Secondary Stroke Prevention: Who Can Benefit from Device Therapies?

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Meeting Summary/Abstract

This article is based on a symposium sponsored by Abbott that took place at ESOC 2021 on Friday 3rd of September 2021. The experts presenting in this symposium focused first on how to identify high-risk patients with cryptogenic stroke that can benefit from patent foramen ovale (PFO) closure and the clinical implications of the procedure. In the second part, they concentrated on discussing how to identify the patients with atrial fibrillation at high-risk of bleeding and reducing that risk while still preventing stroke through left atrium appendage occlusion (LAAO) and the clinical implications of this procedure. Data from several trials reveal how medical devices for PFO closure and LAAO improve patient outcomes. New trials are soon expected to contribute more valuable information.

KEYWORDS: ANTICOAGULATION, ATRIAL FIBRILLATION, LEFT ATRIAL APPENDAGE, PATENT FORAMEN OVALE

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Patent Foramen Ovale Closure – Who Can Benefit?

Dr. Jaime Masjuan

Cryptogenic ischaemic stroke (IS) is more frequent in patients under 60 years of age who usually present fewer stroke risk factors. Paradoxical embolism through a patent foramen ovale (PFO) is a possible mechanism. Epidemiological data have shown that paradoxical embolism is a more common stroke aetiology (5–10%)[1] than previously thought and randomised trials have demonstrated the importance of PFO closure.[2-4] In fact, in well-selected patients with PFO and no other apparent cause, PFO is likely to play a causative role. An international consensus has recently proposed updated nomenclature and classification. The term "PFO-Associated Stroke" is recommended for patients presenting with a superficial, or large and deep, or retinal ischaemic infarction with a medium- to high-risk PFO and no other identified causes.[1]

PFO-associated stroke has a high recurrence rate as reported by an observational study during which stroke recurrence risk was 2.3% in patients with PFO, 15.2% in patients with PFO and atrial septal aneurysm (ASA), and 4.2% in patients with neither of those conditions.[5] As summarised in Table 1, several randomised trials found similar recurrence rates, highlighting the critical need for appropriate secondary prevention. These studies also showed that PFO closure plus antiplatelet treatment is superior to antiplatelet treatment alone to prevent recurrent IS in patients with PFO-associated stroke.[2-4]

In response to these new data, stroke guidelines and practice advisories have been updated given the strength of evidence supporting PFO closure.[6-8]

Table 1. Studies comparing PFO closure with antiplatelet or anticoagulant treatment.[2-4]

Study name	Follow-up (mean or median years)	Number of Patients	Comparator	Recurrence rate	Primary Outcome	Hazard Ratio	P Value†
REDUCE	3.2	664	Antiplatelet	5.4%	IS and new brain infarction on imaging	0.23	0.002
RESPECT	5.9	980	Antiplatelets or warfarin	5.8%	Recurrent nonfatal IS, fatal IS, or early death	0.55	0.046
CLOSE	5.3	663	Antiplatelet or anticoagulation††	6.3%	Stroke	0.03	<0.001

Note: Results from clinical trials are not directly comparable. Information provided for educational purposes only. † The hazard ratio and P value are for the expected probability of stroke or other primary outcome after closure of the PFO vs medical treatment in the intention-to-treat analysis.

†† Anticoagulation refers to any form of anticoagulation (the hazard ratio of 0.03 includes antiplatelet therapy only as a comparator).

In DEFENSE-PFO, 0% vs 12.9% primary endpoint events (stroke, vascular death, or thrombolysis in myocardial infarction-defined major bleeding) occurred in the PFO closure vs medication-only group (P=0.013; study underpowered to provide hazard ratio).[9]

Diagnostic Methods for PFO-Associated Stroke

PFO-related high-risk conditions that should be considered include:

- Presence of ASA
- Increased right-to-left shunt flow (permanently or transiently) indicated by large PFO size, Valsalva manoeuvre, or chronic right atrial hypertension
- Cerebral imaging pattern typical of embolism
- Presence of documented deep venous thrombosis or pulmonary embolism; or predisposition to venous thrombosis (recent immobility due to extended travel, surgery or illness; dehydration; hypercoagulable states; May-Thurner syndrome)
- Absence of risk factors for atherosclerosis

