

NHS England

Evidence review: Percutaneous Patent Foramen Ovale Closure for Secondary Prevention of Cryptogenic Stroke



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1 Introduction

Introduction

- A patent foramen ovale (PFO) occurs when the foramen ovale connecting the left and right atria of the foetal heart does not close spontaneously after birth. Approximately 25% of people have a foramen ovale which remains fully or partially open into adulthood (NICE IPG 472).

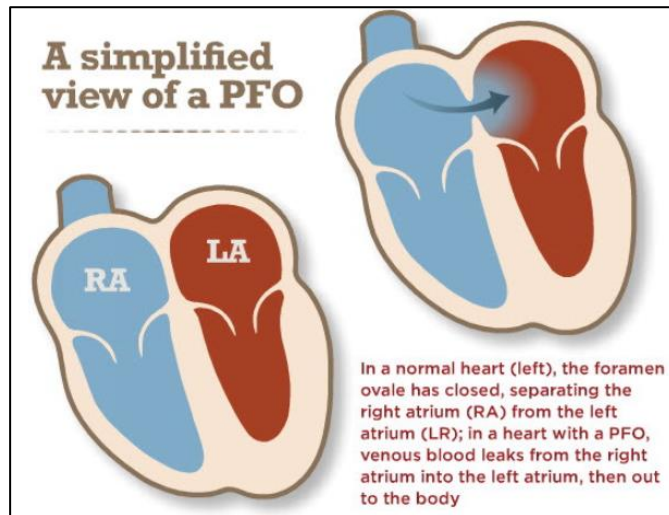


Figure 1: Cross section of the heart showing a patent foramen ovale connecting the right and left atria. Source: American Heart Association.

- Although most people with patent foramen ovale are asymptomatic, it is thought that a PFO increases the risk of blood clots crossing from the right side into the left side of the heart (known as a right to left shunt), and from there into the arterial system where they may block blood vessels. If arteries in the brain become blocked then a stroke or a transient ischaemic attack (TIA) occurs. This passage of material from the right of the circulation to the left is called paradoxical embolism.

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- The NICE Interventional procedure guidance (NICE IPG472) published in December 2013, states that:

“1.1 Evidence on the safety of percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events shows serious but infrequent complications. Evidence on its efficacy is adequate. Therefore, this procedure may be used with normal arrangements for clinical governance, consent and audit.

1.2 The procedure should only be performed in units with appropriate arrangements for urgent cardiac surgical support in the event of complications.

1.3 Clinicians should enter details about all patients undergoing percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events onto the [UK Central Cardiac Audit Database](#).”

The indication and epidemiology

- Ischaemic strokes are due to a blockage of blood supply to the brain. This might be caused by a blood clot in an artery leading to the brain or within one of the vessels inside

the brain (cerebral thrombosis). The blockage may have travelled to the brain from another part of the body (cerebral embolism). Common causes include atherosclerosis and small vessel disease.

- In the UK, there are over 100,000 strokes each year, of which 85% are ischaemic (Stroke Association 2018). There is a range of risk factors for ischaemic stroke, both patient modifiable and non-modifiable (table 1).

Modifiable: risk factors under your control ⁷²	Non modifiable: risk factors out of your control ⁷²
High blood pressure	Age
High blood cholesterol	Ethnicity
Diabetes (type 2)	Gender
Being overweight	Family history of heart disease
Smoking	History of heart disease
Alcohol consumption	PFO (hole in the heart)
Drug use	Diabetes (type 1)
No physical exercise	Atrial Fibrillation

Table 1. Risk Factors for Stroke.

Source: Stroke Association 2018

- Ischemic strokes are labelled as cryptogenic when no probable cause has been established despite a thorough diagnostic evaluation (Saver 2016, Finsterer 2010). 32% of ischemic strokes or TIAs are thought to be cryptogenic (0.36 per 1000 population per year, 95%CI 0.23 to 0.49) with the proportion increasing to 48% in patients younger than 55 years (Linxin et al 2015).
- Diagnostic work-up for cryptogenic stroke (CS) may include transoesophageal echocardiography (TEE), long-term ECG-recordings, CT-/MR-angiography of the aorta, transcranial Doppler-sonography, imaging for venous thrombosis in case of paradoxical embolism, and blood chemical investigations and coagulation tests.
- Cryptogenic strokes have fewer atherosclerotic markers (such as hypertension, diabetes, peripheral vascular disease, hypercholesterolaemia and history of smoking) and no excess of cardioembolic markers such as asymptomatic carotid disease, acute coronary events, minor-risk potential cardioembolic sources on echocardiography, paroxysmal AF or presumed cardioembolic events (Linxin et al 2015)
- The recent RCT by Lee et al (2018) suggests that of 450 patients diagnosed with a cryptogenic stroke with PFO, 38.9% (n=175) were considered to have a high risk PFO. A high-risk PFO was defined as a PFO with an atrial septal aneurysm (protrusion of the dilated segment of the septum at least 15 mm beyond the level surface of the atrial septum), hypermobility (phasic septal excursion into either atrium ≥ 10 mm), or PFO size (maximum separation of the septum primum from the secundum during the Valsalva manoeuvre) ≥ 2 mm on TEE.
- The lack of patient modifiable risk factors for cryptogenic stroke leads clinicians to seek to modify risk factors such as PFO in order to reduce the risk of recurrence, in particular for patients who are unable to reduce their overall risk of stroke themselves (Linxin et al 2015).
- Linxin et al (2015) report that death, dependency at 6 months and 10-year stroke recurrence rates after cryptogenic stroke are all comparable with non-cardioembolic stroke.

Standard treatment and pathway of care

- Medical management of CS with PFO is the current standard care for patients in England. Antiplatelet therapy (for example aspirin) or oral anticoagulation (warfarin or a novel oral anticoagulant such as dabigatran) is used to reduce the risk of further cryptogenic stroke (Finsterer 2010) though the choice of medication may be influenced by concerns about the long-term risk of bleeding.
- Limited access to PFO closure as an alternative to long term medical management has been commissioned via the NHS England Commissioning Through Evaluation programme (Von Klemperer et al 2017).
- Rarely, open surgical closure may be considered for patients in whom medical management has failed or for patients in whom anticoagulant or antiplatelet therapy are contraindicated.

The intervention

- Percutaneous closure of patent foramen ovale is an option for patients who have had a cryptogenic stroke likely to have been caused by paradoxical embolism through patent foramen ovale.
- It is usually performed as an in-patient procedure either using local anaesthesia and intravenous sedation, or with the patient under general anaesthesia. A closure device is introduced using a guide wire and delivery sheath through a small incision in the groin into the femoral vein. It is then passed into the heart and across the patent foramen ovale. The closure device is released to close the defect using image guidance such as echocardiography. Following implantation of the PFO closure device, patients will usually be on antiplatelet or oral anticoagulant medication for up to 6 months, as well as an echocardiogram at 6 months to check that the device is properly implanted. A number of different devices are commercially available (NICE IPG 472), for example the Amplatzer PFO occluder (Figure 2). These are described in the studies included in this review.

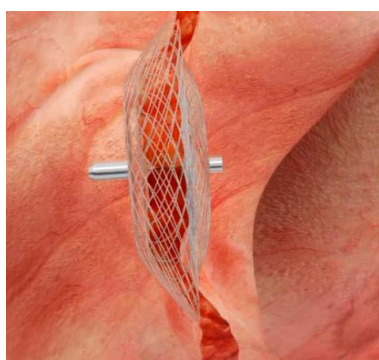


Figure 2: Diagram of the Amplatzer PFO Occluder in situ.

Source: FDA

Rationale for use

- Percutaneous PFO closure for prevention of recurrent cryptogenic stroke is a less invasive and lower risk procedure compared to open surgery in patients for whom medical management has failed or cannot be considered.
- Percutaneous PFO closure performed as a single procedure may be an attractive alternative single intervention to long term medical therapy.

- This review focuses on whether or not percutaneous PFO closure is more clinically and cost effective than long term medical management for the prevention of cryptogenic stroke, in patients for whom long term medical management is currently an option.

2 Summary of results

- Seven studies were included in this review (Shah et al 2018, De Rosa et al 2018, Piccolo et al 2018, Lee et al 2018, Rigatelli et al 2017, Rigatelli et al 2016, Tirschwell et al 2018).
- Two systematic reviews and meta-analyses (SRMAs) (Shah et al 2018, De Rosa et al 2018) and one meta-analysis (Piccolo et al 2018) which compared percutaneous PFO closure (n=1382) and medical therapy alone (MTA) (n=1149) for the prevention of recurrent stroke in patients who had had cryptogenic stroke were suitable for inclusion in this review. They all included the same four randomised controlled trials (RCTs) (PC-TRIAL¹, RESPECT², CLOSE³ and REDUCE⁴ studies). Shah et al (2018) published an update of their SRMA on 25th June 2018, including some amended results, which have been included in this updated RER.
- De Rosa et al (2018) included the shorter-term outcomes (mean follow up 2.6 years) of the RESPECT RCT published by Carroll et al (2013), whereas Shah et al (2018) and Piccolo et al (2018) included the longer-term outcomes (median follow up 5.9 years) of the extended RESPECT RCT (Saver et al 2017), in which there was 27% loss to follow-up. The Shah et al (2018) SRMA was updated on 25 June 2018, and the amended results for all outcomes (recurrent stroke, TIA, major bleeding, atrial fibrillation) are reported in this review.
- In addition, the DEFENSE-PFO RCT (Lee et al 2018) was selected for inclusion as it met the PICO criteria and was not included in any of the SRMAs.
- In addition, two publications from one prospective, non-comparative study of 1000 consecutive patients in Italy (Rigatelli et al 2017, Rigatelli et al 2016) reported median 10.5 year outcomes, longer than were available from the SRMAs or any of the individual RCTs.
- One recent cost-effectiveness study which is relevant to the UK was selected for inclusion (Tirschwell et al 2018).

Clinical Effectiveness

- A 3.3% lower absolute risk of recurrent stroke was found in patients who had PFO closure (RD: -0.033 (95%CI: -0.062- to -0.004), p=0.037) compared to those who were treated with MTA (Shah et al 2018). This is consistent with the 3.1% lower absolute risk of stroke reported in the SRMA by De Rosa et al (2018). It is likely that there is no reduction in the risk of TIA alone following PFO closure (Shah et al 2018), although the result reported in the June 2018 update of this paper is not accurate⁵.

¹ PC-TRIAL: Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism (Meier et al 2013)

² RESPECT: Randomised Evaluation of Current Stroke Comparing PFO Closure of established current Standard of Care Treatment (Carroll et al 2013, Saver et al 2017)

³ CLOSE: Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence (Mas et al 2017)

⁴ REDUCE: GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients (Sondergaard et al 2017)

⁵ This is despite communication between the reviewers and Shah et al via the journal in which the paper was published.

- No statistically significant difference was found between groups in any study for all-cause mortality (De Rosa et al 2018); this outcome was not reported in the Shah et al (2018) meta-analysis due to the low number of events.

Safety

- There was no significant difference in the risk of serious adverse events (SAEs) for patients who had PFO closure compared with MTA [25% vs 24% (RD: -0.006(95%CI: -0.036 to -0.048)), p=0.781, I²=31%], with SAEs occurring in about a quarter of patients in both groups (De Rosa et al 2018). SAEs were not clearly defined.
- There was no significant difference in the incidence of major bleeding in patients who had PFO closure compared with MTA [p=0.24 (Shah et al 2018) and p=0.605 (De Rosa et al 2018)].
- Shah et al (2018) concluded that although there was an increased risk of new onset atrial fibrillation (AF), this could not be quantified due to high levels of heterogeneity (I²=81.98%) among the 4 RCTs. The risk difference ranged from 0.006 in the extended RESPECT RCT (PFO closure vs MTA: 7 events/499 patients vs 4/481) to 0.061 in the REDUCE RCT (PFO closure vs MTA: 29 events/441 patients vs 1/223). However, a 3.3% greater absolute risk of new onset AF or atrial flutter for patients who had PFO closure compared with MTA was reported by De Rosa et al (2018) (PFO closure vs MTA: 4.4%⁶ vs 1.0% (RD: 0.033(95%CI: 0.012 to 0.054), p=0.002, I²=66%). The proportion of new onset AF which required ongoing treatment or was permanent was not reported in either SRMA.
- In the prospective study of 1000 patients receiving a PFO device, immediate procedural success within 30 days was 99.8%. The PFO device was removed intraprocedurally in two patients (Rigatelli et al 2016, 2017).
- Twenty-six (2.6%) of 1000 PFO device recipients experienced non-electrical complications within 30 days of the procedure, the most common of which was groin haematoma (n=10, 1.0%). Fifty-nine (5.9%) PFO device recipients experienced electrical complications⁷, 49 of which resolved within the procedure. Permanent AF and permanent atrioventricular block (AVB) were reported in one and three patients respectively and four out of six patients with supraventricular arrhythmia required pharmacological cardioversion (Rigatelli et al 2016, 2017).
- At median 10.5 year follow up, non-electrical complications occurred in 22 (2.2%) out of 1000 patients. The most common were non-cardiac related death (n=13, 1.3%), recurrent stroke (n=8) and device thrombus (n=5). The long term electrical complication rate was 14/1000 (1.4%) which included permanent AF (n=5), paroxysmal AF (n=4) and supraventricular arrhythmia (n=4) (Rigatelli et al 2016, 2017). The proportion of AF which was permanent is lower in this study than the proportion of new onset AF reported in the SRMA by De Rosa et al (2018), suggesting that the majority of AF is temporary or successfully treated.
- The death of one patient (0.1%) was considered device related although no autopsy was performed to confirm this (Rigatelli et al 2016, 2017).
- Higher complication rates after PFO closure were observed for some device recipients both within the first 30 days after implantation and longer term (Rigatelli et al 2016, 2017):
 - Women were more than twice as likely to have either electrophysiological [OR 2.3 (95%CI 0.5 to 5.1), p<0.001] or acute non-electrophysiological complications [OR 2.1 (95%CI 0.5 to 4.6), p<0.001] within the first 30 days.

