

Patent foramen ovale and cryptogenic stroke: diagnosis and updates in secondary stroke prevention

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The recently published DEFENSE PFO trial was concordant with the results presented here (Lee PH, Song JK, Kim JS, Heo R, *et al*. Cryptogenic stroke and high risk patent foramen ovale: The DEFENSE PFO trial. *J Am Coll Cardiol*. 2018;71(20):2335–42.)

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ABSTRACT

The patent foramen ovale (PFO), given its high prevalence in the general population and especially in patients with cryptogenic stroke, has long generated investigation and debate on its propensity for stroke by paradoxical embolism and its management for stroke prevention. The pendulum has swung for percutaneous PFO closure for secondary stroke prevention in cryptogenic stroke. Based on a review of current evidence, the benefit from PFO closure relies on careful patient selection: those under the age of 60 years with few to no vascular risk factors and embolic-appearing stroke deemed cryptogenic after thorough evaluation. As these data look towards influencing guideline statements and device approvals in the future, patient selection remains the crucial ingredient for clinical decision making and future trials.

INTRODUCTION

The connection between the left and right atria at the fossa ovale in fetal circulation remains open during adulthood in a quarter of the general population, with the prevalence reported higher in those <30 years old and less in those >80 years old.¹ This patent foramen ovale (PFO) has been implicated as an aetiology in cryptogenic stroke, comprising a hefty third of all strokes. The opportunity for risk stratification and secondary stroke prevention in this cohort—cryptogenic stroke with PFO—underscored a number of randomised controlled trials (RCT) leading to a Food and Drug Administration (FDA) approval of the Amplatzer PFO Occluder in October 2016. But at that time, the trials still yielded unconvincing data on the efficacy of PFO closure. Recently a new series of trials have tackled some challenges from previous trials and provided more affirmative data on the utility of PFO closure for a select patient population.

This review will discuss the modalities of diagnosing PFO, strategies to assess the risk of PFO in causing paradoxical embolism, updated evidence on the efficacy of percutaneous PFO closure for secondary stroke prevention of cryptogenic stroke, and

antithrombotic choices in those with PFO and stroke.

DIAGNOSIS OF PFO

A transthoracic echocardiogram (TTE) is part of the routine stroke work-up and a non-invasive way to detect PFO with 99% specificity.² The presence of PFO is determined by agitated saline bubbles shunting to the left atrium within three cardiac cycles (a small shunt 3–10 bubbles, medium 10–20 bubbles and large >20 bubbles),³ often augmented by the Valsalva manoeuvre provoking bubbles to pass with elevated right atrium pressure. However due to the low sensitivity of TTE for PFO detection (46%), a high suspicion for PFO with a negative TTE will often lead to ordering a transoesophageal echocardiogram (TEE), which exhibits high correlation of PFO detection with autopsy findings and is often considered the gold standard (89% sensitivity; 92% specificity).⁴ Although the TEE affords a better look at cardiac structures, it is semi-invasive, with sedation that often limits or precludes the Valsalva manoeuvre.

Transcranial Doppler (TCD) with emboli detection has been shown to be even more sensitive than TEE (96%) and just as specific compared with TTE or TEE.⁵ However TCDs cannot detect additional and potentially relevant structural features such as atrial septal aneurysm (ASA) and septal mobility—features that affect shunt size characterisation—nor really distinguish between intracardiac and intrapulmonary shunts such as pulmonary arteriovenous malformations.^{3 6} An ASA is present when redundant tissue in the fossa ovale causes >10–15 mm of bulging into the left or right atrium during respiration, and may herald a greater recurrent stroke risk compared with PFO alone, although data supporting this are limited and potentially biased.⁷ Still, Tobe *et al*⁸ found that a shunt grade determined by TCD can be a stronger predictor of transient ischaemic attack (TIA) or stroke than shunt detection by TEE, and



