371 (2010).
- Percutaneous closure of patent foramen ovale for recurrent migraine. NICE interventional procedures guidance 370 (2010).
- Transcatheter endovascular closure of perimembranous ventricular septal defect. NIC*E* interventional procedures guidance 336 (2010).
  Endovascular closure of atrial septal defect. NICE interventional procedures guidance 96 (2004).

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 D Hildick-Smith, Dr M Turner (British Cardiovascular Intervention Society); Dr N Baldwin, Professor M Dennis (British Association of Stroke Physicians)

- Three specialist advisers considered the procedure to be established practice and no longer new; 1 adviser considered the procedure to be definitely novel and of uncertain safety and efficacy.

- Standard treatment would be medical therapy with antiplatelet or anticoagulant treatment.

- There is controversy about whether the procedure improves outcomes and whether results vary according to the device used. One particular concern is whether devices may increase the rate of atrial fibrillation, which in itself may increase the risk of embolism 5-fold and offset any reduction in paradoxical embolism.

- Key efficacy outcomes include reduction in the rate of stroke and systemic emboli, increase in oxygenation levels (if appropriate) and complete clinical closure of the PFO.

- The trials to date show only small reductions in the rate of stroke or other emboli associated with closure. These have not been statistically significant on intention-to-treat analyses although they are of borderline statistical significance on per-protocol analyses, which may be biased. In any event the event rate is low in both groups so the number needed to treat to avoid 1 event is high, which calls into question how worthwhile the procedure is.

- Adverse events reported in the literature include stroke, vascular damage, bleeding, perforation of the heart, pericardial effusion, tamponade, arrhythmias during the procedure, increased rate of atrial fibrillation after the procedure, infection, device embolisation, embolism of clots attached to the device, device erosion, and transient worsening of migraine. Theoretical adverse events include death and device misplacement.

- One adviser noted that there is a manufacturer's registry and the NHS device registry.

- One adviser noted that there is a proposed UK dataset for PFO closure that will be put in place by the National Institute for Cardiovascular Outcomes Research (NICOR) if the commissioners agree a Commissioning Through Evaluation policy.

- Two advisers considered the potential impact of the procedure on the NHS to be minor, in terms of numbers of patients eligible for treatment and use of resources; 1 adviser considered the potential impact to be moderate to major and 1 adviser considered the potential impact to be major.

- One specialist adviser noted that many of the stroke events seen in patients with PFO are minor, so we also need to assess the impact on disability and quality of life. Also many patients seem to be psychologically disturbed by the news that they have PFO, which has a detrimental effect on their quality of life. This has to be taken into account if a programme of detection of PFO and of PFO closure is to be rolled out.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- Ongoing randomised controlled trials:
  - CLOSE: RCT started in 2007 to compare any device to close the PFO with antiplatelet therapy for stroke patients (NCT00562289; funded by a French organisation of hospitals; estimated enrolment 900; estimated study completion December 2016).
  - Gore REDUCE: RCT started in 2008 to compare the Gore HELEX device with antiplatelet therapy for stroke patients (NCT00738894; funded by W.L. Gore & Associates; US-based; estimated enrolment 664; estimated study completion August 2015).

References

1. Agarwal S, Bajaj NS, Kumbhani DJ et al. (2012) Meta-analysis of transcatheter closure versus medical therapy for patent foramen ovale in prevention of recurrent neurological events after presumed paradoxical embolism. JACC Cardiovascular Interventions 5: 777–89

2. Furlan AJ, Reisman M, Massaro J et al. (2012) Closure or medical therapy for cryptogenic stroke with patent foramen ovale. New England Journal of Medicine 366: 991–9

3. Carroll JD, Saver JL, Thaler DE et al. (2013) Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. New England Journal of Medicine 368: 1092–100

4. Meier B, Kalesan B, Mattle H et al. (2013) Percutaneous closure of patent foramen ovale in cryptogenic embolism. New England Journal of Medicine 368: 1083–91

5. Wahl A, Juni P, Mono ML et al. (2012) Long-term propensity score-matched comparison of percutaneous closure of patient foramen ovale with medical treatment after paradoxical embolism. Circulation 125: 803–12

6. Personal communication. Unpublished data provided by David Cunningham on behalf of the Central Cardiac Audit Database. March 2013

7. Youssef GS, Allan RM, Manganas C et al. (2006) Case report: a tale of two toes. Heart, Lung, 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: 217–20

9. 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

10. 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

11. 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

12. 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 75: 778–81

Appendix A: Additional papers on percutaneous closure of patent foramen ovale for the prevention of recurrent cerebral embolic events

