**EUROPEAN POSITION PAPER ON PATENT FORAMEN OVALE MANAGEMENT**

**European Association of Percutaneous Cardiovascular Interventions (EAPCI),**

**Association for European Pediatric and Congenital Cardiology (AEPC),**

**European Association for Cardiovascular Imaging (EACVI),**

**European Haematological Society (EHA),**

**European Heart Rythm Association (EHRA),**

**ESC Working group on GUCH,**

**ESC Working group on Thrombosis,**

**European Stroke Organisation (ESO),**

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**PART I - GENERAL APPROACH AND LEFT CIRCULATION SOLID EMBOLISM**

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# INTRODUCTION

The patent foramen ovale (PFO) is implicated as a possible conduit in a number of medical conditions, but we are rarely able to be categoric about its role in any given clinical setting. As such, it has proved elusive to interrogation by standard clinical trial methodology, stressing the need for new clinical and research approaches for complex scenarios (1–5). This interdisciplinary paper, endorsed by 8 European scientific societies, aims to define the principles needed to guide decision-making in this probabilistic milieu.

# METHODS

The European Association for Percutaneous Cardiovascular Interventions (EAPCI) invited European scientific bodies and international experts to develop a shared position statement and recommendations regarding management of PFO. In order to guarantee a strict evidence-based process, a similar methodology was used to develop both recommendations and position statements with the use of a modified GRADE methodology (<http://gdt.guidelinedevelopment.org/app/handbook/handbook.html>), by answering population-intervention-comparator-outcome (PICO) questions to establish recommendations and non-PICO questions to establish position statements.

A detailed review of the methodology used can be found in appendix I. Systematic reviews

and statistical analysis were performed by a dedicated evidence synthesis team. The paper is subdivided in two parts, published separately: the first one related to the methods, general approach and left circulation solid embolism; the second part to decompression sickness, desaturation syndromes, migraine and other clinical settings.

## Statistical Methods

Continuous variables are reported as mean (standard deviation) or median (range). Categorical variables are expressed as n/N (%). In order to support the expression of recommendations and position statements, 4 original meta-analyses were performed for PICO questions and for the accuracy of diagnostic tests for PFO. A meta-regression for assessing the impact on outcomes of the length of dual antiplatelet therapy after closure was also performed. Further details are provided in appendix II.

***Meta-analyses of association studies or of studies on therapy outcomes***

Statistical pooling was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals, using RevMan version 5.3, (The Cochrane Collaboration, The Nordic Cochrane Centre, and Copenhagen, Denmark, <http://community.cochrane.org/tools/review-production-tools/revman>). Hypothesis testing for superiority was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and based on the Cochran Q test, with I2 values of 25%, 50%, and 75% representing, respectively, mild, moderate, and extensive statistical inconsistency.

***Meta-analysis of studies on diagnostic tests accuracy***

Based on the frequencies of true-positive, false-positive, true-negative, and false-negative results in the individual studies, the pooled sensitivity, specificity, and area under the summary receiver operating curve (sROC) were estimated for TCD and TTE (vs TEE, which was treated as the gold standard procedure) (6,7). The area under the sROC values were compared between TCD and TTE using the appropriate z tests. All statistical analyses were performed with Review Manager (RevMan) version 5.3 software (Copenhagen, Denmark, Nordic Cochrane Centre, Cochrane Collaboration, 2014) and STATA/SE version 13 (Stata Corp, College Station, TX). Pooled analysis of sensitivity, specificity and AUC was performed with Meta Disc (version 1.42)

***Evaluation of risk predictors***

Risk estimates were not pooled from individual studies as this approach would have been not feasible and valid given the likelihood of small study effects. We instead adopted Ross et al. approach (8) and appraised the prevalence of studies in which a given predictor proved significantly and independently associated with the outcome of interest in at least 2 studies.

# GENERAL APPROACH TO PFO MANAGEMENT

Position statements on general approach to PFO management are summarised in Table 1.

## **The main axes of evaluation**

In all clinical scenarios, the two main axes guiding assessment and treatment of PFO should be: 1) the probability that any PFO has a relevant role in the observed clinical picture; 2) the likelihood that the observed clinical event will recur. For the highest probability regarding these points, closure of the PFO should be advised. For the lowest probability, medical therapy should be considered. For medium probabilities, all relevant clinical factors should be incorporated to allow good decision-making in liaison with the patient.

