CPAG Summary Report for Clinical Panel – Patent Foramen Ovale Closure for Secondary Prevention of Cryptogenic Stroke

The Benefits of the Proposition – Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	There is no survival benefit [B]	Systematic review of RCTs found no statistically significant difference between treatment groups for all-cause mortality (De Rosa et al 2018). The follow up period in the RCTs may have been too short (mean range 2.6 to 5.3 years), to meaningful differences in all-cause mortality
2.	Progression free survival	Choose an item.	
3.	Mobility	Choose an item.	
4.	Self-care	Choose an item.	
5.	Usual activities	Choose an item.	
6.	Pain	Choose an item.	
7.	Anxiety / Depression	Choose an item.	
8.	Replacement of more toxic treatment	Choose an item.	
9.	Dependency on care giver / supporting independence	Choose an item.	
10.	Safety	Adverse events identified [B]	Serious adverse events (SAEs): any event potentially resulting in significant impairment or death, requiring hospitalization or prolongation of hospitalization. There was no significant difference in these SAEs between those having PFO closure and MTA: 25% vs 24% (De Rosa et al 2018).
11.	Delivery of intervention	Choose an item.	

Other health metrics determined by the evidence review - Percutaneous Patent Foramen Ovale (PFO) Closure Vs. Medical Therapy Alone (MTA) for secondary prevention of cryptogenic stroke.			
No	Metric	Grade of evidence	Summary from evidence review
1.	Recurrent Stroke	Grade A	Absolute risk of recurrent stroke over study period (2.6 to 5.3 yrs) 3.2% lower among patients who had PFO closure than those on MTA (Shah et al 2018) Absolute risk of ischaemic stroke PFO closure vs MTA: 1.2% vs 4.1%. De Rosa et al 2018 The 3.2% absolute reduction in risk for PFO vs MTA should be considered against the risk of stroke for patients on MTA (4.1-4.6% in the study period), equivalent to 28 fewer strokes per 1000 patients undergoing PFO closure. This summary estimate should be treated with caution. There was significant heterogeneity between the four RCTs included in meta-analysis.
2.	TIA	Grade B	Risk of a TIA during the study period (3.2 to 5.9 yrs) Patients who had PFO closure were no more or less likely to have a TIA than those on MTA. Shah et al (2018) This summary estimate should be treated with caution. There was significant heterogeneity between the four RCTs included in meta-analysis.
3.	Composite of stroke or TIA	Grade B	risk of a stroke or a TIA during the study period (2.6 to 5.3 yrs) PFO closure: 3.6% MTA: 6.3% (De Rosa et al 2018) This summary estimate should be treated with caution. There was significant heterogeneity between the four RCTs included in meta-analysis.
4.	Major Bleeding	Grade B	During the follow up period (3.2 to 5.9 yrs), Patients undergoing PFO closure had a (non-significant) lower risk for major bleeding vs MTA. • RD: -0.021 (95%CI: -0.051 to -0.009), p=0.093). Shah et al (2018) • 0.9% vs 1.2% (RD: -0.002, p=0.605) De Rosa et al 2018
5.	New onset AF or Atrial flutter	Grade A	New onset AF or atrial flutter patients undergoing PFO closure: 4.1% compared to MTA 1.0% De Rosa et al (2018).

			Shah et al (2018) found an increased incidence of new onset AF for PFO closure compared with MTA, but considered the heterogeneity (I^2=82.5%) to be too high to pool results.
6.	Cost Effectiveness	Grade C	The cost effectiveness of PFO closure compared to MTA was based on the direct costs and clinical outcomes (in US health care system) of all PFO closure devices and MTA regimes used in the CLOSURE, PC-TRIAL and RESPECT studies (Pickett et al 2014). Compared to MTA, PFO closure was $16,213 more expensive at 2.6 years' post PFO closure procedure: Compared to MTA, PFO closure was less cost-effective at 2.6 years' post PFO closure procedure for a number of outcome measures: • additional $103,607 per life year gained • additional $1,085,334 to prevent 1 combined endpoint (TIA, stroke, death) The estimated time for PFO closure to reach cost effectiveness threshold<$50,000 per QALY was 2.6 yrs (95%CI 1.5 to 44.2yrs). The estimated time for the mean cost of medical therapy to exceed the cost of PFO closure was 30.2yrs (95%CI 28.2 to 36.2yrs).

