Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Advice
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In response to enquiry from the West of Scotland Regional Planning Team

Patent foramen ovale (PFO) closure in patients with cryptogenic ischaemic stroke

Advice for NHSScotland

Percutaneous patent foramen ovale (PFO) closure plus antiplatelet therapy should be considered in carefully selected patients with a diagnosis of cryptogenic ischaemic stroke.

The evidence for PFO closure comes from randomised controlled trials (RCTs) in patients aged 60 or younger, patients considered for this intervention should fall within this age limit. Patients should also have their diagnosis of cryptogenic ischaemic stroke supported by imaging and have a confirmed PFO.

Prior to PFO closure, patients must have had a full investigation to rule out other explanations for ischaemic stroke, and based on these investigations a multi-disciplinary team should agree that paradoxical embolism is the most likely explanation for the stroke.

In exploring patient preferences, the potential benefits and risks of the PFO closure procedure compared with medical therapies alone should be highlighted, including the risk of developing persistent atrial fibrillation or flutter.

PFO closure plus antiplatelet therapy is unlikely to be cost-effective in the short-term (up to 10 years) but becomes cost effective over the lifetime of the patient, with an incremental cost effectiveness ratio (ICER) under £10,000.

PFO closure procedures should be consolidated within a small number of centres with a unified referral pathway to ensure equity of access for eligible patients. Centres offering PFO closure must have on-site access to appropriate facilities and expertise for percutaneous cardiac procedures and transoesophageal echocardiography.

NHSScotland is required to consider the Scottish Health Technologies Group (SHTG) advice.

What were we asked to look at?

The West of Scotland Regional Planning Team asked us to look at the evidence surrounding percutaneous patent foramen ovale (PFO) closure compared with medical therapy alone in patients with cryptogenic ischaemic stroke.

Why is this important?

In 2018, there were 8,388 admissions to hospital for ischaemic stroke in Scotland, and up to one-third of ischaemic strokes are classed as cryptogenic ('of unknown origin'). Currently, the most common treatment for patients who have a cryptogenic ischaemic stroke is long-term medical therapy. Patients who have a cryptogenic ischaemic stroke are typically younger (60 or under) and have fewer comorbidities compared with patients diagnosed with other stroke sub-types. Long-term medical therapy and risk of ischaemic stroke recurrence can place a significant burden on patients and the health service.

Studies suggest there is a potential association between cryptogenic ischaemic stroke and the presence of a PFO. Closing this PFO may provide a way of reducing lifetime risk of ischaemic stroke recurrence in patients with cryptogenic ischaemic stroke. Therefore, percutaneous closure of the PFO using an implantable medical device, alongside medical therapy, is an option in this patient group. Although this procedure has been available for a number of years, three trials published in 2017 and 2018 may help to establish the relative effects of PFO closure.

What was our approach?

We produced SHTG Advice based on published evidence on the clinical effectiveness, cost effectiveness and safety of patent foramen ovale (PFO) closure in patients with cryptogenic ischaemic stroke. We also reviewed the literature for evidence relating to patient and social aspects, and the relationship between procedure volume and outcomes. Information on our SHTG Advice product can be found here.

What next?

The West of Scotland Regional Planning Team will use the SHTG Advice as part of their review of cardiology services. NHS National Services Scotland will also consider this Advice as part of their subsequent national planning or commissioning decisions.

Key points from the evidence review

- The evidence on patent foramen ovale (PFO) closure plus antiplatelet therapy in patients with cryptogenic ischaemic stroke comes from six randomised controlled trials (RCTs) conducted in patients aged 60 years or under.
- A network meta-analysis* (NMA) compared percutaneous PFO closure plus antiplatelet therapy with antiplatelet therapy and with anticoagulant therapy. Data were drawn from six RCTs (n=3,560) comparing PFO closure plus antiplatelet therapy with medical therapy alone, and two RCTs (n=247) comparing antiplatelet therapy with anticoagulant therapy, with median follow-up of 3.9 years. Data for comparisons with oral anticoagulants were limited.
    - Compared with antiplatelet therapy alone, PFO closure plus antiplatelet therapy reduced the risk of recurrent ischaemic stroke (odds ratio (OR) 0.12, 95% credible interval (CrI) 0.04 to 0.27), had no evident effect on mortality (OR 3.28, 95% CrI 0.20 to 174.22) and no evident effect on risk of major bleeding (OR 0.48, 95% CrI 0.20 to 1.12).
    - Compared with anticoagulant therapy alone, PFO closure plus antiplatelet therapy had no evident effect on the risk of recurrent ischaemic stroke (OR 0.44, 95% CrI 0.08 to 3.83) or mortality (OR 0.69, 95% CrI 0.02 to 32.36) but reduced the risk of major bleeding (OR 0.26, 95% CrI 0.07 to 0.82).
- Compared with medical therapy (antiplatelet or anticoagulant therapy) PFO closure plus antiplatelet therapy significantly increased the risk of developing persistent atrial fibrillation or flutter: relative risk (RR) 4.84 (95% confidence interval (CI) 1.91 to 12.26), absolute difference 18 more patients per 1,000 treated.
- Device- and procedure-related complication rates in RCTs comparing PFO closure with medical therapy ranged from 1.5% to 5.9%. The most common adverse events were vascular complications (1.0%), conduction abnormalities (1.0%), device dislocation (0.7%), and device thrombosis (0.5%). Rare but serious adverse events included air embolism (0.4%), cardiac tamponade (0.3%) and cardiac perforation (0.2%).
- The NHS England Commissioning through Evaluation (CtE) programme collected real-world data on percutaneous PFO closure in a single-arm, multicentre registry (n=940). After adjusting for reporting errors, 1.7% of patients in the registry experienced a neurological event. In-hospital major complications (including one death, three neurological events and one myocardial infarction) were reported for 1.0% of patients and minor in-hospital complications were experienced by 2.6% of patients in the registry.

* **Network meta-analysis**: a technique for comparing three or more interventions simultaneously in a single analysis by combining direct and indirect evidence across a network of studies

- Four studies evaluated psychological and quality of life outcomes associated with PFO closure. Studies comparing outcomes for patients who had the PFO procedure with those who had not, found that health-related quality of life was better in the PFO group. The CtE programme in England issued EQ-5D-5L questionnaires to patients at baseline and up to six months follow-up. A marginal improvement in quality of life was demonstrated, with the greatest benefit reported within the anxiety/depression domain of the questionnaire.
- Evidence on the relationship between hospital procedure volume and patient outcomes for PFO closure was limited to one US database cohort study that included data on both percutaneous closure of atrial septal defect (ASD) and PFO closure. An increase in hospital procedure volume was associated with a decrease in odds of the primary outcome (complications and mortality), length of hospital stay and cost of hospitalisation. The study was based on data from 2001 to 2010.
- The NHS England CtE report estimated an overall incremental cost of £5,360 per patient treated with PFO plus antiplatelets compared with medical therapy alone. Published cost-utility studies presented estimated incremental cost effectiveness ratios (ICERs) of £20,951 and £18,584 per quality adjusted life year (QALY) at four years for PFO closure compared with medical therapy. A key uncertainty in published studies is the assumption of a procedure-related utility gain that applies across the lifetime of the model for stable patients. When smaller, short-term utility gains are applied, the ICER increases considerably at four years but is likely to remain cost-effective over the lifetime of the model (20 years).

SHTG Committee considerations

- Over the last 5 years 148 percutaneous PFO closure procedures have been carried out in Scotland, the majority (91.2%) at a single centre. A rough future estimate of 200 to 315 percutaneous PFO closure procedures per year was generated from ISD data and published population studies. The Committee note that this was likely to be a generous estimate.
- Clinical experts indicated to the Committee that historically treatment for cryptogenic ischaemic stroke has involved antiplatelet therapy. Recently there has been a move towards increased use of anticoagulant therapy in this patient group since direct oral anticoagulants offer additional treatment options. The Committee considered this during their deliberations and asked for a brief summary of secondary evidence on effectiveness of oral anticoagulation versus antiplatelet therapy in patients with cryptogenic stroke and a PFO to be added to the SHTG Advice (page 13).
- The importance of selecting patients for PFO closure based on patient characteristics, thorough diagnostic testing, and multidisciplinary team case review was discussed. The Committee highlighted the need for a clear referral pathway and providing PFO closure at a limited number of expert centres in order to optimise outcomes.