## **Pro-active approach: an interdisciplinary collaboration, shared decision-making, and open informed consent.**

Interdisciplinary involvement in decision-making regarding PFO management is axiomatic, and should include an interventional cardiologist and other specialists dictated by the patient’s clinical manifestations. Active involvement of the patient in the decision-making process is mandatory (9,10) and should be documented in an individualised, open, informed consent. Decision aids and narrative tools can be effective in achieving these aims, and can complement the informed consent form (11–16).

## **Diagnosing PFO**

The diagnosis of PFO is useful only if it will influence the treatment in any given clinical scenario. Several techniques can be used to diagnose PFO (17), and their characteristics are summarised in Table 2.

Contrast transoesophageal echocardiography (c-TOE) has been used as a gold-standard in the detection of PFO. It provides unparalleled visualisation of the interatrial septum and other relevant structures. However, a meta-analysis of the accuracy of c-TOE in the diagnosis of PFO compared to autopsy, cardiac surgery, and/or catheterisation yielded a weighted sensitivity of only 89% (18). This is confirmed by other studies (19–32), which show a marked underestimation of the prevalence of PFO compared with historical autopsy studies (33–43) (Figure 1). Inability to perform an adequate Valsalva manoeuvre during transoesophageal echocardiography is probably responsible (44,45). This relatively high false negative result may influence the prediction of recurrence related to the assessment of post-procedural shunt (46,47) and may in part explain the inconsistent results of epidemiological studies (31). c-TOE is necessary to characterise the PFO and stratify the risk in the diagnostic phase (48–53), and systematic reporting of a set of parameters could help in guiding assessment (Table 3). c-TOE can also be used as a first-line investigation when a comprehensive evaluation of other cardiovascular structures is necessary (e.g. the left atrial appendage and/or the aorta and its arch). Three-dimensional TOE is an ideal technique to understand the anatomy of the interatrial septum and guide the interventional procedure (53). Bleeding, aspiration, or oesophageal perforation are rare TOE complications (54).

In an updated meta-analysis of 29 studies comparing contrast-enhanced transcranial Doppler (c-TCD) with c-TOE across 2751 patients (17,55–83), it was found that c-TCD had a sensitivity of 94% and a specificity of 92% (figure 2A) with an area under the receiver operating curve (AUC) 0.97 (figure 2B). In a previous meta-analysis, the specificity of c-CTD was increased to 100% when the threshold for a positive shunt was increased to 10 High Intensity Transient Signals (HITS) (84).

However, in our meta/analysis the quality of evidence was estimated as low because of serious risk of bias and imprecision (Appendix Table 6). Moreover, the inconsistency across studies was 67% for sensitivity and 73% for specificity. These limitations led us to express position statements instead of recommendations. Further details on this meta-analysis can be found in Appendix II.

To summarise available evidence also for contrast-enhanced transthoracic echocardiography (c-TTE), we performed an original meta-analysis of 13 studies across 1360 patients comparing c-TTE against c-TOE (25,61,75,77,85–93). c-TTE was 88% sensitive and 82% specific (Figure 3A). However, the AUC was 0.91, although again with a severe inconsistency among studies (Figure 3B) and a low quality of evidence (Appendix Table 6). Further details on this meta-analysis can be found in Appendix II. Another recent meta-analysis also showed superior overall diagnostic yield of c-TCD compared to c-TTE (94).

Based on the need for first-line investigations to minimise false negative screenings, we propose a diagnostic algorithm in Figure 4 that can be adapted to satisfy disparate clinical and logistic needs.

# SPECIFIC ISSUES AND RECOMMENDATIONS

## **I. LEFT-CIRCULATION SOLID EMBOLISM**

PFO has been associated with solid systemic embolism to cerebral, coronary, ocular, limb, and visceral arteries (95). These clinical scenarios affect large numbers of patients (96–98).

#### DEFINITIONS

We urge to use standardised definitions of outcomes in clinical setting and in the research.

Cryptogenic ischaemic cerebrovascular accidents or systemic embolisms are defined as any definite ischaemia (symptomatic or asymptomatic) occurring in an arterial bed which lacks a known cause despite investigation. Standard definitions of ischaemic cerebrovascular events can be found elsewhere (50). Patients presenting with this clinical scenario should be screened for presence or absence of a PFO. When a PFO is thought likely to be implicated in a cryptogenic embolism, the event should be classified as PFO-related instead of cryptogenic (50). Current classifications do not include this aspect yet (99–102).