⁶ reported by the authors as 4.1%, but corrected by reviewer after checking absolute number of events in the PFO closure group.

⁷ atrial fibrillation, supraventricular tachy-arrhythmias, atrio-ventricular blocks

- Patients who required a device disk larger than 30mm were between four and five times more likely to experience electrophysiological [OR 5.0 (95%CI 1.2 to 7.2), $p < 0.001$] or acute non-electrophysiological complications within the first 30 days [OR 4.0 (95%CI 0.8 to 6.1), $p < 0.001$].
- Patients who had a large atrial septal aneurysm (ASA) had higher risk of both electrophysiological complications (HR 2.2 (95%CI 0.4 to 3.9), $p < 0.001$) and non-electrophysiological complications (OR 2.9 (95%CI 0.4 to 4.3), $p < 0.001$) at median 10.5 year follow up.
- An increased risk for electrophysiological [HR 2.61(95%CI 0.3 to 4.1), $p < 0.001$] and other complications [OR 3.1(95%CI 0.3 to 5.2), $p < 0.001$] was also observed for patients whose implant had a mean device size: septum length ratio greater than 0.8.
- A proportion of patients in the RCTs also had an ASA. However, outcomes for PFO closure in patients with concomitant ASA were not reported separately.
- There was heterogeneity among and within the studies for the interventions used (PFO closure devices and medication), the severity of the index stroke or TIA, the proportion of study participants with a moderate or large PFO size and/or a large ASA, and the proportion who had known risk factors for stroke (e.g. hypertension, diabetes, smoking, obesity and oral contraception). This introduces uncertainty about whether all preceding strokes were cryptogenic and associated with the PFO (Shah et al 2018, De Rosa et al 2018, Piccolo et al 2018, Rigatelli et al 2016, 2017).

Cost Effectiveness

- The only PFO closure device included in the cost-effectiveness study by Tirschwell et al 2018 was the Amplatzer device, which is used in current practice. For an undefined sub-population of patients who were recruited to the RESPECT RCT (Saver et al 2017) in the UK, PFO closure reached a cost-effectiveness threshold lower than the NICE threshold of £20,000 after 4.2 years (no confidence interval reported) post treatment.
- Compared to MTA, the incremental cost-effectiveness ratios (ICERs) for PFO closure at 4, 10 and 20 year time horizons after the procedure were £20,951, £6887 and £2158 respectively. This was based on incremental costs per patient for PFO closure at 4, 10 and 20 year time horizons after the procedure of +£6071, +£4858 and +2848 respectively.
- The costs are all recent UK costs and NHS costs which means that it is highly likely that the results are reliable and generalisable as long as the patient selection criteria are identical to those used in this UK sub-population (which however was not clearly defined). In addition, indirect costs were not included. This means that the cost effectiveness estimates did not take into account the non-NHS costs of stroke care (social care, personal productivity such as employment etc). Inclusion of these wider costs might increase the estimated cost-effectiveness of PFO closure for this subgroup further.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).

- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: PubMed, EMBASE and Cochrane databases (see section 10 for search strategy).
- The searches were conducted on 5th January 2018 and included publications between 5th January 2008 and 5th January 2018. A further search identified papers published between 6th January 2018 and 15th May 2018.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Using established hierarchy of evidence criteria⁸, the best quality and most reliable studies which matched the PICO were selected for inclusion in this review.
- Studies including outcomes for the STARFlex PFO closure device were excluded from this review, following written advice and confirmation from the NHS England Clinical Reference Group that this device is no longer available commercially.
- Individual studies were excluded if they were already included in systematic literature reviews. Due to the availability of two systematic reviews and meta-analyses and one meta-analysis of the same four relevant RCTs, as well as one RCT not included in the SRMAs, prospective uncontrolled studies were only considered for inclusion if they reported additional outcomes or provided information about longer term outcomes not available from the systematic reviews and meta-analyses. Retrospective uncontrolled case series were excluded due to their inferior study design and associated uncertainty of results.
- The outcomes from all papers included were extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4 Results

Two systematic reviews and meta-analyses (SRMAs) (Shah et al 2018, De Rosa et al 2018) and one meta-analysis (Piccolo et al 2018) were included in this review. They included the same four randomised controlled trials (RCTs) (PC-TRIAL⁹, RESPECT¹⁰, CLOSE¹¹ and REDUCE¹²). The four RCTs recruited a total of 2531 subjects who had sustained a cryptogenic stroke, with a mean age across the studies of between 43.3 years and 45.4 years. Patients were treated with either percutaneous PFO closure (n=1382) or medical therapy (n=1149). The follow-up time for the RCTs ranged from a mean of 2.6 years (RESPECT RCT, Carroll et al 2013) to a median of 5.9 years (extended RESPECT RCT, Saver et al 2017). All four RCTs were judged to be of high quality.

⁸ <https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>

⁹ PC-TRIAL: Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism (Meier et al 2013)

¹⁰ RESPECT: Randomised Evaluation of Current Stroke Comparing PFO Closure of established current Standard of Care Treatment (Carroll et al 2013, Saver et al 2017)

¹¹ CLOSE: Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence (Mas et al 2017)

¹² REDUCE: GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients (Sondergaard et al 2017)

The two SRMAs differed in that one (Shah et al 2018) included the longer-term outcomes of the extended RESPECT RCT (Saver et al 2017) whilst the other (De Rosa et al 2018) selected the shorter-term outcomes of the RESPECT RCT (Carroll et al 2013). This was due to concern that the longer-term outcomes were less reliable owing to 27% loss to follow-up of subjects compared to 13% in Carroll et al (2013). The meta-analysis by Piccolo et al (2018) also included the longer-term outcomes of the extended RESPECT RCT (Saver et al 2017). De Rosa et al (2018) only included patients from the CLOSE RCT (Mas et al 2017) who had no contraindications to PFO closure and who were randomised to either PFO closure (n=238) or antiplatelet therapy alone (APT) (n=235), excluding those who received oral anticoagulant therapy alone (OAC). Shah et al (2018) updated their SRMA to also include in their medical therapy group only the 235 patients in CLOSE (Mas et al 2017) who received APT; this SRMA was updated on 25 June 2018, and the published amended outcomes are reported in this review.

In addition, the DEFENSE-PFO RCT (Lee et al 2018) was selected for inclusion as it was not included in any of the SRMAs. We also included two publications from one study of 1000 consecutive patients who received a PFO device and were prospectively followed up for a median of 10.5 years at two centres in Italy (Rigatelli et al 2017, Rigatelli et al 2016). This trial reported much longer term outcomes than were available from the SRMAs or any of the individual RCTs. However, there was considerable heterogeneity among the subjects and interventions in this study and it was not clear what proportion had had a cryptogenic stroke.

One recent cost-effectiveness study was selected for inclusion (Tirschwell et al 2018).

Three of the studies included in this updated review (Piccolo et al 2018, Lee et al 2018, Tirschwell et al 2018) were published after the initial search was carried out on 5th January 2018.

The detailed results for all outcomes reported in these studies are reported in the evidence summary tables in section 7.

a) What is the evidence of clinical effectiveness and safety for PFO closure in patients with a cryptogenic ischaemic stroke and a patent foramen ovale with significant right to left shunt, compared to antiplatelet or anticoagulant therapy?

Clinical effectiveness

Recurrent Stroke and/or TIA. Shah et al (2018) reported a 3.3% lower absolute risk for recurrent stroke in patients who had PFO closure (RD: -0.033 (95%CI: -0.062- to -0.004), p=0.037) compared to those who were treated with medical therapy alone (MTA). This was consistent with the reduced risk of stroke reported by De Rosa et al (2018) which included the shorter term results of RESPECT RCT [PFO closure vs MTA: 1.2% vs 4.1% (RD: -0.031 (95%CI: -0.051 to -0.010), p=0.003, I²=61%)]. Piccolo et al (2018) also reported a significant reduction in the risk of recurrent stroke in the PFO closure group up to 5 years after the procedure (hazard ratio (HR) 0.14 (95% CI 0.04 to 0.55, p=0.005). As the hazard ratio is a relative measure of effect only, it is difficult to interpret with respect to the absolute risk of stroke for patients undergoing PFO closure or MTA.

De Rosa et al (2018) reported a 2.9% lower absolute risk for the composite outcome of a recurrent stroke or TIA [PFO closure vs MTA: 3.6% vs 6.3% (RD: -0.029 (95%CI: -0.050 to -0.007, p=0.008)]. Shah et al (2018) found that PFO closure did not lead to a significant reduction in risk of a TIA only (RD: -0.004(95%CI: -0.017 to 0.010), p=0.46).

Death. De Rosa et al (2018) reported no statistically significant difference between groups in any study for death rate (PFO closure vs MTA: 4/1382 vs 0/1149, no further analysis reported); this outcome was not reported in the Shah et al (2018) meta-analysis due to the low number of events.

Safety

Serious adverse events (SAE). There was no significant difference in the rate of SAEs between the groups undergoing PFO closure or MTA [25% vs 24% (RD: -0.006(95%CI: -0.036 to -0.048), $p=0.781$, $I^2=31\%$)], with SAEs occurring in about a quarter of patients in both groups (De Rosa et al 2018). It was noted that the outcome, 'any serious adverse event' was not clearly defined in this SRMA.

Major Bleeding. Both SRMAs reported no statistical difference in risk for major bleeding for PFO compared to MTA [RD: -0.010, $p=0.24$ (Shah et al 2018); RD: -0.002, $p=0.605$ (De Rosa et al 2018)].

Atrial Fibrillation (AF). One of the SRMAs concluded that although there was an increased risk of new onset AF, this could not be reliably quantified due to high levels of heterogeneity ($I^2=81.98\%$) among the 4 RCTs (Shah et al 2018). The SRMA by De Rosa et al (2018) considered the heterogeneity among the studies to be lower, possibly related to their inclusion of the shorter-term rather than longer-term follow-up data from the RESPECT study. This SRMA found a statistically significant higher incidence of new onset AF or atrial flutter for patients undergoing PFO closure compared to MTA [PFO closure vs MTA: 4.4%¹³ vs 1.0% (RD: 0.033 (95%CI: 0.012 to 0.054), $p=0.002$, $I^2=66\%$)]. The proportion of new onset AF which required treatment or was permanent was not reported.

Asymptomatic new ischaemic lesion. In the DEFENSE-PFO RCT (Lee et al 2018), patients who received the Amplatzer PFO Closure device were significantly less likely to have a new ischaemic lesion detected by MRI brain scan at 6 months (PFO vs MTA: 3/34 (8.8%) vs 7/38 (18.4%), $p=0.024$).

Major Procedural Complications were reported in 2 of the 53 patients who received the Amplatzer PFO Closure device (Lee et al 2018); one patient had pericardial effusion, one patient had a pseudoaneurysm.

The prospective study by Rigatelli et al (2016 and 2017) reported the following outcomes:

Immediate procedural success within 30 days was 99.8%. The PFO device was removed intraprocedurally in two out of 1000 patients.

Complications within 30 days

Non-electrical complications were reported in 26 (2.6%) PFO closure recipients. These comprised:

- device embolization: 2 (0.2%)
- sheath or device entrapment: 3 (0.3%)
- groin haematomas: 10 (1.0%)
- pericardial effusion: 3 (0.3%)
- air embolism: 4 (0.4%)

¹³ reported as 4.1% by the authors but corrected by reviewers following checking of absolute numbers of events in the PFO closure group

Electrical complications were reported in 59 (5.9%) PFO closure recipients. This included 46 with temporary AF and 3 with temporary atrioventricular block (AVB) which resolved within the procedure. Permanent AF and permanent AVB were reported in one and three patients respectively and four out of six patients with supraventricular arrhythmia required pharmacological cardioversion.

Complications at median 10.5 year follow-up

Non-electrical complications occurred in 22 patients. The most common were non-cardiac related death which appeared unrelated to the device (n=13, 1.3%), recurrent stroke (n=8) and device thrombus (n=5).

Electrical complication rate was 14/1000 (1.4%) which included permanent AF (n=5), paroxysmal AF (n=4) and supraventricular arrhythmia (n=4).

Device related death 1 patient died (0.1%) and this was considered device related although no autopsy was performed to confirm this.

Procedure related outcomes were reported, although the authors do not make clear the significance of these:

- Fluoroscopy time: 7.3±4.7 minutes
- Procedural time: 36.5±6.1 minutes
- Total dose area product (Gycm²): 26.7±1.88

b) Is there evidence to identify subgroups of patients who are likely to have a greater capacity to benefit from the procedure?

