

European Stroke Organisation (ESO) Guidelines on the diagnosis and management of patent foramen ovale (PFO) after stroke

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Abstract

Patent foramen ovale (PFO) is frequently identified in young patients with cryptogenic ischaemic stroke. Potential stroke mechanisms include paradoxical embolism from a venous clot which traverses the PFO, in situ clot formation within the PFO, and atrial arrhythmias due to electrical signalling disruption. The purpose of this guideline is to provide recommendations for diagnosing, treating, and long-term managing patients with ischaemic stroke and PFO. Conversely, Transient Ischaemic Attack (TIA) was not considered an index event in this context because only one RCT involved TIA patients. However, this subgroup analysis showed no significant differences between TIA and stroke outcomes. The working group identified questions and outcomes, graded evidence, and developed recommendations following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach and the European Stroke Organisation (ESO) standard operating procedure for guideline development. This document underwent peer-review by independent experts and members of the ESO Guideline Board and Executive Committee. The working group acknowledges the current evidentiary gap in delineating an unequivocal diagnostic algorithm for the detection of PFO. Although transoesophageal echocardiography is conventionally held as the most accurate diagnostic tool for PFO identification, its status as the 'gold standard' remains unsubstantiated by rigorously validated evidence. We found high-quality evidence to recommend PFO closure plus antiplatelet therapy in selected patients aged 18–60 years in whom no other evident cause of stroke is found but a PFO (i.e. PFO-associated stroke). The PASCAL classification system can be used to select such candidates for PFO closure. Patients with both a large right-to-left shunt and an atrial septal aneurysm benefit most from PFO closure. There is insufficient evidence to make an evidence-based recommendation

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Correction (June 2024): This article has been updated to correct the placement of Table I, Expert Consent Statements and Evidence based recommendations.

on PFO closure in patients older than 60 and younger than 18 years. We found low quality evidence to suggest against PFO closure in patients with unlikely PFO-related stroke according to the PASCAL classification, except in specific scenarios (Expert Consensus). We suggest against long-term anticoagulation in patients with PFO-associated stroke unless anticoagulation is indicated for other medical reasons. Regarding the long-term AF monitoring after PFO closure, the working group concluded that there remains significant uncertainty regarding the risks and benefits associated with the use of long-term cardiac monitoring, such as implantable loop recorders. This document provides additional guidance, in the form of evidence-based recommendations or expert consensus statements, on diagnostic methods for PFO detection, and medical management after PFO closure.

Keywords

Patent foramen ovale, stroke, atrial fibrillation, PFO closure, anticoagulation, antiplatelets

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Introduction

One-third of ischaemic strokes are considered to be cryptogenic, indicating that no identifiable cause can be determined, and this tends to be more prevalent among younger patients. The standard evaluation of a symptomatic cerebral infarct relies on the patient's history, physical examination and ancillary investigations.^{1,2} Typically, the work-up begins with brain imaging using MRI or CT to assess the extent and topography of ischaemia, and non-invasive assessment of intracranial and extracranial arteries using ultrasound, MR- or CT- angiography. Routine evaluation also includes assessment of cardiac rhythm and structure by 12-lead ECG, long-term monitoring or inpatient telemetry, transthoracic echocardiography (TTE) or transoesophageal echocardiography (TOE), and laboratory tests for haematology, coagulation, and blood chemistry. In cases where routine tests do not reveal common causes of stroke, such as dissection in younger individuals or significant supra-aortic atherosclerosis, atrial fibrillation (AF), or small vessel disease in older patients, it is advisable to broaden the diagnostic spectrum to include testing for a patent foramen ovale (PFO). Indeed, the persistence into adulthood of a PFO, a normal embryological communication between the cardiac atria,³ has progressively emerged as being causally involved in 10% of all strokes in patients aged 18–60 years.⁴ The involved pathophysiology can be paradoxical thromboembolism through the PFO and/or thrombus formation in the PFO leading to cerebral or systemic embolisation.⁵ However, despite a prevalence of 25% in the general population,⁶ a small minority of individuals with a PFO will develop a PFO related ischaemic stroke in their lifetime. In addition, the rate of recurrence while on medical treatment in patients with no other apparent cause of stroke other than a PFO is low, approximately one event per 100 person-years.^{7,8} This corresponds to a cumulative incidence of 4.6% after 3.8 years of follow-up in the available randomised trials.⁸

Therefore, the major challenge is the identification of patients in whom a PFO can be considered to be the cause

of stroke, as inappropriate treatment may be potentially harmful.⁴ To achieve this aim, an accurate diagnosis of PFO is the first step. Contrast-enhanced transcranial Doppler (c-TCD), TTE, and/or TOE represent established methods for detecting a right-to-left shunt (RLS) and/or a PFO. However, which of these yields the best diagnostic accuracy is still unclear.⁹ After the diagnosis of PFO, structural features can help defining PFO with a causal role in stroke, defined as PFO-related stroke. The first is the presence of an atrial septal aneurysm (ASA), a bulging of the atrial septum into the left and/or right atria, which can facilitate a large inter-atrial shunt which is the second highest-risk feature.¹⁰

Two risk scores have been proposed to assist clinicians in assessing the likelihood of stroke causality from a PFO in patients with cryptogenic stroke, in conjunction with a comprehensive clinical assessment.⁷ The first one, *Risk of Paradoxical Embolism* (RoPE), mainly includes clinical features¹¹ while the second, *PFO-Associated Stroke Causal Likelihood* (PASCAL), is a classification system that includes both the RoPE score and the anatomical features mentioned above.⁷

After a PFO-associated stroke, secondary prevention is required, with options including antiplatelet therapy, anticoagulation, and percutaneous closure of the PFO.⁸ The latter option is based on mechanical prevention of paradoxical embolism and/or local thrombus formation. However, PFO percutaneous closure has been a controversial therapy for most of the past three decades. In 2017, randomised clinical trials (RCT) have demonstrated the superiority of device closure plus medical therapy over medical therapy alone in reducing stroke recurrence in adults up to 60 years of age with no identified alternative cause of stroke.¹² A recent individual patient data meta-analysis (IPDMA) of available RCTs showed a 60% relative risk reduction of recurrent stroke with PFO closure in these patients, although the absolute risk reduction was small (2-year ARR: 1.7%).⁷ Conversely, it is worth noting that there have been more frequent reports of AF following PFO closure. However, it is important to highlight that this increase in AF occurrence

was primarily observed within 45 days following the closure procedure.¹³

The aim of this guideline document is to provide recommendations for physicians on the diagnosis and management of PFO-associated stroke.

Methods

This guideline was prepared according to the ESO standard operating procedure (SOP) for guideline development,¹⁴ which is based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework.¹⁵ The ESO Guideline Board invited two chairs, one neurologist (VC) and one cardiologist (CP), who established a Module Working Group (MWG) consisting of 7 stroke specialists (AHAR, HM, EK, SW, DT, PC, GT), 2 cardiologists (LS, CP) and 2 methodologists (SH, AL). The Guideline Board and the ESO Executive Committee approved the composition of the working group. The full disclosures of all MWG members are listed in Supplemental Table 1.

The MWG developed a list of topics and corresponding questions of greatest clinical interest. Three overarching themes were identified: PFO diagnosis, treatment of PFO-associated stroke and post-procedural management. Questions to be addressed by the MWG were formatted using the Population, Intervention, Comparator, and Outcome (PICO) approach and reviewed by two external reviewers and members of the ESO Guideline Board and Executive Committee. PICO questions on the same subjects were grouped under overarching themes to improve readability. Members of the MWG rated the outcomes as critical, important, or of limited importance according to GRADE criteria. The final decision on outcomes used a Delphi approach. Results of the outcome ratings are presented below. The experts of the MWG discussed and decided by consensus on the PICO questions to be addressed and on the outcomes of interest during virtual meetings. No

face-to-face meetings were organised due to the COVID-19 pandemic.

Literature search

For each question, systematic searches of the MEDLINE, EMBASE, CINAHL and SCOPUS databases, covering the period from the inception of each database to June 2023 were conducted by the ESO Guidelines methodologists. We conducted the research with Medical Subject Headings (MeSH) terms ('Foramen Ovale, Patent' OR 'Patent Oval Foramen' OR 'Oval Foramen, Patent' OR 'Patent Foramen Ovale') AND ('Stroke' OR 'Cerebrovascular Accident' OR 'Cerebrovascular Accidents' OR 'CVA' OR 'CVAs' OR 'Cerebrovascular Apoplexy' OR 'Apoplexy, Cerebrovascular' OR 'Vascular Accident, Brain' OR 'Brain Vascular Accident' OR 'Brain Vascular Accidents' OR 'Vascular Accidents, Brain' OR 'Cerebrovascular Stroke' OR 'Cerebrovascular Strokes' OR 'Stroke, Cerebrovascular' OR 'Strokes, Cerebrovascular' OR 'Apoplexy' OR 'Cerebral Stroke' OR 'Cerebral Strokes' OR 'Stroke, Cerebral' OR 'Strokes, Cerebral' OR 'Stroke, Acute' OR 'Acute Stroke' OR 'Acute Strokes' OR 'Strokes, Acute' OR 'Cerebrovascular Accident, Acute' OR 'Acute Cerebrovascular Accident' OR 'Acute Cerebrovascular Accidents' OR 'Cerebrovascular Accidents, Acute') AND Closure'.

Clinicians of the MWG independently screened titles, abstracts, and full texts for potentially relevant studies for each PICO question. We prioritised RCTs, but where data were limited, we also considered observational studies, and systematic reviews or meta-analyses of observational studies. We excluded publications with only conference abstracts available, narrative reviews, single case reports, or comments.

Data extraction, risk of bias assessment of individual studies and meta-analysis

The ESO methodologists performed data extraction and analysis. The corresponding authors of eligible studies were contacted if relevant data were not reported in original publications. In case of no response, the co-authors of the study were also contacted. If no answer was received, data were considered missing.

The risk of bias of each included RCT was assessed with the Cochrane risk of bias (RoB-2) tool. The ROBINS-I tool was used to assess the risk of bias for observational studies.¹⁶ The risk of bias for studies included in the analysis for the diagnostic PICO was assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool.¹⁷ Where appropriate, fixed or random-effects meta-analyses were conducted using Review Manager (RevMan)

Table 1. Outcomes of interest and judgement of their importance.

Outcome	Importance
Ischaemic stroke recurrence	9
All-cause mortality	7
Transient ischaemic attack	7
Intracranial haemorrhage (intracerebral, subarachnoid, epidural, intraventricular, intraparenchymal, subdural bleeds, epidural bleeds)	7
Major bleedings	7
Minor bleedings	6
Atrial fibrillation in the peri-procedural period ⁶⁸	4
Atrial fibrillation occurring later	5
Myocardial infarction	4

or Stata softwares. The MetaDTA ShinyR app was used for bivariate meta-analyses of diagnostic test accuracy.

All results were presented as estimates of effect with associated 95% confidence intervals (95% CIs). Statistical heterogeneity across studies was assessed using the I^2 statistic, and classified as moderate ($\geq 30\%$), substantial ($\geq 50\%$), or considerable ($\geq 75\%$).¹⁸ The I^2 statistic typically quantifies heterogeneity in meta-analyses, but it was not employed for the diagnostic test accuracy meta-analyses. This is because a certain degree of heterogeneity is anticipated in these studies, and I^2 or similar metrics are rarely used in such contexts.^{19,20}

Evaluation of the quality of evidence and formulation of evidence-based recommendations

Two or three MWG members graded the evidence and wrote the recommendations for each PICO question. As recommended, the evidence synthesis did not use a quality ‘score’ threshold but classified the overall risk of bias at the study level and then in aggregate.²¹ The results of meta-analyses were imported into the GRADE Pro Guideline Development Tool (McMaster University, 2015; developed by Evidence Prime, Inc.) For each PICO question and each outcome, the following were considered: risk of bias based on the type of available evidence (randomised or observational studies); considerations on the inconsistency of results; indirectness of evidence, imprecision of results, and other possible bias. GRADE evidence profiles/summary of findings tables were generated and used to prepare recommendations. The quality of evidence was graded as high, moderate, low, and very low. Strengths of recommendations were graded as strong when the desirable effect of an intervention clearly outweighed the undesirable effects or clearly did not, or weak when the trade-off was less certain, either because of low-quality evidence or because the evidence suggested that desirable and undesirable effects were more closely balanced.^{22,23}

‘Evidence-based recommendations’ were based on the GRADE methodology. The recommendations’ direction, strength, and formulation were determined according to the GRADE evidence profiles and the ESO-SOP.²⁴ All working group members critically revised all recommendations, and discrepancies in grading and recommendations were discussed during regular virtual conferences.

Additional information paragraphs and expert consensus statements

For each PICO question, ‘Additional information’ paragraphs could be added to provide more details on RCTs mentioned in the ‘Analysis of current evidence’

paragraph, summarise observational study results, or provide information on ongoing or future trials. Finally, Expert Consensus Statements were added where the MWG considered that there was insufficient evidence to make Evidence-based Recommendations and where practical guidance for routine clinical practice was needed. The Expert Consensus Statements were based on a Delphi approach and voting by all clinicians of the MWG. Importantly, these Expert Consensus Statements should not be regarded as evidence-based recommendations since they only reflect the opinion of the writing group.^{14,25}

Results

Part 1: PFO DIAGNOSIS

In this section, we address the following **overarching question**:

Which diagnostic test should be used to detect PFO-related right-to-left shunt in patients with cryptogenic stroke?

Accurate diagnosis of PFO-related RLS and PFO characteristics in cryptogenic stroke patients is of paramount importance for risk stratification and therapeutic decision-making. The most commonly used techniques for the detection and evaluation of RLS are contrast-enhanced (c-) transcranial doppler (c-TCD), transthoracic echocardiogram (c-TTE) and transoesophageal echocardiogram (c-TOE).

A large shunt is usually defined by the appearance of >20 microbubbles in the left atrium within 3 cardiac cycles after opacification of the right atrium at c-TTE, >20 bubbles at c-TOE, and >10 high-intensity transient signals (HITS) at c-TCD.^{26–29} During c-TCD, the numbers of hits can be counted using bilateral or unilateral imaging by monitoring either the right or left MCA.³⁰

c-TOE allows for unparalleled visualisation of the interatrial septum and measurement of the size of the PFO. However, TOE renders Valsalva manoeuvre difficult with sub-optimal accuracy and problematic reproducibility. Nevertheless, because of its ability to directly visualise the PFO, TOE has been considered the conventional reference for any PFO-related cardiac assessment and has been used as such in the following analyses.

c-TCD allows for a comfortable procedure for the patient with an easily reproducible Valsalva manoeuvre but is limited by the availability of a good cranial window for ultrasounds and by the impossibility to determine the RLS anatomical location (i.e. cardiac or extracardiac shunting). c-TTE can provide a widely available and easily accessible technique for the detection of PFO-related RLS. ASA is defined as a septum primum excursion of at least 10 mm

from the plane of the atrial septum into the right atrium and/or left atrium and is a critical piece of information for therapeutic decisions.²⁸

PICO 1.1 in patients with cryptogenic stroke, what is the diagnostic performance of c-TCD compared with c-TOE (conventional reference) to screen for a PFO-related right-to-left shunt?

Analysis of current evidence

The literature search identified 34 observational studies evaluating the diagnostic accuracy of *c-TCD* and using *c-TOE* as the conventional reference for the diagnosis of RLS and PFO since 1991^{30–65} (Supplemental Table 2). No RCT was identified. One study performed a retrospective analysis of prospectively collected data,⁵² one study was designed as a case-control analysis, another study described a cross-sectional design,⁴⁹ 10 studies conducted a prospective cohort analysis,^{32,33,35,38,41–43,48,54,63} 21 studies described their design as observational cohort analysis.^{30,31,34,36,37,39,40,45–47,49–51,53,56–60,64,65}

Twenty-three studies included patients after acute ischaemic stroke and/or transient ischaemic attack (TIA).^{38,47,51} The remaining studies also included patients with various other medical conditions such as migraine, vertigo, syncope, myocardial infarction, and peripheral embolism.^{34,38,43–45,47,49,53,59,60}

Acute ischaemic stroke patients included in this analysis presented with suspected cardioembolic stroke^{38,47,51} or cryptogenic stroke.^{32,35,39,41,42,48,52,59,60,65} Cryptogenic stroke was diagnosed when no underlying stroke cause (other than a PFO) could be identified during acute stroke assessment.

Nine studies included patients with various stroke aetiologies.^{33,34,44,46,54–56,64}

Thirteen studies did not describe any aetiological workup and classification.^{30,31,36,37,40,43,45,49,50,53,57,58,63}

Most studies (*N*=16) were conducted before 2000, another seven were conducted before 2010, and only 11 after 2010 (Supplemental Table 2).

The studies used to address this PICO question comprised a total of 3133 patients with a mean age of 48 ± 9 years. Among the analysed patients, 1372 (44%) were women; 2280 (73%) had acute ischaemic stroke, 329 (11%) had TIA, and 50 (2%) had clinically silent cerebral infarcts; 199 (6%) patients had migraine and 17 (0.5%) had vertigo (Supplemental Table 2). In this population, PFOs were detected in 1513 (48%) patients using the conventional standard method of TOE (Table 2).

The RLS was graded following three different criteria: the International Consensus Criteria²⁹ in 11 studies,^{33,38,47,48,51,53,56,59,60,63,64} the Spencer et al.⁶⁶ logarithmic scale in five studies.^{42,51,52,55,58} Twelve studies used 1–5 HITS as a threshold to diagnose RLS.^{35–37,40,41,43–46,49,50,54} These studies were performed before the publication of

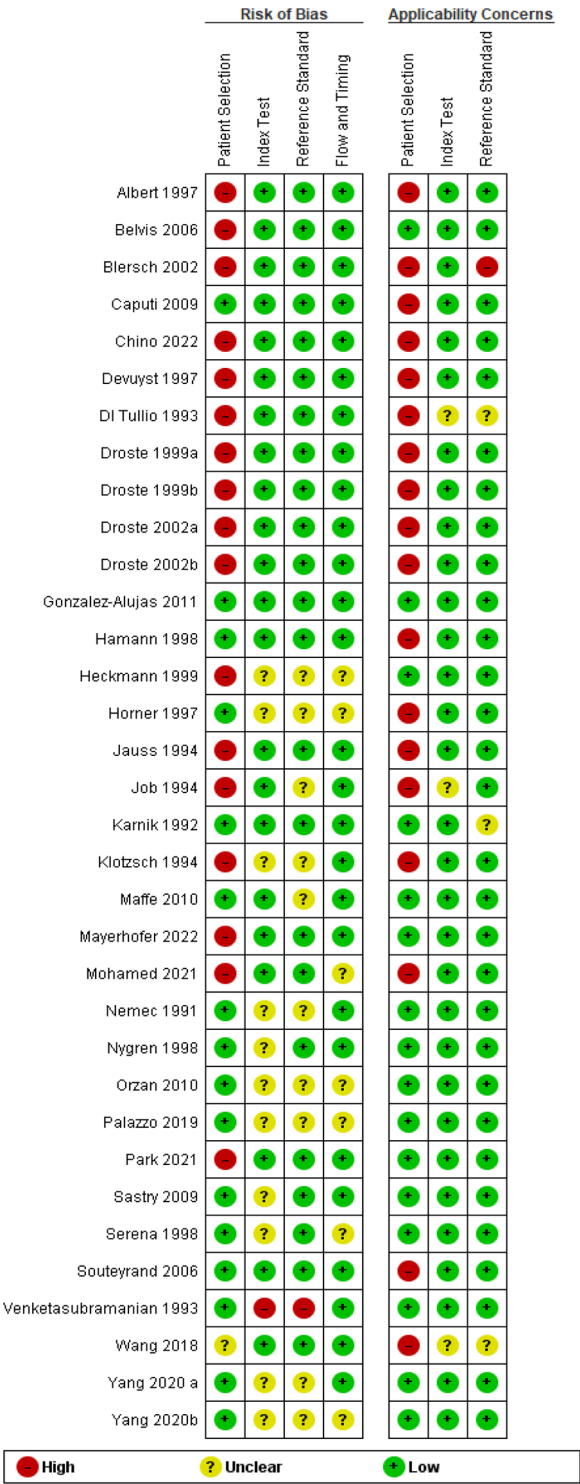


Figure 1. Risk of bias of individual studies included in the analysis of PICO 1.1 using the QUADAS-2 tool.

the consensus recommendations on RLS determination by TCD.²⁹ Two studies used more than 5 HITS as the threshold,^{32,43} two other studies^{31,39} used at least 10 HITS to confirm RLS. Two studies did not describe their criteria.^{30,57}

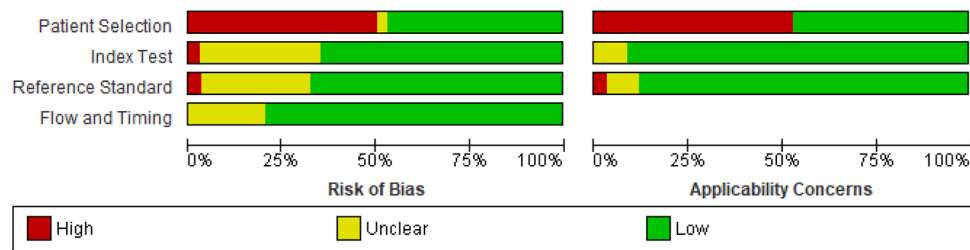


Figure 2. Risk of bias summary for PICO I.I.