#### IS PFO ASSOCIATED WITH CRYPTOGENIC STROKE?

Epidemiological data support an association between PFO and cryptogenic stroke (103–107). Additionally, studies have documented an increased rate of systemic embolization among patients who have venous thrombus or debris and have a PFO. (108–111) (see appendix III). Thirdly, many reports have provided direct evidence of thrombi trapped within a PFO (112–119). Lastly, and most importantly, randomised trials have shown that PFO closure reduces stroke recurrence in comparison with medical therapy (120–122).

However, the causative role of a PFO can vary in different clinical scenarios due to different underlying processes. These include: paradoxical embolism; thrombus forming within the PFO; left atrial dysfunction; and atrial arrhythmias (see appendix III). Research aimed at identifying individual patients' pathophysiology is needed to improve clinical management.

#### IS IT POSSIBLE TO ESTIMATE THE LIKELIHOOD OF A PFO-MEDIATED STROKE?

A PFO is seen in ~25% of the general population, and may therefore coexist by chance in a patient with an unexplained stroke. It is therefore important to assess the probability that the PFO was the conduit in a given case. For a more detailed discussion of each paragraph see appendix III. Position statements are summarised in Table 4A.

***Patient characteristics***

Although observed in patients of almost any age (107), a meta-analysis showed a stronger relative association of PFO with cryptogenic stroke in patients < 55 years as compared to older patients (123). However, despite the comorbidities, in older patients the association is still observed, perhaps due to the increasing prevalence of venous clots or to the increasing size of PFO with age (124).The presence of other clinical risk factors for stroke does not, *per se*, exclude a pathophysiological role of PFO in cryptogenic embolism, though their absence increases the likelihood of its pathogenic role (125).

***Imaging stroke pattern***

Neither the site nor type of infarct pattern in grey or white matter is specific for PFO embolism (125–135). Cortical infarcts are usually embolic even when they are small but a recent patient-level meta-analysis suggests that non-cortical infarcts can also have an embolic origin (136).

***Characteristics of the PFO***

An atrial septal aneurysm (ASA) suggests a more probable causal role of PFO in patients with cryptogenic stroke (121,122,137–140). It is likely that an ASA is simply an indicator of a larger and more frequently open PFO (120,122,141). Other studies have failed to detect these associations however (125,142), underlining the presence of different underlying causative phenotypes and the need to identify them. A Eustachian valve or Chiari network can facilitate paradoxical embolism (143). Also, a long PFO tunnel has been linked to increased stroke risk, although the reason for this is unclear (144).

***Clinical clues***

Documentation of a venous source of embolism around the time of stroke strongly suggests paradoxical embolism in the presence of a PFO. Absence of evidence of venous thrombus is unhelpful because of frequent false negatives (109,145–147). Studies that have attempted to identify an association between inherited thrombophilia and PFO-related stroke have yielded conflicting results (148–151). Simultaneous occurrence of pulmonary and left circulation emboli strongly indicates paradoxical embolism, (110,147) and a history of previous pulmonary embolism supports a paradoxical mechanism (152). Other clinical circumstances such as immobilisation, recent major surgery, an extended car or airplane journey imply possible venous clot development. Activity at the time of the stroke is also relevant - straining manoeuvres, obstructive sleep apnoea and stroke-on-waking should be enquired for. (152–154).

The RoPE (Risk of Paradoxical Embolism) represents an attempt to assign a causal relationship probability to individual PFOs in the setting of stroke of unknown cause (125) and may be useful in helping to guide management decisions. However, it should always be used in conjunction with other parameters because the quality of evidence of internal validation studies has been rated moderate at best (Appendix Table 3) and no large external validation studies have been published.

#### WHAT IS THE RISK OF RECURRENCE IN PFO-ASSOCIATED STROKE?

Meta-analysis suggests that the recurrence rate on medical therapy ranges from 0% to 4.4% for stroke and from 0% to 14% for either TIA or stroke (137,155–157). This wide variability stresses the heterogeneity of patients with these syndromes and the need to obtain more precise phenotypes to identify high risk subjects. Causes of recurrence can of course include non-PFO mediated mechanisms (158,159). Some predictors of stroke recurrence have been identified (46,139,156,160). Table 5 lists features that were statistically significant predictors in at least two studies (105,139–141,160–174). Atrial septal aneurysm anatomy is particularly predictive. (see appendix III). A PRISMA diagram of the selection process in the literature review to obtain these studies is displayed in Appendix Figure 1. In one study (175), a high D-dimer level on admission was an independent predictor of recurrent ischaemic stroke in patients with PFO. Position statements are summarised in Table 4B.

