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European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism

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Abstract

The presence of a patent foramen ovale (PFO) is implicated in the pathogenesis of a number of medical conditions; however, the subject remains controversial and no official statements have been published. This interdisciplinary paper, prepared with involvement of eight European scientific societies, aims to review the available trial evidence and to define the principles needed to guide decision making in patients with PFO. In order to guarantee a strict process, position statements were developed with the use of a modified grading of recommendations assessment, development, and evaluation (GRADE) methodology. A critical qualitative and quantitative evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk/benefit ratio. The level of evidence and the strength of the position statements of particular management options were weighed and graded according to predefined scales. Despite being based often on limited and non-randomised data, while waiting for more conclusive evidence, it was possible to conclude on a number of position statements regarding a rational general approach to PFO management and to specific considerations regarding left circulation thromboembolism. For some therapeutic aspects, it was possible to express stricter position statements based on randomised trials. This position paper provides the first largely shared, interdisciplinary approach for a rational PFO management based on the best available evidence.

Abbreviations

AF atrial fibrillation
AUC area under the receiver operating curve
c-TCD contrast-enhanced transcranial Doppler
c-TOE contrast transoesophageal echocardiography
c-TTE contrast-enhanced transthoracic echocardiography
DOAC direct oral anticoagulants
DVT deep vein thrombosis
ECG electrocardiogram
GRADE Grading of recommendations assessment, development, and evaluation
ICM insertable cardiac monitors
LAE left atrium enlargement
LVH left ventricle hypertrophy
NNH number needed to harm
NNT number needed to treat
OAC oral anticoagulants
OR odds ratio
OSAS obstructive sleep apnoea syndrome
PE pulmonary embolism
PICO population-intervention-comparator-outcome
PFO patent foramen ovale
RCT(s) randomised clinical trial(s)
RoPE risk of paradoxical embolism
R-T-L right-to-left
Rx therapy
TIA transient ischaemic attack

Introduction

The presence of a patent foramen ovale (PFO) is implicated in the pathogenesis of a number of medical conditions. Recent randomised clinical trials (RCTs) have shown evidence of benefit for device closure as compared with medical therapy in patients with cryptogenic stroke. However, we are rarely able to be categoric about the role of PFO in any given clinical setting, stressing the need for specific clinical and research approaches for complex scenarios[1-5]. Moreover, most studies on the subject are observational, with an ensuing low certitude of effects and very disparate, often contradictory, clinical choices in different local realms in the absence of official positions. To address these concerns, the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Scientific Documents and Initiatives Committee invited eight European scientific societies and international experts to develop shared and rational position statements on the management of PFO to help clinicians in decision making. To address that request, this paper aims to define interdisciplinary rational principles needed to guide management of patients with PFO by using a strict methodology to prepare position statements with different underlying quality of evidence, based on systematic literature reviews for each of the considered issues and performing quantitative assessments whenever possible.

The present paper reports the approach to patients with PFO and left circulation thromboembolisms, that affect large numbers of patients[6-8]. A subsequent paper will report on decompression sickness, desaturation syndromes, migraine, and other clinical settings.

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Methods

In order to guarantee a strict evidence-based process, position statements were developed with the use of a modified grading of recommendations assessment, development, and evaluation (GRADE) methodology (http://gdt.guidelinedevelopment.org/app/handbook/handbook.html), by answering population-intervention-comparator-outcome (PICO) questions and non-PICO questions.

A detailed review of the methodology used can be found in **Supplementary Appendix 1**, **Supplementary Appendix 2**, **Supplementary Appendix 3** and **Supplementary Table 12**. Systematic reviews and statistical analysis were performed by a dedicated evidence synthesis team.

IS PFO ASSOCIATED WITH CRYPTOGENIC LEFT CIRCULATION THROMBOEMBOLISM?

The association between PFO and cryptogenic left circulation thromboembolism has mainly been addressed in studies including cryptogenic stroke and is strongly supported by epidemiological data[9-13], clinical observational studies[14-25] **(Supplementary Appendix 4)** and by RCTs showing that PFO closure reduces stroke recurrence in comparison with medical therapy[26-29].

However, the evidence has been controversial due to the different role that a PFO can play in different clinical scenarios and to the lack of adequately dimensioned prospective studies. Pathophysiological processes include paradoxical embolism,

thrombus forming within the PFO, left atrial dysfunction, and atrial arrhythmias **(Supplementary Appendix 4)**. Research aimed at identifying individual patients' phenotypes is needed to improve clinical management.

DEFINITIONS OF PFO-RELATED LEFT CIRCULATION THROMBOEMBOLISM

PFO has been associated with left circulation thromboembolism to several organs[30]; therefore we promote the use of standardised definitions.

Cryptogenic ischaemic left circulation embolisms are defined as any definite ischaemia (symptomatic or asymptomatic) occurring in an arterial bed which lacks a known cause despite investigation. Patients presenting with this clinical picture should be screened for the presence or absence of a PFO. However, when a PFO is thought likely to be implicated in a cryptogenic embolism, the event should be classified as PFO-related instead of cryptogenic[31]. Current classifications do not yet generally include this aspect[32-35].

GENERAL APPROACH TO PFO MANAGEMENT

The management we propose in this paragraph applies to systemic thromboembolism as well as to all PFO-associated syndromes. An overview of the general approach to PFO management is summarised in **Table 1**.

THE MAIN AXES OF EVALUATION

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

PROACTIVE APPROACH: AN INTERDISCIPLINARY COLLABORATION, SHARED DECISION MAKING, AND OPEN INFORMED CONSENT

Interdisciplinary involvement in decision making regarding PFO management is axiomatic and should include an interventional cardiologist and other specialists dictated by the patient's clinical manifestations. Active involvement of the patient in the decision-making process is mandatory[36,37] and should be documented in an individualised, open, informed consent. The development of specific decision aids and the use of narrative tools are encouraged[38-43].

Table 1. Summary of statements.

Position statements	Strength of the statement	Level of evidence	Ref.
General management of PFO-associated syndromes			
Interdisciplinary assessment and decision making should be done	Strong	C	–
The decision making should be done taking into account an estimation of the individual: a) Probability of a causal role of the PFO in the clinical picture b) Risk of recurrence	Strong	C	–
Individual risk stratification should take into account clinical, anatomical and imaging characteristics	Strong	C	–
Shared decision making should be documented in an open, individualised, informed consent	Strong	C	–
Decision aids and narrative tools are suggested to enhance patients' involvement	Conditional	C	38-43
Standardised definitions of candidate events should be adopted in research and clinical settings	Strong	C	–
PFO diagnosis			
To achieve the maximal accuracy in PFO diagnosis, the combined use of different techniques is warranted	Strong	A	45, 54, 55 + Original meta-analyses page 1392 and Supplementary Appendix 4
The technique achieving the highest sensitivity should be used as a first-line investigation in PFO diagnosis	Strong	C	–
c-TCD has a higher sensitivity than c-TTE as a first-line investigation to detect a R-T-L shunt	Conditional	A	55 + Original meta-analyses page 1392 and Supplementary Appendix 4
c-TTE has a lower sensitivity for small shunts than other techniques	Conditional	A	Original meta-analyses page 1392 and Supplementary Appendix 4
c-TOE should be performed by experienced operators in PFO assessment	Strong	C	45-47
A strict methodology should be used performing c-TOE	Strong	C	46-47
c-TOE should be performed to stratify the risk	Strong	C	31, 48-52

DIAGNOSING PFO

The diagnosis of PFO is required only for deciding on a treatment. Several techniques can be used to diagnose PFO[44]. Their characteristics are summarised in **Supplementary Table 1**. High-quality comparative studies are still needed to express a conclusive position on the best diagnostic strategies.

Contrast transoesophageal echocardiography (c-TOE) provides unparalleled visualisation of the interatrial septum and other relevant structures and can show the shunt itself. A meta-analysis of the accuracy of c-TOE in the diagnosis of PFO compared to autopsy, cardiac surgery, and/or catheterisation yielded a weighted sensitivity of only 89%[45]. Inability to perform an adequate Valsalva manoeuvre during transoesophageal echocardiography is probably responsible[46,47] **(Supplementary Figure 1)**. Nonetheless, c-TOE is necessary to characterise the PFO and stratify the risk in the diagnostic phase[31,48-52], and systematic reporting of a set of parameters could help in guiding assessment **(Table 2)**. Bleeding, aspiration, or oesophageal perforation are rare TOE complications[53].

Table 2. PFO variables to be assessed for decision making and interventional treatment.

– PFO morphology: size, location, length of the tunnel
– Spatial relationship and distances between the PFO and the aortic root, vena cava, valves and the free walls of the atrium
– Comprehensive evaluation of the atrial septum, including inspection for atrial septal aneurysms, movement, and other atrial septal defects
– Presence/absence of a Eustachian valve and/or Chiari network
– Thickness of the septum primum and secundum
– Colour Doppler evaluation of the shunt at rest and after a Valsalva manoeuvre

In our updated meta-analysis of 29 studies comparing contrast-enhanced transcranial Doppler (c-TCD) with c-TOE across 2,751 patients **(Supplementary Appendix 3, Supplementary Appendix 4, Supplementary Figure 19)**, c-TCD had a sensitivity of 94% and a specificity of 92% **(Supplementary Figure 2A)** with an area under the receiver operating curve (AUC) of 0.97 **(Supplementary Figure 2B)**. This meta-analysis was limited by the low quality of evidence **(Supplementary Table 2)** and by the inconsistency across studies, being 67% for sensitivity and 73% for specificity. In a previous meta-analysis, the specificity of c-TCD was increased to 100% when the threshold for a positive shunt was increased to 10 high-intensity transient signals[54].

We also performed an original meta-analysis of 13 studies across 1,360 patients comparing contrast-enhanced transthoracic echocardiography (c-TTE) against c-TOE **(Supplementary Appendix 3, Supplementary Appendix 4, Supplementary Figure 20)**. c-TTE was only 88% sensitive and 82% specific with an AUC of 0.91 **(Supplementary Figure 3A)**, a severe inconsistency among studies **(Supplementary Figure 3B)** and a low quality of evidence **(Supplementary Table 2)**. A recent meta-analysis also showed superior overall diagnostic yield of c-TCD compared to c-TTE[55].

At present, grounded on the accrued low-quality evidence, no technique can be considered a gold standard and, in most cases, a precise diagnosis of PFO needs the combined use of different techniques, prescribed according to their different characteristics. As first-line investigations must warrant accuracy by minimising false negative screenings, we propose a diagnostic algorithm in **Figure 1** that can be adapted to satisfy disparate clinical and logistic needs.

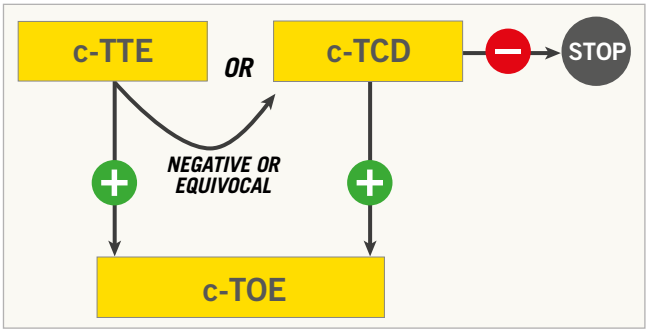

Figure 1. *Algorithm for the diagnosis of PFO. c-TCD: contrast-enhanced transcranial Doppler; c-TOE: contrast-enhanced transoesophageal echocardiography; c-TTE: contrast-enhanced transthoracic echocardiography; – negative test for the presence of right-to-left shunt; + positive test for the presence of right-to-left shunt*

ASSESSMENT OF THE ROLE OF A PFO IN LEFT CIRCULATION EMBOLISM

A PFO is seen in ~25% of the general population and may therefore coexist by chance in a patient with an unexplained left circulation embolism. Due to the complexity and number of the variables influencing the process, and the low scientific quality of the related literature, no position can be expressed regarding the assessment of the role of a PFO in a quantitative way; therefore, this role should be evaluated with critical clinical judgement in an interdisciplinary collaboration between physicians, weighting the following different features on an individual basis. For a more detailed discussion of each of the following paragraphs please refer to **Supplementary Appendix 4**. Position statements are summarised in **Table 3**.

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

Patient characteristics

A meta-analysis of observational studies showed a stronger relative association of PFO with cryptogenic stroke in patients <55 years as compared to older patients[56]. However, the association was also observed in older patients[13,57,58]. The presence of other comorbidities or clinical risk factors for stroke does not, *per se*, exclude a pathophysiological role of PFO in cryptogenic embolism, though their absence increases the likelihood of its pathogenic role[59].

Imaging stroke pattern

Neither the localisation nor type of infarct pattern in grey or white matter was specific for PFO embolism in observational studies[59-69].

Table 3. Summary of statements on the assessment of PFO role in left circulation thromboembolism.

Position statements	Strength of the statement	Level of evidence	Ref.
PFO can play a pathogenic role in cryptogenic left circulation thromboembolism	Strong	A	9-29, 51, 112, 132, Table 5 and Supplementary Table 7
It is essential to evaluate the role of the PFO in any given left circulation thromboembolism	Strong	A	Table 5
No statement is possible regarding the quantification of the role of PFO in left circulation thromboembolism	Strong	C	13, 18, 27-29, 57-98
The evaluation of the role of the PFO in left circulation thromboembolism should be individualised with critical clinical judgement in an interdisciplinary collaboration between physicians, weighting clinical, anatomical and imaging characteristics	Strong	C	13, 18, 27-29, 57-98
Estimating the probability of a PFO being embolism-related			
No single clinical, anatomical or imaging characteristics are sufficient to make a quantitative estimation of the probability of a PFO causal role	Strong	A	26-28, 51, 112, 128, 132, Table 5, 13, 59, 61, 77-79, 171
When a PFO is considered to play a pathogenic role in an embolism, the episode should not be classified as cryptogenic anymore	Strong	A	26-28, 51, 112, 128, 132, Table 5
The presence of other risk factors does not exclude a causative role of PFO; however, it is more likely when patients are young and lack other risk factors	Strong	B	13, 56-59, 78, 79, 90
Cortical infarcts are commonly embolic but, less frequently, also white matter infarcts can be embolic	Strong	B	59, 60-63, 70
No specific imaging pattern has been associated with a causal role of PFO in stroke patients	Strong	C	59-69, 77
ASA, shunt severity and an atrial septal hypermobility can be linked to a causal role of PFO	Strong	A	27-29, 51, 112, 132, Table 5, Supplementary Figure 5; 78, 79, 90, 122, 170, 171, 71-74, 91
PFO sizes, presence of Chiari network or Eustachian valve can be linked to a causal role of PFO	Conditional	C	64, 75, 76, 208, 256
Deep vein thrombosis, immobilisation, long journeys, straining pre-stroke or obstructive sleep apnoea can be linked to a causal role of PFO	Conditional	C	81, 84, 85
Simultaneous pulmonary embolism and/or deep vein thrombosis strongly suggest a causal role of PFO	Strong	C	15, 18, 80-83
The role of thrombophilia cannot be generalised	Strong	C	86-89
The RoPE score should only be part of a comprehensive individual evaluation.			
Further validation studies on the RoPE score are needed	Strong	B	59, Supplementary Table 3
Estimating the risk of recurrences			
The risk of recurrent embolism in unselected patients with PFO is low	Strong	A	90-92, 259
No single variable allows a quantitative prediction of recurrences	Strong	A	94, 95, 26-28, 51, 112, 128, 132, Table 5, Supplementary Table 7
Variables linked to a higher recurrence rate in PFO patients are: – Atrial septal aneurysm and/or PFO diameter – Older age – Coagulation disorders – Stroke at index – D–dimer >1,000 at admission – Acetylsalicylic acid use vs. OAC	Conditional	B	72, 95-98

Cortical infarcts are usually considered embolic but a recent patient-level meta-analysis of RCTs plausibly suggests that non-cortical infarcts can also have an embolic origin[70].

Characteristics of the PFO

An atrial septal aneurysm (ASA) and/or a moderate-to-severe shunt were strongly associated with a causal role of PFO in patients with cryptogenic stroke in observational and randomised studies[27-29,71-74]. Other characteristics associated in randomised studies with a causal PFO are large PFO size and atrial septal hypermobility[29]. A Eustachian valve, Chiari network or a long PFO tunnel was suggested to be linked to PFO-associated strokes but only in retrospective studies[75,76]. Other studies have failed to detect one or more of these associations, however[59,77-79], underlining the heterogeneity of phenotypes and the need to identify them.

Clinical clues

Candidate clinical clues have been addressed in retrospective studies and infrequently in prospective observational studies. Logically, conditions that strongly suggest paradoxical embolism in the presence

of a PFO include the simultaneous or previous occurrence of pulmonary emboli[18,80,81] or the documentation of a venous source of embolism around the time of stroke. Absence of evidence of venous thrombus is unhelpful because of frequent false negatives[15,80,82,83] but immobilisation, recent major surgery, or an extended car or airplane journey implies possible venous clot development. Activity at the time of the stroke is also relevant – straining manoeuvres, obstructive sleep apnoea with stroke-on-waking should be enquired for[81,84,85]. Retrospective studies that have attempted to identify an association between inherited thrombophilia and PFO-related stroke have yielded conflicting results[86-89].

The risk of paradoxical embolism (RoPE) score represents an attempt to assign a causal relationship probability to individual PFOs in the setting of stroke of unknown cause[59] and may be useful in helping to guide management decisions. However, it should always be used in conjunction with other parameters because the quality of evidence of internal validation studies has been rated moderate at best **(Supplementary Figure 15, Supplementary Table 3)**, and no large external validation studies have been published.

In addition, the RoPE score does not account for high-risk PFO features (e.g., septal aneurysm) that have been shown to correlate with higher risk of paradoxical embolisation.

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

Meta-analyses of observational and/or randomised studies suggest that the annual recurrence rate on medical therapy ranges from 0% to 5.8% for stroke and from 0% to 14% for either stroke or transient ischaemic attack (TIA)[90-92]. This wide variability stresses the heterogeneity of phenotypes in these syndromes. Causes of recurrence can of course include non-PFO mediated mechanisms[93,94].

Some predictors of stroke recurrence have been identified prospectively and retrospectively[72,95-97] **(Supplementary Figure 6)**. **Supplementary Table 4** lists features that were statistically significant predictors in at least two studies. Atrial septal aneurysm anatomy is particularly predictive **(Supplementary Appendix 4)**. In one study[98], a high D-dimer level on admission was an independent predictor of recurrent ischaemic stroke in patients with PFO. Therefore, at present, the individual evaluation of the risk of recurrence also cannot be quantitatively scored and should be based on interdisciplinary qualitative clinical evaluation.

UNIFIED DIAGNOSTIC WORKUP IN LEFT CIRCULATION THROMBOEMBOLISM

A diagnostic workup should follow logical steps **(Figure 2)**. **Table 4** summarises position statements. Further details are provided in **Supplementary Appendix 4**.

The diagnostic process should always include interdisciplinary clinical assessments and appropriate imaging.

Identifying atrial fibrillation (AF) is important because recurrences of left circulation embolism are, in the majority of cases, due to left atrial appendage thrombosis instead of paradoxical embolism. However, AF can be difficult to detect. A routine 12-lead electrocardiogram (ECG) and either in-patient cardiac telemetry or 24-hour Holter monitoring are sufficient to diagnose permanent AF and sufficiently long transient AF episodes. However, randomised and observational studies showed that insertable cardiac monitors (ICM) are associated with an increased yield of paroxysmal AF diagnoses relative to standard monitoring also in cryptogenic stroke[99-104] **(Supplementary Appendix 4, Supplementary Figure 16)**. Therefore, in high-risk patients for AF, an ICM period of six months can be reasonably considered to rule out AF before deciding on PFO closure[105]. In **Figure 3** we propose a strategy based on risk stratification of patients to be applied with a critical clinical judgement **(Supplementary Appendix 4)**. During ICM monitoring, patients should be maintained on medical therapy (see below). After six months, whatever the chosen treatment, the monitoring can be extended to the full duration of the ICM life to identify episodes of paroxysmal AF[106-112], to monitor the atrial thrombosis burden in arrhythmic patients, and to aid diagnosis in case recurrent ischaemia occurs.

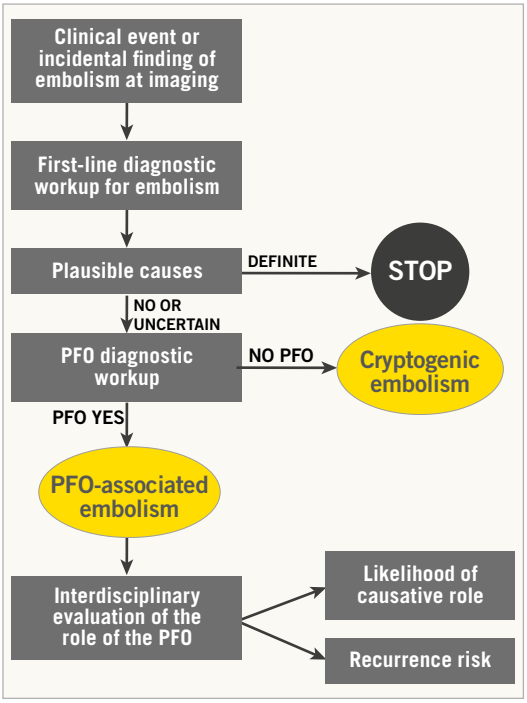

Figure 2. *Algorithm for the diagnostic workup of cryptogenic left circulation thromboembolism.*

MEDICAL AND INTERVENTIONAL MANAGEMENT

Further insights on each of the following paragraphs can be found in **Supplementary Appendix 4**.

PICO questions for the choice of therapy are summarised in **Table 5** and **Supplementary Appendix 5**. **Figure 4** summarises the flow of the choice of the therapy.

EFFICACY AND SAFETY OF MEDICAL THERAPY

A variety of medical treatments has been used, based upon data from secondary prevention studies for stroke in general and from studies on cryptogenic stroke in particular. No adequately dimensioned RCT

Table 4. Summary of statements on the evaluation and treatment of concurrent diseases.

Position statements	Strength of the statement	Level of evidence	Ref.
AF rule-out strategy			
All patients should undergo a routine 12-lead ECG and either in-patient cardiac telemetry or 24-hour Holter monitoring	Strong	B	260, 344
In patients >65 years old with negative routine monitoring, it is reasonable to consider ICM before deciding on PFO closure or permanent OAC	Conditional	C	99-102, 105, 166, 173, 260-263
ICM evaluation period in cryptogenic left circulation embolism should be at least 6 months before deciding on PFO closure or permanent OAC	Conditional	B	99-102,260-263,105
In patients 55 to 64 years old at risk for AF with negative routine monitoring, it is reasonable to consider ICM before deciding on PFO closure or permanent OAC	Conditional	C	173, 264
In patients <55 years old with ≥2 high-risk factors for AF with negative routine monitoring, it is reasonable to consider ICM before deciding on PFO closure or permanent OAC	Conditional	C	–
Patients undergoing diagnostic procedures should be maintained on medical therapy	Strong	B	Table 6
Medical therapy should be decided according to the statements of this position paper	Strong	C	Table 6
In patients with clear evidence of a causal PFO (e.g., simultaneous pulmonary embolism), ICM can be withheld so as not to delay percutaneous closure	Strong	C	Table 5
In patients undergoing ICM, the monitoring should be extended for the full duration of the device life, regardless of the choice of therapy after 6 months	Strong	C	102
Management of PFO in the presence of concomitant diseases			
Patients on temporary OAC, on OAC for pulmonary embolism or those considered at high risk of recurrences despite OAC may undergo PFO assessment for possible closure	Conditional	C	159, 160
Paroxysmal AF episodes >30 seconds detected with intermittent recordings, or ≥5 minutes during ICM can be considered sufficient to evaluate the patient for OAC according to current guidelines on AF	Conditional	B	163-168
ICM results should always be interpreted with other clinical characteristics in order to weigh the AF embolic risk against the PFO embolic risk	Strong	C	102
Routine laboratory tests for prothrombotic states (thrombophilia testing) are not warranted to indicate permanent OAC	Strong	C	161, 162

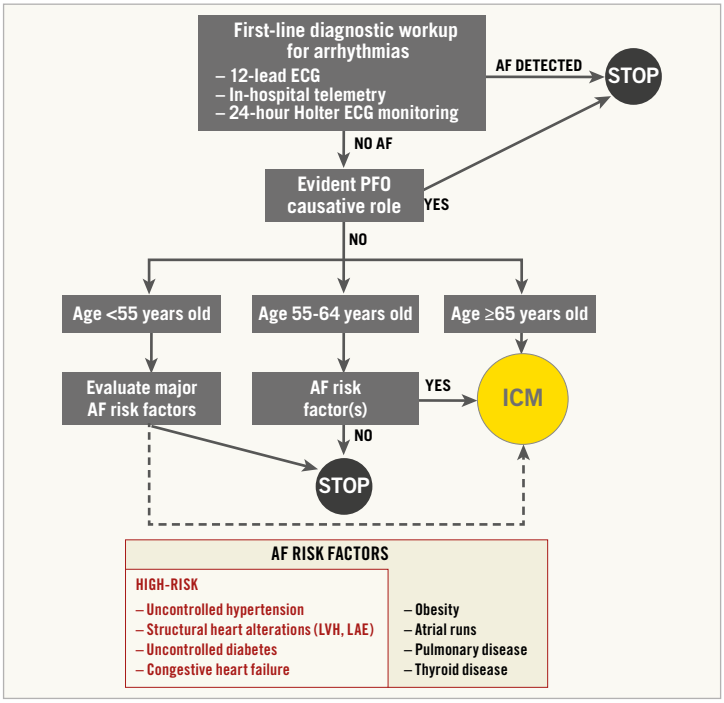

Figure 3. *Flow chart for the screening of overt atrial fibrillation in cryptogenic left circulation thromboembolism. The cut-off ages of 55 and 65 years old have been chosen according to data from large epidemiological studies[166,173]. Patients <55 years may be considered for ICM when they have high clinical suspicion of AF (i.e., ≥2 high-risk factors for AF). ECG: electrocardiography; LAE: left atrium enlargement; LVH: left ventricle hypertrophy*

Table 5. PICO question. Should percutaneous closure of PFO vs. medical therapy be used for secondary prevention of stroke or other left circulation thromboembolism in patients with high-risk PFO features?

Population	Secondary prevention of stroke, TIA, or other left circulation thromboembolism
Intervention	Percutaneous closure of PFO
Comparison	Medical therapy
Main outcomes	Stroke, TIA, death, bleedings, atrial arrhythmias
TYPE OF STATEMENT	**Strong statement for the intervention**
POSITION STATEMENTS	The position of our societies is to perform percutaneous closure of a PFO in carefully selected patients aged from 18 to 65 years with a confirmed cryptogenic stroke, TIA, or systemic embolism and an estimated high probability of a causal role of the PFO as assessed by clinical, anatomical and imaging features. The interventional procedure must be proposed to each patient evaluating the individual probability of benefit based on an assessment of both the role of the PFO in the thromboembolic event (Table 4) and the expected results and risks of a lifelong medical therapy. The role of the patient should be proactive, keeping in highest regard his/her values and preferences regarding outcomes and therapy trade-offs, and informing him/her about the uncertainties of their condition. With the same shared decision-making approach, PFO closure can also be considered in patients >65 or <18 years of age, taking into account on a case-by-case basis the lack of evidence, the age-related confounders and additional risks of interventional and drug therapies. Although no specific data are available to date, consistent with some guidelines on the topic, it seems justified to consider percutaneous closure in patients with a cryptogenic TIA, stroke, or systemic emboli that occurred while on therapy with OAC or antiplatelet agents. The choice of device should take into consideration that most available evidence has been obtained with the AMPLATZER™ PFO Occluder and GORE® HELEX® Septal Occluder (not available anymore) or the GORE® CARDIOFORM Septal Occluder. The use of the latter should be balanced against a lower complete closure rate and a higher risk of AF as compared to medical therapy. The potential use of devices other than AMPLATZER and CARDIOFORM, and the inherent risks, should also be part of the shared decision making with patients, in the light of technical, anatomical, and clinical features.
JUSTIFICATION	**Overall justification** The last, comprehensive, study-level meta-analyses incorporating the most recent randomised trials on patients aged 18-65 years with prior cryptogenic stroke or TIA showed superiority of PFO closure over medical therapy for the prevention of stroke in the first 5 years after the procedure (Supplementary Figure 17, Supplementary Figure 4A). One exploratory analysis of one of these trials extended to a longer follow-up supports a growing benefit of percutaneous closure over medical therapy after that time limit. The CLOSE, and the early-terminated DEFENCE-PFO trials performed in characterised patients with confirmed cryptogenic stroke and high-risk PFO features, and the REDUCE trial which also enrolled higher-risk patients as compared to previous trials, are the main drivers of this evidence (Supplementary Figure 4B and Supplementary Figure 5). The difference in results between studies enrolling higher-risk PFO patients and those enrolling unselected patients with prior cryptogenic cerebral accidents stresses the existence of higher- and lower-risk phenotypes of patients that need to be characterised before deciding on the therapy. This finding is furthermore supported by the cost-effectiveness analysis which demonstrated a benefit over 15 years only in high-risk patients. However, the significant effect in some subgroups, the heterogeneity still present at subgroup analysis even in high-risk patients, and the individual study limitations (Supplementary Appendix 4) enforce the need for carefully informed choices which must be shared with patients and tailored to their personal values and preferences. **Detailed justification** ***Problem.*** PFO-related stroke is an important health problem; therefore, its secondary prevention is a priority. Unfortunately, its management is problematic because high-quality data are lacking in this very heterogeneous class of patients. Nonetheless, the possibility of an efficient secondary prevention should be granted without causing harm with unnecessary treatments. Given the very disparate practices that exist within the medical community in this regard, it is urgent that clinicians follow a balanced approach that is based upon the present level of knowledge, while waiting for more conclusive evidence on better classified populations of patients. ***Desirable effects.*** Our study-level meta-analysis on the 6 RCTs showed a clear superiority of PFO closure over medical therapy in terms of reducing the incidence of stroke recurrence (Supplementary Figure 4A). The two previously published meta-analyses on the 6 RCTs, all of the first five RCTs (hence excluding the DEFENSE-PFO trial) and the highest-quality, patient-level meta-analysis of the first three published RCTs are consistent with our results. Two meta-analyses of comparative observational trials are in keeping with these results (Supplementary Table 7). ***Undesirable effects.*** Interventional treatment does not imply higher complication rates, with the exception of a higher frequency of AF after percutaneous closure relative to medical therapy (Supplementary Figure 9). However, the higher risk of AF with closure versus medical therapy was considerably lowered (Supplementary Figure 10) if an AMPLATZER PFO Occluder was used. In the REDUCE trial using the GORE HELEX or CARDIOFORM septal occluders, the incidence of AF was 6.6% at 5 years, a large proportion of which were only intraprocedural or periprocedural arrhythmias. Bleeding complications were similar in the young cohorts of patients enrolled in RCTs in the short term; however, long-term follow-up data are missing in patients undergoing lifelong medical treatments, which are likely to increase the risk of haemorrhage as patients grow older.