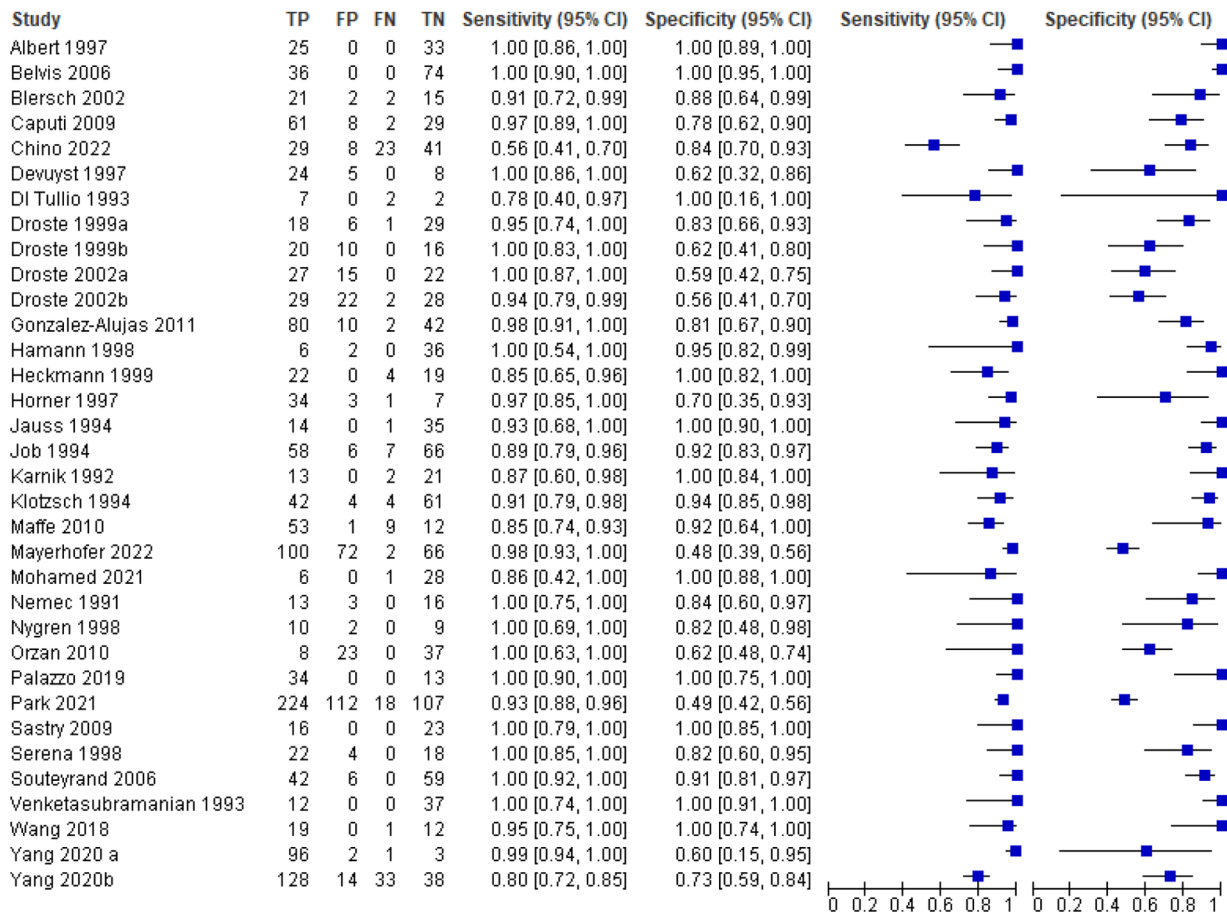


Figure 3. Random-effects meta-analysis comparing the assessment of a right-to-left shunt with c-TCD to c-TOE as a reference test in patients with ischaemic stroke, TIA, silent infarcts migraine and other neurological diseases.

Pooled sensitivity 0.96 (95% CI: 0.93–0.98).

Pooled specificity 0.90 (95% CI: 0.83–0.95).

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) of the studies included in the analysis is shown in Figures 1 and 2. Fourteen (41%) of the 34 studies reported including consecutive patients.^{32–35,41–44,47,48,51,54,59,65} No inappropriate exclusions after recruitment were reported, and no risk of bias in patient selection could be detected.

In 20 (59%) studies, clinicians who performed the c-TCD examinations as index test, were blinded to the results of the c-TOE (reference test) resu

its.^{31–35,38,40,44–48,50,52–54,56,59,63,64} Four of these studies (12% of all) used a double-blind approach, with TOE examiners also blinded to the results of the index test.^{47,48,52,59}

Valsalva manoeuvre was performed before contrast injection in 12 studies.^{30,31,33,35,41,42,45,51,54,57,60,63} In 16 studies, Valsalva manoeuvre followed contrast injections either immediately,^{38,47,53} or 5 s later,^{32,36,37,44,46,48,51,52,56,59,64} or when right atrium opacity was detected.^{39,43} The timing between contrast injection and Valsalva manoeuvre was not reported in six studies.^{35,40,50,55,58}

The contrast medium consisted of air-agitated saline (AS),^{30,32,35,47,53–57} a mixture of blood and saline agitated with air (BAS),^{42,48,49,51,52,59,60,65} a specific echo contrast compound,^{33,36,37,39–41,43–46,50,63,64} a combination of these^{31,34} or was not clearly reported.⁵² When reported, the duration of microbubble detection ranged from 5 to 40 s.

The risk of bias in flow and timing between index tests (TCD) and reference tests (TOE) was unclear in 16 (47%) of the 34 studies.^{31–34,36,37,40,54,56,60,63–65,67} The other studies reported times ranging from simultaneous assessment,^{30,35,38,39,43,44,46,49,50,53,57,58} to the same day^{45,60} within 48 h or the same week^{42,48} or with a median delay of 17 days.⁵⁰ In all studies, all analysed patients received the index and reference tests (Supplemental Table 2).

All 34 studies were included in our quantitative synthesis of sensitivity and specificity (bivariate meta-analysis; Figure 3 and GRADE Table 1). Significant heterogeneity in the included studies was identified. The pooled sensitivity of TCD was 0.96 (95% CI: 0.93–0.98). The pooled specificity of TCD was 0.90 (95% CI: 0.83–0.95). The pooled positive likelihood ratio was 9.74 (95% CI: 5.51–17.22), and the pooled negative likelihood ratio was 0.04 (95% CI: 0.02–0.07). The pooled diagnostic odds ratio for TCD was 236.99 (95% CI: 99.93–562.06). The area under the summary receiver operative characteristic (sROC) curve was 0.96 (95% CI: 0.93–0.98; Figure 4).

In brief, due to its high sensitivity (96%), **c-TCD** it may be regarded as a reliable diagnostic screening tool to detect RLS. The recommendation for this PICO question will be summarised along with the following results and can be found at the end of Part 1.

Additional information

Studies have reported variations in the RLS diagnosis rate when using different contrast agents.^{37,69}

Compared to contrast agents and AS, adding blood increases the sensitivity of c-TCD to as high as 100%.⁷⁰ However, the blood amount in the AS is still controversial, given clinical safety and practices. Gentile et al.⁷¹ reported that 1 mL of blood in agitated saline significantly improved RLS results. Conversely, Hao et al.⁷² reported that adding one drop of blood significantly improved RLS diagnosis of c-TCD by producing more microbubbles. In another study by Li et al.,⁷³ the detection time was much shorter when the BAS compared to AS. There was a trend of more positive and higher RLS levels when using the 10% BAS; however, the differences between the 5% and 10% BAS were not statistically significant.⁷³

Droste et al.³⁷ ranked the performance of TCD with and without echovist by the number of microbubbles detected; the order from highest to lowest was as follows: Echovist with a Valsalva manoeuvre, Echovist with coughing,

Table 2. GRADE evidence profile for PICO 1.1 on TCD detection of a right-to-left shunt compared to c-TOE as reference test.

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease the certainty of evidence				Effect per 1000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 52%
True positives (patients with PFO, RL shunt)	34 Studies	Cross-sectional (cohort-type accuracy study)	Serious ^a	Not serious	Serious ^b	Serious ^c	None	499 (484–510)
False negatives (patients incorrectly classified as not having PFO, RLS)	1467 Patients							21 (10–36)
True negatives (patients without PFO, RLS)	34 Studies	Cross-sectional (cohort-type accuracy study)	Serious ^a	Not serious	Serious ^b	Serious ^c	None	432 (398–456)
False positives (patients incorrectly classified as having PFO, RLS)	1402 Patients							48 (24–82)
								Very low
								Very low

Table shows the number of included studies and participants contributing to the estimates of sensitivity and specificity.

^aDowngraded one level for risk of bias because high proportion of the studies have issues with unclear information on either 'Index Test', 'Reference Standard' or 'Flow and Timing'.

^bDowngraded one level for inconsistency of results from the included studies' results, especially for analysis of the specificity.

^cDowngraded one level for imprecision because high variation in the included studies characteristics.

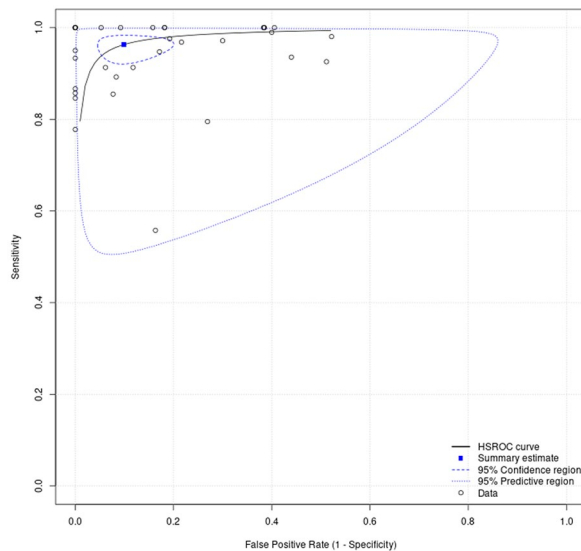


Figure 4. Area under the summary receiver operating characteristic curve (sROC), reflecting the diagnostic accuracy for c-TCD and ROC curve displaying the average value of sensitivity of c-TCD over all possible values of specificity. The area under the ROC curve (AUC) is 0.96.

Echovist with a standardised Valsalva manoeuvre, saline with a Valsalva manoeuvre, Echovist alone, and saline alone.

PICO 1.2: In patients with cryptogenic stroke, what is the diagnostic performance of contrast-enhanced transthoracic echocardiogram (c-TTE) compared with contrast-enhanced transoesophageal echocardiogram (c-TOE, conventional reference) for identifying a PFO-related right-to-left shunt?

Analysis of current evidence

The literature search identified 19 observational studies^{28,30,38,47,49,59–61,74–84} comparing the diagnostic accuracy of TTE with TOE as the conventional reference for the diagnosis of RLS and PFO since 1991 (Supplemental Table 3). No RCT was identified. Seven studies were based on prospective cohorts.^{38,62,74,75,78,79,82} All studies used c-TTE and six studies used harmonic imaging-enhanced TTE to detect RLS.^{28,47,80,81,84} Characteristics of the included studies are presented in Supplemental Table 3. Six studies were conducted before 2000, eight before or on 2010 and only five after 2010. Six studies included patients with acute ischaemic stroke and/or TIA.^{30,49,74,76,79,82}

The studies used to address this PICO question correspond to a total population of 2575 patients with a mean age of 50 ± 7 years with 979 (38%) of the patients being women. A total of 1601 (62%) patients had an acute ischaemic stroke, 202 (8%) had a TIA and 20 (0.8%) had clinically silent cerebral infarcts. Three hundred six (12%) patients had a migraine and 16 (0.6%) had vertigo (Supplemental

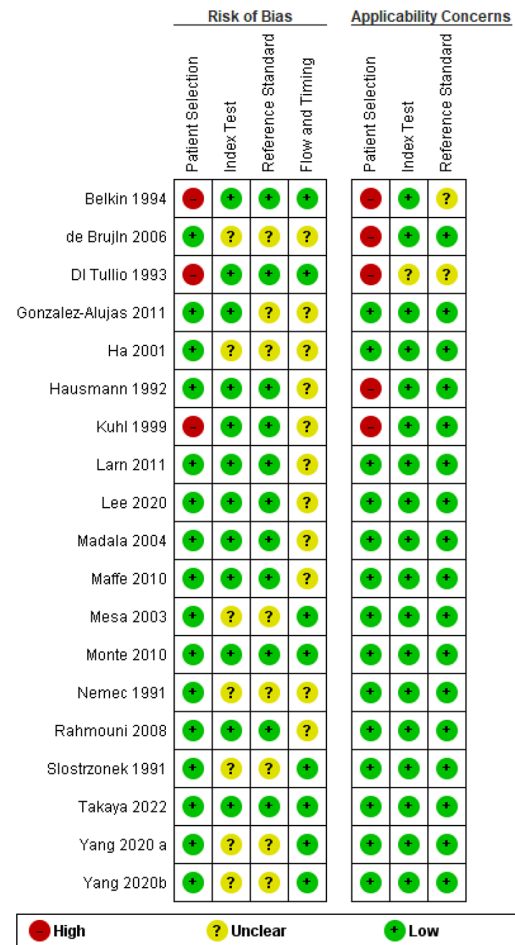


Figure 5. Risk of bias of individual studies used for the analysis of PICO 1.2 using the QUADAS-2 tool.

Table 3). In this population, PFOs were detected in 1029 (40%) patients using the conventional standard method of TOE.

Risk of bias analysis is presented in Figures 5 and 6. The risk of bias in flow and timing between index test (TTE) and reference test (TOE) was unclear in 11 (58%) of the 19 studies.

For our quantitative synthesis (bivariate meta-analysis), significant heterogeneity in the included studies was identified in this setting, c-TTE had a pooled sensitivity of 0.71 (95% CI: 0.50–0.86) Figure 7. The pooled positive likelihood ratio was 60.77 (95% CI: 10.97–336.6) and the pooled negative likelihood ratio was 0.29 (95% CI: 0.16–0.54). The pooled diagnostic odds ratio for c-TTE was 208 (95% CI: 44.8–967.6). The summary area under the ROC curve (sROC) was 0.71 Figure 8, indicating an overall modest diagnostic accuracy of TTE. These results suggest that TTE provides a technique for initial screening of RLS but a poor rule out test (modest sensitivity) for PFO detection in patients with cryptogenic stroke. However, this meta-analysis is limited by the serious inconsistency

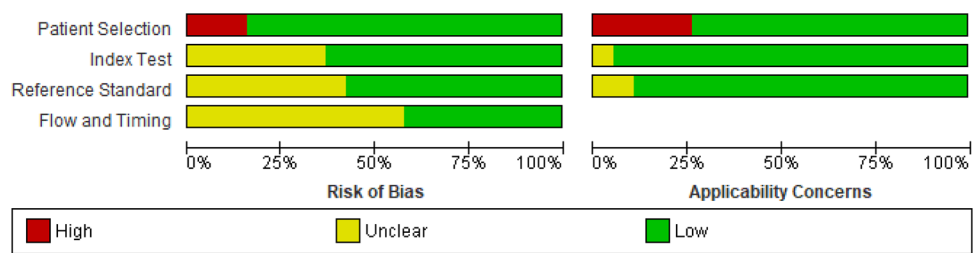


Figure 6. Risk of bias summary.

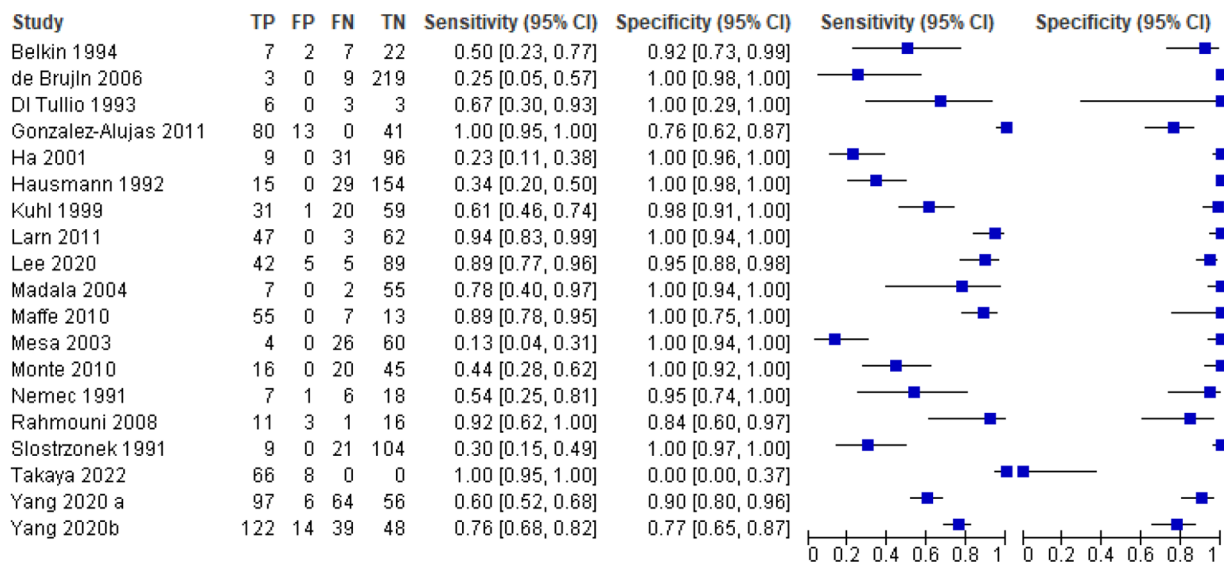


Figure 7. Random-effects meta-analysis comparing the assessment of a right-to-left shunt with c-TTE to c-TOE as a reference test. Pooled sensitivity: 0.71 (95% CI: 0.50–0.86). Pooled specificity: 0.99 (95% CI: 0.93–1.00).