A useful tool to discern any causal relationship between PFO and stroke of unknown cause, and to guide management decisions is the risk of paradoxical embolism (RoPE) score. The score considers patient characteristics such as vascular risk factors, age, and stroke features. For example, a score of ≥7 indicates high probability of a relationship. However, this scoring system does not consider the presence of anatomic factors like septal aneurysm nor the magnitude of the shunt that tend to correlate with higher risk of paradoxical embolisation.[6]

Early diagnosis is facilitated using the embolic stroke of undetermined source (ESUS) diagnosis approach:[10]

- IS detected by CT or MRI that is NOT LACUNAR
- Intra and extra cranial artery imaging to rule out an IS associated with atherosclerotic plaque, arterial dissection, or other vascular diseases
- ECG and prolonged cardiac rhythm monitoring (~30 days) to rule out atrial fibrillation (AF) and other arrhythmias that may be associated with stroke
- Transthoracic echocardiography to rule out major cardio-embolic sources
- No other specific cause of stroke identified (e.g., arteritis, dissection, autoimmune diseases, migraine/vasospasm, drug abuse)[10]

Other diagnostic tests for PFO-related stroke are transoesophageal echocardiogram (TEE) and transcranial doppler. TEE shows the morphology and degree of the shunt; it also shows other features that may lead to a PFO diagnosis (ASA, PFO tunnel length, septum secundum thickness, PFO diameter).[11,12] Transcranial doppler is a simple, non-invasive test that neurologists can perform very early in the stroke unit to quantify the shunt.

Recently, Elgendy et al. proposed grading PFO-risk features in patients with cerebral or retinal infarcts of embolic topography according to an algorithm (Table 2). The greater the PFO-risk grade and the least competition for other possible sources, the more likely the stroke is pathogenically associated with PFO. In patients without other probable sources, the RoPE score, Valsalva at onset, and additional case-specific features enable the clinician to categorise IS as of definite, probable, possible, or unlikely PFO origin.[1]

The European position paper on the management of patients with PFO developed by 8 scientific societies and international experts was the first interdisciplinary approach for rational PFO management based on the available evidence. The recommendation from the paper is that "Percutaneous closure of PFO should be performed in carefully selected patients from 18 to 65 years with confirmed cryptogenic stroke, TIA, or systemic embolism and estimated high probability of causal role of PFO as assessed by clinical, anatomic, and imaging features."[6]

Clinical Implications of PFO Closure

Dr. Rolf Wachter

Patients for whom the evidence is clear

Recent guidelines from the American Heart Association[7] recommend who should undergo PFO closure: "patients 18 to 60 years of age with a nonlacunar IS of undetermined cause despite a thorough evaluation and a PFO with high-risk anatomic features." In these patients, "it is reasonable to choose closure with transcatheter devices and long-term antiplatelet therapy over anti-platelet therapy alone for preventing recurrent strokes."[7]

Table 2. Proposed flexible clinical practice approach to classifying PFO causal association with embolic infarct adapted from Elgendy et al.[1]

Risk Source	Features	Low RoPE Score[a]	High RoPE Score[a]
Very high	A PFO and a straddling thrombus	Definite	Definite
High	(1) Concomitant pulmonary embolism or deep venous thrombosis preceding an index infarct combined with either (2a) a PFO and an atrial septal aneurysm or (2b) a large-shunt PFO	Probable	Highly probable
Medium	Either (1) a PFO and an atrial septal aneurysm or (2) a large-shunt PFO	Possible	Probable
Low	A small-shunt PFO without an atrial septal aneurysm	Unlikely	Possible

Note: The algorithm in this table is proposed for use in flexible clinical practice, when application of an entire formal classification system is not being conducted. [a]The RoPE score includes points for five age categories, cortical infarct, absence of hypertension, diabetes, prior stroke or transient ischaemic attack, and smoking. A higher RoPE score (≥7 points) increases probability of causal association.

These recommendations were based on three trials. The RESPECT Extended follow up (10 years) study revealed a significant benefit of PFO closure vs medical therapy on the composite endpoint of fatal and non-fatal IS and death (HR, 0.55; P=0.046). The subgroup analysis demonstrated that patients who benefitted most from the intervention were those with a substantial shunt size or ASA.[3] The GORE Reduce trial, where shunt size and/or ASA were inclusion criteria, revealed a significant 77% risk reduction in the probability of freedom from recurrent stroke with PFO closure compared with anti-platelet therapy (HR, 0.23; 95% CI: 0.09-0.62; P=0.002).[2] The 5-year outcomes from this study were published recently with similar results.[14] The CLOSE PFO trial showed that PFO closure eliminated stroke for up to 9 years in the PFO group (HR, 0.03; 95% CI: 0–0.26, P<0.001) with a relative risk reduction (RRR) of 97%.[4]

In a meta-analysis that included several PFO studies, earlier trials were less specific and not positive for the IS endpoint. More recent trials show a benefit in this patient population and an average RRR of 62%.[15]

It is worth noting that anticoagulants were more effective than antiplatelets but less effective than PFO closure.[16,17] If a patient qualified for PFO closure, this treatment method may be a better option given it avoids the long-term side effects of OACs.