#### DIAGNOSTIC WORKUP

A diagnostic workup should follow logical steps (Figure 5) and the inherent choices should be done with the patient's active collaboration taking into account the aims and the pros and cons of different tests. Table 6 summarises position statements. Further details are provided in Appendix III.

The diagnostic process begins with a clinical assessment and appropriate imaging. In cases involving a cerebrovascular accident, an accurate neurological evaluation is required. Most TIAs persist less than one hour. Motor and speech deficits are more reliable, while sensory deficits are evanescent (176). In young patients, rare genetic causes of stroke should be excluded (177–180).

Ruling out atrial fibrillation (AF) is important because it is considered to be a possible cause of cryptogenic embolism. A routine 12-lead ECG and either inpatient cardiac telemetry or 24-hour Holter monitoring are usually sufficient to diagnose permanent AF and sufficiently long transient AF episodes. However, randomized and observational studies showed that insertable cardiac monitors (ICM) (181–184) significantly increase AF detection in cryptogenic stroke. ICM monitoring is associated with increased yield of AF diagnoses relative to cardiac monitoring (185,186) (for details see appendix III). Therefore, in older patients with risk factors for atrial fibrillation an ICM monitoring period of six months can be reasonably considered before choosing between medical therapy or percutaneous closure of PFO (187). During ICM monitoring patients should be maintained on medical therapy (see "Secondary prevention" paragraph). Figure 6 shows an “AF rule-out” flow chart for left circulation cryptogenic embolism based on risk stratification of patients including age (> 55 years) (188,189), a CHADS2 or CHA2DS2-VASc score > 1 (182,183,190–194), prior cortical or cerebellar infarction on neuroimaging and other criteria (183,191,195–197). After six months, whatever the chosen treatment, the monitoring can be extended to the full duration of the ICM life to identify episodes of paroxysmal AF (198–204); to monitor the atrial thrombosis burden in arrhythmic patients; and to direct an etiologic diagnosis in cases of recurrent ischaemia.

**Evaluating the need for treatments that question interventions for PFO**

Any indication for long-term OAC may obviate the need for PFO closure. However, in the setting of deep-vein thrombosis and/or pulmonary embolism (205), PFO closure may be considered when there is a high risk of recurrence despite OAC. For patients with paroxysmal AF there is uncertainty regarding the duration of arrhythmic episodes that increases the risk of embolism. According to the HRS/EHRA/ECAS expert consensus statement on AF ablation, AF episodes ≥ 30 seconds constitute clinically significant AF (206). During prolonged monitoring, episodes of AF ≥5 minutes have a predictive value for embolism (207–211). These findings may be combined with a thromboembolic score to evaluate the need for OAC (212). However, the presence of short bursts of AF on an ICM may carry a lower pathogenic value than a high risk PFO. Therefore, ICM results should always be interpreted with other clinical characteristics. Routine laboratory tests for prothrombotic states (thrombophilia testing) are not warranted to indicate permanent anticoagulation (213,214).

## SECONDARY PREVENTION

Further insights on each paragraph can be found in appendix III.

#### EFFICACY AND SAFETY OF MEDICAL THERAPY

A variety of medical treatments has been used, based upon data from secondary prevention studies for stroke at large and from studies on cryptogenic stroke in particular. In PFO-associated cerebrovascular accidents, no trial has yet been published that has specifically assessed the effectiveness of single drugs, but in each trial several drugs were allowed under a class definition, being sometimes also given in combination.

The vast majority of trials were observational and only one randomised comparing OAC and antiplatelet agents. Two meta-analyses of non-randomised data suggested a recurrent stroke rate of 1.3 events per 100 patients-year (215) and a pooled incidence of primary endpoints of 1.8 events per 100 patients-year (216). In a meta-analysis of observational trials, the recurrence rate with mixed medical therapy was 5% per year (217). Meta-analyses of observational studies consistently suggest superiority of OAC over antiplatelet agents in the prevention of stroke (217–220). This is also in keeping with the most recent meta-analysis including the randomised study (Figure 7 and Appendix II). Although the overall quality of the evidence in this meta-analysis was estimated very low (Appendix figure 5), the superiority of OAC vs. antiplatelet agents was also evident when considering studies with multivariate adjustment only (Figure 7). No data are available on persisting disability and quality of life.