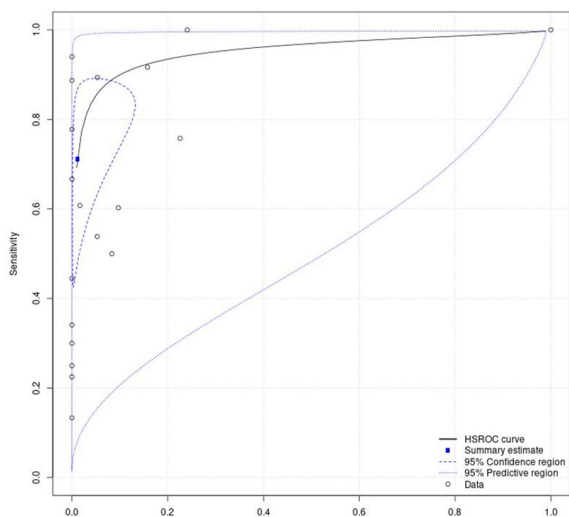


Figure 8. Area under the summary receiver operating characteristic curve (sROC), reflecting the diagnostic accuracy for c-TTE and ROC curve displaying the average value of sensitivity of c-TTE over all possible values of specificity. The area under the ROC curve (AUC) is 0.71, indicating an overall modest diagnostic accuracy of c-TTE.

and severe heterogeneity across studies (especially for sensitivity), which results in a very low overall quality of evidence (Table 3). A previous systematic review analysed 13 studies with 1436 patients to evaluate the accuracy of TTE in detecting RLS compared to TEE, the reference standard. TTE and TEE used a contrast agent and a manoeuvre to provoke RLS. The findings showed that TTE had a weighted mean sensitivity of 46% and a specificity of 99%. The positive likelihood ratio was 20.85, and the negative likelihood ratio was 0.57.⁷⁰

Another systematic literature review analysed 35 studies with 3067 patients; TCD's sensitivity was 96.1% (95% CI: 93.0–97.8) and specificity at 92.4% (95% CI: 85.5–96.1). In contrast, TTE's sensitivity was 45.1% (95% CI: 30.8–60.3) with a specificity of 99.6% (95% CI: 96.5–99.9). TTE showed a higher positive likelihood ratio (LR+ = 106.61, 95% CI: 15.09–753.30) compared to TCD (LR+ = 12.62, 95% CI: 6.52–24.43), but TCD had a lower negative likelihood ratio (LR– = 0.04, 95% CI: 0.02–0.08) than TTE (LR– = 0.55, 95% CI: 0.42–0.72). The area under the curve (AUC) for TCD was 0.98 (95% CI: 0.97–0.99), significantly higher than TTE's 0.86 (95% CI: 0.82–0.89),

Table 3. GRADE evidence profile for PICO 1.2 on c-TTE detection of a RLS using c-TOE as conventional reference test.

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease certainty of evidence				Effect per 1000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 45%
True positives (patients with PFO)	19 Studies	Cross-sectional (cohort type)	Serious ^a	Not serious	Serious ^b	Serious ^c	None	320 (227–385)
False negatives (patients incorrectly classified as not having PFO)	927 Patients	cohort type accuracy study)						130 (65–223)
True negatives (patients without PFO)	19 Studies	Cross-sectional (cohort type)	Serious ^a	Not serious	Serious ^b	Serious ^c	None	543 (511–549)
False positives (patients incorrectly classified as having PFO)	1213 Patients	cohort type accuracy study)						7 (1–39)

Table shows the number of included studies and participants contributing to the estimates of sensitivity and specificity.

^aDowngraded one level for risk of bias because high proportion of the studies have issues with unclear information on either 'Index Test', 'Reference Standard' or 'Flow and Timing'.

^bDowngraded one level for inconsistency of results from the included studies' results, especially analysis on the sensitivity.

^cDowngraded one level for imprecision because high variation in the included studies characteristics.

indicating TCD's greater overall diagnostic yield in detecting PFO in these patients.⁸⁵

Recently, a prospective clinical trial investigated the effectiveness of robot-assisted transcranial Doppler compared to TTE in diagnosing RLS, including patent foramen ovale, in patients suspected of embolic cerebrovascular ischaemia. The study found raTCD significantly more effective, detecting RLS in 64% of cases compared to 20% with TTE. Notably, raTCD identified three times more RLS instances and was particularly more adept at identifying large shunts. This suggests that raTCD could offer a noninvasive, accurate, and accessible means for RLS detection, potentially overcoming the limitations of conventional TCD and TTE.⁸⁶

The recommendation for this PICO question will be summarised with the following results and can be found at the end of Part 1.

Additional information

The diagnostic accuracy of TTE as a screening test for RLS detection in cryptogenic stroke patients can be enhanced by using second harmonic imaging as suggested by a meta-analysis of 15 prospective studies corresponding to 1995 patients. The pooled sensitivity and specificity for TTE with harmonic imaging were 91% and 93%, respectively, with high inconsistency among studies. TTE with harmonic imaging may provide a useful tool for the initial screening test for RLS due to its high accuracy and non-invasiveness. However, TOE is superior to TTE in the identification of specific anatomic features of PFO that guide therapeutic decision-making and interventional procedure planning, such as an atrial septal aneurysm, a moderate or severe shunt (more than 10–20 microbubbles crossing during the first three cardiac cycles).^{8,13,79,87–90}

Other variables that must be evaluated by TOE include PFO size, atrial septal aneurysm and the possible presence of other atrial septal defects, the size of the Eustachian valve and the possible presence of a Chiari network in the right atrium, the thickness of the septum primum and secundum and the atrial rim sizes.^{79,91–94}

PICO 1.3: In patients with cryptogenic stroke, is the diagnostic performance of contrast-enhanced (c)-TCD superior to that of contrast-enhanced transthoracic echocardiogram (c-TTE) to screen for a PFO-related right-to-left shunt using contrast-enhanced transoesophageal echocardiogram (c-TOE) as conventional reference?

The literature search did not identify any study comparing the diagnostic accuracy of c-TCD to c-TTE using c-TOE as the conventional reference for the detection of RLS.

Additional information on TOE as a gold standard

A study-level meta-analysis of the accuracy of c-TOE in the diagnosis of PFO, and therefore of an interatrial shunt, compared to robust reference standards (autopsy, cardiac surgery and/or catheterisation) yielded a weighted sensitivity of only 89%,⁷⁰ probably due to the difficulty of performing an adequate Valsalva manoeuvre.^{95,96} This data highlight the lack of an available non-invasive gold standard for the assessment of PFO-related RLS and the associated challenges in assessing the accuracy of c-TTE, c-TCd and c-TOE.

Additional information on upcoming alternative diagnostic modalities. Regarding alternative diagnostic modalities, cardiac magnetic resonance imaging has been demonstrated to be significantly less effective than TOE in detecting right-to-left shunts.⁹⁷ A comprehensive meta-analysis, encompassing 5 studies with a total of 236 patients, revealed that cardiac magnetic resonance detected only 29.3% (95% CI: 23.6–35.0) compared to 53.7% (95% CI: 47.4–59.9) observed with TOE ($p < 0.001$).⁹⁸ Whereas, the sensitivity of single-phase cardiac computed tomography, for identifying PFO was found to be 85.3%, but its specificity was notably lower at 33.3%, accompanied by a negative predictive value of 33%.⁹⁹ Conversely, in a separate study that involved 70 stroke patients diagnosed with PFO, full-cycle CCT demonstrated enhanced diagnostic performance, boasting a sensitivity of 89.4% and a specificity of 92.3% in comparison to TOE. However, the sensitivity of single-phase CCT in this particular study was considerably reduced at 72.7% ($p = 0.002$), indicating a significant difference in the effectiveness of single-phase and full-cycle CCT in detecting PFOs.¹⁰⁰

Additional information on diagnostic after PFO-closure. The precise protocols and timing for these follow-up assessments to verify the complete PFO closure can differ among medical centres and practitioners as there is no standardised protocol.¹⁰¹ A study between 2000 and 2005 involving 124 patients explored the prevalence of residual interatrial shunting after PFO closure using four types of devices. It reported an 87% closure rate at 2 years, influenced by the device type, PFO canal length, and ASA extent.¹⁰²

Another prospective cohort study of 1078 patients at a single hospital assessed the impact of residual shunts after PFO closure on the recurrence of stroke or TIA. Here, a c-TTE was performed 1 year post-procedure.¹⁰³ A single-centre study with 118 patients evaluating the clinical outcomes and quality of life reported that the total occlusion rate at follow-up (mean 50 months, range 3–100) was 98.1%. The day after closure, a c-TTE was repeated to confirm the proper positioning of the device and exclude

residual shunt, at which point the patient was discharged. Clinical evaluation, complete neurological examination, c-TTE/TOE and c-TCd were scheduled at 1, 6 and 12 months postoperatively and yearly after that.¹⁰⁴

Finally, a retrospective study on medical records and echocardiograms of patients who underwent transcatheter PFO closure, reported a 19.5% incidence of RLS at 4 months post-closure, which decreased to 8.4% by 11 months. Patients were evaluated using c-TTE 2–3 months after a medical procedure. If an RLS was still present, further evaluation occurred 6–12 months post-procedure using c-TEE, chest CT, or assessment in a catheterisation lab with intracardiac echocardiography and angiography to identify additional RLS sources.¹⁰¹

Evidence-based Recommendation for PICO 1.1, 1.2 and 1.3

In patients without an obvious cause of stroke, there is continued uncertainty over the most accurate diagnostic approach for detecting any RLS, because of the lack of a proper gold standard. Therefore, we are unable to offer an evidence-based recommendation. Please see the expert consensus statement below.

Quality of evidence: **Very Low** ⊕

Strength of recommendation: -

Expert Consensus Statements on PFO diagnosis

As there is no technique that can be considered as a gold standard, we advise locally agreed diagnostic algorithms using the available techniques (c-TCd, c-TTE and c-TOE) to diagnose an RLS, keeping into consideration that c-TCd is suggested when c-TTE and/or c-TOE are inconclusive.

Vote: 8/9

In light of the available data, the MMG acknowledges that TCd demonstrates superior sensitivity relative to TTE in the RLS screening.

Vote: 6/9

In patients without an obvious cause of stroke, but with positive diagnosis of RLS on initial assessment, we suggest TOE to gain additional information about the presence and anatomy of the PFO.

Vote: 9/9

Part 2: Treatment of PFO-associated stroke

In this section, to inform clinicians about the different treatment options in stroke prevention in patients with cryptogenic stroke and stroke, we address the following **overarching question**:

Which therapeutic strategy should be used in patients with PFO-associated stroke?

PICO 2: In patients with cryptogenic stroke and PFO, does percutaneous closure of PFO plus antiplatelet therapy, as compared to antiplatelet therapy alone, reduce the risk of stroke recurrence?

Analysis of current evidence and evidence-based recommendation

Patients aged 18–60 years. We identified 6 RCTs comparing PFO closure plus medical therapy versus medical therapy alone (Table 4), several study-level meta-analyses^{4,8,105} and an IPDMA by the Systematic, Collaborative, PFO Closure Evaluation (SCOPE) group, which provides a classification system (PASCAL, see Introduction) to identify which patients with cryptogenic stroke and PFO – or in pathophysiological terms PFO-associated stroke – may benefit most from PFO closure and which ones may not.⁷

CLOSURE I used a clamshell umbrella device that is no longer in production.¹⁰⁶ Double disc devices were employed in the 5 other trials, namely PC Trial, RESPECT, CLOSE, Gore REDUCE and DEFENCE-PFO.^{12,13,79,87} All double disc devices are in clinical use today. Medical anti-thrombotic therapy consisted of antiplatelet therapy in Gore REDUCE and in two of the three arms of CLOSE. In the other trials, antithrombotic therapy was at the discretion of the investigators. About 66%–79% of patients received antiplatelet therapy and 21%–34% anticoagulation.⁸ The trials included patients aged 18–60 years, except for CLOSE, which enrolled patients from 16 to 60 years, and DEFENCE-PFO, which included patients aged 18–80 years.⁸ All studies included patients with a PFO verified by TOE. In addition, CLOSE and DEFENCE PFO only included patients with a large shunt, ASA or both.

Among the six RCTs, DEFENCE PFO, Gore REDUCE, and CLOSE were positive, while CLOSURE I, and PC Trial, and RESPECT were neutral.^{12,13,79,106–108} Their trends also pointed in the direction of the benefit of PFO closure and the results of extended follow up of the RESPECT trial were in favour of PFO-closure.⁸⁷

The RESPECT, REDUCE and CLOSE trials included the Amplatzer and Gore devices which are the only FDA-approved devices.^{12,13,87}

A topical review and an IPDMA by the SCOPE consortium analysed primary and secondary efficacy outcomes of PFO closure plus medical therapy versus medical therapy alone.^{7,8} The median patient age in the device group [$n=1882$] was 46.2 (IQR 39.0–52.7) years and 46.0 (IQR 39.0–53.0) years in the medical group [$n=1846$]. The annualised incidence of stroke was 1.09% (95% CI: 0.88–1.36) with medical therapy and 0.47% (95% CI: 0.35–0.65) with device closure (adjusted HR, 0.41 [95% CI: 0.28–0.60]). All-cause mortality did not differ across treatment groups (Risk ratio 0.98, 95% CI: 0.31–3.11), while information on stroke-associated mortality was not specifically recorded. Regarding safety outcomes, the most common adverse event was AF.⁷ It occurred more often in the PFO closure group (adjusted RR 4.54 [95% CI: 2.78–7.39]), and 46% of the events (50/109) were transient, occurring only in the first 45 days after randomisation.⁷

The SCOPE IPD-MA represents the best available evidence on PFO closure in patients aged 18–60 years. However, SCOPE only indirectly addresses our PICO question because the comparator is not identical to the one, we have chosen (i.e. antiplatelet therapy). In several of the trials included in SCOPE, the comparator was antiplatelet therapy or anticoagulants at the discretion of the investigator (Table 4).⁷ We have therefore conducted a study-level meta-analysis looking only at trials allowing the direct comparison of PFO closure versus antiplatelet therapy (Gore REDUCE and CLOSE), which is presented in Figure 9. The corresponding HR was 0.18 (95% CI: 0.05–0.63), but most patients included in the two trials had a ‘high risk PFO’ with a large shunt, an ASA or both.⁷ The quality of evidence for this comparison of PFO closure versus antiplatelet therapy was deemed to be high (Table 5). The result of the overall comparison between PFO closure plus antithrombotic therapy versus anti-thrombotic therapy (antiplatelets or anticoagulants at the discretion of each investigator) alone align with those of the IPDMA [pooled hazard ratio (HR) 0.38 (95% CI: 0.19–0.77)]. Our results confirm those reported in two previously published study-level meta-analysis considering the same outcome in all the arms.⁴

Not all strokes in patients with PFO (i.e. PFO-associated strokes) are PFO-related.^{4,8,105} Therefore, a clinically relevant question is whether all PFOs in patients with cryptogenic strokes are pathogenic and should be closed. The IPDMA demonstrates that the treatment effect is heterogeneous and depends on the individual patient characteristics.⁷ The probability that a PFO is causally related to the stroke can be estimated with the *Risk of Paradoxical Embolism (RoPE) Score* and the *PFO-Associated Stroke Causal Likelihood (PASCAL)* classification system. The RoPE score is a 10-point scoring system, based on clinical and neuroimaging features only, in which higher scores reflect younger age and the absence of vascular risk factors (Table 6).¹¹⁰ A high score of a patient with a cryptogenic stroke means a greater likelihood that a PFO is present and probably pathogenic, a lower score makes this less likely or unlikely (Table 7).

To further improve the identification of ischaemic strokes due to PFO the SCOPE IPD-MA recently proposed the PFO-Associated Stroke Causal Likelihood (PASCAL) Classification System.⁷ This is different from the other three and directly germane to the current study. Among patients with no major defined cause of ischaemic stroke, the PASCAL classification system integrates information regarding: (1) presence of features that increase likelihood of PFO-stroke mechanisms (high risk PFO physiologic and structural features of large shunt or ASA) and (2) absence of features that increase likelihood of an occult non-PFO stroke mechanisms (older age, vascular risk factors, and stroke topography features) as quantified in the RoPE score. Based on this combination of factors, the original, extended PASCAL Classification System algorithmically

Table 4. Randomised controlled trials comparing PFO closure plus medical therapy versus medical therapy alone (adapted from Kent et al.⁷ and Turc et al.,⁸ JAHA 2018).

Trial	Enrolment/Follow up	Geography	Number of sites	Type of device	Event type for inclusion	PFO type for inclusion	Inclusion timing after event	Age (years)	Patient number	Medical therapy in intervention group	Medical therapy in control group	Follow-up years (mean)/Patient	Ratio of Follow-up Intervention/Control
CLOSURE I 2012 ¹⁰⁶	2003–2008/2003–2010	United States, Canada	87	STARflex (NMT Medical)	Cryptogenic IS or TIA	All TEE verified PFO	≤6 months	18–60	909	ASP for 2 years CLO for 6 months	AP or AC permitted	1.7/1555	1.06
PC Trial 2013 ¹⁰⁷	2000–2009/2000–2012	Europe, Canada, Brazil, Australia	29	Amplatzer	Cryptogenic IS or peripheral embolism	All TEE verified PFO	No restriction	<60	414	ASP > 6 months TIC or CLO ≤6 months	AP or AC permitted	4.1/1681	1.04
RESPECT 2013/2017 ^{87,108}	2003–2011/2003–2016	United States, Canada	69	Amplatzer	Cryptogenic IS	All TEE verified PFO	≤9 months	18–60	980	ASP for 5 months CLO for 1 month	AP or AC permitted	5.8/5688	1.14
CLOSE 2017 ¹³	2007–2014/2007–2016	France, Germany	63	Multiple ^d	Cryptogenic IS	TEE verified PFO, large shunt or ASA	≤6 months	16–60	473 (653) ^b	ASP > 3 months CLO for 3 months	AP	5.3/2507	1.04
Gore REDUCE 2017 ¹²	2008–2015/2008–2016	Europe, Canada, United States	34	Helex or Cardioform (Gore)	Cryptogenic IS	All TEE verified PFO	≤6 months	18–59	664	ASP or ASP + DIP or ASP + CLO	Same per site as in intervention group	3.4/2232	1.10
DEFENCE-PFO 2018 ⁷⁹	2011–2017/2011–2017	South Korea	2	Amplatzer	Cryptogenic IS	TEE verified PFO, large shunt or ASA	≤6 months	18–80	120	ASP ≥ 6 months CLO ≥ 6 months	AP or AC permitted	1.6/≈187 ^c	1.03

IS: ischaemic stroke (includes 'TIA' with visible lesion on imaging); TIA: transient ischaemic attack; AP: antiplatelet therapy; AC: anticoagulation; ASA > 10 mm; ASP: aspirin; CLO: clopidogrel; TIC: ticlopidine.

^aMean duration of follow-up among device patients/mean duration of follow-up among medical patients. Longer follow-up among device patients occurred because of (1) more end point events in medical patients, ending study participation, and (2) more dropouts in medical patients, partly to pursue device placement outside the trials.^bFour Seventy three patients randomised to closure and medical antiplatelet therapy. Additional 180 patients were randomised to AP or AC.

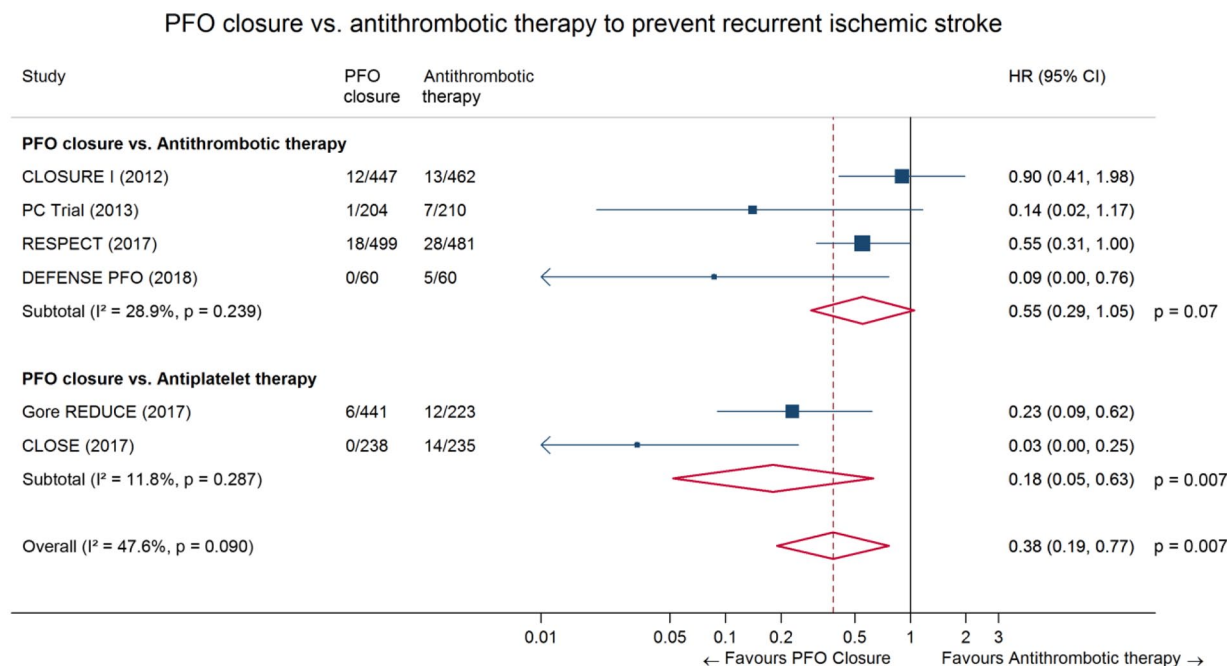


Figure 9. Study-level meta-analysis of the risk of recurrent ischaemic stroke in patients with PFO-associated stroke and randomised to PFO closure versus medical therapy alone (updated from Turc et al.,⁸ JAMA 2018 and Mas et al.¹⁰⁹).

assigns a likelihood of causal relationship among five levels: Definite, Highly Probable, Probable, Possible and Unlikely.¹¹ The PASCAL algorithm was developed using a mixed methods approach incorporating expert judgement, physiologic and epidemiologic data, and the validated RoPE Score.