Table 5 (continued). PICO question. Should percutaneous closure of PFO vs. medical therapy be used for secondary prevention of stroke or other left circulation thromboembolism in patients with high-risk PFO features?

TYPE OF STATEMENT	Strong statement for the intervention
JUSTIFICATION	***Certainty of evidence***. The consistent results of all the meta-analyses performed so far were confirmed when considering OR, RR and AR, even performing sensitivity analysis, and also when including CLOSURE I, the most outdated trial. To date, despite several limitations of individual studies which implied an overall low score in the certainty of evidence (Supplementary Table 9, Supplementary Table 10), in patients with high-risk PFO features the certainty is higher, as shown by the reduction in heterogeneity in meta-analyses and by the recently published sequential analysis of the risk of recurrent stroke[74]. Therefore, future studies are not likely to impact on the certainty of evidence, at least in high-risk populations. ***Values.*** Large variations in preferences of patients indicate the need for tailored informed consent and the explicit evaluation of therapeutic trade-offs with individual patients. ***Balance of effects.*** The NNT with percutaneous closure obtained in RCTs outweighed the NNH for atrial fibrillation after percutaneous closure, especially when an AMPLATZER PFO Occluder was used and when patients with higher-risk PFO were considered. Moreover, based on United States estimates, the cost-effectiveness analysis favours over 15 years percutaneous closure in patients with high-risk PFO features and with the use of an AMPLATZER PFO Occluder.
SUBGROUP CONSIDERATIONS	In published randomised studies, the age of patients was ≤65 years and 18 years. The DEFENSE-PFO trial, strongly positive for PFO closure over medical therapy in the prevention of recurrent stroke, did not have age limitations for enrolment and randomised patients aged up to 66 years old[29]. In our study-level meta-analysis of the 6 RCTs, a statistically significant improvement in stroke recurrence with percutaneous closure was observed only versus antiplatelet therapy (Supplementary Figure 12A), whereas OAT yielded a similar risk of recurrence (Supplementary Figure 12B, Supplementary Figure 12C). Moreover, no differences were noted regarding the outcomes of different pooled clinical inclusion criteria regarding the index event (Supplementary Figure 13). However, some of the previous meta-analyses on the first 5 RCTs consistently found that patients with moderate-to-severe shunt size experienced enhanced outcomes with percutaneous closure relative to medical therapy[78,79,90,122,170,171]. Nonetheless, patients with ASA were associated with better outcomes with percutaneous closure than with medical therapy only in some[171,172] but not in other meta-analyses[78,79]. In our meta-analysis, we found that patients with high-risk PFO features (ASA, hypermobility of atrial septum, moderate-to-severe shunt, or large PFO size) reported enhanced outcomes with percutaneous closure relative to medical therapy, whereas in patients with low-risk PFOs there was no additional benefit with PFO closure vs. medical therapy (Supplementary Figure 4B, Supplementary Figure 5). In our most recent analysis, no device was associated with statistically significant enhanced efficacy versus medical therapy as compared to other devices (Supplementary Figure 14). The risk of new-onset atrial fibrillation was similar with the AMPLATZER PFO Occluder and medical therapy while it was higher for the GORE CARDIOFORM device when compared with medical therapy (Supplementary Figure 10). In some meta-analyses other subgroups experienced enhanced outcomes with percutaneous closure relative to medical therapy. These subgroups include males[70,78,79,90] and age <45 years old[78,79,90]. However, these findings were not confirmed in another meta-analysis[171]. Finally a single previous meta-analysis supported patients with a history of migraines or non-cortical infarcts as having better outcomes with percutaneous closure as compared to medical therapy[70].
IMPLEMENTATION CONSIDERATIONS	PFO closure incurs procedural cost. However, cost-effectiveness studies showed that PFO is associated with economic and QUALY gain after 15 years, provided that the procedure was performed in high-risk patients. Performing the procedure in unselected patients translates into a sharp decrease in cost-effectiveness. Moreover, procedural costs and procedure times may be decreased with the use of sedation instead of general anaesthesia or of intracardiac echocardiography versus transoesophageal echocardiography, thereby eliminating the need for an anaesthesiologist.
MONITORING AND EVALUATION	Each neurological index event should be confirmed by a neurologist or a stroke physician. The cardiologist and the stroke physician must come to the conclusion that the stroke or TIA was cryptogenic and communicate in order to reach consensus regarding therapeutic decisions. Patients should be actively involved at all stages of management and their contribution to choices should be documented.
RESEARCH PRIORITIES	– To verify the existence of additional risk factors and their cut-offs for prediction of events in strict epidemiological series. – To identify new high-risk phenotypes encompassing different clusters of clinical, anatomical and biological characteristics in prospective observational trials (systems and precision approaches) and to perform new randomised trials in these populations. – To design adequately dimensioned RCTs comparing single medical therapies (vitamin K antagonists or DOAC) with percutaneous closure in patients with higher-risk PFO-related left circulation embolism. – To assess outcomes of percutaneous closure vs. OAC. – To assess long-term outcomes (>5 years) with different treatments. – To address the evaluation of persisting disability and quality of life with different treatments. – To design prospective registries to evaluate practices and outcomes in the real world. – To obtain new, cost-effectiveness analyses based on contemporary practices. – To obtain quantitative and qualitative data on patient preferences and values in the setting of cryptogenic stroke or systemic embolism with PFO. – To obtain data on the effectiveness and efficacy of organisational models to manage patients with cryptogenic stroke/systemic emboli.

Table 6. PICO question. Should oral anticoagulants (OAC) vs. antiplatelet therapy be used for secondary prevention of stroke or other left circulation thromboembolism?

Population	Secondary prevention of stroke or other left circulation thromboembolism
Intervention	OAC
Comparison	Antiplatelet therapy
Main outcomes	Stroke; major bleedings
TYPE OF STATEMENT	**Conditional statement for either the intervention or the comparison**
POSITION STATEMENT	In patients in whom a medical therapy only is chosen, the position of our scientific societies is to choose the specific drugs weighing the individual risk of bleeding against the risk of PFO-related stroke recurrence, in close connection with the patient. Long-term OAC with vitamin K antagonists may be preferred if: a) the patient has a low haemorrhagic risk, b) a probable good therapeutic compliance is foreseen, and c) a proper anticoagulant monitoring can be guaranteed. In patients in whom these conditions are not satisfied, or the risk of stroke recurrence is deemed low, an antiplatelet therapy should be prescribed. Reassessment of the risk/benefit ratio should be performed on a regular basis, especially with advancing age and the increase in comorbidities which can affect both risk and benefit issues. No position can be expressed for DOAC, although intuitively their reduced bleeding risk compared with vitamin K antagonists in other clinical conditions is appealing.
JUSTIFICATION	**Overall justification** The randomised CLOSE trial shows a statistically non-significant reduction of stroke with OAC as compared to antiplatelet therapy. However, a single trial enrolling only 300 patients reporting outcomes with wide confidence intervals cannot be considered conclusive. Meta-analyses consistently indicate a statistically significant reduction in the risk of stroke with OAC as compared to antiplatelet therapy, at the cost of a significantly higher risk of major bleeding. However, the overall uncertainty of the evidence remains very high (Supplementary Table 11) and the inconsistency across studies is severe (Supplementary Figure 7). Therefore, only a conditional statement for either OAC or antiplatelets can be expressed, with the choice between them being guided by individual safety and expected risk of recurrence variables. **Detailed justification** ***Desirable effects***. The randomised CLOSE trial shows a statistically non-significant reduction of stroke with OAC as compared to antiplatelet therapy. Our meta-analysis indicates a statistically significant reduction of the odds ratio for stroke of approximately 12% with OAC over antiplatelet therapy (Supplementary Figure 18). These results are in keeping with previous meta-analyses. ***Undesirable effects.*** An approximately 5-fold higher risk of major bleeding emerged from our meta-analysis with OAC as compared to antiplatelet therapy. Also, these results are in line with previous analysis. ***Certainty of evidence.*** The certainty of evidence is very low, because the results are mainly derived from non-randomised comparisons (Supplementary Table 11), and the included randomised trial, enrolling only approximately 300 patients, reported wide confidence intervals in effect estimates. Therefore, further RCTs will probably impact on effect estimates. ***Values.*** Patients undergoing secondary pharmacological prevention for stroke appear to accept higher risk of bleeding if a considerable certitude can be provided regarding the prevention of stroke. ***Balance of effects.*** The balance of desirable and undesirable effects of therapy varies according to the expected benefits of the therapy, as the risk of bleeding appears to be homogenous across studies. Therefore, therapy should be as individualised as possible. ***Feasibility.*** Feasibility of implementation of a safe OAC regimen with vitamin K antagonists is largely dependent on availability of monitoring facilities of proper anticoagulation and on the possibility of accessing them by patients.
SUBGROUP CONSIDERATIONS	No subgroup consideration can be derived from the accrued data. However, given the inconsistency of the studies and the variability of results, subgroups should be identified for new study.
IMPLEMENTATION CONSIDERATIONS	No cost-effectiveness studies have been performed in this field. However, as the costs of OAC and antiplatelet therapy are low, the cost-effectiveness profile is dependent mainly on the costs of adverse events in the follow-up. The available evidence shows that bleeding complications increase with age, rendering even more uncertain the cost-effectiveness of this therapy in the long term.
MONITORING AND EVALUATION	In antithrombotic therapy the risk/benefit ratio is highly dependent on time. It is therefore advised to reassess risks and benefits of the chosen therapy on a regular basis, especially with advancing age and the increase in comorbidities. Local registries for prospective evaluations of outcomes are strongly encouraged.
RESEARCH PRIORITIES	– To assess more precise risk factors and their cut-offs for prediction of events. – To identify new high-risk phenotypes encompassing different clusters of clinical, anatomical and biological characteristics in prospective observational trials (systems and precision approaches). – To design adequately dimensioned head-to-head RCTs comparing single medical therapies (e.g., acetylsalicylic acid, clopidogrel, vitamin K antagonists, DOAC, etc.) in patients in whom percutaneous therapy has been excluded. – To assess long-term outcomes (>5 years) with different treatments. – To address the evaluation of persisting disability and quality of life with different treatments. – To design prospective registries to evaluate practices and outcomes in the real world. – To obtain new, cost-effectiveness analyses based on contemporary practices. – To obtain quantitative and qualitative data on patient preferences and values in the setting of cryptogenic stroke or systemic embolism with PFO. – To obtain data on the effectiveness and efficacy of organisational models to manage patients with cryptogenic stroke/systemic emboli.

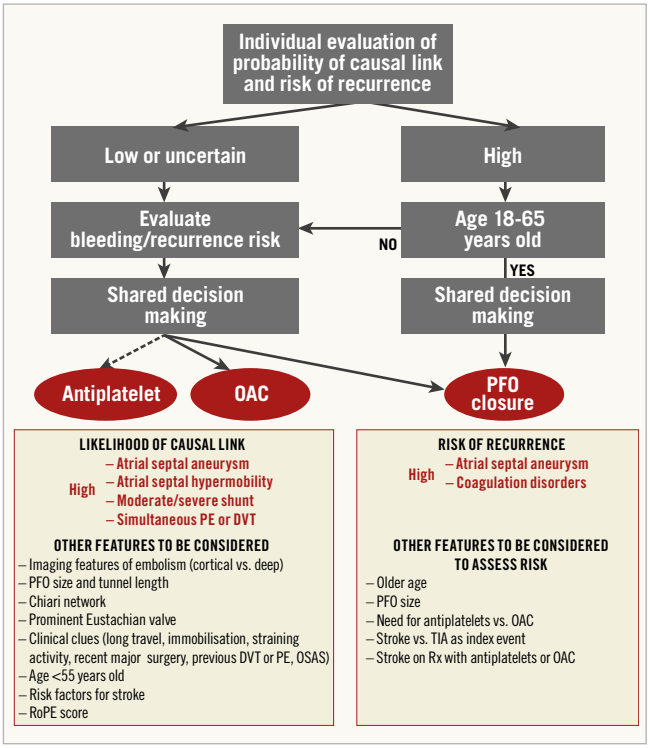

Figure 4. *Treatment algorithm for secondary prevention of left circulation cryptogenic thromboembolism. DVT: deep vein thrombosis; OAC: oral anticoagulants; OSAS: obstructive sleep apnoea syndrome; PE: pulmonary embolism; Rx: therapy; TIA: transient ischaemic attack*

has yet been published that has assessed the effectiveness of individual drugs specifically in PFO-associated cerebrovascular accidents.

Trials were almost exclusively observational with only one adequately dimensioned RCT comparing oral anticoagulants (OAC) and antiplatelet agents. One meta-analysis of RCTs showed a recurrent stroke rate of 1.27 events per 100 patient-years with drugs only[74]. In our meta-analysis of the RCTs, the incidence of recurrent stroke on medical therapy was 4.6% after 3.8 years of follow-up **(Supplementary Figure 4A, Supplementary Figure 4B, Supplementary Appendix 3)**, whereas in a meta-analysis of observational trials the recurrence rate was 5% per year[113].

Despite a severe heterogeneity of results, the most recent meta-analysis including the randomised study is consistent with previous meta-analyses of observational studies[113-116], suggesting superiority of OAC over antiplatelet agents in the prevention of stroke **(Supplementary Figure 7, Supplementary Appendix 3)**. Although the overall quality of the evidence in this meta-analysis was estimated to be very low **(Supplementary Table 11)**, the superiority of OAC vs. antiplatelet agents was also evident when considering studies with multivariate adjustment only **(Supplementary Figure 7)**. No data are available on persisting disability and quality of life.

Reports on safety have often been incomplete or have yielded inconsistent results. In a meta-analysis of observational studies, 1.1% of patients receiving medical therapy experienced a bleeding complication[113]. This surprisingly low proportion of bleeding episodes can be explained by the young age of the patients and the short follow-up and, thus, must be interpreted with caution because most of these patients will undergo a lifelong medical therapy with an incremental risk of bleeding with age. Indeed, in our meta-analyses on PFO patients, an odds ratio (OR) of 4.57 was found for major bleeding with OAC relative to antiplatelet drugs **(Supplementary Figure 8)**. A previous meta-analysis considering secondary prevention of stroke in general revealed that the potential benefit of OAC might be outweighed by the risk of both intracranial haemorrhage (OR 2.54) and major extracranial haemorrhage (OR 3.43)[117]. In this respect, direct oral anticoagulants (DOAC) may alter the risk-benefit ratio[118,119], although no data exist in these patients.

SAFETY AND EFFICACY PROFILE OF PFO CLOSURE

Percutaneous procedure

Primary technical success approaches 100%[78,113] and complete closure is seen in 93-96% at one year[122]. The use of larger devices has a higher risk of residual shunts[113,123-125]; the AMPLATZER™ PFO Occluder (St. Jude Medical, St. Paul, MN, USA) may have lower residual shunt rates than other devices[123,125-130]. Individual randomised data show a relative risk reduction of up to 80% for recurrent strokes[131,132]. One meta-analysis of RCTs has shown the stroke recurrence rate to be 0.29 per 100 person-years[74] **(Supplementary Appendix 3)**. In our study-level meta-analysis of RCTs with an average 3.8 years of follow-up, the incidence of recurrent stroke was 2% in the closure arms, and the number needed to treat (NNT) with PFO closure to prevent one stroke overall was 37 (95% confidence interval [CI]: 26 to 68) **(Supplementary Figure 4A)**, and 21 in patients with high-risk PFO features (95% CI: 16 to 61) **(Supplementary Figure 5)**. Results on TIA and on death were neutral (**Supplementary Figure 4C**, **Supplementary Figure 4D**, respectively). An increase of the treatment effects over time can be expected[28,133,134]. No data are available on persisting disability and quality of life.

Complications are summarised in **Supplementary Table 5**. Procedural complications had a 2.6% incidence in RCTs[74]. The most frequent late complication is device thrombosis, which is seen in 1.0-2.0%[135]. Device embolism is a serious event and occurs at a rate of 0.9-1.3%[135,136]. Atrial wall erosions are serious events that have been reported anecdotally. The risk of long-term mortality or the need for cardiac surgery is less than one in 1,000. Minor complications occur only in 1.0-1.7%.

The most frequent undesirable event following transcatheter percutaneous closure is AF in RCTs and observational trials[28,78,106-111,113]. In a meta-analysis of RCTs, a 4.6% incidence was reported after 3.8 years of follow-up[74]. In our meta-analysis, for incident AF, the overall number needed to harm (NNH) was 25 **(Supplementary Figure 9A)**, whereas beyond 45 days there was no increased risk for AF with PFO closure **(Supplementary Figure 9B, Supplementary Figure 9C)**. The incidence of these events was lowest with the AMPLATZER PFO Occluder **(Supplementary Figure 10)**. Interestingly, a statistically significant reduction of AF prevalence after

percutaneous closure of PFO was also shown in other studies, suggesting some antiarrhythmic effect of the procedure[137].

Management after percutaneous closure

No data on best management strategies after PFO closure are available. Position statements are summarised in **Table 7**.

Drug treatments

To decide on post-procedural therapy one should consider that: a) endocardialisation of the device can continue up to five years post implantation[128,138-140]; b) one of the most frequent complications after closure is device thrombosis; and c) premature discontinuation of therapy may cause minor cerebrovascular events after PFO closure, as suggested by a marked trend towards association between duration of dual antiplatelet therapy after PFO closure and the incidence of TIA in our study-level meta-regression analysis **(Supplementary Figure 11)**.

It is reasonable to decide on the post-procedural therapy according to the strategies used in RCTs. Overall, 5/6 RCTs prescribed or recommended a dual antiplatelet therapy in the first one to six months after closure, continuing with a single drug beyond two years in 3/4 RCTs that had a longer follow-up after that limit. In all positive trials, an antiplatelet therapy was prolonged for the entire duration of the study in the majority of patients (in 2/4 studies it was prescribed for five years). In one negative trial, only 50% and 41% of patients were still taking an antiplatelet therapy after one and five years, respectively[132].

Delayed complications

Supplementary Table 5 displays the main tools available to detect complications. At present, no relationship between PFO patency after closure and the incidence of recurrence has been found **(Supplementary Table 6)**[124,141-147], but studies were small, often plagued by partially incomplete follow-up, and problematic regarding shunt detection accuracy[139]. Also, a persistent shunt after closure may reveal other sources of paradoxical embolism which were missed during the diagnostic phase[148].

No high-quality data are available to guide the optimal management of a residual moderate-to-severe PFO patency. The literature on acute and long-term results after repeat device implantation for a residual shunt is scarce, but retrospective evaluations are encouraging[149-156].

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

Surgical closure of PFO

There are no current indications for surgical closure of a PFO as first-line treatment. Closure of incidental PFOs is usually undertaken during valvular surgery or in the rare cases when surgery is indicated for other conditions in which the PFO plays a role, such as a straddling thrombus in the PFO, or seldom when complications of percutaneous closure occur which cannot be managed by percutaneous means.

Management in the presence of concomitant diseases

Position statements are summarised in **Table 4**.

In the setting of hypercoagulability, deep vein thrombosis and/or pulmonary embolism[159], PFO closure may be considered when there is the need for only temporary OAC or a high risk of recurrence despite permanent OAC, particularly in pulmonary

Table 7. Summary of statements on the management after percutaneous closure of PFO.

Position statements	Strength of the statement	Level of evidence	Ref.
Drug therapy and follow up after percutaneous closure			
It is reasonable to propose dual antiplatelet therapy for 1 to 6 months after PFO closure	Conditional	A	27, 29, 51, 112, 132, Supplementary Figure 11
We suggest a single antiplatelet therapy be continued for at least 5 years	Conditional	C	27-29, 51, 112, 132, 128, 138-140
The extension of the therapy with single antiplatelet beyond 5 years should be based on the balance between patient's overall risk of stroke for other causes and haemorrhagic risk	Strong	C	–
The choice of the type of antiplatelet drug in the follow-up is currently empiric	Strong	A	27-29, 51, 112, 132
The value of residual shunt after percutaneous closure cannot be deduced from available studies	Strong	C	124, 141-47
Systematic, high-quality data on follow-up are needed	Strong	C	–
To obtain comparable data we propose to perform: a) a TTE prior to hospital discharge b) c-TCD at least once beyond six months to assess effective PFO closure and thereafter, if residual shunt persists, annually until closure c) c-TOE or c-TTE in case of severe residual shunt at c-TCD, or recurrent events, or symptoms during follow-up	Conditional	C	124, 141-147, 55 + Original meta-analyses page 1392 and Supplementary Appendix 4
Patients should undergo antibiotic prophylaxis for any invasive procedure performed in the first six months from PFO closure	Conditional	C	–

embolism, where PFO was reported to be an independent predictor of new brain lesions in the follow-up, despite optimal OAC[160].

Routine laboratory tests for prothrombotic states (thrombophilia testing) are not generally warranted to guide the need for permanent OAC[161,162].

Although no study has assessed this issue as yet, it is reasonable that excluding patients with AF from PFO closure and treating them with permanent OAC should translate into an increased effectiveness of secondary prevention of left circulation thromboembolism. However, as in the CRYSTAL-AF study, a higher incidence of AF at ICM did not translate into a higher stroke incidence[102]; the presence of short bursts of AF on an ICM may carry a lower pathogenic value than a high-risk PFO. Therefore, the burden of AF should be weighed against the burden of PFO by considering other clinical characteristics to decide for or against PFO closure. For patients with paroxysmal AF, there is uncertainty regarding the duration of arrhythmic episodes which increases the risk of embolism. According to the HRS/EHRA/ECAS expert consensus statement on AF ablation, AF episodes ≥30 seconds constitute clinically significant AF[163]. During prolonged monitoring, episodes of AF ≥5 minutes have a predictive value for embolism[164-168]. These criteria should be combined with a thromboembolic score to evaluate the need for OAC[169].

Conclusions

The management of patients with cryptogenic left circulation thromboembolism and PFO has been controversial, giving rise to heterogeneous strategies across different local realms in Europe. Based on the best available evidence, we were able to reach, in this interdisciplinary position paper, a consensus among eight European scientific societies on key diagnostic, therapeutic and research issues, from the index event to follow-up. It was possible to express strict position statements based on randomised trials for some therapeutic aspects, whereas other aspects were often based on limited and non-randomised data. This position paper provides the first largely shared approach for a rational PFO management based on the best available evidence. This may help physicians to offer coherent strategies throughout Europe and focus the research on high-priority subjects.

Guest Editor

This paper was guest edited by David R. Holmes, MD, MACC; Department of Cardiology, Mayo Clinic, Rochester, MN, USA.

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Conflict of interest statement

H. Sievert reports institutional fees from Carag and Lifetech, outside the submitted work. B. Dalvi reports being a consultant to Abbott. B. Meier declares a conflict of interest in the form of speaker fees received from Abbott. M. Chessa reports personal fees from Abbott and Occlutech. D. Toni reports personal fees from Boehringer Ingelheim, Bayer, Pfizer Bristol-Myers Squibb, Daiichi Sankyo, and Medtronic. P. Scacciatella reports personal fees from Abbott Medical and Gore Medical. J. Thomson reports being a proctor and consultant for Abbott Medical and Gore Medical. D. Hildick-Smith reports having consultancy/advocacy for Abbott, Gore and Occlutech. D. Sibbing reports personal fees outside the submitted work from Roche Diagnostics, Daiichi Sankyo, Eli Lilly, Bayer Healthcare, Sanofi, Pfizer and AstraZeneca. S. Kasner reports personal fees from Bristol-Myers Squibb, Boehringer Ingelheim, Medtronic and AbbVie, grants from W.L. Gore, and grants and personal fees from Janssen and Bayer, outside the submitted work. G. Biondi-Zoccai reports having been a consultant for Abbott Vascular and Bayer. J. Carroll reports personal fees from AGA Medical, St. Jude Medical, and Abbott. The Chairman of the task force and all the other authors have no conflicts of interest to declare. The Guest Editor has no conflicts of interest to declare.

References

The references can be found in the Supplementary data document.

Supplementary data

Supplementary Appendix 1. Detailed methods.

Supplementary Appendix 2. Statistical methods.

Supplementary Appendix 3. Systematic review of evidence, assessment of its quality and meta-analyses.

Supplementary Appendix 4. Detailed evaluation of specific issues.

Supplementary Appendix 5. GRADE evaluation of evidences for PICO questions.

Supplementary Figure 1. Comparison of the rate of PFO detection in studies using TOE or autopsy.

Supplementary Figure 2. Meta-analysis of diagnostic accuracy studies comparing c-TCD vs. c-TOE.

Supplementary Figure 3. Meta-analysis of diagnostic accuracy studies comparing c-TTE vs. c-TOE.

Supplementary Figure 4. Outcomes in patients undergoing percutaneous closure or medical therapy.

Supplementary Figure 5. Subgroup analysis according to PFO features.

Supplementary Figure 6. PRISMA flow chart for the review of studies on the predictors of stroke in patients with cryptogenic stroke and a PFO.

Supplementary Figure 7. Forest plot for the risk of stroke recurrence in studies comparing OAC with antiplatelet therapy for cryptogenic solid systemic embolism.

Supplementary Figure 8. Forest plot for the risk of major bleedings in studies comparing OAC with antiplatelet therapy for cryptogenic cerebral or systemic embolism.

Supplementary Figure 9. Risk of atrial fibrillation in studies comparing PFO closure with medical therapy for cryptogenic cerebral or systemic embolism.

Supplementary Figure 10. Forest plot for the risk of atrial fibrillation according to the type of device used for PFO closure in studies comparing PFO closure with medical therapy for cryptogenic cerebral or systemic embolism.

Supplementary Figure 11. L'Abbé plots for the risk of TIA and stroke after PFO closure according to the length of dual antiplatelet therapy.

Supplementary Figure 12. Risk of stroke recurrence in patients undergoing OAC or antiplatelet therapy in studies comparing PFO closure with medical therapy for cryptogenic cerebral or systemic embolism.

Supplementary Figure 13. Risk of stroke recurrence according to the type of index event in studies comparing PFO closure with medical therapy for cryptogenic cerebral or systemic embolism.

Supplementary Figure 14. Risk of stroke recurrence according to the type of device used for PFO closure in studies comparing PFO closure with medical therapy for cryptogenic cerebral or systemic embolism.

Supplementary Figure 15. PRISMA flow chart for the review of studies on the RoPE score.

Supplementary Figure 16. PRISMA flow chart.

Supplementary Figure 17. PRISMA flow chart for the review of RCTs comparing PFO closure with medical therapy.

Supplementary Figure 18. PRISMA flow chart for the review of studies comparing OAC with antiplatelet therapy for secondary prevention of stroke, TIA or systemic solid embolism in patients with previous cryptogenic left embolism.

Supplementary Figure 19. PRISMA flow chart for the review of studies investigating the accuracy of PFO diagnostic tests.

Supplementary Figure 20. PRISMA flow chart for the review of studies investigating the accuracy of PFO diagnostic tests.

Supplementary Figure 21. Simplified scheme of the interacting network of processes underlying clinical manifestations associated with PFO.

Supplementary Table 1. PFO diagnostic methods.

Supplementary Table 2. Qualitative evaluation of diagnostic studies.

Supplementary Table 3. Qualitative evaluation of the studies on RoPE score.

Supplementary Table 4. Predictors of cryptogenic stroke recurrence in the presence of a PFO.

Supplementary Table 5. Complications of percutaneous closure.

Supplementary Table 6. Prognosis of patients with PFO patency.

Supplementary Table 7. Summary of meta-analyses on closure vs. medical therapy trials.

Supplementary Table 8. Observational studies comparing PFO closure with medical therapy.

Supplementary Table 9. RCTs comparing percutaneous closure and medical therapy.

Supplementary Table 10. Qualitative and quantitative assessment of the evidence on the comparison between PFO closure versus medical therapies.

Supplementary Table 11. Qualitative assessment of the evidence on the comparison between antiplatelet versus OAC therapies.

Supplementary Table 12. Quality of evidence grades.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/146th_issue/252

Supplementary data

Supplementary Appendix 1. Detailed methods.

General outline of the process

The European Association for Percutaneous Cardiovascular Interventions (EAPCI) planned to create position statements on PFO management. Relevant European scientific bodies were invited to collaborate, and task force members were chosen by each society. External international experts were also asked to join the initiative as reviewers. Systematic reviews and statistical analysis were performed by a dedicated evidence synthesis team. Grading of recommendations assessment, development, and evaluation (GRADE) methodology (http://gdt.guidelinedevelopment.org/app/handbook/handbook.html) was used to develop patients-interventions-comparators-outcomes (PICO) questions, evaluate evidence and formulate position statements. Not all topics could be addressed by the PICO methodology and therefore additional non-PICO questions were developed. Some PICO questions were reclassified as non-PICO after the literature search, due to a lack of clear evidence. Non-PICO questions were formally defined by e-mail exchange.

The evidence synthesis team undertook relevant systematic literature searches for each question using a combination of controlled vocabulary and free text terms. The databases searched for this purpose were: Pubmed, Scopus, Google Scholar and ISI. Preliminary literature searches were performed in September/October 2016 with an update in March 2018.

Evidence was evaluated qualitatively and where possible by quantitative methods. Each evaluation was performed according to a pre-defined ranking of outcomes made by the task force. Grading of the quality of evidence was made by consensus by the evidence synthesis team and the task force using the following criteria: the type of studies included, limitations in study design and methodology (i.e., risk of bias), inconsistency (or else: heterogeneity) of results, indirectness of evidence, imprecision, reporting bias, the magnitude of the treatment effect, evidence of a dose–response relationship, and the effect of all plausible confounding. Quality of evidence was evaluated by the means of GRADE-PRO GDT online tool (https://gradepro.org) and graded as high, moderate, low and very low (**Supplementary Table 12**). When several outcomes were assessed for a clinical question, the grade for the overall quality of evidence was based on the grade for the most important outcome(s).

Quantitative absolute risk reduction, as classically performed in the GRADE method, was not deemed sufficient to formulate position statements because of the low event rate frequency. Therefore, original meta-analyses were undertaken for all PICO questions and some non-PICO topics.

Subsequently, the task force was structured in working groups, each addressing one question and writing the relevant draft. These drafts were merged and distributed to the task force members for individual editing in three consecutive editing rounds. Discrepancies were resolved by consensus and the final manuscript

underwent a formal approval by the task force, before being distributed to the relevant scientific societies for the final endorsement. The final version was approved July 22nd 2018 and submitted for publication July 23rd 2018.

