Clinical Commissioning Policy Proposition:

Percutaneous patent foramen ovale closure for the prevention of recurrent cerebral embolic stroke (up to the age of 60 years)

Reference: NHS England 1770

Prepared by NHS England Specialised Services Clinical Reference Group for Cardiac Services

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Contents

1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About: Patent Foramen Ovale (PFO) closure for the prevention of recurrent cerebral embolic stroke

The foramen ovale is a small natural channel which allows blood to flow between the two upper chambers of the foetal heart (the left and right atria). In the majority of people this channel closes shortly after birth but in approximately 25% it remains open or 'patent' and is referred to as a Patent Foramen Ovale or PFO.

In the vast majority of people a PFO never causes any problems at all. However in a small minority the channel could be large enough to allow a blood clot which has formed in the veins that return blood to the heart to bypass the lungs (which normally act to safely filter such clots out) and instead pass directly into the left side of the heart. From here a clot could travel along the blood vessels to different parts of the body and may cause a blockage. A stroke may occur if the blockage happens in a vessel in the brain. If the blockage here is only temporary a brief stroke-like episode called a transient ischaemic attack (TIA) is the result.

About current treatments

Most people who have had a stroke or TIA because of a PFO take regular medications to reduce the clotting tendency of the blood to reduce the chance of

another event. These medications are usually anti-platelet drugs such as aspirin or clopidogrel or anti-coagulants such as warfarin or an equivalent.

About the new treatment

An alternative approach to preventing recurrent strokes is to block up the PFO using a small closure device. This device is passed through the skin (i.e. percutaneously) into a large vein in the groin and then threaded up into the heart. The device is then positioned across the PFO and deployed so that both ends of the channel are blocked.

What we have decided

NHS England has carefully reviewed the evidence to treat patent foramen ovale with percutaneous PFO closure in those patients who have had a previous stroke. We have concluded that there is enough evidence to consider making the treatment available.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission patent foramen ovale (PFO) closure for the prevention of recurrent cerebral embolic stroke.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether PFO closure for the prevention of recurrent cerebral embolic stroke will be routinely commissioned will made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Percutaneous PFO closure refers to a minimally-invasive procedure to close a foramen ovale which is a defect in the atrial septum, the structure that separates the two upper chambers of the heart. The foramen ovale normally closes at birth but remains open (patent or persistent) in some people. In those who have a stroke of undetermined cause (often referred to as a cryptogenic stroke), there is a greater likelihood that the foramen ovale is patent and its closure may reduce the probability of a further stroke.

Percutaneous closure is achieved using an occluder device that is placed under ultrasound and X-ray guidance in a cardiac catheterisation laboratory by a cardiology team with appropriate expertise. During the procedure patients may be sedated or given a general anaesthetic to facilitate transoesophageal echocardiography (TOE).

Percutaneous PFO closure is normally undertaken in patients who have already had an embolic stroke for which no other cause can be identified despite extensive investigations i.e. in an otherwise cryptogenic stroke. The most likely mechanism by which PFO causes stroke is paradoxical embolism: the passage of a small venous

thrombus from the right to the left side of the heart being carried in the blood that by-passes the filtering action of the lungs. Once in the arterial system the thrombus may lodge in an artery in the brain and cause a stroke.

Patients would normally only be considered for percutaneous PFO closure if they had been proven to have stroke or TIA by brain imaging, have no other evidence of other causes of stroke and been shown to have a PFO with appropriate characteristics to make it the most likely explanation of stroke.

The clinical problem is that some patients with PFO associated cryptogenic stroke can go on to have further strokes despite anti-thrombotic medication. Exposure to the risk of recurrent stroke due to paradoxical embolism may continue over several decades.

The National Institute for Health and Care Excellence (NICE) IPG 472 had no concerns about the safety of percutaneous PFO closure. They concluded that doctors should use their normal arrangements for clinical governance (hospital approval to do the procedure), patient consent and audit (reviewing results and outcomes of patients treated with this procedure).

4 Definitions

Patent Foramen Ovale (PFO)

The foramen ovale is a small natural channel which allows blood to flow between the two upper chambers of the foetal heart (the left and right atria). In the majority of people this channel closes shortly after birth but in approximately 25% it remains open or ‘patent’ and is referred to as a Patent Foramen Ovale or PFO.