The SCOPE group derived the PASCAL classification system to assess the individual treatment effect.⁷ The main results for individual treatment effects are given in Table 8.

Evidence-based recommendation

In patients undergoing PFO we suggest dual antiplatelet therapy to reduce the risk of recurrent stroke, based on the protocol of available RCTs (please see the Expert consensus below for details).

Quality of evidence: Very Low ⊕

Strength of recommendation: Weak against intervention ↓?

Expert consensus statement

In patients with PFO-related stroke who underwent percutaneous closure, according to the protocol design of the majority of positive randomised controlled trials this panel suggests prescribing a dual antiplatelet therapy for 1–6 months and to continue a single antiplatelet therapy in the long term, for at least 5 years after percutaneous closure.

Vote 9/9 experts agree

unlikely, possible, and probable using the PASCAL Classification System had HRs of 1.14 (95% CI: 0.53–2.46), 0.38 (95% CI: 0.22–0.65), and 0.10 (95% CI: 0.03–0.35), respectively (P for interaction=0.003). The 2-year absolute risk reduction was −0.7% (95% CI: −4.0 to 2.6), 2.1% (95% CI: 0.6–3.6), and 2.1% (95% CI: 0.9–3.4) in the unlikely, possible, and probable PASCAL categories, respectively. An additional analysis of the IPDMA data showed that patients with large shunts plus ASA derived the greatest benefit from PFO closure.⁷ At 2 years, their absolute risk reduction of recurrent stroke was 5.5% (95% CI: 2.7–8.3) and at 5 years it was 7.1% (95% CI: 3.7–10.6), indicating an NNT of 14 (95% CI: 9–27).

Device-associated adverse events were generally higher among patients classified as unlikely; the absolute risk increases for AF beyond day 45 after PFO closure were as follows: 4.41% (95% CI: 1.02–7.80) in the unlikely PASCAL category, 1.53% (95% CI: 0.33–2.72) in the possible, and 0.65% (95% CI: −0.41 to 1.71%) in the probable PASCAL category. Major bleeding events included access site or retroperitoneal haemorrhage in 1%, pericardial tamponade in 0.17%, and cardiac perforation in 0.06%.⁷

We acknowledge that the use of risk stratification tools was not prespecified in the present PICO question and therefore no systematic review was conducted with regard to the PASCAL classification system. Nevertheless, we chose to use PASCAL for our evidence-based recommendations because one of the three prespecified aims of the main SCOPE collaboration paper was to examine whether the PASCAL system was associated with a differential treatment effect, and which was clearly demonstrated

Patients with low versus high RoPE Scores had HRs of 0.61 (95% CI: 0.37–1.00) and 0.21 (95% CI: 0.11–0.42), respectively (P for interaction=0.02). Patients classified as

Table 5. GRADE evidence profile for PICO 2 (PFO closure plus antiplatelet therapy vs antiplatelet therapy alone).

Certainty assessment			No. of patients		Effect		Certainty	Importance				
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			PFO closure	no PFO closure	Relative (95% CI)	Absolute (95% CI)
Ischaemic stroke recurrence												
6	Randomised trials	Not serious	Not serious	Serious ^a	Not serious	Strong association	39/1889 (2.1%)	82/1851 (4.4%)	HR 0.41 (0.28–0.60)	2-Year absolute difference: 17 fewer per 1000 (from 27 fewer to 7 fewer)	⊕⊕⊕⊕ High	Critical
All-cause mortality												
6	Randomised trials	Not serious	Not serious	Serious ^a	Not serious	None	6/1889 (0.3%)	4/1851 (0.2%)	Not provided in the SCOPE IPD-MA	Not provided in the SCOPE IPD-MA	⊕⊕⊕ Moderate	Critical
TIA												
6	Randomised trials	Not serious	Not serious	Serious ^a	Not serious	None	43/1889 (2.3%)	41/1851 (2.2%)	Not provided in the SCOPE IPD-MA	Not provided in the SCOPE IPD-MA	⊕⊕⊕ Moderate	Critical
Major bleeding												
6	Randomised trials	Not serious	Not serious	Serious ^a	Not serious	None	25/1762 (1.4%)	10/1956 (0.5%)	RR 0.80 (0.47–1.40)	3 fewer per 1000 (from 11 fewer to 5 more)	⊕⊕⊕ Moderate	Critical
Atrial fibrillation (all events)												
6	Randomised trials	Not serious	Not serious	Serious ^a	Not serious	Strong association	88/1762 (5.0%)	21/1956 (1.1%)	RR 4.54 (2.78–7.39)	38 more per 1000 (from 27 more to 49 more)	⊕⊕⊕⊕ High	Important
Atrial fibrillation present beyond 45 days												
6	Randomised trials	Not serious	Not serious	Serious ^a	Not serious	Strong association	43/1762 (2.4%)	16/1956 (0.8%)	RR 2.60 (1.44–4.70)	14 more per 1000 (from 6 more to 22 more)	⊕⊕⊕⊕ High	Important

CI: confidence interval; RR: risk ratio; TIA: transient ischaemic attack.

^aIn most of these trials the comparator was not antiplatelet therapy but either antiplatelet therapy or anticoagulants at the discretion of the investigator.**Table 6.** RoPE score.¹¹⁰

Characteristic	Points
No history of	
Hypertension	+1
-Diabetes	+1
-Stroke or transient ischaemic attack	+1
Non-smoker	+1
Cortical infarct on imaging	+1
Age (in years)	
- 18–29	+5
- 30–39	+4
- 40–49	+3
- 50–59	+2
- 60–69	+1
- >70	+0
Total RoPE score = sum of individual points (maximum = 10 points)	

Table 7. PASCAL classification system.⁷

High RoPE score (≥7)	High-risk PFO feature (large shunt and/or ASA) ^a	Stroke related to PFO
Absent	Absent	Unlikely
Absent	Present	Possible
Present	Absent	Possible
Present	Present	Probable

^aLarge shunt size is defined as >20 bubbles in the left atrium on TOE; ASA defined as >10 mm of excursion from midline.

by the analysis. In this guideline, the quality of evidence for using the PASCAL classification system was rated down by one level (please see the corresponding recommendation box) because this system was not used as an inclusion criterion or stratification variable in any of the six RCTs, nor was it prospectively validated.

Additional information

Patients qualified for inclusion in the DEFENCE-PFO, CLOSURE I, CLOSE and GORE REDUCE trials if their index stroke occurred 6 months before the potential intervention.^{12,13,79,106} However, the actual timing of inclusion varied among these studies. Specifically, the RESPECT trial saw patient enrolment at a mean time of 2.6–3.3 months post-stroke,⁸⁷ the GORE REDUCE trial around 3.4 months,¹² the CLOSE trial approximately 3.1 months, and the PC Trial at about 4.3 months following the index stroke.¹⁰⁷

None of the trials were powered to explore the very early timing of PFO closure.

Patients over 60 years of age. Hospital-based and population-based studies show that RLS in older patients with cryptogenic strokes are more common than in patients with known cause of stroke, similar to patients at aged 18–60 years.⁴ However, data on PFO closure from RCTs are

Table 8. Recurrent ischaemic stroke in the individual patient data meta-analysis^{7,111}.

Category		Hazard ratio (95% CI)	PFO closure, events at 2 years/ no of patients (%)	Medical therapy, events at 2 years/ no of patients (%)	Absolute risk reduction at 2 years	No. needed to treat at 2 years (95% CI)
PASCAL unlikely ^a	RoPE score < 7, no large shunt, no ASA	1.14 (0.53–2.46)	11/293 (4.1)	8/254 (3.4)	–0.7 (–4.0 to 2.6)	–153 (–25 to 38)
PASCAL possible ^a	RoPE score ≥ 7 or large shunt or ASA	0.038 (0.22–0.65)	13/897 (1.5)	31/914 (3.6)	2.1 (0.6–3.6)	47 (27–166)
PASCAL probable ^a	RoPE score ≥ 7 and large shunt or ASA or both	0.10 (0.03–0.35)	2/700 (0.3)	16/683 (2.5)	2.1 (0.9–3.4)	47 (29–111)
PFO anatomy (disregarding RoPE score) ^b	large shunt and ASA ^c	0.15 (0.06–0.35)	0.4%	5.9%	5.5 (2.7–8.3)	18 (12–37)

^aFrom Kent et al.⁷^bFrom Mas et al.¹¹¹^cThe median RoPE score in this series was 6 (IQR 5–7), the mean 6.1 (SD 1.3), but on a RoPE scale of 9 points without counting radiology findings. This indicates that this series comprises patients of PASCAL possible and probable categories.

scarce in this age group. Only the DEFENCE-PFO Trial allowed randomisation of patients older than 60 years, but only 13 patients were randomised to PFO closure and 21 to medical therapy alone in this age group.^{8,79,112} During follow-up, no patients experienced a recurrent stroke or TIA after PFO closure, while 4 events occurred in the control group ($p=0.07$). At 2 years, the event rate was 24.6% in the medical group, corresponding to a HR of 0.14 (95% CI: 0.005–3.57, $p=0.23$). Because of the very low number of randomised patients, we believe that no evidence-based recommendation can reasonably be provided for this age group. It would be important to include these patients in RCTs if possible, or at least in a prospective clinical registry. Examples are the PFO Closure, Oral Anticoagulants or Antiplatelet Therapy After PFO-associated Stroke in Patients Aged 60–80 years trial (CLOSE-2, NCT05387954) or the Prospective Registry of Elderly ESUS with PFO (COACH_ESUS, NCT05238610).

Patients younger than 18 years. How to manage teenagers after PFO-associated stroke is another relevant clinical question. Patients had to be at least 16 years old to be enrolled in CLOSE and at least 18 years old in the other five RCTs. However, in CLOSE only one patient younger than 18 years, who did not have an outcome event, was included. Therefore, data from those trials do not address whether PFO closure should be recommended in patients younger than 18 years with PFO-associated stroke. A retrospective study identified 31 children who underwent PFO closure after stroke.¹¹³ Their median age was 14.9 years and median follow-up was 568 days. No recurrent stroke occurred.

Additional information

There are many clinical variables with a putative association with paradoxical embolism.⁴ None and no other abnormal clinical condition caused by PFO was part of the inclusion criteria of the RCTs and they all are omitted in the PASCAL score. Nevertheless, a history of non-cerebral embolism, deep venous thrombosis, pulmonary embolism,

pulmonary arterial hypertension, history of sleep apnoea or other hypoxaemic conditions associated with PFO, Valsalva at stroke onset, recent history of prolonged immobility, recent airline travel, presence of venous thrombophilia, decompressive illness in divers, straddling thrombus through the PFO, platypnea-orthodeoxia syndrome or an Eustachian valve or other anatomical features on echocardiography possibly enhancing the risk of paradoxical embolism, may be taken in consideration when managing patients after PFO-associated strokes.^{7,9}

Evidence-based recommendations

In patients aged 18–60 years in whom no other evident cause of stroke is found but a PFO (i.e. PFO-associated stroke), we recommend PFO closure in selected patients, in addition to antiplatelet therapy (please see below for details).

Quality of evidence: High ⊕⊕⊕⊕

Strength of recommendation: Strong for intervention ↑↑

In patients aged 18–60 years with possible or probable PFO-related stroke according to the PASCAL classification, we recommend PFO closure in addition to antiplatelet therapy.

Quality of evidence: Moderate ⊕⊕⊕

Strength of recommendation: Strong for intervention ↑↑

In patients aged 18–60 years with unlikely PFO-related stroke according to the PASCAL classification, we suggest against PFO closure unless there is a high probability of clinical causality (please see the Expert consensus below).

Quality of evidence: Low ⊕⊕

Strength of recommendation: Weak against intervention ↓?

In patients older than 60 and younger than 18 years, no evidence-based recommendation can be provided. Please see the expert consensus statements below.

Quality of evidence: Very Low ⊕

Strength of recommendation: -

Table 9. GRADE evidence profile for PICO 3 (PFO closure vs anticoagulation).

Certainty assessment		No. of patients					Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PFO closure + Antiplatelets	Anticoagulants	Relative (95% CI)	Absolute (95% CI)
Ischaemic stroke										
1	Randomised trials	Not serious	Not serious	Not serious	Very serious ^a	None	0/238 (0.0%)	3/187 (1.6%)	RR 0.11 (0.01–2.16)	14 Fewer per 1000 (from 16 fewer to 19 more)
Death										
1	Randomised trials	Not serious	Not serious	Not serious	Very serious ^a	None	0/238 (0.0%)	1/187 (0.5%)	RR 0.26 (0.01–6.40)	4 Fewer per 1000 (from 5 fewer to 29 more)
TIA										
1	Randomised trials	Not serious	Not serious	Not serious	Very serious ^a	None	8/238 (3.4%)	5/187 (2.7%)	RR 1.26 (0.42–3.78)	7 More per 1000 (from 16 fewer to 74 more)
Major bleeding										
1	Randomised trials	Not serious	Not serious	Not serious	Serious ^b	None	2/238 (0.8%)	10/187 (5.3%)	RR 0.16 (0.03–0.71)	45 Fewer per 1000 (from 52 fewer to 16 fewer)
									$\oplus\oplus\oplus$ Moderate	Critical

CI: confidence interval; RR: risk ratio; TIA: transient ischaemic attack.

^aWide confidence interval and optimal information size not met (very few events and small sample size).^bOptimal information size not met (very few events and small sample size).**Table 10.** GRADE evidence profile for PICO 3 (antiplatelets vs anticoagulants).

Certainty assessment			No. of patients				Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anticoagulants	Antiplatelets	Relative (95% CI)	Absolute (95% CI)
Stroke recurrence										
5	Randomised trials	Not serious	Not serious	Not serious	Serious ^a	None	33/751 (4.4%)	48/811 (5.9%)	RR 0.76 (0.43–1.32)	14 fewer per 1000 (from 34 fewer to 19 more)
Major bleeding										
4	Randomised trials	Not serious	Not serious	Not serious	Serious ^a	None	19/709 (2.7%)	12/755 (1.6%)	RR 1.63 (0.77–3.43)	10 more per 1000 (from 4 fewer to 39 more)
TIA										
1	Randomised trials	Not serious	Not serious	Not serious	Very serious ^b	None	5/187 (2.7%)	6/174 (3.4%)	RR 0.78 (0.24–2.50)	8 fewer per 1000 (from 26 fewer to 52 more)
Composite outcome (stroke/TIA/death)										
3	Randomised trials	Not serious	Not serious	Not serious	Very serious ^b	None	21/250 (8.4%)	27/253 (10.7%)	RR 0.93 (0.41–2.09)	7 fewer per 1000 (from 63 fewer to 116 more)
Death										
3	Randomised trials	Not serious	Not serious	Not serious	Very serious ^b	None	4/250 (1.6%)	3/253 (1.2%)	RR 1.46 (0.36–5.95)	5 more per 1000 (from 8 fewer to 59 more)

CI: confidence interval; RR: risk ratio; TIA: transient ischaemic attack.

Explanations

^aWide confidence interval.^bOptimal information size not met (less event and small sample size) and wide confidence interval.

Expert consensus statement

Expert consensus statements on PFO closure in patients older than 60 years old and patients aged between 13 and 17

This panel encourages the inclusion of patients **older than 60 years old** with stroke and PFO in randomised trials whenever possible, or at least in a registry. If this is not possible, the majority of the module working group members suggest using the PASCAL Classification System and clinical judgement to guide therapy.

Vote: 8/9 experts agree

This panel suggests PFO closure in selected patients aged between 13 and 17 with PFO-related stroke according to PFO anatomy.

Vote: 9/9 experts agree

Expert consensus statement on PFO closure in patients with unlikely PFO-related stroke according to the PASCAL classification

In patients aged 18–60 years with unlikely PFO-related stroke according to the PASCAL classification, this panel suggests PFO closure in various combinations of the following situations, which suggest a high probability of clinical causality: non-cerebral embolism, deep venous thrombosis and/or pulmonary embolism close to index stroke, pulmonary arterial hypertension, history of sleep apnoea or other hypoxaemic conditions associated with PFO, Valsalva at stroke onset, recent history of prolonged immobility, recent airline travel, presence of venous thrombophilia, decompressive illness in divers, platypnea-orthodeoxia syndrome or a Eustachian valve or other anatomical features on echocardiography to enhance the risk of paradoxical embolism.

Vote: 7/9

Expert consensus statement

This panel encourages the inclusion of patients **older than 60 years old** with stroke and PFO in randomised trials whenever possible, or at least in a registry. If this is not possible, the majority of the module working group members suggest using the PASCAL Classification System and clinical judgement to guide therapy.

Vote: 8/9 experts agree

This panel suggests PFO closure in selected patients aged between 13 and 17 with PFO-related stroke according to PFO anatomy.

Vote: 9/9 experts agree

Expert consensus statements on the timing of the PFO closure

Given the lack of evidence for the timing of PFO closure, the panel suggests considering PFO closure within 6 months post-index stroke, based on randomised studies. However, as secondary prevention procedures are time-dependent, PFO closure should be performed as soon as possible based on each patient's clinical scenario, including stroke lesion size and risk profile.

Vote: (9/9) experts agree

PICO 3: In patients with cryptogenic stroke and PFO, does percutaneous closure of the PFO plus antiplatelet therapy compared with oral anticoagulants (VKA or DOACs) reduce the risk of stroke recurrence?

Analysis of current evidence and evidence-based recommendation

The 3-arm CLOSE study was the only one in which patients were randomised to PFO closure or oral anticoagulation, but the head-to-head comparison of these 2 groups was not prespecified in the study statistical analysis plan (Table 9).¹³ Overall, 238 patients were randomised to PFO closure and 187 to anticoagulants, of which 92.8% were vitamin K antagonists (VKA) and only 7.2% were direct oral anticoagulants (DOAC). In the anticoagulation group, 3 patients had a recurrent stroke over a follow-up of 967 patient-years, compared with none in the PFO closure group over a follow up of 963 patient-years, which were not statistically significant in the post-hoc analysis, HR 0.14; 95% CI: 0.00–1.45; $p=0.08$ for log-rank test.⁸ The outcome events are listed in Figures 10–12. However, CLOSE was underpowered for this comparison (Figures 13 and 14).

Additional information

A non-randomised comparison between PFO closure and anticoagulation is available from the CLOSURE¹⁰⁶ and RESPECT trials.^{87,108} A meta-analysis of those data reported an OR of 1.19 (95% CI: 0.43–3.26) for stroke recurrence with oral anticoagulants. Also including data from CLOSE trial in the meta-analysis, the OR for stroke recurrence with oral anticoagulants was 0.74 (95% CI: 0.20–2.74).⁴

In a prospective cohort of 591 patients with cryptogenic ischaemic stroke or TIA and PFO, 134 (22.7%) had thrombophilia [(protein C deficiency (13.4%), protein S deficiency (32.1%), Factor V Leiden (11.9%), G2021A mutation (7.5%), anticardiolipin antibody (21.6%), hyperhomocysteinaemia (23.9%), antithrombin III deficiency (11.2%), positive lupus anticoagulant (8.2%), high factor VIII levels (11.2%)].¹¹⁴ In a mean duration follow-up of 53 months, thrombophilia significantly increased the risk for recurrent events (HR 1.85; 95% CI: 1.09–3.16; $p=0.024$). PFO closure was performed in 383 (65%) patients, who had a reduced risk of stroke or TIA recurrence (HR 0.16; 95% CI: 0.09–0.30; $p<0.001$). Of the 134 patients with thrombophilia, 89 underwent PFO closure and 45 received only medical therapy (anticoagulants or antiplatelets), with a difference in the risk for recurrent events in favour of PFO closure (HR 0.25; 95% CI: 0.08–0.74; $p=0.012$).¹¹⁵

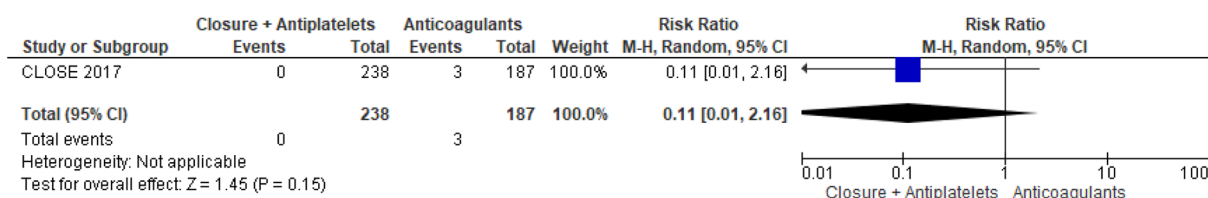


Figure 10. Risk of ischaemic stroke (only one study included).