There is no evidence from the SRMAs or the meta-analysis, the DEFENSE-PFO RCT or the prospective long term follow up study to clearly identify subgroups of patients with PFO who have had a cryptogenic stroke who will benefit more from PFO closure. The SRMAs confirmed that there was no difference in the pooled outcomes between PFO closure and either antiplatelet or anticoagulant medication considered separately.

The prospective observational study by Rigatelli et al (2016 and 2017) of 1000 consecutive patients suggests that some patients have higher complication rates after PFO closure within the first 30 days after implantation:

- women were more than twice as likely to have either electrophysiological [OR 2.3 (95%CI 0.5 to 5.1), p<0.001] or acute non-electrophysiological complications [OR 2.1 (95%CI 0.5 to 4.6), p<0.001] within the first 30 days.
- patients who required a device disk larger than 30mm were between four and five times more likely to experience electrophysiological [OR 5.0 (95%CI 1.2 to 7.2), p<0.001] or acute non-electrophysiological complications [OR 4.0 (95%CI 0.8 to 6.1), p<0.001].

Rigatelli et al (2016 and 2017) also reported that some patients had higher complication rates at median 10.5 year follow up:

- patients whose implant had a mean device size: septum length ratio greater than 0.8 had an increased risk for electrophysiological [HR 2.61 (95%CI 0.3 to 4.1), p<0.001] and other complications [OR 3.1 (95%CI 0.3 to 5.2), p<0.001].
- patients who had a large atrial septal aneurysm (ASA) had higher risk of both electrophysiological complications (HR 2.2 (95%CI 0.4 to 3.9), p<0.001) and non-electrophysiological complications (OR 2.9 (95%CI 0.4 to 4.3), p<0.001).

While a proportion of patients in the RCTs also had ASA, the SRMAs did not report subgroup analysis for these patients.

Each of the four RCTs had different proportions of patients with a moderate or large PFO size, but outcomes were not reported separately for these patients.

Although the DEFENSE-PFO RCT (Lee et al 2018) only included patients who were confirmed to have an explicit and objectively defined high-risk PFO, the results from this population are not suitable for comparison with the results of the SRMAs as the characteristics of this population were more tightly defined than in the four RCTs in the SRMAs, follow-up time was much shorter (median 2.8 years) and the study was underpowered to detect the primary outcome.

c) What is the evidence of cost effectiveness for PFO closure in patients with a cryptogenic ischaemic stroke and a patent foramen ovale with significant right to left shunt, compared to antiplatelet or anticoagulant therapy?

Two cost effectiveness studies (Pickett et al 2014, Tirschwell et al 2018) met the criteria in the PICO. However, only the more recent cost effectiveness evaluation by Tirschwell et al (2018) was selected for inclusion as the outcomes and assumptions were all highly relevant to the UK NHS setting, whereas the study by Pickett et al (2014) used USA costs from 2011 which are not generalisable to the UK.

Tirschwell et al (2018) reported the estimated time for PFO closure (using the Amplatzer PFO Closure device) to reach the NICE accepted cost effectiveness threshold of £20,000 per QALY to be 4.2 years, although no confidence intervals were reported.

At 4 years post PFO closure procedure, the findings for PFO with Amplatzer compared with MTA were:

- Incremental cost per patient: +£6071 (no CI reported)
- Incremental quality adjusted life years (QALYS): 0.29
- Incremental cost effectiveness ratio (ICER): £20,951

At 10 years post PFO closure procedure, the findings for PFO with Amplatzer compared with MTA were:

- Incremental cost per patient: +£4858 (no CI reported)
- Incremental QALYS: 0.71
- ICER: £6887

89% of probabilistic sensitivity analysis (PSA) iterations were cost effective

At 20 years post PFO closure procedure, the findings for PFO with Amplatzer compared with MTA were:

- Incremental cost per patient: £2848 (no CI reported)
- Incremental QALYS: 1.32
- ICER: £2158

The ICER estimates are therefore well below the NICE threshold of £20,000 over a lifetime.

The Tirschwell et al (2018) cost effectiveness model was based only on the outcomes from an undefined UK 'subpopulation' of PFO patients recruited to the RESPECT RCT: ie those who have had a 'cryptogenic stroke and a large degree of right to left shunt or atrial septal aneurysm'. The median follow up time for the extended RESPECT RCT (Saver et al 2017) was 5.9 years, so the clinical effectiveness and cost outcomes and assumptions were estimated using a Markov model for up to a 20-year time horizon. The costs took into account the direct costs associated with either percutaneous PFO closure or medical therapy regimens, as well as the probability of

complications and their associated costs. Procedure costs and drug therapy were based on UK NHS costs. This means that it is highly likely that the results are reliable and generalisable as long as the patient selection criteria are identical to those used in this UK subpopulation (rather than the wider RESPECT cohort). In addition, indirect costs were not included. Although this is the conventional method used by NICE, the value of avoiding a stroke may be underestimated resulting in a conservative estimate of cost effectiveness which does not take into account the wider, non-NHS, societal costs of caring for people who have had a stroke such as social care, personal productivity such as employment etc. Inclusion of these wider costs might increase the estimated cost-effectiveness of PFO closure for this subgroup further.

The authors did not report other potentially useful cost effectiveness outcomes such as

- cost per life year gained
- cost to prevent one combined endpoint of a TIA, stroke or death
- time before the median cost of medical therapy exceeds the cost of PFO Closure.

A number of potential conflicts of interest were identified: the manuscript was funded by Amplatzer PFO device manufacturer (Abbott), one of the authors is employed by Abbott, and an individual employed by 'Technomics Research' undertook the modelling assistance and editing; it is not clear whether there was any relationship between this organisation and the manufacturer.

5 Discussion

The primary outcome of interest is whether PFO closure for patients who have had cryptogenic stroke is superior to medical therapy alone (MTA) in preventing stroke recurrence, without causing harm.

There is high quality evidence from five recent RCTs, the most recent being the DEFENSE-PFO RCT (Lee et al 2018). For the RESPECT RCT, both shorter and longer-term outcomes are available (Carroll et al 2013, Saver et al 2017). Two SRMAs and one meta-analysis reported the pooled outcomes from the same four RCTs, excluding the DEFENSE-PFO RCT which was published subsequently. Shah et al (2018) noted that individually, two of the RCTs did not show a statistically significant reduction in stroke recurrence following PFO closure [(PC-TRIAL (Meier et al 2013), RESPECT (Saver et al 2017)]. However, when pooled there was a reduction in the risk of recurrent stroke of between 3.1% (De Rosa 2018) and 3.3% (Shah et al 2018), compared with a baseline risk of recurrent stroke among patients on MTA of between 4.1% and 4.6% (De Rosa et al 2018 and Shah et al 2018 respectively). The authors do not report the absolute risk reduction but given the total event rate reported by Shah et al (2018), this appears equivalent to approximately 33 fewer recurrent stroke events per 1000 PFO closure recipients than would be expected if all patients received MTA. This is the equivalent of a number needed to treat (NNT) of approximately 30 PFO closures to prevent one stroke.

The two SRMAs took different approaches to one of the RCTs. De Rosa et al (2018) included the shorter-term outcomes from the RESPECT RCT (Carroll et al 2013) while Shah et al (2018) included longer-term outcomes (Saver et al 2017) in which there was 27% loss to follow-up. While inclusion of the longer-term outcomes in Shah et al (2018) resulted in a slightly larger risk reduction for reduction in stroke recurrence, the risk reduction found in the two SRMAs was statistically similar.

The proportion of missing data (due to subject withdrawal or loss to follow up) at longest reported follow-up for all four RCTs was reported in the SRMA by Shah et al (2018). The highest proportion of missing data was in the extended RESPECT RCT by Saver et al (2017) (PFO closure vs MTA:

20.8% vs 33.3%) which had the longest follow-up, a median of 5.9 years. In comparison, the CLOSE RCT with the next longest follow-up (mean 5.3 years) had the lowest proportion of missing data (PFO closure vs MTA: 8.8% vs 11%) (Mas et al 2017). The REDUCE RCT ((Sondergaard et al 2017), with median 3.2 year follow-up, had 8.8% (PFO closure) and 14.8% (MTA) missing data, and the PC-TRIAL (Meier et al 2013), with 4.0-4.1 year follow-up, had 15.2% (PFO closure) and 20.0% (MTA) missing data. All analyses were based on the intention to treat approach. However, it is unknown if the event rate for each outcome would remain unchanged if data from these missing subjects were available for inclusion.

There was heterogeneity among the RCTs in a number of respects.

Interventions used A number of different PFO closure devices were used; three of the RCTs [PC-TRIAL (Meier et al 2017), RESPECT (Carroll et al 2013, Saver et al 2017) and DEFENSE-PFO RCT (Lee et al 2018)] used the Amplatzer device only (combined n=763), but the REDUCE RCT (Sondergaard et al 2017) used the HELEX Septal Occluder and the CARDIOFORM Septal Occluder devices, and clinicians in the CLOSE RCT (Mas et al 2017) used 11 different devices. Another important difference between the trials which may have affected the results were the differences in medication prescribed for patients who received a PFO closure device as well as the different medication regimes used as the comparator. Whilst some of the studies report the use of warfarin, it is not clear if any of the novel oral anticoagulants were included as part of any of the MTA regimes.

Indication Although the indication specified was cryptogenic stroke, the severity of the index event varied between the RCTs. For example, 18.1% in PC-TRIAL and 9.5% in REDUCE had a TIA rather than a stroke that lasted longer than 24 hours. The patients selected for inclusion in DEFENSE-PFO RCT were subject to stringent and objective measures to confirm the high risk morphology of the PFO.

In addition, although not fully reported in the SRMAs by Shah et al (2018) and De Rosa et al (2018), the individual RCTs report a proportion of study subjects who also had known risk factors for stroke. These included hypertension, diabetes, smoking, obesity and oral contraception. This was also the case in the prospective uncontrolled study by Rigatelli et al (2016, 2017). This introduces some uncertainty about whether all preceding strokes were cryptogenic and associated with the PFO. The ongoing management of these modifiable risk factors such as smoking cessation also confounds the results in that it brings into question whether or not the benefits or harms observed are directly and solely attributable to the PFO closure procedure.

Results for patients with a large PFO or an ASA and PFO were not reported separately in the SRMAs. In the RCTs included in the SRMAs, between 20.1% and 94.3% patients had a severe/substantial shunt and 23% to 36.1% patients had an ASA. The authors did not report what proportion of patients had both a severe/substantial shunt and an ASA, and it is not clear whether these were investigated and defined using the same criteria across all four RCTs. Over 90% of patients in the CLOSE RCT had a severe/substantial shunt, but the question about whether patients with these anatomical features have a greater capacity to benefit from PFO closure cannot be answered from this study. This is due to the study design and to its confounding factors (differences in device used, antithrombotic medication, definition of cryptogenic stroke, presence of stroke risk factors). Rigatelli et al (2016, 2017) reported a higher likelihood of long term complications in patients with a large (grade 3-5) ASA.

Safety The acute and long-term complication rates were low in all the studies. While De Rosa et al (2018) found no difference in risk of death or major bleeding for patients undergoing PFO closure or MTA, they did find a 3.3% greater risk [RD: 0.033 (95%CI 0.012 to 0.054)] of new

onset atrial fibrillation (AF) or atrial flutter. This outcome was not analysed by Shah et al (2018) due to the significant heterogeneity among the studies, which was also acknowledged by De Rosa et al (2018) who recognised the uncertainty of their finding for this outcome. Neither systematic review reported what proportion of the new onset AF or atrial flutter was temporary or required further treatment. There is lower quality evidence from the long term prospective study by Rigatelli et al (2017) which reported only 5 patients with permanent AF and 4 with paroxysmal AF out of 1000 patients at median 10.5 year follow up, suggesting that the majority of new onset AF is temporary or successfully treated.

No studies carried out formal analyses of benefits against risks and there remains some uncertainty about the balance between them. The reduction in absolute risk of recurrent stroke following PFO closure of between 3.1% and 3.3% (De Rosa 2018, Shah et al 2018), needs to be considered against the possible increased absolute risk of new onset AF of 3.3% (De Rosa et al, 2018) and the proportion of AF which might be permanent.

We noted that quality of life was not measured in any of the RCTs. Neither Shah et al (2018) nor De Rosa et al (2018) reported gender differences in the baseline populations or the outcomes.

Cost effectiveness

The reported estimated time for PFO closure (using the Amplatzer PFO Closure device) to reach the cost effectiveness threshold of £20,000 per QALY was 4.2 years, although no confidence intervals were reported. The reported ICERS of £20,951 at 4 years, £6887 at 10 years and £2158 at 20 years are all well within the accepted cost effectiveness threshold for NICE.

This cost effectiveness outcomes model should be treated with some degree of caution.

- The model is based on the results from a UK sub-population recruited to the extended RESPECT RCT (Saver et al 2017) - those who have had a 'cryptogenic stroke and a large degree of right to left shunt or atrial septal aneurysm'. The sub-population is not objectively defined; although the authors state that anatomical features of the PFO were considered, it is not clear if the right to left inter-atrial shunt size was objectively defined or open to local interpretation.
- The baseline characteristics for the UK sub-population are not reported, so there might have been pre-treatment differences between the PFO closure and MTA treatment arms.
- The international RESPECT cohort included some patients who had stroke-related risk factors such as hypertension and smoking. We do not know the patient characteristics of the two treatment arms of the UK sub-population, although the authors have reported the annual probability of stroke for this specific group.
- The discussion reported that when the model was applied to the entire RESPECT cohort (rather than the UK sub-population), this resulted in higher ICERS at 4, 10 and 20 years. However, the ICERS reported at 10 and 20 years for the entire cohort and the sub-population appear to be identical. It is not clear if this is a reporting error.