Atrial fibrillation (AF)

A heart condition that causes an irregular heartbeat. It results from loss of co-ordinated contraction of the two atria (the upper receiving chambers of the heart). Non-valvular AF is AF which occurs in the absence of rheumatic mitral valve disease or a metallic mitral prosthesis.

PFO closure

The use of a device to close a PFO to prevent the flow of blood between the upper chambers of the heart.

Occluder

A medical device designed to close a hole in the heart.

Stroke

A focal area of brain injury due to a disruption in its blood supply.

Ischaemic stroke

A stroke due to blockage of an artery that supplies blood to part of the brain.

Cardio-embolic stroke

A cardio-embolic stroke is one that results from debris or clot in the heart moving into the circulation and blocking a blood vessel supplying brain tissue.

Cryptogenic stroke

A cerebral ischemia of obscure or unknown origin. The cause of cryptogenic stroke remains undetermined because the event is transitory or reversible, investigations did not look for all possible causes, or because some causes truly remain unknown. In the context of young patients this is where the cause of the stroke remains unknown despite extensive investigations to exclude cardiac and large and small artery sources of thrombo-embolism and pro-thrombotic states or events.

Transient ischaemic attack (TIA)

An episode of focal neurological dysfunction due to a transient interruption in blood supply with symptoms lasting less than 24 hours and without evidence of infraction on brain imaging.

Transoesophageal echocardiography (TOE)

A transoesophageal echocardiogram is an alternative way to perform an echocardiogram. A specialised probe containing an ultrasound transducer at its tip

is passed into the patient's oesophagus.

Paradoxical embolus/embolism

A clot which passes from a vein to an artery.

Anti-thrombotic medication

There are two classes of anti-thrombotic drugs: anticoagulants and antiplatelet drugs. Anticoagulants slow down clotting, thereby reducing fibrin formation and preventing clots from forming and growing. Antiplatelet agents prevent platelets from clumping and also prevent clots from forming and growing.

5 Aims and Objectives

This policy proposition considered: The clinical criteria under which NHS England will routinely commission percutaneous PFO closure for the prevention of recurrent stroke.

The objectives were to:

- Determine the clinical effectiveness and safety of percutaneous PFO closure in the prevention of recurrent stroke
- Determine the patient eligibility criteria for percutaneous PFO closure, ensuring the best clinical and cost-effective use and taking account of patient risk stratification
- Ensure robust monitoring and follow up arrangements to enable audit of stroke/other thromboembolic event rate and procedure/device related complications

6 Epidemiology and Needs Assessment

In the UK, there are over 100,000 strokes each year, of which 85% are ischaemic (Stroke Association, 2018). 15-20% occur in people under the age of 60.

PFO is the most common association (40-50%) of cryptogenic stroke in patients younger than 55 years (Gonzalez-Alujas et al., 2011; Tobis et al., 2005). The lack of patient modifiable risk factors for cryptogenic stroke leads clinicians and patients 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 (Li et al., 2015).

PFO is far more common among cryptogenic cases than in explained cases (OR 6.0 (95%CI 3.7 to 9.7)) (Overell et al., 2000).

However, prospective studies of people with PFO have provided inconsistent findings about stroke risk (Mas et al., 2001; Almekhlafi, 2009).

The recent publication of long term outcomes from randomised controlled trials now provides a much firmer basis for the evaluation of potential treatment benefits.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

In coming to this view NHS England has considered the findings of both:

a) a review of the research literature, and

b) an observational registry study commissioned from NICE of patients undergoing PFO closure in NHS England's Commissioning through Evaluation (CtE) scheme

The review of the research literature found:

Two systematic reviews and meta-analyses (SRMAs) (Shah et al., 2018, De Rosa et al. 2018) of four randomised controlled trials (RCTs) which compared percutaneous PFO closure (n=1382) and medical therapy alone (n=1339) for the prevention of recurrent stroke in patients who had had cryptogenic stroke were suitable for inclusion in this review. Both meta-analyses included the same four recent RCTs (PC-TRIAL, RESPECT, CLOSE and REDUCE studies).

