

Cerebrovascular Events in Older Patients With Patent Foramen Ovale: Current Status and Future Perspectives

Julio I. Farjat-Pasos,¹ Angel Chamorro,² Sylvain Lanthier,³ Mathieu Robichaud,¹ Siddhartha Mengi,¹ Christine Houde,⁴ Josep Rodés-Cabau^{1,5}

¹Department of Cardiology, Quebec Heart & Lung Institute, Laval University, Quebec City, Canada

²Department of Neuroscience, Hospital Clinic, University of Barcelona, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain

³Neurovascular Program and Research Center, Montreal Sacre Coeur Hospital; Montreal, Canada

⁴Department of Pediatric Cardiology, Laval University Hospital Center, Quebec City, Canada

⁵Department of Research & Innovation, Clínic Barcelona, Barcelona, Spain

Patent foramen ovale (PFO) closure, along with medical therapy, has emerged as the therapeutic gold standard in younger (<60-year-old) patients with a PFO-related stroke for preventing recurrent events. However, PFO management guidelines lack definite recommendations for older (>60 years) patients with a PFO-related cerebrovascular event, a complex group of patients who were mostly excluded from PFO closure clinical trials. Nevertheless, several studies have shown a higher prevalence of PFO among older patients with cryptogenic stroke, and its presence has been associated with an increased risk of recurrent events. Furthermore, older patients exhibit a higher prevalence of high-risk PFO anatomical features, present inherent age-related risk factors that might increase the risk of paradoxical embolism through a PFO, and have a higher incidence of ischemic events after a PFO-related event. Additionally, observational studies have shown the safety and preliminary efficacy of PFO closure in older PFO-related stroke patients. Yet, higher rates of recurrent cerebrovascular events and new-onset atrial fibrillation were observed in some studies among older patients compared to their younger counterparts. After careful case-by-case evaluation, including the assessment of hidden potential cardioembolic sources of a cryptogenic stroke other than PFO, transcatheter PFO closure might be a safe and effective therapeutic option for preventing recurrent thromboembolic events in patients >60 years with a high-risk PFO-associated stroke. Ongoing trials will provide important insights into the role of PFO closure in the elderly population.

Correspondence: Josep Rodés-Cabau
Quebec Heart and Lung Institute, Laval University, 2725, Chemin Sainte-Foy, G1V 4G5, Quebec City, Quebec, Canada
Tel: +1-418-6568711
E-mail: josep.rodés@criucpq.ulaval.ca
<https://orcid.org/0000-0001-8237-7095>

Received: May 15, 2023

Revised: August 18, 2023

Accepted: August 21, 2023

Keywords Patent foramen ovale; Cryptogenic stroke; Elderly population

Introduction

The presence of a patent foramen ovale (PFO) has been identified as an important source of cardioembolic cerebrovascular events in younger (<60 years old) patients and multiple randomized trials have shown the efficacy of transcatheter PFO closure (vs. medical treatment alone) for preventing recurrent ischemic

stroke events in such patients.¹⁻⁵ Still, current national and international clinical PFO management guidelines lack definite recommendations about transcatheter PFO closure for patients >60 years.⁶⁻¹¹ However, observational data have shown a higher prevalence of PFO among older patients diagnosed with cryptogenic stroke,^{12,13} and the presence of PFO in the elderly population has been associated with an increased risk of recurrent

cerebrovascular events.^{12,14-16} Also, several studies have shown the safety and preliminary efficacy of transcatheter PFO closure in older cryptogenic stroke patients;¹⁷⁻²¹ nevertheless, in some of these studies, a higher rate of recurrent thromboembolic events and new-onset atrial fibrillation (AF) episodes at follow-up have been observed following PFO closure in older patients compared to their younger counterparts, highlighting the differences and increased complexity of cerebrovascular events in this population.^{17,21} This review provides an overview of (1) the epidemiology of ischemic stroke in the elderly, particularly cardioembolic and PFO-related stroke, (2) the limitations of PFO causality risk scores and ischemic stroke classification systems in the elderly, and current clinical guidelines recommendations about PFO closure in older patients, and (3) current clinical evidence regarding transcatheter PFO closure in older patients, ongoing clinical trials and future perspectives in the field.