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
Alaeddini J, Feghali G, Jenkins S et al. (2006) Frequency of atrial tachyarrhythmias following transcatheter closure of patent foramen ovale. Journal of Invasive Cardiology 18:365-368	Case series n=71 (cryptogenic stroke in 70) Mean follow-up=248 days	Atrial fibrillation: 3 patients Atrial flutter: 2 patients	Comparative studies in table 2.
Alameddine F and Block PC. (2004) Transcatheter patent foramen ovale closure for secondary prevention of paradoxical embolic events: acute results from the FORECAST registry.[see comment]. Catheterization & Cardiovascular Interventions 62:512-516	Case series n=272 Follow-up=not reported	Initial complete shunt closure rate: 74.3% Periprocedural complication rate: 6.6% No deaths or pericardial tamponade	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Anzai HC. (2004) Incidence of thrombus formation on the CardioSEAL and the Amplatzer interatrial closure devices. American Journal of Cardiology 93: 426–31	Case series n=57 patients with PFO (some patients also had ASD)	No events in follow-up. Thrombus formation occurred more in CardioSEAL than Amplatzer device (22% [5/23] vs 0% [0.27]; p = 0.02).	Difficult to separate results for patients with ASD/PFO.
Anzola GP, Morandi E, Casilli F et al. (2004) Does transcatheter closure of patent foramen ovale really "shut the door?" A prospective study with transcranial Doppler. Stroke 35:2140-2144	Case series n=140 Follow-up=1 year	Implantation successful in all patients. Large shunt at 12 months: 9% (9/104) Atrial fibrillation: 8% Scintillating scotomata: 6% TIA: 1 patient with paroxysmal atrial fibrillation and complete PFO closure	Comparative studies in table 2.
Anzola GP. (2006) Can patent foramen ovale closure using the Cardia PFO occluder reduce the occurrence of thromboembolic events? Nature Clinical Practice Cardiovascular Medicine 3:186-187	Case series n=403 Follow-up=6 months	Loss to follow-up: 10.4% (42/403) 12 thromboembolic events (5 recurrent stroke, 8 TIAs). Annual recurrence rate: 2.0% Residual shunt at 6 months: 10.8% (39/361) Device thrombi: 10 patients Asymptomatic wire fracture: 14 patients	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Aslam F, Iliadis AE, and Blankenship JC. (2007) Percutaneous closure of patent foramen ovale: success and outcomes of a low-volume procedure at a rural medical center. Journal of Invasive Cardiology 19:20-24	Case series n=52 Follow-up=28 months	All had successful deployment but 10 had mild residual shunt at discharge. Pre-discharge events: bleeding in 4, arrhythmia in 3 At 28-month follow-up: 4 had spells of uncertain aetiology, 1 had atrial fibrillation No TIAs or strokes. 1 death of renal failure and sepsis not related to the procedure.	Comparative studies in table 2.
Aytemir K, Oto A, Ozkutlu S et al. (2012) Early-mid term follow-up results of percutaneous closure of the interatrial septal defects with occlutech figulla devices: A single center experience. Journal of Interventional Cardiology.25: 375-381	Case series n=143 Mean follow-up=15 months	During the follow-up, all patients were asymptomatic and no ischemic stroke, cardiac perforation, device erosion, embolization, thrombus formation, or malposition of the device was observed.	Comparative studies in table 2.
Babic UU. (2000) Experience with ASDOS for Transcatheter Closure of Atrial Septal Defect and Patent Foramen Ovale. Current Interventional Cardiology Reports 2: 177–83	Case series n=89 patients with PFO (also 261 patients with ASD)	In all patients treated with closure (ASD or PFO), 91% (218) were successful; failure in 9% (32), 7% (26) were retrieved. Perforation in 6, thromboembolism in 3, infection in 2, early dislodgement in 3, transient arteriovenous block in 2.	Difficult to separate results for patients with ASD/PFO.
Balbi M, Casalino L, Gnecco G et al. (2008) Percutaneous closure of patent foramen ovale in patients with presumed paradoxical embolism: periprocedural results and midterm risk of recurrent neurologic events. American Heart Journal 156:356-360	Case series n=128 Mean follow-up= 32 months	Implantation successful in all patients. Complete PFO closure at 6 months (transcranial doppler examination): 82.5%. No death, device embolisation or thrombosis, need for cardiac surgery. Complications:7% No recurrent thromboembolic events during follow-up period.	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Banerjee A, Bengur AR, Li JS et al. (1999) Echocardiographic characteristics of successful deployment of the Das AngelWings atrial septal defect closure device: initial multicenter experience in the United States. American Journal of Cardiology 83: 1236–41	Case series n=70 patients (some patients also had ASD)	95% (65) had successful device deployment.	Difficult to separate results for patients with ASD/PFO.
Bartz PJ, Cetta F, Cabalka AK et al. (2006) Paradoxical emboli in children and young adults: role of atrial septal defect and patent foramen ovale device closure. Mayo Clinic Proceedings 81: 615-619	n=45 FU=5 months (median)	No major procedural complications occurred. Forty-four patients (98%) had no recurrent neurologic events and no residual atrial shunt by contrast transthoracic echocardiography.	Small case series.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Becker M, Frings D, Schroder J et al. (2009) Impact of occluder device type on success of percutaneous closure of atrial septal defects-a medium-term follow-up study. Journal of Interventional Cardiology 22:503-510	Case series n=309 (PFO or ASD) Mean follow-up=31 months	16 thromboembolic events. Annual recurrence: 2.1% Presence of atrial septal defect was a significant risk factor for thromboembolic events (p=0.0168)	Comparative studies in table 2.
Berdat PA, Chatterjee T, Pfammatter JP et al. (2000) Surgical management of complications after transcatheter closure of an atrial septal defect or patent foramen ovale. Journal of Thoracic & Cardiovascular Surgery 120: 1034–9	Case series n=76 patients with PFO (report on 10 patients with complications)	8/10 of patients who required operations after transcatheter closure had a significant shunt because of persistent malposition or dislocation of the device 1 patient died of **left ventricular perforation** after device dislocation.	Larger studies in table 2.
Bialkowski J, Wawrzynczyk M, Karwot B et al. (2012) Medium-term results of transcatheter closure of patent foramen ovale (PFO) with Amplatzer PFO and Cribriform occluders. Kardiologia Polska 70: 1142-1146	Case series n=56 Follow-up=6 months	Results of randomised trials are necessary to confirm the effectiveness of transcatheter therapy in patients with PFO and a paradoxical thromboembolic event	Larger studies in table 2.
Bijl JM, Ruygrok PN, Hornung TS et al. (2005) Percutaneous closure of patent foramen ovale. Internal Medicine Journal 35: 706-711	n=40 FU=11 months (mean)	No complications were encountered. No further neurological events occurred in 39 patients at a mean follow-up time of 11 ± 7 months (3–25 months) nor was a significant shunt detected in the 34 who underwent follow-up echocardiography.	Small case series.
Billinger, K, Ostermayer, SH, Carminati, M, et al. (2006) HELEX Septal Occluder for transcatheter closure of patent foramen ovale: multicentre experience. Eurointervention 1 (4) 465-471	Case series n=128 Follow-up=21 months	127 had successful implantation No recurrent events in follow-up Complete PFO closure with one device achieved in 90% (114/128) Device embolisation, wire-frame fracture, retrieval cord breaks (each had 2 occurrences with no sequelae)	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Bissessor N, Wong AW, Hourigan LA et al. (2011) Percutaneous patent foramen ovale closure: Outcomes with the Premere and Amplatzer devices. Cardiovascular Revascularization Medicine 12: 164-169	Case series n=70 Median follow-up=11 months	PFO causing presumed paradoxical embolism can be closed percutaneously with a low rate of significant residual shunting and very few complications. Recurrent index events are uncommon at medium-term (up to 4 years) follow-up.	Larger studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bonvini RF, Sztajzel R, Dorsaz P-A et al. (2010) Incidence of atrial fibrillation after percutaneous closure of patent foramen ovale and small atrial septal defects in patients presenting with cryptogenic stroke. International Journal of Stroke 5:4-9	Non randomised comparative study n=143 (92 percutaneous PFO closure vs 51 medically treated) patients with cryptogenic stroke Follow-up=12 months	Incidence of atrial fibrillation was similar in both groups at 12 months (7.6% vs 7.8%, p=1.0)	Larger studies in table 2.
Braun M, Gliech V, Boscheri A et al. (2004) Transcatheter closure of patent foramen ovale (PFO) in patients with paradoxical embolism. Periprocedural safety and mid-term follow-up results of three different device occluder systems. European Heart Journal 25:424-430	Case series n=307 (paradoxical embolism) Median follow-up=24 months	Implantation successful in all patients Perinterventional complications: 9 patients (5 ST-segment elevations, 1 arteriovenous fistula, 2 TIA and 1 device dislodged – all successfully reversed) Annual risk of recurrence: 0.6% for TIA, 0% for stroke ad 0.2% for peripheral embolism.	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Bronzetti G, D'Angelo C, Donti A et al. (2011) Role of atrial fibrillation after transcatheter closure of patent foramen ovale in patients with or without cryptogenic stroke. International Journal of Cardiology 146: 17–21	Case series n=276 Mean follow-up=17 months	New-onset atrial fibrillation was documented in 10 patients (4%), all included in the group with a previous cryptogenic cerebrovascular ischaemic event, at a mean of 1.6 months post-procedure.	Comparative studies in table 2.