- Having a clear understanding and agreement on the suite of diagnostic tests required to rule out known causes or risk factors for ischaemic stroke, and therefore to define cryptogenic ischaemic stroke, was acknowledged as important.
- The Committee discussed the consequences of patients developing persistent atrial fibrillation after PFO closure and the impact this could have on future ischaemic stroke risk. It was also noted that patients may need to take antiplatelets or anticoagulants for a prolonged period after PFO closure, due to the relatively young age of this population.
- The Committee accepted that, despite some uncertainty surrounding the appropriateness of inputs to the published economic models, the long-term cost effectiveness of the PFO closure procedure had been demonstrated.

Contents

Definitions

Atherosclerosis: a potentially serious condition in which fatty substances, called plaques or atheroma, accumulate in arteries causing them to narrow and become blocked[1].

95% credible interval: the treatment effect of interest has a 95% probability of lying within the interval.

Network meta-analysis: a technique for comparing three or more interventions simultaneously in a single analysis by combining direct and indirect evidence across a network of studies[2].

Paradoxical embolism: when a blood clot passes from the right side of the heart to the left side through a patent foramen ovale. These clots can enter the systemic arterial circulation without having passed through the pulmonary circulation where they may otherwise have been filtered out[3].

Patent foramen ovale: a small, flap-like hole in the heart that did not close the way it should after birth[4].

Literature search

A 2019 health technology assessment (HTA) published by the Norwegian Institute of Public Health (NIPH) was identified in the initial scoping search for this topic in May 2019[5]. The NIPH HTA forms the basis of this SHTG Advice on patent foramen ovale (PFO) closure in patients with cryptogenic ischaemic stroke.

To supplement the Norwegian HTA, the primary literature was systematically searched between 22 and 24 July 2019 using the following databases: Medline, Embase, Cinahl, Web of Science and PsycINFO. Results were limited to English language and studies published in the past ten years (2009-2019). Search filters were applied to identify literature on the following: cost effectiveness, volume and outcome, patient issues. Details of the search filters used are available on request.

Concepts used in all searches included: cryptogenic stroke, patent foramen ovale, transcatheter closure. A full list of resources searched and terms used are available on request.

Research question

What is the clinical effectiveness, cost effectiveness and safety of transcatheter patent foramen ovale (PFO) closure compared with antiplatelet and/or anticoagulant therapy in patients with cryptogenic ischaemic stroke?

Introduction

In 2018 there were 8,388 admissions to hospital for ischaemic stroke in Scotland[6]. When the source of the thromboembolism that causes an ischaemic stroke cannot be identified, the stroke is classed as cryptogenic ('of unknown origin')[7]. The point at which an ischaemic stroke should be considered cryptogenic varies and has not been universally agreed. In Scotland, patients would be deemed to have had a cryptogenic ischaemic stroke if they have had a computed tomography (CT) or magnetic resonance imaging (MRI) brain scan to rule out haemorrhagic stroke and detect ischaemic lesions, and have undergone extensive testing to rule out other known stroke aetiologies. Extensive testing may include echocardiography or electrocardiography to detect sources of cardiac embolism, extended heart rhythm monitoring for atrial fibrillation, duplex ultrasound to exclude large artery atheroma, CT or MRI imaging to rule out small vessel disease, and blood tests to eliminate rare causes of stroke. In some cases a CT or magnetic resonance (MR) angiogram of the large arteries and extracranial arteries may be performed to exclude aortic arch atheroma, and atheroma at sites other than the carotid bifurcation (Prof. M Dennis, Professor of Stroke Medicine, University of Edinburgh. Personal communication, 16 Aug 2019).

A number of observational studies have suggested an association between cryptogenic ischaemic stroke and the presence of a patent foramen ovale (PFO)[8]. All human fetuses have a foramen ovale – a hole between the right and left atria of the heart – that allows fetal blood to bypass the lungs *in utero*[9]. When a baby takes its first breath after birth the foramen ovale closes and is permanently sealed within a few months of birth in 75% of people. For 25% of people the foramen ovale remains open (patent). This is not a problem for most people, but in a small proportion a blood clot can pass through the PFO and enter the systemic arterial circulation instead of being filtered out by tiny capillaries in the lungs as blood passes through the pulmonary arterial circulation. This 'paradoxical embolism' is thought to be one of the causes of cryptogenic ischaemic stroke, when a blood clot that passes through the PFO blocks an artery in the brain[5].

Traditional risk factors for stroke, such as hypertension or diabetes, are less likely to be present in patients presenting with cryptogenic ischaemic stroke, while these patients are more likely to have a PFO than patients with stroke of known aetiology[3]. Cryptogenic ischaemic strokes also tend to be more common among younger adults (≤60 years) compared with other stroke sub-types[5]. In older patients who present with known stroke risk factors, clinicians may conclude the PFO is an incidental finding rather than the primary source of a thromboembolism (Prof. M Dennis, Professor of Stroke Medicine, University of Edinburgh. Personal communication, 16 Aug 2019).

Currently, the most common treatment for patients in Scotland who have a cryptogenic ischaemic stroke is long-term antiplatelet therapy[5]. Now that direct oral anticoagulants are available, a proportion of patients may be offered anticoagulant therapy instead. A potential addition to medical therapy in the cryptogenic ischaemic stroke population is percutaneous closure of the PFO using an implantable medical device.

Health technology description

Percutaneous PFO closure is performed under local anaesthesia plus sedation or general anaesthesia, depending on the patient and cardiologist[10, 11]. Echocardiography is used to guide the procedure and can also be used to assess the size of device needed. Using a catheter, guide wire and delivery sheath, the PFO closure device is inserted into the femoral vein in the groin, passed into the heart and through the PFO. Once in place, straddling the PFO, the device is released to become a permanent implant that closes the defect. In the Commissioning through Evaluation (CtE) programme in England, PFO closure procedures used the AMPLATZER® PFO Occluder, Septal Occluder or Cribriform (54.5%), the CARDIOFORM Septal Occluder (30.1%), the Figulla Flex range (13.1%), or other/combination of these devices (2.3%)[10].

The AMPLATZER® PFO Occluder (Abbott) comprises two expandable discs made of a metal alloy and polyester mesh[11]. The two discs are held together by a 'waist' that will hold the discs at each side of the PFO after implantation. The CARDIOFORM Septal Occluder (GORE®) is similar in appearance, with two discs made of metal alloy covered in a thin layer of Gore-Tex®[11]. Over time the patient's tissues will grow around and into the device.

Approximate costs for a PFO closure device in NHSScotland, based on the AMPLATZER® PFO Occluder, are £3,295 for the device and £235 for the delivery system, plus VAT (Dr D Northridge, Consultant Cardiologist, Royal Infirmary of Edinburgh. Personal communication, 20 Aug 2019).

Epidemiology

Patent foramen ovale (PFO)

An estimated 1 in 4 adults have a patent foramen ovale[9], with no reported sex predominance in incidence[12, 13]. Large epidemiological studies have suggested potential race- and ethnicity-related differences in incidence[12].

The true prevalence of PFO in adult ischaemic stroke patients is uncertain, with estimates ranging from 36% to 54%[13]. In adults who have a cryptogenic ischaemic stroke, the estimated prevalence of PFO is 40% to 50%, which is higher than in people of the same age who have not had a stroke[5, 9, 13].

Cryptogenic ischaemic stroke

Approximately 80% of strokes in the UK are ischaemic[10] and up to one-third of these ischaemic strokes are classed as cryptogenic[5]. Cryptogenic ischaemic strokes typically occur in a younger population (≤60 years), with fewer comorbidities, compared with other stroke sub-types[10, 14]. Also, the odds of having a cryptogenic ischaemic stroke are higher in men compared with women: odds ratio (OR) 1.50, 95% confidence interval (CI) 1.08 to 2.08, p=0.015[7].

In a large population-based cohort study in Oxfordshire (OXVASC), consecutive patients with a first transient ischaemic attack (TIA) or ischaemic stroke were followed up for a period of 10 years[14]. Of 2,555 patients with a first ischaemic event, 32% were classed as cryptogenic. Incidence of cryptogenic ischaemic stroke in the OXVASC cohort was 0.36 per 1,000 population per year (95% CI 0.23 to 0.49). Among patients aged <55 years, cryptogenic events accounted for 48% of all ischaemic events. Patients with cryptogenic ischaemic events had the lowest prevalence of risk factors for atherosclerosis, including hypertension, diabetes, hypercholesterolaemia, and history of smoking, compared with patients who had an ischaemic event of known aetiology.

Scottish estimates

In the last 5 years, the total number of percutaneous PFO closure procedures in Scotland was 148. Of these, 85 were in patients from Lothian, Fife or Tayside; 43 were in patients from Grampian; and 20 patients resided in other board areas (Mr G Hecht, Principal Information Analyst, ISD Scotland. Personal communication, 22 Aug 2019). The majority of percutaneous PFO closure procedures (91.2%) were performed in NHS Lothian (Mr J Connor, Principal Information Analyst, ISD Scotland. Personal communication, 27 Nov 2019).