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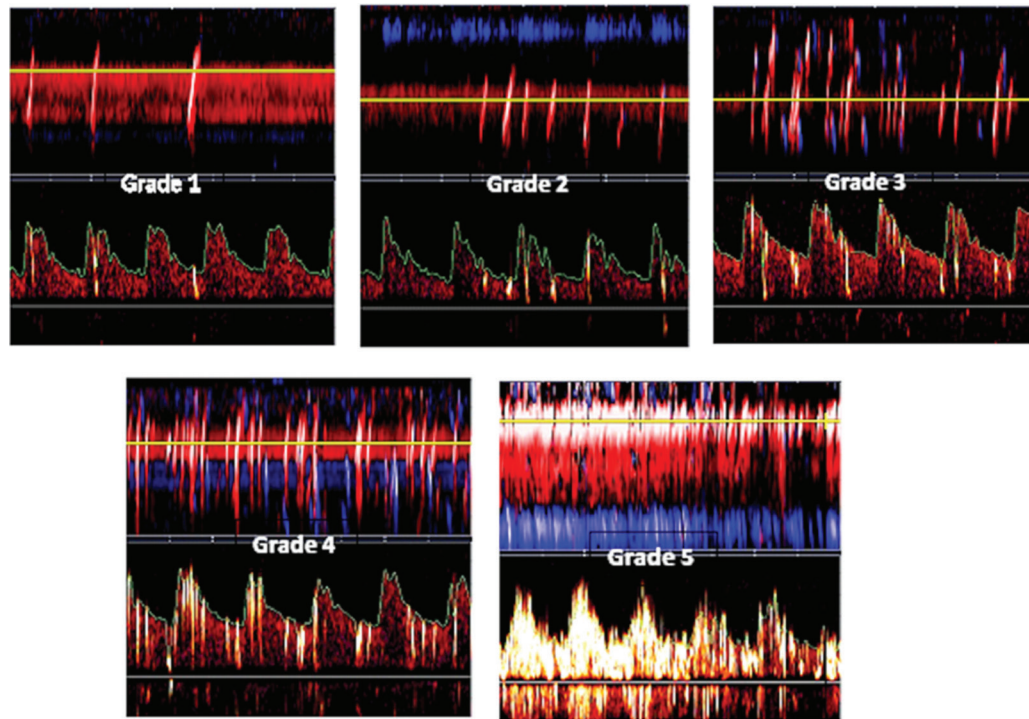


Figure 1 Transcranial Doppler detection of the right-to-left shunt missed by transoesophageal echocardiography with sedation. Microemboli identified as high-intensity transient signals related to the injection of bubbles (agitated saline) can be graded as follows: grade 0, no microemboli detected in 60s; grade 1, 1–10 microemboli; grade 2, 11–30 microemboli; grade 3, 31–100 microemboli; grade 4, 101–300 microemboli; grade 5, >300 microemboli. (Reproduced from Tobe *et al*⁶ with permission from Elsevier.)

that TEE missed 15% of the shunts caught by TCD, and of those 40% were large shunts (grade 3 and higher). The authors postulated the importance of an awake Valsalva manoeuvre in shunt detection. TCD should not replace echocardiographic techniques to detect PFO and other shunt features, but can be a complementary and highly sensitive technique when performed by a properly trained and experienced operator (figure 1).

PARADOXICAL EMBOLISM VIA PFO AS STROKE AETIOLOGY

Cryptogenic stroke is often broadly defined to include patients with no clear source of stroke, but for this review cryptogenic stroke is diagnosed only after a thorough evaluation excluded other relevant aetiologies. PFO prevalence is up to 40% in patients with cryptogenic stroke, suggesting that it may be conduit for stroke caused by paradoxical embolism rather than just an incidental finding.^{8,9} However the stroke recurrence rate in patients with cryptogenic stroke with PFO is low, estimated at 1–2 strokes per 100 patient-years, and it is difficult to determine if those recurrent strokes are causally related to PFO.^{10,11} A PFO is postulated to serve as a conduit for paradoxical embolism to the brain from deep vein thrombosis (DVT) with pulmonary embolism (PE). Other mechanisms include thrombus in transit in the atrial septum and atrial arrhythmias causing thrombus formation and embolisation to the brain via PFO.¹²