Bruch L, Parsi A, Grad MO et al. (2002) Transcatheter closure of interatrial communications for secondary prevention of paradoxical embolism: single-center experience. Circulation 105: 2845–8	Case series n=54 patients with PFO (also patients with ASD) Follow-up=122.2 patient-years	Successful and without complications in all patients. After 3 months, 2 had residual shunt but this disappeared at 12 months. At 112.2 patient-years, no recurrences.	Difficult to separate results for patients with ASD/PFO.
Buscheck F, Sievert H, Kleber F et al. (2006) Patent foramen ovale using the Premere device: the results of the CLOSEUP trial. Journal of Interventional Cardiology 19:328-333.	Case series n=73 Follow-up=6 months	No shunt on contrast echocardiography: 86% Transient atrial fibrillation (resolved in 3 months): 1 patient No thrombus, stroke or deaths.	Comparative studies in table 2.
Caputi L, Butera G, Parati E et al. (2012) Italian patent foramen ovale survey (I.P.O.S.): Early results. Perspectives in Medicine 1: 236-240	Case series n=1035 (243 at 12 months and 31 at 24 months)	The rate of neurological events and cardiac and extra-cardiac complications were around 3% and 9% up to the 24-month follow-up respectively. A large permanent residual RLS and no RLS were observed in less than 1% and in 82% of patients at the 1-year follow-up, respectively.	Larger studies are included.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Casaubon L, McLaughlin P, Webb G et al. (2007) Recurrent stroke/TIA in cryptogenic stroke patients with patent foramen ovale. Canadian Journal of Neurological Science 34:74–80	Non-randomised comparative study n=121 Follow-up=32 months	PFO closure (device and surgical) had fewer strokes than medical therapy (p = 0.014).	Included in Agarwal et al, 2012 meta-analysis.
Cecconi M, Quarti A, Bianchini F et al. (2006) Late cardiac perforation after transcatheter closure of patent foramen ovale. Annals of Thoracic Surgery 81: e29–30	Case report n=1	**Left atrial wall perforation and aortic root erosion** 16 months after the procedure. This was successfully treated with emergency surgery. Uneventful post-operative course.	Event reported in table 2.
Cerrato P, Priano L, Imperiale D et al. (2006) Recurrent cerebrovascular ischaemic events in patients with interarterial septal abnormalities: a follow-up study. Neurological Science 26: 411–8	Non-randomised comparative study n=86 Follow-up=2.6 years	Rate of recurrent events: • Percutaneous PFO closure=0% (0/0) • Antiplatelet therapy=19% (9/48; 4 TIA, 5 strokes) • Anticoagulation=12% (2/17; 1 TIA, 1 stroke)	Larger comparative studies are included in table 2. Included in Agarwal et al, 2012 meta-analysis.
Cetta F, Arruda MJ, Graham LC. (2003) Large left atrial thrombus formation despite Warfarin therapy after device closure of a patent foramen ovale. Catheterization and Cardiovascular Interventions 59: 396–8	Case report n=1	**Thrombus** detected at 6 month echocardiogram. Both device and thrombus were removed without complications.	Event reported in table 2.
Chatterjee T, Petzsch M, Ince H et al. (2005) Interventional closure with Amplatzer PFO occluder of patent foramen ovale in patients with paradoxical cerebral embolism. Journal of Interventional Cardiology 18:173-179	Case series n=55 Mean follow-up=19 months	Procedure success in all. Complete occlusion on TOE and colour doppler in 96% 3 to 6 months after. 2 had trivial residual shunt. 1 had cardiac tamponade in hospital requiring successful pericardiocentesis. No recurrent events.	Comparative studies in table 2.
Chiam PTL, Schneider LM, Ruiz CE. (2008) Cardiac perforation during patent foramen ovale closure sealed with an Amplatzer PFO Occluder. Journal of Invasive Cardiology 20: 665–8	Case report n=1	**Perforation of right atrial wall** caused when patient attempted to sit up during procedure. Successfully treated percutaneously.	Event reported in table 2.
Chintala K, Turner DR, Leaman S et al. (2003) Use of balloon pull-through technique to assist in CardioSEAL device closure of patent foramen ovale. Catheterization & Cardiovascular Interventions 60:101-106.	Retrospective comparative case series (2 techniques) n=51 Follow-up=17.5 months	4 had partial deployment. No complications associated with the technique.	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Christen T, Mach F, Didier D et al. (2005) Late cardiac tamponade after percutaneous closure of patent foramen ovale. European Journal of Echocardiography 6: 465–9	Case report n=1	1 year after procedure patient developed **cardiac tamponade** from haemorrhagic pericardial effusion. The aortic root had been impinged by a strut from the device. Removal by open heart surgery with uneventful recovery.	Event reported in table 2.
Cifarelli A, Musto C, Parma A et al. (2010) Long-term outcome of transcatheter patent foramen ovale closure in patients with paradoxical embolism. International Journal of Cardiology 141:304–10	Case series n=202 Follow-up=3 years	Device migration in 1 patients after 24 hours No death or stroke in follow-up but 3 recurrent TIAs in first 6 months. Thromboembolism-free survival rates: 99% in patients less than or equal to 55 years and 84% in greater than 55 years.	Comparative studies in table 2.
Delaney JW, Li JS, Rhodes JF. (2007) Major complications associated with transcatheter atrial septal occluder implantation: a review of the medical literature and the manufacturer and user facility device experience (MAUDE) database. Congenital Heart Disease 2: 256–64	Review of complications for patients treated with ASD (also searched for reports with patients treated for PFO)	Comparison of events in different devices. Embolisation rates in MAUDE database (FDA) for some devices were lower than some European studies but this may be because of restrictions in the US. MAUDE database showed a higher estimated major complication than the medical literature, including death.	Review was for both ASD and PFO so difficult to separate results for patients treated with PFO.
Diaz T, Cubeddu RJ, Rengifo-Moreno, PA et al. (2010) Management of residual shunts after initial percutaneous patent foramen ovale closure: A single center experience with immediate and long-term follow-up. Catheterization and Cardiovascular Interventions 76:145–50	Case series n=424 Follow-up=2.9 years	21 had moderate to severe residual shunt 6 months after closure, 20 required a second device 95% (19/20) success rate in these patients.	Comparative studies in table 2.
Dubiel M, Bruch L, Liebner M et al. (2007) Exclusion of patients with arteriosclerosis reduces long-term recurrence rate of presumed arterial embolism after PFO closure. Journal of Interventional Cardiology 20:275-281	Case series n=180 (124 PFO, 24 PFO-like ASD and 31 ASD) Mean follow-up=40 months	Trivial residual shunt at 18 months: 5 patients Paradoxical embolism: 1 patient	Comparative 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	Outcomes related to presence of migraine 24% (46) had migraine with aura; in 24% (11/46), this had disappeared completely at follow-up and 63% (29/46) had improved	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Egred M, Andron M, Albouaini K et al. (2007) Percutaneous closure of patient foramen ovale and atrial septal defect: Procedural outcome and medium-term follow-up. Journal of Interventional Cardiology 20:395–401	Case series n=185 with PFO or ASD closure Mean follow-up=16.9 months	96.8% (179/185) with successful closure Residual shunt before discharge in 20% (37/185). At 6 months, this was only 5.4% (10/185). No recurrences or deaths. Retroperitoneal haematoma requiring transfusion in 1, pericardial effusion requiring aspiration in 2.	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Fischer D, Fuchs M, Schaefer A et al. (2008) Transcatheter closure of patent foramen ovale in patients with paradoxical embolism. Procedural and follow-up results after implantation of the Starflex occluder device with conjunctive intensified anticoagulation regimen. Journal of Interventional Cardiology 21:183-189	Case series n=154 Mean follow-up=26 months	Significant residual shunt: 5 patients Thrombus formation on occlude: 5 patients (removed in 3) Stroke: 2 patients TIA: 7 patients 2 deaths 3 patients with bleeding complications	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Ford MA, Reeder GS, Lennon RJ et al. (2009) Percutaneous Device Closure of Patent Foramen Ovale in Patients With Presumed Cryptogenic Stroke or Transient Ischemic Attack. The Mayo Clinic Experience. Jacc: Cardiovascular Interventions 2:404-411	Case series n=352 (cryptogenic stroke: 63.9% and TIA:36.1%) Mean follow-up=37 months	Recurrence rate: 0.6% (2.1% for stoke, 0.3% for TIA at 1 year and 0.7% for TIA at 4 years)	Comparative studies in table 2.
Gaul C, Heckmann JG, Bremer J et al. (2004) Thrombus am Sideris-Okklerduersystem nach 6 Jahren. Deutsche Medizinische Wochenschrift 129:87–90	Case report n=1	**Left atrial thrombus** attached to occluder 6 years after implantation. Resolved with anticoagulation.	Event reported in table 2.
Giardini A, Donti A, Formigari R et al. (2004) Comparison of results of percutaneous closure of patent foramen ovale for paradoxical embolism in patients with versus without thrombophilia. American Journal of Cardiology 94:1012-1016	Case series n=72 (cerebral stroke: 51% and TIA: 49%) Follow-up=20 months	Patients with thrombophilia: 20%. PFO closure successful in all patients. Residual shunt at 6 months: 5 patients.	Comparative studies in table 2.
Giardini A, Donti A, Formigari R et al. (2007) Spontaneous large right-to-left shunt and migraine headache with aura are risk factors for recurrent stroke in patients with a patent foramen ovale. International Journal of Cardiology 120:357-362	Case series n=140 Follow-up=2.2 years	At least 1 recurrent event: 31% (44/140), commonly female (p=0.0001) and more often had associated thrombophilia (p=0.0077)	Comparative studies in table 2.