Reports on safety have often been incomplete or yielded inconsistent results. In a meta-analysis of observational studies, 1.1% of patients receiving medical therapy experienced a bleeding complication (217). This surprisingly low proportion of bleeding episodes can be explained by the young age of the patients and the short follow-up and, thus, must be interpreted with caution. Indeed, in our meta-analyses on PFO patients, an OR of 4.57 was found for major bleeding with OAC relative to anti-platelet drugs (figure 8). A previous meta-analysis considering secondary prevention of stroke at large revealed that the potential benefit of OAC might be outweighed by the risk of both intracranial haemorrhage (OR 2.54) or major extracranial haemorrhage (OR 3.43) (221). In this respect direct oral anticoagulants (DOACs) may be an alternative (222,223), although no data exist in these patients.

#### SAFETY AND EFFICACY PROFILE OF PFO CLOSURE

#### PERCUTANEOUS PROCEDURE

The initial report on percutaneous PFO closure pertained to an atrial septal defect device (224). The first dedicated PFO closure device was implanted in 1997 (225). Primary technical success approaches 100% (217) and complete closure is seen in 85-95% at one year. The use of larger devices has a higher risk of residual shunts (217,226–228) and the Amplatzer occluder may have lower residual shunt rates than other devices (59,226,228–232). Freedom from recurrent embolism is ~97% at five years (233). Individual randomized data show a relative risk reduction of up to 80% for recurrent strokes (161,234). Two meta-analyses of three randomized trials have shown the stroke recurrence rate to be 0.76 per 100 person-years (215) and a pooled incidence of primary endpoints of 1.2 per 100 person-years (216) (see appendix III). In the most recent meta-analysis, including all available five RCTs, the number needed-to-treat (NNT) with PFO closure to prevent one stroke during 3 to 5 years follow-up was 41 (figure 9 A and B). Results on TIA and on death were neutral (figure 9 C and D, respectively). An increase of the treatment effects over time can be expected (122,235). No data are available on persisting disability and quality of life.

Complications are infrequent and are summarised in Table 7. Device embolism occurs at a rate of 0.9-1.3% (233,236). Minor complications occur only in 1.0-1.7%. The most frequent late complication is device thrombosis, which is seen in 1.0-2.0% (236). The risk of long-term mortality or the need for cardiac surgery is less than one in 1000.

The most frequent undesirable events following transcatheter percutaneous closure are atrial arrhythmias, especially AF (122,198–203,217). Considering AF, in the last meta-analysis the number needed to harm (NNH) was 29 (figure 10 A). Although post-procedural AF may reflect a higher atrial vulnerability related to the PFO (198–203,237), the majority of the reported events in RCTs appeared to be related to the procedure and did not recur later in the follow-up (120–122,199,200). Indeed, in our meta-analysis, for AF occurring in the first 45 days after the procedure the NNT was 38 (figure 10 B), whereas the risk of AF occurring beyond 45 days was similar to patients on medical therapy (figure 10 C). The incidence of these events was lowest with Amplatzer PFO occluders (<1%) (136,238–241) (figure 11). Interestingly, a statistically significant reduction of AF prevalence after percutaneous closure of PFO was also shown in other studies, suggesting some antiarrhythmic effect of the procedure (242).

#### MANAGEMENT AFTER PERCUTANEOUS CLOSURE

No data on best management strategies after FPO closure are available. Position statements are summarised in Table 8.

**Drug Treatments**

To decide on post-procedural therapy one should consider that: a) endothelialisation of the device peaks between six months and one year, but can continue up to five years post implantation (47,230,243,244); b) one of the most frequent complications after closure is device thrombosis; and c) premature discontinuation of therapy may cause minor cerebrovascular events after PFO closure, as suggested by a marked trend towards duration of dual antiplatelet therapy after PFO closure and the incidence of TIA in our study-level meta-regression (figure 12).

It is reasonable to decide on the post-procedural therapy according to the prescription policies in RCTs. Overall, 4/5 RCTs prescribed a dual antiplatelet therapy in the first 1-6 months after closure, continuing with a single drug beyond 2 years in 3/5 RCTs. Among positive trials, 2/3 prescribed an antiplatelet therapy for 5 years. In one negative trial, only 50% and 41% of patients were still taking an antiplatelet therapy after 1 and 5 years respectively (234).

**Delayed complications**

Table 7 displays the main tools available to detect complications. At present, no relationship between PFO patency after closure and the incidence of recurrence has been found (Table 9) (79,227,245–250) but studies were small and often plagued by partially incomplete follow-up. Moreover, some data show that residual shunts can also re-appear after a first negative study during follow-up (47), thereby casting doubt on the reliability of these data.