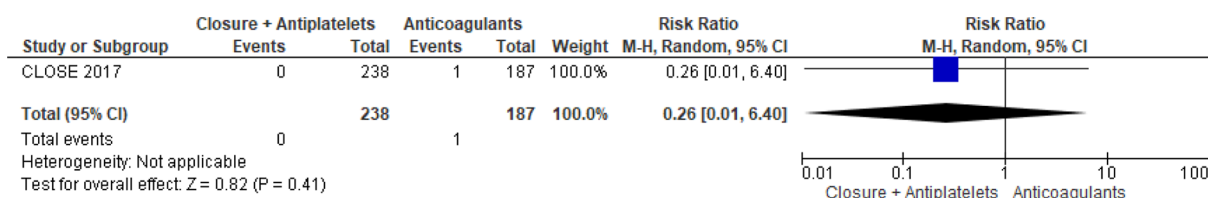


Figure 11. Risk of death (only one study included).

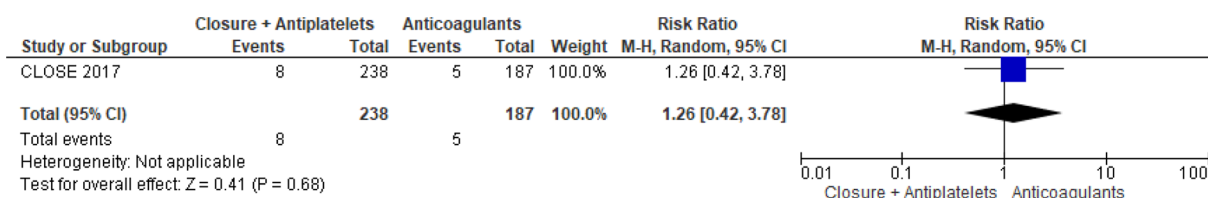


Figure 12. Risk of TIA (only one study included).

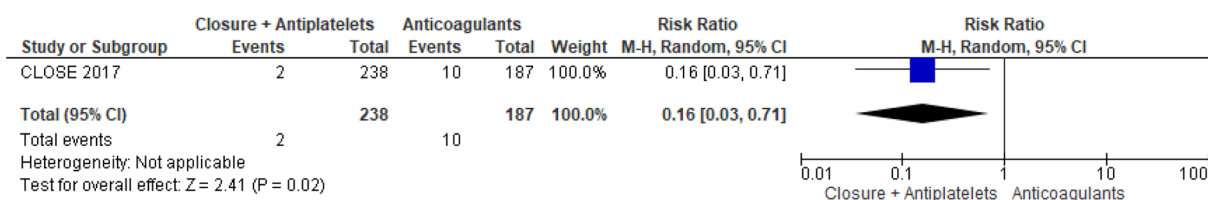


Figure 13. Risk of major bleeding.

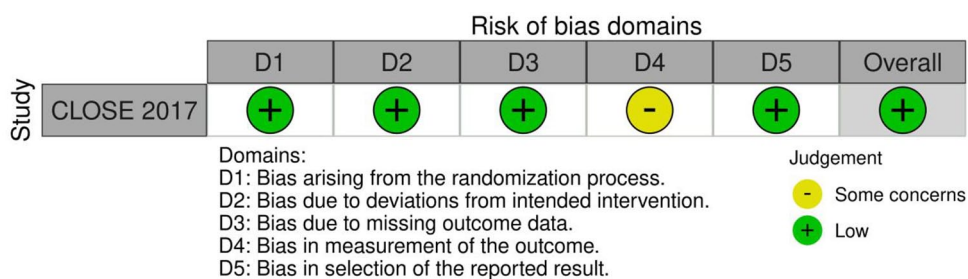


Figure 14. Risk of bias of randomised controlled trial (outcomes: Ischaemic stroke, Death, TIA, Major bleeding).

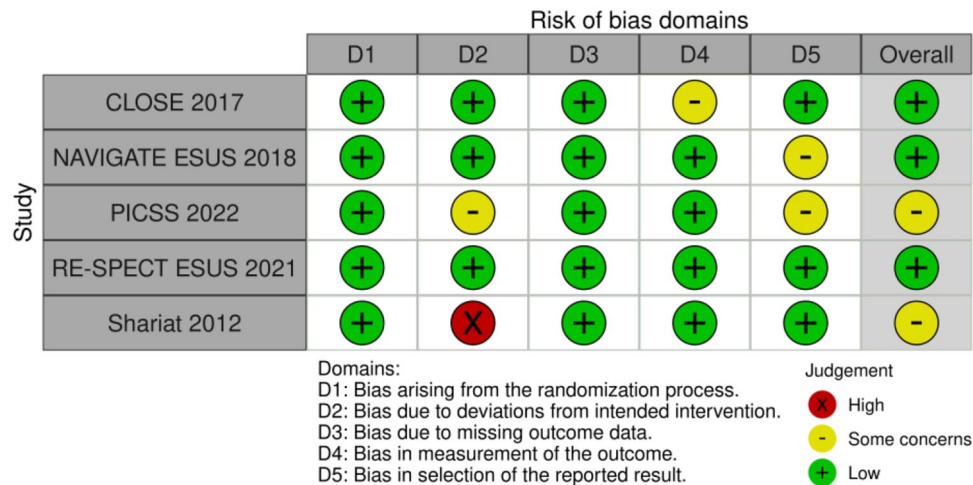


Figure 15. Risk of bias of randomised controlled trials.

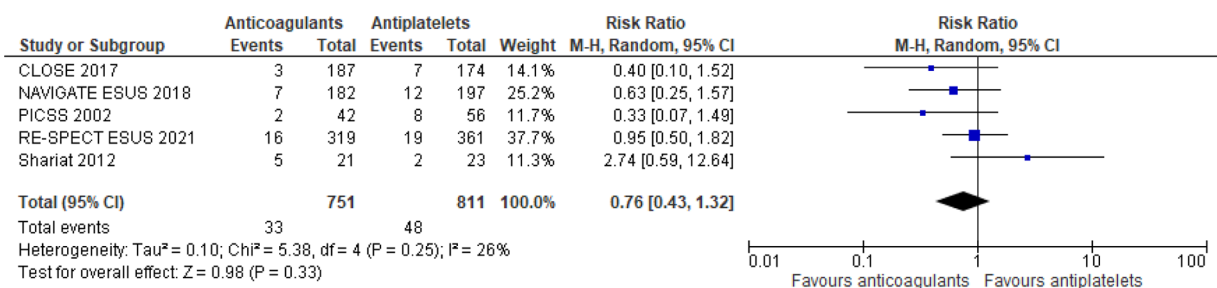


Figure 16. Risk of stroke recurrence restricted to RCTs (antiplatelets vs anticoagulants) stroke recurrence.

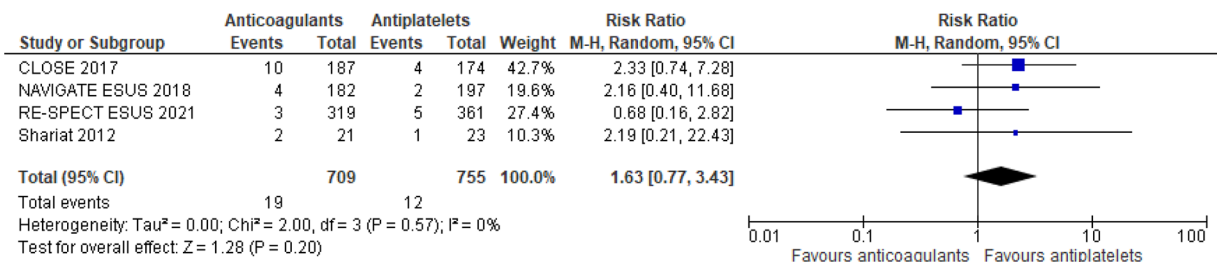


Figure 17. Risk of major bleeding restricted to RCTs (antiplatelets vs anticoagulants).

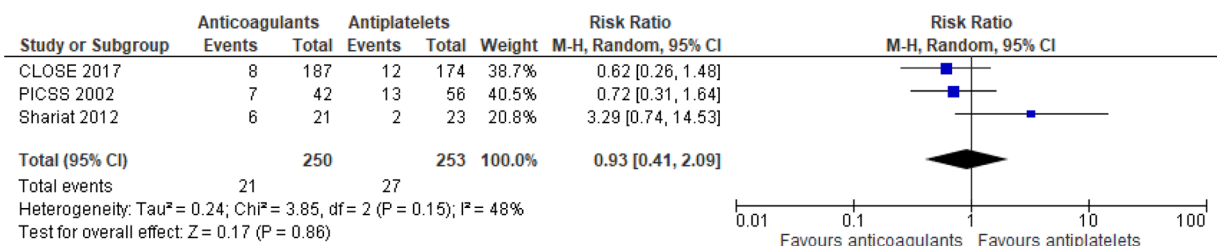


Figure 18. Risk of composite outcome (stroke/TIA/death) restricted to RCTs (antiplatelets vs anticoagulants).

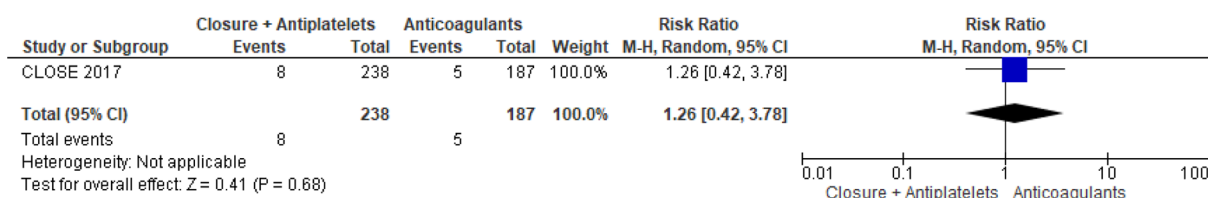


Figure 19. Risk of TIA restricted to RCTs (antiplatelets vs anticoagulants) TIA.

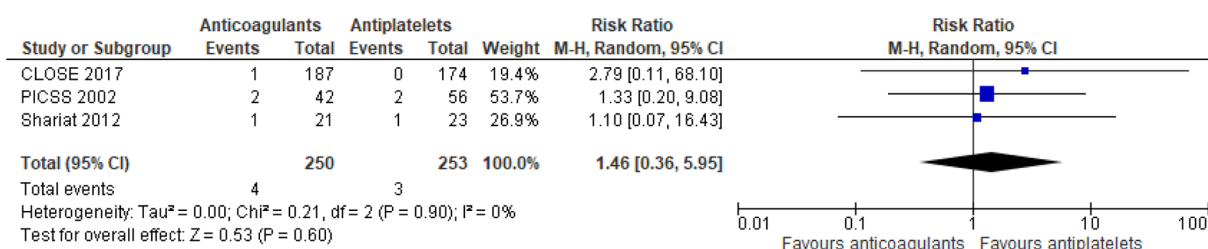


Figure 20. Risk of death restricted to RCTs (antiplatelets vs anticoagulants) death.

Evidence-based recommendation

In patients aged 18–60 years with possible or probable PFO-related stroke, there is insufficient evidence regarding the risks and benefits of long-term anticoagulation vs PFO closure. Nonetheless, we suggest PFO closure in addition to antiplatelet therapy rather than long-term oral anticoagulants alone, based on the (1) superiority of PFO closure over antithrombotic therapy demonstrated in the pivotal RCTs and (2) the cumulative risk of major bleedings associated with long-term anticoagulation.

Quality of evidence: Low ⊕⊕

Strength of recommendation: Weak for intervention ↑?

In contrast, anticoagulants had a higher risk for major bleeding; RR: 1.63 (95% CI: 0.77–3.43); for the composite of recurrent stroke/TIA and death there was a minimal difference; RR: 0.93 (95% CI: 0.41–2.09) (Figures 16–20)

Overall, the data suggests a slightly lower risk of stroke recurrence with anticoagulants compared to antiplatelets but with a higher risk of major bleeding. The evidence for other outcomes like TIA, composite outcomes, and death is of low quality with considerable uncertainty (Figure 20).

Additional information

A previously published study-level meta-analysis including the CLOSE study as well as adjusted and non-adjusted observational comparisons found a statistically significant reduction of recurrent stroke risk in patients with PFO undergoing oral anticoagulation as compared to antiplatelet therapy (OR: 0.88; 95% CI: 0.83–0.92) at the expense of an increased major bleeding rate (OR: 4.57; 95% CI: 2.10–9.93).⁸ In another recent meta-analysis on cerebrovascular event recurrences and/or death in patients with PFO treated with oral anticoagulation (OAC) or antiplatelet therapy for secondary prevention of cryptogenic stroke, the efficacy endpoints were stroke recurrence and the composite of stroke, TIA, or all-cause death. Major bleedings represented the safety endpoint. Sixteen studies with 3953 patients (OAC=1527, APT=2426) were included. The weighted mean follow-up was 2.9 years. OAC was associated with a significant reduction in the risk of stroke compared with APT (RR: 0.65; 95% CI: 0.44–0.95; ARR 2%, NNT 49), while no difference was found regarding the composite outcome (RR: 0.78; 95% CI: 0.57–1.07) and the safety outcome (RR: 1.57; 95% CI: 0.85–2.90; $p = 0.15$).¹²⁰

PICO 4: In patients with cryptogenic stroke and PFO, does oral anticoagulation compared with antiplatelet therapy reduce the risk of recurrent stroke?

Analysis of current evidence

Two RCTs that enrolled patients with cryptogenic stroke and PFO and three prespecified analyses of non-randomised subgroups of patients with cryptogenic stroke and PFO enrolled in otherwise RCTs compared anticoagulant therapy and antiplatelet therapy outcomes.^{12,13} The duration of follow-up was different among studies: 5 years in the CLOSE trial,¹³ 11 months in NAVIGATE ESUS,¹¹⁶ 2 years in PICSS,¹¹⁷ 19 months in RESPECT-ESUS¹¹⁸ and 13.5 months in patients receiving anticoagulants and 14.6 months in those treated with antiplatelets in the trial by Shariat et al.¹¹⁹ (Table 10). In our meta-analysis of these study-level data on 1562 patients, for stroke recurrence anticoagulants had a lower recurrence risk versus antiplatelets (RR: 0.76 [95% CI: 0.43–1.32] (Figure 15).

Table 11. Grade evidence profile table for PICO 5: In patients with cryptogenic stroke and PFO, does dual antiplatelets compared with single antiplatelet therapy reduce the risk of recurrent stroke after PFO closure?.

Certainty assessment		No. of patients			Effect		Certainty	Importance				
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Anticoagulants	Antiplatelets	Relative (95% CI)	Absolute (95% CI)
Major bleeding												
I	Cohort studies	Serious ^a	Not serious	Serious ^b	Serious ^c	None	0/105 (0.0%)	6/445 (1.3%)	RR 0.71 (0.04 to 12.46)	4 Fewer per 1000 (from 13 fewer to 155 more)	⊕○○○ Very low	Critical
Myocardial infarction												
I	Cohort studies	Serious ^a	Not serious	Serious ^b	Serious ^c	None	0/105 (0.0%)	6/445 (1.3%)	RR 0.71 (0.04 to 12.46)	4 Fewer per 1000 (from 13 fewer to 155 more)	⊕○○○ Very low	Critical

CI: confidence interval; RR: risk ratio.

^aModerate to serious risk of bias.^bVariation in outcome definition.^cOptimal information size not met (less event and small sample size) and very wide confidence interval.

Part 3. Post-procedural management

In this section, we address the following overarching question.

Evidence-based recommendation

There is continued uncertainty over the risks and benefits of the use of anticoagulation vs. antiplatelet therapy in patients in whom no other evident cause of stroke is found but a PFO (i.e., PFO-associated stroke). Please see the Expert Consensus Statement below.

Quality of evidence: Low ⊕⊕

Strength of recommendation: -

Expert consensus statement

In light of the results of the meta-analyses including both randomised trials and observational studies, we suggest an individualised approach to the choice of antithrombotic therapy for patients with PFO-related stroke who refuse PFO closure. The choice of anticoagulation over antiplatelet therapy should balance the expected lower risk of PFO-related stroke recurrence with a possible increase in the long-term risk of major bleeding and take into account the patient's preference.

Vote:9/9 experts agree

What should be the long-term management after PFO closure in patients with cryptogenic stroke?

PICO 5. After percutaneous closure in patients with PFO-related stroke, does dual antiplatelet therapy after the procedure compared with single antiplatelet therapy reduce the risk of recurrent stroke?

Analysis of current evidence

The coagulation system is part of the normal and crucial sealing process of PFO occluders by facilitating fibrous tissue growth within the meshes of the device.^{121,122} Therefore, it is not surprising that minor cerebrovascular events have been estimated with an incidence up to 1.0%–2.0%, within the first 4 weeks after PFO closure.^{123,124} Based on animal models and isolated reports in humans a complete device endothelialization is expected to be achieved within 6 months after PFO closure in the majority of patients, however the process may require up to 5 years.¹²⁵ Diagnostics cannot visualise this process on many types of implanted devices because it is a layer that is often only a few cells thick.¹²⁶ The understanding of endothelialisation, albeit incomplete, comes from the rare cases when devices were inspected at the time of autopsy or open heart surgery. These devices often had incomplete tissue covering the large surface of the device, filling the crevices at the edge of the discs, and bridging the gap between the device edge and the adjacent tissue.^{127,128}

Antiplatelet therapy after closure may have a role to facilitate this endothelialisation and to prevent ischaemic events. Our literature search failed to identify any RCT of

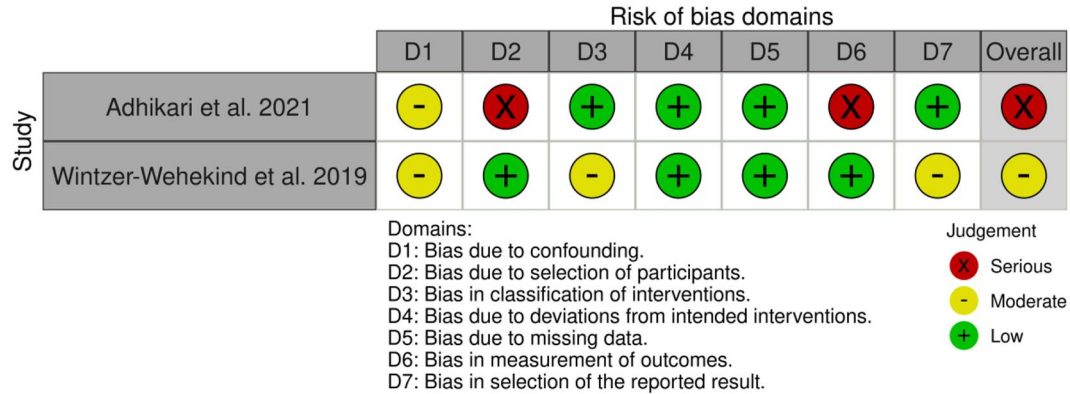


Figure 21. Risk of bias assessment (ROBINS-I tool) of observational studies reporting data on dual antiplatelet therapy versus single antiplatelet therapy for reducing the risk of recurrent stroke after PFO closure.