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 89: 1649–51	Case report n=1 Time of occurrence=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.
Goel R, Hatler C, and Heuser R. (2008) Effects of percutaneous closure of patent foramen ovale on atrial fibrillation. Vascular Disease Management 5:37-40	Case series n=68 Follow-up not reported	3 of 4 with atrial fibrillation before the procedure had resolution after. 4 developed new-onset atrial fibrillation after the procedure.	Comparative studies in table 2.
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	Case report n=1	Contrast bubbles and a TIA (after 5 months) developed in a patient despite PFO closure and anticoagulation. A residual defect was supposed. A pulmonary arteriovenous fistula was discovered in the left lower lobe.	Device failure 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=130 (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% (26/135) (>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	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Harrer JU, Wessels T, Franke A et al. (2006) Stroke recurrence and its prevention in patients with patent foramen ovale. Canadian Journal of Neurological Science 33: 39–47	Non-randomised comparative study n=124 Follow-up=50 months	Rate of stroke after percutaneous closure=3% per year The differences in the rates of recurrent ischaemic events was reported not to be significant between the treatment groups.	Included in Agarwal et al, 2012 meta-analysis.
Harms V, Reisman M, Fuller CJ et al. (2007) Outcomes after transcatheter closure of patent foramen ovale in patients with paradoxical embolism. American Journal of Cardiology 99:1312-1315	Case series n=237 Mean follow-up=568 days	Recurrent stroke: 3.4% Event free survival (freedom from stroke, death or explantation):0.92 Mortality: 3% (7/237) Complete closure or minimal residual RLS: 66%	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Herrmann HC, Silvestry FE, Glaser R et al. (2005) Percutaneous patent foramen ovale and atrial septal defect closure in adults: results and device comparison in 100 consecutive implants at a single center. Catheterization & Cardiovascular Interventions 64:197-203	Case series n=100 (94% paradoxical embolism) Follow-up=6 months	Implantation success: 94% Complications: 2.8% Readmission for atrial arrhythmias during follow-up: 2 patients Neurological event: 1 patient Moderate and severe shunt at 6 months (confirmed by echocardiography): 33% (83 patients tested)	Comparative studies 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 Interventions 1:287–91	Case series n=124 (70 had standby intracardiac echocardiography) Follow-up not reported	Procedural success in all 64 who had contrast-fluoroscopy without significant complications. All were shown to have correct placement.	Comparative studies in table 2
Hong TE, Thaler D, Brorson J et al. (2003) Transcatheter closure of patent foramen ovale associated with paradoxical embolism using the amplatzer PFO occluder: initial and intermediate-term results of the U.S. multicenter clinical trial. Catheterization & Cardiovascular Interventions 60:524-528	Case series n=50 Mean follow-up=16.5 months	Procedural successful in 49 (1 was discovered not to have PFO). 17 had minimal residual shunt, 4 had moderate and 2 had large shunts. At last follow-up, only 1 minimal, 1 moderate and 1 large shunt. No device-related complications. 1 arteriovenous fistula at catheter site requiring repair No recurrences.	Comparative studies in table 2
Hubbard R, Blankenship J, Haldis T. (2007) Rescue of CardioSEAL PFO closure device malposition with Amplatzer PFO closure device at time of initial implantation. Catherization and Cardiovascular Interventions 69:285–8	Case report n=1	**Device prolapsed into right atrium** immediately after it was placed. It was successfully captured percutaneously.	Event reported in table 2.
Hung, J., Landzberg, M. J., Jenkins, K. J et al. (2000) Closure of patent foramen ovale for paradoxical emboli: intermediate-term risk of recurrent neurological events following transcatheter device placement. Journal of the American College of Cardiology 35: 1311–7	Case series n=63 Follow-up=2.6 years	86% (54/63) with effective closure (trivial or no residual shunt) 11% (7/63) had mild shunt and 3% (2/63) had moderate shunt 4 recurrent events: 1 stroke and 3 TIAs.	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Jesurum JT, Fuller CJ, Renz J et al. (2009) Diagnosis of secondary source of right-to-left shunt with balloon occlusion of patent foramen ovale and power M-mode transcranial Doppler. Jacc: Cardiovascular Interventions 2: 561-567	Case series n=88 Mean follow-up=192 days	At follow-up (n=66), 93%(13/14) patients with secondary RLS and 44% (23/52) without secondary RLS had residual RLS (p=0.002).	Comparative studies 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.	Comparative studies in table 2.
Jamshidi P, Wahl A, Windecker S et al. (2007) Percutaneous Closure of Patent Foramen Ovale without Echocardiographic Guidance. Indian Heart Journal 59(6):459-462	Case series n=420 Follow-up=not reported	25% had an associated atrial septal aneurysm. Implantation successful:99% (418/420) Complications: 3% (12/420) Of these: Embolisation of device or of parts of it (successfully treated by removal): 5 patients Pericardial tamponade requiring pericardiocentesis: 1 patient Air embolisation with transient symptoms: 3 patients Vascular access problems: 3 patients Residual shunt at 24 hours: 19% patients	Comparative studies in table 2.
Karagianni A, Abrahamsson P, Furenas E et al. (2011) Closure of persistent foramen ovale with the BioSTAR biodegradable PFO closure device: Feasibility and long-term outcome. Scandinavian Cardiovascular Journal 45: 267-272	Case series n=59	The BioSTAR device could be selected for use in small shunts less than 10 mm while the Amplatzer may be chosen for larger defects or more complicated anatomy.	Larger studies are included.
Kay JD, O'Laughlin MP, Ito K et al. (2004) Five year clinical and echocardiographic evaluation of the Das Angel Wings atrial septal occluder. American Heart Journal 147:361–8	Case series n=30 patients (some patients also have ASD) Follow-up=5 years	No device embolisation and no clinical complications. Residual shunt in 44% at 24 hours, 20% at 1 year, 18.8% at 2 years.	Difficult to separate results for patients with ASD/PFO.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Khositseth A, Cabalka AK, Sweeney JP et al. (2004) Transcatheter Amplatzer device closure of atrial septal defect and patent foramen ovale in patients with presumed paradoxical embolism.[see comment]. Mayo Clinic Proceedings 79:35-41	Case series n=103 Mean follow-up=8.3 months	No deaths Atrial fibrillation: 2 patients Vessel injury: 3 patients Profound sinus node dysfunction: 1 patient Trivial residual shunt at 3 months: 7.4% (7/95) Recurrent TIA: 2 patients Recurrent retinal artery occlusion: 1 patient Average annual occurrence of all events: 3.6 at 23 months. Mean freedom from recurrence of all events at 12 months: 98.9%	Comparative studies in table 2.
Khositseth A, Cabalka AK, Sweeney JP et al. (2004) Transcatheter Amplatzer device closure of atrial septal defect and patent foramen ovale in patients with presumed paradoxical embolism. Mayo Clinic Proceedings 79: 35–41	Case series n=81 patients transcatheter closure of PFO (10 patients transcatheter closure of PFO and ASD) Mean follow-up=8.3 months	All successfully deployed with no deaths Complications: atrial fibrillation (2), vessel injury (3), sinus node dysfunction (1), device embolisation with successful retrieval (1). At 3 months, 7 had residual shunt. 3 recurrent events (2 TIA and 1 retinal artery occlusion) over mean 8.3 months	Difficult to separate results for patients with ASD/PFO. Devices used for both ASD/PFO.
Kiblawi FM, Sommer RJ, and Levchuck SG. (2006) Transcatheter closure of patent foramen ovale in older adults. Catheterization and Cardiovascular Interventions 68:136-142	Case series n=456 Mean follow-up=17.8 months	Procedural complication similar in patients> 55 years compared to younger patients [3.8% (7/184) vs 4.4% (12/272), p=NS] Incidence of new onset atrial fibrillation significantly higher in older patients [35% (14/40) vs 4.3% (2/47), p<0.025)	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Knebel F, Gliech V, Walde T et al. (2004) Percutaneous closure of interatrial communications in adults - prospective embolism prevention study with two- and three-dimensional echocardiography. Cardiovascular Ultrasound 2: 5	Case series n=161 Follow-up=13-19 months	Minor complications: 2.5% Residual shunt at 6 months: 2 patients Recurrent thromboembolic events: 1 patient	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Koenig P, Cao Q, Heitschmidt M et al. (2003) Role of intracardiac echocardiographic guidance in transcatheter closure of atrial septal defects and patent foramen ovale using the AMPLATZER device. Journal of Interventional Cardiology 16:51–63	Case series n=29 Follow-up=6 months	All had immediate complete closure. 54 of 55 patients with PFO or ASD had complete closure at 6 month follow-up (one continues to have a small residual shunt)	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Krumsdorf U, Keppeler P, Horvath K et al. (2001) Catheter closure of atrial septal defects and patent foramen ovale in patients with an atrial septal aneurysm using different devices. Journal of Interventional Cardiology 14:49-55	Case series n=51 Mean follow-up=10.4 months	Procedural success in all. 1 device embolisation 12 hours after the procedure Residual shunts in 4 after 2 weeks and 1 after 6 months. Thrombus on device in 3 (treated with anticoagulation) 2 TIAs and 1 stroke during follow-up	Comparative studies in table 2.
Krumsdorf U, Ostermayer S, Billinger K et al. (2004) Incidence and clinical course of thrombus formation on atrial septal defect and patent foramen ovale closure devices in 1,000 consecutive patients. Journal of the American College of Cardiology 43: 302–9	Case series n=593 (plus 407 with ASD closure	This occurred in 2.5% 15/593) of those with PFO closure. 3 required surgical removal. Post-procedure atrial fibrillation and persistent ASA are significant predictors of thrombus formation.	Event reported in table 2.
Kutty S, Brown K, Asnes JD et al. (2008) Causes of recurrent focal neurologic events after transcatheter closure of patent foramen ovale with the CardioSEAL septal occluder. American Journal of Cardiology 101:1487-1492	Case series n=216 Mean follow-up=2.1 years	4 recurrent strokes (0.9% per year) TIA: 10 patients Combined stroke and TIA event rate: 3.4% per year	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Lai DW, Saver JL, Araujo JA et al. (2005) Pericarditis associated with nickel hypersensitivity to the Amplatzer Occluder device: a case report. Catherization and Cardiovascular Interventions 66: 424–6	Case report n=1	Patient developed **pericarditis, atrial fibrillation and increased migraine** after closure. He later tested positively for nickel hypersensitivity. He was treated with beta blockers for the atrial fibrillation and prednisone for the pericarditis. The device was not removed but the patient had resolution after 2 months.	Event reported in table 2.
Lisignoli V, Lanzone AM, Zavalloni D et al. (2007) Closure of patent foramen ovale: when and how? Current Vascular Pharmacology 5:322–7	Case series n=98 Follow-up not reported	Successful deployment in all Major complications included heparin-induced thrombocytopenia in 1, device dislodgement in 1	Comparative studies in table 2.