However, the analysis used a UK study population, UK NHS direct costs, and transition probabilities which means that it is highly likely that the results are reliable and generalisable enough as long as the patient selection criteria are identical to those used in this UK sub-population.

The model uses direct costs only: although this is the conventional method used by NICE, the value of avoiding a stroke may be underestimated resulting in a conservative estimate of cost effectiveness which does not take into account the non-NHS costs of stroke care (social care,

personal productivity such as employment). Inclusion of these wider costs might increase the estimated cost-effectiveness of PFO closure for this subgroup further. Other cost effectiveness outcomes were not reported.

A number of potential conflicts of interest were identified among the authors of this study and it is not clear to what extent the work was independent of the manufacturer.

There are currently significant uncertainties for patients and clinicians who need to make decisions about the best course of treatment to prevent a recurrent stroke for people with a PFO who have had a cryptogenic stroke. Reductions in risk of recurrent stroke have been reported in SRMAs of RCTs comparing PFO closure with MTA, but further research would be helpful to more clearly identify the balance of benefits and risks of PFO closure compared to specific regimens of MTA in patients with cryptogenic stroke only (as opposed to those with concomitant modifiable risk factors for stroke). This should include separate consideration of those with concomitant ASA which appears to be both a risk factor for recurrent stroke and a risk predictor for higher incidence of complication rates. Research would also need to evaluate the impact of the percutaneous PFO closure or MTA on the quality of life of those who have already had a cryptogenic stroke. This would also inform future QALY estimates.

Greater transparency of the cost effectiveness model (including the reporting of confidence intervals) and clarity over the patient baseline characteristics, including the baseline PFO risk, would help to address the outstanding uncertainty about the confidence with which the estimated ICERS can be considered, and the subgroup of patients to which these estimates might apply.

6 Conclusion

The evidence from recently published RCTs, and the systematic reviews and meta-analyses of the pooled outcomes from these RCTs, indicates that for a period of up to median 5.9 years, there is a reduction in risk of up to 3.3% for recurrent stroke for patients with cryptogenic stroke who received a PFO closure device compared with medical therapy alone (MTA) (Shah et al 2018). This compares with a baseline risk of recurrent stroke for patients on MTA of between 4.1% (De Rosa et al 2018) and 4.6% (Shah et al 2018).

There is no evidence from the studies on the lifetime benefit of PFO closure compared with MTA. However, as the risks of adverse events of long term medication are ongoing whereas the risks of adverse events from PFO closure are likely to be more closely associated with the procedure, it is plausible that the risk difference between the two interventions might increase over time.

However, some uncertainty remains about the balance of risks and benefits, and in particular about the impact of the reported 3.3% increased risk of new onset atrial fibrillation (AF) in patients receiving a PFO closure device (Shah et al 2018), and the proportion of this which might be permanent.

In the cost-effectiveness analysis by Tirschwell et al (2018) the ICER estimates for PFO closure are well within the NICE threshold of £20,000 per QALY at 10 and 20 years. However, there remains some uncertainty about the cost-effectiveness of PFO closure compared with MTA. This is due to the lack of clarity about the patient selection criteria for the UK sub-population included in this study, the lack of confidence intervals and the lack of reporting of other cost effectiveness outcomes.

This uncertainty about long term benefits and harms needs to be considered in the context of the use of PFO closure as a preventative procedure rather than to treat symptoms, and the relatively low baseline risk of stroke recurrence with MTA cited above. However, if the risk of complications was acceptable to patients, a reduction in the incidence of recurrent stroke would be highly valuable in the context of the overall burden of stroke in younger people to the NHS and social care services, as well as the impact on their lives and the lives of their families.

7 Evidence Summary Tables

For abbreviations see list at the end of section 7.

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Shah et al 2018 ¹⁴	Systematic review and meta-analysis of 4 RCTs comparing PFO closure and medical therapy alone (MTA) Search date 'to October 2017'	n=2531 Patients with PFO and cryptogenic stroke Mean age range: 43.3 to 45.4yrs Male: 49% Smokers 17.9% Diabetes (4.9%)	Transcatheter PFO Closure plus antithrombotic medication ¹⁹ (n=1382) Or Medical therapy alone (MTA) (n=1149) Absolute numbers and % of patients receiving antiplatelet	Primary Clinical effectiveness	Recurrent Stroke	Risk difference (RD): -0.033 (95%CI: -0.062- to -0.004), p=0.037 based on 25/1382 events /patient in the PFO closure group and 59/1149 events/patient in the MTA group.	8	Direct	These results are updated following corrections by the author published on 25.06.2018 which led to a slightly larger risk difference for recurrent stroke, and smaller risk difference for major bleeding, compared with the original analysis (which had double-counted a number of patients from the CLOSE study). The updated reported result for TIA is not accurate as although the risk difference between PFO closure and MTA had changed from 0.002 to 0.000 for the CLOSE study results, the overall risk difference, CI and p value reported remained the same. The authors explained that the ' <i>absolute numbers (both denominators and nominators) are different for the MTA groups, but event rates are similar. Therefore pooled estimates for the outcome of TIA are similar</i> '.
				Secondary Clinical effectiveness	TIA	RD: -0.004 (95%CI: -0.017 to 0.010), p=0.46 based on 31/1382 events /patient in the PFO closure group and 39/1149 events/patient in the MTA group.			
				Secondary Safety	Risk for Major Bleeding (based on 3 RCTs only)	RD: -0.010 (95%CI: -0.037 to 0.016), p=0.24 based on 11/883 events /patient in the PFO closure group and			

¹⁴ Results updated 29 June to reflect corrections made to the analysis by the authors and reported in the Journal commentary.

Variable	PC, 2013 (7)	RESPECT Extended, 2017 (12)	CLOSE, 2017 (10)	REDUCE, 2017 (11)
Protocol for antithrombotic therapy				
Device group	Aspirin (5 or 6 mo) and ticlopidine or clopidogrel (1-6 mo)	Aspirin (6 mo) and clopidogrel (1 mo) after 6 mo, antithrombotic therapy was at the discretion of the site investigator	Aspirin (2 mo) and clopidogrel (2 mo) after 2 mo, single antiplatelet therapy, was at the discretion of the site investigator	Clopidogrel (2 d). After 2 d, use of antiplatelet therapy was at the discretion of the site investigator
MTA group	Antiplatelet therapy, or oral anticoagulation at the discretion of the site investigator, provided >1 antithrombotic therapy was used	Aspirin or warfarin or clopidogrel or aspirin and dipyridamol at the discretion of the site investigator	Antiplatelet group: Aspirin or clopidogrel or aspirin and dipyridamol* Anticoagulant group: Vitamin K antagonists or direct oral anticoagulants*	Aspirin or clopidogrel or aspirin and dipyridamol at the discretion of the site investigator

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a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	No language restriction Follow up ranged from mean 3.2 yrs to median 5.9yrs RCTs: PC-TRIAL 2013 ¹⁵ CLOSE 2017 ¹⁶ REDUCE 2017 ¹⁷ RESPECT extended 2017 ¹⁸	Hypercholesterolaemia (22.3%) Hypertension (25.2%) Large PFO (n=1267, 43.9%) Atrial Septal aneurysm (ASA) in addition to PFO (n=654, 22.6%)	therapy or OAC (or both) at randomisation or at discharge for both the device and MTA arms was not reported by Shah et al 2018. Absolute numbers not retrievable for the pooled population after accessing the individual RCT publications.	Secondary Safety	Risk for New onset AF	14/668 events/patient in the MTA group. Increased risk in PFO closure group but magnitude of increased risk is not reported Pooled analysis not undertaken as authors considered heterogeneity for this outcome to be too high (Q=16.65; P<0.001; I ² =81.98%) Based on 53/1382 events /patient in the PFO closure group and 9/1149 events/patient in the MTA group.			Excluded studies with STARFlex device (no longer available): therefore, more generalisable to current clinical practice. All RCTs classed as high quality: multicentre, randomised, multicentre open label, superiority trials However, none of the RCTs were double blinded. The forest plots indicate that individually 2 of the 4 RCTs (Extended RESPECT, PC-TRIAL) do not clearly favour PFO closure for reduction in risk of recurrent stroke. All RCTs reported missing data ranging from 8.8% and 20.8% for the device group and 11% and 33.3% in the MTA group. The greatest loss to follow-up (overall 27%: 20.8% PFO/ 33.3% MTA) was in RESPECT 2017. All analyses based on intention to treat approach Heterogeneity among the 4 RCTs for <ul style="list-style-type: none"> • Antithrombotic medication at discharge • Antithrombotic medication at last follow up • Type of PFO closure device • Differences in definition of recurrent stroke • Variance in anatomical features of study subjects e.g. size of inter-atrial shunt (IAS), presence of ASA, large IAS (higher risk of PFO related stroke) • % subjects with other risk factors for stroke

¹⁵ PC-TRIAL: Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism (Meier et al 2013)

¹⁶ CLOSE: Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence (Mas et al 2017)

¹⁷ REDUCE: GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients (Sondergaard et al 2017)

¹⁸ RESPECT: Randomised Evaluation of Current Stroke Comparing PFO Closure of established current Standard of Care Treatment (Saver et al 2017)

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
									<p>Meta-analysis included patients from two of the three randomisation groups from the CLOSE study only ie a comparison of PFO device and APT.</p> <p>Mean follow up not reported but ranged from mean 2.6 years to median 5.9 years across the RCTs.</p> <p>All RCTs industry sponsored apart from CLOSE (sponsored by French Ministry of Health).</p>
De Rosa et al 2018	<p>S1</p> <p>Systematic review and meta-analysis of 4 RCTs comparing PFO closure and medical therapy alone (MTA)</p> <p>Search date: 1 Dec 2004 to 14 Sept 2017</p> <p>PC-TRIAL 2013</p> <p>CLOSE 2017</p>	As for Shah et al 2018 above.	<p>Transcatheter PFO Closure (n=1382)</p> <p>Or</p> <p>Medical therapy alone (n=1149)</p>	<p>Primary Clinical effectiveness</p> <p>Secondary Clinical effectiveness</p> <p>Secondary Clinical effectiveness</p> <p>Secondary Safety</p> <p>Secondary Safety</p>	<p>Composite of Stroke or TIA</p> <p>Ischaemic stroke</p> <p>Death</p> <p>New onset AF or Atrial flutter</p> <p>Major bleeding</p>	<p>PFO closure vs MTA: 3.6% vs 6.3% (RD: -0.029(95%CI: -0.050 to -0.007), p=0.008, I²=34%)</p> <p>PFO closure vs MTA: 1.2% vs 4.1% (RD: -0.031(95%CI: -0.051 to -0.010), p=0.003, I²=61%)</p> <p>No statistically significant difference found between groups in any study (risk difference and p value not reported) [PFO closure: 4 deaths/1382 PFO device recipients MTA: 0 deaths/1149 on MTA]</p> <p>PFO closure vs MTA: 4.4%²¹ vs 1.0% (RD: 0.033(95%CI: 0.012 to 0.054), p=0.002, I²=66%)</p> <p>PFO closure vs MTA: 0.9% vs 1.2% (RD: -0.002(95%CI: -0.012 to 0.007), p=0.605, I²=28%)</p>	8	Direct	<p>SRMA of same RCTs as Shah et al (2018) EXCEPT for <u>exclusion</u> of RESPECT RCT long term outcomes at median 5.9 yrs (Saver et al 2017). Only included outcomes from RESPECT 2013 trial because there was complete f/up of all patients (mean f/up 2.6 yrs).</p> <p>Mean follow up for the pooled outcomes were not reported.</p> <p>Excluded studies with STARFlex device (no longer available): therefore, more generalisable to current clinical practice.</p> <p>All RCTs classed as high quality: multicentre, randomised, multicentre open label, superiority trials None of the RCTs were double blinded.</p> <p>Heterogeneity among the 4 RCTs for:</p> <ul style="list-style-type: none"> • Antithrombotic medication at discharge • Antithrombotic medication at last follow up • Type of PFO closure device • Some differences in definition of recurrent stroke • Variance in anatomical features of study subjects e.g. size of inter-atrial shunt (IAS),

²¹ reported by the authors as 4.1%, but corrected by reviewer after checking absolute number of events in the PFO closure group.