GRADE process and position statements

Formulation of the PICO questions was suggested and concluded by consensus among the members of the working group. Twenty-two PICO questions were initially formulated. Only two of these could be addressed by a modified GRADE methodology after the evidence evaluation ("Should percutaneous closure of PFO vs. medical therapy be used for secondary prevention of stroke or other left-circulation thromboembolism ?" and "Should oral anticoagulants (OAC) vs. antiplatelet therapy be used for secondary prevention of stroke or other left-circulation thromboembolism ?").

The nature and strength of position statements was agreed by task force consensus.

Specifications of PICO are detailed in the relevant sections and tables of the document.

Population

These position statements refer to patients with PFO with various forms of putatively associated syndromes and are specified throughout the text.

Interventions

Interventions addressing PFO-associated syndromes vary according to the relevant clinical scenario. We have focused on percutaneous closure, pharmacological interventions and behavioural measures. Pharmacological interventions include: oral anticoagulants, antiplatelet agents, and combinations of these interventions. Behavioural measures consist in change of specific activities when they expose subjects to risk. These activities include: lifestyle, surgical techniques when an operation is required, and habits or working activities.

Comparators

As no gold standard therapies are available in PFO-associated syndromes, we compared different interventions among those that are commonly used.

Outcomes

The GRADE methodology recommends that evidence-based guidelines consider outcomes which are of importance to patients and/or their families and that more emphasis is placed on outcomes of greatest importance to them. Therefore, we focussed on patients' chance of survival, quality of life, working status, and functional outcome. However, apart from death risk, those outcomes have seldom been considered in published literature regarding PFO-related syndromes. We also considered the risks of adverse effects of therapies (e.g., haemorrhage or arrhythmias). The position statements of this position paper are expressed on

agreement by consensus and on a grading of outcomes performed with a formal online poll. Therefore, the priority is based on the lone judgement of the task force.

Non-PICO questions definition and position statements

Originally, 7 non-PICO questions were formulated for each PFO-associated clinical syndrome: four of which are indicated in the chapter titles of the manuscript, two are incorporated into "Diagnostic workup" and one in the "Efficacy and safety of therapies" chapters. After evidence evaluation, 20 questions formerly identified as PICO questions were changed into non-PICO questions. Each question underwent the above described process for developing position statements which were finally incorporated into the chapters of the position paper.

Position statements were formulated by consensus among the members of the task force, based on the evidence evaluation in the 3 Delphi editing rounds. Tables summarising position statements indicate the strength of the position statement – strong or conditional (depending on patient values, physician opinion, resources available or setting) according to GRADE method. We also indicated the quality of the data: A) data derived from multiple RCTs or meta-analyses; B) data derived from single RCT or large non-randomised studies; C) consensus of opinion of experts and/or small studies, retrospective studies and registries. Despite a "C" level of evidence, some statements have been classified as "strong". The reasons for this are because it is the low quality of evidence that supported the direction of the statement (e.g., more research is needed in a sector because the lack of evidence) or because there were few or no specific studies addressing the issue but the evidence on the PFO subject as a whole supported the statement (e.g., interdisciplinary assessment and decision making should be done in PFO-related syndromes although no studies were performed comparing interdisciplinary approach with single professional management). Conversely, in other situations, a statement may have been classified as "conditional" despite a level of evidence "A" if the underlying evidence had a low quality despite being derived from randomised studies. For strong statements, we use the terminology ‘should. . .’ or definitely affirmative sentences. In case of conditional/discretionary statements, we used a wording implying that doctors and patients should consider more carefully whether the suggested option is the right choice or case for that particular patient.
In the tables summarising position statements, "Ref." denotes both bibliography and/or original evidence which has been produced in this document.

LIST OF PICO AND NON-PICO QUESTIONS

1. Should analytical risk factors (clinical or anatomical) be used to diagnose causal or high-risk PFO in cryptogenic stroke or other left-circulation thromboembolism?
2. Should the risk of paradoxical embolism (ROPE) score be used to diagnose causal or high-risk PFO in cryptogenic stroke?
3. Should insertable cardiac long-term monitoring be used to diagnose atrial fibrillation in patients with PFO-associated ischaemic cryptogenic stroke or other left-circulation thromboembolism?
4. Should transcranial Doppler with bubble test vs. transthoracic contrast echography be used to

diagnose PFO in suspected PFO-associated clinical syndromes?

5. Should transoesophageal contrast-echocardiography vs. transthoracic contrast echocardiography be used to diagnose PFO in suspected PFO-associated clinical syndromes?

6. Should transcranial Doppler vs transoesophageal contrast-echocardiography be used to diagnose PFO in suspected PFO-associated clinical syndromes?

7. Should transcranial Doppler vs transoesophageal contrast-echocardiography be used to diagnose PFO patency in patients who underwent percutaneous closure?

8. Should transcranial Doppler vs. transthoracic contrast echocardiography be used to diagnose PFO patency in patients who underwent percutaneous closure?

9. Should transoesophageal contrast-echocardiography vs. transthoracic contrast echocardiography be used to diagnose PFO patency in patients who underwent percutaneous closure?

10. Should percutaneous closure of PFO vs. medical therapy be used for secondary prevention of stroke or left-circulation thromboembolism? **(PICO question)**

11. Should oral anticoagulants (OAC) vs. antiplatelet therapy be used for secondary prevention of stroke or other left-circulation thromboembolism? **(PICO question)**

12. Should percutaneous closure of PFO vs. medical therapy be used for pregnant women with indication to secondary prevention of stroke or other left-circulation thromboembolism?

13. Should primary prevention vs. no prevention measures be used in patients with PFO and very high risk of paradoxical embolisation or cryptogenic ischaemic stroke?

14. Should percutaneous closure of PFO vs. diving avoidance be used for secondary prevention of decompression sickness in professional divers?

15. Should percutaneous closure of PFO vs. diving avoidance be used for secondary prevention of decompression sickness in recreational divers?

16. Should percutaneous closure of PFO vs. flying avoidance be used for secondary prevention of decompression sickness or asymptomatic embolisation in airplane pilots?

17. Should percutaneous closure of PFO vs. diving avoidance be used for primary prevention of decompression sickness in professional divers?

18. Should percutaneous closure of PFO vs. diving avoidance be used for primary prevention of decompression sickness in recreational divers?

19. Should percutaneous closure of PFO vs. flying avoidance be used for primary prevention of decompression sickness in airplane pilots?

20. Should percutaneous closure of PFO vs. medical therapy be used for platypnoea-orthodeoxia syndrome?

21. Should percutaneous closure of PFO + medical therapy vs. medical therapy alone be used for migraine with aura?

22. Should percutaneous closure of PFO vs. no therapy alone be used in patients scheduled for surgery in the sitting position?

GRADING OF OUTCOMES FOR THE POSITION STATEMENTS

Position statements were expressed evaluating the relevant outcomes in each particular setting. Before the systematic literature reviews, task force members formally defined outcomes for each questions using Delphi rounds and successively, with an online poll, graded their importance for making a decision regarding the position statements. Outcomes were graded as: critical, important but not critical or of limited importance for decision making. Grading was performed by each member of the task force rating each outcome numerically on a 1 to 9 scale (7 to 9 – critical; 4 to 6 – important; 1 to 3 – of limited importance). The final grading of outcomes was the average of the individual grading. If for a question, no outcome reached an average rate ≥ 7, we considered critical for decision making those items that had the highest prevalence of individual scores ≥ 7 in the poll. If some outcomes had more than four votes ≤3, the item was ranked as of limited importance for expressing a position. When, comparing similar questions, the poll vote resulted to be inconsistent, the most reliable vote was considered.

After the evidence review was performed, a reassessment of importance was necessary. **Supplementary Table 13** summarise the final grading of outcomes used for this position document.

LITERATURE SEARCH QUERIES

1. Should analytical risk factors (clinical or anatomical) be used to diagnose causal or high-risk PFO in cryptogenic stroke or other left-circulation thromboembolism?

((pfo) OR (patent foramen ovale)) and ((risk factor) OR (aneurysm) OR (septal pouch) OR (deep vein thrombosis)) and ((stroke) OR (transient ischaemic attack) OR (TIA) OR (migraine) or (embolism)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

2. Should ROPE score be used to diagnose causal or high-risk PFO in cryptogenic stroke?

((pfo) OR (patent foramen ovale)) and ((risk factor) OR (aneurysm) OR (septal pouch) OR (deep vein thrombosis)) and ((stroke) OR (transient ischaemic attack) OR (TIA) OR (migraine) or (embolism)) and ((score) or (ROPE)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

3. Should insertable cardiac long-term monitoring be used to diagnose atrial fibrillation in patients with PFO-associated ischaemic cryptogenic stroke or other left-circulation thromboembolism?

((pfo) OR (patent foramen ovale)) and ((ischaemic) OR (cryptogenic) OR (stroke) or (TIA) or (transient ischaemic attack) or (embolism) or (migraine)) and ((atrial fibrillation) or (AF) or (asymptomatic) OR (loop recorder) or (ILR) OR (insertable cardiac long-term monitoring)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

4. Should transcranial Doppler with bubble test vs. transthoracic contrast echography be used to diagnose PFO in suspected PFO-associated clinical syndromes?

((pfo) OR (patent foramen ovale)) and ((ischaemic) OR (cryptogenic) OR (stroke) or (TIA) or (transient ischaemic attack) or (embolism) or (migraine)) and ((transcranial Doppler) or (bubble) or (transthoracic contrast echography) or (echocardiography)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

5. Should transoesophageal contrast-echocardiography vs. transthoracic contrast echocardiography be used to diagnose PFO in suspected PFO-associated clinical syndromes?

((pfo) OR (patent foramen ovale)) and ((ischaemic) OR (cryptogenic) OR (stroke) or (TIA) or (transient ischaemic attack) or (embolism) or (migraine)) and ((transcranial Doppler) or (bubble) or (transthoracic contrast echography) or (echocardiography)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

6. Should transcranial Doppler vs transoesophageal contrast-echocardiography be used to diagnose PFO in suspected PFO-associated clinical syndromes?

((pfo) OR (patent foramen ovale)) and ((ischaemic) OR (cryptogenic) OR (stroke) or (TIA) or (transient ischaemic attack) or (embolism) or (migraine)) and ((transcranial Doppler) or (bubble) or (transthoracic contrast echography) or (echocardiography)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

7. Should transcranial Doppler vs transoesophageal contrast-echocardiography be used to diagnose PFO patency in patients who underwent percutaneous closure?

((pfo) OR (patent foramen ovale) OR (patency)) AND ((closure) OR (percutaneous) or (Amplatzer) OR (Watchman) OR (device) OR (Cardioseal/STARFlex) OR (Helix)) and ((ischaemic) OR (cryptogenic) OR (stroke) OR (TIA) OR (transient ischaemic attack) OR (migraine) or (embolism)) and ((transcranial Doppler) OR (bubble) OR (transthoracic contrast echography) OR (echocardiography) OR (trans oesophageal)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

8. Should transcranial Doppler vs. transthoracic contrast echocardiography be used to diagnose PFO patency in patients who underwent percutaneous closure?

((pfo) OR (patent foramen ovale) OR (patency)) AND ((closure) OR (percutaneous) or (Amplatzer) OR (Watchman) OR (device) OR (Cardioseal/STARFlex) OR (Helex)) and ((ischaemic) OR (cryptogenic) OR (stroke) OR (TIA) OR (transient ischaemic attack) OR (migraine) or (embolism)) and ((transcranial Doppler) OR (bubble) OR (transthoracic contrast echography) OR (echocardiography) OR (trans oesophageal)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

9. Should transoesophageal contrast-echocardiography vs. transthoracic contrast echocardiography be used to diagnose PFO patency in patients who underwent percutaneous closure?

((pfo) OR (patent foramen ovale) OR (patency)) AND ((closure) OR (percutaneous) or (Amplatzer) OR (Watchman) OR (device) OR (Cardioseal/STARFlex) OR (Helex)) and ((ischaemic) OR (cryptogenic) OR (stroke) OR (TIA) OR (transient ischaemic attack) OR (migraine) or (embolism)) and ((transcranial Doppler) OR (bubble) OR (transthoracic contrast echography) OR (echocardiography) OR (trans oesophageal)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

10. Should percutaneous closure of PFO vs. medical therapy be used for secondary prevention of stroke or other left-circulation thromboembolism?

((pfo) OR (patent foramen ovale)) AND ((closure) OR (percutaneous) or (Amplatzer) OR (Watchman) OR (device) OR (Cardioseal/STARFlex) OR (Helex)) and ((ischaemic) OR (cryptogenic) OR (stroke) OR (TIA) OR (transient ischaemic attack) OR (embolism)) and ((medical) or (drug) or (aspirin) or (clopidogrel) or (warfarin) or (antiplatelet) or (anticoagulation)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

11. Should oral anticoagulants (OAC) vs. antiplatelet therapy be used for secondary prevention of stroke or other left-circulation thromboembolism?

((pfo) OR (patent foramen ovale)) AND ((ischaemic) OR (cryptogenic) OR (stroke) OR (TIA) OR (transient ischaemic attack) OR (embolism)) and ((medical) or (drug) or (aspirin) or (clopidogrel) or (warfarin) or (antiplatelet) or (anticoagulation)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

12. Should percutaneous closure of PFO vs. medical therapy be used for pregnant women with indication to secondary prevention for left circulation embolism?
((pregnancy) OR (pregnant) OR (postpartum) OR (caesarean)) and ((pfo) OR (patent foramen ovale)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

13. Should primary prevention vs. no prevention measures be used in patients with PFO and very high risk of paradoxical embolisation or cryptogenic ischaemic stroke?
((primary prevention) or (primary) or (asymptomatic)) and ((pfo) OR (patent foramen ovale)) AND ((closure) OR (percutaneous) or (Amplatzer) OR (Watchman) OR (device) OR (Cardioseal/STARFlex) OR (Helex)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

14. Should percutaneous closure of PFO vs. diving avoidance be used for secondary prevention of decompression sickness in professional divers?
((decompression) or (sickness) or (professional) or (recreational) or (amateur) or (divers) or (diver) or (scuba diving)) and ((pfo) OR (patent foramen ovale)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

15. Should percutaneous closure of PFO vs. diving avoidance be used for secondary prevention of decompression sickness in recreational divers?
((decompression) or (sickness) or (professional) or (recreational) or (amateur) or (divers) or (diver) or (scuba diving)) and ((pfo) OR (patent foramen ovale)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

16. Should percutaneous closure of PFO vs. flying avoidance be used for secondary prevention of decompression sickness or asymptomatic embolisation in airplane pilots?
((decompression) or (sickness) or (airplane) or (pilot) or (fighter)) and ((pfo) OR (patent foramen ovale)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

17. Should percutaneous closure of PFO vs. diving avoidance be used for primary prevention in professional divers?
((decompression) or (sickness) or (airplane) or (pilot) or (fighter)) and ((pfo) OR (patent foramen ovale)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

18. Should percutaneous closure of PFO vs. diving avoidance be used for primary prevention in recreational divers?
(decompression) or (sickness) or (professional) or (recreational) or (amateur) or (divers) or (diver) or (scuba diving)) and ((pfo) OR (patent foramen ovale)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

19. Should percutaneous closure of PFO vs. flying avoidance be used for primary prevention in airplane pilots?
((decompression) or (sickness) or (airplane) or (pilot) or (fighter)) and ((pfo) OR (patent foramen ovale)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

20. Should percutaneous closure of PFO vs. medical therapy be used for platypnea-orthodeoxia syndrome?

((platypnea) OR (orthodeoxia) or (platypnea-orthodeoxia syndrome)) and ((pfo) OR (patent foramen ovale)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

21. Should percutaneous closure of PFO + medical therapy vs. medical therapy alone be used for migraine with aura?

(migraine) and ((pfo) OR (patent foramen ovale)) AND ((closure) OR (percutaneous) or (Amplatzer) OR (Watchman) OR (device) OR (Cardioseal/STARFlex) OR (Helex)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

22. Should percutaneous closure of PFO vs. no therapy be used in patients scheduled for surgery in the sitting position?

((sitting) or (sitting position) or (semisitting position)) and ((pfo) OR (patent foramen ovale)) NOT ((review[pt] OR editorial[pt] OR letter[pt]))

Supplementary Appendix 2. Statistical methods.

Continuous variables are reported as mean (standard deviation) or median (range). Categorical variables are expressed as n/N (%). In order to support the expression of position statements, 4 original meta-analyses were performed for PICO questions and for the accuracy of diagnostic tests for PFO. A meta-regression for assessing the impact on outcomes of the length of dual antiplatelet therapy after closure was also performed. Further details are provided in **Supplementary Appendix 3.**

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

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

Meta-analysis of studies on diagnostic tests accuracy

Based on the frequencies of true-positive, false-positive, true-negative, and false-negative results in the individual studies, the pooled sensitivity, specificity, and area under the summary receiver operating curve (sROC) were estimated for TCD and TTE (vs TEE, which was treated as the gold standard procedure) [174,175]. The area under the sROC values were compared between TCD and TTE using the appropriate z tests. All statistical analyses were performed with Review Manager (RevMan) version 5.3 software (Copenhagen, Denmark, Nordic Cochrane Centre, Cochrane Collaboration, 2014) and STATA/SE version 13 (Stata Corp, College Station, TX). Pooled analysis of sensitivity, specificity and AUC was performed with Meta Disc (version 1.42).

Evaluation of risk predictors

Risk estimates were not pooled from individual studies as this approach would have been not feasible and valid given the likelihood of small study effects. We instead adopted Ross et al. approach [176] and appraised the prevalence of studies in which a given predictor proved significantly and independently associated with the outcome of interest in at least 2 studies.

Supplementary Appendix 3. Systematic review of evidence, assessment of its quality and meta-analyses.

A systematic review of evidence was performed for each question. **Supplementary Figure 6**, **Supplementary Figure 15**, **Supplementary Figure 16, Supplementary Figure 17, Supplementary Figure 18, Supplementary Figure 19, Supplementary Figure 20,** display PRISMA diagrams of the selection of the main searches. PRISMA diagrams were not produced for the questions that yielded a low number of publications.

High quality evidence is generally lacking in PFO-associated syndromes. An evaluation of the quality of evidence was formally performed with GRADE method for: all the meta-analyses that have been performed for the aims of this document and for the studies addressing internal ROPE score validation (**Supplementary Table 3**).

We performed two original meta-analyses for supporting decisions on each PICO question and a meta-regression of RCTs aimed at assessing the effects of the length of dual antiplatelet therapy after closure on stroke and TIA recurrence. We also performed two meta-analyses aimed at assessing accuracy of testing: a) Transcranial Doppler with bubble test vs. Transoesophageal contrast-echocardiography in the diagnosis of PFO and b) Transthoracic contrast-echocardiography vs. Transoesophageal contrast-echocardiography in the diagnosis of PFO.

Supplementary Figure 17 and **Supplementary Table 10** respectively display the PRISMA diagram and the GRADE evaluation of the quality of evidence of the studies included in the meta-analysis comparing PFO closure with medical therapies for secondary prevention of stroke, TIA or other left-circulation thromboembolism in patients with previous cryptogenic left embolism.

Supplementary Figure 18 and **Supplementary Table 11** respectively display the PRISMA diagram and the GRADE evaluation of the quality of evidence of the meta-analysis of the studies comparing OAC with antiplatelet for secondary prevention of stroke, TIA or other left-circulation thromboembolism in patients with previous cryptogenic left embolism.

Supplementary Figure 19 and **Supplementary Figure 20** display the PRISMA diagram of the meta-analysis of the studies investigating the accuracy of PFO diagnostic tests. Supplementary Table 2 displays the GRADE evaluation of the quality of evidence included in the meta-analysis of the same studies.
The main results of these meta-analyses are displayed in the published text.

Supplementary Appendix 4. Detailed evaluation of specific issues.

The issue of complexity in PFO related syndromes

Even though its causal involvement in several diseases has been well-documented, the role of PFO in most causal mechanisms remains intrinsically elusive. Two reasons for this are: a) because it can only be presumed in most cases as its causal role is often transient and the medical observation is delayed; and b) because of the "statistical noise" that is caused by the high prevalence of PFO in the general population and competing causes. Moreover, some of the candidate PFO-associated clinical syndromes (e.g., decompression sickness and transient ischaemic attacks) are themselves difficult to diagnose, which increases the probabilistic nature of the argument.

Additionally, PFO is not simply a yes or no condition, and different anatomical variations and degrees of patency might interfere with its causative role, thereby multiplying the possible phenotypes. To this, one must add the fact that the anatomical characteristics of any PFO can vary according to changing clinical and physiological conditions (e.g., a PFO can be more or less open depending on atrial pressure). As such, existing diagnostic procedures might not be reliable or reproducible enough to assess the value and role of the dynamic features of PFO in all its possible configurations (see "diagnosing PFO" paragraph in the published text). Furthermore, as demonstrated by the accrued literature cited in this paper, clinical classifications lump together populations of patients who are, in actuality, very heterogeneous from pathophysiological, prognostic and therapeutic points of view. Indeed, the complex interacting network of processes underlying clinical manifestations varies considerably between individuals, as well as within the same person over the course of time, thereby masking the role of each individual node in studies performed on large numbers of patients which are insufficiently characterised [1,2,112] (**Supplementary Figure 21**).

All of these characteristics, some improvable (i.e., due to imperfect knowledge or technology) and others not (i.e., intrinsic factors), upsurge exponentially the incertitude of the system, and explain why randomised studies performed in such patients have often yielded conflicting results [1] rendering assessments of the role of PFO a complex paradigm in medicine. This complexity has important consequences because complex systems are highly non-linear and cannot be addressed with classic deterministic approaches [177]. A breakthrough is therefore warranted to define new classifications of patients with similar clinical characteristics, prognosis, and therapeutic needs in a non-deterministic environment. Systems science and precision medicine approaches are the major candidates to address these issues, because they have the potential to guide decisions at the individual patient level [4,178].
While awaiting fresh systems medicine evidence-guiding decisions, individuals suffering from candidate PFO-associated syndromes need to be approached within a multidisciplinary framework, wherein shared decision making becomes essential.

Further details on diagnostic accuracy studies

Contrast transoesophageal echocardiography (c-TOE) has a lower sensitivity than previously believed. A meta-analysis on this topic is discussed in the main text. This is confirmed by other studies [179–192], which

show a marked underestimation of the prevalence of PFO compared with historical autopsy studies [193–203] (**Supplementary Figure 1**). This relatively high false negative result may influence the prediction of recurrence related to the assessment of post-procedural shunt [96,139] and may in part explain the inconsistent results of epidemiological studies [183].

Nonetheless, three-dimensional TOE is an ideal technique to understand the anatomy of the interatrial septum and guide the interventional procedure [52].

Additionally, we performed an updated meta-analysis of 29 studies comparing contrast-enhanced transcranial Doppler (c-TCD) with c-TOE across 2751 patients (**Supplementary Appendix 3**) [44,126,147,204–230] and an original meta-analysis of 13 studies across 1360 patients comparing contrast-enhanced transthoracic echocardiography (c-TTE) against c-TOE (**Supplementary Appendix 3**) [189,216,218,229,231–239]. Results are discussed in the published text.

In a previous meta-analysis of 27 studies with 1,968 patients, the weighted mean sensitivity and specificity for contrast-enhanced transcranial Doppler (c-TCD) in detecting right-to-left shunts, as compared to c-TOE, were 97% (95% CI: 94%-98%) and 93% (95% CI: 86%-97%), respectively. However, when the threshold for a positive shunt was increased from 1 high-intensity transient signal (HITS) to 10 HITS, c-TCD specificity was increased to 100% without affecting sensitivity [54].

A recent meta-analysis of 35 studies comparing c-TCD and c-TTE to c-TOE in 3067 patients also showed a superior overall diagnostic yield of c-TCD compared to that of c-TTE. In this study the AUC was significantly greater ($p < 0.001$) in c-TCD (AUC = 0.98, 95% CI = 0.97-0.99) compared to c-TTE studies (AUC = 0.86, 95% CI = 0.82-0.89), with a a higher sensitivity and lower specificity of c-TCD as compared to c-TTE [55].

Is PFO associated with cryptogenic stroke? What are the underlying processes?

Clinical studies supporting a key role for PFO in paradoxical embolisation.

In one study that involved over 205,000 subjects, after either deep vein thrombosis or pulmonary artery embolism, the relative risk (RR) of stroke during the first year in patients with PFO increased 2.2-fold and 2.9-fold respectively, relative to patients without a PFO [14]. Another study identified a greater proportion of pelvic deep vein thrombosis in patients with cryptogenic stroke and PFO than in patients with stroke of determined reason [15]; while an additional study showed that the presence of a PFO was associated with diffusion-weighted MRI-detected silent strokes in patients with recent pulmonary embolism [18].

Clinical studies supporting different pathophysiologic processes in PFO-associated embolism.

Pathogenic processes attributable to PFO presence include: paradoxical embolism [240]; thrombus forming within the PFO [96,241]; left atrial dysfunction [242]; and atrial arrhythmias [56,243–245]. Indeed, prevalence rates of atrial arrhythmias ranging from 1% to 10% were reported in a meta-analysis of a small number of prospective observational and retrospective studies that were conducted in candidates for percutaneous closure of PFO [137]; while new-onset atrial fibrillation following transcatheter percutaneous closure, in rates ranging from 0.5% to 15%, has been detected in other studies [106–111]. Therefore, at least

in some patients, pre-existing misdiagnosed AF may become clinically evident only after PFO closure, possibly unmasked by the irritating local stimuli of the device [111,246] .

IS IT CLINICALLY POSSIBLE TO ESTIMATE THE PROBABILITY OF A CAUSAL RELATIONSHIP BETWEEN A PFO AND STROKE?

Patient characteristics

Although observed in patients of almost any age [13], in a meta-analysis of 23 case-control studies examining the prevalence of PFO in patients with cryptogenic stroke versus controls with a stroke of known cause, the OR for younger (< 55 years) and older patients (≥ 55 years) were 5.1 (3.3 to 7.8) and 2.0 (>1.0 to 3.7), respectively [56]. However, despite the comorbidities, in older patients the association is still observed, perhaps due to the increasing prevalence of venous clots or to the increasing size of PFO with age [13,57]. Some meta-analyses of RCTs not including DEFENSE-PFO trial suggest that younger age and male gender may be associated to a more probable causal role of PFO [78,79,90], however this was not found by another meta-analysis [171].

During their patient-level meta-analysis of observational cohorts of cryptogenic stroke patients, the RoPE (Risk of Paradoxical Embolism) group [59] found that patients who were younger; who did not have hypertension, diabetes, smoking, or a prior stroke or TIA; and who had a cortical stroke on neuroimaging were more likely to have a PFO and, thus, had a higher likelihood that the index event was related to a PFO rather than to other causes.

Imaging stroke pattern

Cortical ischaemic lesions, whether symptomatic or asymptomatic, suggest probable embolisation even when they are small [59]. However, deep white matter lesions can also be embolic [60,62,63], even though they are more likely due to lipohyalinosis [247]. Indeed, in a recent patient-level meta-analysis of randomised clinical trials (RCT) comparing percutaneous closure of PFO and medical therapy, patients with non-cortical infarcts had a lower rate of recurrence after PFO closure than those on medical therapy, suggesting an embolic origin of the index event [70].

No pattern in grey or white matter has been specifically observed in PFO-associated strokes [61,64–69], though a single study identified an inverse relationship between PFO size and number of brain lesions observed on MRI and a direct relationship between PFO size and infarct volume [77].
An embolisation pattern in the posterior circulation has been described in PFO-associated strokes in retrospective studies [248–250]. However, another report did not find any topographical association with PFO-associated embolisms [61].
Taken together, these data again indicate the heterogeneity of the underlying pathophysiologic processes in PFO-caused strokes. No studies have been performed regarding imaging patterns of PFO-associated non-cerebral cryptogenic embolism.

Characteristics of the PFO

The association between PFO and cryptogenic stroke has been reported to be stronger in patients who have an atrial septal aneurysm (ASA) in addition to a PFO (with odds ratios as high as 33.3) [71–73,91]. However, in one study, the risk of recurrent stroke or TIA at four years of follow-up was 0% in patients with an ASA but no PFO; 5.6% in patients with a PFO alone; and 19.2% in patients with both a PFO and ASA [72]. Given that other studies have shown that the extent of the interatrial septum deviation correlates with the anatomical size of a PFO [251,252], it is possible that a statistical interaction exist between ASA and the size of the associated PFO and its aggregated time of gaping. Indeed, several studies have found that patients with a more severe right-to-left shunt, a larger PFO opening, or the presence of right-to-left shunting at rest are more likely to have had a cryptogenic stroke than controls lacking these [64,76,208,253–256].

Consistently, the recent interventional sub-study of the CLOSE trial performed in patients with an ASA or a severe shunt showed that the closure of the PFO resulted in a statistically significant higher reduction of stroke recurrences as compared to medical therapy [27]. The DEFENSE-PFO trial, performed in patients with ASA or a severe shunt or a wide PFO opening or a interatrial septal hyper-mobility, also showed similar outcomes [29]. Supplementary to this observation, also subgroup analysis of long term RESPECT study results showed that patients with ASA or a larger shunt had a greater risk reduction with PFO closure [28]. Moreover, patients with a moderate-to-severe shunt were more likely to experience better outcomes with percutaneous closure of PFO as compared to medical therapy alone in all meta-analyses of RCTs not including DEFENSE-PFO study, suggesting a more probable causal PFO in these patients [78,79,90,122,170,171].

However, as expected in heterogeneous patient populations, other studies have failed to detect these associations, while others have shown that even small PFO can be causative, likely with different underlying processes than large ones [59,77], stressing the need for multi-parametric risk stratification and phenotypisation of patients.

The presence of anatomic atrial variants (e.g., a Eustachian valve or Chiari network) that can promote flow from the inferior vena cava toward the PFO may favour the persistence of a patent foramen ovale and the formation of an atrial septal aneurysm, thereby facilitating paradoxical emboli [75]. A long PFO tunnel has also been linked to increased stroke risk in retrospective studies [76]

Clinical clues

Documentation of a venous source of embolism is a key criterion for a presumed diagnosis of paradoxical embolism; but one first needs to exclude the possibility that the venous thrombosis is secondary to the immobilisation that often results after the embolism becomes clinically manifest. The search for venous thrombosis is often negative [80,82,83], though this may be due to an inability to detect small venous clots [15]. Several acquired and hereditary pro-thrombotic states increase the risk of deep vein thrombosis [257] (**Supplementary Table 13**) and may translate into a higher risk of PFO-associated emboli. Studies that have attempted to identify an association between inherited thrombophilia and PFO-related stroke have yielded conflicting results [87–89,258]. Indeed, in one meta-analysis, a significant association was identified

between factor II G20210A and PFO-related stroke [OR 3.9; (95% CI 2.2 to 6.7) relative to those patients without a PFO (2.3; 95% CI 1.2 to 4.4) [87], but a more recent study failed to confirm this finding [88]. Moreover, in a study by Pezzini et al., patients having either the factor V Leiden (G1691A) mutation or the prothrombin G20210A variant exhibited an odds ratio for stroke of 1.98 versus controls [87]. Another study failed to detect a significantly-increased risk of cerebrovascular events in subjects with the combined presence of elevated antiphospholipid antibodies levels and a PFO [89].