Luermans JG, Plokker HW, ten Berg JM 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=83 Follow-up=1.9 years	Stroke recurred in 1.2% and TIA in 3.6%, peripheral embolism in none. Major complications in 1.2% (in 1, device did not unfold which became lost requiring minimal surgical procedure, inguinal haematoma in 1)	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Luermans JG, Post MC, Temmerman F et al. (2008) Closure of a patent foramen ovale is associated with a decrease in prevalence of migraine: a prospective observational study. Acta Cardiologica 63:571-577	Case series n=92 Follow-up=6 months	Patient questionnaire before and 6 months after procedure. Decrease in any type of migraine from 28.6% preoperatively to 10.7% postoperatively (p=0.001) Decrease in migraine without aura from 16.7% preoperatively to 8.3% postoperatively (p=0.07) Decrease in migraine with aura from 11.9% preoperatively to 2.4% postoperatively (p=0.02)	Comparative studies in table 2.
Luermans JG, Post MC, Schrader R et al. (2008) Outcome after percutaneous closure of a patent foramen ovale using the Intrasept device: a multi-centre study.[see comment]. Catheterization & Cardiovascular Interventions 71:822-828	Case series n=430 (cryptogenic stroke:69.8%, TIA: 23.5%, peripheral embolism: 3.3% and other: 3.5%) Median follow-up=0.8 years	Storke:0.5% TIA: 2.5% Peripheral embolism: none Periprocedural complications: 11.5% patients (0.2% defined as major) Residual shunt: 12.5% in patients with no recurrent events and 36.4% in patients with an event (p=0.04)	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Luermans JG, Budts W, Ten Berg JM et al. (2011) Comparison of outcome after patent foramen ovale closure in older versus younger patients. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 7: 209-215	Case series n=335 Mean follow-up=4 years	Percutaneous PFO closure appears to be effective for secondary prevention of cryptogenic stroke in younger patients but seems to be related with less beneficial outcome in elderly.	Larger studies are included.
MacDonald ST, Daniels MJ, Ormerod OJ (2013) Initial use of the new GORE() septal occluder in patent foramen ovale closure: implantation and preliminary results. Catheterization & Cardiovascular Interventions 81: 660-665	n=20 FU=1 month	Removal and repositioning of two devices was performed on two occasions after uncertainty about device locking. At 1 month follow-up, two patients had brief self-terminating episodes of suspected atrial fibrillation, all had normal resting ECGs. No thromboembolic/neurological events were reported	Small case series.
Mareedu RK, Shah MS, Mesa JE et al. (2007) Percutaneous closure of patent foramen ovale: a case series and literature review. Clinical Medicine & Research 5: 218-227	n=14 FU=15 months (mean)	No immediate or late bleeding complication occurred in any patient. One patient developed paroxysmal atrial fibrillation and one patient developed thrombotic complications at 7 months post-procedure secondary to the progression of her anal carcinoma and subsequently died.	Small case series.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Motreff P, Dauphin C, Souteyrand Geraud. (2008) Cardiac perforation and tamponade 3 months after transcatheter PFO closure by STARFlex device: a case report. Catherization and Cardiovascular Interventions 71: 412–6	Case report n=1	**Cardiac tamponade** 3 months later with large pericardial effusion. Device had 'moved' and had perforated the right atrial wall. Pericardiocentesis performed and device was explanted 5 days later with no further sequelae.	Event reported in table 2.
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	Case report n=1	**Pericardial effusion with cardiac tamponade requiring pericardiocentesis**. 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.	Event reported in table 2.
Nkomo VT, Theuma P, Maniu CV et al. (2001) Patent foramen ovale transcatheter closure device thrombosis. Mayo Clinic Proceedings 76: 1057–61	Case reports n=2	**Bilateral thrombosis** on the device in 2 patients at 1 and 3 months after the procedure. Both were removed surgically with no long-term sequelae.	Event reported in table 2.
Nusser T, Hoher M, Merkle N et al. (2006) Cardiac magnetic resonance imaging and transoesophageal echocardiography in patients with transcatheter closure of patent foramen ovale. Journal of the American College of Cardiology 48:322-329	Case series n=75 Follow-up=12 months	Shunting detected by CMRI: 66.6% (48/72) Coronary anomalies: 2 patients	Comparative studies in table 2
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=265 Follow-up=19 months	Total occlusion rate on TTE or TOE: 98% at follow-up. No significant recurrent neurological events	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Opotowsky AR, Landzberg MJ, Kimmel SE et al. (2009) Percutaneous closure of patent foramen ovale and atrial septal defect in adults: The impact of clinical variables and hospital procedure volume on in-hospital adverse events. American Heart Journal 157(5):867-874	Case series (registry data) n=2555 (patients >20 years with PFO / ASD closure) Follow-up=discharge from hospital	8.2% involved an adverse event. Older patients and those with comorbidities were more likely to have an adverse event.	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Palma G, Rosapepe F, Vicchio M et al. (2007) Late perforation of right atrium and aortic root after percutaneous closure of patent foramen ovale. The Journal of Thoracic and Cardiovascular Surgery 134: 1054–5	Case report n=1	13 months after procedure, patient had pericardial effusion without tamponade. Device had **perforated left atrium and aortic root**. Emergency surgery was performed with uneventful postoperative recovery.	Event reported in table 2.
Post MC, Van DK, and Budts W. (2005) Percutaneous closure of a patent foramen ovale: single-centre experience using different types of devices and mid-term outcome. Acta Cardiologica 60:515-519	Case series n=112 (91.9% cryptogenic stroke) Median follow-up=1.9 years	Stroke: 1.8% TIA: 2.8% Dislocation of device: 0.9% transient arrhythmias: 15.5%, aspiration pneumonia: 0.9%, inguinal haematoma: 3.6%, allergic reaction to medication: 1.8%, Device perforation: 0.9%, persistent arrhythmias: 6.3%, thrombus formation on device: 0.9%	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
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.
Praz F, Beney S, Wahl A et al. (2012) Long-term follow-up after percutaneous closure of patent foramen ovale for secondary prevention of paradoxical embolism in elderly patients (>=70 years). European Geriatric Medicine 3: 23-27	Case series n=58 Mean follow-up=5 years	Freedom from recurrent ischaemic stroke, transient ischaemic attack, or peripheral embolism was 100% at 1 year, 86% at 5 years, and 82% at 10 years. The risk of recurrent thromboembolic events was significantly higher as compared to the patients <70 years old (p<0.001).	Larger studies are included.
Presbitero P, Lanzone AM, Albiero R et al. (2009) Anatomical patterns of patent foramen ovale (PFO): Do they matter for percutaneous closure? Minerva Cardioangiologica 57:275-284	Case series n=216 (mostly cryptogenic stroke or TIA) Mean follow-up=19 months	All procedures successful Recurrent TIA at follow-up: 2 patients Residual shunt: 4.9% Palpitations: 4%	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Recto M, Sobczyk W, Hadley T et al. (2003) Left atrial thrombus formation on a CardioSeal Septal Occlusion device in a patient with elevated factor VIII: resolution with medical therapy. Journal of Invasive Cardiology 15: 594–6	Case report n=1	Case of **left atrial thrombus on device** 12 days after treatment. Medical therapy with heparin and aspirin was successful.	Outcome reported in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion 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, $p < 0.001$)	Comparative intervention studies in table 2.
Ries MW, Kampmann C, Rupprecht HJ et al. (2003) Nickel release after implantation of the Amplatzer occluder. American Heart Journal 145:737-741	Case series n=67 with closure of ASD or PFO	Closure success in all. Rise in mean serum of nickel after implantation and increased 24 hours after. No allergic or toxic reactions.	Comparative studies in table 2.
Rigatelli G, Dell'Avvocata F, Cardaioli P et al. (2011) Permanent right-to-left shunt is the key factor in managing patent foramen ovale. Journal of the American College of Cardiology 58: 2257-2261	Case series n=180	The presence of permanent shunt confers the highest risk of recurrent stroke (odds ratio: 5.9, 95% confidence interval: 2.0 to 12, $p<0.001$).	Larger studies in table 2.
Rigatelli G, Dell'Avvocata F, Giordan M et al. (2009) Embolic implications of combined risk factors in patients with patent foramen ovale (the CARPE criteria): consideration for primary prevention closure? Cardiology 22:398–403	Matched comparative study n=120 (36 'high-risk' patient group vs 84 not 'high-risk') Follow-up=24.8 months	No difference in immediate success (100%), complications (0%) or occlusion rates (88.9% and 91.6%) at mean 24.8 months follow-up. Residual small shunts in both groups. No cerebral events in either group.	Larger studies in table 2.
Rigatelli, G., Dell'avvocata, F., Ronco, F et al. (2010) Patent oval foramen transcatheter closure: results of a strategy based on tailoring the device to the specific patient's anatomy. Cardiology in the Young 20:144–9	Case series n=109 Follow-up=up to 34 months	Pre-discharge occlusion rate: 91% Occlusion rates at mean 24 months follow-up: 96%	Comparative studies in table 2.
Rigatelli G, Cardaioli P, Dell'avvocata F et al. (2008) The association of different right atrium anatomical-functional characteristics correlates with the risk of paradoxical stroke: an intracardiac echocardiographic study. Journal of Interventional Cardiology 21:357-362	Case series n=114 Follow-up=28.7 months	After TEE and ICE study and measurements, a prominent EV or CN was diagnosed on ICE in 73%, a basal shunt in 48%, a moderate to severe ASA in 47% and a multiperforated FO in 34% patients.	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Rigatelli G, Dell'avvocata F, Braggion G et al. (2008) Persistent venous valves correlate with increased shunt and multiple preceding cryptogenic embolic events in patients with patent foramen ovale: An intracardiac echocardiographic study. Catheterization and Cardiovascular Interventions 72:973-976	Case series n=98 Follow-up=12 months	Prominent EV or CN diagnosed on ICE in 73.4% (72/98) and on TEE in 45.9% (45/98) (p<0.01)	Comparative studies in table 2.
Rigatelli G, Cardaioli P, Giordan M et al. (2009) Transcatheter intracardiac echocardiography-assisted closure of interatrial shunts: Complications and midterm follow-up. Echocardiography 26:196-202	Case series n=100 with PFO Follow-up=36.6 months	Procedural success rate: 99% Predischarge occlusion rate: 90.7% Complication rate: 12% Occlusion rate at follow-up: 96.5% No aortic erosion or device thrombosis observed	Comparative studies in table 2.
Rigatelli G, Dell'avvocata F, Giordan M et al. (2009) Safety and long-term results of patent foramen ovale transcatheter closure in patients with thrombophilia. Minerva Cardioangiologica 57:285-289	Case series n=98 Mean follow-up=24.8 months	Success rate: 100% No device thrombosis or recurrent cerebral ischaemia or stroke observed. Patients with thrombophilia had a higher incidence of atrial septal aneurysm, migraine with aura and deep venous thrombosis in the previous medical history compared to patients without.	Comparative studies in table 2.