De Rosa et al. (2018) included the shorter-term outcomes of the RESPECT RCT published in 2013 (Carroll et al.), whereas Shah et al. (2018) included the longer-term outcomes of the extended RESPECT RCT (Saver et al., 2017), in which there

was 27% loss to follow-up. In their analysis of the CLOSE RCT (Mas et al., 2017) Shah et al. (2018) appear to have double counted 171 of the patients who received antiplatelet therapy. Whilst it is not possible to say precisely what the impact of this is on their estimates of risk difference, it is notable that their findings are similar to those of De Rosa et al. (2018) and so any bias is likely to be small.

One prospective study of 1000 consecutive patients in Italy (Rigatelli et al., 2016; Rigatelli et al., 2017) reported median 10.5 year outcomes.

One cost-effectiveness study was available for inclusion (Pickett et al., 2014).

Clinical Effectiveness from the literature review

Patients undergoing PFO closure had a lower risk of stroke than those treated with medical therapy alone (MTA) over a follow-up period of 3.2 to 5.9 years:

- 3.2% lower absolute risk of recurrent stroke (RD: -0.032 (95%CI: -0.5- to -0.014), p=0.011) (Shah et al., 2018).
- 3.1% lower absolute risk of recurrent ischaemic stroke (De Rosa et al., 2018).

No reduction in the risk of TIA alone was seen (Shah et al., 2018).

No statistically significant difference for all-cause mortality was seen (De Rosa et al., 2018).

Adverse events

Serious adverse events (SAEs) of treatment were common in the follow up period among patients undergoing either PFO closure or sustained MTA (25% vs 24% (RD: -0.006(95%CI: -0.036 to -0.048), but were not significantly different (p=0.781, I2=31%).

One of the two SMRAs found that new onset atrial fibrillation or flutter was significantly more frequent in patients undergoing PFO closure compared to those on MTA [PFO closure vs MTA: 4.1% vs 1.0% (RD: 0.033 (95%CI: 0.012 to 0.054), p=0.002, I2=66%)].

There was no significant difference in the incidence of major bleeding in patients

who had PFO closure compared with MTA (p=0.605, Shah et al., 2018) and p=0.093, De Rosa et al., 2018)).

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.

Cost-effectiveness from the evidence review

One cost effectiveness study (Pickett et al., 2014) met the criteria in the Population, Intervention, Comparison and Outcomes framework (PICO). This was a cost effectiveness model based on the combined outcomes from three RCTs (CLOSURE, PC-TRIAL and RESPECT trials) for a male, mean age 45.7 years. One of the two devices included in this study (Pickett et al., 2014) is currently used in the UK; the Amplatzer PFO closure device. This model is based on short term outcomes only (2.6 years) and does not include outcomes from the most recent trials. It also uses USA based costs for device, procedure and drugs from 2011 which differ from current UK costs.

This study estimated the incremental cost of using the Amplatzer device to prevent one stroke as $648,044 (95% CI $486,799 to $856,615), but this estimate does not take account of the cost of stroke treatment, rehabilitation and care costs and indirect costs to the patient and their carers; none of which are included in the model. The time to reach a cost effectiveness threshold lower than $50,000 was 2.38 years (95% CI 0.5 to 10.0 years).

Commissioning through Evaluation study

To clarify the potential benefits of this treatment in NHS settings, 940 patients with PFO were recruited from 19 centres across England, 901 of whom underwent closure through NHS England's CtE scheme. Patients in this scheme were followed

up for up to two years.

At the time of reporting to NHS England, analysis was available for the third (notional 1 year) follow up; data were available on 417 (59%) of the 702 eligible patients who had reached this assessment. The adverse events experienced by these patients during a median follow up of 212 days (approx. 7 months) were:

- 2.2 neurological events per 100 patient years
    - 95% confidence interval 1.2 to 3.6 events
- 2.6 neurological events or deaths per 100 patient years
    - 95% confidence interval 1.5 to 2.4 events