Using ISD stroke data and estimates from the published literature, there would be approximately 200 to 315 people in Scotland, aged 64 years or younger, who have a PFO and experience a cryptogenic ischaemic each year. This estimate is based on the following assumptions:

- The annual number of incident cases of stroke (any type) in Scotland remains similar to the 2,101 recorded in people aged 0 to 64 years in 2017-18[15]
- 87% of incident cases of stroke are ischaemic[6]
- Approximately 32% of ischaemic strokes will be classed as cryptogenic[14]
- Between 36% and 54% of patients who have an ischaemic stroke have a PFO[13].

These patient volume estimates are likely to be overestimates because the ISD data includes incident stroke of any sub-type; the age groups available in the ISD data are not an exact match for the population of interest (0 to 64 rather than ≤60 years); the cryptogenic ischaemic stroke and PFO prevalence estimates are derived from published studies; and some patients of the correct age, stroke type and who have a PFO, may still be unsuitable for the PFO closure procedure.

Clinical effectiveness and safety

Evidence on clinical effectiveness and safety of PFO closure in adults with cryptogenic ischaemic stroke comes from a recent Norwegian HTA[5], which was based on a network meta-analysis (NMA) by Mir *et al* (2018)[3]. The following review draws from both the HTA and NMA publications.

Following a systematic literature search, the Mir *et al* (2018) NMA was selected for inclusion in the Norwegian HTA on the basis that it addressed the most relevant research question, was judged to be of high methodological quality, included the largest number of randomised controlled trials (RCTs) and patients, and had the most up-to-date literature search. The network of RCTs in the NMA allowed for direct and indirect comparisons between three interventions: PFO closure plus antiplatelet therapy, antiplatelet therapy, and anticoagulant therapy. The network consisted of a single, closed loop, with PFO closure used as the reference treatment in analyses (figure 1). Unlike pairwise meta-analyses, the NMA and HTA report results separately for PFO closure plus antiplatelet therapy compared with antiplatelet therapy alone and PFO closure plus antiplatelet therapy compared with anticoagulant therapy alone.

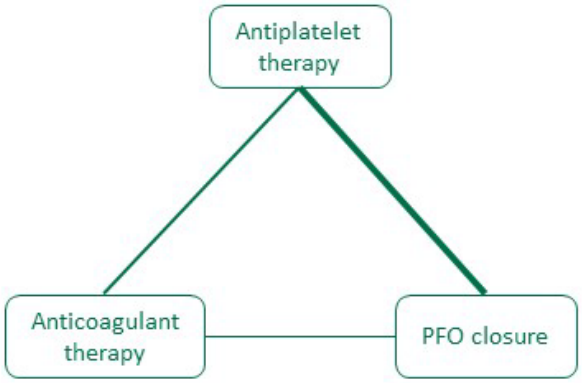

Figure 1: network of interventions for prevention of recurrence following cryptogenic ischaemic stroke

Mir *et al* (2018) performed a fixed-effect Bayesian NMA, adjusting for correlation between treatment effects in multi-arm trials. The goodness-of-fit of this model was not discussed by the NMA authors. Heterogeneity was only assessed for direct evidence comparing PFO closure with antiplatelet therapy (low heterogeneity). The transitivity assumption - the assumption that all studies in an NMA have similar patient groups, outcomes, methodologies, etcetera - may not be met in this analysis because patients in individual studies could be suitable for any of the three interventions, could be unsuitable for PFO closure, or could have contraindications to anticoagulation. The NMA and HTA authors do not address transitivity in their reports. The final assumption of NMA, consistency, refers to consistency of effect estimates derived from direct and indirect evidence in the network. Mir *et al* (2018) assessed consistency using the node-splitting approach and found no suggestion of inconsistency between direct and indirect effect estimates.

Six RCTs (n=3,560) comparing PFO closure plus antiplatelet therapy with medical therapy (antiplatelet or anticoagulant) alone, and two RCTs (n=247) comparing antiplatelet therapy with anticoagulant therapy, contributed data to the NMA. Mir *et al* (2018) considered most of these RCTs to be at risk of bias due to lack of blinding of patients and personnel, and incomplete outcome data. The risk of bias due to lack of blinding is likely to be small because study outcomes were objective and outcome assessment was blinded.

Key characteristics and findings from the six RCTs comparing PFO closure plus antiplatelet therapy with medical therapy alone are presented in appendix 2. Overall, the trials appear to have recruited participants with similar characteristics. Two trials (CLOSURE I, PC Trial) incorporated patients with TIA. These patients comprised less than 30% of each intervention group in the two trials. In four RCTs (CLOSURE I, PC Trial, RESPECT, DEFENSE PFO) patients in the medical therapy group received either antiplatelet or anticoagulant therapy, with a minority (20% to 34%) receiving anticoagulants. The PFO closure devices used in the CLOSURE I trial and in some patients in the REDUCE trial, are no longer available. Despite similarities in patient selection between trials, RCT results varied in statistical significance for the same outcomes (appendix 2). These differing findings may be due to variation in length of follow-up, differences in the diagnostic work-up for cryptogenic ischaemic stroke, or developments in manufacturing of PFO closure devices.

In the NMA, mean age of trial participants was 45 years, approximately 50% to 60% were male, and the median duration of follow-up was 3.9 years (range 1.2 to 5.9). Odds ratios were calculated for most outcomes due to the low number of events recorded. Using the GRADE system, evidence quality for each outcome was considered to be low or moderate by Mir *et al* (2018). Evidence quality was generally downgraded due to imprecision or indirectness. External clinical experts consulted by the Norwegian HTA authors agreed with these GRADE assessments.

Absolute and relative effect estimates from comparisons of PFO closure plus antiplatelet therapy with antiplatelet therapy alone and PFO closure plus antiplatelet therapy versus anticoagulant therapy alone are reported in table 1. Compared with antiplatelet therapy alone, PFO closure plus antiplatelet therapy was associated with a reduction in the risk of further ischaemic stroke events, with no evident increase in risk of death or major bleeding. Compared with anticoagulant therapy alone, there was no difference in risk of ischaemic stroke or death with PFO closure plus antiplatelet therapy. The risk of major bleeding was lower in patients treated with PFO closure plus antiplatelet therapy compared with patients on anticoagulant therapy alone. In a meta-analysis using only direct evidence, PFO closure plus antiplatelet therapy was associated with a significant increase in the risk of developing persistent atrial fibrillation within 1 year compared with medical therapy alone (antiplatelet or anticoagulant): risk ratio (RR) 4.84, 95% CI 1.91 to 12.26, risk difference 18, 95% CI 5 to 56, moderate evidence quality.

Table 1: clinical effectiveness and safety outcomes reported in the Mir *et al* (2018) NMA of RCTs[3]

Outcome	Relative effect	Absolute effect (per 1,000)		Absolute difference (per 1,000)	GRADE evidence quality
		Medical	PFO		
PFO closure + antiplatelets versus antiplatelets only					
Ischaemic stroke (within 5 years)	OR 0.12 (95% CrI 0.04 to 0.27)	100	13	87 fewer	Moderate
Mortality (within 5 years)	OR 3.28 (95% CrI 0.20 to 174.22)	3	9	6 more	Moderate
Major bleeding (within 5 years)	OR 0.48 (95% CrI 0.20 to 1.12)	14	7	7 fewer	Moderate
PFO closure + antiplatelets versus anticoagulants only					
Ischaemic stroke (within 5 years)	OR 0.44 (95% CrI 0.08 to 3.83)	29	13	16 fewer	Low
Mortality (within 5 years)	OR 0.69 (95% CrI 0.02 to 32.36)	13	9	4 fewer	Moderate
Major bleeding (within 5 years)	OR 0.26 (95% CrI 0.07 to 0.82)	27	7	20 fewer	Moderate
Anticoagulation versus antiplatelet therapy					
Ischaemic stroke (within 5 years)	OR 0.27 (95% CrI 0.03 to 1.21)	OAC 29	AP 100	71 fewer*	Low
Mortality (within 5 years)	OR 4.81 (95% CrI 0.31 to 224.43)	OAC 13	AP 3	10 more*	Low
Major bleeding (within 5 years)	OR 1.9 (95% CrI 0.68 to 5.53)	OAC 26	AP 14	12 more*	Moderate

*Credible intervals for anticoagulation versus antiplatelet therapy absolute differences all included both fewer events and more events with oral anticoagulation due to high levels of imprecision.
PFO = patent foramen ovale; OR = odds ratio; CrI = credible interval

In pairwise meta-analysis using only direct evidence, Mir *et al* (2018) reached similar conclusions to those reported in their NMA[3]. Compared with antiplatelet therapy alone, PFO closure plus antiplatelet therapy was associated with significant reductions in the risk of recurrent ischaemic stroke (OR 0.13, 95% CI 0.06 to 0.31), no significant difference in mortality (risk difference (RD) 0.00, 95% CI -0.00 to 0.01) and no significant difference in risk of major bleeding (OR 0.54, 95% CI 0.23 to 1.25). The Norwegian HTA authors compared findings from their NMA with published pairwise meta-analyses from 2018 and concluded the results were consistent, although there was variation in the

estimated magnitude of effect. This conclusion appears to be supported by comparison of the NMA results with those of three recent pairwise meta-analyses (2019) that incorporated the same six RCTs (appendix 3)[16-18].