The Benefits of the Proposition – Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Choose an item.	
2.	Progression free survival	Choose an item.	
3.	Mobility	Choose an item.	
4.	Self-care	Choose an item.	
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8.	Replacement of more toxic treatment	Choose an item.	

9.	Dependency on care giver / supporting independence	Choose an item.	
10.	Safety	Choose an item.	
11.	Delivery of intervention	Choose an item.	

Other health metrics determined by the evidence review - Percutaneous Patent Foramen Ovale (PFO) Closure for secondary prevention of cryptogenic stroke (uncontrolled studies).			
No	Metric	Grade of evidence	Summary from evidence review
1.	Immediate procedural success within 30 days	Grade C	Immediate procedural success: device remaining in situ and effectively closing the PFO within the first 30 days after the procedure. 99.8% devices and device procedures were successful This outcome is based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012.
2.	Complications within 30 days	Grade C	Electrical complications and non-electrical complications that occurred within 30 days of PFO device implantation were reported. Among 1000 PFO closure device recipients, 59 (5.9%) experienced electrical complications (Rigatelli et al 2017), most commonly Temporaneous AF: 46 (4.6%) all resolved within procedure 26/1000 (2.6%) experienced non-electrical complications (Rigatelli et al 2016): most commonly groin haematomas:10(1.0%) These complication rates are based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012.
3.	Predictors of complications within 30 days	Grade C	Analysis of the characteristics of patients who experienced complications following PFO closure implantation was reported. Females were more than twice as likely to experience complications within 30 days of PFO closure: People who required a PFO device disk larger than 30mm were 4-5 times more likely to experience complications within 30 days These predictors of complications are based on

			one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012.
4.	Complication rate at median 10.5 yr f/up	Grade C	Longer term electrical complications and non-electrical complications that had occurred at the median follow up time of 10.5 years after PFO closure device implant were reported. 14/1000 (1.4%) of the 1000 PFO closure device recipients experienced long-term electrical complications (Rigatelli et al 2017) comprising, most commonly AF (0.9%) 22/1000 (2.2%) experienced long-term non-electrical complications (Rigatelli et al 2016): most commonly in 13 (1.3%) (11 neoplastic related, 2 car accident related) These complication rates are based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012.
5.	Predictors of complications at median 10.5 yr f/up	Grade C	Analysis of the characteristics of patients who experienced long-term complications following PFO closure implantation was reported. Patients with a large (3-5 grade) ASA as well as PFO were 2 to 3 times more likely to experience complications in the longer term: Patients for whom the mean ratio between device size and entire septum length was >0.8 were 2 to 3 times more likely to experience complications: These predictors of complications should be treated with caution. They are based on one uncontrolled study of 1000 patients who received a PFO device between 1999 and 2012. It is not clear what proportion of subjects had cryptogenic stroke: a high proportion had known risk factors for stroke (eg diabetes, hypertension, smoking). There was heterogeneity between subjects (including PFO size, presence of ASA), PFO devices and concomitant medication.

Abbreviations: AF: atrial fibrillation, ASA: atrial septal aneurysm, AVB: atrioventricular block, f/up: follow up, HR: hazard ratio, I^2: measure of heterogeneity, MTA: medical therapy alone, OR: odds ratio, PFO: patent foramen ovale, QALY: quality adjusted life year, RD = risk difference, TIA: transient ischaemic attack; yrs: years

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

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

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

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