No high-quality data are available regarding the management of a significant residual shunt. The literature on acute and long-term results after repeat device implantation for a residual shunt is scarce, but the reported results are encouraging (251–257). The largest series encompasses 100 patients with initial PFO closure and a residual shunt at follow-up TOE that was considered significant enough for a second device (258). Procedural success was 98%. There were no early or late complications, and a 6-month follow-up TOE was available for 91% of the patients, revealing complete closure in 73%.

Empirically, antibiotic prophylaxis against endocarditis before an invasive procedure or surgical intervention should also be recommended routinely in all cases within the first six months after the implantation and it may be considered beyond six months in patients with a residual shunt.

#### SURGICAL CLOSURE OF PFO

There are no current indications for surgical closure of a PFO as first-line treatment. Standalone surgery has yielded varying results (259,260), with a high complication rate (~20%) (259)and an unsatisfying closure rate (261). Closure of incidental PFOs is not generally advocated during coronary artery bypass surgery because of the higher risk of postoperative stroke (262), but during valvular surgery incidental PFO closure is usually undertaken. Surgical PFO is also done in rare cases when surgery is indicated for other conditions in which the PFO plays a role, such as a straddling thrombus in the PFO or a right-sided cardiac tumours causing hypoxaemia or paradoxical embolism through a PFO (263). Finally**,** PFO should be closed during surgery performed for rare complications which cannot be managed by percutaneous means, such as infected or misplaced PFO devices or erosion of the atrial free wall caused by a PFO device.

**Should percutaneous closure of PFO vs. medical therapy be used for secondary prevention of stroke or systemic solid embolism?**

|  |  |
| --- | --- |
| **Population:** | secondary prevention of stroke, TIA, or systemic solid embolism  |
| **Intervention:** | percutaneous closure of PFO |
| **Comparison:** | medical therapy |
| **Main outcomes:** | Stroke, TIA, death, bleedings, atrial arrhythmias |
| **Setting:** hospital |