A number of studies have examined the clinical clues that predict PFO's propensity for paradoxical embolism. Those with cryptogenic stroke and PFO have significantly lower prevalence of traditional stroke risk factors, such as diabetes, hypertension and coronary artery disease.^{7,13} A history of DVT or PE, prolonged travel, migraine, Valsalva manoeuvre preceding onset of stroke symptoms, sleep apnoea and waking up with stroke/TIA have been described as independent risk factors for PFO-associated cerebrovascular events.¹² In a retrospective study of 284 subjects with cryptogenic stroke, shunt grade ≥ 3 (defined as >31 microemboli per 60s) predicted TIA and stroke-free survival at ~3.4 years, while the presence of right-to-left shunt on TEE and ASA and septal mobility on TEE did not.⁵ Limitations included a small sample size with septal defect, and the results were possibly affected by TCD and TEE done on different days.

The data on shunt size and risk of stroke have been nebulous: while some studies suggest larger shunt increases the risk of stroke, others note no difference based on shunt size.^{7,14–16} This might be attributed to the poor reliability of shunt measurement by TCD or TEE. Investigators in the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) found no association between the presence of PFO and ASA with stroke or death. In fact, there was a higher trend towards recurrence in small-sized shunts, with the 2-year stroke rate for no, small and large shunts being 15.4%, 18.5% and 9.5%, downplaying the significance of

paradoxical embolism as a risk factor for stroke.¹⁶ However, one crucial limitation is that the study, contrary to its name, included all strokes, including atherosclerotic and lacunar strokes, most of which are not likely attributable to PFO. Further, the PICSS had limited power to fully characterise the impact of combined PFO and ASA on stroke risk. Recent RCTs have included variables such as large shunt size and associated ASA; however, the verdict on how PFO closure affects those with large shunt size is incongruent among RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) (those with ASA and large shunts fare better),¹⁷ Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism (PC) Trial (opposite of RESPECT),¹⁸ REDUCE (no difference)¹⁹ and CLOSE (more effective for large shunts).²⁰

A meta-analysis by Almekhlafi *et al*²¹ found that recurrent stroke or TIA rates of cryptogenic stroke with PFO did not increase compared with cryptogenic stroke without PFO (relative risk (RR)=1.1, 95% CI 0.8 to 1.5). However, these data do not negate PFO as a risk factor for stroke, just that it is just as likely to cause recurrent stroke as other occult mechanisms. Kent and Thaler¹⁴ developed a PFO propensity scale in which the probability of merely incidental PFO in cryptogenic stroke is much lower in younger patients aged <55 than in patients >55 (20%, CI 16% to 25% vs 48%, CI 34% to 66%).

The difficulty with attributing PFO as the actual cause of stroke has led to the development of the Risk of Paradoxical Embolism (RoPE) score in cryptogenic stroke, drawing from a database of 3023 patients with cryptogenic stroke who had PFO studied by TEE or TCD, where cryptogenic stroke was defined by the Trial of Org 10172 for Acute Stroke Treatment (TOAST) classification.²² Younger age, the absence of traditional vascular risk factors and the presence of a superficially located lesion are consistently associated with increasing prevalence of PFO (table 1).

PFO-attributable fraction of cryptogenic stroke is >60% in those with RoPE score of 6 or higher, with scores 9–10 reaching almost 90% (figure 2); however, recurrence rate was only 2% at 2 years, thus creating challenges for RCTs in powering their studies to account for low outcome rate.²² Because the RoPE score predicted PFO as an outcome, it was not possible to examine PFO characteristics (such as shunt size). The heterogeneity and inconsistent data collection across the component databases prevented the RoPE model from including some predictive variables cited in previous studies, such as obesity index, stroke severity,²² DVT or PE history, hypercoagulable states, prolonged travel/forced immobility, migraine, sleep apnoea, Valsalva at stroke onset and ‘wake up’ stroke/TIA.¹²

PERCUTANEOUS CLOSURE OF PFO

PFO closure devices

Surgical closure of atrial septal defects (ASD) had been around since the 1950s, but it was not until 1992 that the

Table 1 The Risk of Paradoxical Embolism score (maximum of 10 points)