Device- and procedure-related complication rates in the RCTs comparing PFO closure plus antiplatelet therapy with medical therapy alone ranged from 1.5% to 5.9% (appendix 2). The NMA of these trials reported relative and absolute risk differences for any serious device- and procedure-related complication within 1 year: RD 0.04, 95% CI 0.02 to 0.05, 0 events per 1,000 treated with medical therapy versus 36 events per 1,000 treated with PFO closure plus antiplatelet therapy, high certainty evidence. It is unclear how valid these differences in effect are given that device- and procedure-related adverse events are not likely to occur in the medical therapy arm of trials. The most common device- and procedure-related adverse events were vascular complications (1.0%), conduction abnormalities (1.0%), device dislocation (0.7%), and device thrombosis (0.5%). Rare but serious adverse events included air embolism (0.4%), cardiac tamponade (0.3%) and cardiac perforation (0.2%).

A random effects meta-regression by Mir *et al* (2018) indicated that the reduction in risk of recurrent ischaemic stroke following PFO closure decreased as the proportion of patients receiving anticoagulant therapy increased (p=0.036). In other words, the beneficial effects of PFO closure on risk of recurrent ischaemic stroke were greater in patients treated with antiplatelet therapy. Meta-regression analyses also suggested that PFO closure was more effective in patients with a moderate or large right-to-left cardiac shunt (p=0.047).This result should be interpreted with caution due to potential confounding because trials that recruited a high proportion of patients with moderate or large right-to-left cardiac shunts, also had a higher proportion of patients treated with antiplatelet therapy.

Antiplatelet versus anticoagulant therapy

Following discussion with clinical experts at the SHTG Committee meeting, this section was added to the current review to clarify the relative effectiveness of the two medical therapy options for patients with cryptogenic ischaemic stroke and a PFO. The NMA by Mir *et al* (2018) included comparison of anticoagulant and antiplatelet therapy in patients with cryptogenic stroke and a PFO (table 1)[3]. These comparisons were based on one (n=361) or two (n=408) RCTs, and the evidence quality was rated low due to serious imprecision for the outcomes of stroke recurrence and mortality. No significant differences in risk of recurrent ischaemic stroke, mortality or major bleeding were found for patients treated with anticoagulation compared with antiplatelet therapy.

A second NMA and a direct pairwise meta-analysis, based on an overlapping set of RCTs, also compared oral anticoagulation with antiplatelet therapy in patients with cryptogenic ischaemic stroke and a PFO[19, 20]. The NMA by Saber *et al* (2018) was a Bayesian analysis that stated it would assess goodness of model fit, heterogeneity and inconsistency but did not reported these in the results[19]. The Saber *et al* (2018) NMA incorporated six RCTs (n=1,542 in relevant comparisons), but it

is not clear which studies contributed data for each outcome. Saber *et al* (2018) used antiplatelet therapy as the reference treatment in their network. Oral anticoagulation was associated with a lower risk of recurrent ischaemic stroke compared with antiplatelet therapy in this NMA: OR 0.42, 95% CrI 0.22 to 0.78. There was a lower risk of major bleeding with antiplatelet therapy compared with oral anticoagulation: OR 0.16, 95% CrI 0.04 to 0.56.

The pairwise meta-analysis incorporated five RCTs (n=1,720) that compared oral anticoagulation with antiplatelet therapy in patients with cryptogenic stroke and a medically-managed PFO[20]. Results of this meta-analysis showed no significant difference between oral anticoagulation and antiplatelet therapy in risk of stroke recurrence (HR 0.68, 95% CI 0.32 to 1.48) or major bleeding (HR 1.61, 95% CI 0.72 to 3.59). The authors note that the studies included in the meta-analysis were likely underpowered for this comparison, terminated prematurely or had a very small sample size. Therefore the authors did not consider the meta-analysis results sufficient to support a change in clinical practice towards increased use of oral anticoagulation in this patient population.

Commissioning through Evaluation (CtE) registry data

The English Commissioning through Evaluation (CtE) programme collected real-world data on percutaneous PFO closure in a single-arm, multicentre observational registry[10]. Consecutive patients were recruited at 20 specialist cardiac centres and followed up for a maximum of 2 years. Patients were considered for inclusion in the registry if they had one or more ischaemic neurological events confirmed with brain imaging; symptoms were considered by a multi-disciplinary team to be due to a right-to-left cardiac shunt; thorough diagnostic investigation had found no other likely source of thromboembolism; a PFO was demonstrated either spontaneously or on Valsalva manoeuvre; and informed consent was given by the patient.

A total of 940 patients were included in the registry, of whom 907 (96.5%) had device implantation attempted. Of these 907 implantation procedures, 901 were successful (similar to observed success rates in RCTs) and six resulted in failure to implant. Median age of patients in the registry was 45 years (inter-quartile range (IQR) 36 to 51) with higher body mass index (BMI) and older age associated with lower PFO device implantation success rates. The proportion of patients available for follow-up declined rapidly, with 81.9% available at 6 weeks and 39.1% by 2 years follow-up. However, there were no statistically significant differences in patient characteristics of responders compared with non-responders to follow-up.

Results from the CtE registry were reported as events per 100 person-years (table 2). After adjustment for reporting errors, 1.7% of patients in the registry experienced a neurological event. In-hospital major complications were reported for 1.0% of patients and minor in-hospital complications were experienced by 2.6% of patients in the registry. Major in-hospital complications included one death, three neurological events, three device embolisation events, one myocardial infarction, one case of major bleeding and one requirement for additional surgery to retrieve an embolised device. In-hospital complications categorised as minor included nine new or worsening cases of atrial

fibrillation, five minor vascular complications, four device malposition events, five minor bleeds, three new or worsening migraine cases and one minor cardiac structural complication.

Following hospital discharge 5.2% (95% CI 3.8% to 7.0%) of patients experienced a major complication and 3.5% (95% CI 2.3% to 5.0%) developed new onset atrial fibrillation. Other major complications post-discharge include two deaths, 23 neurological events, 13 major bleeds, one myocardial infarction, one major cardiac structural complication, one major vascular complication and four people requiring additional surgery. Minor post-discharge complications occurred in 14.6% of patients: 61 minor cardiac structural complications, 21 new or worsening migraine, seven minor bleeds, five minor vascular complications and two air embolisms. Ten percent of patients available for follow-up 1 year after PFO closure had a residual cardiac shunt, which may have left them at risk of further paradoxical embolisms. In univariate analysis, the only covariate significantly associated with in-hospital major complications was right-to-left cardiac shunt without provocation.

Table 2: combined in-hospital and post-discharge event rates at any follow-up in the CtE registry[10]

Event	N patients with event (%)	Event rate per 100 person-years (95% CI)
Neurological	23 (2.5)	3.4 (2.1 to 5.0)
Neurological (revised)*	15 (1.7)	2.2 (1.2 to 3.6)
Death	3 (0.3)	0.4 (0.1 to 1.3)
Composite of mortality and neurological events	–	2.6 (1.5 to 4.1)
Ischaemic	9 (1.0)	1.3 (0.6 to 2.5)
Device embolisation	3 (0.3)	0.4 (0.1 to 1.3)
Additional surgery	5 (0.5)	0.7 (0.2 to 1.7)

* Errors in reporting of outcomes in the registry were manually corrected by registry owners following consultation with clinicians

Patient and social aspects

Living with stroke

Two stroke charities describe the effects having a stroke has on patients and their lives[21, 22]. According to a report produced by the Stroke Association, in 2017 there were over 1.2 million stroke survivors living in the UK[22]. The impact stroke has on patients depends on which part of the brain is affected and the size of the damaged area, but almost two-thirds of stroke patients leave hospital with some form of disability. In a survey of over 1,000 patients, four out of every ten people felt that the physical effects of stroke were the hardest to cope with. These physical effects include visual problems (20%), dysphasia (33%), arm or leg weakness (75%), fatigue (50%), swallowing difficulties

(50%) and problems with bladder control (50%). In Scotland, over half of patients leaving hospital after having a stroke need help to walk. Anxiety (>50%), depression (33%) and difficulty controlling emotional responses (20%) are also common after a stroke. People who have had a stroke report negative effects on relationships with their partner (42%) and family (25%), as well as on their daily life. Although 90% of patients return home within 6 months of having a stroke, many live alone (25%) and/or need help with daily activities (40%). Among people of working age, those that have had a stroke are 2-3 times more likely to be unemployed 8 years after their stroke, and approximately 1 in 6 patients experience a loss of income after a stroke.