The relevance of only observing patients with high-risk anatomical features was highlighted in a meta-analysis. In this patient group there was a significant RRR of 73% (pooled relative risk (RR) for PFO closure, 0.27 [95% CI: 0.1–0.7; P=0.01; I^2=42%]) compared with low-risk patients where there was no significant difference between those who had a PFO closure and those who did not (pooled RR for PFO closure, 0.80 [95% CI: 0.43–1.47; P=0.41; I^2=12%]).[17]

Clinical scenarios when PFO closure could be considered might include a patient over 61 years with nonlacunar stroke but with high-risk anatomic features (at least moderate PFO). The stroke risk from PFO is not eliminated once individuals are past 61 years of age. Then, if all other criteria are fulfilled and high-risk features are present, PFO closure may be an option. Another scenario might be a patient between 18–60 years with nonlacunar stroke and high-risk anatomic features with a competing cause of stroke (for example, carotid artery sclerosis without stenosis and at least moderate PFO) but not a treatable one. In this case, it would be hard to determine if the reason for the stroke is the competing cause or the PFO. Then, if the PFO is high-risk, closure could be considered.

Gaps in knowledge

As noted in the AHA guidelines, more information is needed regarding patients ≥60 years of age with ESUS, whether they

should have PFO closure or medical management. In the subgroup of patients ≤60 years of age, there are questions surrounding which additional parameters can identify patients who benefit most and the role of anticoagulation vs PFO closure regarding long-term bleeding risks.[7]

Age and AF will be important factors to consider in the future. A prospective study found an association between the presence of PFO and cryptogenic stroke in both older and younger patients suggesting that paradoxical embolism is a cause of stroke in both age groups.[18] Also, a better understanding on how to identify patients ≥60 years of age who may have a PFO-derived stroke is needed. The Find-AF 2 Study currently underway aims to provide more information.[19]

PFO Q&A Discussion Session

Dr. Hans C Diener, Dr. Peter Rothwell, Dr. George Ntaios, Dr. Rolf Wachter, Dr. Jaime Masjuan

The panel discussed if PFO should be removed from the ESUS definition. Dr. George Ntaios stated that given the findings to date, this should be removed for younger patients, but for patients >60 years of age more evidence is needed from PFO trials in this age group.

On the question of what percentage of patients >60 years of age could potentially be candidates for PFO closure, Dr. Rothwell shared his experience from published studies in the UK. In patients >60 years of age, the proportion with a large PFO is similar to patients <60 years of age, as is the excess of PFO and cryptogenic stroke vs non-cryptogenic stroke. Epidemiology between the two age groups is also remarkably similar.

Neurologists worry about the risk of AF after PFO closure and how to manage it. Dr. Rolf Watcher explained that the PFO closure procedure acts as a stress test for the left atrium (LA). If the LA produces AF during the procedure (5–10% of patients), although most likely paroxysmal, these patients may have a higher risk of persistent AF later. If AF is observed, and the patient fulfils the criteria from the RCTs, he recommended to close the PFO; if the patient is borderline (moderate PFO, 65 years of age), his view was that it is probably better to prescribe OACs. After PFO closure, patients should be monitored for AF. In stroke patients, the recommendation is to monitor for 72 hrs. If the patient has risk factors for AF such as supraventricular ectopic beats and larger LA, then monitoring should be longer.

Dr Watcher continued with some advice regarding patients with high-risk PFO and antiphospholipid antibody syndrome who require anticoagulation, stating that if the patient is <60 years of age, the PFO should be closed. The rationale is that competing risks always have to be considered because patients may have more than one stroke mechanism. Patients who have two strokes often have a change in aetiology in 50% of the cases between the first stroke and the recurrence. Nonetheless, if the signs of the PFO are clear, it should be closed.

Left Atrial Appendage Occlusion - Who Can Benefit?