Characteristics	Points
Vascular risk factors	
No hypertension	1
No diabetes mellitus	1
No prior stroke or transient ischaemic attack	1
Non-smoker	1
Age (years)	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
≥70	0
Stroke features	
Cortical infarction	1

first percutaneous PFO closure was successfully completed in 36 patients with paradoxical embolism.³ CardioSEAL and STARFlex devices (NMT Medical, Boston, Massachusetts) had been used off-label for ASD and PFO closures with relatively good clinical experience, although reports of device fracture and atrial thrombus and ultimately the failure of their clinical trial CLOSURE-1 (described further below) led to the parent company ceasing operations in 2011.^{23 24} Currently in North America, the Amplatzer Septal Occluder (St Jude Medical, St Paul, Minnesota) and the Amplatzer Multifenestrated Septal Occluder are available for ASD closures and off-label for PFO closure, and since October 2016 the Amplatzer PFO Occluder has been the only FDA-approved device for PFO closure.³ The Gore HELEX Septal Occluder (Gore and Associates, Flagstaff, Arizona) and the retrievable Gore CARDIOFORM Septal Occluder are FDA-approved for ASD closures, and the latter has just been approved by the FDA for PFO closure in April 2018. Other devices have been approved for closure in Europe, Canada and Asia. Occlusion success is reported to be >95% in all devices.³

Evidence for percutaneous closure of PFO in cryptogenic stroke

Decades of observational data up to 2012 have suggested the benefit of PFO closure in secondary stroke prevention of cryptogenic stroke (incident rate ratio 0.19, CI 0.07 to 0.54) compared with medical therapy arm,²⁵ but these observational studies were likely biased by patient selection, differential ascertainment of recurrent events and publication bias. Professional organisations such as the American Academy of Neurology recommended that patients with PFO and cryptogenic stroke should be encouraged to participate in randomised clinical trials.²⁶ Subsequently, beginning with the CLOSURE trial in 2012, followed by the RESPECT and PC trials in 2013,

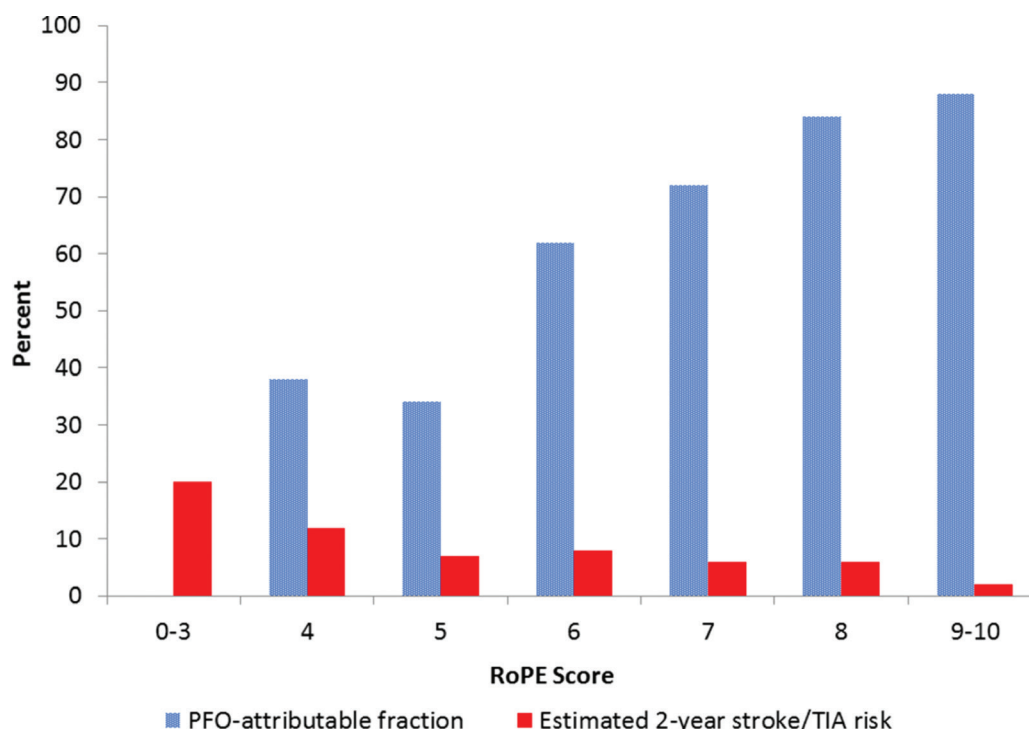


Figure 2 Relationship between the RoPE score and both the PFO-attributable stroke fraction (blue bars) and estimated risk of recurrent cerebral ischaemic events (red bars). Higher RoPE scores are associated with a greater likelihood that the stroke was causally related to PFO, but are also associated with a lower risk of subsequent stroke. PFO, patent foramen ovale; RoPE, Risk of Paradoxical Embolism; TIA, transient ischaemic attack.