Although many elements of stroke recovery and rehabilitation are the same regardless of age, Chest Heart & Stroke Scotland highlight issues that are of particular relevance to the younger stroke population[21]:

- Symptoms may not be recognised as stroke because the individual is deemed 'too young for a stroke', which can cause delays in treatment.
- Many people who have a stroke are able to return to work, but some may not be able or feel it is not the right thing for them.
- Of the people who do return to work, it may not be in the same capacity due to issues with fatigue, memory and concentration.
- Finances can become a problem if people can no longer work or have to work fewer hours.
- Family members may also have to take time off from work to provide care.
- The lasting effects of stroke may not be visible, particularly in younger people.

Many stroke survivors fear having another stroke[23]. A study conducted in Scotland in 2000-2001 explored the fear of stroke recurrence through structured and semi-structured interviews with stroke survivors[24]. Participants had been admitted to a specialist stroke unit and had a confirmed diagnosis of stroke. Patients with aphasia or substantial cognitive impairment were excluded. The median age of participants was 71 years (range 32 to 90). One month after a stroke over half of the participants (56%, 50/89) agreed or strongly agreed with the statement 'I worry about my stroke returning'. At nine months post-stroke the proportion was 48% (39/81). In semi-structured interviews with 60 participants one month after a stroke, over three-quarters of respondents discussed fearing the consequences of having another stroke. Fear of dying, of not being able to communicate, or of increasing disability and dependence, emerged in these qualitative interviews. Awareness of the potential for stroke recurrence was reflected on with reference to the experiences of family, friends and other patients.

PFO closure

Four studies were identified that evaluated psychological and quality of life outcomes associated with PFO closure: a retrospective observational study[25], CtE registry data from England[10], and two cross-sectional studies involving the same group of patients who had PFO closure[26, 27].

The retrospective observational study assessed health-related quality of life (HRQoL) in three groups: patients who had percutaneous PFO closure following a cryptogenic ischaemic stroke or TIA, patients with a PFO that was not closed because their ischaemic stroke or TIA was considered unrelated to the PFO, and a 'normal' Swedish population[25]. The SF-36 questionnaire was used to assess HRQoL in eight domains: physical function, role impairment (physical), bodily pain, general health, vitality, social function, role function (emotional aspects) and mental health. Out of 402 patients with a PFO and a suspected diagnosis of ischaemic stroke or TIA, 344 patients (208 with PFO closure, 136 without) returned a completed HRQoL SF-36 questionnaire at mean follow-up of 5.5 years (range 3 to 13). The age- and gender-matched reference group came from the Swedish SF-36 normative database. Patients in the PFO closure group were significantly younger than those in the non-closure group: 49 ± 10.7 years versus 57 ± 11.7 years, $p \leq 0.05$.

No statistically significant differences were detected for any of the SF-36 domains in comparisons between the PFO closure group and the reference group. In comparisons of the non-closure and the reference groups, HRQoL was significantly worse in the non-closure group on four out of eight domains in the SF-36 questionnaire. The non-closure group also had significantly worse HRQoL compared with the PFO closure group, after adjusting for age, in the SF-36 domains for role limitation (physical), vitality, mental health, and general health[25].

The CtE programme in England, issued EQ-5D-5L questionnaires to patients at baseline and at all follow-up visits[10]. The CtE report noted that since PFO closure is a preventative procedure rather than a therapeutic one, it is unclear whether patients' symptoms or quality of life would improve, other than the possibility of reductions in anxiety and drug-related adverse effects. Pre-procedure, EQ-5D-5L scores were available for 432/940 people included in the registry. The mean pre-procedure utility value was 0.87. At 6 weeks, 241 paired scores were available and showed a mean utility gain of 0.03, with 34% of patients reporting improved quality of life, 50% no change and 17% a deterioration. At 6 months follow-up, paired data for 207 patients were available and the marginal improvement was maintained, with a similar percentage of patients (35%) reporting improved quality of life, 18% no change and 47% a deterioration. The domain showing the greatest benefit from the procedure was for anxiety and depression.

Of the two cross-sectional studies, the most recent (2011) compared psychological outcomes in post-cryptogenic ischaemic stroke or TIA patients who had undergone PFO closure, with a group of post-stroke patients who were not considered for PFO closure [27]. The study aim was to compare levels of functioning, depression and anxiety in 89 post-PFO closure patients and 56 age-matched stroke/TIA patients. Patients who had undergone PFO closure reported better levels of functioning and substantially lower levels of depression and anxiety compared with age-matched controls. This

result may be affected by confounding as functioning level was the strongest predictor of depression and anxiety in this study. Better psychological wellbeing in the PFO closure group may be ascribed to their better health and higher functioning status. The higher levels of psychological wellbeing in this group may also be attributed to patients who undergo PFO closure being otherwise relatively healthy, without additional uncontrolled diseases or cardiovascular risk factors.

The second cross-sectional study, by the same authors but published a year earlier, compared the same group of patients who had PFO closure (n=89) with 60 age-matched controls who had not had an ischaemic stroke or TIA[26]. The aim of this study was to evaluate levels of psychological distress, quality of life, and optimism in these two groups. Both groups scored similarly for measures of quality of life, depression and anxiety. Older participants in both groups reported higher levels of depression than younger participants. In addition, older participants in the age-matched control group reported higher levels of depression than older participants in the PFO closure group. Higher levels of optimism were reported in the PFO closure group. The authors concluded that PFO closure may enhance quality of life and psychological wellbeing. However, they also noted the need for larger longitudinal studies before robust conclusions are possible.

Volume-outcome

Published evidence on the relationship between hospital PFO procedure volume and patient outcomes was limited to one database cohort study[28]. This study was not restricted to patients who had undergone percutaneous PFO closure, but included data on percutaneous atrial septal defect (ASD) closure. The study did not distinguish between ASD and PFO closure due to the same procedure code being used for both interventions in the database.

Singh *et al* (2015) gathered data on 7,107 patients who had undergone percutaneous ASD or PFO closure between 2001 and 2010. Data were retrieved from the Nationwide Inpatient Sample (NIS) dataset which contains 20% of inpatient records from 1,051 hospitals in the US. Mean age of the study population was 52.8 years (standard error (SE) 0.2) with 57% women. Annual hospital ASD/PFO procedure volume was divided into tertiles: 1-13 procedures, 14-37 procedures and 38-162 procedures. A multivariate analysis showed that an increase in hospital procedure volume was associated with a decrease in the odds of the composite primary outcome of in-hospital complications and mortality, and a reduction in the odds of staying in hospital more than two days (table 3). Annual hospital procedure volume in both the second (14-37 procedures) and third (>38 procedures) tertile was associated with reduced odds of the composite primary outcome (for second tertile: OR 0.72, 95% CI 0.57 to 0.91, p<0.01; for third tertile: OR 0.61, 95% CI 0.44 to 0.86, p<0.01) when compared with the first tertile (<13 procedures).

Table 3: effects of annual hospital ASD/PFO procedure volume on patient outcomes[28]

Annual procedure volume	In-hospital complications and mortality OR (95% CI)	Length of hospital stay >2 days OR (95% CI)
First tertile (1-13 procedures)	Referent	Referent
Second tertile (14-37 procedures)	0.72 (0.57 to 0.91) p<0.01	0.95 (0.92 to 0.98) p<0.01
Third tertile (>38 procedures)	0.61 (0.44 to 0.86) p<0.01	0.92 (0.89 to 0.96) p<0.01

The study authors noted that patients undergoing ASD/PFO closure would experience a 4.6% absolute risk reduction in the composite primary outcome (in-hospital complications and mortality), after adjustment for other clinical variables, when the procedure is performed in a hospital with an annual volume of 10-25 procedures compared with hospitals with an annual procedure volume of <10. A further 2.1% absolute risk reduction was noted in hospitals performing >25 procedures/year compared with hospitals which performed 10-25 procedures/year.