Rigatelli G, Dell'avvocata F, Giordan M et al. (2010) Transcatheter patent foramen ovale closure in spite of interatrial septum hypertrophy or lipomatosis: a case series. Journal of Cardiovascular Medicine 11:91-95	Case series n=140 Mean follow-up=36.6 months	Small residual shunt at follow-up: 2 patients No recurrence of stroke or aortic erosion or device thrombosis was observed.	Comparative studies in table 2.
Rigatelli G, Dell'Avvocata F, Giordan M et al. (2009) Embolic implications of combined risk factors in patients with patent foramen ovale (the CARPE criteria): consideration for primary prevention closure? Journal of Interventional Cardiology 2:398–403	Case control comparing group with a large number of risk factors to another matched group (all treated with percutaneous PFO closure) n=120 (36 high-risk vs 84) Mean follow-up=24.8 months	Risk factors included large PFO, large ASA, coagulation abnormalities, and prominent Eustachian valve. No difference in immediate success rate between groups. Female gender and concomitance of the defined features were the only predictors of recurrent paradoxical embolism	Larger studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Rigatelli G, Braggion G, Chinaglia M et al. (2006) Setting up a multidisciplinary program for management of patent foramen ovale-mediated syndromes. Journal of Interventional Cardiology 19: 264–8	Non-randomised comparative study n=25 (15 medical therapy , 11 percutaneous PFO closure) Follow-up=10.8 months	No recurrent PFO syndromes in patients treated with devices at follow-up.	Larger studies with longer follow-up in table 2.
Rigatelli G, Braggion G, Chinaglia M et al. (2006) Setting up a multidisciplinary program for management of patent foramen ovale-mediated syndromes. Journal of Interventional Cardiology 19: 264–8	Non-randomised comparative study n=25 (15 medical therapy , 11 percutaneous PFO closure) Follow-up=10.8 months	No recurrent PFO syndromes in patients treated with devices at follow-up.	Larger studies with longer follow-up in table 2.
Rodes-Cabau J, Mineau S, Marrero A et al. (2008) Incidence, timing, and predictive factors of new-onset migraine headache attack after transcatheter closure of atrial septal defect on patent foramen ovale. American Journal of Cardiology 101:688–692	Case series n=185 out of 260 who had ASD or PFO closure and no previous history of migraine Mean follow-up=2 years	New-onset headache in 7% (13) after a median of 10 days (aura was present in 9); in 9 this was still present at last follow-up. Patients who developed migraine with aura were significantly younger and more likely to have had ASD over PFO closure.	Comparative studies in table 2. Mixed indication (ASD and PFO).
Schoen SP, Boscheri A, Lange SA et al. (2008) Incidence of aortic valve regurgitation and outcome after percutaneous closure of atrial septal defects and patent foramen ovale. Heart 94(7):844-847	Case series n=240 (PFO or ASD) Follow-up=27 months (mean)	Successful implantation: 98% Sufficient closure without residual shunt: 92% with PFO Overall major complication rate: 0.8% Newly developed or worsened aortic valve regurgitation: 10% patient with PFO	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Schrader R. (2003) Indication and techniques of transcatheter closure of patent foramen ovale. Journal of Interventional Cardiology 16:543-551	Case series n=457 (patients with embolic events) Mean follow-up= 19.6 months	Residual shunt at 6 months: 13% (36/277) Residual shunt at 12 months: 6.3% (7/111) Transient asymptomatic thrombi developed in 13 devices Asymptomatic wire fracture detected in 21 devices. Pericardial effusion: 4 patients (treated medically in 2, by pericardiocentesis in 1 and surgically without device removal in 1) Occluder system removed due to partial unbuttoning: 1 patient Mortality: 2 deaths from pneumonia, 1 from pulmonary embolism, 1 from stroke. 13 patients had recurrent events. Annual incidence of recurrent stroke: 0.8%, annual incidence of recurrent TIA: 1.1%	Comparative studies in table 2.
Schuchlenz HW, Weihs W, Berghold A et al. (2005) Secondary prevention after cryptogenic cerebrovascular events in patients with patent foramen ovale. International Journal of Cardiology 101: 77–82	Non-randomised comparative study n=280 Follow-up=3 years	Closure of PFO decreased the risk for recurrent cerebrovascular attacks over anticoagulation (HR 0.06, 95% CI 0.012 – 0.29, p<0.001) and antiplatelet therapy had an increased rate of recurrence (HR 2.3, 95% CI 0.9 – 5.5, p=0.055).	Included in Agarwal et al, 2012 meta-analysis.
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.	Comparative studies in table 2.
Schwerzmann 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	Comparative case series (of different devices) n=100 (50 STAR, 50 Amplatzer) Follow-up=3.5 years	Actuarial risk of recurrence was 16.8% in the STAR group and 2.7% in the Amplatzer group after 3 years.	Comparative intervention studies in table 2.
Shafi NA, McKay RG, Kiernan FJ et al. (2009) Determinants and clinical significance of persistent residual shunting in patients with percutaneous patent foramen ovale closure devices. International Journal of Cardiology 137:314-316	Case series n=51 Follow-up=3 years	Procedural success in all 10 had residual shunt (3 mild, 2 moderate, 3 severe, 2 on color Doppler) 96% remained event free at 3 years	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Shammas NW, Dippel EJ, Fagan T et al. (2004) Protruding umbrella into the left atrium associated with recurrence of a stroke: a possible late complication of the CardioSEAL occluder. The Journal of Invasive Cardiology 16: 76–7	Case report n=1	6 months after the procedure the patient was shown to have **protruded left atrial umbrella of the device**. There was no shunt and the device appeared stable. The patient was given anticoagulation in addition to aspirin and there were no events over next 6 months.	Event reported in table 2.
Sievert H, Fischer E, Heinisch C et al. (2007) Transcatheter closure of patent foramen ovale without an implant: initial clinical experience. Circulation 116 (15) 1701-1707	n=30 FU=6 months (mean)	Technical success (ie, successful application of radiofrequency energy) was achieved in 27 patients. The remaining 3 patients received an implantable closure device. All 30 patients were free from serious procedure-related adverse events. No recurrent strokes, deaths, or perforations occurred as a result of the procedure. 13 (43%) of the 30 patients experienced PFO closure after the first procedure.	Small case series.
Sievert H, Babic UU, Hausdorf G et al. (1998) Transcatheter closure of atrial septal defect and patent foramen ovale with ASDOS device (a multi-institutional European trial). American Journal of Cardiology 82: 1405–13	Case series n=46 patients with PFO (some patients also had ASD)	13% (26/200) failure rate Complications necessitating removal included device embolisation (2), device entrapment within Chiari network (1), frame fracture (1), perforation of atrial wall (2). Thrombus formation in 9 patients in 1 to 4 weeks after procedure.	Difficult to separate results for patients with ASD/PFO.
Slavin L, Tobis JM, Rangarajan K et al. (2007) Five-year experience with percutaneous closure of patent foramen ovale. American Journal of Cardiology 99:1316–20	Case series n=116 patients with previous embolic events Mean follow-up=30 months	No recurrence of any thromboembolic event in follow-up. Temporary problems after the procedure including chest discomfort and palpitations.	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Spies C, Reissmann U, Timmermanns I et al. (2008) Comparison of contemporary devices used for transcatheter patent foramen ovale closure.[see comment]. Journal of Invasive Cardiology 20:442-447	Case series n=795 presumed paradoxical embolism) Mean follow-up=26 months	Procedure successful in all patients. Annual incidence of recurrent thromboembolic events: 1.4% Complication rate: 1.8% Residual shunt immediately after procedure higher in patients treated with Cardia PFO occlude (24% vs 14% [Intrasept] vs 16% [Amplatzer], p=0.004)	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Spies C, Timmermanns I, Reissmann U et al. (2008) Patent foramen ovale closure with the Intrasept occluder: Complete 6-56 months follow-up of 247 patients after presumed paradoxical embolism. Catheterization & Cardiovascular Interventions 71:390-395	Case series n=247 Median follow-up=14 months	Atrial septal aneurysm: 51% (127/247) Acute complications: 4 patients (2 air embolism, 1 pericardial effusion and 1 supraventricular tachycardia) Residual shunt at 6 months: 13% Residual shunt at 1 year: 10% Recurrent TIA: 4 patients Recurrent CVA: 3 patients	Comparative studies in table 2.
Spies C, Khandelwal A, Timmemans I et al. (2008) Recurrent events following patent foramen ovale closure in patients above 55 years of age with presumed paradoxical embolism. Catherization and Cardiovascular Interventions 72: 966–70	Case series n=1055 Follow-up=18 months	Residual shunt in 10% of patients over 55 years and 8.4% in those below 55 years (p = 0.325). Annual incidence of recurrent events in patients above 55 was 1.8% and 1.3% in those below 55.	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Stackhouse KA, Goel SS, Qureshi AM et al. (2012) Off-label closure during CLOSURE study. Journal of Invasive Cardiology 24: 608-11	Case series n=133	Comparison of patients enrolled into CLOSURE I to off-label closures performed during the study recruitment period at a single large institution. Large shunts were considerably more common in off-label patients, suggesting that higher-risk patients may have been preferentially closed off-label. These results suggest that the results of CLOSURE I may not apply to all patients with initial cryptogenic stroke.	Larger studies are included.
Staubach S, Steinberg DH, Zimmermann W et al. (2009) New onset atrial fibrillation after patent foramen closure. Catheterization and Cardiovascular Interventions 74: 889– 95	Case series n=1349 Follow-up=38.1 months	3.9% (53) patients developed new-onset atrial fibrillation (77% within 0 to 6 months: 33 within 4 weeks, 8 within 6 months) 56.6% (30) of these developed chronic atrial fibrillation.	Event reported in table 2.
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	RCT of different device n=660 (220 each to Amplatzer, CardioSEAL-STARFlex or Helex Occluder) Follow-up=30 days	PFO closure can be performed safely with each device. The Helex occluder embolised more frequently. Device thrombus formation and paroxysmal atrial fibrillation were more common with the CardioSEAL-STARflex occluder.	Included in Agarwal et al, 2012 meta-analysis.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Tande AJ, Knickelbine T, Chavez I et al. (2005) Transseptal technique of percutaneous PFO closure results in persistent interatrial shunting. Catheterization & Cardiovascular Interventions 65:295-300	Case series n=120 Mean follow-up=11 months	Device closure successful in all patients TIA: 4 patients Complete closure at 6 months (confirmed by transoesophageal echocardiography): 40% (4/10) transseptal group and 73.4% (58/79) tunnel group.	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Thanopoulos BD, Dardas PD, Karanasios E et al. (2006) Transcatheter closure versus medical therapy of patent foramen ovale and cryptogenic stroke. Catheterization and Cardiovascular Interventions 68: 741–6	Non-randomised comparative study n=92 Follow-up=24 months	Immediate complete closure in 91% (44/48) after closure. At 6-month follow-up, complete closure was confirmed by contrast bubble study in all 48 patients. Average annual incidence of embolic events was 0% for PFO closure group and 15% for antiplatelet therapy group ($p<0.001$).	Included in Agarwal et al, 2012 meta-analysis.