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | ○  | ○  | ●  | ○  |

 |
| **RecommendationS** | We recommend percutaneous closure of a PFO in carefully-selected patients aged from 18 to 60 years with a confirmed cryptogenic stroke, TIA or systemic embolism and an estimated high probability of a causal role of the PFO as assessed by clinical, anatomical and imaging features. The interventional procedure must be proposed to each patient with different degrees of probability of benefit, according to the individual probability of a causal role of PFO and the probability of recurrence and balanced with the expected results and risks of a life-long medical therapy. The role of the patient should be pro-active, keeping in highest regard his/her values and preferences regarding outcomes and therapy trade-offs, and informing him/her about the uncertainties of their condition. With the same shared-decision making approach, PFO closure can also be considered in patients >60 or < 18 years of age, taking into account on a case by case basis the lack of evidence, the age-related confounders and additional risks of interventional and drug therapies.Although no specific data are available to date, consistent with some guidelines on the topic, it seems justified to consider percutaneous closure in patients with a cryptogenic TIA, stroke or systemic emboli that occurred while on therapy with OAC or antiplatelet agents.The choice of device should take into consideration that most available evidence has been obtained with the Amplatzer occluder and Helex (not available any more) or Cardioform device. The use of the latter should be balanced against a higher risk of AF as compared to medical therapy in the majority of available meta-analyses. The potential use of devices other than Amplatzer and Cardioform, and the inherent risks, should also be part of the shared decision-making with patients, in the light of technical, anatomical, and clinical features. |
| **Justification** | **Overall justification**The last, comprehensive, meta-analysis incorporating the most recent trials on patients aged 18-60 years showed a statistically significant advantage of PFO closure over medical therapy for the prevention of stroke in the first 5 years after the procedure. One exploratory analysis of one of these randomised trials extended to a longer follow up, support a growing benefit of percutaneous closure over medical therapy after that time limit. The CLOSE and REDUCE trials, performed in carefully characterised patients with confirmed cryptogenic stroke and high risk features, had a pivotal role in this evidence. However, the overall moderate certainty of evidence due to the heterogeneity across studies and the low quality of evidence weaken the strength of the recommendation (i.e. "conditional for the intervention"), enforcing the need for carefully-informed choices which must be shared with patients and tailored to their personal values and preferences.**Detailed justification***Problem*PFO-related stroke is an important health problem; therefore, its secondary prevention is a priority. Unfortunately, its management is problematic because high-quality data are lacking in this very heterogeneous class of patients. Nonetheless, the possibility of an efficient secondary prevention should be granted without causing harm with unnecessary treatments. Given the very disparate practices that exist within the medical community in this regard, it is urgent that clinicians follow a balanced approach that is based upon the present level of knowledge, while waiting for more conclusive evidence on better classified populations of patients.*Desirable Effects*Our meta-analysis, the first on the 5 RCTs, and the highest-quality, patient-level, meta-analysis of the first three published RCTs showed a clear benefit of PFO closure over medical therapy, in terms of reducing the incidence of stroke recurrence and the primary adverse composite endpoint (Figure 9A and B). Other study-level meta-analyses have revealed superiority of PFO closure in other-than-ITT analyses or in sensitivity analyses when an Amplatzer device was used. A minority of study-level meta-analyses detected no superiority of one therapy over another. A meta-analysis of comparative observational trials demonstrated marked superiority of PFO closure (Table 10). *Undesirable Effects*Interventional treatment does not imply higher complication rates, with the exception of a higher frequency of AF after percutaneous closure relative to medical therapy (Figure 10). However, the higher risk of AF with closure versus medical therapy was considerably lowered (Figure 11), and in many other meta-analyses abolished, if an Amplatzer device was used. In the REDUCE trial using GORE Helex or Cardioform septal occluder the incidence of AF was 6.6% at 5 years, a large proportion of which were only intra- or peri-procedural arrhythmias. Bleeding complications were similar in the young cohorts of patients enrolled in RCTs in the short term; however, long-term follow-up data are missing in patients undergoing life-long medical treatments, which are likely to increase the risk of haemorrhage as patients grow older.*Certainty of evidence*The certainty of evidence is overall still moderate, because of wide confidence intervals, the lower-than-expected incidence of outcomes in randomised studies, and the low quality of the majority of individual RCTs and observational trials included in different meta-analyses (Table 11 and Appendix Table 4). As future studies are likely to impact the certainty of evidence, this leads to weaker recommendation strength for the overall population*Values*Large variations in preferences of patients indicate the need for tailored informed consent and the explicit evaluation of therapeutic trade-offs with individual patients.*Balance of effects*Despite the uncertainty of estimates, the NNT with percutaneous closure obtained in RCTs out-weighed the NNH for atrial fibrillation after percutaneous closure, especially when an Amplatzer device was used.  |
| **Subgroup considerations** | In the available randomised studies, the age of patients was ≤60 years. In our study-level meta-analysis of the 5 RCTs no differences were noted regarding the outcomes of different pooled clinical inclusion criteria. (Figure 14). In several previous meta-analyses, the use of an Amplatzer device was associated with statistically-significant enhanced efficacy versus medical therapy as compared to other devices (Table 10) but this was not confirmed in our most recent analysis (figure 15). The risk of new-onset atrial fibrillation was similar with the Amplatzer device and medical therapy while it was higher for the GORE device when compared with medical therapy (figure 11). In some meta-analyses, other subgroups also experienced enhanced outcomes with percutaneous closure relative to medical therapy. These subgroups include males (136,264,265), and patients with a history of migraines or non-cortical infarcts (136). In an exploratory, long term, analysis of the RESPECT trial PFO closure was associated with better outcomes in patients with an atrial septal aneurysm or a large R-t-L shunt. (122).  |
| **Implementation considerations** | PFO closure incurs procedural cost. However, this cost may be offset over time by reduced event rates and costs of long-term medical treatment. In younger patients, PFO closure may be cost effective in the long term. Procedural costs and procedure times may be decreased with use of sedation or intracardiac echocardiography versus transoesophageal echocardiography, thereby eliminating the need for an anaesthesiologist.  |
| **Monitoring and evaluation** | Each neurological index event should be confirmed by a neurologist or a stroke physician. The Cardiologist and the Stroke Physician must come to the conclusion that the stroke or TIA was cryptogenic, and communicate in order to reach consensus regarding therapeutic decisions. Patients should be actively involved at all stages of management and their contribution to choices should be documented.  |
| **Research priorities** | - To identify high risk-phenotypes encompassing different clusters of clinical, anatomical and biological characteristics in prospective observational trials (systems and precision approaches) and to perform new randomised trial in these populations- To assess long-term outcomes (>5 years) with different treatments - To address the evaluation of persisting disability and quality of life with different treatments- To design prospective registries to evaluate practices and outcomes in the real world- To obtain new, cost-effectiveness analyses based on contemporary practices- To obtain quantitative and qualitative data on patient preferences and values in the setting of cryptogenic stroke or systemic embolism with PFO- To obtain data on the effectiveness and efficacy of organisational models to manage patients with cryptogenic stroke/systemic emboli  |

A detailed meta-analytic methodology and assessment of evidences can be found in appendix II and III.