Simultaneous occurrence of symptomatic or asymptomatic pulmonary and left circulation emboli should strongly indicate paradoxical embolism, [18,80] while a history of previous single or recurrent pulmonary embolism can support a paradoxical mechanism with recurrent clinical or asymptomatic cryptogenic embolisms [81].

Circumstances that predispose someone to DVT — like an immobilising injury/surgery or an extended automobile or airplane ride — or activities that promote paradoxical embolism — like straining to defecate, heavy lifting, and other activities associated with a Valsalva manoeuvre immediately prior to stroke onset, strengthen the hypothesis that a given stroke is due to paradoxical embolism and should be investigated further. With a similar mechanism, also obstructive sleep apnea can cause a paradoxical embolism and this possibility should be enquired for in case of cryptogenic stroke-on-awakening [84]. However, it is not clear whether these predisposing factors are more frequent in cryptogenic stroke patients with than without a PFO [81,85].

Clinical risk scores

The RoPE score represents an attempt to assign a causal relationship probability to individual PFOs, based on the assumption that identifying subjects with similar characteristics to subgroups in which a PFO was found to be more prevalent implies a greater probability of causation [59]. Variables associated with a PFO in cryptogenic stroke patients included younger age, the presence of a cortical stroke, and the absence of diabetes, hypertension, smoking, or a prior stroke or TIA. RoPE developers incorporated these factors into the 10-point RoPE score, whereby the higher the score (i.e., the fewer atherosclerotic vascular risk factors a given patient has), the more likely it is that the patient has a PFO, with a cut-off of more than 6 points on a 10-point scale indicating a higher probability of association between PFO and the stroke [59]. However, external validation studies still are to be published; and even the imprecision of internal validation studies has been judged severely (**Supplementary Table 3**). Moreover, paradoxically, a higher causation probability of a PFO as assessed by the RoPE score seem to be associated to a lower rate of recurrence [59], which is in contrast to the findings of the most recent randomised studies.

RISK OF RECURRENCE IN PFO-ASSOCIATED STROKE

Risk of recurrence is a pivotal factor to consider during decision making in patients with a PFO-associated stroke. One meta-analysis that incorporated one RCT, three case-control studies, and 11 case series, identified a rate of recurrent stroke or TIA of four events per 100 patient-years (95% CI 3.0–5.1) and a rate

of recurrent stroke of 1.6 events per 100 patient-years (95% CI 1.1–2.1), while the pooled absolute rate of recurrent ischaemic stroke or TIA was 4.0 events per 100 person-years overall [91]. However, in different studies, these figures ranged 0 to 4.4% for stroke and 0 to 14% for either TIA or stroke [259], emphasising the heterogeneity of the risk and of the characteristics of patients in these populations, and the need to discriminate between them.
In another meta-analysis that assessed 14 observational studies encompassing 4251 patients, cryptogenic stroke patients with a PFO exhibited no increased risk either of recurrent stroke alone of either stroke or TIA recurrence, when compared to cryptogenic stroke patients without a PFO [95]. The finding that cryptogenic stroke patients with and without a PFO have similar rates of stroke seems odd, but might just reflect that, in patients without a PFO, other occult causes of stroke might similarly increase the risk of recurrence [92].

A few studies have examined the aetiology of recurrent cerebrovascular events in PFO patients [93,94]. One important finding is that an alternative cause of stroke (e.g., large artery disease, small artery disease, cardio-embolism, other causes), unrelated to PFO, was identified in many patients with recurrent stroke. This finding does not exclude PFO as causal for the first (or recurrent) episode but shows that the causes of recurrence may change over time, adding a dynamic pattern to the complexity of the overall picture. In particular, in the CLOSURE 1 trial [94], in both arms of the study an aetiological alternative to paradoxical embolism was frequently (37%) responsible for recurrent events.

The systematic review of literature revealed that few specific predictors of stroke recurrence in patients with a PFO have been identified. A PRISMA diagram of the selection process in the literature review to obtain these studies is displayed in **Supplementary Figure 6**. Some features were found to be statistically-significant predictors in at least two studies (Table 3 in the published text). ASA seems to have a particular role with this respect. In the RoPE database, septal hypermobility was a significant predictor of stroke recurrence [97]. In the PFO-ASA study, cryptogenic stroke patients with both PFO and an atrial septal aneurism (ASA) were more likely to have a recurrent stroke than cryptogenic stroke patients without a PFO. The risk of recurrent stroke in this group was four times higher than in patients with no PFO, but the confidence interval for this estimate was large[72]. Moreover, two meta-analyses not including DEFENSE-PFO study, suggest that the subgroup patients with ASA had a greater risk reduction with PFO closure than patients without these characteristics, hence supporting the role of ASA in stroke recurrences [170,171].

With regards to the size of the PFO, all studies that have examined this potential predictive factor have found that cryptogenic stroke patients with small and large shunts have roughly equivalent stroke recurrence rates [72,95,96], though this may reflect the unreliability of transoesophageal echocardiography in the prediction of future events [96]. Indeed, the subgroup analysis of the randomised controlled trial RESPECT, supported large shunts to be associated with more frequent stroke recurrences [28]. However, unexpectedly, in the RoPE database [97] a small shunt was a significant predictor of stroke recurrence in patients who had a high probability that their PFO was stroke-related rather than an incidental finding.

DIAGNOSTIC WORKUP

The diagnostic process must begin with a clinical assessment, based upon the clinical presentation or the organ involved, as well as organ-specific and appropriate vessel imaging (colour-Doppler ultrasound, CT or MRI angiography, or invasive angiography). Additional clinical assessments and imaging can be performed to detect sub-clinical embolism in other organs, including pulmonary scans or scintigraphy, organ-specific CT scans or abdominal sonography (e.g., spleen or kidney).
Whatever the embolism site, thorough transthoracic echocardiographic and neurological evaluation should be performed.

In cases involving a cerebrovascular accident, an accurate neurological evaluation is required to differentiate a TIA from syncope, peripheral vertigo, or transient focal deficits, such as those that may occur after a seizure or associated with a migraine attack. Most TIAs persist less than one hour.

Assessing asymptomatic paroxysmal AF

Paroxysmal AF occurs without specific symptoms in the vast majority of patients with cryptogenic stroke [102] and is under-detected after spontaneous resolution [99]. Randomised and observational studies performed using insertable cardiac monitors [99–102] and external ECG monitoring [260,261] have consistently demonstrated that prolonged monitoring and the selection of high-risk populations increases AF detection in cryptogenic stroke, albeit at highly variable rates [164]. A systematic review of all the studies conducted on detection of AF after ischaemic stroke or transient ischaemic attack with various monitoring systems (inpatient cardiac monitoring, 24-hours, 48-hours and 72-hours Holter, external loop recorder, mobile cardiac outpatient telemonitoring) demonstrated a highly variable rate of AF detection with considerable heterogeneity among studies [260]. However, in this meta-analysis, a prolonged non-invasive monitoring (>24 hours) increased yield of AF detection in patients with cryptogenic stroke and old age. These data were confirmed by the randomised controlled trial Embrace, assessing the detection of AF with external ECG monitoring in cryptogenic stroke [261]. Based on these data, the selection of candidates for ICM monitoring based on risk factors for AF has been proposed, leading to silent AF detection in up to 35% of patients at six months and 46% at a median follow-up of 14.5 months [262,263].

Given that, in the Cristal AF study, the insertable cardiac monitor (ICM) removal rate was 2.4%, due to infection at the insertion site or pocket erosion, while the number of implanted ICM needed to detect a first episode of AF was 14 over six months of monitoring, 10 over 12 months, and four over 36 months, an ICM-based rule-out protocol of paroxysmal AF is a reasonable option in selected high-risk patients after a cryptogenic stroke. Patients may be considered at high risk if: ≥55 years old, given the very low incidence of AF in patients <55 years old in large cohorts [173,264]; or with an history of prior cortical or cerebellar infarction on neuroimaging and a CHADS2 or CHA2DS2-VASc score > 1 [100,101,265]. However, the CHA2DS2-VASc score was designed for stroke prediction in AF patients rather than for AF risk prediction, but four of its six individual items have been repeatedly identified as strongly associated with AF, therefore they can also be considered high risk markers: congestive heart failure [266,267], hypertension [268], advanced patient age [101,265,266], and diabetes mellitus [267,269]. Furthermore, also frequent atrial runs

and left atrial dilation are known predictors of AF in patients with cryptogenic stroke [101,266,270,271]. Finally, left ventricular hypertrophy, pulmonary or thyroid disease, and obesity are also associated with an increased AF risk [272] and can be considered high risk features. Likely, the same considerations apply to any form of left-circulation thromboembolism.

Evaluating the need for anticoagulants in AF

The higher sensitivity of extensive monitoring poses the question that the detection of extremely brief harbinger episodes alone may be less critical. Indeed, in a recent meta-analysis involving 1149 patients across four randomised studies, despite the higher recognition rate of 30-second AF episodes with monitoring prolonged over six days versus ≤ 48 hours, the outcomes of patients in the two groups were similar [164]. In the Mode Selection Trial (MOST), high-rate atrial arrhythmic episodes lasting at least five minutes predicted a higher incidence of the composite outcome of death or nonfatal stroke [165]. In the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT), an episode of high-rate atrial arrhythmia lasting more than six minutes conferred a relative risk of 2.5 for subsequent ischaemic stroke or systemic embolism. A higher AF threshold duration, as indicated by the SOS-AF study (1 hour), TRENDS trial (5.5 hours), and AT500 Registry (24 hours), may be inappropriate for secondary stroke prevention [166–168]. Patients with cryptogenic stroke and PFO, and having a pre-stroke CHA2DS2-VASc score >1, are a cohort at elevated risk of atrial fibrillation recurrence. Therefore, the relevance of transient episodes of AF may be greater in this group than AF detected incidentally in patients without a prior stroke. The ICM-detected arrhythmia duration may be combined with the baseline CHADS2 score to evaluate the risk of thromboembolic events. In patients with a CHADS2 score ≥2, AF episodes lasting more than five minutes appear to significantly increase the risk of stroke [169].

ADDITIONAL INSIGHTS ON EFFICACY AND SAFETY OF MEDICAL THERAPIES

Contemporary medical treatments are based upon the extrapolation of data from secondary prevention studies for stroke at large, from studies on cryptogenic stroke at large, or from their sub-group analysis. In the different studies that have been published, medical therapy has always been heterogeneous, even within each study. In most studies, the oral anticoagulants (OAC) used have consisted of vitamin K inhibitors while direct oral anticoagulants (DOAC) were also allowed in CLOSE trial. Antiplatelet therapy has also been very variable, consisting of acetylsalicylic acid, clopidogrel, and extended-release dipyridamole, alone or in different combinations, and sometimes in conjunction with OAC.

Prior to the publication of CLOSE, REDUCE and DEFENSE-PFO trials, one meta-analysis of randomised trials, comparing a mixed medical therapy to the percutaneous closure of PFO, identified in its medical therapy arm a pooled incidence of primary endpoints of 1.8 events per 100 patients/year (95% CI, 0.7-2.9) [273].

In the individual trials assessed in these meta-analyses, the event rate of stroke, TIA, peripheral embolism, and/or death ranged between 2.5% (OAC) in the RESPECT trial [131] and 7.9% (acetylsalicylic acid) in the

CLOSURE I study [274]. In a meta-analysis of observational trials, mixed medical therapy yielded a pooled incidence rate of recurrent neurological events of 5.0 per 100 person-years (95% CI: 3.6 to 6.9) [113]. One of the last, comprehesive, meta-analyses of RCTs reported a stroke incidence of 1.27 events per 100 patients/year (95% CI, 0.84–1.78)[74].

Only one recent randomised sub-study, part of a larger one, has compared the use of OAC (vitamin K inhibitors or DOAC) and antiplatelet therapy (acetylsalicylic acid, clopidogrel or a combination of acetylsalicylic acid+dipyridamole) in 361 patients with cryptogenic stroke with a large PFO and/or an atrial septal aneurism showing, after an average 5 years of follow-up, a statistically non-significant lower incidence of stroke in patients receiving OAC as compared to those who received antiplatelet therapy [1.6% vs 4.0%, respectively; p=0.21; OR=0.34 (95% CI: 0.10 to 1.53)] [27].

Five meta-analyses, not including CLOSE trial, have been published to date comparing antiplatelet therapy and OAC for PFO-associated cryptogenic strokes. Four study-level meta-analyses (the first three involving observational studies only and the last one both observational and randomised studies not comparing directly OAC and antiplatelet therapy), incorporating up to 3311 patients, consistently found a statistically-significant advantage of OAC over antiplatelet therapy, including an OR = 0.37 for stroke or TIA (95% CI: 0.23 to 0.60) [114], an incidence rate ratio of 0.42 (95% CI, 0.18–0.98) for stroke and/or TIA [115], a relative risk of pooled recurrent neurological events of 0.58 (95% CI: 0.41 to 0.82) [113], and event rates for stroke and/or TIA at or beyond 12 months of 7.7% versus 9.8%, respectively, p = 0.03 [116]. In a patient-level meta-analysis of 12 databases and 2385 patients not including CLOSE trial, a point estimate of the reduction of strokes, TIAs or death and stroke alone was noted with OAC of approximately 25% as compared to antiplatelet therapy, but this reduction was not statistically significant [275]. However, similar to the results of medical substudy of CLOSE trial, the number of events identified during follow-up was small, underlining imprecision in the estimation of effects [275]. These findings may also be due, as for many other of the aforementioned factors in this population, to heterogeneity within the populations classified as having PFO-associated cryptogenic emboli, even when they are deemed to be at higher risk according to a few indicators, such those enrolled in CLOSE trial. Indeed, OAC had a statistically-significant beneficial effect on the primary composite outcome in analyses that were standardised to only include patients who had actually received antiplatelet therapy (adjusted HR: 0.64, 95% CI 0.42–0.99) [275].

Overall the quality of the available evidence for safety issues is low. In the first three randomised studies on PFO excluding CLOSE, REDUCE and DEFENSE-PFO trials, only 7/11 bleeds were major haemorrhages amongst patients receiving medical therapy. In a meta-analysis of observational studies, 1.1% of the patients receiving medical therapy experienced a bleeding complication [113]. The young age of patients and the short follow-up may influence the estimate of bleedings. Indeed, in one of the above-mentioned meta-analyses on PFO patients, an OR of 6.49 (95% CI: 3.25 to 12.99) was reported for major bleeding with OAC relative to antiplatelet drugs [116]. In addition, another meta-analysis of 11 trials involving 2487 patients and considering the secondary prevention of stroke at large revealed that the potential benefit of OAC might be

outweighed by the risk of both intracranial haemorrhage (OR 2.54, 95% CI 1.19 to 5.45) and major extracranial haemorrhage (OR 3.43, 95% CI 1.94 to 6.08) [117].

ADDITIONAL INSIGHTS ON THE SAFETY AND EFFICAY OF PERCUTANEOUS CLOSURE

The initial report on percutaneous PFO closure pertained to an atrial septal defect device [120]. The first dedicated PFO closure device was implanted in 1997 [121].
The main quantitative and quantitative characteristics of the RCTs are summarised in **Supplementary Table 9** and in **Supplementary Table 10**.
Regarding more detailed qualitative characteristics, despite the fact that all these studies are RCT, therefore the highest ranked source of evidence, all individual studies shared important limitations.
All studies were underpowered due to a lower incidence of outcomes as compared to forecasts and therefore also reported wide confidence intervals in their results. It is likely that this probably also due to the short duration of follow up for these kind of endpoints (usually 2 years, except in PC and the extended Respect post-hoc analysis). All the studies also had a lower-than expected rate of recruitment which accounts for a high risk of referral bias. All the studies were therefore concerned by the possibility of a high attrition bias, with the possibility of some patients at higher risk treated outside the study. Moreover, all studies compared PFO closure with mixed medical therapies. No study had a comprehensive AF rule-out strategy with ICM before the randomisation, so that overt AF may be reliably excluded. Finally, the stroke risk attributable to atrial fibrillation induced by PFO closure is unknown, therefore the impact of post-procedural AF in patients undergoing percutaneous closure (mostly transient) is unclear.

The Closure I trial [51]was the first study to be published and evaluated the STARFlex PFO closure system (now out of market) against the administration of warfarin, acetylsalicylic acid, or combined acetylsalicylic acid and warfarin at the physician's choice. It had a long enrolment phase from 2003 to 2008, which also caused the need to amend the original protocol to lower the number of patients. Finally, 909 patients aged 18–60 with a cryptogenic stroke (including lacunar patern at imaging) or TIA and a PFO, were randomised 1:1: 447 to PFO closure (72.6 % stroke, 27.4 % TIA) and 462 to medical therapy (71.4 % stroke, 28.6 % TIA). The primary endpoint was a composite of recurrent stroke or TIA at 2 years, any death within 30 days, or death from neurologic causes at 2 years. Moderate to substantial shunts and atrial septal aneurysm prevalence was similar in study arms (on average approximately 52 % and 36%, respectively). No relevant deaths occurred. Procedural success was 89.4 % for implantation and 86.1 % for effective closure at 6 months of followup. In the follow-up 52 cerebrovascular outcome events occurred: 25 ischaemic strokes and 30 transient ischaemic attacks. There was no evidence that endovascular PFO closure was superior to medical therapy alone in the prevention of stroke or TIA (5.5 % vs 6.8 %, HR 0.78, 95 % CI 0.45–1.35, p00.37), stroke (2.9 % vs 3.1 %, HR 0.90, 95 % CI 0.41–1.98, p00.79), or TIA (3.1 % vs 4.1 %, HR 0.75, 95 % CI 0.36–1.55, p00.44). This lack of benefit persisted when the analysis was confined to modified intent-to-treat or per-protocol patients only. However, there was a significant increase in the risk of major vascular procedural complications after PFO closure (3.2 % vs 0, p=0.001). Among the main limitations of this study: the high risk of referral bias due to the low number of enrolled patients per centre, the risk of selection bias

due to the low risk of patients, the short follow-up, the inclusion of interventional centres with low volume of activity, the use of an outdated and probably less-effective device, the inclusion of TIA as index events and as outcome measure, the inclusion of lacunar syndrome,.

The Respect trial [112] compared the Amplatzer PFO Occluder with four treatment regimens: monotherapy with warfarin, acetylsalicylic acid or clopidogrel, or a combination of acetylsalicylic acid with extended-release dipyridamole. Also this study suffered an 8 years enrolment phase, caused, among other factors, by a double amendment in the protocol, needing an increase in patients to be included. At the end, 980 patients aged 18–60 with a cryptogenic stroke only and a PFO were randomised 1:1: 499 to PFO closure and 481 to medical therapy. The primary efficacy endpoint was a composite of recurrent nonfatal ischaemic stroke, fatal ischaemic stroke, or early death after randomisation in the time span necessary to 25 events to occur. A similar proportion of patients with an atrial septal aneurysm (36.1 % vs 35.1 %) and presence of substantial shunting (defined as more than 10 microbubbles of right-to-left shunt, 77.9 % vs 74.1 %) was observed. Procedural success was 96.1 % for implantation and 93.5 % for effective closure at 6 months of follow-up. The primary publication in 2013 reported a total of 25 primary endpoint events (nine in the closure group and 16 in the medical therapy group), all of which were recurrent nonfatal stroke (0.66 events per 100 patient-years, HR with closure = 0.49, 95 % CI: 0.22–1.11; p=0.08). The primary analysis showed similar results in the prevention of stroke in the 2 arms (1.33 % vs 1.73 % at 1 year, 1.60 % vs 3.02 % at 2 years, and 2.21 % vs 6.40 % at 3 years, HR 0.492, 95 % CI 0.217–1.114, p=0.083. However, the per-protocol analysis of 20 events suggested benefit for PFO closure (HR 0.366, 95 % CI 0.141–0.955, p=0.032). Subgroup analyses suggested a benefit in the presence of a substantial shunt or atrial septal aneurysm. Atrial fibrillation occurred in 0.6 % of patients in both groups. There were no cases of device thrombus or embolisation. Major vascular complications were exclusively seen in the device group, but without a statistically significant difference as compared to medical therapy.
In a second publication in 2017,[28] the investigators reported that after 10 years, in an intention-to-treat analysis, PFO closure with the Amplatzer PFO Occluder resulted in a 62 % relative risk reduction (RRR) for recurrent ischaemic stroke compared to medical management (HR 0.38; 95 % CI: 0.18–0.79; 10-year event rates 2.3 % versus 11.1 %; p=0.007). Similar results were seen in patients <60 years of age (58 % RRR; HR 0.42; 95 % CI: 0.21–0.83; 10-year event rates 3.0 % versus 13.2 %; p=0.01). The rates of atrial fibrillation, major bleeding, and death from any cause were comparable or lower in the device study arm. Specific limitations of this trial are: a different drop-out rate in the two study arms and the caution to be used in per-protocol analysis instead of in intention-to-treat analysis.

The PC trial [132]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. Also in this study a low enrolment rate was observed (9 years). 414 patients aged 18-60 years old with neuroradiologically verified cryptogenic stroke or TIA or peripheral thromboembolism and a PFO were randomised 1:1: 204 to closure and 210 to medical therapy groups. The primary endpoint was a composite of death, nonfatal stroke, TIA, or peripheral embolism at 4.5 years Device implantation was successful in

95.9% of patients and effective in 95.9% of those. The prevalence of moderate-to-severe shunt and of ASA was similar in the two study arms (on average approximately 65% and 24%, respectively). Eighteen primary endpoint occurred (6 strokes, 12 TIA): 3.4% in the closure group and 5.2% in the medical therapy group (hazard ratio for closure vs. medical therapy, 0.63; 95% confidence interval [CI], 0.24 to 1.62; P = 0.34). No relevant deaths occurred. At subgroup analysis no significant differences emerged in the two study arms. Except for a statistical trend towards a higher minor atrial fibrillation rate in PFO closure (2% vs. 0%, p=0.058), the overall complication rate was similar in the two study groups.
Specific limitations of this trial were: a possible high attrition bias, the inclusion of TIA as index events and as outcome measure and the considerable risk of selective reporting by the clinical event committee in this open label trial.

The Reduce trial [26], evaluated PFO closure with the Gore Helex (not available any more) or Gore Cardioform septal occluder plus antiplatelet therapy versus to antiplatelet treatment alone. Antiplatelet could consist of: acetylsalicylic acid, a combination of acetylsalicylic acid and dipyridamole or clopidogrel, Enrolment lasted 6 years. 664 patients with a cryptogenic ischaemic stroke a PFO aged 18-59 years old were randomly 2:1: 441 patients to PFO closure group and 223 to medical therapy only group. The first co-primary endpoint was freedom from clinical evidence of an ischaemic stroke (clinical ischaemic stroke) through at least 24 months. The second co-primary endpoint, derived from a secondary endpoint with a protocol amendment, was the incidence of new brain infarction (composite of clinical ischaemic stroke or silent brain infarction detected by MRI). In 7.3% of patients of the interventional group no device was implanted. In those who received the device, the implantation was successful in 98.8% of patients and effective at 12 months in 75.6% of those. ASA was present in 20% of patients undergoing closure, whereas this data is not available for patient on medical therapy only. A moderate-to large shunt was present in approximately 80% of patients in both arms. Primary endpoint clinical ischaemic stroke occurred in 18 patients. The incidence of new brain infarctions was significantly lower in the PFO closure group than in the antiplatelet-only group (5.7% vs. 11.3%; P = 0.04), but the incidence of silent brain infarction did not differ significantly between the study groups (P = 0.97). Serious adverse events were similar in the two groups. Atrial fibrillation occurred in 6.6% of patients after PFO closure vs 0.4% ($p<0.001$). Also in this study a different dropout rate was observed in the two study arms, accounting for a possible selective reporting bias.

The Close study [27]was a 3 arm randomised study. The 3 arm of the study were: 1) antiplatelet therapy plus trans-catheter PFO closure with any CE-mark of PFO closure device; 2) antiplatelet therapy alone; 3) anticoagulant therapy alone (with OAC or DOAC). Antiplatelet therapy consisted of: acetylsalicylic acid, clopidogrel or acetylsalicylic acid combined with extended release dipyridamole. Enrolment was stopped at 8 years, before reaching the planned target of 900 patients, because of budget limitations. As a compensation for this, the follow-up period was prolonged. The study finally included 663 patients aged 16-60 years old, with a cryptogenic ischaemic stroke and a PFO with an associated ASA or large interatrial shunt. Patients were randomised 1:1:1: 235 to antiplatelet only, 238 to PFO closure and the remaining to anticoagulants. Pre-specified comparisons included only the comparisons of closure vs. antiplatelets and antiplatelets vs.

anticoagulants. Primary endpoint was the occurrence of fatal or nonfatal stroke at 3 years. With the 11 different devices used (with a large majority being Amplatzer PFO occluder), the closure procedure was successful in 98.6% of patients and the rate of effective PFO closure was 93.0%. ASA was present in approximately 32% of patients in both arms, a large shunt was present in approximately 72% of patients in both arms.

Recurrent fatal or non-fatal stroke occurred in 14 patients, but none in the PFO-closure group. Therefore, the risk of recurrent stroke was significantly reduced in the PFO closure group as compared with the antiplatelet therapy alone group (97 % RR; HR 0.03; 95 % CI: 0.00–0.26; $p<0.001$). A significantly higher rate of new-onset paroxysmal atrial fibrillation in the PFO closure group compared to the antiplatelet only group was also reported (4.6 % versus 0.9 %; $p<0.02$). In a post-hoc analysis comparing PFO closure vs. anticoagulation, 3 patients on anticoagulants 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 (intention-to-treat analysis), which was statistically non-significant at the survival analysis.

The Defense-PFO study [29]compared PFO closure with Amplatzer PFO Occluder or medical therapy alone as chosen by the caring physician (acetylsalicylic acid, acetylsalicylic acid in combination with clopidogrel, acetylsalicylic acid in combination with cilostazol or warfarin). Enrolment lasted 6 years, when it was terminated for the advantage in PFO closure arm which was evident before the end of the planned enrolment. The study randomised, 1:1, 120 patients who experienced a cryptogenic ischaemic stroke and had a high risk PFO (ASA, PFO width >2 mm or moderate-to-large shunt): 60 to percutaneous closure and 60 to medical therapy only. ASA was present in approximately 10% of patients in both arms, atrial septal hypermobility in 45% and a large shunt in 90% of patients.

The primary endpoint was a composite of stroke, vascular death, or Thrombolysis In Myocardial Infarction (TIMI)–defined major bleeding during 2 years of follow-up, and occurred in 6 patients undergoing medical therapy only, and in none undergoing PFO closure ($p=0.013$). The study reports 2 cases of AF in the group undergoing closure and none in the medical therapy-group. Specific limitation of this trial is the low number of enrolling centres (i.e. two).

SURGICAL CLOSURE OF PFO

There are no current indications for surgical closure of a PFO as first-line treatment. Closure of incidental PFOs at the time of coronary artery bypass surgery is not generally advocated because of the higher risk of postoperative stroke [157], but during valvular surgery incidental PFO closure is usually undertaken. Surgical PFO is also done in rare cases when surgery is indicated for other conditions in which the PFO plays a role, such as a straddling thrombus in the PFO or a right-sided cardiac tumours causing hypoxaemia or paradoxical embolism through a PFO [158]. Finally**,** PFO should be closed during surgery performed for rare complications which cannot be managed by percutaneous means, such as infected or misplaced PFO devices or erosion of the atrial free wall caused by a PFO device.

Supplementary Appendix 5. GRADE evaluation of evidences for PICO questions.

Should percutaneous closure of PFO vs. medical therapy be used for secondary prevention of stroke or other left-circulation thromboembolism?

POPULATION:	Secondary prevention of stroke, TIA, other left-circulation thromboembolism
INTERVENTION:	Percutaneous closure of PFO
COMPARISON:	Medical therapy
MAIN OUTCOMES:	Stroke, TIA, death, bleedings, atrial arrhythmias
SETTING:	Hospital

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Stroke is an important cause of morbidity and persistent disability, with 16.9 million people suffering a stroke each year. The incidence of stroke in young adults and in low-income countries is increasing. Cryptogenic strokes represent 30-40% of all strokes and there is evidence demonstrating a causal role of PFO in this figure, varying from 25% to approximately 50% of the total.	Based on these data, PFO is causal in between approximately 1.2 million and 3 million strokes each year worldwide. Cryptogenic non-cerebral systemic embolism is similar to cryptogenic embolic stroke, thereby increasing the number of people affected yearly. Finding an effective PFO treatment would translate into a substantial population effect.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Unknown	Currently data are available on 7137 patients in 11 nonrandomised comparisons, six randomised studies, 3 study-level meta-analysis of the 6 RCTs, 2 study-level meta-analysis of 5 RCTs and observational comparisons, 10 study-level meta-analyses of 5 RCTs, one patient-level meta-analysis of the 3 first published RCTs, one meta-analysis performed on observational trials only	Studies are available for cryptogenic stroke only; however cryptogenic non-cerebral embolism can be considered a variant of this condition.

UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	ans 17 meta-analyses of the 3 first published RCTs(**Supplementary Table 7**, **Supplementary Table 8**). Three of the six RCTs (CLOSE, REDUCE and DEFENSE-PFO trials) showed superiority of PFO closure plus medical therapy vs. medical therapy alone for reducing recurrent strokes. The remaining 3 studies showed a similar efficacy with interventional or medical therapies, although one reported the superiority of PFO closure only on pre-specified as-treated analysis [112]. In this study an exploratory analysis at extended 5.9 years' follow-up yielded a superiority of PFO closure over medical therapy [28]. Our study-level meta-analysis performed on the 6 published RCTs, shows superiority of PFO closure over medical therapy for stroke recurrence on ITT analysis with an odds ratio (OR) = 0.38 (95% CI: 0.18-0.80), with a heterogeneity across studies which is borderline between moderate and significant (χ^2=10.7, p=0.06; I^2=53%) (**Supplementary Figure 4A**). However, when considering subgroups classified as per risk characteristics of the PFO, in the low risk subgroup this heterogeneity disappeared (I^2=0%) and was reduced in the high-risk subgroup (I^2=40%) (**Supplementary Figure 5**). Moreover, in the same analysis, the superiority of percutaneous closure was clearly driven by the high-risk patients (**Supplementary Figure 5**). This was also true when considering altogether the studies which selected high risk patients upstream (CLOSE, DEFENSE-PFO and REDUCE), without subgroup analysis (**Supplementary Figure 4B**). The superiority of PFO closure was confirmed also for the stroke reduction of the studies when compared with antiplatelet therapy with an OR = 0.38 (95% CI:0.17-0.84) (**Supplementary Figure 12A**) but not with OAC, although only 3 RCTs could be analysed for the latter comparison (**Supplementary Figure 12B**). Of note, the only RCT of those allowing the direct comparison of percutaneous closure with OAC in a post-hoc analysis, found no statistically significant difference in stroke incidence in the follow-up [74].	The NNH for atrial fibrillation is likely to increase substantially with more adequate screening strategies for AF before treatment allocations.