Van den Branden BJL, Post MC, Plokker HW et al. (2011) Percutaneous atrial shunt closure using the novel occlutech figulla device: 6-month efficacy and safety. Journal of Interventional Cardiology 24: 264-271	n=82 FU=6 months	No major complications or reoccurrences of cerebral thromboembolic events occurred. Seven patients (8.9%, 6 PFO and 1 ASD patient) experienced a new SVT. One patient developed a recurrent cerebral hemorrhage 5 months after ASD closure, which appeared not to be related to the procedure. Using contrast transthoracic echocardiography 6 months after PFO closure (n = 45), a residual shunt was present in 30% of the patients (small 26%, moderate 4%).	Small case series.
Van Den Branden BJ, Post MC, Plokker HW et al. (2010) Patent foramen ovale closure using a bioabsorbable closure device: safety and efficacy at 6-month follow-up. Jacc: Cardiovascular Interventions 3: 968-973	Case series n=62 Follow-up=6 months	Closure of PFO using the bioabsorbable device is associated with a low complication rate and a low recurrence rate of embolic events. However, a relatively high percentage of mild or moderate residual shunting is still present at 6-month follow-up.	Larger studies are included.
Van Den Branden BJ, Luermans JG, Post MC et al. (2010) The BioSTAR device versus the CardioSEAL device in patent foramen ovale closure: Comparison of mid-term efficacy and safety. EuroIntervention 6: 498-504	Case series n=81 Follow-up=6 months	There is no difference in safety and efficacy at six months between the CardioSEAL and BioSTAR device used for PFO closure. However, using the BioSTAR device tends to be associated with a higher percentage of moderate shunting.	Larger studies are included.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Vanderheyden M, Willaert W, Claessens P et al. (2002) Thrombosis of a patent foramen ovale closure device: thrombolytic management. Catheterization and Cardiovascular Interventions 56: 522–6	Case report n=1	**Bilateral device thrombosis** successfully treated with pharmacotherapeutic approach (thrombolytics and glycoprotein IIb/IIIa receptor blockers).	Event reported in table 2.
van de Wyngaert F, Kefer J, Hermans C et al. (2008) Absence of recurrent stroke after percutaneous closure of patent foramen ovale despite residual right-to-left cardiac shunt assessed by transcranial Doppler. Archives of cardiovascular diseases 101:435-441	Case series n=66 Mean follow-up=3.73 years	Closure successful in all with no major side effects. No recurrences in follow-up. Residual shunts on transcranial doppler detected residual shunt in 41.7% (25/60) of those followed-up at 12 months (20% had more than 50 microbubbles)	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Varma C, Benson LN, Warr MR et al. (2004) Clinical outcomes of patent foramen ovale closure for paradoxical emboli without echocardiographic guidance. Catheterization & Cardiovascular Interventions 62:519-525	Case series n=92 Mean follow-up=402 days	All patients had successful device deployment Residual shunt at 1 year (confirmed by echocardiography): 1 patient Cumulative event free survival rate for paradoxical embolus at 1 year: 97.3%	Comparative studies in table 2.
Vigna C, Inchingolo V, Giannatempo G et al. (2008) Clinical and brain magnetic resonance imaging follow-up after percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. American Journal of Cardiology 101:1051-1055	Case series n=71 Follow-up=16 months	Recurrent neurologic event: 1%	Comparative studies in table 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	Case series n=825 Follow-up at least 6 months	Residual shunt 24 hours later was present in 15%. At ≥ 6 months, minimal, moderate or large residual shunts persisted in 7%, 3% and 2% of patients. Device embolisation with percutaneous removal in 5, pericardial tamponade requiring pericardiocentesis in 1, thrombus on device in 5	Comparative studies in table 2.
Wahl A, Krumsdorf U, Meier B et al. (2005) Transcatheter treatment of atrial septal aneurysm associated with patent foramen ovale for prevention of recurrent paradoxical embolism in high-risk patients. Journal of the American College of Cardiology 45:377-380	Case series n=141 Follow-up=ASA + PFO: 2.5 years (mean), PFO only: 2.3 years (mean)	At 6 months shunt abolished ion 86% patients with ASA a+ PFO and 85% of patients with PFO only Freedom from recurrent TIA, stroke and peripheral embolism at 4 years: 95% for patients with ASA and PFO and 94% for patients with PFO only.	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Wahl A, Kunz M, Moschovitis A et al. (2008) Long-term results after fluoroscopy-guided closure of patent foramen ovale for secondary prevention of paradoxical embolism.[see comment]. Heart 94:336-341	Case series n=525 (cryptogenic stroke) Mean follow-up=2.9 years	35% (186/525) had >1 clinically apparent embolic events. Mean events per patient:1.7 Implantation failed: 0.4% (2/525) Procedural complications: 2.5% (13/525) Complete closure at 6 months=86% Minimal, moderate and large shunt of 9%, 3% and 2% respectively. During follow-up 6 ischaemic strokes, 9 TIAs and 2 peripheral emboli. Freedom from recurrent stroke, TIA or peripheral embolism was 98% at 1 year, 97% at 2 years and 96% at 5 and 10 years. Residual shunt hazard ratio:3.4 (95% CI: 1.3–9.2)	Comparative studies in table 2.
Wahl A, Tai T, Praz F et al. (2009) Late Results After Percutaneous Closure of Patent Foramen Ovale for Secondary Prevention of Paradoxical Embolism Using the Amplatzer PFO Occluder Without Intraprocedural Echocardiography. Effect of Device Size. Jacc: Cardiovascular Interventions 2:116-123	Case series n=620 (presumed paradoxical embolism) Mean follow-up=3 years	All procedures successful 5 procedural complications (0.8%): 4 arteriovenous fistulae requiring elective surgical correction and 1 TIA. Complete closure in 91% patients at 6 months confirmed by contrast transoesophageal echocardiography. Minimal, moderate or large residual shunt persisted in 6%, 2% and 1% respectively. During follow-up 5 ischaemic attacks, 8 TIAs and no peripheral emboli reported. Freedom from recurrent ischaemic stroke, TIA or peripheral embolism was 99% at 1 year and 2 years and 97% at 5 years.	Comparative studies in table 2. Included in Agarwal et al, 2012 meta-analysis.
Weimar C, Holle DN, Benemann J et al. (2009) Current management and risk of recurrent stroke in cerebrovascular patients with right-to-left cardiac shunt. Cerebrovascular Disease 28: 349–56	Case series n=1126 (including 117 with percutaneous closure and 234 with medical treatment) Follow-up=28.4 months	Study was to look at prognosis in patients with shunting. Not all patients were reported to have had treatment. Outcomes were not separated by treatment regime.	Outcomes were not separated by treatment regime. Included in Agarwal et al, 2012 meta-analysis.
Wilmshurst P, Nightingale S, Pearson M et al. (2006) Relation of arterial shunts to migraine in patients with ischemic stroke and peripheral emboli. American Journal of Cardiology 98:831–3	Case series n=35 with PFO (4 ASD) for stroke and migraine	This study first did contrast echo to determine if paradoxical embolism was a cause of ischaemic stroke. Then performed an analysis of 60 patients for clinically relevant shunts but did not appear to give outcomes of the patients treated with closure	Comparative studies in table 2.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion 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 for PFO and ASD closure Follow-up not reported	57% (21/37, 20 with PFO) of patients had no residual shunt after 6 weeks No patients without migraine before shunt closure developed migraine during long-term follow-up.	Comparative studies in table 2.
Windecker S, Wahl A, Nedeltchev K et al. (2004) Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. Journal of the American College of Cardiology 44: 470–8	Non-randomised comparative study n=308 Follow-up=2 years	Univariate analysis showed that patients with complete PFO occlusion had a significantly lower risk of stroke or TIA than medically treated patients (6.5% vs 22.2%, p=0.04; RR 0.37; 95% CI 0.14 to 0.99).	A more recent publication with longer follow-up is included. Included in Agarwal et al, 2012 meta-analysis.
Wohrle J, Bertrand B, Soondergaard L et al. (2012) PFO closuRE and CryptogenIc StrokE (PRECISE) registry: A multi-center, international registry. Clinical Research in Cardiology 101: 787-793	Case series n=267 Mean follow-up=11 months	In this prospective, international, multicenter PRECISE registry, the use of the Premere™ PFO closure device for closure of PFO after stroke or TIA resulted in good clinical results with no recurrent event.	Larger studies are included.
Wohrle J, Kochs M, Spies J et al. (2009) Impact of Percutaneous Device Implantation for Closure of Patent Foramen Ovale on Valve Insufficiencies. Circulation 119(23):3002-3008	Case series n=129 (cryptogenic ischaemic events) Follow-up=12 months	Median regurgitation fraction for pulmonary valve: 5.4% at device implantation, 4.3% at 12 months.	Comparative studies in table 2.
Youssef GS, Allan RM, Manganas C et al. (2006) Case report: a tale of two toes. Heart, Lung, Circulation 15: 267–8	Case report n=1	27-year old woman had large influx of bubbles into the left atrium, despite the PFO being closed. A **large arteriovenous fistula** was found in the right lung. No neurological events had occurred at 6 months follow-up	Device failure has already been reported in table 2.
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 29: 814-816	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.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Zajarias A, Thanigaraj S, Lasala J et al. (2006) Predictors and clinical outcomes of residual shunt in patients undergoing percutaneous transcatheter closure of patent foramen ovale.[see comment]. Journal of Invasive Cardiology 18:533-537	Case series n=101 Follow-up=6 months	Closure with total elimination of shunt: 63% At 6 months residual shunt was resolved in all but 3 patients. One of these patients had a recurrent nonfatal TIA.	Comparative studies in table 2.
Zanchetta M, Pedon L, Olivieri A et al. (2008) Randomized study comparing mechanical with electronic 2-dimensional intracardiac ultrasound monitoring (MEDIUM) during percutaneous closure of patent foramen ovale in adult patients with cryptogenic stroke. Echocardiography 25:496-503	RCT (comparing diagnostic methods) n=82 Follow-up=12 months	Residual shunt rate at 12 months: 97.5% vs 94.7%, p=0.951)	Comparative studies in table 2.
Zhang C-J, Huang Y-G, Huang X-S et al. (2010) Transcatheter closure of patent foramen ovale with the Spider patent foramen ovale occluder: A prospective, single-center trial. Chinese Medical Journal 123:834–7	Case series n=55 Follow-up=35 months	All had successful implantation No residual shunt of the atrial level on TOE and no latent arrhythmia or cerebral vessel events during follow-up	Comparative studies in table 2.
Zhang CJ, Huang YG, Huang X et al. (2011) Transcatheter closure of patent foramen ovale in Chinese patients with paradoxical embolism. - Immediate results and long-term follow-up. Circulation Journal 75: 1867-1871	Case series n=192 Median follow-up=49 months	Transcatheter PFO closure is a minimally invasive procedure with a high success rate, low complication rate and an excellent long-term outcome, and appears to be a wise approach for secondary prevention of recurrent embolic events in symptomatic patients	Larger studies are included.