**Should oral anticoagulants (OAC) vs. antiplatelet therapy be used for secondary prevention of stroke or systemic solid embolism?**

|  |  |
| --- | --- |
| **Population:** | secondary prevention of stroke or systemic solid embolism |
| **Intervention:** | OAC |
| **Comparison:** | antiplatelet therapy |
| **Main outcomes:** | stroke; major bleedings |

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | ○  | ●  | ○  | ○  |

 |
| **Recommendation** | In patients in whom a medical therapy is chosen, the position of our scientific societies is to choose the specific drugs weighing the individual risk of bleeding against the risk of PFO-related stroke recurrence, in close connection with the patient. Long-term OAC with vitamin K antagonists may be preferred if: a) the patient has a low haemorrhagic risk and b) a probable good therapeutic compliance is foreseen and c) a proper anticoagulant monitoring can be guaranteed. In patients in whom these conditions are not satisfied, or the risk of stroke recurrence is deemed low, an antiplatelet therapy should be prescribed. Reassessment of the risk/benefit ratio should be performed on a regular basis, especially with advancing age and the increase in comorbidities which can affect both risk and benefit issues. No recommendations can be made for DOACs. |
| **Justification** | **Overall justification**Meta-analyses indicate a statistically significant reduction in the risk of stroke with OAC as compared to antiplatelet therapy, at the cost of a significantly higher risk of major bleeding. The only randomised comparison shows a statistically non-significant reduction of stroke with OAC as compared to antiplatelet therapy. However, the uncertainty of the evidence remains very high (Appendix Table 5) and the inconsistency across studies severe (Figure 7).**Detailed justification***Desirable Effects*Our meta-analysis indicates a statistically significant reduction of the odds ratio for stroke of approximately 12% with OAC over antiplatelet therapy. These results are in keeping with previous meta-analyses.*Undesirable Effects*An approximately 5-fold higher risk of major bleeding emerged from our meta-analysis with OAC as compared to antiplatelet therapy. Also these results are in line with previous analysis.*Certainty of evidence*The certainty of evidence is very low, because the results are mainly derived from nonrandomised comparisons (Table 15 and Appendix Table 5).*Values*Patients undergoing secondary pharmacological prevention for stroke appear to accept higher risk of bleeding if a considerable certitude can be provided regarding the prevention of stroke.*Balance of effects*The balance of desirable and undesirable effects of therapy varies according to the expected benefits of the therapy, as the risk of bleeding appears to be homogenous across studies. Therefore therapy should be as individualised as possible.*Feasibility*Feasibility of implementation of a safe OAC regimen with vitamin K antagonists is largely dependent on availability of monitoring facilities of proper anticoagulation and on the possibility to access them by patients. |
| **Subgroup considerations** | No subgroup consideration can be derived from the accrued data. However, given the inconsistency of the studies and the variability of results, subgroups should be identified for new study.  |
| **Implementation considerations** | No cost-effectiveness studies have been performed in this field. However, as the costs of OAC and antiplatelet therapy are low, the cost-effectiveness profile is dependent mainly on the costs of adverse events in the follow-up. The available evidence shows that bleeding complications increase with age rendering even more uncertain the cost/effectiveness of this therapy in the long term.  |
| **Monitoring and evaluation** | In antithrombotic therapy the risk/benefit ratio is highly dependent on time. It is therefore recommended to reassess risks and benefits of the chosen therapy on a regular basis, especially with advancing age and the increase in comorbidities. Local registries for prospective evaluations of outcomes are strongly encouraged. |
| **Research priorities** | - To identify high risk-phenotypes encompassing different clusters of clinical, anatomical and biological characteristics in prospective observational trials (systems and precision approaches)- To design adequately-dimensioned head-to-head RCTs comparing single medical therapies (e.g., acetylsalicylic acid, clopidogrel, vitamin K antagonists, DOACs, etc.) in patients in whom percutaneous therapy has been excluded- To assess long-term outcomes (>5 years) with different treatments - To address the evaluation of persisting disability and quality of life with different treatments- To design prospective registries to evaluate practices and outcomes in the real world- To obtain new, cost-effectiveness analyses based on contemporary practices- To obtain quantitative and qualitative data on patient preferences and values in the setting of cryptogenic stroke or systemic embolism with PFO- To obtain data on the effectiveness and efficacy of organisational models to manage patients with cryptogenic stroke/systemic emboli |

Figure 16 summarises the recommended treatment algorithm.

A detailed meta-analytic methodology and assessment of evidences can be found in appendix II and III.

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