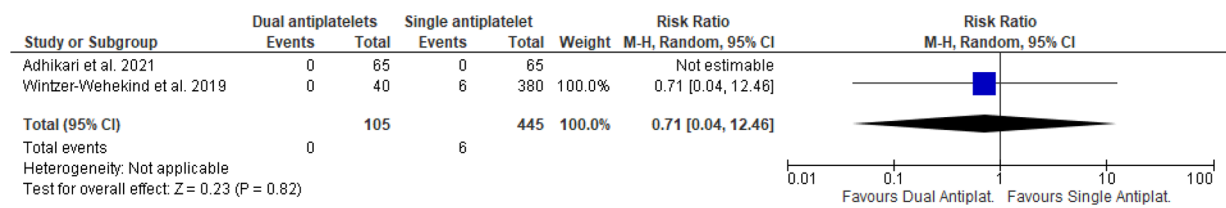


Figure 22. Dual antiplatelet therapy versus single antiplatelet therapy and risk of recurrent stroke.

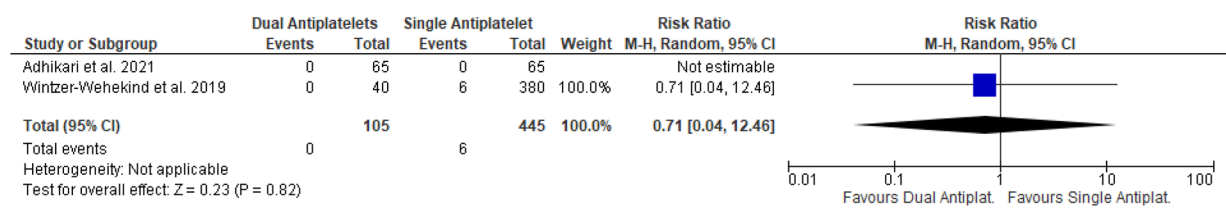


Figure 23. Dual antiplatelet therapy versus single antiplatelet therapy and risk of MI.

dual antiplatelet therapy versus single antiplatelet therapy after PFO closure. Only two observational studies were found to be relevant for this comparison.^{129,130} These two observational studies were found to be relevant for our meta-analysis of major bleeding outcome after PFO closure following stroke (Figure 21); only one study was included in our analysis.¹³⁰ Our analysis showed non-significant benefit of single antiplatelet therapy (Aspirin or Clopidogrel) over dual antiplatelets therapy (Aspirin + Clopidogrel) in reducing the risk of major bleeding ($p=0.82$, Figure 22).^{129,130} At the same time, no significant benefit of dual antiplatelet therapy (Aspirin + Clopidogrel) over single antiplatelet therapy (Aspirin or Clopidogrel) was observed in reducing the risk of myocardial infarction ($p=0.82$, Figure 23).

In a meta-analysis including all the six RCTs, major bleeding occurred in 1.8% and 1.7% of the patients randomised to PFO closure and medical treatment, respectively.⁸ In the CLOSE trial, there was no stroke during

follow-up in the closure group, but up to 24 bleeding events were described under antiplatelet therapy.¹³

Additional information

In a hospital-based cohort, 453 consecutive patients who underwent PFO closure due to a cryptogenic ischaemic event were followed up and assessed at a median follow-up of 8 (IQR: 4–11) years. All patients were on antithrombotic treatment following PFO closure. Stroke and TIA occurred in 4 (0.9%) and 12 (2.6%) patients, respectively. Six percent of patients had bleeding events (major in 1.3% of patients) (Table 11). A propensity score-matched analysis of 46 patients who discontinued antithrombotic therapy within 1-year of PFO closure and 120 patients who continued antithrombotic therapy showed similar rates of ischaemic events between groups (0 vs 0.2 stroke/transient ischaemic attack per 100 patient-years in those who discontinued vs those who continued antithrombotic therapy).¹³⁰

In patients undergoing PFO we suggest dual antiplatelet therapy followed by single antiplatelet therapy to reduce the risk of recurrent stroke, based on the protocol of available RCTs (please see the Expert consensus below for details).

Quality of evidence: Low ⊕⊕

Strength of recommendation: –

No evidence-based recommendation can be formulated regarding the duration of the single antiplatelet treatment.

Quality of evidence: Low ⊕⊕

Strength of recommendation: Weak against intervention ↓?

PICO 6: In patients with PFO-related stroke who have undergone percutaneous closure, does prolonged cardiac monitoring compared with no prolonged cardiac monitoring, reduce the risk of recurrent stroke?

Analysis of current evidence

In RCTs, new-onset AF was 4.3 times more frequent in patients assigned to the closure group than in those assigned to the antithrombotic group.⁴

In a recent meta-analysis, a 4.6% incidence of AF was reported in a follow-up period of 3.8 years. However, the Authors did not clarify whether the AF episodes were symptomatic or identified through ILR monitoring.⁸ Additionally, a meta-analysis of 14 studies (13,245 patients, mean age 61.2 years), the rate of AF detection was lower in patients with stroke and PFO compared to those without (RR=0.52, 95% CI: 0.41–0.63). In line with this, AF detection was lower in patients with PFOs found on TTE versus TOE, suggesting that the yield of AF monitoring is further reduced with increasing PFO size.¹³¹

A meta-analysis reported that beyond 45 days after closure there was no increased risk for AF with PFO closure.⁷ The incidence of these events appeared lowest with the Amplatzer and GORE occluders.^{4,132}

Moreover, there is growing evidence from RCTs and observational studies that using data from RCTs and observational studies, the implantable loop recorder (ILR) reduces the risk of first-ever and recurrent (combined) stroke.^{133,134}

We were unable to identify RCTs or comparative observational studies on patients with PFO closure that compared the detection of AF with prolonged cardiac monitoring compared with non-prolonged cardiac monitoring. However, our literature search identified five observational studies in which prolonged monitoring was conducted after PFO closure, without a control arm. These five observational studies involving 2076 patients were included in our meta-analysis to estimate the long-term incidence of AF after PFO closure. Of note, four of these studies had as endpoint only the detection of AF with prolonged monitoring^{135–138} whereas only one study included

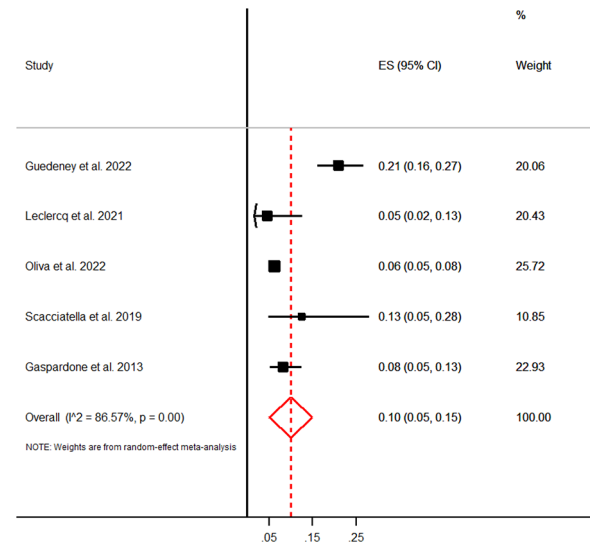


Figure 24. Meta-analysis of the incidence of AF after PFO closure in patients who underwent long-term cardiac monitoring.

recurrent ischaemic stroke as endpoint.^{136–139} No recurrent stroke was recorded (Figure 24).

The pooled AF detection rate was 10% (95% CI: 5–15) in patients who underwent cardiac monitoring.¹⁴⁰ Two studies utilised ILR in patients over 55 years and associated cardiovascular risk factors.^{135,138} A previously published study reported a median delay from procedure to arrhythmia of 14.0 days (IQR: 6.5–19.0 days), and one-half of these patients reported symptomatic episodes.¹³⁸ Determinants for AF were older age (adjusted OR: 1.67 per 10-year increase; 95% CI: 1.18–2.36), device left disc diameter of 25 mm compared to smaller diameter (adjusted OR: 2.67; 95% CI: 1.19–5.98) and male sex (adjusted OR: 4.78; 95% CI: 1.96–11.66). Data from Canadian administrative health data recorded new-onset AF following PFO closure in patients having diabetes and age 60 years with an HR of 2.49; 95% CI: 1.48–4.18; $p=0.001$ and 2.82; 95% CI: 1.76–4.51; $p=0.001$, respectively.¹³⁹

Another study also detected a statistically higher rate of AF in PFO patients independently from PFO closure.¹³⁷

Additional information

In one cohort, oral anticoagulation was prescribed in 29 (56.9%) patients.¹³⁹ Electric and pharmacologic cardioversion was performed in one and eight patients, respectively. Percutaneous ablation was performed in four patients. Among the 19 ILR-monitored patients presenting with more than 1 episode of supraventricular arrhythmia, there were seven cases of recurrence more than 3 months after the index event. One TIA occurred in one patient 1 month after admission for symptomatic flutter, despite adherence to oral anticoagulation. Among patients without supraventricular arrhythmia, 1 stroke and 1 TIA occurred in ILR

monitored patients.¹³⁸ Other studies showed a statistically significant reduction of AF prevalence after percutaneous closure of PFO, suggesting some antiarrhythmic effect of the procedure.¹⁴¹

Several ongoing studies are investigating the role of prolonged cardiac monitoring after PFO closure and the clinical implications of AF occurrence on the risk of recurrent stroke such as PFO-AF Observational Cohort Study (France, NCT04926142); ALFA ROMEO Observational Cohort Study (Switzerland, NCT04881578), PREDICT-AF-PFO Nonrandomized Clinical Trial (Germany, NCT04898361) and DEFENCE-ELDERLY Observational Cohort Registry (South Korea, NCT04285918).

Additional information

We decided not to develop a PICO question regarding the screening for subclinical AF in patients below 60 years of age who have experienced a cryptogenic stroke and PFO as Rubiera et al. already addressed these topics in the ESO screening guidelines. However, we listed this chapter's relevant expert opinion statements to support physicians in the PFO management.¹⁴²

Evidence-based recommendations:

In patients aged 18–60 years in whom no other evident cause of stroke is found but a PFO, there is continued uncertainty over the risks and benefits of the use of long-term cardiac monitoring (i.e. ILR)

Please see the Expert Consensus Statement below.

Quality of evidence: Very Low ⊕

Strength of recommendation: –

Expert consensus statements

In line with the ESO guidelines on screening for AF after cryptogenic stroke,¹⁴² this panel suggests that in patients <55 year old in whom no other evident cause of stroke is found but a PFO (i.e. PFO-associated stroke), a basic cardiac monitoring during 24 h by telemetry or Holter-ECG should be performed before closure.

Vote 8/9 experts agree

In line with the ESO guidelines on screening for atrial fibrillation after cryptogenic stroke,¹⁴² we suggest using an ILR to detect paroxysmal AF in patients with cryptogenic stroke and PFO older than 60 years.

Vote 7/9 experts agree

We suggest that patients that have been implanted a loop recorder before PFO closure continue monitoring AF until the end-of-life of the recorder.

Vote 8/9 experts agree

We advise against systematic implantation of monitoring devices after PFO closure.

Vote 8/9 experts agree

We advise in favour of a systematic use of ILR in patients with recurrent stroke after PFO closure who have negative short-term ECG monitoring and no other obvious causes for recurrence, regardless of age.

Vote 8/9 experts agree

Discussion

This guideline document was developed following the GRADE methodology and aims to assist physicians in decision-making regarding cryptogenic stroke and PFO. All recommendations and Expert consensus statements are summarised in Table 12.

Although accurate diagnosis of PFO and associated anatomical characteristics such as the presence of an ASA are very important for risk stratification and decisions on PFO closure, we were unable to provide an evidence-based recommendation on the best diagnostic strategy in patients with recent ischaemic stroke. Indeed, although TOE is usually considered to be the conventional reference to diagnose a PFO, its sensitivity against robust invasive techniques is imperfect. Bayesian methods have been suggested to deal with meta-analysis of diagnostic test accuracy in the context of imperfect reference standards but were considered to be beyond the scope of this guideline.^{143,144} However, we provide a pragmatic expert consensus statement to use c-TOE to gain additional information about the presence and anatomy of the PFO after an initial assessment based on locally available techniques (c-TTE or c-TCd, in case TOE is not considered part of first-line investigations). In line with this pragmatic approach, we did not include recommendations on the preparation of the AS with and without blood, even if there are data showing that the addition of blood increases the sensitivity.^{37,73} The same pragmatic approach should be applied for longterm follow up examinations for residual RLS as no standardised protocols could be established for the lack of gold standards.

In order to increase the number of studies on PFO diagnosis, we included our study population, not only acute ischaemic strokes and TIAs, but also patients with migraine, vertigo, syncope, myocardial infarction, and peripheral embolism.

In addition, we did not include a comprehensive diagnostic protocol for patients with cryptogenic stroke to rigorously exclude other rare aetiologies beyond a PFO, as this protocol should follow international and national clinical guidelines.¹⁴⁵

We found high-quality evidence to recommend PFO closure plus antiplatelet therapy in selected patients aged 18–60 years in whom no other evident cause of stroke is found but a PFO (i.e. PFO-associated stroke). The PASCAL classification system can be used to select such candidates for PFO closure. Patients with both a large right-to-left shunt and an ASA benefit most from PFO closure. There is insufficient evidence to make an evidence-based recommendation on PFO closure in patients older than 60 and younger than 18 years. Whereas, for patients between 18 and 60 years whose stroke is considered unlikely to be related to PFO as per the PASCAL classification, PFO closure is generally not recommended unless there is substantial clinical

Table 12. Synoptic table of all recommendations.

Topic/PICO question	Recommendation	Expert consensus statement
Evidence-based recommendation for PICO 1.1, 1.2 and 1.3		
1.1 In patients with cryptogenic stroke, what is the diagnostic performance of c-TCD compared with c-TOE (conventional reference) to screen for a PFO-related right-to-left shunt?	In patients without an obvious cause of stroke, there is continued uncertainty over the most accurate diagnostic approach for detecting any RLS, because of the lack of a gold standard. Therefore, we are unable to offer an evidence-based recommendation. Quality of evidence: Very Low ⊕ Strength of recommendation: -	As there is no technique that can be considered as a gold standard, we advise locally agreed diagnostic algorithms using the available techniques (c-TCD, c-TTE, and c-TOE) to diagnose an RLS, keeping into consideration that c-TCD is suggested when c-TTE and /or c-TOE is inconclusive. Vote: 8/9
1.2 In patients with cryptogenic stroke, what is the diagnostic performance of contrast-enhanced transthoracic echocardiogram (c-TTE) compared with contrast-enhanced transoesophageal echocardiogram (c-TOE, conventional reference) for identifying a PFO-related right-to-left shunt?		In light of the available data, the MMG acknowledges that TCD demonstrates superior sensitivity relative to TTE in the RLS screening. Vote: 6/9
1.3 In patients with cryptogenic stroke, is the diagnostic performance of c-TCD superior to that of contrast-enhanced transthoracic echocardiogram (c-TTE) to screen for a PFO-related right-to-left shunt using contrast-enhanced transoesophageal echocardiogram c-TOE as conventional reference?		In patients without an obvious cause of stroke, but with positive diagnosis of RLS on initial assessment, we suggest TOE to gain additional information about the presence and anatomy of the PFO. Vote: 9/9
Overarching question: Which diagnostic test should be used to detect PFO-related right-to-left shunt in patients with cryptogenic stroke?		
PICO 2 In patients with cryptogenic stroke and PFO, does percutaneous closure of PFO plus antiplatelet therapy, as compared to antiplatelet therapy alone, reduce the risk of stroke recurrence?	In patients aged 18–60 years in whom no other evident cause of stroke is found but a PFO (i.e. PFO-associated stroke), we recommend PFO closure in selected patients, in addition to antiplatelet therapy (please see below for details). Quality of evidence: High ⊕⊕⊕⊕ Strength of recommendation: Strong for intervention ↑↑	Expert consensus statements on PFO closure in patients older than 60 years old and patients aged between 13 and 17 We encourage the inclusion of patients older than 60 years old with stroke and PFO in randomised trials whenever possible, or at least in a registry. If this is not possible, the majority of the module working group members suggest using the PASCAL Classification System and clinical judgement to guide therapy. Vote: 8/9 experts agree
	In patients aged 18–60 years with possible or probable PFO-related stroke according to the PASCAL classification, we recommend PFO closure in addition to antiplatelet therapy. Quality of evidence: Moderate ⊕⊕⊕ Strength of recommendation: Strong for intervention ↑↑	We suggest PFO closure in selected patients aged between 13 and 17 with PFO-related stroke according to PFO anatomy. Vote: 9/9 experts agree
	In patients aged 18–60 years with unlikely PFO-related stroke according to the PASCAL classification, we suggest against PFO closure unless there is a high probability of clinical causality Quality of evidence: Low ⊕⊕ Strength of recommendation: Weak against intervention ↓?	In patients aged 18–60 years with unlikely PFO-related stroke according to the PASCAL classification, a majority of MWG members suggest PFO closure in various combinations of the following situations, which suggest a high probability of clinical causality: Non-cerebral embolism, deep venous thrombosis and/or pulmonary embolism close to index stroke, pulmonary arterial hypertension, history of sleep apnoea or other hypoxaemic conditions associated with PFO, Valsalva at stroke onset, migraine aura, recent history of prolonged immobility, recent airline travel, presence of venous thrombophilia, decompressive illness in divers, platypnea-orthodeoxia syndrome or a Eustachian valve or other anatomical features on echocardiography to enhance the risk of paradoxical embolism Vote: 7/9 experts agree

(Continued)

Table 12. (Continued)

Topic/PICO question	Recommendation	Expert consensus statement
PICO 3 In patients with cryptogenic stroke and PFO, does percutaneous closure of the PFO plus antiplatelet therapy compared with oral anticoagulants (VKA or DOACs) reduce the risk of stroke recurrence?	In patients aged 18–60 years old with possible or probable PFO-related stroke according to the PASCAL classification, there is continued uncertainty regarding the risks and benefits of long-term anticoagulation vs. PFO closure. Nonetheless, we suggest PFO closure in addition to antiplatelet therapy instead of long-term oral anticoagulants alone, based on (1) the cumulative risk of major bleedings associated with long-term anticoagulation; (2) superiority of PFO closure over antithrombotic therapy demonstrated in the pivotal RCTs. Quality of evidence: Low ⊕⊕ Strength of recommendation: Weak for intervention ↑?	
PICO 4: In patients with cryptogenic stroke and PFO, does oral anticoagulation compared with antiplatelet therapy reduce the risk of recurrent stroke?	There is continued uncertainty over the risks and benefits of the use of anticoagulation vs. antiplatelet therapy in patients in whom no other evident cause of stroke is found but a PFO (i.e., PFO-associated stroke). Quality of evidence: Low ⊕⊕ Strength of recommendation: -	In light of the results of the meta-analyses including both randomised trials and observational studies, the majority of this panel suggest an individualised approach to the choice of antithrombotic therapy for patients with PFO-related stroke who refuse PFO closure. The choice of anticoagulation over antiplatelet therapy should balance the expected lower risk of PFO-related stroke recurrence with a possible increase in the long-term risk of major bleeding and take into account the patient's preference. Vote: 9/9 experts agree
PICO 5 After percutaneous closure in patients with PFO-related stroke, does dual antiplatelet therapy after the procedure compared with single antiplatelet therapy reduce the risk of recurrent stroke?	In patients undergoing PFO we suggest dual antiplatelet therapy followed by single antiplatelet therapy to reduce the risk of recurrent stroke, based on the protocol of available RCTs (please see the Expert consensus below for details). Quality of evidence: Low ⊕⊕ Strength of recommendation: Weak against intervention ↓? No evidence-based recommendation can be formulated regarding the duration of the single antiplatelet treatment. Quality of evidence: Very Low ⊕ Strength of recommendation: -	In patients with PFO-related stroke who underwent percutaneous closure, according to the protocol design of the majority of positive randomised controlled trials this panel suggests prescribing a dual antiplatelet therapy for 1–6 months and to continue a single antiplatelet therapy in the long term, for at least 5 years after percutaneous closure. Vote: 9 /9 experts agree
PICO 6: In patients with PFO-related stroke who have undergone percutaneous closure, does prolonged cardiac monitoring compared with no prolonged cardiac monitoring, reduce the risk of recurrent stroke?	In patients aged 18–60 years in whom no other evident cause of stroke is found but a PFO, there is continued uncertainty over the risks and benefits of the use of long-term cardiac monitoring (i.e. ILR) to increase the detection of subclinical AF. Quality of evidence: Very Low ⊕ Strength of recommendation: -	In line with the ESO guidelines on screening for AF after cryptogenic stroke,¹⁴² this panel suggests that in patients aged 18–60 years in whom no other evident cause of stroke is found but a PFO (i.e. PFO-associated stroke), a basic cardiac monitoring during 24 h by telemetry or Holter-ECG should be performed before closure. Vote 8/9 experts agree In line with the ESO guidelines on screening for atrial fibrillation after cryptogenic stroke,¹⁴² we suggest using an ILR to detect paroxysmal AF in patients with cryptogenic stroke and PFO older than 60 years. Vote 7/9 experts agree We suggest that patients that have been implanted a loop recorder before PFO closure continue monitoring AF until the end-of-life of the recorder. Vote 8/9 experts agree We advise in favour of a systematic use of ILR in patients with recurrent stroke after PFO closure, negative short-term ECG monitoring and no other obvious causes for recurrence, regardless of age. Vote 8/9 experts agree We advise against systematic implantation of monitoring devices after PFO closure. Vote 8/9 experts agree

evidence suggesting a causal relationship (see Expert Consensus).