		On the contrary, interventional and medical therapy yielded similar results in preventing TIA and Death (**Supplementary Figure 4C**, **Supplementary Figure 4D**). On patient-level meta-analysis not including CLOSE, REDUCE and DEFENSE-PFO trials, PFO closure was superior to medical therapy on ITT analysis for stroke recurrence, with a hazard ratio (HR) = 0.58 (95%CI: 0.34–0.98), and for the primary composite endpoint (stroke, TIA or death) only after adjusting for covariates with an HR = 0.68 (95%CI: 0.46–1.00) [70]. The 3 comprehensive study-level meta-analyses and 11 study-level meta-analyses not including DEFENSE-PFO trials (**Supplementary Table 7**), all showed superiority of PFO closure over medical therapy only. One of the study-level meta-analyses of the 6 published RCTs revealed an incidence rate of 1.27 per 100 patients/year with medical therapy (95% CI, 0.84– 1.78; I2= 53%) and of 0.29 strokes per 100 person-years with percutaneous closure (95% CI, 0.02–0.76; I2= 83%) in the PFO closure group [74]. Death rates were similar in medical and interventional arms (pooled RR 0.79, 95% CI, 0.39– 1.60, P= 0.51; I2= 0%)[74]. No deaths were associated to stroke. Incidence rates for haemorrhage and overall adverse events were similar in the intervention and medical therapy arms in all meta-analyses. However, it should be taken into account that most of the patients were young and follow-up not very long, therefore a life-long medical therapy may cause an underdetected late rise in haemorrhages with advancing age. The risk of atrial arrhythmias, particularly atrial fibrillation, was higher after PFO closure than after medical therapy in our meta-analysis of the 6 RCTs with an OR= 4.15 (95%CI: 2.42-7.13) (**Supplementary Figure 9A**) and also in all meta-analyses of the first 5 RCTs [78,79,90,122,170,171,276–278]. However, this difference was influenced by the type of device received by patients. With the use of Amplatzer	

		device, no difference in the risk of postprocedural AF was found in our meta-analysis (**Supplementary Figure 10**) and in four previous meta-analyses including less studies than the last one. Moreover a less significant difference in AF risk war reported with Amplatzer device in other three previous meta-analyses [70,172,279–283]. Among the 6 RCTs, the use of GORE septal occluders, in the REDUCE trial, was associated with the highest probability of AF with OR=15.6 (95%CI: 2.11-115.48) (**Supplementary Figure 10**).	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	All individual RCTs were underpowered (**Supplementary Table 9**), mainly because of the discrepancy between the expected vs. observed incidence of events, and meta-analyses should be interpreted accordingly. Moreover, individual RCTs have low internal and external validity (**Supplementary Table 10**). Indeed, event rates were low and confidence intervals wide. Moreover, innumerable data from meta-analyses and randomised and observational studies (see text) show that substantial heterogeneity exists in the populations studied. However, part of this heterogeneity disappeared when considering the subgroups of patients according to PFO risk features, suggesting that in part the PFO characteristics may account for the observed difference in study results. Therefore, the conclusion in this subgroups of patients are likely not to change with new trials. Nonethelss, more precise phenotyping with multidimensional data is warranted to design more appropriate randomised trials indentifying new subgroups of responders vs. non-responders to each therapy.	
VALUES	**Is there significant uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or	No study addressed the issue of patient preferences or values regarding outcomes and treatments for cryptogenic stroke with PFO. A systematic review recently addressed these issues stroke prevention with medical therapy in patients with atrial fibrillation across 27 studies [284]. Generally speaking, most patients were willing to accept even high risks of a therapy if a certain threshold in stroke risk reduction could be reached. This acceptance went in many cases	

	variability	beyond the judgement of physicians. Moreover, significant differences in preferences appeared also between patients.	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	See the "desirable effects" and "undesirable effects" sections of this table for a summary of evidence. On our study-level meta-analysis of the 6 RCTs, the number needed to treat (NNT) over 3.9 years follow-up with percutaneous closure was 37 to avert one stroke as compared to medical therapy on ITT analysis (**Supplementary Figure 4A**), but it was only 21 in high risk PFOs and 27 to avert one primary endpoint as compared to antiplatelet therapy only (**Supplementary Figure 5, Supplementary Figure 12A**, respectively). On patient-level meta-analysis of the first 3 published RCTs, NNT with percutaneous closure over 2.5 years was 50 to avoid 1 primary composite outcome event; to avoid 1 ischaemic stroke, the NNT was 67 [70]. On study-level meta-analysis, the NNT for an Amplatzer device to prevent one stroke at 5 years was 29, while to prevent one TIA it was 49 [282]. This benefit continues to grow beyond 5 years [28,70,133]. On our meta-analysis, the NNH to cause an atrial fibrillation over 3.9 years is 25 as compared to medical therapy (**Supplementary Figure 9A**), but this value appears to be influenced by the kind of device (**Supplementary Figure 10**).	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Based on a meta-analysis of the first 5 published randomised trials (therefore excluding Defense-PFO trial), a recent study showed that over a 15-year time horizon, PFO closure resulted in a gain of 0.33 QALYs at cost savings of $3568 as compared to medical therapy only, representing an incremental net monetary benefit of $52 761 (95% interval −$8284 to $158 910). However this gain only applies when the hazard ratio for stroke remains low (i.e. in higher risk populations). With the rise of HR, a sharp decline in cost-effectiveness occurs [285] Previous data from the three first published RCTs comparing PFO closure with medical therapy, showed that, at 31.0 years (29. 6- 33.6), the per-patient	Calculations of the cost/effectiveness in the Stortecky meta-analysis were based on the overall costs of one procedure with Amplatzer in the UK, which ranges from 6,300 to 10,000 Euros.

		mean cost of medical therapy exceeded that of PFO closure. Among studies utilising only the Amplatzer device, the cost analysis more strongly favoured closure: cost to prevent one stroke = 652,392 USD (318,955-26,888,272); time to less than 50,000 USD/QALY-gained, 2.4 years (1.3 to 10.1); time to medical cost exceeding closure cost, 22.7 years (19.75 to 26.7)[273] In another meta-analysis of the first 3 published trials, the costs to prevent one stroke through PFO closure with an Amplatzer device ranged between 182,000-290,000 Euros, whereas the incremental cost-effectiveness ratio would range from 40,000-63,000 Euros/QALY-gained [282].	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Should oral anticoagulants (OAC) vs. antiplatelet therapy be used for secondary prevention of stroke or other left-circulation thromboembolism?

POPULATION:	Secondary prevention of stroke or other left-circulation thromboembolism
INTERVENTION:	OAC
COMPARISON:	Antiplatelet therapy
MAIN OUTCOMES:	Stroke; major bleedings

Assessment

	JUDGEMENT	RESEARCH EVIDENCE
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	PFO-related stroke, TIA and peripheral embolisms impact a considerable proportion of patients yearly with deaths and persisting disability. At present the pharmacological therapy for secondary prevention has been derived from stroke studies at large with no reference therapy for PFO-related left circulation thromboembolism.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	Only one randomised study has compared the use of OAC (vitamin K antagonists or DOACS) and antiplatelet therapy (acetylsalicylic acid, clopidogrel or a combination of acetylsalicylic acid and dipyridamole) in 361 patients with cryptogenic stroke with a large PFO and/or an atrial septal aneurism showing, after an average 5 years of follow-up, a statistically non-significant difference of stroke in patients receiving OAC as compared to those who received antiplatelet therapy [1.6% vs 4.0%, respectively; p=0.21; OR=0.34 (95% CI: 0.10 to 1.53)] [27]. Only one meta-analysis including CLOSE study has been performed to date and it is reported in this document. It includes 20 studies (1 randomised, 4 adjusted observational and 15 non-adjusted studies, including sub-analysis of 3 randomised studies) and 3509 patients. We report a statistically significant OR: 0.85 (95%CI: 0.81-0.90) for stroke in favour of OAC (Supplementry Figure 7). However, we found a severe inconsistency across both studies (I2: 98%) and subgroups (I2: 96.5%) with statistically significant heterogeneity (p<0.00001). Moreover, the quality of evidence was estimated very low, because of risk of bias and imprecision (**Supplementary Table 11**) and because most of the evidence was
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ● Varies ○ Don't know	

		derived from nonrandomised comparisons, although some were adjusted comparisons. As compared to antiplatelet therapy, in a previous patient-level meta-analysis of non-randomised trials, OAC yielded a statistically non-significant reduction of strokes, TIAs or death and stroke alone [275]. Four previous study-level meta-analyses incorporating up to 3311 patients, again not including CLOSE trial, (the first three involving observational studies only and the last one both observational and non-randomised comparisons of randomised studies), also consistently found a statistically-significant advantage of OAC over antiplatelet therapy, including an OR = 0.37 for stroke or TIA (95% CI: 0.23 to 0.60)[114], an incidence rate ratio of 0.42 (95% CI, 0.18–0.98) for stroke and/or TIA [115], a relative risk of pooled recurrent neurological events of 0.58 (95% CI: 0.41 to 0.82) [113], and event rates for stroke and/or TIA at or beyond 12 months of 7.7% versus 9.8%, respectively, p = 0.03 [116]. In our meta-analysis on 14 studies and 1426 patients we found an OR 4.57 (95%CI: 2.10-9.93) for increased bleeding with OAC as compared to antiplatelet therapy, with no inconsistency at all across studies (**Supplementary Figure 8**). This is in-keeping with a previous meta-analysis of non-randomised comparisons only where an OR of 6.49 (95% CI: 3.25 to 12.99) was reported for major bleeding with OAC relative to antiplatelet drugs [116].
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	Overall, the available meta-analyses are consistent with an advantage of OAC over antiplatelet therapy as a secondary prevention in patients with previous PFO-related stroke or TIA. Also in our meta-analysis, including the only randomised study performed so far, most of the benefit of OAC was due to non-randomised studies, although in 4 of them the comparisons were adjusted. In the CLOSE study, a trend was observed towards an advantage of OAC over antiplatelet therapy, but it was not statistically significant. However, this study was underpowered due to a lower than expected incidence of primary endpoint in the control arm. Moreover, other individual studies had a low quality

		of evidence because of imprecision and risk of bias. Therefore, more adequately powered studies are needed to obtain a higher certitude of the estimate of effects.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No study addressed the issue of patient preferences or values regarding outcomes and treatments during medical therapy for cryptogenic stroke with PFO. A systematic review addressed these issues for stroke prevention in patients with atrial fibrillation across 27 publication describing the results of studies conducted in 12 different countries [284]. Most studies showed that patients were willing to accept higher bleeding risks if a certain threshold in stroke risk reduction could be reached, resulting in the fact that physicians appeared to be more sensitive to bleeding risk than patients. Moreover, patients preferred easy-to-administer treatments, such as treatments that are applied once daily without any food/drug interactions and without the need for bridging and frequent blood controls, implying a preference for DOACs.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ● Varies ○ Don't know	Despite the high statistical significance of our meta-analysis favouring OAC, and its narrow confidence intervals, the severe inconsistency among studies disallows generalisations (**Supplementary Figure 7**). On the contrary the higher risk of bleeding with OAC was consistent across all the considered studies (**Supplementary Figure 8**). This translates in that the balance between desirable and undesirable effects varies mainly according to the magnitude of the benefit OAC, the risk of major bleeding being similar across subgroups.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Cost effectiveness evaluation of different medical therapies has not been performed in patients with PFO-related cryptogenic stroke, TIA, and peripheral embolism.

FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Feasibility of implementation appears evident but the feasibility of a safe OAC in comparison to vitamin K antagonists is largely dependent on the availability of monitoring facilities of proper anticoagulation and on the possibility to access them by patients.

Supplementary Table 1. PFO diagnostic methods.

DIAGNOSIS METHOD	USE	DIAGNOSTIC CRITERIA	ADVANTAGES	LIMITATIONS
Transthoracic Echocardiography (TTE)	• Evaluation of cardiac structures, interatrial septum motility • Evaluation of potential causes of cardiac embolism (e.g. left atrial mass or thrombus, left ventricular thrombus, etc) • Diagnosing a clinically relevant intracardiac shunt at rest and after a Valsalva maneuver (With Bubble Test)	• Constrast in left atrium in the first 3-5 cardiac cycles • <20 bubbles mild/moderate • >20 bubbles severe	• Well tolerated by the patient. • Low cost and reproducible. • Ease for Valsalva manoeuvre, sniff, coughing • Visualisation and semi-quantification of the right-to-left shunt • Comparative follow-up method	• Reduced sensitivity for mild interatrial shunts • Need for a sufficient echographic thoracic window • Semi-quantitative assessment of the shunt • Need for training in sonographers
Transesophageal Echocardiography (TEE)	• Morphological characterisation of interatrial septum, atrial structures • Evaluation of ascending aorta • Anatomical details of PFO indicated for intervention	• Constrast in left atrium in the first 3-5 cardiac cycles • <20 bubbles: mild/moderate • >20 bubbles: severe	• Gold standard for visualisation of cardiac and aortic structures and sources of embolism (tumors, thrombi, vegetations, complex aortic plaques) Semi-quantitative assessment of the shunt	• Patient discomfort • Impossibility to perform proper Valsalva manoeuvre • Training requested
Transcranial Doppler (TCD)	• Diagnosing right-to-left shunts at rest and after a Valsalva maneuver	• 3-10 HITS: mild/moderate • >10 HITS / shower/curtain: severe	• Well tolerated by the patient • Low cost and reproducible.	• Unable to be performed in 20% of the patient for bone thickness • Impossibility of directly visualise shunt location

			• High sensitivity for any right-to-left shunt • Semi-quantitative assessment of the shunt • Contrast improves feasibility loss due to bone thickness • Magnitude of shunt is predictor of relapse	• Lack of standardisation • Methodology influences results

Supplementary Table 2. Qualitative evaluation of diagnostic studies.

A: Transcranial Doppler with bubble test vs. Transoesophageal contrast-echocardiography in the diagnosis of PFO

№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Test accuracy QoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
29 studies 2751 patients	Cohort & case-control type studies	Serious [a]	Not serious	Not serious	Serious [b]	None	⊕⊕◯◯ LOW

Explanations
a. high risk of adjudication bias
b. no sample size calculation

B. Transthoracic costrast-echocardiography vs. Transoesophageal contrast-echocardiography in the diagnosis of PFO

№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Test accuracy QoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
13 studies 1360 patients	Cross-sectional (cohort type accuracy study)	Serious [a]	Not serious	Not serious	Serious [b]	None	⊕⊕◯◯ LOW

Explanations
a. High risk of adjudication bias b. No sample size calculation

Supplementary Table 3. Qualitative evaluation of the studies on RoPE score.

№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Test accuracy QoE
		Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
4 studies 6362 patients	Cohort and case-control type studies	Not serious	Not serious	Not serious	Very serious [a,b]	Strong association	⊕⊕⊕◯ MODERATE

Explanations
a. 2 on 4 studies with multivariate analysis.
b. No studies with sample size calculation

Supplementary Table 4. Predictors of cryptogenic stroke recurrence in the presence of a PFO.

Kind of predictor	**N. of pts**	**N. of studies**	**OR/HR**	**LCI**	**UCI**
Older Age [73,97,286,287]	2171	4	1.47	1.2	1.8
Septal aneurysm [288–292]	630	5	3.0	1.8	4.8
Acetylsalicylic acid use vs. OAC [11,72,293–295]	1235	5	2.5	1.1	6.1
Coagulation disorders [296,297]	258	2	2.75	1.17	6.49
Stroke at index [298,299]	367	2	3.0	1.4	6.5
PFO diameter (continuous variable) [11,290]	334	2	3	1.9	4.6

All predictors significant at multivariate analysis in 2 studies or more have been included, along with number of studies. OR/HRs (Odds ratio/Hazard ratio) have been reported of the study with the smallest confidence interval. LCI: Lower confidence interval, UCI: upper confidence interval

Supplementary Table 5. Complications of percutaneous closure.

COMPLICATION	INCIDENCE	PATHOPHYSIOLOGY	SYMPTOMS/SIGNS	DIAGNOSTIC WORKUP
Residual shunt [123,124,300,301]	10-15%	• Temporary or persistent mild to severe device leak due to device-PFO mismatch and/or incomplete endocardial coverage	• Possibly asymptomatic • Recurrent systemic embolism • Observed in different positions	• c-TCD • c-TTE • c-TOE
Atrial arrhythmias [106–111,302]	0.5-15%	• Related to age and/or ASA • Mechanical irritation related to device type and size • Inflammatory reaction • Electrical barrier by the device • P-wave dispersion	• Possibly asymptomatic • Atrial Fibrillation • Superaventricular tachyarrhythmias • Recurrent systemic embolism	• Holter ECG • ICM
Device thrombosis [135,303]	1-2%	• Thrombosis of device arms not covered by endocardium	• Possibly asymptomatic • Systemic embolism	• TTE • TOE
Pericardial effusion/ tamponade [48,49,301,303–305]	0.5-1%	• Perforation during procedure • Early(24-48h) and late erosion • Allergic reaction (mild effusion)	• Possibly asymptomatic • Dyspnea • Chest pain	• TTE • TOE (erosion)
Device embolisation [135,136,301,306–309]	0.9-1.3% (early) Rare (late)	• Early and late mobilisation due to erosion of the atrial septum or to device-PFO mismatch	• Possibly asymptomatic • Pulmonary embolism	• TTE • TOE • Chest X-ray
Endocarditis [127,310,311]	Anecdotal	• Colonisation of device arms not covered by endothelium	• Unexplained fever • Systemic septic embolism	• TOE
Atrio-aortic fistula [312]	Anecdotal	• Erosion of aortic wall	• New onset murmur	• TOE

c-TTE: contrast-enhanced transthoracic echocardiogram; c-TOE: contrast-enhanced transoesophageal echocardiogram; c-TCD: contrast-enhanced transcranial doppler; ICM: internal cardiac monitor; ASA: aceytlsalycilic acid; ECG: electrocardiogram

Supplementary Table 6. Prognosis of patients with PFO patency.

Author	Nr. of patients	Follow-up (months)	% of positive TCD	% of positive TOE	N of events in patients with positive TCD	N of events in patients with positive TOE	N of events in patients with negative TCD	N of events in patients with negative TOE
Anzola, 2004 [143]	112	12	9,00%	9,00%	0	0	1	1
Balbi, 2008 [144]	109	6	17,5% (6 months)	21, 6 % (3 months)	0	0	0	0
Cifarelli, 2010 [141]	202	6	4%	4%	0	0	0	0
Caputi, 2013 [124]	243	12	32,00%	32,00%	4	4	8	8
de Cillis, 2010 [145]	72	6	6.9%	5,5%	0	0	0	0
Donti, 2006 [146]	11	1	36,00%	-	0	0	0	0
Orzan, 2010 [147]	68	6	25,00%	11,76%	0	0	0	0
Ussia, 2009 [142]	14	6 (TCD) 12 (TOE)	21%	0%	0	0	1	1

TOE: transesophageal echocardiogram; TCD: transcranial Doppler;

Supplementary Table 7. Summary of meta-analyses on closure vs. medical therapy trials.

Study	Design of the study	N of study (patients)	N of RCT (patients)	N of observational studies (patients)	Stroke, TIA; all cause death	Stroke, TIA	Stroke
Turc, 2018 [74]	Pairwise, study level	6 (3560)	6 (3560)	-	-	-	PFO closure reduced incidence of stroke (RR 0.36; 95%CI: 0.17-0.79)
Wang, 2018 [313]	Pairwise, study level	6 (3560)	6 (3560)	-	PFO closure reduced incidence of stroke and TIA and all cause death (HR 0.60: 95%CI:0.42-0.85)	PFO closure reduced incidence of stroke (2.0% versus 4.5%, OR 0.41, 95%CI: 0.19–0.90	PFO closure reduced incidence of stroke (HR 0.4; 95%CI:0.19-0.88)
Saber, 2018 [337]	NMA, study level	6 (3497)	5 (3497)	-			PFO closure reduced incidence of stroke (RR 0.30; 95%CI: 0.17-0.49)
Tsivgoulis, 2018 [338]	NMA, study level	6 (3497)	5 (3497)	-			PFO closure reduced incidence of stroke (RR 0.42; 95%CI: 0.20-0.91)
Lattanzi, 2018 [339]	Pairwise, study level	5 (3440)	5 (3440)	-			PFO closure reduced incidence of stroke (RR 0.43; 95%CI: 0.21-0.90)
Smer, 2018 [340]	Pairwise, study level	5 (3440)	5 (3440)	-			PFO closure reduced incidence of stroke (RR 0.48; 95%CI: 0.27-0.87)

Shah, 2018 [277]	Pairwise, study level *[Closure I trial was excluded because using Starflex]	4 (3216)	4 (3216)	-			PFO closure decreased the AR for recurrent stroke by 3.2% (RD, -0.032; 95%CI: -0.05 to -0.014) compared with medical therapy
De Rosa, 2018 [122]	Pairwise, study level *[Closure I trial was excluded because using Starflex]	4 (3216)	4 (3216)	-	PFO closure reduced the risk for the main outcome of stroke or TIA (RD: −0.029 95%CI: −0.050 to −0.007])		
Abdelaziz, 2018 [341]	Pairwise, study level	5 (3440)	5 (3440)	-			PFO closure reduced incidence of stroke (RR 0.43; 95%CI: 0.19-0.91)
Ahmad, 2018 [342]	Pairwise, study level	5 (3440)	5 (3440)	-			PFO closure reduced incidence of stroke (RR 0.32 95%CI: 0.13-0.82)
Reinthaler, 2018 [343]	Pairwise, study level	5 (3440)	5 (3440)	-			PFO closure reduced incidence of stroke (RR 0.32 95%CI: 0.13-0.80)
Anantha-Narayanan, 2018 [314]	Pairwise, study level	5 (3440)	5 (3440)	-	-	-	PFO closure reduced incidence of stroke (RR 0.59 95%CI: 0.40-0.87)
Palaiodimos, 2018 [315]	Pairwise, study level	5 (3440)	5 (3440)	-	-	-	PFO closure reduced incidence of stroke (HR 0.29 95%CI: 0.02-0.56)

Chen, 2018 [316]	Pairwise, study level	19 (6301)	5 (3440)	14 (2861)	-	-	PFO closure reduced incidence of stroke (HR 0.38 95%CI: 0.24-0.60)
Darmoch, 2018 [317]	Pairwise, study level	5 (3440)	5 (3440)	-	-	-	PFO closure reduced incidence of stroke (HR 0.42 95%CI:0.20-0.91)
Alushi, 2018 [318]	Pairwise, study level	5 (3440)	5 (3440)	-	PFO closure reduced the composite of stroke, TIA, all cause death and peripheral embolism (HR 0.52; 95%CI: 0.36-0.77)		PFO closure reduced incidence of stroke (HR 0.39 95%CI: 0.19-0.83)
Ando, 2018 [278]	Pairwise, study level	5 (3440)	5 (3440)	-		PFO closure did not reduce the risk of transient ischaemia attack (RR 0.78; 95%CI:0.53-1.15)	PFO closure reduced the risk of recurrent str oke (RR 0.42; 95%CI:0.20-0.91)
Hakeem, 2018 [78]	Pairwise, study level	5 (3440)	5 (3440)	-			The cumulative incidence of recurrent stroke was 2.02% in the PFO closure arm and 4.4% in the medical therapy group (RR 0.42; 95%CI:0.20-0.91).

Ntiatos, 2018 [170]	Pairwise, study level	5 (3627)	5 (3627)	-			PFO closure reduce ischaemic stroke recurrence (0.53 vs 1.1 per 100 patient-years; OR: 0.43; 95%CI: 0.21-0.90)
Abo Salem, 2018 [90]	Pairwise, study level	5 (3627)	5 (3627)	-			PFO closure reduced stroke: 2.0% vs. 4.2% RR 0.48; 95%CI: 0.3-0.7
Zhang, 2018 [171]	Pairwise, study level	20 (6921)	5 (3627)	5 (3294)	PFO closure was associated with a significantly lower incidence of the composite outcome of ischaemic stroke, TIA, or all-cause death (OR: 0.57; 95%CI: 0.38-0.85		PFO is associated with lower incidence of stroke (OR: 0.39; 95%CI:0.24-0.63)
Schulze, 2018 [276]	Pairwise, study level	5 (3440)	5 (3440)	-		PFO closure reduced the combination of recurrent stroke + TIA (OR 0.53, 95%CI: 0.36-0.80)	PFO closure significantly reduced recurrent stroke (OR: 0.41, 95%CI: 0.19-0.90]
Kheiri, 2018 [79]	Pairwise, study level	5 (3440)	5 (3440)	-			Pooled analysis showed a statistically significant reduction in the rate of recurrent stroke with PFO closure in comparison to medical therapy (OR 0.41; 95%CI: 0.19-0.90)

Stortecky, 2015 [282]	Network, study level	4 (2963)	4 (2963)	-	NA	NA	Superiority of Amplatzer for stroke RR (0.39; 95%CI:0.17–0.84) No difference for Starflex (RR 1.01; 95%CI:0.44-2.41)
Bin Riaz, 2013 [319]	Pairwise, study level	3 (2303)	3 (2303)	-	Superiority of PFO closure at per protocol (HR: 0.64, 95%CI: 0.41-0.98) and not at intention to treat analysis (HR: 0.66, 95%CI:0.43-1.01)	NA	NA
Capodanno, 2014 [280]	Pairwise, study level	14 (4634)	3 (2303)	11 (2331)	NA	NA	No difference for RCTs and for observational studies with adjustement (HR 0.62; 95%CI:0.34-1.11) Superiority of RCTs with Amplatzer Occluder (HR 0.44, 95%CI: 0.20-0.95)
Li, 2015 [320]	Pairwise, study level	3 (2303)	3 (2303)	-	NA (RR 0.73, 95%CI:0.45-1.17)	NA	No difference also for Amplatzer occluder. (only intention to treat) (RR 0.61, 95%CI:0.29-1.27)
Hakeem, 2013 [321]	Pairwise, study level	3 (2303)	3 (2303)	-	No difference (RR 0.7; 95%CI: 0.48–1.06)	NA	No difference (RR 0.66; 95%CI:0.35–1.24)

Kent, 2013 [322]	Pairwise, patient level	3 (2303)	3 (2303)	-	No difference at intention to treat analysis, superiority of PCO closure at as-treated, persisting aftger adjustment. (HR: 0.68 95%CI:0.46-1.00)	NA	Superiority of PFO closure at intention to treat, at as-treated and after adjustement. (HR: 0.58; 95%CI: 0.34-0.99)
Khan, 2013 [279]	Pairwise, study level	3	3	-	NA	No difference at intention to treat analysis (OR 0.67; 95%CI:0.44-1.0) superiority of PFO closure at as protocol (OR 0.62; 95%CI: 0.40-0.95) and as treated (OR 0.61; 95%CI:0.40-0.95)	
Kitsios, 2012 [115]	Pairwise, study level	9 (8916)	1 (909)	8 (8007)	NA	Superiority of PFO closure (HR 0.19; 95%CI: 0.07–0.54)	
Kwong, 2013 [323]	Pairwise, study level	3 (2303)	3 (2303)	-			No difference (OR:0.65; 95%CI:0.36–1.20)
Rengifo- Moreno, 2013 [324]	Pairwise, study level	3 (2303)	3 (2303)	-	No difference at ITT analysis (HR:0.67; 95%CI:0.44–1.00)	Superiority of PFO closure at ITT (HR:0.60; 95%CI:0.36-0.98)	
Nagaraja, 2014 [325]	Pairwise, study level	3 (2303)	3 (2303)	-	NA	No difference	No difference (OR: 0.654; 95%CI:0.3-61.19)

Ntaios, 2013 [172]	Pairwise, study level	3 (2303)	3 (2303)	-	NA	NA	No difference overall (OR: 0.64, 95%CI:0.37–1.1). Superiority for Amplatzer device (OR: 0.46: 95%CI:0.21–0.9) (ITT analysis) but not STARFLEX (OR: 0.93; 95%CI:0.45–2.11)
Pandit, 2014 [326]	Pairwise, study level	3 (2303)	3 (2303)	-	NA	NA	No difference. Superiority for Amplatzer device (ITT analysis) (HR:0.44; 95%CI:0.21-0.9)
Pickett, 2013 [273]	Pairwise, study level	3 (2303)	3 (2303)	-	No difference (HR 0.67; 95%CI:0.44–1.01)	No difference	No difference. Superiority for Amplatzer device (ITT analysis) (HR:0.44; 95%CI:0.21–0.95)
Pineda, 2013 [327]	Pairwise, study level	3	3	-		No difference. Superiority for PFO closure only at as-treated analysis (OR:0.70; 95%CI:0.47–1.0)	No difference (OR 5 0.65; 95%CI:0.36–1.20)
Udell, 2014 [283]	Pairwise, study level	3	3	-	NA	No difference (RR:0.73; 95%CI:0.50-1.0)	

Wolfrum, 2014 [328]	Pairwise, study level	14 (2303)	3 (2303)	11 (2032)	NA	NA	No difference for RCTS (HR 0.58; 95%CI:0.33-0.99), superiority of PFO closure for observational studies (RR 0.66; 95%CI:0.37-1.19)
Agarwal, 2012 [113]	Pairwise, study level	48 (10327)	-	48 (10327)	NA	Superiority of PFO closure (pooling univariate analysis) (RR:0.25; 95%CI:0.11-0.58]	NA

RR: relative risk; AR: absolute risk; OR: odds ratio; ITT: intention-to-treat; HR: hazard ratio; RD: risk difference; CI: confidence interval;

Supplementary Table 8. Observational studies comparing PFO closure with medical therapy

Study	Type	N of pts	Follow up (mo)	Control	PE	Follow up (yrs)	ORE (PFO vs. medical therapy)	ERE (PFO vs. medical therapy)	Overall results	ITT	PP	PFO closure vs. APL	PFO closure vs. AC
Thanopoulos, 2006 [329]	P	92	24	antiplatelet		2	NA		Superiority of PFO closure at univariate analysis	NA	NA	Superiority of PFO closure at univariate analysis	NA
Harrer, 2006 [330]	P	124	52	ASA		2.1	NA		No difference at multivariate analysis			No difference at multivariate analysis	
Paciaroni, 2011 [331]	P	238	24	antiplatelet		2			No difference at multivariate analysis for stroke/TIA and for stroke			No difference at multivariate analysis for stroke/TIA and for stroke	
Casaubon, 2006 [332]	R	121	70	medical therapy	5.8				No difference at multivariate analysis				
Lee, 2010 [290]	R	181	48	Surgical Pfo Closure vs. medical therapy	3.5				Aspirin increased risk of recurrence at multivariate analysis			Aspirin increased risk of recurrence at multivariate analysis	
Mirzada, 2015 [333]	P	314	60	medical therapy		6.8	NA		No difference at multivariate analysis				

Pezzini, 2016 [334]	R	521	100	medical therapy	Stroke, TIA	8.3	NA		No difference at multivariate analysis			No difference at multivariate analysis	No difference at multivariate analysis
Wahl, 2016 [133]	P	308	180	medical therapy	Stroke, TIA	15			Superiority of PFO closure at multivariate analysis				
Weimar, 2009 [335]	P	899	28	medical therapy					No difference at multivariate analysis				
Schuchlenz, 2005 [252]	R	280		medical therapy	Stroke, TIA				Superiority of PFO closure at multivariate analysis			Superiority of PFO closure at multivariate analysis	Superiority of PFO closure at multivariate analysis
Windecker, 2004 [336]	P	308	48	medical therapy	Stroke, TIA	4			Superiority of PFO closure at multivariate analysis				

PTS: patients; APL: antiplatelet drugs; AC: anticoagulant drugs; P: prospective: R: retrospective ; PP: per-protocol: ITT: itention-to-treat; ORE: observed rate of events; ERE: expected rate of events; PE: primary endpoint; TIA: transitory ischemic attack

Supplementary Table 9. RCTs comparing percutaneous closure and medical therapy.