Organisational issues/Context

Commissioning policy in NHS England

In July 2019, NHS England commissioned PFO closure for prevention of recurrent cerebral embolic stroke in adults[29]. The criteria outlined for selecting patients for PFO closure are as follows:

- Patient is aged 60 years or younger, as per RCT inclusion criteria.
- A diagnosis of ischaemic stroke or TIA has been indicated on clinical assessment and brain imaging.
- There is no significant atrial fibrillation requiring oral anticoagulant therapy.
- A full investigation has failed to identify known risk factors/explanations for the ischaemic stroke or TIA, such as vascular disease or hypertension.
- The presence of a PFO with a clinically significant right-to-left shunt or atrial septal aneurysm has been confirmed using bubble contrast transthoracic echocardiography, including provocative manoeuvres if there is no cardiac shunt through the PFO at rest. Alternatively, transoesophageal bubble contrast echocardiography or bubble contrast transcranial Doppler may be used to exclude the presence of a PFO, if appropriate.
- A multi-disciplinary team, that includes a stroke specialist and an interventional cardiologist, considers paradoxical embolism to be the most likely cause of the ischaemic stroke or TIA.

Survey of UK cardiologists, stroke specialists and neurologists

In 2015, a survey of 120 UK cardiologists, stroke specialists and neurologists highlighted an inconsistent approach, particularly between specialties, to the selection of patients for PFO closure, with cardiologists evincing a less conservative approach[8]. Not all respondents answered every question, but key findings include:

- 90% (108/120) of respondents felt there was a role for PFO closure in selected patients with cryptogenic ischaemic stroke.
- 64.5% (71/110) of respondents said they would consider PFO closure after one cerebrovascular event, 20.9% (23/110) after two events, and 14.5% (16/110) after three or more events.
- Overall, cardiologists had a significantly lower threshold for considering PFO closure after a single cerebral event compared with non-cardiologists (60.0% versus 81.0%, p=0.041).
- 80.7% (92/114) of respondents required evidence of ischaemic stroke on CT or MRI prior to consider PFO closure. Cardiologists were significantly less likely than neurologists to require such evidence (73.1% versus 82.6%, p=0.04).
- 25.7% (29/113) of respondents did not consider an age cut-off for PFO closure and cardiologists were significantly more likely to consider patients of any age for PFO closure (52% versus 17%, p<0.001).
- 97.4% (111/114) of respondents felt the presence of a PFO should be confirmed with a transthoracic echocardiogram (TTE) bubble study.

Norwegian HTA organisational issues

The 2019 NIPH HTA included a section on organisational aspects, based on consultation with clinical experts and other stakeholders[5]. The HTA authors noted that introducing PFO closure at a national level required investment in new facilities and human capital, and could affect general, stroke and cardiology units. The following factors would need to be considered if a PFO closure service was to be developed:

- Suitable diagnosis of patients with cryptogenic ischaemic stroke and a PFO.
- Adequate referral for PFO closure requiring clinicians to first refer eligible patients for transoesophageal echocardiography to determine the presence and size of a PFO, and extent of the right-to-left cardiac shunt.
- The service would need cardiologist expertise and capacity for both the PFO procedure and transoesophageal echocardiography. This may include training for cardiologists in hospitals not used to offering PFO closure, and for PFO closure teams, for example interventional cardiologists, imaging cardiologists and nurses.
- There may be an initial backlog of patients, who are eligible for PFO closure but who were not referred at the time of their cryptogenic ischaemic stroke.

- Hospitals need to have the necessary facilities for performing percutaneous PFO closure, for example catheterisation laboratories, and access to transoesophageal echocardiography services.

Cost effectiveness

The most relevant economic evidence on PFO closure consisted of three studies[10, 30, 31]. The NHS England CtE report presents a cost-consequence analysis comparing PFO closure plus medical therapy with medical therapy alone[10]. A further two published economic evaluations from the perspective of the UK healthcare system provide cost-utility analyses of PFO closure plus medical therapy compared with antiplatelet therapy alone[30, 31].

CtE cost-consequence analysis

The CtE report presents a *de novo* economic model consisting of a decision tree followed by a Markov state transition model[9]. The decision tree was used to explicitly model device-related serious adverse events. The subsequent Markov model included five health states in a cohort of 1,000 patients with a mean age of 45 years. Model time horizon was 45 years. Patients could remain stroke-free, experience a neurological event (ischaemic stroke, haemorrhagic stroke, TIA), develop atrial fibrillation, bleed, or die. In the PFOC arm of the model, patients had procedure-related risks and experienced strokes and bleeds at the rates observed at discharge in the CtE registry. After that estimates for PFO closure procedure-related outcomes (as observed upon discharge) were extrapolated using data from the RESPECT trial up to 5.9 years (trial follow-up period), and from 5.9 until lifetime of the model (90 years) using parametric models thereafter. Clinical event rates for the comparator arm (medical therapy alone) were also modelled on data from the RESPECT trial.

The study conducted detailed bottom-up costing of the PFO closure procedure using average costs from NHS sources and device manufacturers. Procedural costs included pre-operative assessment costs, peri-operative costs (time in theatre, medical specialists, anaesthesia, imaging, PFO device and consumables) and costs of post-operative patient management. The cost of the PFO devices and consumables constituted the highest proportion of the total cost of the PFO closure procedure (approximately 40%). Overhead costs, such as procurement, stores, finance and general management, were included in the analysis. Depending on the costing assumptions, the cost of PFO closure ranged from £6,939 to £9,251, with a central estimate of £8,233.

Over the model time horizon, the total discounted cost per patient receiving PFO closure was £12,956, of which 64% constituted PFO procedure-related costs, 23% subsequent stroke management costs, and 13% the cost of medicines and management in primary care. This represents an additional £5,360 per patient treated with PFO closure plus medical therapy compared with medical therapy alone. The key driver of the results is the PFO closure procedure cost, which is only partially offset by a reduction in the cost of subsequent stroke management (owing to a reduction in recurrent stroke cases). Discounted and undiscounted costs are presented in table 4.

Table 4: estimated total NHS procedural and health state costs per patient with cryptogenic ischaemic stroke over a 45-year time horizon[10]

	Discounted costs			Undiscounted costs		
	PFO	Medical	Difference*	PFO	Medical	Difference*
Procedures and bleeds	£8,233	£0	+£8,233	£8,233	£0	+£8,233
Medication and primary care	£1,737	£2,574	-£837	£3,048	£4,442	-£1,393
Ischaemic stroke (NHS)	£2,809	£4,686	-£1,877	£5,465	£8,989	-£3,524
Haemorrhagic stroke (NHS)	£8	£169	-£160	£16	£321	-£305
TIA	£101	£148	-£47	£174	£250	-£76
Bleeds	£68	£19	+£49	£117	£29	+£87
Total	**£12,956**	**£7,596**	**+£5,360**	**£17,053**	**£14,031**	**+£3,022**

*A plus sign indicates a higher cost with PFO closure. Numbers in these columns are rounded.

The CtE economic model predicted a 40% reduction in subsequent ischaemic strokes per 1,000 patients receiving a PFO closure over 45 years. This is a decrease of 182 ischaemic strokes, including avoidance of 54 deaths, in patients receiving PFO closure plus medical therapy, translating into an expected incremental cost of £29,451 per future ischaemic stroke episode avoided and £99,259 per death avoided.

Quality of life (QoL) data were collected as part of the CtE registry and show a significant short-term increase in QoL after PFO closure that is mainly associated with reduced anxiety and improved physical functioning. However, the data were not included in the economic model and the value of the baseline utility score is higher than the population norms for the UK for this age group (mean value 0.85)[32], which undermines the validity of the QoL findings and may explain why they were not incorporated into the economic model.

Cost utility analyses

One published UK cost-utility analysis presented a Markov cohort model using clinical data on ischaemic stroke recurrence rates for a sub-population in the RESPECT trial[31]. The anatomical features (large degree of right-to-left shunt or atrial septal aneurysm) of the modelled RESPECT sub-population are likely to be consistent with those required for cryptogenic ischaemic stroke patients to be considered for PFO closure in Scotland (Prof. M Dennis, Professor of Stroke Medicine, University of Edinburgh. Personal communication, 11 Oct 2019). In this subgroup analysis, the

AMPLATZER® PFO Occluder device was used in the PFO closure procedure, followed by aspirin plus clopidogrel for one month, and aspirin only thereafter (doses not specified). Individuals in the medical therapy arm received 75mg clopidogrel daily as per NHS guidelines. In the model, patients could transition between four health states – stable, minor recurrent ischaemic stroke, moderate recurrent ischaemic stroke and dead – every 3 months over a 20-year time horizon. Thirty percent of the recurrent ischaemic strokes in the base case were assumed to be of moderate severity and 70% minor. The mean age of the modelled sub-population was 46 years to reflect the overall population in the RESPECT trial.