Appendix B: Related NICE guidance for percutaneous closure of patent foramen ovale for the prevention of recurrent cerebral embolic events

Guidance	Recommendations
Interventional procedures	**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. **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).

Appendix C: Literature search for percutaneous closure of patent foramen ovale for the prevention of recurrent cerebral embolic events

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	30/07/2013	Issue 6 of 12, June 2013
Database of Abstracts of Reviews of Effects – DARE (CRD website)	31/07/2013	-
HTA database (CRD website)	31/07/2013	-
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	30/07/2013	Issue 6 of 12, June 2013
MEDLINE (Ovid)	30/07/2013	1946 to July Week 3 2013
MEDLINE In-Process (Ovid)	30/07/2013	July 29, 2013
EMBASE (Ovid)	30/07/2013	1974 to 2013 Week 30>
CINAHL (NLH Search 2.0/EBSCOhost)	30/07/2013	1981 to present

Trial sources searched on 5 December 2012:

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- Evidence Updates (NHS Evidence)
- General internet search

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

1 Foramen Ovale, Patent/

2 PFO.tw.
3 exp Heart Septal Defects, Atrial/
4 ((heart* or atrial* or cardiac*) adj3 sept* adj3 defect*).tw.
5 Foramen Ovale/
6 (Foramen* adj3 Ovale*).tw.
7 or/1-6
8 Intracranial Embolism/
9 ((Intracranial* or cerebral* or brain* or paradox*) adj3 (embol* or stroke* or infract* or ischem*)).tw.
10 Ischemic Attack, Transient/
11 TIA.tw.
12 (ischemic adj3 (stroke* or attack*)).tw.
13 Embolism, Paradoxical/
14 (cross* or paradoxical* adj3 embolis*).tw.
15 Brain Ischemia/
16 (Brain* adj3 isch?em*).tw.
17 or/8-16
18 7 and 17
19 ((clos* or block* or shut* or plug*) adj4 (percutan* or transcathet* or device* or system)).tw.
20 Heart Catheterization/
21 ((heart* or atrial* or cardiac*) adj3 cathet*).tw.
22 STARFlex.tw.
23 Amplatzer.tw.
24 CARDIOSeal.tw.
25 Solysafe.tw.
26 Biostar*.tw.
27 Gore Helex.tw.
28 occluder.tw.
29 (Amplatzer* adj sept* occluder*).tw.
30 or/19-29
31 18 and 30
32 Animals/ not Humans/
33 31 not 32
34 limit 33 to ed=20100801-20121231