Dr. Matthias Endres

AF causes up to 25% of all IS, and when left untreated stroke recurrences are frequent (up to 50% over 5 years), very severe, and with high mortality.[20] The European AF Trial (EAFT) showed that oral anticoagulation (OAC) very effectively reduces stroke risk (relative risk reduction of 66%) in patients with AF compared with antiplatelet drugs such as aspirin 300 mg/day (14%).[21] Direct anticoagulants (DOACs) are also associated with a lower risk for intracranial haemorrhage. However, drug persistence is a challenge, as even in clinical trials for DOACs the dropout rate was approximately 20% (Table 3).

Table 3. Persistence rates of different OACs and Aspirin[22-25]

Clinical trial	Anticoagulant	Drop-out rate
RELY	Dabigatran (110 mg)	20.7%
	Dabigatran (150 mg)	21.2%
	Warfarin (INR 2-3)	16.7%
ROCKET AF	Rivaroxaban (20 mg)	23.7%
	Warfarin (INR 2-3)	22.2%
ARISTOTLE	Apixaban (5 mg)	25.3%
	Warfarin (INR 2-3)	27.5%
AVERROES	Apixaban (5 mg)	17.5%
	Aspirin (81-324 mg)	20.5%

It is also important to consider the many contraindications for long-term OAC which include major bleeding/intracranial haemorrhage, cerebral tumours, end-stage liver disease, and renal failure/chronic dialysis. Recent practical guides provide pathways for the use of DOACs according to liver or renal function to identify high-risk patients where OAC is not recommended.[26] Additionally, the role of anticoagulation in patients with AF who also have multiple cerebral microbleeds is a controversial issue.[27]

Left Atrial Appendage Occlusion

As >90% of the thrombi in AF emerge in the left atrial appendage (LAA),[28,29] LAA Occlusion (LAAO) has been developed as an alternative treatment to anticoagulation in patients with AF. PROTECT AF was the first study to demonstrate that mechanical closure with a device produced fewer primary efficacy events (stroke, systemic embolism, or cardiovascular death [8.4%; RR, 0.60]) than warfarin (13.9%) and met the study's criteria of noninferiority and superiority. In the device group, there were 3.6 safety events per 100 patient-years compared with 3.1 in the warfarin group (RR, 1.17). Adverse events with the device were pericardial effusion, procedure-related stroke, and device embolisation during the periprocedural period, vs major bleeding with warfarin.[30]

In addition, combined 5-year outcomes from the PREVAIL and the PROTECT AF trials showed that utilising devices in LAAO prevents AF-related stroke similarly to warfarin, but because it reduces major bleeding events, there are less haemorrhagic strokes and mortality.[31] With these data, LAAO was included in the European Society of Cardiology guideline as an alternative for patients with clear contraindications for OACs.[32]

Many devices are currently available to perform LAAO.[33] The recently published results of a prospective global registry showed that when LAAO was performed, the rate of IS was 67% lower than the expected stroke rate. Closure was complete in 98.4% of cases (peri device flow <3 mm) and device-related thrombus occurred in 1.6%.[34] There are more large studies underway including Amulet IDE,[35] CATALYST,[36] Closure AF,[37] and Strokeclose[38] seeking to compare LAAO devices with each other and with DOACs or best medical care, and the results of these studies will provide valuable information (Table 4).

Table 4. Ongoing and finalised studies comparing LAAO devices with each other and with DOACs or best medical care

Randomised clinical trials	
COMPARE-LAAO (on-going) (ISS)[39]	**AIM:** Comparing effectiveness and safety of LAAO for non-valvular AF patients at high stroke risk unable to use oral anticoagulation therapy **STUDY DESIGN:** Open-label, national multicentre RCT where patients will be randomised in a 2:1 fashion to the device arm or the usual care arm **ENROLMENT:** 609 patients **FOLLOW-UP:** up to 5 years **LOCATIONS:** the Netherlands **ENROLMENT FINALISATION:** 2026
OCCLUSION-AF (on-going) (ISS)[40]	**AIM:** Assess the effect of LAAO to reduce the incidence of stroke, systemic embolism, major bleeding and all-cause mortality in AF patients with a prior ischaemic stroke or TIA **STUDY DESIGN:** Open-label study with blinded outcome assessment by an independent clinical event committee. Amulet or Watchman device vs NOAC drugs; apixaban, dabigatran, edoxaban or rivaroxaban. **ENROLMENT:** 750 patients **FOLLOW UP:** up to 10 years **LOCATIONS:** Denmark, Finland, Norway, Sweden **ENROLMENT FINALISATION:** 2024