Major cost components in the model included the PFO closure procedure, PFO device, medications, serious adverse events, follow-up care and cost of recurrent ischaemic stroke. The cost of the PFO closure procedure and device was obtained from the NHS England CtE report. All treatment-specific cost data were obtained from published NHS sources. The cost of recurrent ischaemic stroke came from a UK population-based cohort study, which reported 5-year mean hospital care costs after an ischaemic stroke. Health state utility values after a recurrent ischaemic stroke were derived from a UK population-based study which reported EQ-5D utility values for minor, moderate and severe ischaemic strokes over 5 years. Initial health state utility weights for stable patients were based on expert opinion. Utilities for the PFO closure arm were assumed to increase by 5% from baseline in the first 3-6 months, and 10% thereafter if patients remained in the stable state. A discount rate of 3.5% was applied to all benefits and costs.

In the base case, at 4.2 years PFO closure was within the willingness-to-pay threshold of £20,000-£30,000 per quality adjusted life year (QALY), with an estimated incremental cost effectiveness ratio (ICER) of just over £20,000. At this time point, the PFO closure procedure generated 0.29 additional QALYs and was associated with an incremental cost of £6,071 compared with medical therapy alone. At 10 and 20 years, a substantial reduction in the ICER was observed, with the cost per QALY falling to £6,887 and £2,158 respectively (table 5). Probabilistic sensitivity analysis performed at 10 years found PFO closure to be cost-effective in 89% of the performed model iterations.

Table 5: cost-effectiveness results of PFO closure plus medical therapy compared with medical therapy alone based on a sub-population from the RESPECT trial[31]

	PFO	Medical	Incremental
At 4 years			
Total costs	£6,847	£776	£6,071
Total QALYs	3.25	2.96	0.29
ICER			£20,951
At 10 years			
Total costs	£7,287	£2,429	£4,858
Total QALYs	7.29	6.59	0.71
ICER			£6,887
At 20 years (base case)			
Total costs	£8,084	£5,237	£2,846
Total QALYs	12.12	10.80	1.32
ICER			£2,158
Annual rate of ischaemic stroke recurrence	0.0036	0.0131	

QALY = quality-adjusted life year, ICER = incremental cost-effectiveness ratio

The second UK cost-utility analysis compared PFO closure using the CARDIOFORM Septal Occluder plus standard medical management compared with medical therapy alone[30]. The analysis was based on a six health state Markov cohort decision model with a cycle duration of 3 months and a 5-year base case time horizon. Patients could transition between the following health states: stable after index ischaemic stroke, TIA, post-TIA, clinical ischaemic attack, post-clinical ischaemic attack, and death. The definition of the modelled cohort and comparators were in accordance with the REDUCE trial protocol. Quarterly transition probabilities were also derived from the REDUCE trial. The utility values and costs included were very similar to those used in the other UK-specific economic evaluation described above[31].

In the base case (at 5 years), PFO closure was associated with an incremental cost of £5,983 and 0.41 additional QALYs compared with medical therapy alone, resulting in an incremental cost effectiveness ratio (ICER) of £14,571, which is below the commonly accepted willingness-to-pay threshold of £20,000 to £30,000/QALY. Results were presented for 4, 10 and 20 years, yielding ICERs of £18,584, £5,812 and £833 respectively (table 6). In a probabilistic sensitivity analysis, PFO closure was cost-effective in 76.9% of the performed model iterations.

Table 6: cost-effectiveness of PFO closure plus medical therapy compared to medical therapy alone based on the REDUCE trial[30]

	PFO	Medical	Incremental
At 5 years (base case)			
Total costs	£7,744	£1,761	£5,983
Total QALYs	4.20	3.79	0.41
ICER			£14,571
At 4 years			
Total costs	£7,546	£1,313	£6,233
Total QALYs	3.48	3.14	0.34
ICER			£18,584
At 10 years			
Total costs	£8,831	£4,423	£4,408
Total QALYs	7.29	6.53	0.76
ICER			£5,812
At 20 years			
Total costs	£10,936	£9,869	£1,067
Total QALYs	11.21	9.93	1.28
ICER			£833
Annual rate of ischaemic stroke recurrence	0.0044	0.0172	

QALY = quality-adjusted life year, ICER = incremental cost-effectiveness ratio

It is not clear if the population in the REDUCE trial reflects the population most likely to be considered for PFO closure in Scotland, meaning this study is potentially less relevant for decision-making. It appears that serious adverse events were associated with costs only, and it is not clear if utility decrements were applied, which may have led to an overestimate of the relative cost-effectiveness of PFO closure. However, because the proportion of patients who reported serious adverse events was relatively small in the REDUCE trial (1.4%) the lack of utility decrements is not expected to have a big impact on the base case results.

Discussion

In the published cost-utility analyses, the main driver of cost-effectiveness was the higher QoL associated with lower annual ischaemic stroke recurrence rates for the PFO closure arm in the UK sub-population of the RESPECT trial (0.36% versus 1.31%) and the full REDUCE trial (0.44% versus 1.72%). Lower ischaemic stroke recurrence rates are also associated with decreased follow-up costs.

There are major uncertainties around the magnitude and duration of the QoL utility gain for PFO closure patients compared with those on medical therapy who have not experienced any recurrent ischaemic strokes. Clinical experts noted that the assumption of 10% higher utility for patients who were stable following PFO closure compared with medical therapy 6 months post-procedure appears arbitrary (Prof. M Dennis, Professor of Stroke Medicine, University of Edinburgh. Personal communication, 11 Oct 2019). Although patients may feel less anxious after their procedure, their quality of life 6 months later is likely to be similar to that of patients on medical therapy, as demonstrated by the results from the CtE utility assessment. To partially explore this uncertainty, the second cost-utility analysis included a one-way sensitivity analysis that indicated if the PFO closure-specific utility increment for the stable state was 5% instead of 10%, the ICER increased beyond £30,000 at 5 years[30].

To assess the impact of equal utility for stable patients 6 months after treatment, the economic model used in the cost-effectiveness study by Tirschwell *et al* (2018)[31] was closely replicated by the SHTG assessment team (table 7). The replicated model demonstrated that, where only a 5% higher utility was used for stable PFO closure patients in the first 6 months, followed by an equal utility in both treatment arms thereafter, the ICER was in excess of £100,000/QALY in the short term (up to 10 years). Cost-effectiveness substantially improved after 10 years, reaching the acceptable cost-effectiveness threshold (£30,000/QALY) approximately 13.5 years post-procedure. PFO closure plus medical therapy remained cost-effective compared to medical therapy alone over the lifetime of the patient, yielding an ICER of under £10,000 at 20 years. However, given the relatively young patient group, it is worth noting that the long term effects of the increased risk of atrial fibrillation post PFO closure leading to an increased risk of subsequent stroke on the cost-effectiveness of PFO closure are unknown.

Table 7: sensitivity analyses using a closely replicated model, with reduced utility gains

	PFO	Medical	Incremental
At 4 years			
Total costs	£6,835	£790	£6,046
Total QALYs	2.99	2.96	0.02
ICER			£248,659
At 10 years			
Total costs	£7,274	£2,446	£4,829
Total QALYs	6.68	6.59	0.08
ICER			£59,558
At 20 years			
Total costs	£8,058	£5,210	£2,848
Total QALYs	11.11	10.83	0.29
ICER			£9,979

QALY = quality-adjusted life year, ICER = incremental cost-effectiveness ratio

It should also be noted that utility weights for post-stroke health states in the published economic models were derived from an older population (mean age 75 years) whose index stroke was not necessarily cryptogenic. It is likely that recurrent ischaemic stroke in people of working age has a bigger negative impact on quality of life due to decreased earnings and social activities. As such, the incremental benefit following a reduction in ischaemic stroke rates may be underestimated in the published studies.

Both cost utility analyses used peri-operative costs for PFO closure from the CtE report (£6,300). This included the device and consumables cost, which was based on a device 'bundle' used in the CtE registry in NHS England (approximately £3,400). These estimated device costs are consistent with quoted costs from manufacturers in Scotland. However, conflicting data are available that suggest device costs in NHSScotland may be higher.

Overall, the economic evidence suggests that PFO closure plus medical therapy is a cost-effective option in the long-term compared with medical therapy alone in patients with cryptogenic ischaemic stroke, driven by the reduction in recurrent ischaemic stroke episodes. Scenario analyses suggest PFO closure plus medical therapy may not be cost-effective in the short-term compared to medical therapy alone, but is likely to be cost-effective over the lifetime of the patient.