Study	N of patients	Follow-up (months)	Comparison	Primary endpoint	Follow-up for sample size calculation (years)	Median follow up (years)	Observed rate of events (Closure vs. medical therapy)	Expected rate of events (Closure vs. medical therapy)
CLOSURE I, 2012 [51]	909	48	medical therapy	Stroke/tia and death from neurologica causes	2	2	5.5% vs. 6.8%	3.0% vs.6.0%
PC TRIAL, 2013 [132]	414	48	medical therapy	Death, stroke, TIA, peripheral embolims	4.5	4.1	3.4% vs. 5.2%	4.5% vs. 13.5%
RESPECT, 2012, 2017 [28,112]	980	84	medical therapy	Stroke,TIA, death	2*	5.9	1.9% vs. 3.3%*	1.05% vs. 4.3%*
REDUCE, 2017 [26]	664	38	medical therapy	Stroke or imaging-confirmed TIA at 24 months post-randomisation	2	3.2	1.4% vs. 5.4%	3.6% Vs. 8%
CLOSE, 2017 [27]	473	64	medical therapy	Fatal or non-fatal stroke	3	5.4	0% vs.6.2%	5.3%vs. 10.5%
DEFENSE-PFO, 2018 [29]	120	24	medical therapy	Stroke, vascular death and TIA	2	2.8	0% vs. 12.9%	4% vs. 15%

* These data refer to 2-year follow-up on which sample size computation was performed.
TIA: transient ischaemic attack

Supplementary Table 10. Qualitative and quantitative assessment of the evidence.

Percutaneous closure of PFO compared to medical therapy for secondary prevention of stroke or systemic solid embolisation in pts with cryptogenic stroke or TIA and a PFO											
Certainty assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With medical therapy	**With percutaneous closure of PFO**		**Risk with medical therapy**	**Risk difference with percutaneous closure of PFO**
RCT											
3,441 (7 RCTs)	serious [a,b,c]	not serious	serious [d]	serious [e]	all plausible residual confounding would reduce the demonstrated effect	⨁⨁◯◯ LOW	85/1612 (5.3%)	46/1829 (2.5%)	**HR 0.38** (0.18 to 0.80)	**Study population**	
										53 per 1.000 **32 fewer per 1.000** (43 fewer to 10 fewer)	

COHORT STUDIES										
2,481 (8 observational studies)	serious [f,g]	not serious	not serious	serious [h]	all plausible residual confounding would suggest spurious effect, while no effect was observed	⨁◯◯◯ VERY LOW				
CASE-CONTROL STUDIES **CI:** Confidence interval; **HR:** Hazard Ratio										
902 (3 observational studies)	very serious [i]	not serious	not serious	serious [h]	all plausible residual confounding would suggest spurious effect, while no effect was observed	⨁◯◯◯ VERY LOW				

Explanations

a. 7 available randomised trials have limitations: a) Different definitions of key terms (e.g., cryptogenic stroke. b) There may have been a significant patient self-selection bias, whereby patients with a higher risk of recurrent stroke may opt out of clinical trials, and thus are not represented in this trial. This is reflected in the fact that the inclusion of patients was very slow, especially in the CLOSURE, PC and RESPECT, and the number of patients included was significantly lower than the number of patients treated with PFO occlusion in the respective centers. This means that patients with an expected high risk of stroke recurrence were treated outside the study. And just these patients were the most likely to show a difference in the treatment procedures. In particular, the CLOSURE I study shows considerable weaknesses. In CLOSURE I are potential bias that have influenced the study: a) The trial was underpowered to detect small differences in the event rates. b) Patient selecti

b. 2/7 studies likely enrolled patients with misdiagnosed Atrial Fibrillation

c. 4/7 studies enrolled patients with TIA and used TIA as main outcome measure, instead of stroke

d. 6/7 studies with heterogeneity of drug treatments according to the physician preference

e. wide confidence intervals in CLOSURE, PC and RESPECT studies and lower than expected incidence of outcomes for 7/7 studies

f. high or unclear risk of blinding and of follow-up assessment

g. half of studies with high risk of incomplete reporting

h. most of studies without sample size calculation

i. high risk of unclear risk of blinding and of allocation concealment

Supplementary Table 11. Qualitative assessment of the evidence on the comparison between antiplatelet versus OAC therapies

Quality assessment						
№ of participants (studies) follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
OUTCOME: STROKE						
361 (20 observational studies) [a]	Serious [b]	Not serious	Not serious	Serious [b]	None	⊕◯◯◯ VERY LOW
OUTCOME: MAJOR BLEEDING						
1436 (14 observational studies) [c]	Serious [c]	Not serious	Not serious	Serious [d]	None	⊕◯◯◯ VERY LOW

Explanations
a. 1 RCT on ASA vs. OAT, 3 studies with multivariate adjustement and 16 observational studies.
b. Due to large number of studies without randomisation or multivariate adjustement (16/20)
c. 1 RTC, 13 studies without multivariate adjustement
d. Only one RCT

Supplementary Table 12. Quality of evidence grades.

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Supplementary Figure legends

Supplementary Figure 1. Comparison of the rate of PFO detection in studies using TOE or autopsy.
Top: TOE studies yielded a significantly lower prevalence of PFO 13% (95% CI: 8%-18%) as compared to autopsy studies 25% (95% CI: 20%-29%), p=0.004.
Bottom: Results of the single studies [179–203]. For details see the text in **Supplementary Appendix 4**.

Supplementary Figure 2. Meta-analysis of diagnostic accuracy studies comparing c-TCD vs. c-TOE.
A. Forest plot for sensitivity and specificity. As compared with c-TOE, c-TCD yielded a sensitivity of 0.94 (0.92-0.95) and a specificity 0.92 (0.91-0.93). The inconsistency estimates were 67% for sensitivity and 73% for specificity.
B. At receiver operating characteristics (ROC) curve analysis, the AUC was 0.97.

Supplementary Figure 3. Meta-analysis of diagnostic accuracy studies comparing c-TTE vs. c-TOE.
A. Forest plot for sensitivity and specificity. As compared with c-TOE, c-TTE yielded a sensitivity 0.88 (0.86-0.89) and a specificity of 0.82 (0.78-0.84). The inconsistency estimates were 78% for sensitivity and 83% for specificity.
B. At ROC curve analysis, the AUC was 0.91.

Supplementary Figure 4. Outcomes in patients undergoing percutaneous closure or medical therapy.

A. Forest plot for the risk of stroke recurrence in overall RCTs
B. Forest plot for the risk of stroke recurrence in RCTs with a high prevalence of high-risk PFO patients vs. those in which patients were unselected for PFO features
C. Forest plot for the risk of TIA recurrence
D. Forest plot for the risk of Death

Supplementary Figure 5. Sub-group analysis according to PFO features.
Overall, in this subgroup of patients selected only on the PFO characteristics [atrial septal aneurism, moderate-to-severe shunt (i.e. "relevant shunt"), PFO size >2 mm, atrial septal hypermobility], percutaneous closure yielded a lower risk reduction than observed in Panel A (OR 0.54 vs. 0.38), suggesting that additional risk resides in other clinical and/or anatomical parameters.
In patients with high-risk PFO characteristics, PFO closure yielded a statistically significant lower risk of stroke as compared to medical therapy. Moderate heterogeneity was still present in this high-risk subgroup, suggesting different roles of the considered PFO features in different patients.
In patients with low-risk PFO characteristics, PFO closure did not yield statistically significant differences as compared to medical therapy. No heterogeneity was found across the subgroups of different studies.

Supplementary Figure 6. PRISMA flow chart for the review of studies on the predictors of stroke in patients with cryptogenic stroke and a PFO.

Supplementary Figure 7. Forest plot for the risk of stroke recurrence in studies comparing OAC with antiplatelet therapy for cryptogenic solid systemic embolism.

Supplementary Figure 8. Forest plot for the risk of major bleedings in studies comparing OAC with antiplatelet therapy for cryptogenic cerebral or systemic embolism.

Supplementary Figure 9. Risk of atrial fibrillation in studies comparing PFO closure with medical therapy for cryptogenic cerebral or systemic embolism.
A. Forest plot for the risk of atrial fibrillation
B. Forest plot for the risk of atrial fibrillation in the first 45 days after the procedure
C. Forest plot for the risk of atrial fibrillation beyond 45 days after the procedure

Supplementary Figure 10. Forest plot for the risk of atrial fibrillation according to the type of device used for PFO closure in studies comparing PFO closure with medical therapy for cryptogenic cerebral or systemic embolism.

Supplementary Figure 11. L'Abbé plots for the risk of TIA and stroke after PFO closure according to the length of dual antiplatelet therapy.
A. TIA (β=-8.10; 95% CI: -10.11 to 0.45; p=0.98)
B. Stroke (β=0.061; 95% CI: -0.14 to 0.25; p=0.57)

Supplementary Figure 12. Risk of stroke recurrence in patients undergoing OAC or antiplatelet therapy in studies comparing PFO closure with medical therapy for cryptogenic cerebral or systemic embolism.
A. Forest plot for the risk of recurrent stroke in patients undergoing antiplatelet therapy or percutaneous closure
B. Forest plot for the risk of recurrent stroke in patients undergoing OAC or percutaneous closure (excluding CLOSE trial data)
C. Forest plot for the risk of recurrent stroke in patients undergoing OAC or percutaneous closure (including CLOSE trial published data)

Supplementary Figure 13. Risk of stroke recurrence according to the type of index event in studies comparing PFO closure with medical therapy for cryptogenic cerebral or systemic embolism.

Supplementary Figure 14. Risk of stroke recurrence according to the type of device used for PFO closure in studies comparing PFO closure with medical therapy for cryptogenic cerebral or systemic embolism.

Supplementry Figure 15. PRISMA flow chart for the review of studies on the RoPE score.

Supplementary Figure 16. PRISMA flow chart for the review of RCTs comparing inseartable cardiac monitors with intermittent recordings to diagnose atrial fibrillation in patients with PFO-associated left circulation thromboembolism

Supplementary Figure 17. PRISMA flow chart for the review of RCTs comparing PFO closure with medical therapy.

Supplementary Figure 18. PRISMA flow chart for the review of studies comparing OAC with antiplatelet therapy for secondary prevention of stroke, TIA or systemic solid embolism in patients with previous cryptogenic left embolism.

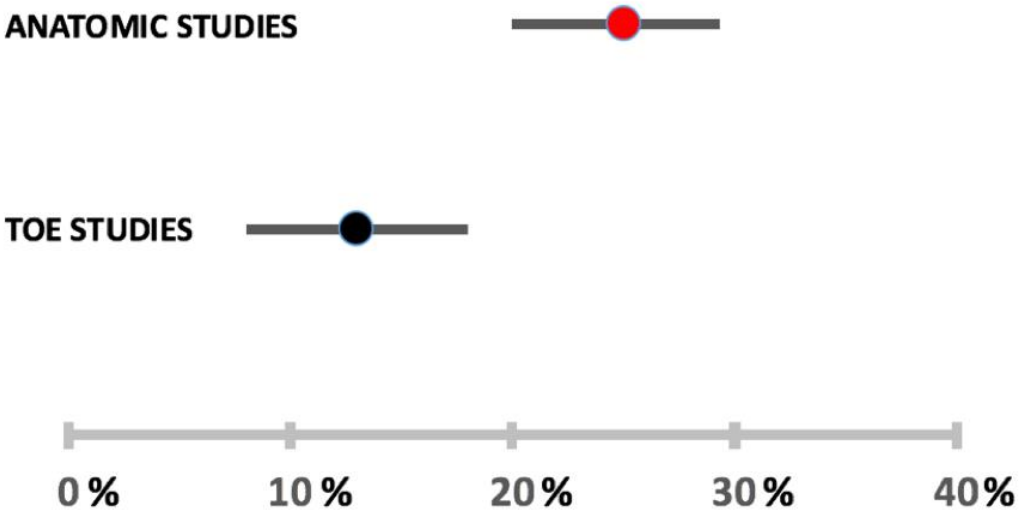
Supplementary Figure 19. PRISMA flow chart for the review of studies investigating the accuracy of PFO diagnostic tests.

Supplementary Figure 20. PRISMA flow chart for the review of studies investigating the accuracy of PFO diagnostic tests.

Supplementary Figure 21. Simplified scheme of the interacting network of processes underlying clinical manifestations associated with PFO.

Supplementary Figures

Supplementary Figure 1.



C-TOE STUDIES

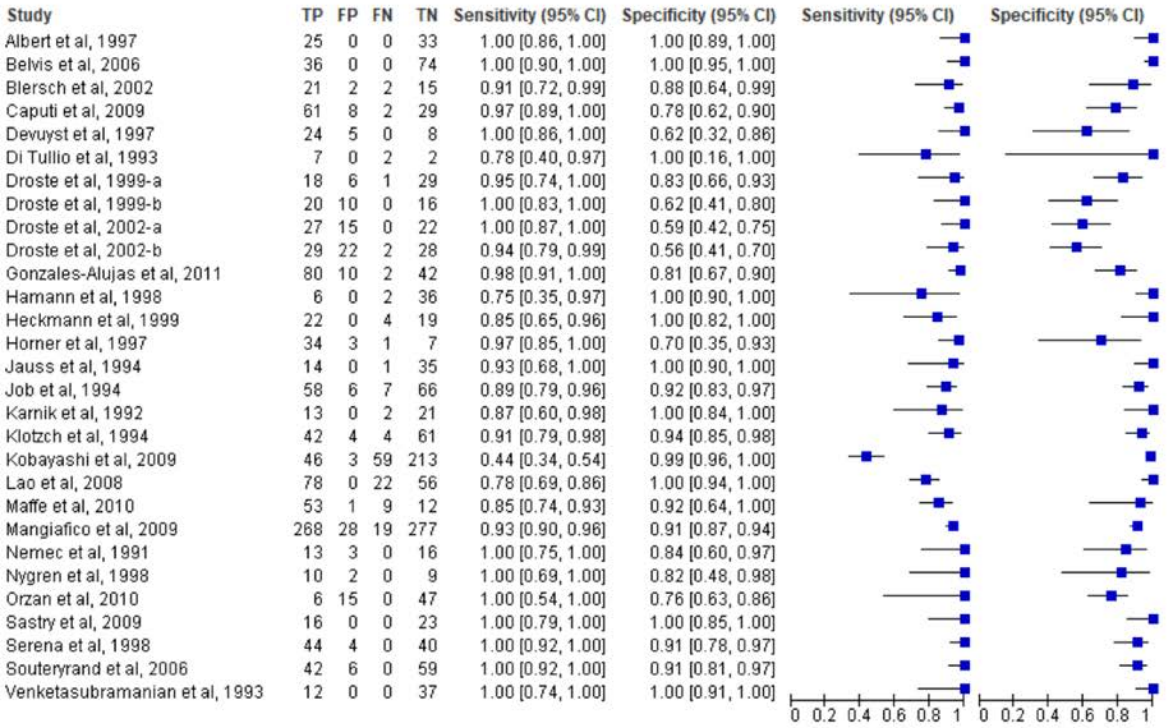
Year	Hearts	PFO (%)
1988	40	2.5
1989	50	12
1989	64	27
1989	479	6.1
1991	50	26
1991	50	8
1991	150	20
1991	79	17
1991	63	3.2
1995	1000	9.2
1999	581	25.6
2003	1365	5.3
2006	939	15.6
2013	20	10
TOTAL	2025	12

AUTOPSY STUDIES

Year	Hearts	PFO (%)
1897	399	26
1900	306	32
1918	1809	29
1931	4083	25
1934	500	17
1948	492	23
1972	144	35
1979	64	31
1984	965	27
1994	500	15
2015	103	13.6
TOTAL	9365	25

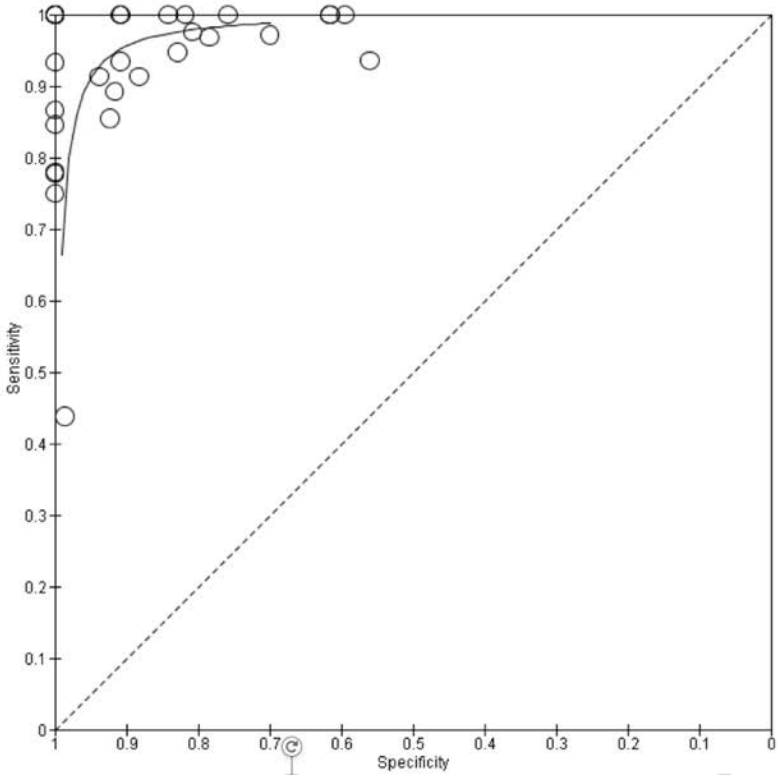
Supplementary Figure 2.

A



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Albert et al, 1997	25	0	0	33	1.00 [0.86, 1.00]	1.00 [0.89, 1.00]
Belvis et al, 2006	36	0	0	74	1.00 [0.90, 1.00]	1.00 [0.95, 1.00]
Blersch et al, 2002	21	2	2	15	0.91 [0.72, 0.99]	0.88 [0.64, 0.99]
Caputi et al, 2009	61	8	2	29	0.97 [0.89, 1.00]	0.78 [0.62, 0.90]
Devuyst et al, 1997	24	5	0	8	1.00 [0.86, 1.00]	0.62 [0.32, 0.86]
Di Tullio et al, 1993	7	0	2	2	0.78 [0.40, 0.97]	1.00 [0.16, 1.00]
Droste et al, 1999-a	18	6	1	29	0.95 [0.74, 1.00]	0.83 [0.66, 0.93]
Droste et al, 1999-b	20	10	0	16	1.00 [0.83, 1.00]	0.62 [0.41, 0.80]
Droste et al, 2002-a	27	15	0	22	1.00 [0.87, 1.00]	0.59 [0.42, 0.75]
Droste et al, 2002-b	29	22	2	28	0.94 [0.79, 0.99]	0.56 [0.41, 0.70]
Gonzales-Alujas et al, 2011	80	10	2	42	0.98 [0.91, 1.00]	0.81 [0.67, 0.90]
Hamann et al, 1998	6	0	2	36	0.75 [0.35, 0.97]	1.00 [0.90, 1.00]
Heckmann et al, 1999	22	0	4	19	0.85 [0.65, 0.96]	1.00 [0.82, 1.00]
Horner et al, 1997	34	3	1	7	0.97 [0.85, 1.00]	0.70 [0.35, 0.93]
Jauss et al, 1994	14	0	1	35	0.93 [0.68, 1.00]	1.00 [0.90, 1.00]
Job et al, 1994	58	6	7	66	0.89 [0.79, 0.96]	0.92 [0.83, 0.97]
Karnik et al, 1992	13	0	2	21	0.87 [0.60, 0.98]	1.00 [0.84, 1.00]
Klotzch et al, 1994	42	4	4	61	0.91 [0.79, 0.98]	0.94 [0.85, 0.98]
Kobayashi et al, 2009	46	3	59	213	0.44 [0.34, 0.54]	0.99 [0.96, 1.00]
Lao et al, 2008	78	0	22	56	0.78 [0.69, 0.86]	1.00 [0.94, 1.00]
Maffe et al, 2010	53	1	9	12	0.85 [0.74, 0.93]	0.92 [0.64, 1.00]
Mangiafico et al, 2009	268	28	19	277	0.93 [0.90, 0.96]	0.91 [0.87, 0.94]
Nemec et al, 1991	13	3	0	16	1.00 [0.75, 1.00]	0.84 [0.60, 0.97]
Nygren et al, 1998	10	2	0	9	1.00 [0.69, 1.00]	0.82 [0.48, 0.98]
Orzan et al, 2010	6	15	0	47	1.00 [0.54, 1.00]	0.76 [0.63, 0.86]
Sastry et al, 2009	16	0	0	23	1.00 [0.79, 1.00]	1.00 [0.85, 1.00]
Serena et al, 1998	44	4	0	40	1.00 [0.92, 1.00]	0.91 [0.78, 0.97]
Souteyrand et al, 2006	42	6	0	59	1.00 [0.92, 1.00]	0.91 [0.81, 0.97]
Venketasubramanian et al, 1993	12	0	0	37	1.00 [0.74, 1.00]	1.00 [0.91, 1.00]

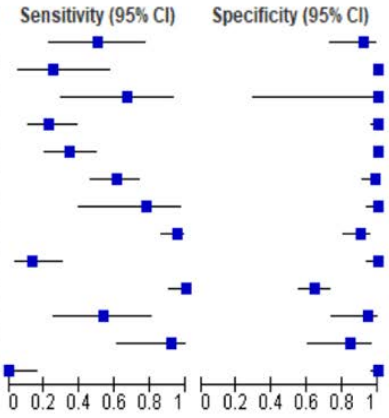
B



Supplementary Figure 3.

A

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Belkin et al, 1994	7	2	7	22	0.50 [0.23, 0.77]	0.92 [0.73, 0.99]
de Bruijn et al, 2006	3	0	9	219	0.25 [0.05, 0.57]	1.00 [0.98, 1.00]
Di Tullio et al, 1993	6	0	3	3	0.67 [0.30, 0.93]	1.00 [0.29, 1.00]
Ha et al, 2001	9	0	31	96	0.23 [0.11, 0.38]	1.00 [0.96, 1.00]
Hausmann et al, 1992	15	0	29	154	0.34 [0.20, 0.50]	1.00 [0.98, 1.00]
Kuhl et al, 1999	31	1	20	59	0.61 [0.46, 0.74]	0.98 [0.91, 1.00]
Madala et al, 2004	7	0	2	55	0.78 [0.40, 0.97]	1.00 [0.94, 1.00]
Maffe' et al, 2010	58	7	3	62	0.95 [0.86, 0.99]	0.90 [0.80, 0.96]
Mesa et al, 2003	4	0	26	60	0.13 [0.04, 0.31]	1.00 [0.94, 1.00]
Monte et al, 2010	36	45	0	81	1.00 [0.90, 1.00]	0.64 [0.55, 0.73]
Nemec et al, 1991	7	1	6	18	0.54 [0.25, 0.81]	0.95 [0.74, 1.00]
Rahmouni et al, 2008	11	3	1	16	0.92 [0.62, 1.00]	0.84 [0.60, 0.97]
Siostrzonek et al, 1991	0	0	21	104	0.00 [0.00, 0.16]	1.00 [0.97, 1.00]



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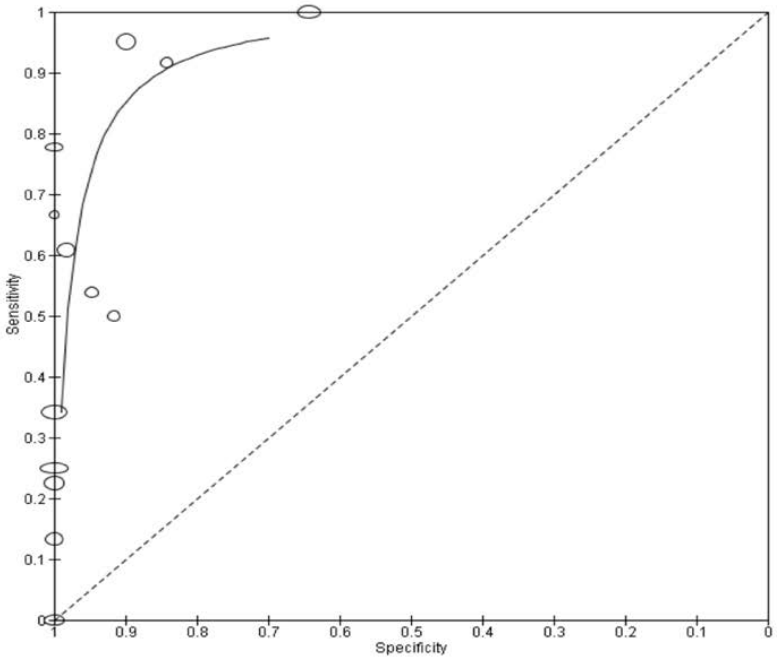
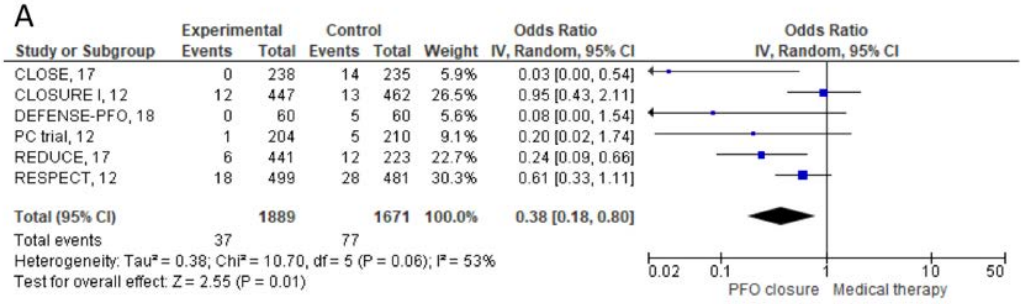


Supplementary Figure 4.