SWISS-APERO (on-going) (ISS)[41]	**AIM:** Comparison of Amplatzer™ Amulet™ and Watchman device in patients undergoing LAA closure **ENROLMENT:** 200 patients **FOLLOW UP:** up to 5 years **LOCATIONS:** Belgium, France, Italy, Switzerland **ENROLMENT FINALISATION:** 2021
CATALYST (on-going) Amplatzer™ Amulet™ LAAO vs. NOAC (AVSS)[36]	**AIM:** Indication expansion study for Amplatzer™ Amulet™ compared to NOACs **STUDY DESIGN:** Prospective randomised, multicentre active control worldwide trial where Amplatzer™ Amulet™ is randomised to commercially available NOAC **ENROLMENT:** 2650 patients **FOLLOW-UP:** up to 5 years **LOCATIONS:** Worldwide **ENROLMENT FINALISATION:** 2024
STROKECLOSE (on-going) Prevention of Stroke by Left Atrial Appendage Closure in AF Patients After Intracerebral Haemorrhage (ISS)[38]	**AIM:** To assess the effect of LAAO to reduce the incidence of stroke, bleeding, and cardiovascular mortality in patients with non-valvular AF and prior intracranial haemorrhage **STUDY DESIGN:** Interventional, randomised (2:1), multicentre, parallel assignment where Amplatzer™ Amulet™ is randomised to medical therapy **ENROLMENT:** 750 patients **FOLLOW-UP:** Enrolment over 3 years, follow-up up to 10 years **LOCATION:** Nordics **ENROLMENT FINALISATION:** 2022
CLOSURE-AF (on-going) LAA CLOSURE in Patients with Atrial Fibrillation Compared to Medical Therapy (ISS)[37]	**AIM:** To assess benefit of LAA closure in patients with non-valvular AF at high risk of stroke as well as high risk of bleeding as compared to best medical care **STUDY DESIGN:** Patients randomised to LAAO and to medical therapy **ENROLMENT:** 1512 patients **FOLLOW-UP:** up to 2 years **LOCATION:** Germany **ENROLMENT FINALISATION:** 2021
Amulet IDE Amplatzer™ Amulet™ vs Watchman (AVSS)[35]	**AIM:** To evaluate safety and efficacy by demonstrating non-inferior performance to comparator device in patients with non-valvular AF **STUDY DESIGN:** Prospective, global, multi-centre trial with 1-1 randomisation to evaluate the safety and effectiveness of the Amplatzer™ Amulet™ by demonstrating that the device is non-inferior to the Watchman LAA closure device (Control) in subjects with non-valvular AF. **ENROLMENT:** 1878 patients **FOLLOW-UP:** up to 5 years after implant **LOCATION:** up to 180 sites Worldwide **ENROLMENT FINALISATION:** 2019
PRAGUE-17 Left Atrial Appendage Closure vs. Novel Anti-coagulation Agents in Atrial Fibrillation (ISS)[43]	**AIM:** To compare the LAAO to NOAC pharmacological treatment in a RCT of AF patients at high risk of a cardioembolic event **STUDY DESIGN:** Randomised, parallel, open label. Patients with nonvalvular AF were randomised to LAAO (n=201) versus a NOAC (n=201) **ENROLMENT:** 415 patients **FOLLOW UP:** up to 4 years **LOCATIONS:** Czechia **ENROLMENT FINALISATION:** 2019

Left Atrial Appendage Occlusion – Clinical Implications

Dr. Jens Erik Nielsen-Kudsk

LAAO is a mechanical stroke prevention method currently being used in selected AF patients with high bleeding risk, and its use in a broader AF population as an alternative to DOAC is being considered. The clinical advantage is that it provides life-long stroke protection without the continued bleeding risk from long-term OAC. However, there are contraindications to LAAO such as LAA thrombus, infection, mitral stenosis, and severe left ventricular dysfunction.