Conclusion

In patients aged 60 or younger, who have a confirmed cyptogenic ischaemic stroke and PFO, compared with medical therapy alone, closure of the PFO plus antiplatelet therapy reduced the risk of further ischaemic strokes, with no evidence of an increased risk of mortality or major bleeding. The procedure appears to be relatively safe, although there is as increased risk of developing persistent atrial fibrillation or flutter following PFO closure compared with patients treated with medical therapy alone.

Published economic evaluations suggest that PFO closure plus medical therapy is a cost-effective treatment option in patients aged 60 or under. Uncertainty surrounding the accuracy of long-term procedure-related utility benefits mean that these findings should be treated with caution.

Identified research gaps

RCT evidence directly comparing PFO closure plus medical therapy with oral anticoagulants alone in adult patients with cryptogenic ischaemic stroke would supplement the current evidence on the clinical effectiveness of PFO closure.

Future RCTs could explore potential benefits of PFO closure plus medical therapy compared with medical therapy alone in different age groups of patients with cryptogenic ischaemic stroke, for example patients aged over 60 years.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

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References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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Appendix 1: abbreviations

ASD	atrial septal defect
BMI	body mass index
CI	confidence interval
CrI	credible interval
CT	computed tomography
CtE	Commissioning through Evaluation
DOAC	direct oral anticoagulant
DVT	deep venous thrombosis
ECG	electrocardiogram
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost effectiveness ratio
IQR	inter-quartile range
MRI	magnetic resonance imaging
NIPH	Norwegian Institute of Public Health
NMA	network meta-analysis
NR	not reported
OR	odds ratio
OXVASC	Oxford vascular study
PFO	patent foramen ovale
QALY	quality adjusted life-years
QoL	quality of life
RCT	randomised controlled trial
RD	risk difference
RR	relative risk/risk ratio
SD	standard deviation

SE	standard error
TIA	transient ischaemic attack
TOE	transoesophageal echocardiography
TTE	transthoracic echocardiography

Appendix 2: RCTs comparing PFO closure plus antiplatelet therapy with medical therapy

Trial (publication year)	CLOSURE I (2012)[33]	PC Trial (2013)[34]	RESPECT (2013)[35]	CLOSE (2017)[36]	REDUCE (2017)[37]	DEFENSE PFO (2018)[38]
Study design/methodology characteristics						
N	909	414	980	473*	664	120
Years	2003-2008	2000-2009	2003-2011	2007-2016	2008-2015	2011-2017
Countries (n sites)	USA, Canada (87)	Europe, Canada, Brazil, Australia (29)	USA, Canada (69)	France (32), Germany (2)	Canada, Denmark, Finland, Norway, Sweden, UK, USA (63)	South Korea (2)
Patient selection criteria	Age 18-60; Ischaemic stroke or TIA in past 6 months; PFO on TOE; Right-to-left shunt	Age <60; PFO on TOE; Ischaemic stroke, TIA or thromboembolic event	Aged 18-60; Cryptogenic ischaemic stroke; PFO on TOE; Moderate-large shunt	Aged 16-60; Ischaemic stroke in past 6 months; PFO with atrial septal aneurysm or large shunt	Aged 18-59; Cryptogenic ischaemic stroke in past 6 months; PFO with right-to-left shunt	Ischaemic stroke in past 6 months; High risk PFO with right-to-left shunt
Diagnostic testing	Excluded arterial stenosis, atheroma, ventricular dysfunction or aneurysm, and atrial fibrillation	12-lead ECG, TOE, MRI or CT, Duplex ultrasound, blood tests	TOAST criteria of cryptogenic ischaemic stroke	Arterial imaging, blood tests, echocardiography, ECG	MRI or CT of brain, arterial imaging, echocardiography	Arterial imaging, Holter monitoring or prolonged cardiac rhythm monitoring (ECG)
Comparison	PFO closure (STARFlex) + antiplatelets	PFO closure (AMPLATZER® PFO Occluder) + antiplatelets for 6 months	PFO closure (AMPLATZER® PFO Occluder) + antiplatelets for 6 months	PFO closure (multiple devices) + antiplatelets Antiplatelets only	PFO closure (HELEX or CARDIOFORM) + antiplatelets	PFO closure (AMPLATZER® PFO Occluder) + antiplatelets for 6 months

	Medical therapy (warfarin, aspirin or both) Subgroup analysis for antiplatelets & anticoagulants for primary outcome	Medical therapy (antiplatelets or anticoagulants)	Medical therapy (antiplatelets or warfarin) Subgroup analysis for antiplatelets & warfarin for recurrent stroke	Anticoagulants only (warfarin or DOAC)	Antiplatelets only	Medical therapy (antiplatelets or warfarin)
Primary outcome(s)	Composite of stroke, TIA, and mortality	Composite of mortality, non-fatal stroke, TIA and peripheral embolism	Composite of non-fatal ischaemic stroke, fatal ischaemic stroke, and early death	Fatal or non-fatal stroke	Co-primary endpoints: ischaemic stroke recurrence and new brain infarction	Composite of stroke, vascular death, and major bleeding
Follow-up (years)	Mean 2.0	Mean 4.1	Median 5.9 (IQR 4.2 to 8.0)	Mean 5.3 (SD 2.0)	Median 3.2 (IQR 2.2 to 4.8)	Mean 2.0
Study results and conclusions						
Mean age (years)	46.0	44.5	45.9	43.4	45.1	51.5
% Male	51.8	49.8	54.7	59.0	60.6	55.8
Key results (95% CI)	Recurrent stroke HR 0.90 (0.41 to 1.35) Major bleeding§ RR 2.43 (0.77 to 7.69) Atrial fibrillation§ RR 7.92 (2.40 to 26.21)	Recurrent stroke HR 0.20 (0.02 to 1.72) Major bleeding§ RR 0.34 (0.04 to 3.27) Atrial fibrillation§ RR 3.15 (0.64 to 15.6)	Recurrent stroke HR 0.55 (0.31 to 0.999) Major bleeding NR Atrial fibrillation 0.4% PFO group	Recurrent stroke HR 0.03 (0.00 to 0.26) Major bleeding NR Atrial fibrillation§ RR 5.43 (1.22 to 24.24)	Recurrent stroke HR 0.23 (0.09 to 0.62) Major bleeding§ RR 0.87 (0.41 to 2.48) Atrial fibrillation§ RR 14.64 (2.01 to 106.9)	Recurrent stroke 0 events PFO 5 events Medical Major bleeding 0 events PFO 2 events Medical Atrial fibrillation 3.3% PFO group

	Device/procedure complications 3.2%	Device/procedure complications 1.5%	Device/procedure complications 4.2%	Device/procedure complications 5.9%	Device/procedure complications 3.9%	Complications 3.3%
Conclusion from RCT	No benefit of PFO closure compared with medical therapy (including in subgroup analyses)	No benefit of PFO compared with medical therapy	Significant reduction in stroke recurrence with PFO closure Subgroup analyses: stroke recurrence significantly reduced only in comparisons of PFO closure compared with antiplatelets	Significant reduction in stroke recurrence with PFO closure; significant increase in new atrial fibrillation with PFO closure	Significant reduction in stroke recurrence with PFO closure; significant increase in new atrial fibrillation with PFO closure	Significant reduction in composite outcome and stroke recurrence with PFO closure

*Total patients recruited to CLOSE RCT = 663. However, some patients were randomised to anticoagulants and were only compared with the antiplatelet group. In the randomisation to PFO closure or antiplatelets there were 473 patients.

§Relative risk calculated by NIPH

CT = computed tomography, DOAC = direct oral anticoagulant, ECG = electrocardiogram, HR = hazard ratio, IQR = inter-quartile range, MRI = magnetic resonance imaging, NR = not reported, PFO = patent foramen ovale, RCT = randomised controlled trial, RR = relative risk, SD = standard deviation, TIA = transient ischaemic attack, TOE = transoesophageal echocardiography

Appendix 3: results from direct pairwise meta-analysis

Table: findings from three pairwise meta-analyses, published in 2019, that incorporated the same six RCTs as the network meta-analysis by Mir *et al* (2018)[3]

	Dahal (2019)[16]	Vidale (2019)[17]	Vukadinović (2019)[18]
Recurrent ischaemic stroke	OR 0.34 95% CI 0.15 to 0.78	RR 0.58 95% CI 0.44 to 0.76	RR 0.38 95% CI 0.18 to 0.82
Mortality	OR 0.74 95% CI 0.28 to 1.93	–	–
Major bleeding	OR 0.81 95% CI 0.42 to 1.56	–	RR 0.91 95% CI 0.60 to 1.38
Atrial fibrillation	OR 4.79 95% CI 2.35 to 9.77	RR 5.57 95% CI 2.98 to 10.39	RR 5.54 95% CI 3.00 to 10.20