A



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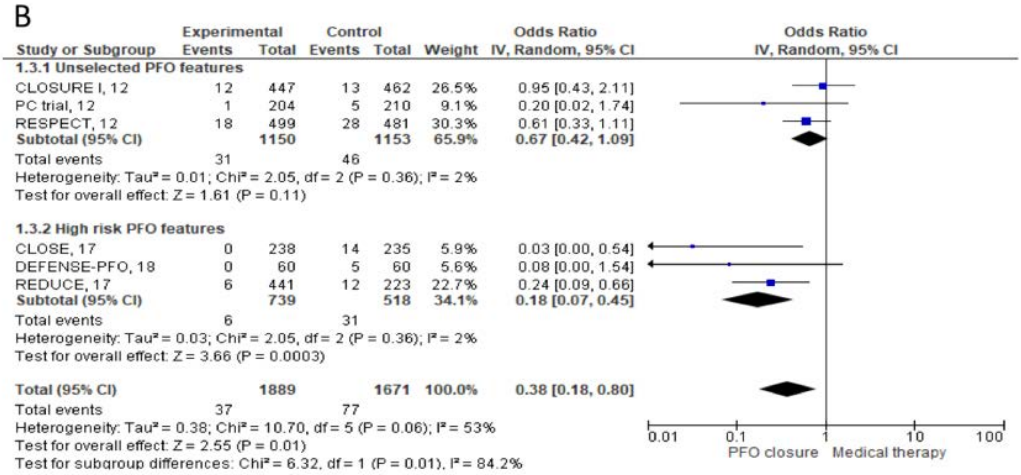
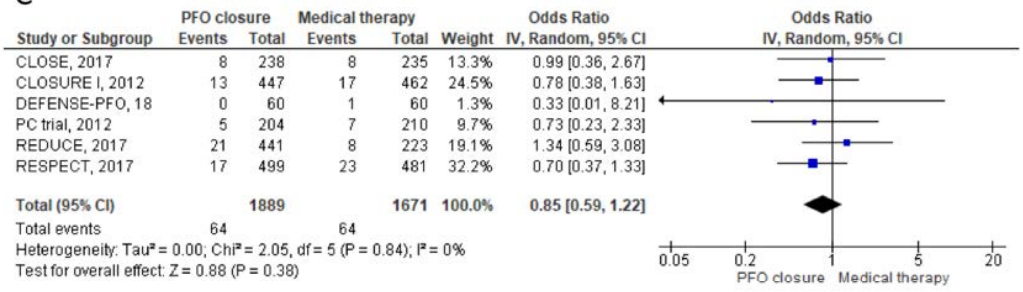
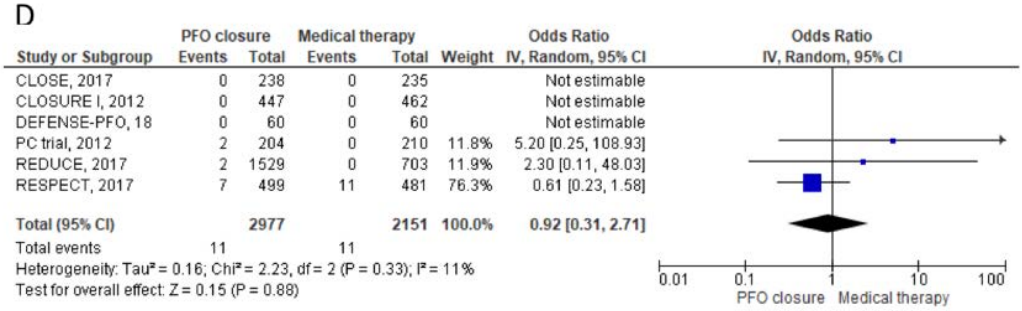


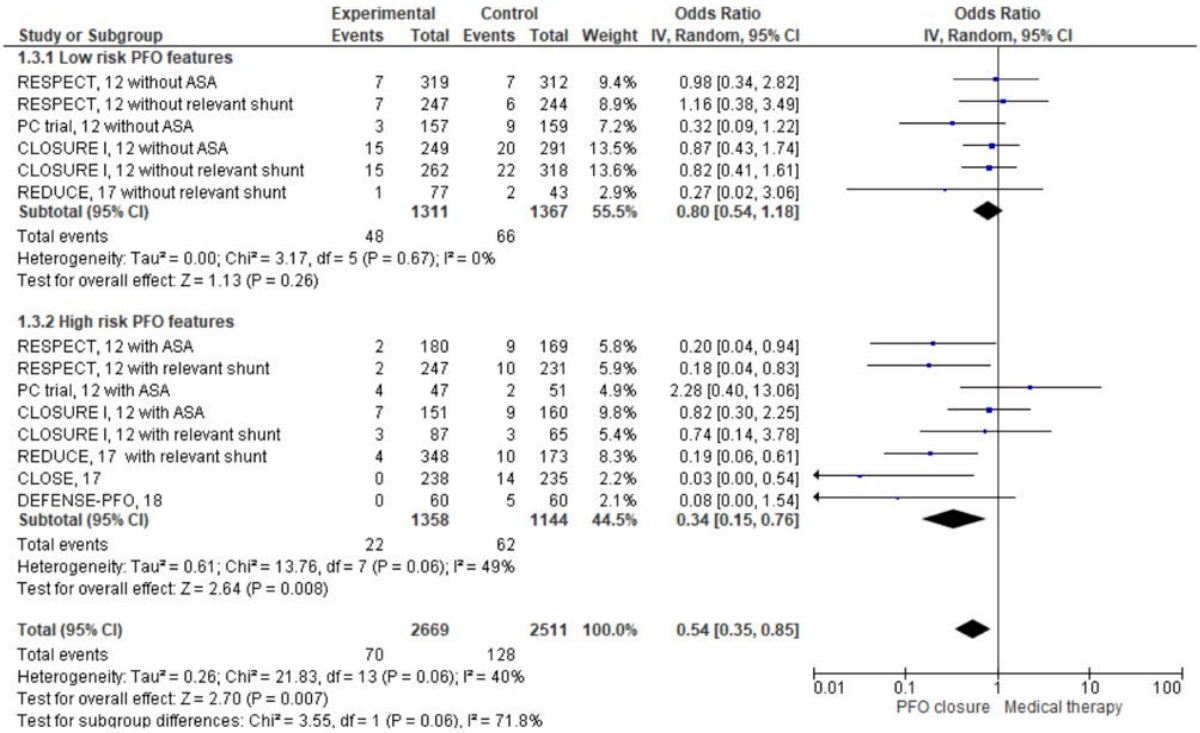
C



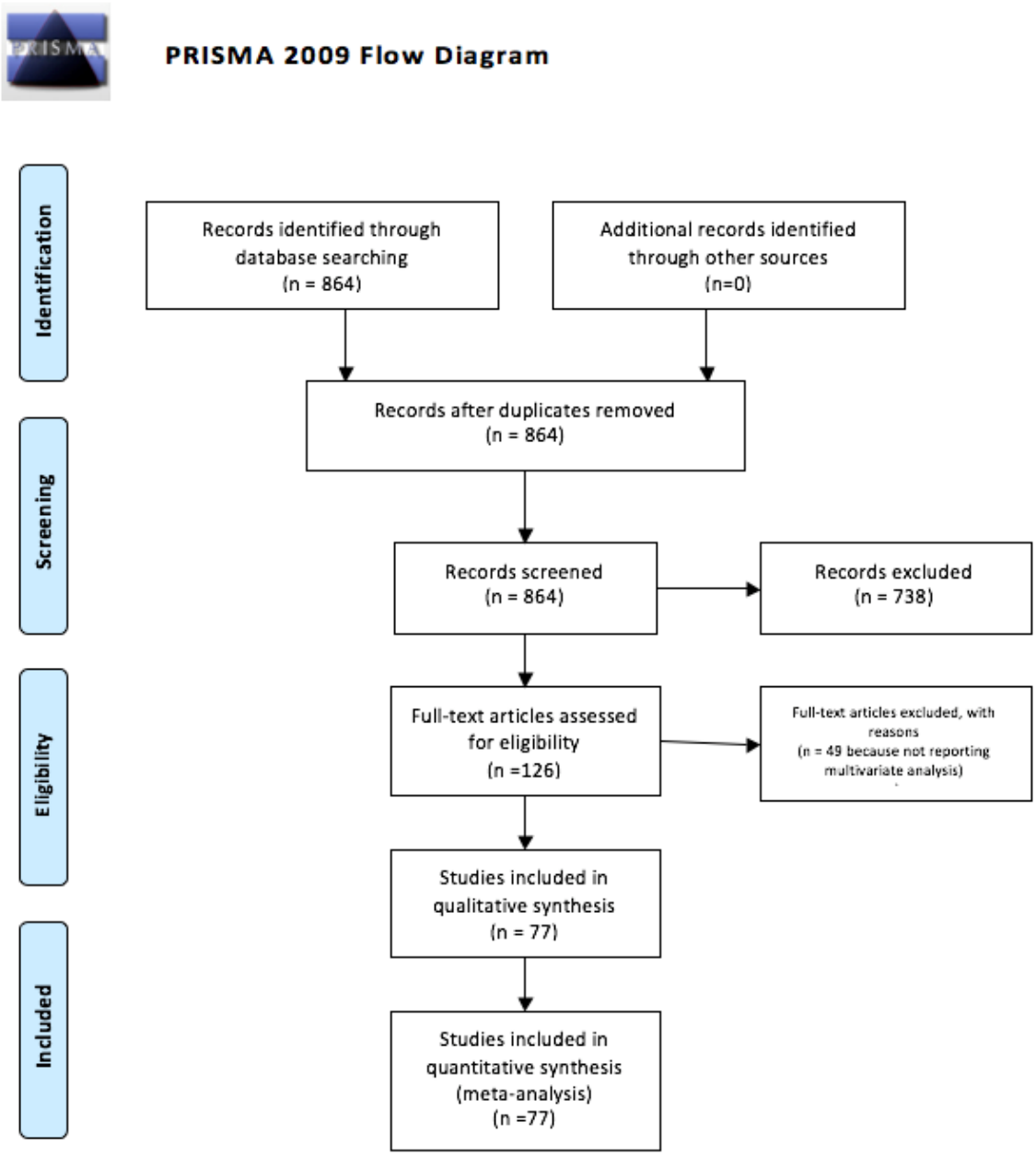
D



Supplementary Figure 5.



Supplementary Figure 6.



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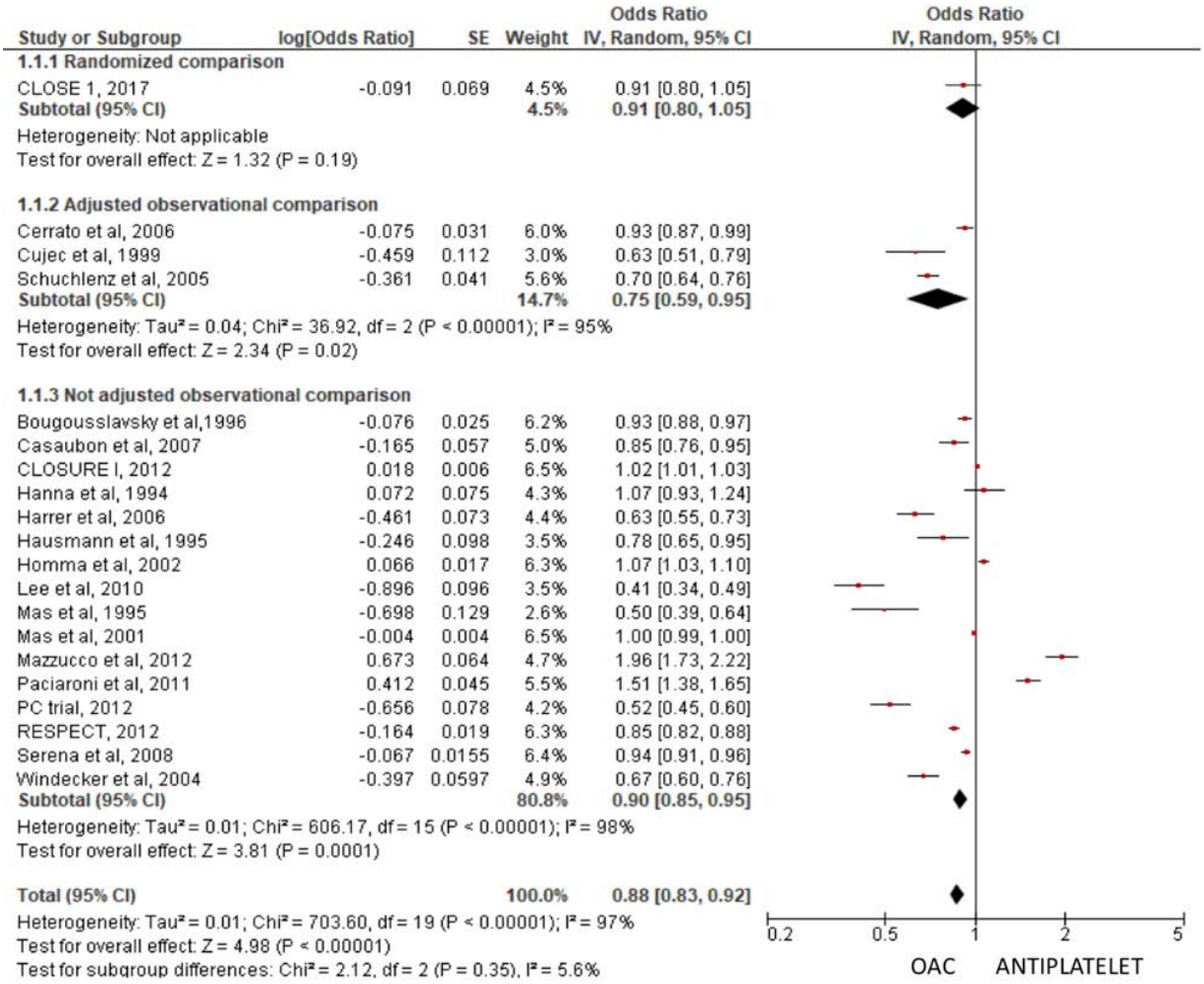
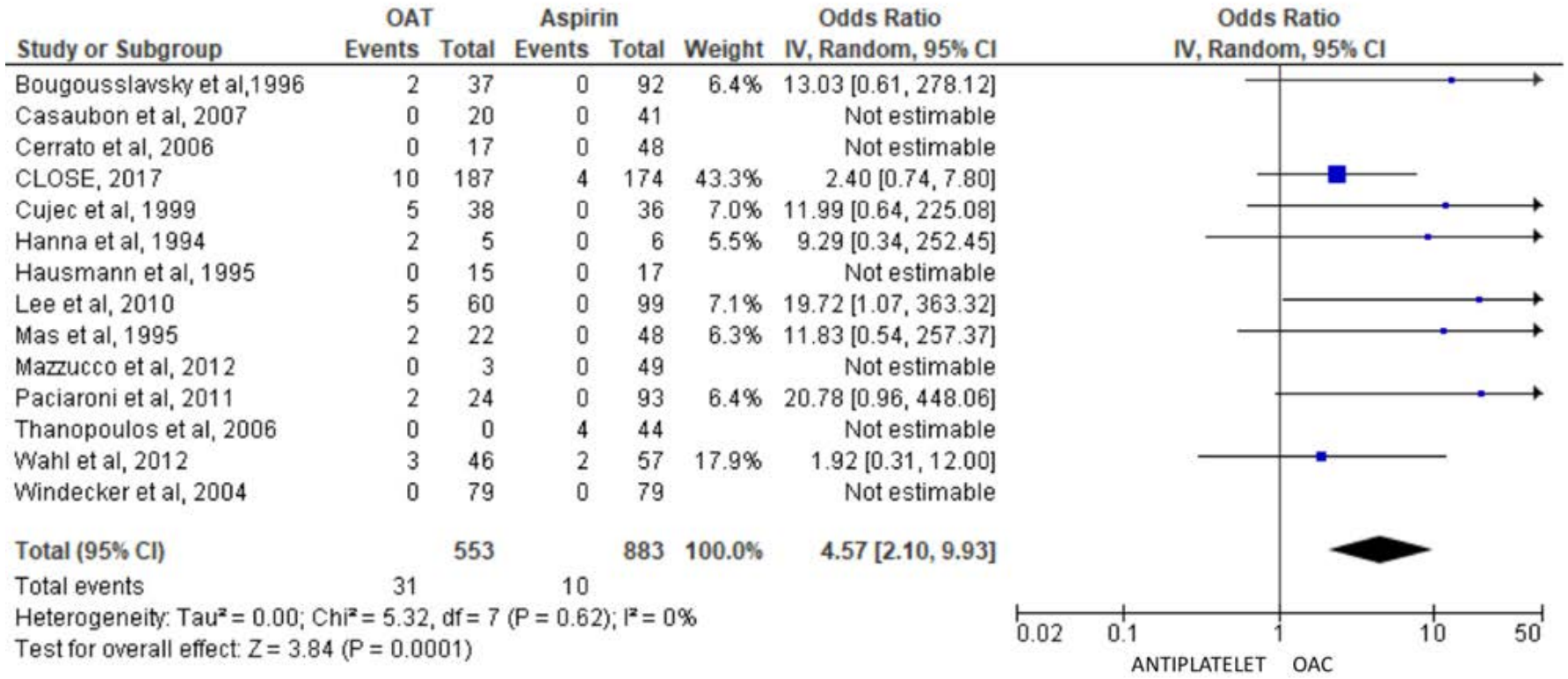
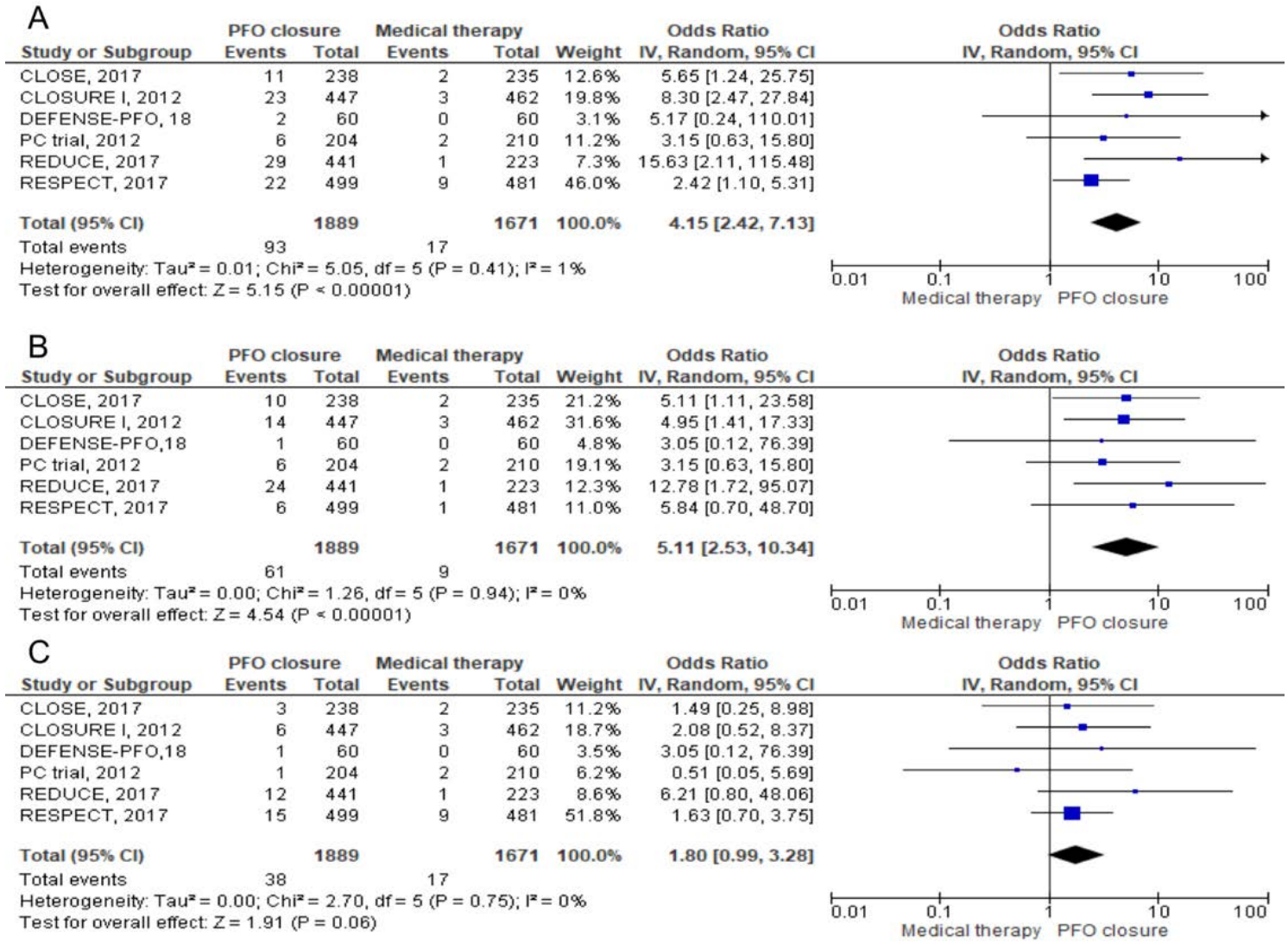
Supplementary Figure 7.



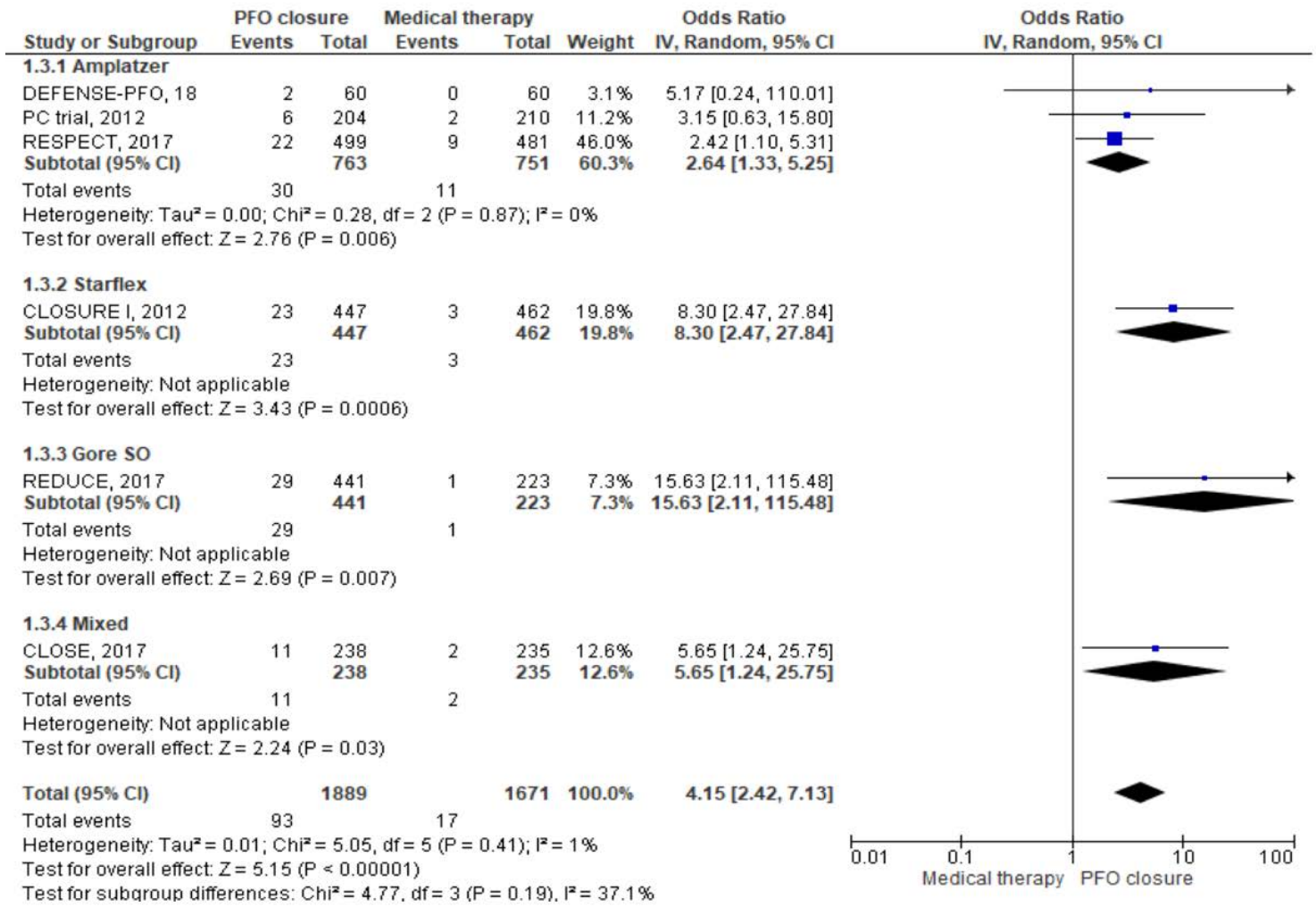
Supplementary Figure 8.



Supplementary Figure 9.

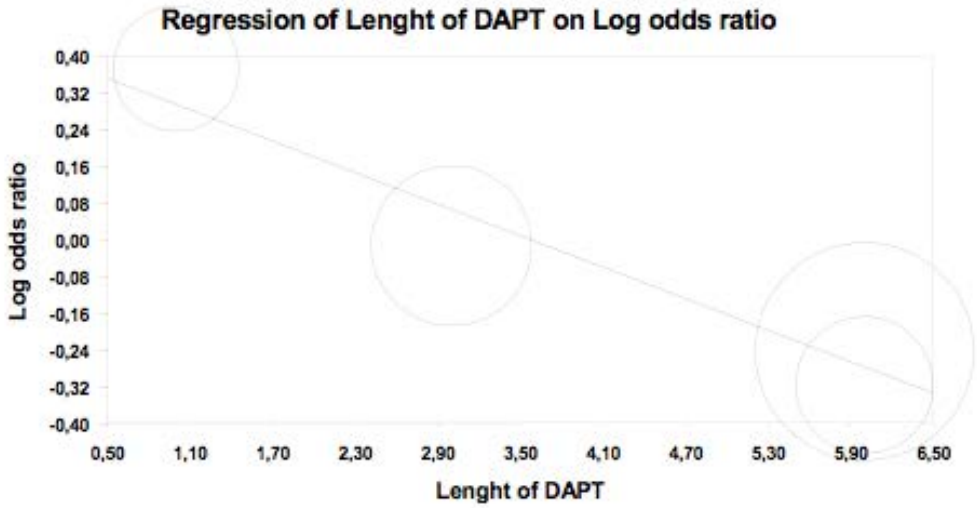


Supplementary Figure 10.

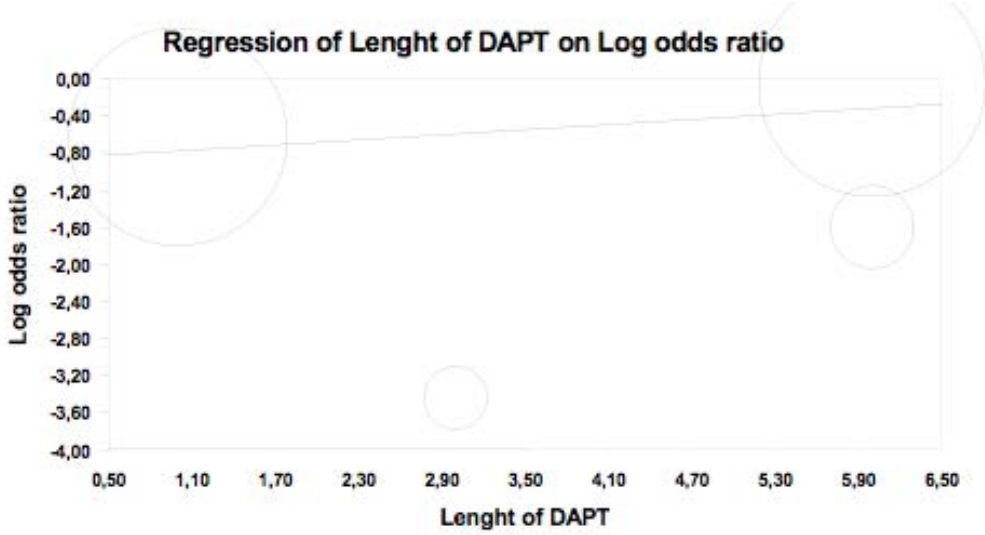


Supplementary Figure 11.

A. TIA



B. STROKE



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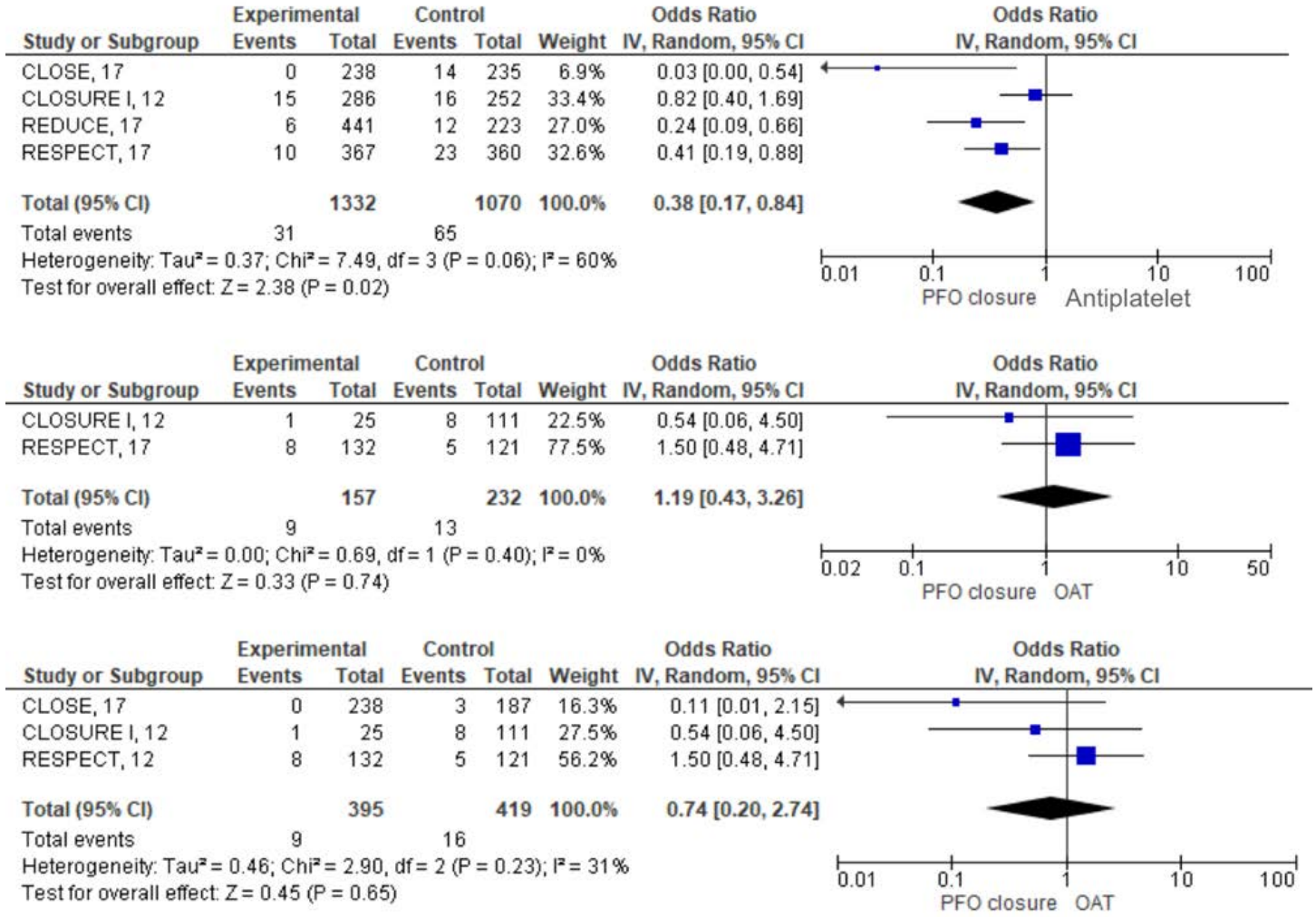