Outcomes from LAAO vs DOACs have been reported in different studies. In a propensity score-matched study, the primary outcome of IS, major bleeding or mortality in LAAO was 256 events per 100 patient-years (14.5%) vs 461 (25.7%) for DOAC (HR, 0.57; 95% CI: 0.49–0.67).[42] Results from Prague-17, a small (n=402), non-inferiority RCT revealed that LAAO was noninferior to DOAC in preventing major AF-related cardiovascular, neurological, and bleeding events among patients at high-risk for stroke and increased risk of bleeding (P=0.004).[43] Most recently, findings of a large RCT (n=4770) revealed that stroke or systemic embolism occurred in 4.8% of patients with AF who received LAAO during cardiac surgery vs 7.0% who did not (HR, 0.67; 95% CI: 0.53–0.85; P=0.001), representing approximately 33% reduction in the risk of stroke or systemic embolism.[44]

LAAO Q&A Discussion Session

Dr. Hans Christoph Diener, Dr. Peter Rothwell, Dr. George Ntaios, Dr. Matthias Endres, Dr. Jens Erik Nielsen-Kudsk

The panel discussed whether the procedural risk of LAAO in routine practice was something for neurologists to be concerned about. Dr. Nielsen-Kudsk explained that a 1% risk of pericardial effusion is present due to the LAA being a thin-walled, fragile structure. However, device technology has improved through small retention hooks and better design, and the risk is now comparable to that of ablation procedures for AF. In addition, interventionalists are more skilled than in the past. Post-procedure bleeding risk is still a concern even though patients are transitioned from OAC to double anti-platelet therapy and then anti-platelet monotherapy over time.

Continuing, Dr. Nielsen-Kudsk explained the results of a recently published head-to-head comparison between LAAO devices in high-risk patients (Amulet IDE trial, N=1878). The IS rate was low for both devices (Amulet and Watchman) (1.67%/year vs 1.94%/year) and "a very good signal in this patient population" indicating high efficacy and good safety results.[45]

For patients with cerebral amyloid angiopathy, and whether they should be systematically treated with LAAO, Dr. Endres explained that these patients have a high bleeding risk which is even higher with OACs. Therefore, if a patient with amyloid angiopathy has AF it's a difficult treatment decision. Trials with patients after intracerebral haemorrhage are ongoing (Closure AF[37] or Strokeclose[38]), and until the data are available LAAO is a good alternative for patients with high bleeding risk. Also, for cancer patients with hypercoagulation and AF, life expectancy and the degree of hypercoagulation need to be considered as part of individualised treatment decisions in the absence of trial evidence. On the other hand, the major risk for these patients is deep venous thrombosis and pulmonary embolism, so they should primarily be anticoagulated.

On a question of what happens if a patient has a recurrent stroke after LAAO, Dr. Nielsen-Kudsk replied that it is necessary to find out if the new stroke might be related to the device implantation, or to an incomplete LAAO through the use of CT scan or TEE. These patients often have other stroke risks and vascular-related strokes to consider. Nevertheless, the device should be checked after implantation for possible device-related thrombi in these patients.

Finally, a question on the rates of incomplete closure after LAAO was discussed, and Dr Nielsen-Kudsk confirmed how in the Amulet IDE trial the closure rates for the devices were 98.9% and 96.8% (threshold leak >5 mm). No correlation has been found yet between small leaks <5 mm and clinical outcomes, although if the leak is >5 mm, he indicated it should be closed with a vascular plug during a low-risk catheter procedure.

Summary

In some cases, 'PFO-associated stroke' defines the underlying mechanism of stroke more precisely than the term ESUS. Diagnostic assessment should be performed early with the ESUS diagnostic approach and with the combination of TEE and transcranial doppler. There appears

to be clear evidence supporting PFO closure in patients 18–60 years with non-lacunar stroke and high-risk anatomic features. PFO closure could also be considered for patients 61–69 years of age with high-risk anatomic features, and in patients 18–60 years of age with other potential causes of stroke. Highlighted gaps in knowledge include how to better define patients who benefit from PFO closure, especially in those ≥60 years of age, and with AF as a competing risk factor. Patients benefitting from LAAO are those with IS or TIA, plus AF, and one of the following: intracranial haemorrhage, severe chronic kidney disease/chronic dialysis, and other lifelong contraindications for OACs. Considering the evidence to date, LAAO is likely to be applied more widely for AF in the future. Several RCTs (Occlusion-AF,[46] CATALYST,[36,47] CHAMPION-AF, OPTION[48]) are evaluating whether LAAO could replace DOAC, and other studies are needed to investigate whether transcatheter LAAO can add to the effect of DOAC and further reduce the risk of stroke. Clinicians should strive to include patients in clinical trials to provide them with access to promising therapies and to help build the body of evidence in this area of medicine. As PFO-associated stroke management requires a multidisciplinary approach, neurologists and cardiologists need to work closely together to improve stroke prevention and patient outcomes.

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