We suggest against long-term anticoagulation in patients with PFO-associated stroke unless anticoagulation is indicated for other medical reasons. Moreover, our guidelines did not specifically address the management of anticoagulation therapy for concurrent deep venous thrombosis in patients with PFO and PFO related stroke. We defer to the existing specialised guidelines currently in place for the type, dosages, and duration of anticoagulation treatment.¹⁴⁶ These existing guidelines advocate for deferral elective procedures, such as PFO closure, to mitigate the risk of recurrent thromboembolic events. Additionally, it is important to note that there is a lack of data regarding the simultaneous management of anticoagulation treatment and PFO closure.¹⁴⁶

In our guidelines we did not address the issue of detection for subclinical AF in patients with PFO and cryptogenic stroke as the recent ESO guideline on screening for subclinical atrial fibrillation after stroke or TIA of undetermined origin addressed this thoroughly.¹⁴²

Regarding the detection of AF after PFO, we observed that, consistent with the IPDMA, the patients likely to derive greater benefit from PFO closure also appeared to be at lower risk of device-associated adverse events such as atrial fibrillation, making the harm benefit trade-offs of device closure more clearly favourable in the possible and probable groups according to PASCAL classification.⁷ The lower risk of adverse events in the patients with potential high benefit is in line with prior evidence showing a higher risk of incident AF in patients with lower RoPE scores,¹⁴⁷ who are older and have more vascular risk factors. This increased risk may reflect occult AF being a more likely mechanism for the index stroke in these patients, stressing the need for an accurate AF rule-out at the diagnostic stage, but may also reflect a greater susceptibility to arrhythmogenic effects of device-tissue contact.

The MWG rated late-onset AF post-stroke as a lower priority, particularly in the context of patients who have undergone PFO when selected by PASCAL criteria. In such cases, late-onset AF detected after the cerebrovascular incident may be incidental and not directly related to the initial stroke event. To this regard, Sposato et al. reported that AF detected after a stroke is associated with a 26% lower risk of future strokes compared to AF that was known prior to the stroke. This may be because AF before a stroke is typically more severe and is detected through ECG. On the other hand, AF, identified after a stroke, is usually discovered during short-term or extended monitoring, suggesting a lesser severity.¹⁴⁸ Furthermore, patients who are diagnosed with AF after a stroke generally present with fewer risk factors and less cardiac disease, which contributes to a reduced risk of stroke.

Another open issue is the long-term effects of postprocedural AF on the remodelling of the left atrium, as well as the progression of left atrial fibrosis and the increased risk

of AF, remain areas that require further investigation.⁹⁷ Therefore, a personalised approach to cardiac rhythm monitoring in PFO patients after closure needs to be addressed.¹⁴⁹

In this guideline, we have not addressed which antiplatelet agent is superior for long-term treatment as only the PC trial compared the Amplatzer PFO Occluder with any antiplatelet or anticoagulation therapy of the physician's choice, which resulted to be acetylsalicylic acid, ticlopidine, clopidogrel and warfarin.¹¹¹ Regarding anticoagulation, the current evidence incorporated a variety of anticoagulants for comparison, such as warfarin and DOACs in order to assess the outcomes of anticoagulant therapy.^{13,119} Therefore, the choice of the antithrombotic agent may be personalised, based on individual clinical characteristics which may prompt to opt for a specific agent.

An open question is the management of the patients who underwent PFO and have residual RLS. The percentages and impact of RLS vary from 0% to 19%^{101–103} based on the different case series. Some Authors reported that residual RLS was influenced by the device type, PFO canal length, and ASA extent.¹⁰³ The incidence of right-to-left shunting (RLS) was 19.5% at a mean of 4 months' follow-up, which reduced to 8.4% at 11 ± 2 months.¹⁰¹ Moreover, in the same study alternative causes for residual RLS were detected such as pulmonary arteriovenous malformation.

We decided not to develop a PICO question regarding the screening for subclinical AF in patients below 60 years of age who have experienced a cryptogenic stroke and PFO as Rubeira et al. already addressed these topics in the screening guidelines.

There are also contrasting results on the embolic risk of residual RLS. Hammerstingl et al.¹⁰² reported no increased risk of thromboembolic events, as 3.2% of patients experienced arterial embolic events unrelated to residual PFO shunting or device-related thrombus formation. Another single-centre study of 118 patients reported a 98.1% total occlusion rate at a mean follow-up of 50 months, with no recurrent neurological events observed.¹⁰⁴ Contrastingly, a large prospective cohort study revealed that patients with residual shunts had a higher rate of stroke or TIA recurrence compared to those with complete PFO closure – 2.32 versus 0.75 events per 100 patient-years, respectively.¹⁰³ These studies collectively suggest that while residual shunt post-PFO closure is possible, the correlation with recurrent thromboembolic events is inconsistent across studies. Patients should be informed about these possible risks before performing PFO closure.

We decided not to include TIA as the index event in our guideline. This decision was based on the fact that RCTs except for the Closure trial, did not include TIA as index events.¹⁰⁶ However, it is noteworthy that the TIA subgroup in CLOSURE 1 constituted less than 30% of the participants, and the subgroup analysis revealed no significant distinctions.¹⁰⁶ However, international guidance papers, including the European Action Plan and the European

Position paper on the management of patients with PFO, often grouped TIAs and strokes in the same management pathway.^{4,145} PFO patients tend to be younger in comparison to patients with other well-defined causes of stroke. This age difference can potentially result in the overdiagnosis of TIAs due to the higher prevalence of conditions that mimic strokes in this particular age group. Conversely, relying solely on the low ABCD2 score may exclude certain patients from the diagnostic evaluation process. Therefore, based on current clinical practice, individuals presenting with sudden transient clinical symptoms such as motor deficits or speech disturbances may be considered as vascular patients when other conditions such as migraine with aura or seizures are excluded.

Moreover, we did not address sex-specific issues, such as PFO-related stroke during pregnancy. These specific concerns necessitate dedicated pathways and a multidisciplinary approach to provide comprehensive and tailored care, particularly in the context of managing delivery. In such cases, close collaboration between obstetricians, neurologists, cardiologists, and other relevant specialists is essential to ensure the safest and most appropriate management of both the pregnancy and the associated medical condition.

In conclusion, in patients with PFO-related stroke aged 18–60 years, PFO closure plus time-limited antiplatelet therapy is the recommended strategy for secondary prevention of recurrent stroke, with a low rate of complications. Further RCTs are required to test whether and in which patients over 60 years of age with stroke and PFO should be treated with PFO closure.

Plain language summary

This guideline is intended for individuals who have experienced an ischaemic stroke and have been diagnosed with a patent foramen ovale (PFO). A PFO is a heart condition where a small hole between the heart's two upper chambers, which usually closes after birth, remains open. Most people with a PFO never know they have it, and it does not cause problems. Rarely, this hole can let blood clots travel to the brain, which might cause a stroke.

Objective: The guideline's primary aim is to offer healthcare professionals recommendations on how to diagnose, treat, and provide long-term care for these patients. The recommendations were developed by experts who considered the best available evidence. They assessed the quality of the evidence and used a standardised method to make their recommendations.

These are the treatment recommendations:

PFO closure: It is recommended to close the PFO using a special procedure ('percutaneous PFO closure') for patients aged 18–60 years who do not have any other apparent reason for their stroke except the PFO. This indicates that PFO closure reduces the risk of recurrent strokes in the average of patients in this specific age group.

Candidate selection: The guideline outlines criteria to determine which patients are the best candidates for PFO closure, which may include factors like the size of the PFO and the presence of an atrial septal aneurysm, an abnormal protrusion or bulging of the interatrial septum, which is the wall between the left and right atria of the heart. This bulge can move back and forth with the heartbeats.

Age consideration: For patients with a large PFO and an atrial septal aneurysm, closing the PFO is strongly recommended aged 18–60 years. However, there is insufficient evidence to support or discourage PFO closure for patients younger than 18 or older than 60. This suggests that the procedure's effectiveness in these age groups has not been sufficiently investigated yet.

PFO closure for unlikely stroke causes: It's generally not recommended to close the PFO for individuals unlikely to have had a stroke because of their PFO unless there are special circumstances. This suggests that PFO closure should be primarily considered for stroke prevention in relevant cases.

Long-term medication: After the PFO closure patients should be treated with two types of antiplatelets for 6-month followed by a single antiplatelet treatment for at least 5 years. In selected cases the treatment with anticoagulation is preferred to antiplatelets.

Diagnosis and post-procedure care: The guideline provides recommendations on how to diagnose PFO and outlines protocols for the care and follow-up of patients who have undergone PFO closure.

This guideline offers a structured approach for healthcare professionals to manage patients with ischaemic stroke and PFO, considering age, other medical conditions, and the potential benefits of PFO closure and medication. It emphasises evidence-based decision-making and individualised care. However, it is important to note that medical guidelines can evolve over time based on new research findings and clinical experiences.

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Contributorship

Valeria Caso, Guillaume Turc, and Christian Pristipino wrote and supervised the manuscript, which included overall oversight and ensuring the integrity of the work. Silke Walter, Abdul-Rahim, Pedro Castro, and Eleni Korompoki were responsible for writing PICO 1 of the manuscript. Salman Hussain and Avtar Lal performed the statistical analysis for the guidelines. Heinrich Mattle, Lars Søndergaard, Danilo Toni wrote PICO 2, 3, and 4. Valeria Caso prepared PICO 5 and 6, suggesting a focus on additional specific clinical questions or components of the research. All members developed a list of topics and corresponding questions of most significant clinical interest, identified three overarching themes (PFO diagnosis, treatment of PFO-associated stroke, and post-procedural management), and performed literature research.

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Supplemental material

Supplemental material for this article is available online.

References

1. Saver JL. Cryptogenic stroke. *New Engl J Med* 2016; 375: e26.
2. Saver JL, Mattle HP and Thaler D. Patent foramen ovale closure versus medical therapy for cryptogenic ischemic stroke: a topical review. *Stroke* 2018; 49: 1541–1548.
3. Thaler DE, Di Angelantonio E, Di Tullio MR, et al. The risk of paradoxical embolism (RoPE) study: initial description of the completed database. *Int J Stroke* 2013; 8: 612–619.
4. Pristipino C, Sievert H, D'Ascenzo F, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *Eur Heart J* 2019; 40: 3182–3195.
5. Alsheikh-Ali AA, Thaler DE and Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? *Stroke* 2009; 40: 2349–2355.
6. Hagen PT, Scholz DG and Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984; 59: 17–20.
7. Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke. *JAMA* 2021; 326: 2277–2286.
8. Turc G, Calvet D, Guérin P, et al. Closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. *J Am Heart Assoc* 2018; 7: e008356.
9. Elgendy AY, Saver JL, Amin Z, et al. Proposal for updated nomenclature and classification of potential causative mechanism in patent foramen ovale-associated stroke. *JAMA Neurol* 2020; 77: 878–886.
10. Turc G, Lee JY, Brochet E, et al. Atrial septal aneurysm, shunt size, and recurrent stroke risk in patients with patent foramen ovale. *J Am Coll Cardiol* 2020; 75: 2312–2320.
11. Messé SR and Kent DM. Still no closure on the question of PFO closure. *New Engl J Med* 2013; 368: 1152–1153.
12. Søndergaard L, Kasner SE and Rhodes JF. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *New Engl J Med* 2020; 382: 978–1042.
13. Mas JL, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *New Engl J Med* 2017; 377: 1011–1021.
14. Steiner T, Dichgans M, Norrving B, et al. European Stroke Organisation (ESO) standard operating procedure for the preparation and publishing of guidelines. *Eur Stroke J* 2021; 6: CXXII–CXXXIV.
15. Guyatt GH, Oxman AD, Sultan S, et al. GRADE guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol* 2011; 64: 1311–1316.
16. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; 355:i4919.
17. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; 155: 529–536.
18. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol* 2011; 64: 1303–1310.
19. Beishon LC, Elliott E, Hietamies TM, et al. Diagnostic test accuracy of remote, multidomain cognitive assessment (telephone and video call) for dementia. *Cochrane Database Syst Rev* 2022; 4: CD013724.
20. Deeks JJ. Systematic reviews in health care: systematic reviews of evaluations of diagnostic and screening tests. *BMJ* 2001; 323: 157–162.
21. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol* 2011; 64: 1294–1302.
22. Prada-Ramallal G, Takkouche B and Figueiras A. Bias in pharmacoepidemiologic studies using secondary health care

- databases: a scoping review. *BMC Med Res Methodol* 2019; 19: 53.
23. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane handbook for systematic reviews of interventions. *Cochrane Database Syst Rev* 2019; 10:ED000142.
 24. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol* 2011; 64: 1277–1282.
 25. Ntaios G, Bornstein NM, Caso V, et al. The European stroke organisation guidelines: a standard operating procedure. *Int J Stroke* 2015; 10 Suppl A100: 128–135.
 26. Webster MW, Chancellor AM, Smith HJ, et al. Patent foramen ovale in young stroke patients. *Lancet* 1988; 2: 11–12.
 27. Van Camp G, Schulze D, Cosyns B, et al. Relation between patent foramen ovale and unexplained stroke. *Am J Cardiol* 1993; 71: 596–598.
 28. Kühl HP, Hoffmann R, Merx MW, et al. Transthoracic echocardiography using second harmonic imaging: diagnostic alternative to transesophageal echocardiography for the detection of atrial right to left shunt in patients with cerebral embolic events. *J Am Coll Cardiol* 1999; 34: 1823–1830.
 29. Jauss M and Zanette E. Detection of right-to-left shunt with ultrasound contrast agent and transcranial Doppler sonography. *Cerebrovasc Dis* 2000; 10: 490–496.
 30. Di Tullio M, Sacco RL, Venketasubramanian N, et al. Comparison of diagnostic techniques for the detection of a patent foramen ovale in stroke patients. *Stroke* 1993; 24: 1020–1024.
 31. Albert A, Müller HR and Hetzel A. Optimized transcranial Doppler technique for the diagnosis of cardiac right-to-left shunts. *J Neuroimaging* 1997; 7: 159–163.
 32. Belvis R, Leta RG, Martí-Fàbregas J, et al. Almost perfect concordance between simultaneous transcranial Doppler and transesophageal echocardiography in the quantification of right-to-left shunts. *J Neuroimaging* 2006; 16: 133–138.
 33. Blersch WK, Draganski BM, Holmer SR, et al. Transcranial duplex sonography in the detection of patent foramen ovale. *Radiology* 2002; 225: 693–699.
 34. Caputi L, Carriero MR, Falcone C, et al. Transcranial Doppler and transesophageal echocardiography: comparison of both techniques and prospective clinical relevance of transcranial Doppler in patent foramen ovale detection. *J Stroke Cerebrovasc Dis* 2009; 18: 343–348.
 35. Devuyt G, Despland PA, Bogousslavsky J, et al. Complementarity of contrast transcranial Doppler and contrast transesophageal echocardiography for the detection of patent foramen ovale in stroke patients. *Eur Neurol* 1997; 38: 21–25.
 36. Droste DW, Reisener M, Kemény V, et al. Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts. Reproducibility, comparison of 2 agents, and distribution of microemboli. *Stroke* 1999; 30: 1014–1018.
 37. Droste DW, Kriete JU, Stypmann J, et al. Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts: comparison of different procedures and different contrast agents. *Stroke* 1999; 30: 1827–1832.
 38. González-Alujas T, Evangelista A, Santamarina E, et al. Diagnosis and quantification of patent foramen ovale. Which is the reference technique? Simultaneous study with transcranial Doppler, transthoracic and transesophageal echocardiography. *Rev Esp Cardiol* 2011; 64: 133–139.
 39. Hamann GF, Schätzer-Klotz D, Fröhlig G, et al. Femoral injection of echo contrast medium may increase the sensitivity of testing for a patent foramen ovale. *Neurology* 1998; 50: 1423–1428.
 40. Heckmann JG, Niedermeier W, Brandt-Pohlmann M, et al. [Detection of patent foramen ovale. Transesophageal echocardiography and transcranial Doppler sonography with ultrasound contrast media are “supplementary, not competing, diagnostic methods”]. *Med Klin* 1999; 94: 367–370.
 41. Horner S, Ni XS, Weihs W, et al. Simultaneous bilateral contrast transcranial doppler monitoring in patients with intracardiac and intrapulmonary shunts. *J Neurol Sci* 1997; 150: 49–57.
 42. Chino S, Mochizuki Y, Mizuma K, et al. Transcranial Doppler for stratification of high-risk morphology of patent foramen ovale in patients with cryptogenic stroke. *Heart Vessels* 2022; 37: 2119–2127.
 43. Jauss M, Kaps M, Keberle M, et al. A comparison of transesophageal echocardiography and transcranial Doppler sonography with contrast medium for detection of patent foramen ovale. *Stroke* 1994; 25: 1265–1267.
 44. Job FP, Ringelstein EB, Grafen Y, et al. Comparison of transcranial contrast Doppler sonography and transesophageal contrast echocardiography for the detection of patent foramen ovale in young stroke patients. *Am J Cardiol* 1994; 74: 381–384.
 45. Karnik R, Stöllberger C, Valentin A, et al. Detection of patent foramen ovale by transcranial contrast Doppler ultrasound. *Am J Cardiol* 1992; 69: 560–562.
 46. Klötzsch C, Janssen G and Berlit P. Transesophageal echocardiography and contrast-TCD in the detection of a patent foramen ovale: experiences with 111 patients. *Neurology* 1994; 44: 1603–1606.
 47. Maffè S, Dellavesa P, Zenone F, et al. Transthoracic second harmonic two- and three-dimensional echocardiography for detection of patent foramen ovale. *Eur J Echocardiogr* 2010; 11: 57–63.
 48. Mayerhofer E, Kanz D, Guschlbauer B, et al. Bubble test and carotid ultrasound to guide indication of transesophageal echocardiography in young patients with stroke. *Front Neurol* 2022; 13: 836609.
 49. Nemec JJ, Marwick TH, Lorig RJ, et al. Comparison of transcranial Doppler ultrasound and transesophageal contrast echocardiography in the detection of interatrial right-to-left shunts. *Am J Cardiol* 1991; 68: 1498–1502.
 50. Nygren AT and Jogestrand T. Detection of patent foramen ovale by transcranial Doppler and carotid duplex ultrasonography: a comparison with transoesophageal echocardiography. *Clin Physiol* 1998; 18: 327–330.
 51. Orzan F, Liboni W, Bonzano A, et al. Follow-up of residual shunt after patent foramen ovale closure. *Acta Neurol Scand* 2010; 122: 257–261.
 52. Park S, Oh JK, Song JK, et al. Transcranial Doppler as a screening tool for high-risk patent foramen ovale in cryptogenic stroke. *J Neuroimaging* 2021; 31: 165–170.
 53. Sastry S, MacNab A, Daly K, et al. Transcranial Doppler detection of venous-to-arterial circulation shunts: criteria for patent foramen ovale. *J Clin Ultrasound* 2009; 37: 276–280.