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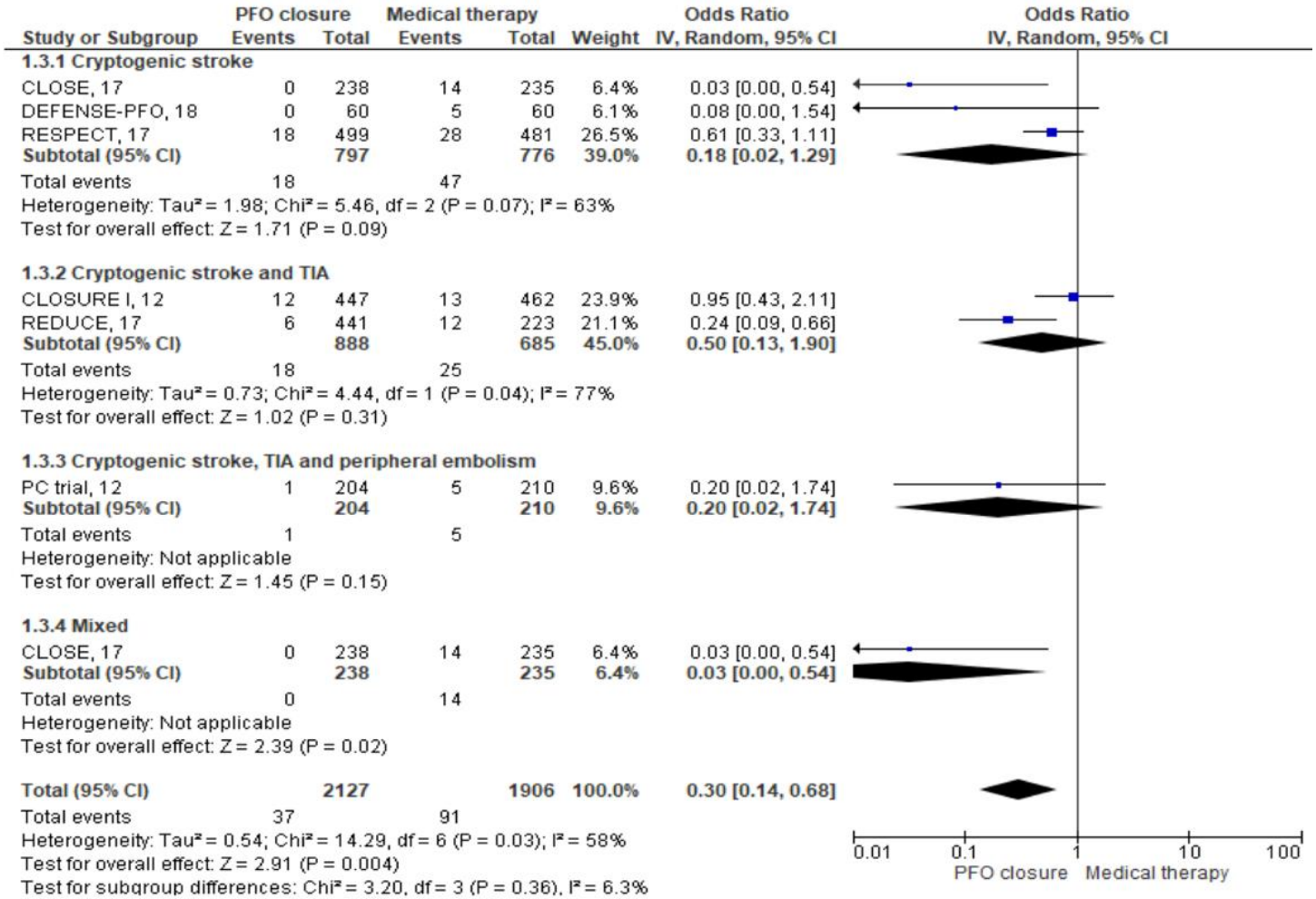
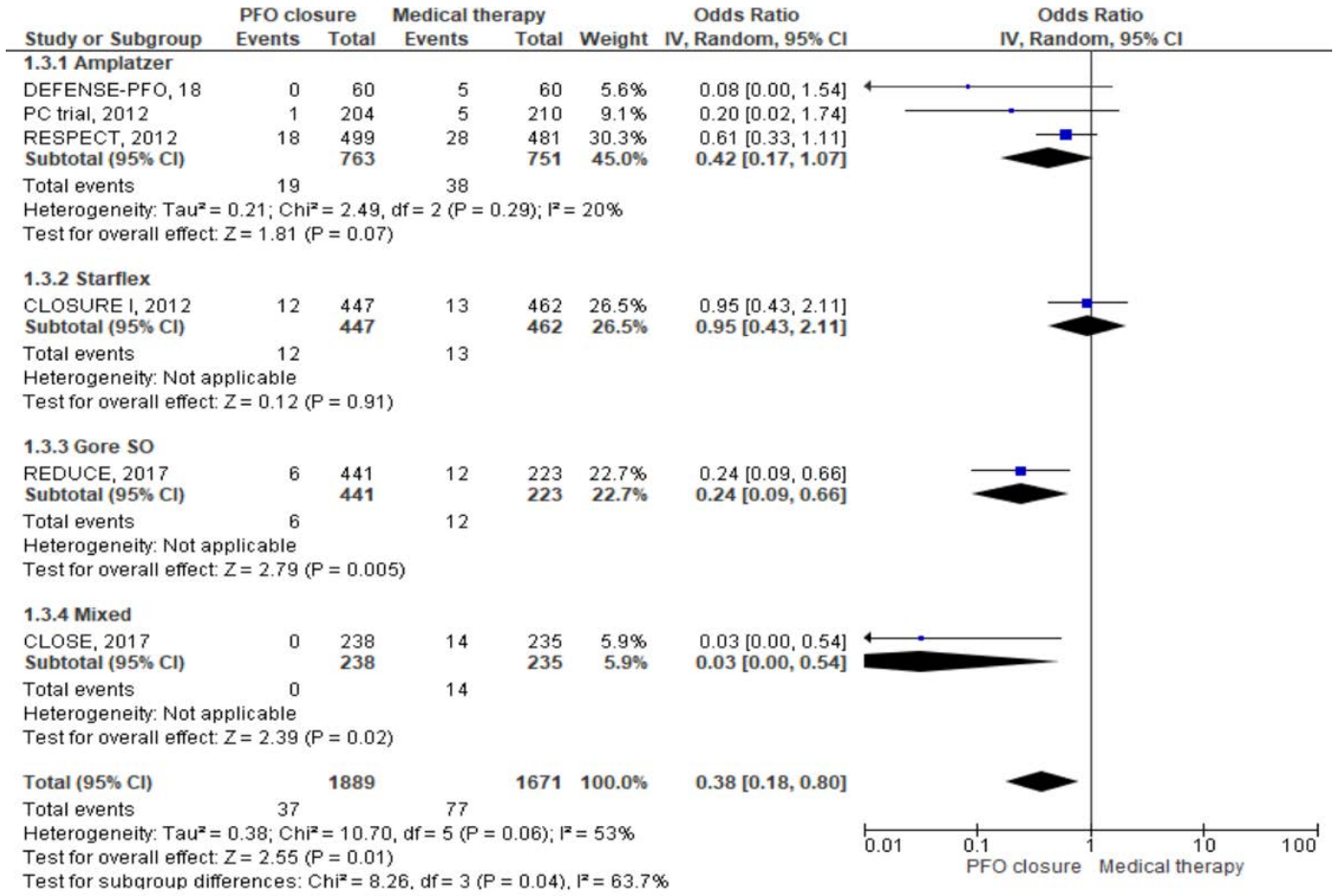
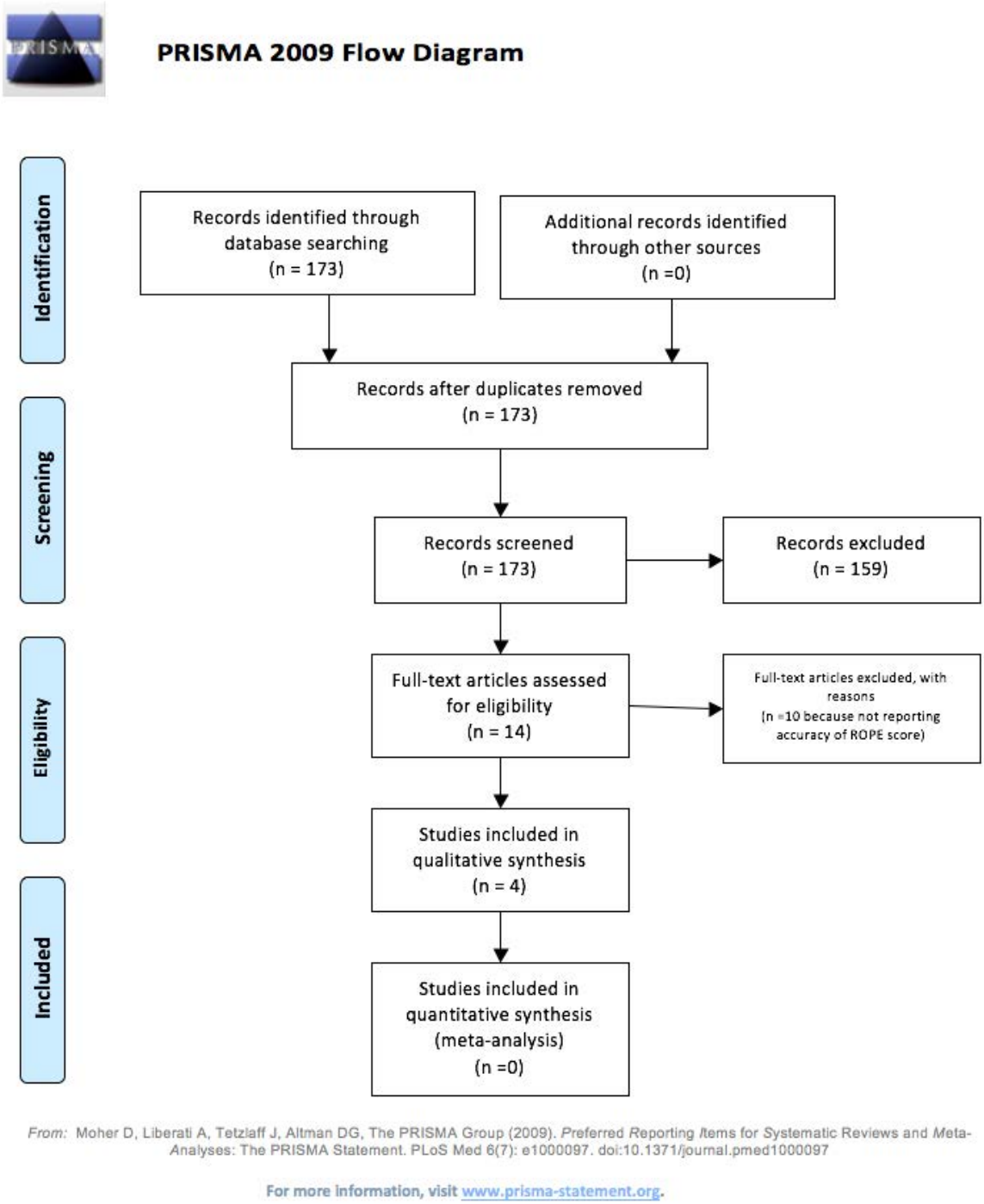


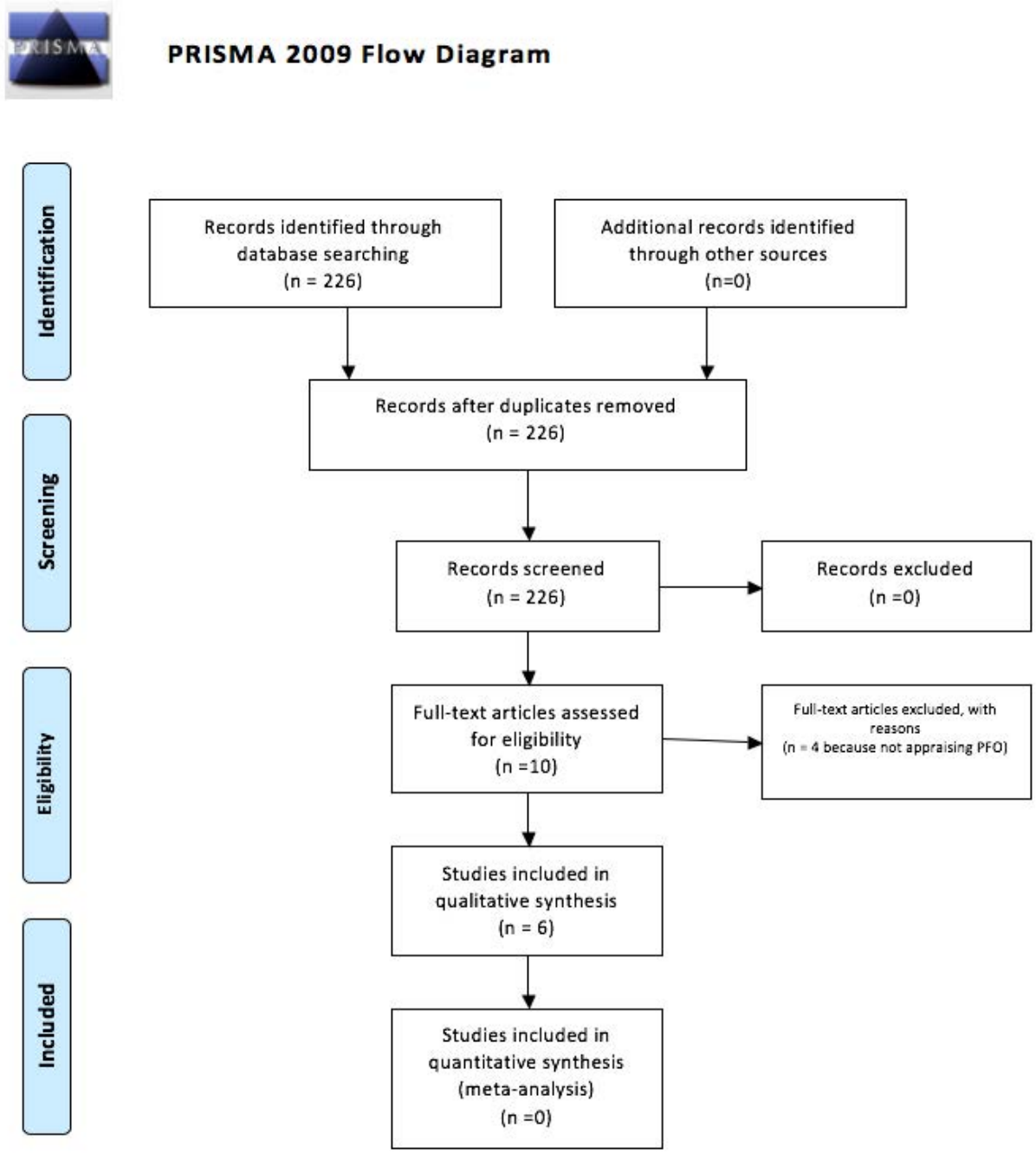
Supplementary Figure 14.



Supplementary Figure 15.



Supplementary Figure 16.



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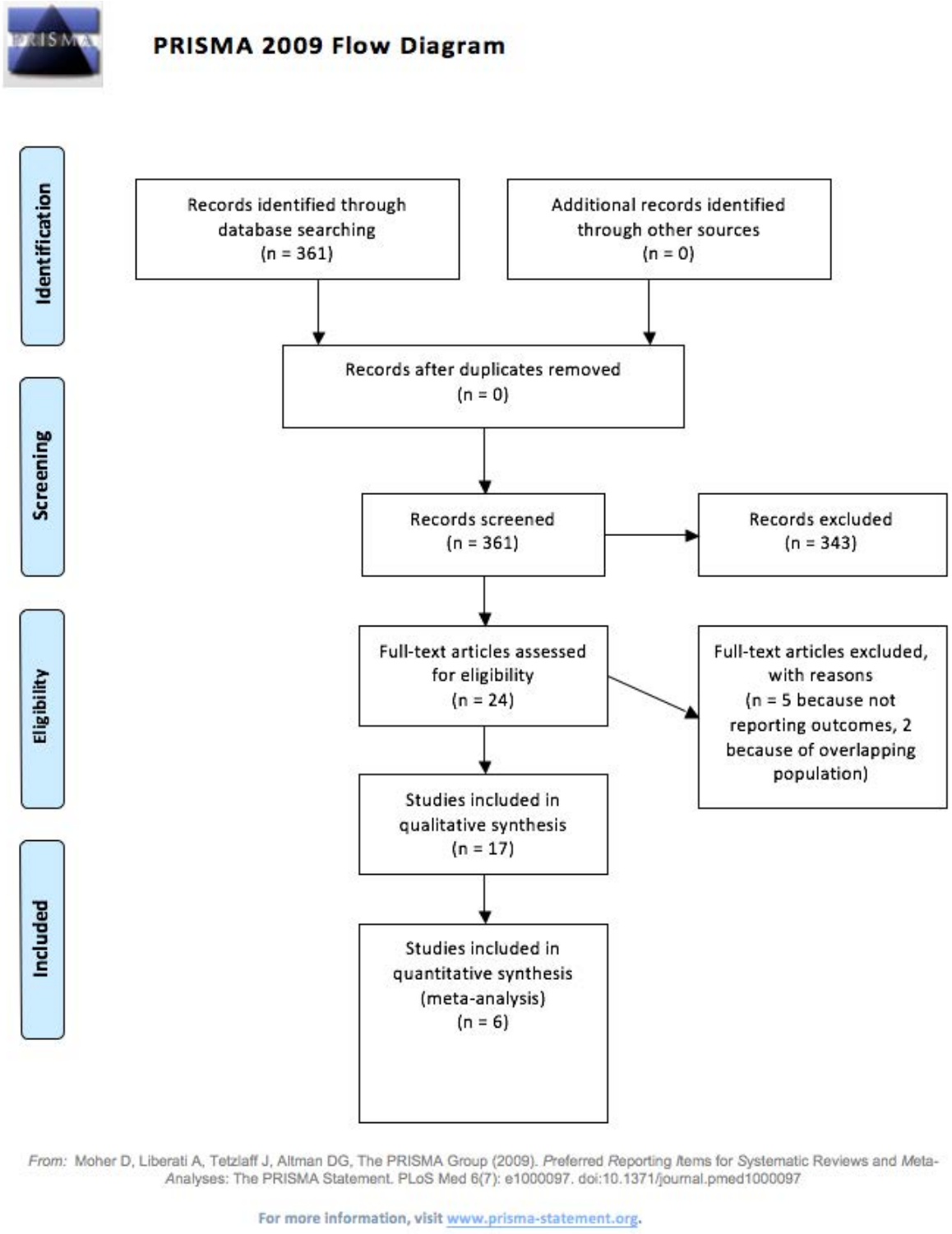
Supplementary Figure 17.



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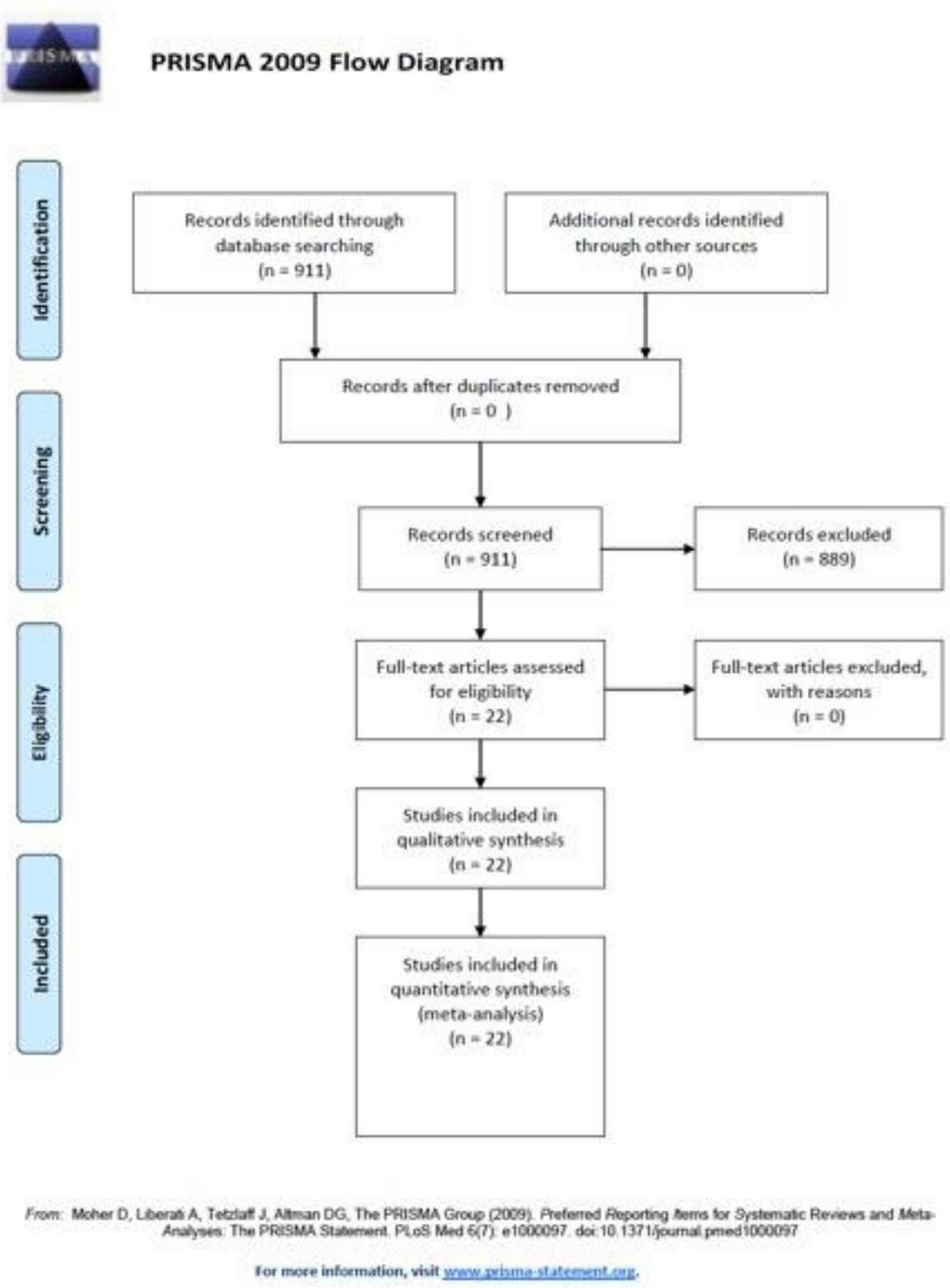

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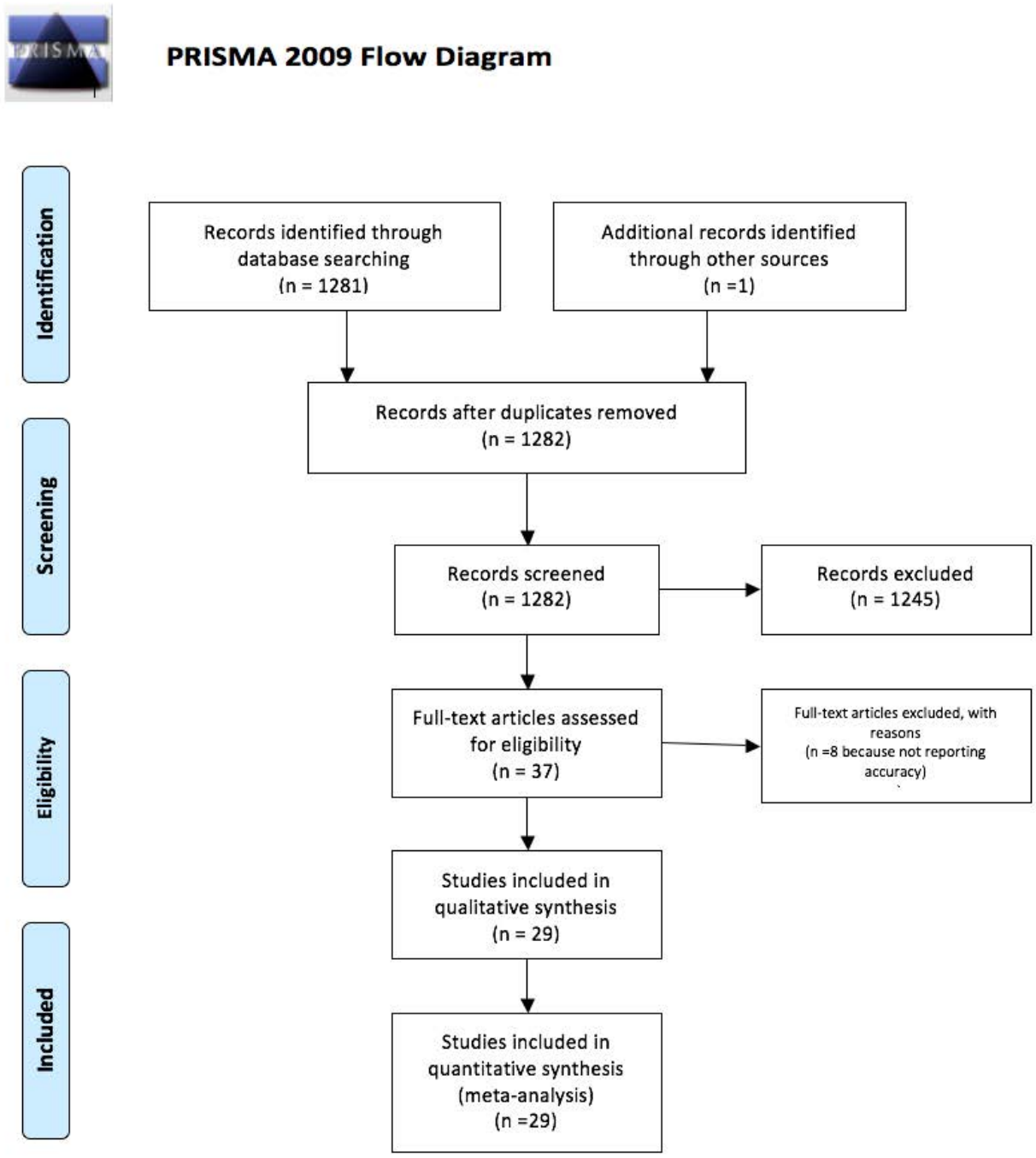

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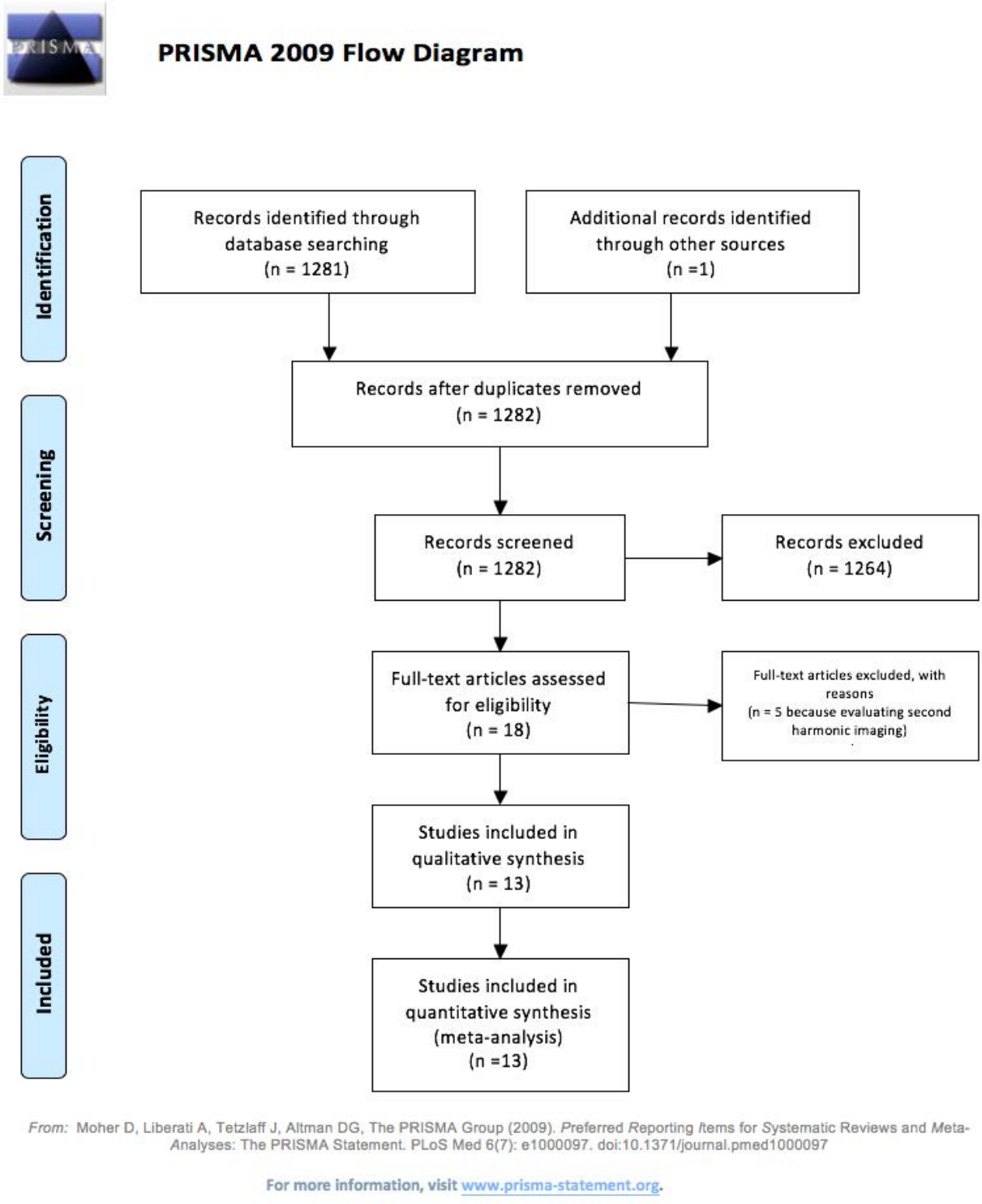
Supplementary Figure 20.



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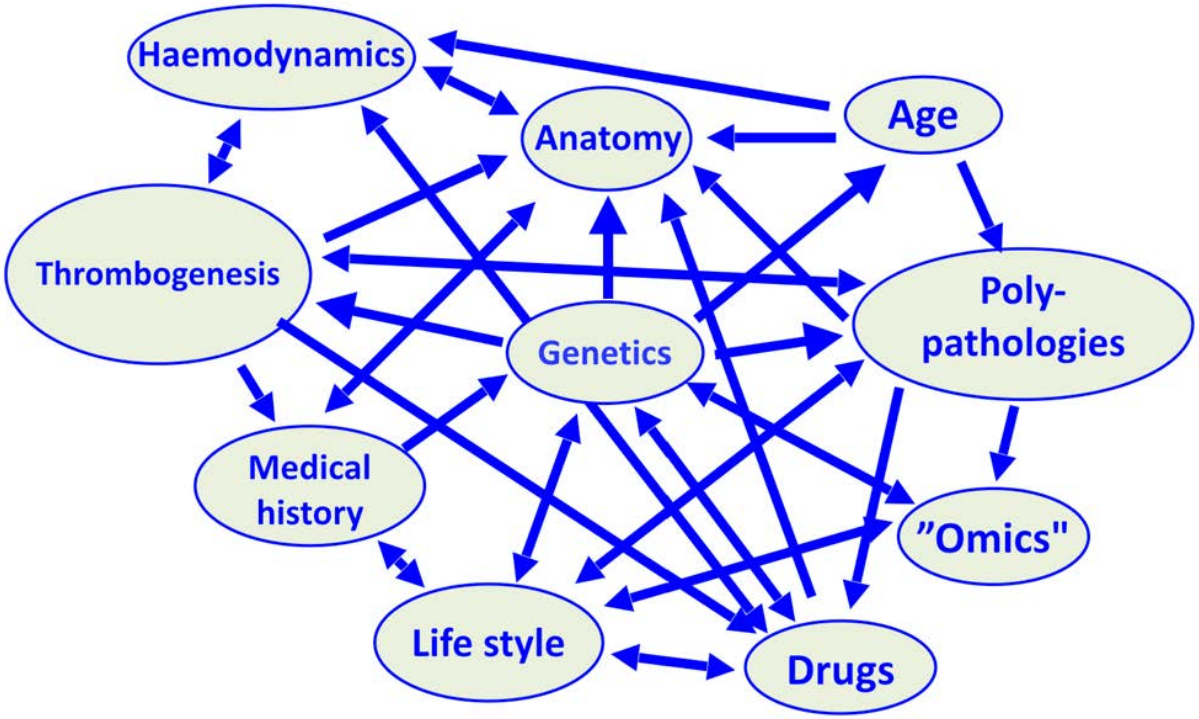

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