these randomised trials failed to show a benefit of percutaneous PFO closure in stroke prevention in cryptogenic stroke. In 2017, the tides have turned with evidence from two newer RCTs, CLOSE and REDUCE, and the longer term results of RESPECT that all showed PFO closure to be beneficial in a specific patient population with cryptogenic stroke. The results of the trials are summarised in table 2.

CLOSURE was a multicentre trial that randomised subjects to STARFlex and CardioSEAL devices (plus aspirin and clopidogrel) or medical therapy (aspirin, warfarin or both at the investigators' discretion) in 909

subjects with cryptogenic stroke or TIA with 2 years of follow-up. The primary outcome of stroke, TIA and death was 5.5% in the device arm and 6.8% in the medical arm, and was not statistically different. Recurrent stroke or TIA rates were low in both groups (2.9% closure vs 3.1% medical, Risk Difference -0.13% , CI -2.2% to 2%) and largely unattributed to PFO. Criticisms of the study were many: TIA did not require imaging confirmation and is at times difficult to define; the trial inclusion criteria allowed lacunar strokes that are less likely attributable to PFO as an aetiology of stroke; and 2-year follow-up was deemed not long enough. Moreover, the STARFlex device also

Table 2 Summary of results from five randomised trials of PFO closure

Trial (year)	N	PFO closure device (incidence rate)	Medical therapy (incidence rate)	HR (95% CI)	P values
CLOSURE-1 (2012)	909	STARFlex (2.6)	AP/AC (3.1)	0.78 (0.45 to 1.35)	0.37
PC Trial (2013)	414	Amplatzer (0.8)	AP/AC (1.3)	0.63 (0.24 to 1.62)	0.34
RESPECT (long term) (2017)	980	Amplatzer (0.6)	AP/AC (1.1)	0.55 (0.31 to 1.0)	0.046
CLOSE (2017)	473	Multiple (0.0)	AP/AC (1.2)	0.03 (0.00 to 6.18)	<0.001
REDUCE (2017)	664	Gore HELEX or CARDIOFORM (0.4)	AP (1.7)	0.23 (0.09 to 0.62)	0.002

Incidence rate indicates the trial's primary endpoint rate per 100 person-years.

AC, anticoagulant; AP, antiplatelet; PFO, patent foramen ovale; RESPECT, Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; PC, Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism Trial.

exhibited relatively low rate of closure success (86%) in this trial and high rates of complications. Both devices used in this study are no longer available in the USA.²⁷

Next, the PC trial and the RESPECT trial examined the Amplatzer PFO Occluder device. The PC trial included a younger age cut-off (<60 years) with cryptogenic stroke or TIA and randomised 414 subjects to device closure (plus aspirin and ticlopidine or clopidogrel for 1–6 months) versus medical therapy (oral anticoagulant (AC) or antiplatelet (AP) at the investigators' discretion). Even with longer follow-up of 4 years, the recurrent stroke or TIA rates were still low (2.5% in the closure group and 5.2% in the medical group, HR 0.45 (0.16 to 1.29), $p=0.14$).¹⁸ Atrial fibrillation (AF) was reported in 2.9% of the closure arm and 1% of the medical arm. Criticisms included low recruitment and low event rate, causing inadequate power for meaningful secondary analyses.¹⁸