54. Serena J, Segura T, Perez-Ayuso MJ, et al. The need to quantify right-to-left shunt in acute ischemic stroke: a case-control study. *Stroke* 1998; 29: 1322–1328.
55. Mohamed SA, Saleh MA, ELKhawas HM, et al. Right to left shunting detection by contrast-enhanced transcranial color-coded duplex among patients with cryptogenic stroke. *Egypt J Neurol Psychiatry Neurosurg* 2021; 57: 24.
56. Souteyrand G, Motreff P, Lusson JR, et al. Comparison of transthoracic echocardiography using second harmonic imaging, transcranial Doppler and transesophageal echocardiography for the detection of patent foramen ovale in stroke patients. *Eur J Echocardiogr* 2006; 7: 147–154.
57. Venketasubramanian N, Sacco RL, Di Tullio M, et al. Vascular distribution of paradoxical emboli by transcranial Doppler. *Neurology* 1993; 43: 1533–1535.
58. Wang H, Chu W, Kou Y, et al. Clinical value of cryptogenic stroke associated with small patent foramen ovale detected jointly by TEE and cTCD. *Int J Clin Exp Med* 2018; 11: 4178–4182.
59. Yang X, Wang H, Wei Y, et al. Diagnosis of patent foramen ovale: the combination of contrast transcranial Doppler, contrast transthoracic echocardiography, and contrast transesophageal echocardiography. *Biomed Res Int* 2020; 2020: 8701759.
60. Yang J, Zhang H, Wang Y, et al. The efficacy of contrast transthoracic echocardiography and contrast transcranial Doppler for the detection of patent foramen ovale related to cryptogenic stroke. *Biomed Res Int* 2020; 2020:1513409.
61. Lao AY, Sharma VK, Tsigoulis G, et al. Detection of right-to-left shunts: comparison between the international consensus and spencer logarithmic scale criteria. *J Neuroimaging* 2008; 18: 402–406.
62. Belkin RN, Pollack BD, Ruggiero ML, et al. Comparison of transesophageal and transthoracic echocardiography with contrast and color flow Doppler in the detection of patent foramen ovale. *Am Heart J* 1994; 128: 520–525.
63. Droste DW, Jekentaite R, Stypmann J, et al. Contrast transcranial Doppler ultrasound in the detection of right-to-left shunts: comparison of echovist-200 and echovist-300, timing of the Valsalva maneuver, and general recommendations for the performance of the test. *Cerebrovasc Dis* 2002; 13: 235–241.
64. Droste DW, Lakemeier S, Wichter T, et al. Optimizing the technique of contrast transcranial Doppler ultrasound in the detection of right-to-left shunts. *Stroke* 2002; 33: 2211–2216.
65. Palazzo P, Ingrand P, Agius P, et al. Transcranial Doppler to detect right-to-left shunt in cryptogenic acute ischemic stroke. *Brain Behav* 2019; 9: e01091.
66. Spencer MP, Moehring MA, Jesurum J, et al. Power m-mode transcranial Doppler for diagnosis of patent foramen ovale and assessing transcatheter closure. *J Neuroimaging* 2004; 14: 342–349.
67. Kermer P, Eschenfelder CC, Diener HC, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany-updated series of 120 cases. *Int J Stroke* 2020; 15: 609–618.
68. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; 42: 373–498.
69. Puledda F, Toscano M, Pieroni A, et al. Right-to-left shunt detection sensitivity with air-saline and air-succinyl gelatin transcranial Doppler. *Int J Stroke* 2016; 11: 229–238.
70. Mojadidi MK, Bogush N, Caceres JD, et al. Diagnostic accuracy of transesophageal echocardiogram for the detection of patent foramen ovale: a meta-analysis. *Echocardiography* 2014; 31: 752–758.
71. Gentile M, De Vito A, Azzini C, et al. Adding blood to agitated saline significantly improves detection of right-to-left shunt by contrast-transcranial color-coded duplex sonography. *Ultrasound Med Biol* 2014; 40: 2637–2641.
72. Hao N, Liu K, Guo ZN, et al. Comparison of two contrast agents for right-to-left shunt diagnosis with contrast-enhanced transcranial Doppler. *Ultrasound Med Biol* 2014; 40: 2317–2320.
73. Li F, Shen Q, Deng X, et al. Agitated saline with 10% blood increases number and stability of microbubbles in detection right-to-left shunt by contrast-enhanced transcranial Doppler: an in vitro and in vivo observational study. *J Thorac Dis* 2023; 15: 1970–1977.
74. de Bruijn SF, Agema WR, Lammers GJ, et al. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. *Stroke* 2006; 37: 2531–2534.
75. Mesa D, Franco M, Suárez de, Lezo J, et al. [Prevalence of patent foramen ovale in young patients with cerebral ischemic accident of unknown origin]. *Rev Esp Cardiol* 2003; 56: 662–668.
76. Ha JW, Shin MS, Kang S, et al. Enhanced detection of right-to-left shunt through patent foramen ovale by transthoracic contrast echocardiography using harmonic imaging. *Am J Cardiol* 2001; 87: 669.
77. Hausmann D, Mügge A, Becht I, et al. Diagnosis of patent foramen ovale by transesophageal echocardiography and association with cerebral and peripheral embolic events. *Am J Cardiol* 1992; 70: 668–672.
78. Lam YY, Yu CM, Zhang Q, et al. Enhanced detection of patent foramen ovale by systematic transthoracic saline contrast echocardiography. *Int J Cardiol* 2011; 152: 24–27.
79. Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO Trial. *J Am Coll Cardiol* 2018; 71: 2335–2342.
80. Madala D, Zaroff JG, Hourigan L, et al. Harmonic imaging improves sensitivity at the expense of specificity in the detection of patent foramen ovale. *Echocardiography* 2004; 21: 33–36.
81. Monte I, Grasso S, Licciardi S, et al. Head-to-head comparison of real-time three-dimensional transthoracic echocardiography with transthoracic and transesophageal two-dimensional contrast echocardiography for the detection of patent foramen ovale. *Eur J Echocardiogr* 2010; 11: 245–249.

82. Rahmouni HW, Keane MG, Silvestry FE, et al. Failure of digital echocardiography to accurately diagnose intracardiac shunts. *Am Heart J* 2008; 155: 161–165.
83. Siostrzonek P, Zangeneh M, Gössinger H, et al. Comparison of transesophageal and transthoracic contrast echocardiography for detection of a patent foramen ovale. *Am J Cardiol* 1991; 68: 1247–1249.
84. Takaya Y, Nakayama R, Akagi T, et al. Importance of saline contrast transthoracic echocardiography for evaluating large right-to-left shunt in patent foramen ovale associated with cryptogenic stroke. *Int J Cardiovasc Imaging* 2022; 38: 515–520.
85. Katsanos AH, Psaltopoulou T, Sergentanis TN, et al. Transcranial Doppler versus transthoracic echocardiography for the detection of patent foramen ovale in patients with cryptogenic cerebral ischemia: a systematic review and diagnostic test accuracy meta-analysis. *Ann Neurol* 2016; 79: 625–635.
86. Rubin MN, Shah R, Devlin T, et al. Robot-assisted transcranial Doppler versus transthoracic echocardiography for right to left shunt detection. *Stroke* 2023; 54: 2842–2850.
87. Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *New Engl J Med* 2017; 377: 1022–1032.
88. Mas JL, Arquizán C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *New Engl J Med* 2001; 345: 1740–1746.
89. Handke M, Harloff A, Olschewski M, et al. Patent foramen ovale and cryptogenic stroke in older patients. *New Engl J Med* 2007; 357: 2262–2268.
90. Cabanes L, Coste J, Derumeaux G, et al. Interobserver and intraobserver variability in detection of patent foramen ovale and atrial septal aneurysm with transesophageal echocardiography. *J Am Soc Echocardiogr* 2002; 15: 441–446.
91. Schuchlenz HW, Saurer G, Weihs W, et al. Persisting eustachian valve in adults: relation to patent foramen ovale and cerebrovascular events. *J Am Soc Echocardiogr* 2004; 17: 231–233.
92. Goel SS, Tuzcu EM, Shishehbor MH, et al. Morphology of the patent foramen ovale in asymptomatic versus symptomatic (stroke or transient ischemic attack) patients. *Am J Cardiol* 2009; 103: 124–129.
93. Lapergue B, Decroix JP, Evrard S, et al. Diagnostic yield of venous thrombosis and pulmonary embolism by combined CT venography and pulmonary angiography in patients with cryptogenic stroke and patent foramen ovale. *Eur Neurol* 2015; 74: 69–72.
94. Katsanos AH, Giannopoulos S, Frogoudaki A, et al. The diagnostic yield of transesophageal echocardiography in patients with cryptogenic cerebral ischaemia: a meta-analysis. *Eur J Neurol* 2016; 23: 569–579.
95. Johansson MC, Eriksson P, Guron CW, et al. Pitfalls in diagnosing PFO: characteristics of false-negative contrast injections during transesophageal echocardiography in patients with patent foramen ovales. *J Am Soc Echocardiogr* 2010; 23: 1136–1142.
96. Rodrigues AC, Picard MH, Carbone A, et al. Importance of adequately performed Valsalva maneuver to detect patent foramen ovale during transesophageal echocardiography. *J Am Soc Echocardiogr* 2013; 26: 1337–1343.
97. Sposato LA, Albin CSW, Elkind MSV, et al. Patent foramen ovale management for secondary stroke prevention: state-of-the-art appraisal of current evidence. *Stroke* 2024; 55: 236–247.
98. Meinel TR, Eggimann A, Brignoli K, et al. Cardiovascular MRI compared to echocardiography to identify cardioaortic sources of ischemic stroke: a systematic review and meta-analysis. *Front Neurol* 2021; 12: 699838.
99. Xiong L, Zeng Y, Gan T, et al. Assessing patent foramen ovale on coronary computed tomographic angiography: a comparison with transesophageal echocardiography. *Jpn J Radiol* 2022; 40: 689–695.
100. Lee S, Kim IC, Kim YD, et al. The role of cardiac CT throughout the full cardiac cycle in diagnosing patent foramen ovale in patients with acute stroke. *Eur Radiol* 2021; 31: 8983–8990.
101. Shah AH, Osten M, Benson L, et al. Incidence and outcomes of positive bubble contrast study results after transcatheter closure of a patent foramen ovale. *JACC Cardiovasc Interv* 2018; 11: 1095–1104.
102. Hammerstingl C, Bauriedel B, Stüsser C, et al. Risk and fate of residual interatrial shunting after transcatheter closure of patent foramen ovale: a long term follow up study. *Eur J Med Res* 2011; 16: 13–19.
103. Deng W, Yin S, McMullin D, et al. Residual shunt after patent foramen ovale closure and long-term stroke recurrence: a prospective cohort study. *Ann Intern Med* 2020; 172: 717–725.
104. Evola S, Camarda EA, Triolo OF, et al. Clinical outcomes and quality of life after patent foramen ovale (PFO) closure in patients with stroke/transient ischemic attack of undetermined cause and other PFO-associated clinical conditions: a single-center experience. *J Clin Med* 2023; 12: 20230905.
105. Abo-Salem E, Chaitman B, Helmy T, et al. Patent foramen ovale closure versus medical therapy in cases with cryptogenic stroke, meta-analysis of randomized controlled trials. *J Neurol* 2018; 265: 578–585.
106. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *New Engl J Med* 2012; 366: 991–999.
107. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *New Engl J Med* 2013; 368: 1083–1091.
108. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *New Engl J Med* 2013; 368: 1092–1100.
109. Mas JL, Derex L, Guérin P, et al. Reprint of: transcatheter closure of patent foramen ovale to prevent stroke recurrence in patients with otherwise unexplained ischaemic stroke: expert consensus of the French Neurovascular Society and the French Society of Cardiology. *Rev Neurol* 2020; 176: 53–61.
110. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology* 2013; 81: 619–625.
111. Mas JL, Saver JL, Kasner SE, et al. Association of atrial septal aneurysm and shunt size with stroke recurrence and

- benefit from patent foramen ovale closure. *JAMA Neurol* 2022; 79: 1175–1179.
112. Kwon H, Lee PH, Song JK, et al. Patent foramen ovale closure in old stroke patients: a subgroup analysis of the DEFENSE-PFO trial. *Stroke* 2021; 23: 289–292.
113. Miton N, Godart F, Milani G, et al. Patent foramen ovale closure in children without cardiopathy: child-PFO study. *Arch Cardiovasc Dis* 2020; 113: 513–524.
114. Liu K, Song B, Palacios IF, et al. Patent foramen ovale attributable cryptogenic embolism with thrombophilia has higher risk for recurrence and responds to closure. *JACC Cardiovasc Interv* 2020; 13: 2745–2752.
115. Joosten LPT, van Doorn S, van de Ven PM, et al. Safety of switching from a vitamin K antagonist to a Non-Vitamin K antagonist oral anticoagulant in frail older patients with atrial fibrillation: results of the FRAIL-AF randomized controlled trial. *Circulation* 2024; 149: 279–289.
116. Hart RG, Sharma M and Mundl H. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *New Engl J Med* 2018; 379: 986–987.
117. Homma S, Sacco RL, Di Tullio MR, et al. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in cryptogenic stroke study. *Circulation* 2002; 105: 2625–2631.
118. Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *New Engl J Med* 2019; 380: 1906–1917.
119. Shariat A, Yaghoubi E, Farazdaghi M, et al. Comparison of medical treatments in cryptogenic stroke patients with patent foramen ovale: a randomized clinical trial. *J Res Med Sci* 2013; 18: 94–98.
120. Angelini F, Fortuni F, Tsivgoulis G, et al. Comparison of antithrombotic strategies in patients with cryptogenic stroke and patent foramen ovale: an updated meta-analysis. *Cardiovasc Drugs Ther* 2021; 35: 987–993.
121. Bédard E, Rodés-Cabau J, Houde C, et al. Enhanced thrombogenesis but not platelet activation is associated with transcatheter closure of patent foramen ovale in patients with cryptogenic stroke. *Stroke* 2007; 38: 100–104.
122. Brandt RR, Neumann T, Neuzner J, et al. Transcatheter closure of atrial septal defect and patent foramen ovale in adult patients using the amplatzer occlusion device: no evidence for thrombus deposition with antiplatelet agents. *J Am Soc Echocardiogr* 2002; 15: 1094–1098.
123. Abaci A, Unlu S, Alsancak Y, et al. Short and long term complications of device closure of atrial septal defect and patent foramen ovale: meta-analysis of 28,142 patients from 203 studies. *Catheter Cardiovasc Interv* 2013; 82: 1123–1138.
124. Krumdorf U, Ostermayer S, Billinger K, et al. Incidence and clinical course of thrombus formation on atrial septal defect and patent foramen ovale closure devices in 1,000 consecutive patients. *J Am Coll Cardiol* 2004; 43: 302–309.
125. Chessa M, Drago M, Krantunkov P, et al. Differential diagnosis between patent foramen ovale and pulmonary arteriovenous fistula in two patients with previous cryptogenic stroke caused by presumed paradoxical embolism. *J Am Soc Echocardiogr* 2002; 15: 845–846.
126. Carroll JD. A positive bubble test post-patent foramen ovale closure: was satisfaction-of-search to blame? *JACC Cardiovasc Interv* 2018; 11: 1105–1107.
127. Massarenti L and Yilmaz A. Incomplete endothelialization of left atrial appendage occlusion device 10 months after implantation. *J Cardiovasc Electrophysiol* 2012; 23: 1384–1385.
128. Ahn E, Luk A, Mezody M, et al. Early morphological changes of an amplatzer septal occluder explanted at heart transplant. *Cardiovasc Pathol* 2009; 18: 57–60.
129. Adhikari CM, Prajapati D, Bogati A, et al. Safety and efficacy of single vs dual antiplatelets therapy after atrial septal defect device closure. *J Nepal Health Res Counc* 2021; 19: 295–299.
130. Wintzer-Wehekind J, Alperi A, Houde C, et al. Long-term follow-up after closure of patent foramen ovale in patients with cryptogenic embolism. *J Am Coll Cardiol* 2019; 73: 278–287.
131. Chen JZ and Thijs VN. Presence of atrial fibrillation in stroke patients with patent foramen ovale: systematic review and meta-analysis. *Front Neurol* 2021; 12: 613758.
132. Tsivgoulis G, Katsanos AH, Mavridis D, et al. Percutaneous patent foramen ovale closure for secondary stroke prevention: network meta-analysis. *Neurology* 2018; 91: e8–e18.
133. Tsivgoulis G, Palaodimou L, Triantafyllou S, et al. Prolonged cardiac monitoring for stroke prevention: a systematic review and meta-analysis of randomized-controlled clinical trials. *Eur Stroke J* 2023; 8: 106–116.
134. Tsivgoulis G, Triantafyllou S, Palaodimou L, et al. Prolonged cardiac monitoring and stroke recurrence: a meta-analysis. *Neurology* 2022; 98: e1942–e1952.
135. Scacciatella P, Jorfida M, Biava LM, et al. Insertable cardiac monitor detection of silent atrial fibrillation in candidates for percutaneous patent foramen ovale closure. *J Cardiovasc Med* 2019; 20: 290–296.
136. Leclercq F, Odorico X, Marin G, et al. Atrial fibrillation screening on systematic ambulatory electrocardiogram monitoring after percutaneous patent foramen ovale closure: a prospective study. *Int J Cardiol Hear Vasc* 2021; 37: 100919.
137. Gasparone A, Giardina A, Iamele M, et al. Effect of percutaneous closure of patent foramen ovale on post-procedural arrhythmias. *J Am Coll Cardiol* 2013; 62: 2449–2450.
138. Guedeney P, Laredo M, Zeitouni M, et al. Supraventricular arrhythmia following patent foramen ovale percutaneous closure. *JACC Cardiovasc Interv* 2022; 15: 2315–2322.
139. Oliva L, Huszti E, Hall R, et al. Incidence of new-onset atrial fibrillation after transcatheter patent foramen ovale closure using 15 years of Ontario administrative health data. *Heart Rhythm* 2022; 19: 1414–1420.
140. Noble S, Bonvini RF, Rigamonti F, et al. Percutaneous PFO closure for cryptogenic stroke in the setting of a systematic cardiac and neurological screening and a standardised follow-up protocol. *Open Heart* 2017; 4: e000475.
141. Jarral OA, Saso S, Vecht JA, et al. Does patent foramen ovale closure have an anti-arrhythmic effect? A meta-analysis. *Int J Cardiol* 2011; 153: 4–9.
142. Rubiera M, Aires A, Antonenko K, et al. European Stroke Organisation (ESO) guideline on screening for subclinical

- atrial fibrillation after stroke or transient ischaemic attack of undetermined origin. *Eur Stroke J* 2022; 7: VI.
143. Cerullo E, Sutton AJ, Jones HE, et al. MetaBayesDTA: code-less Bayesian meta-analysis of test accuracy, with or without a gold standard. *BMC Med Res Methodol* 2023; 23: 127.
144. Menten J, Boelaert M and Lesaffre E. Bayesian meta-analysis of diagnostic tests allowing for imperfect reference standards. *Stat Med* 2013; 32: 5398–5413.
145. Norrving B, Barrick J, Davalos A, et al. Action plan for stroke in Europe 2018-2030. *Eur Stroke J* 2018; 3: 309–336.
146. Hornor MA, Duane TM, Ehlers AP, et al. American college of surgeons' guidelines for the perioperative management of antithrombotic medication. *J Am Coll Surg* 2018; 227: 521–536.X.
147. Strambo D, Sirimarco G, Nannoni S, et al. Embolic stroke of undetermined source and patent foramen ovale: risk of paradoxical embolism score validation and atrial fibrillation prediction. *Stroke* 2021; 52: 1643–1652.
148. Sposato LA, Field TS, Schnabel RB, et al. Towards a new classification of atrial fibrillation detected after a stroke or a transient ischaemic attack. *Lancet Neurol* 2024; 23: 110–122.
149. Diener HC, Wachter R, Wong A, et al. Monitoring for atrial fibrillation prior to patent foramen ovale closure after cryptogenic stroke. *Int J Stroke* 2023; 18: 400–407.