In contrast all recent trials, bar one, report that patients undergoing PFO closure experience less than one adverse event per 100 patient years. This suggests that adverse outcomes following PFO closure are more common among procedures undertaken as part of the evaluation scheme than among patients undergoing PFO closure in recently published RCTs. The outcomes of patients within the evaluation scheme appear more comparable with patients in the control (MTA) arms of trials, where the estimated adverse event rates range from 1.3 to 3.4 per 100 patient years albeit that the trial follow up periods (for both MTA and PFO closure groups) are considerably longer (2 to 6 years), giving longer for cumulative adverse events. Comparisons between the NHS CtE study and published RCTs provides some insight into the likelihood of gains in routine practice. Interpretation is not straightforward, not least because patients entering trials are carefully selected and different methods are used for follow up, assessment of outcome and for analysis.

The CtE investigators were unable to identify a UK based model that would assist the economic assessment of CtE; they therefore developed their own Markov model, using clinical data from the RESPECT trial. This analysis concluded that for every 1,000 patients undergoing PFO closure there could be 275 fewer strokes over a lifetime (45-year time horizon). The cost-consequences model indicates that each PFO procedure would cost the NHS £5,360 more per patient undergoing the procedure than MTA (over these 45 years); this after taking account of the costs of treatment, the likelihood of sustaining a stroke and the costs of treatment and care

for such events. The additional cost above MTA reduced to £3,733 per patient undergoing PFO when taking into account the societal costs of stroke. This analysis did not however attempt to value the quality of life losses attributable to sustaining a stroke.

8 Proposed Criteria for Commissioning

PFO closure will be commissioned for patients who have suffered stroke or TIA with brain imaging abnormalities confirming ischaemic damage, due to paradoxical embolus (where a venous clot has passed through a PFO and caused a stroke).

The age ranges of patient cohorts studied in the RCTs were between 16 and 60 years. The evidence confirms that age is a very good predictor of atherosclerotic disease, which dominates the risk of recurrent stroke in the general population. The impact of a PFO on recurrent stroke risk is clearly discernible in a 50-year-old but far more difficult to establish in patients over 60 where risk of atherosclerotic disease is increasing and the risk of stroke from other causes. The policy therefore uses the same age criteria as were used for trial entry of 60 years or below. If a PFO closure for secondary prevention of stroke is proposed in patients under the age of 18 years they should be referred to a Children's Cardiac Surgical Centre and considered by the relevant MDT. It is recognised that new referral of patients over 16 may also be referred to an adult cardiac centre commissioned to undertake percutaneous closure.

It is also anticipated that the diagnosis of stroke or TIA will be supported by clinical assessment and brain imaging and that patients will have undergone comprehensive evaluation for the presence of usual stroke risk factors such as hypertension, vascular disease, atrial fibrillation and smoking.

Assessment of PFO

It is anticipated that all patients will be discussed at a MDT and the final decision regarding intervention will be taken there.

Stroke or TIA patients where there is a suspicion of PFO should undergo bubble contrast transthoracic echocardiography, including provocative manoeuvres to open

a PFO that has no right to left shunt at rest. Transoesophageal bubble contrast echocardiography may be used as an alternative and bubble contrast transcranial Doppler may be used to exclude a PFO. Large PFOs and those associated with atrial septal aneurysm are more likely to have caused a stroke.

Criteria for PFO closure

1. Stroke or TIA with clinical and imaging evidence to support diagnosis
2. Presence of a PFO with large shunt or atrial septal aneurysm
3. Absence of significant atrial fibrillation or other indications for anti-coagulation
4. Full investigation to identify other explanations for stroke, such as vascular disease (including dissection), hypertension or other risk factors
5. MDT including stroke clinician and interventional cardiologist consider paradoxical embolus to be the most likely cause of stroke, and do not consider that there are other likely causes
6. Age 60 or under as per the clinical trial criteria

PFO closure procedure

The PFO closure procedure should be undertaken, following fully informed consent, by a cardiologist experienced in percutaneous procedures on the atrial septum, such as PFO and ASD closure. They should also be trained in managing potential complications of the procedure, such as percutaneous device retrieval and pericardial drainage (even though these are very rare complications). Ultrasound guidance should be used to access the femoral vein and transoesophageal echocardiography or intracardiac echocardiography coupled with X-ray fluoroscopy should be used to guide the positioning of the PFO occluder. Centres should comply with previous Adult Congenital Heart Disease Guidelines which were supported by British Cardiac Society, British Cardiac Intervention Society and British Congenital Cardiac Association.