In RESPECT, 980 subjects between the ages of 18 and 60 were randomised to PFO closure (plus aspirin and clopidogrel for 1 month, followed by aspirin only for 5 months at the investigators' discretion) versus medical therapy (at the investigators' discretion, involving mostly a combination of AP or AC therapy). The intention-to-treat (ITT) analysis did not show benefit of closure in reducing stroke or TIA risk (1.8% device vs 3.3% medical, HR 0.49, CI 0.22 to 1.11, $p=0.08$), but the as-treated analysis showed statistically significantly lower recurrence in the closure group (1.1% vs 3.3%, HR 0.27, CI 0.1 to 0.75, $p=0.007$) at 2 years. The rates of new-onset AF were similarly low in both groups and no device embolisation or thrombus events were reported. In a subgroup analysis, closure was favourable in those with large shunts and associated ASA.²⁸

Despite these overall negative results, a pooled analysis of individual data from the three RCTs showed that recurrent strokes were significantly fewer with PFO closure than with medical therapy alone (adjusted HR 0.58, 95% CI 0.34 to 0.99, $p=0.04$), with the effect size larger when limited to the Amplatzer PFO Occluder alone (adjusted HR 0.41, 95% CI 0.20 to 0.88, $p=0.02$).²⁹ In October 2016, the FDA approved the Amplatzer PFO Occluder for patients with cryptogenic stroke between 18 and 60 years old. Contraindications included intracardiac mass, vegetation or thrombus at implantation site, active endocarditis, anatomical challenges and presence of other right-to-left shunts such as ASD.³ By 2016, both cardiology and neurology societies' guidelines still cautioned on routinely recommending percutaneous PFO closure in patients with cryptogenic stroke. Messé *et al*²⁶ reported the number needed to treat (NNT) to prevent one stroke in 3–4 years is 56, with a wide 95% CI (31 to 526), and recommended continuing to refer patients to ongoing clinical trials hoping to obtain stronger evidence.

The RESPECT trial extended its follow-up to a median of 5.9 years and published the results in September 2017. The ITT analysis yielded 3.6% of the subjects in the closure arm with primary endpoint (all of which were non-fatal recurrent strokes) vs 5.8% in the medical arm

(HR 0.55, 95% CI 0.31 to 0.99, $p=0.046$).¹⁷ The difference was more apparent with the outcome of recurrent embolic stroke of undetermined source (ESUS) (HR 0.38, 95% CI 0.18 to 0.79, $p=0.007$).¹⁷ Subgroups that benefited from PFO closure over medical therapy alone remained similar to those in the initial RESPECT trial: those with ASA and large shunt (grade 3), and now additionally those assigned to AP therapy only. There was no difference in recurrent stroke in the AC group versus the closure group (HR 1.32, CI 0.43 to 4.03, $p=0.63$). The NNT to prevent one stroke in 5 years with the Amplatzer device was now at an estimated 42 years.¹⁷ However, DVT/PE events were higher in the PFO group, possibly due to lower intensity antithrombotic given in that group. Notably, there were significantly more subjects who were lost to follow-up in the medical therapy group (33%) compared with the PFO closure group (21%).¹⁷

The CLOSE trial investigators incorporated relevant past findings to define a stringent patient selection criteria: 663 patients with cryptogenic stroke aged 16–60 years with large (grade 3) shunt or ASA (≥ 10 mm excursion) were randomised 1:1:1 into three groups—PFO closure (11 different devices were used, followed by 3 months of aspirin and clopidogrel and then single AP), AP only (aspirin, clopidogrel or aspirin-dipyridamole) and AC only (warfarin or direct oral anticoagulants: DOACs). At a follow-up of 5.3 years, no stroke occurred in the PFO group, while 6% of the AP group suffered recurrent stroke (HR 0.03, 95% CI 0 to 0.26, $p<0.001$).²⁰ Recurrent stroke occurred in 1.6% of the AP-only group and 4% of the AC-only group, but the rates were not statistically different (HR 0.44, 95% CI 0.11 to 1.48).²⁰ Interestingly the PFO group was not compared with the AC group. This trial allowed investigator discretion on the choice of closure device, showing generalisability of the successful closure rate (93%) and procedural complication rate (5.9%)—similar to some previous trials. More AF was noted in PFO closure group as well (4.6% vs 0.9%, $p=0.02$), demonstrating inherent risks in all PFO closure devices.²⁰