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	REDUCE 2017 RESPECT 2013 ²⁰ (only used RESPECT extended f/up for sensitivity analyses) Follow up ranged from mean 2.6 to 5.3 yrs.			Secondary Safety	Serious adverse events (not defined)	PFO closure vs MTA: 25%(345 events/1382 pts) vs 24%(281/1149) (RD: -0.006(95%CI: -0.036 to -0.048), p=0.781, I ² =31%)			presence of ASA, large IAS (higher risk of PFO related stroke) <ul style="list-style-type: none"> % subjects with other risk factors for stroke <p>All analyses based on intention to treat approach. All constituent RCTs had patients who withdrew or were lost to f/up. At mean f/up of 2.6yrs, 86.8% subjects recruited to RESPECT RCT remained in active f/up compared to 73.1% in active f/up at median 5.9yrs.</p> <p>Only included patients from the PFO and APT randomisation groups from the CLOSE study.</p> <p>All RCTs industry sponsored apart from CLOSE (sponsored by French Ministry of Health).</p>
Piccolo et al 2018	S1 Meta-analysis of Estimates of risk based on Kaplan-Meier curves from 4 RCTs comparing PFO closure and medical therapy alone (MTA)	As for Shah et al 2018 above	Transcatheter PFO Closure using range of devices (n=1382) Or Medical therapy alone (MTA) using oral antiplatelet therapy in the CLOSE and REDUCE trials, oral anticoagulation therapy in	Primary Clinical effectiveness	Recurrent ischaemic stroke	At longest follow-up ²⁶ PFO vs MTA: 25/1382 (1.81%) vs 59/1149 (5.13%) had at least 1 ischaemic stroke HR 0.18 (95% CI 0.06 to 0.59), p=0.005 At 1 year: PFO(n=1290) vs MTA(n=1048): HR 0.40 (95% CI 0.20 to 0.80), p=0.010 Between 1 and 5 years PFO vs MTA: HR 0.14 (95% CI 0.04 to 0.55), p=0.005 Beyond 5 years PFO vs MTA:	8	Direct	Excluded studies with STARFlex device (no longer available): therefore, more generalisable to current clinical practice. All RCTs classed as high quality: multicentre, randomised, multicentre open label, superiority trials None of the RCTs were double blinded. Heterogeneity among the 4 RCTs for <ul style="list-style-type: none"> Antithrombotic medication at discharge Antithrombotic medication at last follow up Type of PFO closure device Differences in definition of recurrent stroke Variance in anatomical features of study subjects e.g. size of inter-atrial shunt (IAS), presence of ASA, large IAS (higher risk of PFO related stroke) % subjects with other risk factors for stroke

²⁰ RESPECT: Randomised Evaluation of Current Stroke Comparing PFO Closure of established current Standard of Care Treatment (Carroll et al 2013)

²⁶ The 2531 patients included in the analysis had been exposed to treatment for variable lengths of time (up to 9 years).

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary																		
	Follow up ranged from mean 3.2 yrs to median 5.9yrs RCTs: PC-TRIAL 2013 ²² CLOSE 2017 ²³ REDUCE 2017 ²⁴ RESPECT extended 2017 ²⁵		the PC and RESPECT trials. (n=1149)			HR 0.20 (95% CI 0.03 to 1.19), p=0.077			Included long term f/up of RESPECT trial (median f/up 5.9 yrs) which had c.27% dropout leading to incomplete dataset. Absolute number of events not reported for three time intervals (1yrs, 1-5yrs, beyond 5yrs). Wide confidence intervals after 5 years, due to decreasing numbers of patients at risk in either treatment group. <table border="1"> <thead> <tr> <th>No at risk</th> <th>5yrs</th> <th>6yrs</th> <th>7yrs</th> <th>8yrs</th> <th>9yrs</th> </tr> </thead> <tbody> <tr> <td>PFO</td> <td>903</td> <td>516</td> <td>479</td> <td>478</td> <td>143</td> </tr> <tr> <td>MTA</td> <td>675</td> <td>307</td> <td>271</td> <td>176</td> <td>67</td> </tr> </tbody> </table> At the longest follow up time of 9 years, a HR of 0.18 indicates that 18% of patients who had a PFO closure had a stroke compared to the proportion of the MTA group. It should be noted that the hazard ratio is a relative measure of effect only and tells us nothing about absolute risk. This analysis did not assess any other outcomes such as transient or permanent adverse events.	No at risk	5yrs	6yrs	7yrs	8yrs	9yrs	PFO	903	516	479	478	143	MTA	675	307	271	176	67
No at risk	5yrs	6yrs	7yrs	8yrs	9yrs																						
PFO	903	516	479	478	143																						
MTA	675	307	271	176	67																						
Lee et al 2018	P1 RCT South Korea Multicentre,	n=120 Patients with cryptogenic stroke and	PFO Closure using Amplatzer PFO Occluder & medication (n=60)	Primary Clinical Effectiveness	K-M 2yr cumulative estimate of the composite of stroke, vascular death or TIMI-defined ²⁹ major	PFO vs MTA: 0/60vs 6/60 (2 year event rate 12.9%, 95%CI 3.2 to 22.6; SE 5.0, p=0.013)	7	Direct	Standardised protocol using CT or MR angiography or ultrasonography to rule out other mechanisms of stroke and confirm cryptogenic stroke, as well as establish if the PFO is high risk: stringent and objective criteria for enrolment to the study. These patients were more highly selected (with greater PFO risk) than those recruited to the RCTs included																		

²² PC-TRIAL: Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism (Meier et al 2013)

²³ CLOSE: Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence (Mas et al 2017)

²⁴ REDUCE: GORE HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients (Sondergaard et al 2017)

²⁵ RESPECT: Randomised Evaluation of Current Stroke Comparing PFO Closure of established current Standard of Care Treatment (Saver et al 2017)

²⁹ TIMI is a recognised definition of bleeding used in clinical trials. A major bleed is classed as any intracranial bleeding (excluding microhaemorrhages <10 mm evident only on gradient-echo MRI), clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL or fatal bleeding (bleeding that directly results in death within 7 days (Mehran et al 2011))

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	randomised, open label superiority trial DEFENSE-PFO ²⁷ Median F/up 2.8yrs, IQR 0.9 to 4.1 yrs	high risk PFO ²⁸ . Mean age 51.8 yrs Recruited Sept 2011 to October 2017	7 declined intervention Or Medication only (n=60) Using antiplatelet or anticoagulation therapy.		bleeding during 2 years f/up				in the SRMAs (Shah et al 2018, De Rosa et al 2018).
				Secondary	K-M cumulative estimate of the probability of ischaemic stroke	PFO vs MTA: 0/60 vs 5/60 (10.5%), 95%CI 1.68 to 19.32; SE 4.5, p=0.023)		Only 2 centres from one country: possible selection bias	
				Clinical Effectiveness	Vascular death	None occurred		Study recruitment terminated early (following publication of the CLOSE RCT (Mas et al 2018). Planned target recruitment (n=105 in each arm) was not reached. The study results are therefore underpowered.	
				Secondary	K-M cumulative estimate of TIMI-defined major bleeding	PFO vs MTA: 0/60 vs 2/60 (4.9%), p=0.15		We note that the number of patients included in the ITT analysis at 2 years is 40/60 for PFO and 37/60 for MTA.	
				Clinical Effectiveness	K-M cumulative estimate of Haemorrhagic stroke	PFO vs MTA: 0/60 vs 1/60 (2.5%), p=0.30		7/60 selected for PFO declined the procedure; 4/60 patients randomised to MTA had PFO closure during the f/up period. The authors note that none of these 11 patients experienced the primary endpoint.	
				Secondary	K-M cumulative estimate of TIA	PFO vs MTA: 0/60 vs 1/60 (2.0%), p=0.32		The authors state in the discussion that the number of patients needed to treat to avoid one stroke at 2 years is 10, although it is not clear how they arrived at this. Reviewer calculations indicate that the NNT is 12.	
				Clinical Effectiveness	Systematic embolism	None occurred			
				Secondary	Asymptomatic new ischaemic brain lesion on	PFO vs MTA: 3/34 (8.8%) vs 7/38 (18.4%), p=0.024			
				Clinical Effectiveness					

²⁷ DEFENSE-PFO: Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients with High Risk Patent Foramen Ovale

²⁸ High risk PFO defined as a PFO with an atrial septal aneurysm (protrusions of the dilated septum at least 15mm beyond the level surface of the atrial septum), hypermobility (phasic septal excursion into either atrium>10mm) or PFO size (maximum separation of the septum primum from the secundum during the Valsalva manoeuvre)>2mm on TEE.

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
				Clinical Effectiveness	f/up MRI at 6 months				
				Secondary Safety	Non-fatal procedural complications	Atrial fibrillation, n=2 Pericardial effusion, n=1 Pseudo aneurysm, n=1			
Tirschwell et al 2018	S2 Cost effectiveness Markov model based on outcomes for a UK subgroup of patients (starting age 46 yrs) recruited to RESPECT RCT 2017 (Saver et al 2017)	The model assumption were partly based on a UK 'sub-population' ³⁰ of pts in the RESPECT RCT who all had "cryptogenic ischaemic stroke and putative high risk anatomical features of the PFO ASA and/or substantial right to left inter-atrial shunt who required no anticoagulation for their concomitant conditions and could	Amplatzer PFO Occluder or MTA	Primary Cost effectiveness	Time to reach WTP threshold of £20,000 per QALY	4.2 years	8	Direct	High quality cost effectiveness analysis using UK study population, UK NHS direct costs, and transition probabilities. Assumptions clearly reported with credible references. Sensitivity analysis reported. Confidence intervals not reported. This model focuses on a UK 'subpopulation' of PFO patients recruited to the RESPECT RCT: ie those who have had a 'cryptogenic stroke and a large degree of right to left shunt or atrial septal aneurysm'. It is not clear how other causes of stroke were investigated in this UK subgroup in order to confirm that the index stroke was cryptogenic. In addition, it is not clear if the right to left inter-atrial shunt size was objectively defined or open to local interpretation. The international RESPECT cohort included some patients who had stroke-related risk factors such as hypertension and smoking. We do not know the patient characteristics of the two treatment arms of the UK sub-population, although the authors have reported the annual probability of stroke for this specific group. The model uses direct costs only: this is the conventional method used by NICE. The value of
				Primary Cost effectiveness	Cost effectiveness at 4 years	PFO vs MTA: Incremental costs: £6071 Incremental QALYS: 0.29 ICER: £20,951			
				Primary Cost effectiveness	Cost effectiveness at 10 years	PFO vs MTA: Incremental costs: £4858 Incremental QALYS: 0.71 ICER: £6887 89% of PSA iterations were cost effective			
				Primary Cost effectiveness	Cost effectiveness at 20 years	PFO vs MTA: Incremental costs: £2848 Incremental QALYS: 1.32 ICER: £2158			
				Secondary Clinical effectiveness	Annual probability of stroke per year for PFO vs MTA for this UK subpopulation	PFO vs MTA: 0.36% vs 1.31%			

³⁰ Subgroup used to model the cohort for the cost-effectiveness study was based on a survey of UK specialists (Von Klemperer et al 2017)

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		<p>be managed on ant-platelet medication'</p> <p>RESPECT pts: 18-60 yrs</p> <p>PFO confirmed by TEE Paradoxical embolization only</p>							<p>avoiding a stroke may be underestimated resulting in a conservative estimate of cost effectiveness which does not take into account the wider, real-life costs of caring for stroke or the QoL impact of stroke on people of working age.</p> <p>The discussion reports that the model applied to the entire ITT RESPECT cohort resulted in higher ICERS at 4,10 and 20 years. However, the ICERS reported at 10 and 20 years for the entire RESPECT cohort appear to be identical to the ICERS reported for the UK subpopulation. It is not clear if this is a reporting error.</p> <p>The manuscript was funded by PFO device manufacturer (Abbott). One of the authors is employed by Abbott. An individual employed by 'Technomics Research' undertook the modelling assistance and editing; It is not clear to what extent this individual was independent of the manufacturer.</p>

b. Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Rigatelli et al 2017	P1 Prospective observational study of 1000 consecutive patients Mean f/up: 12.3 +/- 0.6yrs (median 10.5yrs, range: 4 to 17yrs) Cardiologic examination planned for 1,6,12 months and annually. TEE: 3months, 12month TCD: 1 month	n=1000, consecutive patients (mean age 47.3 +/-17.1 yrs) 56% female n=851(85.1%) stroke enrolled in 2 centres in Italy between February 1999 and February 2012 for R-L shunt catheter – based closure All had medium (n=301, 30.1%) or large PFO (n=699, 69.9%) on TTE. Unspecified proportion did not have cryptogenic stroke	Different devices used: • Amplatzer PFO Occluder (n=463, 46.3%) • Amplatzer ASD Cribriform Occluder (n=420, 42.0%) • Premere occlusion system (n=95, 9.5%) • Biostar occlude (n=22, 2.2%) PLUS Medication: • Premere or Amplatzer devices: 100mg aspirin for 6 months	Primary Clinical effectiveness Primary Safety Primary Safety Primary Clinical effectiveness	Immediate procedural success within 30 days Complications within 30 days Predictors of electrophysiological complications within 30 days Follow up occlusion at median 10.5 yr f/up	99.8% device was intraprocedurally removed in 2/1000 pts Non-electrical complications 22(2.2%) (not described) Electrical complications: 59 (5.9%) comprising • Temporaneous AF: 46 (4.6%)* • Permanent AF: 1 (0.1%) • Temporaneous AVB I or II grade: 3 (0.3%)* • Permanent AVB I or II grade: 3(0.3%) • Temporaneous or permanent AVB III: 0 • Supraventricular arrhythmias: 6 (0.6%)** *spontaneously resolved within procedure **4 resolved with pharmacological cardioversion, 2 spontaneously resolved Female gender: OR 2.3 (95%CI 0.5 to 5.1), p<0.001 Device disk>30mm: OR 5.0 (95%CI 1.2 to 7.2), p<0.001 93.8% comprising 35 trivial shunts, 16 small shunts, 11 moderate shunts	8	Indirect	Heterogeneity among subjects with mixture of PFO size, initial incident (15% TIA vs 85% stroke) and the study suggests that a proportion (not specified) did not have cryptogenic stroke: 25.3% were smokers, 21.2% had high blood pressure, 27.8% had hypercholesterolaemia, 21.3% were on oral contraception, 24.4% have MTHFR mutation Non-randomised, uncontrolled study. Different devices used with different concomitant medication. No pts lost to follow-up for long term f/up of median 10.5 yrs. Multivariate sensitivity analysis performed to identify predictors of complications: age, sex, grade of ASA, shunt, rim thickness, tunnel length, device disk, device size relative to AS length, device type. 42% had ASD occlusion devices (not PFO closure device). 606/1000 patients who had PFO closure also had an atrial septal aneurysm. 312 of these were graded 4-5.

b. Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	TTE: 12months and yearly (every 2 yrs if no events reported) Holter 24hr monitoring: 1month		<ul style="list-style-type: none"> Biostar device: aspirin 100mg + clopidogrel 75mg for 6 months Or <ul style="list-style-type: none"> warfarin for 6 months if coagulation abnormalities present (any device) 	Primary Safety Primary Safety	Electrical complication rate at median 10.5 yr f/up Predictors of electrophysiological complications at median 10.5 yr f/up	14/1000 (1.4%) comprising <ul style="list-style-type: none"> permanent AF: 5 (0.5%) paroxysmal AF: 4 (0.4%) complete AVBlock: 1 (0.1%) supraventricular arrhythmias: 4 (0.4%) Large (3-5 grade) ASA (HR 2.2 (95%CI 0.4 to 3.9), p<0.001 Mean ratio between device size and entire septum length>0.8 (HR 2.61(95%CI 0.3 to 4.1), p<0.001			
Rigatelli et al 2016	P1 Prospective observational study of 1000 consecutive patients Mean f/up: 12.3 +/- 0.6yrs (median 10.5yrs, range: 4 to 17yrs)	n=1000, consecutive patients (mean age 47.3 +/-17.1 yrs) 56% female n=851(85.1 %) stroke enrolled in 2 centres in Italy between February 1999 and February 2012 for R-L shunt catheter – based closure	Different devices used: <ul style="list-style-type: none"> Amplatzer PFO Occluder (n=463, 46.3%) Amplatzer ASD Cribriform Occluder (n=420, 42.0%) Premere occlusion system (n=95, 9.5%) 	Primary Clinical effectiveness Primary Safety Secondary Safety Secondary	Immediate procedural success within 30 days Non-electrical complications within 30 days Fluoroscopy time Procedural time	Reported above 26 (2.6%) comprising <ul style="list-style-type: none"> device embolization: 2(0.2%) sheath or device entrapment: 3(0.3%) groin haematomas:10(1.0) pericardial effusion: 3(0.3%) air embolism: 4(0.4%) death:0(0) (electrophysiological outcomes already reported above) 7.3+/-4.7minutes 36.5+/-6.1minutes	8	Indirect	Same study as above, focusing on non-electrophysiological outcomes.

b. Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
	Cardiologic examination planned for 1,6,12 months and annually. TEE: 3months, 12month TCD: 1 month TTE: 12months and yearly (every 2 yrs if no events reported) Holter 24hr monitoring: 1month	All had medium (n=301, 30.1%) or large PFO (n=699, 69.9%) on TTE. Unspecified proportion did not have cryptogenic stroke	<ul style="list-style-type: none"> • Biostar Occluder (n=22, 2.2%) PLUS Medication: <ul style="list-style-type: none"> • Premere or Amplatzer devices: 100mg aspirin for 6 months • Biostar device: aspirin 100mg + clopidogrel 75mg for 6 months Or <ul style="list-style-type: none"> • warfarin for 6 months if coagulation abnormalities present (any device) 	Safety					
				Secondary Safety	Total dose area product (Gycm2)	26.7+/-1.88			
				Primary Safety	Predictors of acute complications within 30 days	Female gender: OR 2.1 (95%CI 0.5 to 4.6), p<0.001 Device disk>30mm: OR 4.0 (95%CI 0.8 to 6.1), p<0.001			
				Primary Clinical effectiveness	Cardiac related death	1(0.1%) no autopsy but death was counted as device related – possibly due to ventricular tachycardia during exercise.			
				Primary Safety	complication rate at median 10.5 yr f/up For outcomes not already reported above	2.2% comprising <ul style="list-style-type: none"> • atrial fibrillation: 5(0.5%) • device thrombosis: 5(0.5%) • erosion: 0(0) • mitral valve regurgitation: 2(0.2) • recurrent stroke (minor/major): 6/2(0.8) • device embolization/removal: 1(0.1%) • device fracture: 0(0) • cardiac related death: 1(0.1%) • non-cardiac related death: 13 (1.3%) (11 neoplastic related, 2 car accident related) 			
				Primary Safety	Predictors of complications at median 10.5 yr f/up	Large (3-5 grade) ASA (OR 2.9 (95%CI 0.4 to 4.3), p<0.001 Mean ratio between device size and entire septum length>0.8			

b. Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						(OR 3.1(95%CI 0.3 to 5.2), p<0.001			

Abbreviations:

AF: atrial fibrillation, APT: antiplatelet therapy, ASA: atrial septal aneurysm, ASD: Atrial septal defect, AVB: atrioventricular block, HR: hazard ratio, IAS: inter atrial shunt; ICE: intracardiac echocardiography, ICER: incremental cost effective ratio, IQR: interquartile range; ITT: intention to treat population, I²: measure of heterogeneity, K-M: Kaplan-Meier estimate, MTA: medical therapy alone, MTHFR: methylenetetrahydrofolate reductase gene mutation, OAC: oral anticoagulant medication, OR: odds ratio, PFO: patent foramen ovale, PSA: probabilistic sensitivity analysis, QALY: quality adjusted life year, QoL: quality of life, RCT: randomised controlled trial, RD: risk difference, TCD: transcranial Doppler scan, TEE: transoesophageal echocardiography, TIA: transient ischaemic attack; TTE: transthoracic echocardiography, TIMI: thrombolysis in myocardial infarction, WTP: willingness to pay, yrs: years

8 Grade of Evidence Tables

For abbreviations see list at the end of section 8.

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Recurrent Stroke	Shah et al 2018	8	Direct	A	<p>This outcome is the risk of a recurrent stroke during the study period (ranging from mean 3.2 yrs to median 5.9 yrs) for those people who had PFO closure compared to those who were treated with medication alone (MTA).</p> <p>Shah et al 2018 found that patients who had PFO closure had a 3.3% lower risk of recurrent stroke than those on medication alone [RD: -0.033 (95%CI: -0.062- to -0.004), p=0.037]. This was based on 25/1382 events /patients in the PFO closure group and 59/1149 events/patient in the MTA group.</p> <p>A similar reduction in risk was reported by De Rosa et al 2018 for PFO closure vs MTA: risk of ischaemic stroke 1.2% vs 4.1% (RD: -0.031(95%CI: -0.051 to -0.010), p=0.003, I²=61%).</p> <p>The meta-analysis by Piccolo et al 2018 of the same 4 RCTs as Shah et al 2018 (including the extended follow-up results of the RESPECT RCT) also reported a reduced risk of recurrent stroke in patients who had PFO closure (HR 0.14 (95% CI 0.04 to 0.55), p=0.005) up to 5 years follow up.</p> <p>The 3.3% reduction in risk for PFO vs MTA reported by Shah et al 2018 should be considered against the relatively low risk of stroke for patients on MTA (between 4.1% and 4.6%). The absolute benefit is not reported by the authors but reviewer analysis of the event rates indicate that compared to MTA, there might be 33 fewer strokes per 1000 patients who undergo PFO closure for cryptogenic stroke. This is the equivalent of an NNT of 30 PFO closures to prevent one stroke.</p> <p>These estimates should be treated with caution. There was significant heterogeneity among the four RCTs (different devices used, differences in medication, as well as variation in the baseline characteristics of subjects including existing risk factors for stroke (e.g. diabetes, hypertension, size of interatrial shunt, presence of an ASA). Two of the four RCTs (RESPECT extended, PC-TRIAL) did not individually show a statistically significant difference between treatment groups for risk of recurrent stroke.</p>
	De Rosa et al 2018	8	Direct		
	Piccolo et al 2018	8	Direct		
	Lee et al 2018	7	Direct		
TIA	Shah et al 2018	8	Direct	A	<p>This outcome is the risk of a TIA during the study period (ranging from mean 3.2 yrs to median 5.9 yrs) for those people who had PFO closure compared to those who were treated with MTA.</p> <p>The SRMA by Shah et al (2018) found that patients who had PFO closure were no more or less likely to have a TIA than those on medication alone [RD: -0.004 (95%CI: -0.017 to 0.010), p=0.46].</p> <p>A reduction in risk for TIA would be welcome to patients. Although transient, a TIA is sometimes associated with a non-transient stroke event soon after.</p> <p>This result should be treated with caution. The study results by Shah et al 2018 were amended in June 2018 but the results for TIA do not appear to have been amended to</p>
	Lee et al 2018	7	Direct		

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					reflect the corrected MTA population from the CLOSE trial. The impact of this on their estimate of reduction of risk is not clear although the authors confirm that the results are 'similar' ³¹ . In addition, there was significant heterogeneity among the four RCTs (different devices used, differences in medication, as well as variation in baseline characteristics of subjects including existing risk factors for stroke (e.g. diabetes, hypertension, PFO morphology and presence of an ASA).
Death	De Rosa et al 2018	8	Direct	B	<p>For the duration of the RCTs [up to mean follow up of 5.3 years (Mas et al 2017)], all-cause mortality (death) was recorded for all subjects regardless of cause.</p> <p>In their SRMA of RCTs, De Rosa et al 2018 found that there was no statistically significant difference between treatment groups for all-cause mortality (PFO 4 deaths/1382; MTA 0 deaths/1149; risk difference and p value were not reported).</p> <p>This is a very important outcome for patients but the reduction in the relatively low risk of stroke (4.1-4.6% risk of stroke on MTA) did not translate into reduced risk of death within the duration of the RCTs. After receiving a PFO device, no additional patients were alive who would not otherwise have been compared to medical therapy alone.</p> <p>The follow up period in the RCTs may have been too short (range mean of 2.6 to 5.3 years), and the incidence of death too low to be able to assess if the risk of all-cause mortality was significantly different in patients receiving PFO compared to MTA.</p>
Composite of Stroke or TIA	De Rosa et al 2018	8	Direct	B	<p>This outcome is the risk of either a stroke or a TIA event occurring during the study period (mean follow-up ranging from 2.6 to 5.3 yrs) for those people who had PFO closure compared to those who were treated with medication alone.</p> <p>The SRMA by De Rosa et al (2018) found that patients who had PFO closure were less likely to have a TIA or stroke than those on medication alone. PFO closure vs MTA: 3.6% vs 6.3% (RD: -0.029(95%CI: -0.050 to -0.007), p=0.008, I²=34%).</p> <p>A reduction in risk for TIA or stroke would be welcome to patients. Although transient, a TIA is sometimes associated with a non-transient stroke event soon after.</p> <p>There was heterogeneity among the four RCTs (different devices used, differences in medication, as well as variation in baseline characteristics of subjects including existing risk factors for stroke (e.g. diabetes, hypertension, size of interatrial shunt and presence of an ASA).</p>
Composite of stroke, vascular death or Thrombolysis in	Lee et al 2018	7	Direct	B	<p>This outcome is the K-M cumulative estimate of risk of either a stroke, vascular death or TIMI-defined major bleeding during the 2 year follow up for those people who had PFO closure compared to those who were treated with medication alone.</p>

³¹ In a private communication via the Annals of Internal Medicine, dated 30.07.2018 the authors state, "In the original paper, total event rates were 0.022 (31/1382) for the Device group and 0.033 (50/1510) for the MTA group. In the corrected version, total event rates are 0.022 (31/1382) for the Device group and 0.033(39/1149) for the MTA group. Although absolute numbers (both denominators and nominators) are different for the MTA groups, but event rates are similar. Therefore pooled estimates for the outcome of TIA are similar."