The procedure should be performed with arrangements for cardiac surgical back up, even though complications requiring this are extremely rare.

Transthoracic echocardiography should be performed prior to patient discharge to exclude any complications of the procedure.

Anti-platelet, or in some patients, anti-coagulant drugs will usually be continued for 6 months post procedure. Long term aspirin is often indicated.

Procedural Complications

Serious complications are very rare. Vascular damage occurred in 0.8% of patients in the RESPECT study, but can be reduced by vascular ultrasound to guide the venous puncture. Device embolisation is rare with current devices but follow up echocardiography is required to confirm device position. Atrial arrhythmia is the most common complication but is usually self-limiting and occurs in the first few weeks after the procedure. It remains unclear if there is any excess atrial arrhythmia in the very long term; in the longest and largest study (RESPECT) at mean 2.5 years follow up there was no difference in atrial arrhythmia. There was a slight excess of atrial arrhythmia at mean 5.9 years follow up but this was not statistically significant (p=0.3).

Follow up after PFO closure

Follow up may include management of other stroke risk factors if present such as smoking, hypertension and elevated serum cholesterol, as clinically appropriate. Repeat transthoracic bubble contrast echocardiogram, usually after 6 to 12 months or transoesophageal echocardiogram if felt necessary by the cardiology team, should be performed.

9 Proposed Patient Pathway

Patients with stroke or TIA will be assessed by a neurologist or stroke specialist who will confirm the diagnosis by clinical evaluation and appropriate imaging. Common cause of stroke will be sought but when none can be found and the pattern of stroke disease is consistent with an embolic mechanism, transthoracic bubble contrast echocardiography should be considered or transoesophageal echocardiography if felt to be indicated.

Individuals with a PFO with features suggesting that it may be the cause of stroke should be considered by a MDT consisting of a stroke specialist and an interventional cardiologist with expertise in the management of PFO patients.

Eligibility for PFO closure should be considered based on the patient selection criteria discussed in section 8.

10 Proposed Governance Arrangements

It is a requirement that sites will produce information leaflets (clinical indications, clinical benefits, complications, need for follow up, current evidence base and its limitations) for patients about percutaneous PFO closure. Alternatively, implanting sites will have information available via their website.

Follow up will likely be undertaken in the centre in which the procedure was carried out and it is anticipated that patients will be seen at least once, including a repeat transthoracic bubble contrast echocardiogram 6 to 12 months after device implantation. Transoesophageal echocardiogram may be appropriate if there is clinical suspicion of device malposition, thrombosis or other complication.

NICE has previously indicated that normal governance arrangements are appropriate as there are no safety concerns about the procedure.

The use of a Percutaneous PFO occlusion device will subject to the NHS England prior approval system.

A suspected problem ('adverse incident') with the medical device should be reported using the Yellow Card Scheme as soon as possible at the following link: https://www.gov.uk/report-problem-medicine-medical-device

11 Proposed Mechanism for Funding

The device is excluded from the national tariff and will be funded by pass through payments made against invoices raised by provider Trusts or through the high costs device programme.

The procedure is included in tariff and will be funded through the routine contract procedures. A specific code exists for percutaneous PFO closure (K16.5 Percutaneous transluminal closure of patent ovale foramen with prosthesis) and maps to HRGs EY22, EC12, EC13 and EC14. All activity must be recorded using these codes.

12 Proposed Audit Requirements

Centres must undertake an annual audit of their percutaneous PFO closure programme, reporting efficacy and safety outcomes within the clinical governance structure of their hospital and network. They should benchmark themselves against existing and developing regional, national and international data. These audits should include the appropriate procedure code. The audits and their findings should be made available to commissioners.

13 Documents That Have Informed This Policy Proposition

This document updates and replaces Clinical Commissioning Policy Statement: Patent Foramen Ovale (PFO) Closure April 2013 (Reference: NHSCB/A09/PS/a).

For all other indications percutaneous PFO closure is not routinely commissioned.

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

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