The Gore REDUCE trial enrolled 664 subjects aged 18–59 with cryptogenic stroke and moderate to large shunts and was more stringent on the medical therapy group to only allow AP (aspirin, aspirin-dipyridamole or clopidogrel-only options). The Gore HELEX or CARDIOFORM devices were used. At a median follow-up of 3.2 years, clinical recurrent stroke was again significantly lower in the closure group (HR 0.23, 95% CI 0.09 to 0.62, $p=0.002$),¹⁹ as was the composite of clinical strokes and silent infarcts, but the incidence of silent infarcts by MRI was not different between the groups. Of note, new-onset AF was higher in the Gore devices (6.6%) than noted in the Amplatzer trials, and effective closure was similar while complete closure at 12 months was lower (75.6%). Most AF events were transient, and clinical ramifications of transient AF post-PFO closure procedure have yet to be described. The NNT to prevent one stroke at 24 months was 28.¹⁹ CLOSE and

Gore REDUCE are the only RCTs that showed efficacy at primary ITT analysis as well as per-protocol analysis. In making a clean comparison with an AP-only group, the Gore investigators compared exploratory intervention with current guideline-based practice, thus reducing confounding to the medical therapy efficacy. It is also worth noting that discontinuing AP therapy was allowed in the PFO closure group in previous trials before CLOSE and REDUCE, which may have increased overall stroke risk in that group.^{19 20}

A caveat to all the clinical trials is that most trials did not require prolonged cardiac monitoring to rule out AF as a stroke aetiology to consider inclusion into the 'cryptogenic stroke' category. Although the argument can be made that most of those aged 18–60 years old have low risk of AF, the presence of undetected AF would definitely skew the rates of AF postprocedure and question the mechanism of recurrent strokes in this group and whether PFO closure is related at all. The ESUS subset of cryptogenic stroke is radiographically selective and requires thorough diagnostic testing to ensure truly no underlying explanation for stroke. The ESUS definition does not exclude presence of PFO, and so limiting inclusion to ESUS might zone in on the cleanest patient population to target.

All primary outcomes from the clinical trials included recurrent strokes of all causes and not just cryptogenic stroke. It would also be difficult to determine PFO-attributable stroke for all individual subjects. The secondary outcome of recurrent ESUS in the long-term RESPECT trial is especially intriguing, as ESUS suggests no other likely aetiology for stroke besides the presence of PFO. Recurrent ESUS as an outcome would further enrich future studies on the efficacy of PFO closure versus various antithrombotic therapies.

In a recent meta-analysis of the four RCTs (excluding CLOSURE given the death of the STARFlex device) enrolling 2892 patients, PFO closure decreased the absolute recurrent stroke risk by 3.2% (risk difference -0.032 (95% CI -0.050 to -0.014)) compared with medical therapy. The treatment strategies did not differ in rates of TIA or major bleeding.³⁰ A meta-analysis including all five RCTs showed PFO closure reduced composite stroke/TIA/death (0.7 vs 1.48 events per 100 patient-years, RR 0.52, 95% CI 0.29 to 0.91, $I^2=55\%$) and recurrent stroke/TIA (1.04 vs 2.00 events per 100 patient-years, RR 0.55, 95% CI 0.37 to 0.82, $I^2=42.2\%$) compared with medical therapy.¹¹ Therefore based on the RESPECT per-protocol and subgroup analysis, and the Gore REDUCE, CLOSE and long-term RESPECT trial results, for patients 18–60 years old with cryptogenic stroke, few vascular risk factors, and high-risk PFO characteristics such as large shunt and ASA, percutaneous PFO closure will reduce recurrent stroke risk, provided that the institutional procedural complication rate is low and minor risk of AF is understood.