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Myocardial Infarction (TIMI)-defined major bleeding					<p>Lee et al 2018 reported that during the 2 year follow up period, patients were less likely to have a stroke, vascular death or TIMI-defined major bleeding than those on medication alone. PFO closure vs MTA: 0/60 vs 6/60 (12.9%), (95%CI 3.2 to 22.6; SE 5.0, p=0.013).</p> <p>A reduction in risk for stroke, vascular death or major bleeding is important outcome for patients.</p> <p>These results are based on one RCT only (n=120) and a short follow up period (2 years). The study was underpowered to detect this primary end point. The study was conducted in only 2 centres, both in South Korea which may have resulted in selection bias. This study did not recruit all patients with a cryptogenic stroke which was presumably due to PFO; rather, the population recruited was considered to have a <u>high risk</u> PFO³² confirmed by a TEE protocol to assess morphological features. These results may not be generalisable to a wider patient group.</p>
Serious Adverse Events	De Rosa et al 2018	8	Direct	B	<p>Serious adverse events are any untoward clinical event that results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, requires intervention to prevent permanent impairment or damage.</p> <p>During the follow up period of the 4 RCTs included in this SRMA (mean 2.6-5.3 yrs), there was no significant between group difference in SAE between PFO closure and MTA: 25% vs 24% (RD: -0.006(95%CI: -0.036 to -0.048), p=0.781).</p> <p>This indicates that PFO closure is not more harmful for SAEs compared to MTA, although the SAE rate is not insignificant for either the MTA or the PFO closure groups.</p> <p>The study duration was relatively short (mean 2.6 – 5.3 yrs). There was heterogeneity among the four RCTs for this outcome (different devices used, differences in medication, as well as variation in baseline characteristics of subjects including existing risk factors for stroke (e.g. diabetes, hypertension), PFO morphology and presence of an ASA).</p>
Major bleeding	Shah et al 2018 (based on 3 RCTs only)	8	Direct	A	<p>A major bleed includes bleeding which results in death, bleeding in a critical area or organ, or bleeding causing a fall in haemoglobin level, or leading to transfusion of whole blood or red cells.</p> <p>During the follow up period (mean 3.2 to median 5.9 yrs), the SRMA by Shah et al 2018 reported no difference in risk for major bleeding for PFO closure compared to</p>
	De Rosa et al 2018	8	Direct		
	Lee et al 2018	7	Direct		

³² A high-risk PFO was defined as a PFO with an atrial septal aneurysm (protrusion of the dilated segment of the septum at least 15 mm beyond the level surface of the atrial septum), hypermobility (phasic septal excursion into either atrium ≥ 10 mm), or PFO size (maximum separation of the septum primum from the secundum during the Valsalva manoeuvre) ≥ 2 mm on TEE.

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					<p>MTA (RD: -0.010 (95%CI: -0.037 to 0.016), p=0.24). This was consistent with the SRMA by De Rosa et al 2018 (PFO closure vs MTA: 0.9% vs 1.2% (RD: -0.002(95%CI: -0.012 to 0.007), p=0.605).</p> <p>The avoidance of major bleeding at any time is an important outcome for patients.</p> <p>De Rosa et al found relatively low heterogeneity among the four RCTs for this outcome (despite different devices used, differences in medication, as well as variation in baseline characteristics of subjects including existing risk factors for stroke (e.g. diabetes, hypertension, presence of an ASA).</p> <p>However, the low event rate and limited duration of the RCTs mean that it is not certain if over a longer duration, the difference in risk of bleeding associated with PFO closure might be considered statistically and clinically significant given the potential ongoing annual risk of bleeding associated with exposure to oral anticoagulant (OAC) and antiplatelet medication (APT) in the MTA group.</p>
Asymptomatic new ischaemic lesion	Lee et al 2018	7	Direct	B	<p>This outcome is the number of patients who were found to have a new ischaemic brain lesion following an MRI scan 6 months after either PFO closure or starting MTA, but who had experienced no symptoms.</p> <p>Lee et al 2018 reported that at 6 months follow up, patients who had received a PFO closure device were less likely to have an asymptomatic ischaemic lesion compared to those on medication alone. PFO closure vs MTA: 3/34 (8.8%) vs 7/38 (18.4%), p=0.024</p> <p>It is not clear from the study what proportion of asymptomatic lesions are likely to develop into a TIA or stroke. It is therefore not clear if this outcome is meaningful to patients.</p> <p>These results are based on one RCT only (n=120) and a short follow up period (2 years). The study was underpowered to detect the primary end point. The study was conducted in only 2 centres, both in South Korea which may have resulted in selection bias. This study did not recruit all patients with a cryptogenic stroke which was presumably due to PFO; rather, the population recruited was considered to have a high risk PFO confirmed by a TEE protocol to assess morphological features. These results may not be generalisable to a wider patient group.</p>
Non-fatal major procedural complications	Lee et al 2018	7	Direct	B	<p>At median duration of follow up of 2.8 years, major procedure related complications were observed in patients who had received an Amplatzer PFO Closure device.</p> <p>Lee et al 2018 reported that 2 out of 53 patients who had received the Amplatzer PFO Closure device had a major procedural complication ie: Pericardial effusion, n=1 Pseudo aneurysm, n=1</p>

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					<p>Procedure related adverse events are of importance to patients but if the event is peri-procedural and can be managed successfully prior to discharge without risking explanation of the device or requiring further intervention, then this may be acceptable, compared to the possibility of future stroke prevention.</p> <p>These results are based on one RCT only (n=120) and a short follow up period. Only 53 of the 60 patients randomised to have PFO closure had the procedure (7 declined). The study was underpowered to detect the primary end point. The study was conducted in only 2 centres, both in South Korea which may have resulted in selection bias. This study did not recruit all patients with a cryptogenic stroke which was presumably due to PFO; rather, the population recruited was considered to have a high risk PFO confirmed by a TEE protocol to assess morphological features. These results may not be generalisable to a wider patient group.</p>
New onset atrial fibrillation (AF) or Atrial flutter	Shah et al 2018	8	Direct	A	<p>New onset AF is a chaotic and irregular atrial arrhythmia that may occur following the introduction of the PFO closure device. AF is known to cause significant morbidity and mortality including palpitations, dyspnoea, angina, dizziness or syncope, and features of congestive heart failure, tachycardia-induced cardiomyopathy, stroke, and death.</p> <p>De Rosa et al (2018) reported a statistically significant increased incidence of new onset AF or atrial flutter for PFO closure compared with MTA: 4.4%³³ vs 1.0% (RD: 0.033 (95%CI: 0.012 to 0.054), p=0.002, I²=66%). Shah et al (2018) found an increased risk of new onset AF in the PFO group but considered the heterogeneity among the RCTs for new onset AF (I²=81.98%) to be too high to allow meta-analysis of the pooled results. These findings suggest that the evidence on the magnitude of the increased risk of AF associated with PFO closure is inconclusive.</p> <p>Given that AF is, by itself a known risk factor for stroke, whether or not it is an adverse effect associated with PFO closure device implantation, the rationale for which is to prevent recurrence of stroke, is of great importance to patients. It is also important whether the AF persists or is transient or managed effectively; however the studies did not provide these details.</p> <p>The two SRMAs are of similar quality. De Rosa et al (2018) includes the more complete RCT results of the initial RESPECT study (Carroll et al 2013) whereas Shah et al (2018) included RESPECT extended follow-up (Saver et al 2017) in which missing data and loss to follow-up were much higher (missing data: 13.2% vs 26.9% respectively). This may account for the higher estimate for heterogeneity in Shah et al (2018), although the authors' explanation for the heterogeneity is that it is most likely due to the different types of devices used across all the trials. It is not clear why the range of devices used did not therefore result in heterogeneity for other outcomes reported by Shah et al 2018. Given that even the lower estimate of I² for this outcome in De Rosa et al (2018) was 66% and may still represent substantial heterogeneity, these results should be treated with great caution.</p>
	De Rosa et al 2018	8	Direct		
	Lee et al 2018	7	Direct		

³³ reported by the authors as 4.1%, but corrected by reviewer after checking absolute number of events in the PFO closure group.

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Cost Effectiveness of Amplatzer device compared to MTA	Tirschwell et al 2018	8	Direct	B	<p>The cost effectiveness of PFO closure compared to MTA was based on the UK and NHS direct costs and clinical outcomes (both benefits and complications) of the Amplatzer PFO device and MTA regimes used in a UK subpopulation of the RESPECT RCT.</p> <p>Tirschwell et al 2018 reported that the estimated time for PFO closure to reach a cost effectiveness threshold of <£20,000 per QALY was 4.2 yrs (no CI reported)</p> <p>At 4 years post PFO closure procedure, the findings for PFO with Amplatzer compared with MTA were:</p> <ul style="list-style-type: none"> • Incremental cost per patient: +£6071 (no CI reported) • Incremental QALYS: 0.29 • ICER: £20,951 <p>At 10 years post PFO closure procedure, the findings for PFO with Amplatzer compared with MTA were:</p> <ul style="list-style-type: none"> • Incremental cost per patient: +£4858 (no CI reported) • Incremental QALYS: 0.71 • ICER: £6887 <p>89% of probabilistic sensitivity analysis (PSA) iterations were cost effective</p> <p>At 20 years post PFO closure procedure, the findings for PFO with Amplatzer compared with MTA were:</p> <ul style="list-style-type: none"> • Incremental cost per patient: £2848 (no CI reported) • Incremental QALYS: 1.32 • ICER: £2158 <p>Cost effectiveness may not be a priority to individual patients; it is an important outcome for decision makers. It reflects the incremental clinical effectiveness of PFO closure compared to MTA as well as the acquisition cost of the device and related procedure.</p> <p>The cost effectiveness outcomes modelled in this study should be treated with some degree of caution. It reflects the results from a UK sub-population recruited to the extended RESPECT RCT (Saver et al 2017). The sub-population is not clearly defined. The authors state that anatomical features of the PFO were considered but the criteria for PFO closure is not explicit, and it may have been open to local interpretation. The baseline characteristics for the UK sub-population are not clear, so there might be pre-treatment differences between the PFO closure and MTA treatment arms. No confidence intervals were reported. However, the costs are all recent UK and NHS based which means that as the ICER estimates are well below the NICE threshold of £20,000 over a lifetime, it is highly likely that the results are reliable and generalisable as long as the patient selection criteria are identical to that used in this UK subpopulation. In addition, indirect costs were not included. This means that the cost effectiveness estimates did not take into account the non-NHS costs of stroke</p>

a. Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					care (social care, personal productivity such as employment etc). Inclusion of these wider costs might reduce the ICER estimate further (i.e. improve cost-effectiveness).

b. Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Immediate procedural success within 30 days	Rigatelli et al 2017	8	Indirect	C	<p>Immediate procedural success was defined as the device remaining in situ and effectively closing the PFO within the first 30 days after the percutaneous procedure.</p> <p>99.8% devices and device procedures were successful (998 patients of the 1000 consecutive subjects). The device was intraprocedurally removed in 2/1000 patients. The reasons were not explained.</p> <p>The procedural complication rate within 30 days of implantation is low. This is of modest importance given that the endpoint outcome of interest is prevention of recurrent stroke.</p> <p>This outcome is based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012. It is not clear what proportion of subjects had cryptogenic stroke: a high proportion had known risk factors for stroke (eg diabetes, hypertension, smoking). There was heterogeneity among subjects (eg PFO size, presence of ASA), PFO devices and concomitant medication.</p>
	Rigatelli et al 2016	8	Indirect		
Complications within 30 days	Rigatelli et al 2017 Rigatelli et al 2016	8	Indirect	C	<p>Electrical complications and non-electrical complications that occurred within 30 days of PFO device implant were reported.</p> <p>59 (5.9%) of the 1000 PFO closure device recipients experienced electrical complications (Rigatelli et al 2017) comprising</p> <ul style="list-style-type: none"> • Temporaneous AF: 46 (4.6%) all resolved within procedure • Permanent AF: 1 (0.1%) • Temporaneous AVB I or II grade: 3 (0.3%) all resolved within procedure • Permanent AVB I or II grade: 3(0.3%) • Temporaneous or permanent AVB III: 0 • Supraventricular arrhythmias: 6 (0.6%). 4 required pharmacological cardioversion. <p>26/1000 (2.6%) experienced non-electrical complications (Rigatelli et al 2016):</p> <ul style="list-style-type: none"> • device embolization: 2(0.2%) • sheath or device entrapment: 3(0.3%)

b. Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					<ul style="list-style-type: none"> • groin haematomas:10(1.0) • pericardial effusion: 3(0.3%) • air embolism: 4(0.4%) • death:0(0) <p>Complications due to the PFO closure device or procedure, particularly those which are not temporary, are important factors for patients to consider especially given that the PFO closure treatment is a preventative strategy rather than a treatment for a symptomatic condition.</p> <p>These complication rates should be treated with caution. They are based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012. It is not clear what proportion of subjects had cryptogenic stroke: a high proportion had known risk factors for stroke (e.g. diabetes, hypertension, smoking). There was heterogeneity among subjects (e.g. PFO size, presence of ASA), PFO devices and concomitant medication.</p>
Predictors of complications within 30 days	Rigatelli et al 2017 Rigatelli et al 2016	8	Indirect	C	<p>Analysis of the characteristics of patients who experienced complications following PFO closure implantation was reported.</p> <p>Females were more than twice as likely to experience complications within 30 days of PFO closure: electrophysiological complications: OR 2.3 (95%CI 0.5 to 5.1), p<0.001(Rigatelli et al 2017) Non-electrical complications: OR 2.1 (95%CI 0.5 to 4.6), p<0.001 (Rigatelli et al 2016)</p> <p>People who required a PFO device disk larger than 30mm were 4-5 times more likely to experience complications within 30 days electrophysiological complications: OR 5.0 (95%CI 1.2 to 7.2), p<0.001 (Rigatelli et al 2017) Non-electrical complications: OR 4.0 (95%CI 0.8 to 6.1), p<0.001 (Rigatelli et al 2016)</p> <p>Female patients and patients who require a larger PFO closure device would wish to know the absolute risk to which they are exposed, rather than the overall risk to a wider population. Complications due to the PFO closure device or procedure, particularly those which are not temporary, are important factors for patients to consider especially given that the PFO closure treatment is intended as a preventative strategy rather than a treatment for a symptomatic condition.</p> <p>These predictors of complications should be treated with caution. They are based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012. It is not clear what proportion of subjects had cryptogenic stroke: a high proportion had known risk factors for stroke (eg diabetes, hypertension, smoking).</p>

b. Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					There was heterogeneity among subjects (eg PFO size, presence of ASA), PFO devices and concomitant medication.
Complication rate at median 10.5 yr f/up	Rigatelli et al 2017 Rigatelli et al 2016	8	Indirect	C	<p>Longer term electrical complications and non-electrical complications that had occurred at the median follow up time of 10.5 years after PFO closure device implant were reported.</p> <p>14/1000 (1.4%) of the 1000 PFO closure device recipients experienced electrical complications (Rigatelli et al 2017) comprising</p> <ul style="list-style-type: none"> • permanent AF: 5 (0.5%) • paroxysmal AF: 4 (0.4%) • complete AVBIII: 1 (0.1%) • supraventricular arrhythmias: 4 (0.4%) <p>22/1000 (2.2%) experienced non-electrical complications (Rigatelli et al 2016):</p> <ul style="list-style-type: none"> • device thrombosis: 5(0.5%) • erosion: 0(0) • mitral valve regurgitation: 2(0.2) • recurrent stroke (minor/major): 6/2(0.8) • device embolization/removal: 1(0.1%) • device fracture: 0(0) • cardiac related death: 1(0.1%) • non-cardiac related death: 13 (1.3%) (11 neoplastic related, 2 car accident related) <p>Complications due to the PFO closure device or procedure, particularly those which are not temporary, are important factors for patients to consider especially given that the PFO closure treatment is a preventative strategy rather than a treatment for a symptomatic condition.</p> <p>These complication rates should be treated with caution. They are based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012. It is not clear what proportion of subjects had cryptogenic stroke: a high proportion had known risk factors for stroke (e.g. diabetes, hypertension, smoking). There was heterogeneity among subjects (including PFO size, presence of ASA), PFO devices and concomitant medication.</p>
Predictors of complications at median 10.5 yr f/up	Rigatelli et al 2017 Rigatelli et al 2016	8	Indirect	C	<p>Analysis of the characteristics of patients who experienced complications following PFO closure implantation was reported.</p> <p>Patients with a large (3-5 grade) ASA as well as PFO were 2 to 3 times more likely to experience complications in the longer term:</p> <ul style="list-style-type: none"> • electrophysiological complications: HR 2.2 (95%CI 0.4 to 3.9), p<0.001 (Rigatelli et al 2017) • Non-electrical complications: OR 2.9 (95%CI 0.4 to 4.3), p<0.001 (Rigatelli et al 2016)

b. Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
					<p>Patients for whom the mean ratio between device size and entire septum length was >0.8 were 2 to 3 times more likely to experience complications:</p> <ul style="list-style-type: none"> • electrophysiological complications: HR 2.61(95%CI 0.3 to 4.1), p<0.001 (Rigatelli et al 2017) • Non-electrical complications: OR 3.1(95%CI 0.3 to 5.2), p<0.001 (Rigatelli et al 2016) <p>Patients with a large ASA as well as a PFO, as well as those who require a large PFO closure device relative to the length of their septum, would wish to know the absolute risk to which they are exposed, rather than the overall risk to a wider population. Complications due to the PFO closure device or procedure, particularly those which are not temporary, are important factors for patients to consider especially given that the PFO closure treatment is intended as a preventative strategy rather than a treatment for a symptomatic condition.</p> <p>These predictors of complications should be treated with caution. They are based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012. It is not clear what proportion of subjects had cryptogenic stroke: a high proportion had known risk factors for stroke (e.g. diabetes, hypertension, smoking). There was heterogeneity among subjects (including PFO size, presence of ASA), PFO devices and concomitant medication.</p>
Procedure related outcomes	Rigatelli et al 2016	8	Indirect	C	<p>A number of procedural related outcomes were reported. This included the time that it took for the percutaneous PFO closure procedure, the continuous medical imaging time required to implant the PFO device (fluoroscopy time) and the total dose area product which is a measure of radiation risk (defined as the absorbed dose multiplied by the area irradiated, expressed in gray-centimetres squared (Gy-cm²).</p> <p>Procedure time: 36.5+/-6.1 minutes Fluoroscopy time: 7.3+/-4.7 minutes Total dose area product: 26.7+/-1.88 Gy-cm²</p> <p>It is not clear what the significance of these outcomes are to patients, although the procedure time and exposure to radiation contribute to both the overall procedure costs and potential safety outcomes.</p> <p>These results are based on one uncontrolled study, the procedure and duration and dose of radiation exposure may vary depending on provider, device used and experience of the interventional cardiologist, patients with PFO who are treated with medical therapy would not be exposed to the PFO device implant procedure or the radiation associated with the procedure.</p>

Abbreviations:

AF: atrial fibrillation, ASA: atrial septal aneurysm, AVB: atrioventricular block, f/up: follow up, CI: confidence interval, HR: hazard ratio, ICER: incremental cost effectiveness ratio, I²: measure of heterogeneity, K-M: Kaplan-Meier estimate, MTA: medical therapy alone, OR: odds ratio, PFO:

patent foramen ovale, PSA: probabilistic sensitivity analyses, QALY: quality adjusted life year, RCT: randomised controlled trial, RD = risk difference, TEE: transoesophageal echocardiography, SRMA: systematic review and meta-analysis, TIA: transient ischaemic attack; TIMI: thrombolysis in myocardial infarction, yrs: years

9 Literature Search Terms

Search strategy Indicate all terms used in the search	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Adults who have sustained a cryptogenic ischaemic stroke (of presumed embolic origin) and a patent foramen ovale with demonstrable right to left shunt with or without atrial septal aneurysm
I – Intervention Which intervention, treatment or approach should be used?	Transcatheter PFO closure and short term dual antiplatelet therapy
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Antiplatelet or anti-coagulant therapy
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	<u>Any including:</u> <u>Critical to decision-making:</u> Recurrent stroke Disability Death <u>Important to decision-making:</u> Short and longer term adverse treatment effects (including incidence of atrial fibrillation, atrial arrhythmia) Bleeding risks Cost effectiveness
Assumptions / limits applied to search	
<i>Inclusion and exclusion criteria e.g. study design, date limits, patients, intervention, language, setting, country etc.</i> <i>Include: Peer reviewed studies published in the last 10 years, English language only</i> <i>Exclude: conference papers, posters, abstracts, letters, unpublished literature</i>	

10 Search Strategy

We searched PubMed, Embase and Cochrane Library limiting the search to papers published in English language in the last 10 years. We excluded conference abstracts, commentaries, letters, editorials and case reports. In addition, we were advised by email communication from NHS England received on 10th January 2018 of two more recent publications (systematic reviews and meta-analyses of RCTs) published on 9th January 2018. These were included in the abstracts for selection.

This search was re-run following request by NHS England to update this evidence review due to the subsequent publication of a new and relevant cost-effectiveness study.

Search date: 5th January 2018, updated 15th May 2018.

Embase

1 patent foramen ovale/
2 (patent foramen ovale or persistent foramen ovale or pfo).ti,ab.
3 1 or 2
4 ((percutaneous* or transcatheter* or trans-catheter*) adj5 (clos* or repair*)).ti,ab.
5 ((percutaneous* or transcatheter* or trans-catheter*) adj5 (device* or implant*)).ti,ab.
6 ((occluder or occlusion) adj5 (device* or implant*)).ti,ab.
7 clos*.ti.
8 4 or 5 or 6 or 7
9 3 and 8
10 patent foramen ovale/su [Surgery]
11 ((patent foramen ovale or persistent foramen ovale or pfo) adj5 clos*).ti,ab.
12 9 or 10 or 11
13 limit 12 to (english language and "reviews (maximizes specificity)" and yr="2008 -Current")
14 conference*.pt.
15 13 not 14
16 cerebrovascular accident/
17 stoke*.ti,ab.
18 ((cerebrovascular or cerebral or neurolog* or brain) adj5 (event* or mortality or death*)).ti,ab.
19 16 or 17 or 18
20 12 and 19
21 limit 20 to (english language and yr="2008 -Current")
22 conference*.pt.
23 21 not 22
24 15 or 23

11 Evidence Selection

- Total number of publications reviewed: 217
- Total number of publications considered potentially relevant: 31
- Total number of publications selected for inclusion in this briefing: 7

12 References

American Heart Association.

http://www.heart.org/HEARTORG/Conditions/CongenitalHeartDefects/AboutCongenitalHeartDefects/Atrial-Septal-Defect-ASD_UCM_307021_Article.jsp#.WoWDCmacY_M. accessed 16 February 2018

Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med*. 2013 Mar 21;368(12):1092-100.

De Rosa S, Sievert H, Sabatino J, Polimeni A, Sorrentino S, Indolfi C. Percutaneous Closure Versus Medical Treatment in Stroke Patients With Patent Foramen Ovale: A Systematic Review and Meta-analysis. *Ann Intern Med*. doi:10.7326/M17-3033

Finsterer J. 2010. Management of cryptogenic stroke. *Acta Neurol Belg*. 2010 Jun;110(2):135-47. <https://www.ncbi.nlm.nih.gov/pubmed/20873443> accessed 19 February 2018

FDA. https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120021d.pdf accessed 20 February 2018

Furlan A, Reisman M, Massaro J, Mauri L, Adams H, Albers G, Felberg R, M.D., Howard Herrmann H, Kar S, Landzberg M, Raizner A, Wechsler L. Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale. *N Engl J Med* 2012; 366:991-999 DOI: 10.1056/NEJMoa1009639

Lee PH, Song JK, Kim JS, Heo R, Lee S, Kim DH, et al. Cryptogenic Stroke and High-Risk Patent Foramen Ovale: The DEFENSE-PFO Trial. *J Am Coll Cardiol*. 2018 Feb 28.

Linxin Li, Gabriel S Yiin, Olivia C Geraghty, Ursula G Schulz, Wilhelm Kuker, Ziyah Mehta, Peter M Rothwell. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol* 2015; 14: 903–13

Mas JL, Derumeaux G, Amarenco P, Arquizan C, Aubry P, Barthelet M, et al. Close: Closure of patent foramen ovale, oral anticoagulants or antiplatelet therapy to prevent stroke recurrence: Study design. *Int J Stroke*. 2016 Aug;11(6):724-32.

Mehran R, Sunil V. Rao SV et al. Standardized Bleeding Definitions for Cardiovascular Clinical Trials *Circulation*. 2011;123:2736-2747. <https://doi.org/10.1161/CIRCULATIONAHA.110.009449> accessed online 23.07.2018

Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med*. 2013 Mar 21;368(12):1083-91.

NICE Interventional Procedure Guidance 472. Percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events. NICE 2013. www.nice.org.uk/guidance/ipg472. Accessed 10 January 2018.

Piccolo R, Franzone A, Siontis GCM, Stortecky S, Pilgrim T, Meier B, et al. Patent foramen ovale closure vs. medical therapy for recurrent stroke prevention: Evolution of treatment effect during follow-up. *Int J Cardiol*. 2018 Mar 15;255:29-31.

Pickett CA, Villines TC, Ferguson MA, Hulten EA. Cost effectiveness of percutaneous closure versus medical therapy for cryptogenic stroke in patients with a patent foramen ovale. *Am J Cardiol* 2014 Nov 15;114(10):1584-9.

Rigatelli G, Zuin M, Pedon L, Zecchel R, Dell'Avvocata F, Carrozza A, et al. Clinically apparent long-term electric disturbances in the acute and very long-term of patent foramen ovale device-based closure. *Cardiovasc Revasc Med*. 2017 Mar;18(2):118-22.

Rigatelli G, Pedon L, Zecchel R, Dell'Avvocata F, Carrozza A, Zennaro M, et al. Long-Term Outcomes and Complications of Intracardiac Echocardiography-Assisted Patent Foramen Ovale Closure in 1,000 Consecutive Patients. *J Interv Cardiol*. 2016 Oct;29(5):530-8.

Saver J, Carroll J, Thaler D, Smalling R, Macdonald L, Marks D, et al. Long term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med*. [serial on the Internet]. 2017; 377(11): Available from:

<http://onlinelibrary.wiley.com/doi/10.1002/ane.1466>

Saver JL. CLINICAL PRACTICE: Cryptogenic Stroke. *N Engl J Med*. 2016 May 26;374(21):2065-74. doi: 10.1056/NEJMc1503946.

Shah R, Nayya M, Jovin I, Rashid A, Bondy B, Fan T-H, Flaherty M, Sunil V, Rao S. Device Closure Versus Medical Therapy Alone for Patent Foramen Ovale in Patients With Cryptogenic Stroke: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2018;168(5):335-342. Commentary posted on 25.06.2018

Sondergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, et al. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. *N Engl J Med*. 2017 Sep 14;377(11):1033-42.

Stroke Association. State of the nation: Stroke statistics February 2018. https://www.stroke.org.uk/system/files/sotn_2018.pdf accessed 19th February 2018

Stroke Association. State of the nation: Stroke statistics January 2017. https://www.stroke.org.uk/sites/default/files/state_of_the_nation_2017_final_1.pdf. accessed 20th February 2018

Tirschwell DL, Turner M, Thaler D, Choulerton J, Marks D, Carroll J, et al. Cost-effectiveness of percutaneous patent foramen ovale closure as secondary stroke prevention. *J Med Econ*. 2018 Apr 13:1-10.

Von Klemperer K, Kempny A, Pavitt CW, Janssen JC, Uebing A, Nicol E. Device closure for patent foramen ovale following cryptogenic stroke: a survey of current practice in the UK. *Open Heart*. 2017;4(2):e000636.