Overall safety

Across the five RCTs, the major complication rate (pericardial effusion with tamponade, device embolisation needing surgery, device erosion, thrombus on device, stroke/TIA) was 2.4%–5.9%, and serious adverse events were not significantly different between the closure and medical arms.³¹ In a recent meta-analysis of the five trials, the risk of AF was higher in the closure group (4% vs 0.7%, RR=4.55, 95% CI 2.16 to 9.6, $I^2=25\%$, $p<0.01$), although the risk was not significant with Amplatzer PFO Occluder (RR=2.10, 95% CI 0.8 to 5.56, $I^2=0\%$, $p=0.13$), but significantly more so with STARFlex (RR=7.92, 95% CI 2.4 to 26.21, $p<0.01$) and Gore (RR=14.66, 95% CI 2.01 to 106.95, $p<0.01$) devices.¹⁰ Postimplant AF usually occurs within 6 months, with only 3.8% of these progressing to persistent AF.¹⁰ RESPECT showed that most new-onset AF post procedure resolved prior to discharge from the hospital.¹⁷ All-cause mortality was low in both the PFO closure and medical arms with the Amplatzer PFO Occluder (0.17 vs 0.24 deaths per 100 patient-years).¹¹ Although patients need to be aware of the real risk of AF post procedure, its often self-limited nature may not warrant long-term anticoagulation. In addition to careful patient selection, shared decision making between the stroke neurologist and the interventional cardiologist is important to patient outcomes.

ANTITHROMBOTIC THERAPY IN STROKES WITH PFO

Given the overlap of clinical characteristics in those with PFO with high stroke propensity and those with ESUS, AC has been compared with AP to determine which is the better antithrombotic for secondary stroke prevention. A systematic review pooled observational data and used propensity scoring methods to study 2385 subjects (804 on AC and 1581 on AP) with 227 composite endpoints of recurrent stroke/TIA/death. The difference between AC and AP was not statistically significant for the composite outcome (adjusted HR 0.76, 95% CI 0.52 to 1.12) or for the secondary outcome of stroke alone (adjusted HR 0.75, 95% CI 0.44 to 1.27).³² In alternative weighting schemes, the AC group had a beneficial effect on the composite outcome compared with the AP group (adjusted HR 0.64, 95% CI 0.42 to 0.99).³² Subgroup analyses again did not show a significant difference in stroke prevention.

In the practice advisory by the American Academy of Neurology, there was insufficient evidence supporting superiority of AC therapy based on two randomised class II studies comparing aspirin and warfarin in recurrent stroke risk.^{33 34} The summary estimate of effect from these two studies was an RD of 2% favouring AP therapy (95% CI -21% to 25%).²⁶

The CLOSE study was underpowered to detect a difference in stroke recurrence risk between AC-only and AP-only groups; however, both the ITT and per-protocol analyses showed a trend towards lower rates of recurrent stroke at 5 years in the AC group. Only 7% of patients in the AC group received DOACs, while the rest received

vitamin K antagonists.²⁰ DOACs have become more popular, have a lower risk profile compared with warfarin and are the subjects of ongoing trials involving ESUS, and thus should be part of future studies examining the efficacy of DOACs versus AP therapy in stroke prevention in subjects with cryptogenic stroke. While many patients would likely choose a one-time procedure over a lifelong course of AC treatment, there are undoubtedly some who are more averse to invasive procedures, and we should have data to inform patients of the likely outcomes of their preferences.

CONCLUSIONS AND FUTURE DIRECTIONS

High-risk features of PFO that increase its risk for causing paradoxical embolism can be detected with high sensitivity and specificity with TEE and TCD. Those with ESUS and clinical clues to paradoxical embolism as discussed above are more likely to have their stroke be attributable to PFO; nevertheless, the recurrence rate of stroke via PFO is low. Percutaneous PFO closure is beneficial and relatively safe for secondary stroke prevention among adults <60 years, with few conventional vascular risk factors, who have undergone a thorough work-up of their stroke aetiology and are deemed cryptogenic except for the presence of PFO, and who may have large shunts or associated ASA. Patients should be aware of the risk of postprocedure AF, although its ramifications on long-term antithrombotic management are still unclear. The decision to proceed with PFO closure should be made in conjunction with the patient, stroke neurologist and cardiologist. There are insufficient data on the efficacy of AP versus AC in stroke prevention in patients with cryptogenic stroke with PFO, so barring another reason for anticoagulation, starting with AP therapy as long-term therapy is reasonable, regardless of whether PFO is closed. Future studies examining AC (including DOACs) versus PFO closure in subjects with cryptogenic stroke and the clinical significance of transient AF post procedure would be of great value. We look forward to future improvement in device complication rates and possible updated practice guidelines in the wake of new evidence.

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