Ischemic Stroke Epidemiology in the Elderly Population

In the United States, each year, approximately 795,000 people experience a new or recurrent stroke. Approximately 610,000 of these are first attacks, 185,000 are recurrent attacks, and most importantly, 87% are ischemic strokes.²² Ischemic stroke incidence increases with age, especially in women ≥ 50 years.²³ The lifetime risk for an incident stroke is 14.5% for a person 65 years of age,²² and its mortality ranges from 74.6 to 254.2 per 100,000 in a 65- to 84-year-old population.²² Overall, one-third of ischemic strokes have a cardioembolic source,⁸ and this proportion increases with age.²⁴

Classification of Ischemic Stroke

According to the latest stroke management guidelines, in the overall population, the distribution of ischemic stroke causes is 23% lacunar (small vessel disease) and 77% non-lacunar. Among the non-lacunar strokes, 45% are cryptogenic and 35% cardioembolic,⁸ with the latter (including PFO-related strokes) showing an increasing temporal trend among white people (2.4% annually between 1993 and 2015, 95% confidence interval [CI], 0.6%–4.3%).²² Interestingly, among the large proportion of patients with cryptogenic stroke, 50% are considered as an embolic stroke of undetermined source (ESUS), implying that the stroke is embolic in origin but with an unknown source of the thrombi, and the other 50% are considered non-embolic or non-ESUS.⁸ Besides a PFO, other potential cardioembolic sources include valvular heart disease, atrial fibrillation, left ventricular disease, malignancy, aortic arch atherosclerotic plaques, as well

as other intracardiac shunts.²⁴ Despite this, it is estimated that PFO is likely responsible for approximately 5% of all ischemic strokes and 10% of those occurring in young and middle-aged adults.²⁵ However, the position of PFO inside stroke classification systems can be very overlapping or confusing, leading to not-so-accurate statistics in PFO-related stroke patients. In an effort to overcome such limitations, based on all stroke classification systems limitations and the latest evidence around PFO, Elgendy et al.²⁵ recently proposed the term PFO-associated stroke to “all patients presenting with superficial, large deep, or retinal infarcts in the presence of a medium-risk to high-risk PFO and no other identified likely cause.”²⁵

PFO and Its Role in Ischemic Stroke in the Elderly

Overall and age-specific prevalence of PFO among healthy subjects

The spontaneous closure of foramen ovale usually occurs within the first year of life but only in three-fourths of the population, leaving approximately 25%^{26,27} of the adult population with a PFO, which translates to about 1.9 billion people globally.²⁸ The prevalence of PFO differs according to patients' age, from 34.3% during the first three decades of life to 20.2% during the 9th and 10th decades.²⁶ Additionally, in autopsy studies of healthy hearts, the PFO size is larger in the 10th decade of life compared to the 1st decade of life,²⁶ which is clinically relevant since large-size PFOs have a stronger causal relationship with a PFO-related stroke.³

Prevalence of PFO among younger and older patients with cryptogenic stroke

In young patients (<55 years) diagnosed with cryptogenic stroke, multiple studies have shown an increased prevalence of PFO compared to their stroke of known origin counterparts,^{29,30} as much as four times higher than patients with stroke of known causes³⁰ among all diagnostic modalities.²⁷

Although the initial effort in the search for an association between a PFO and cryptogenic stroke among the elderly population failed (vaguely defined as having a stroke without a predetermined cause),³¹ more recent studies have shown an increasing association within this population. Alsheikh-Ali et al.²⁹ performed a systematic review identifying 23 case-control studies, showing an OR of 2 (>1 to 3.7) for PFO in patients older than 55 years diagnosed of cryptogenic stroke. However, one important limitation of that study was the diagnostic method of PFO since in 74% of the studies was transesophageal echocardiogram (TEE),

but in 26% was transcranial Doppler. More recently, Handke et al.¹² reported a TEE prevalence of PFO in 28.3% of older patients with cryptogenic stroke, compared to 11.9% in patients of the same age with a known cause of stroke. In the multivariable analysis, PFO was independently associated with cryptogenic stroke in the younger and older groups. Likewise, in a population-based study nested in the Oxford Vascular (OXVASC) study, compared to patients with transient ischemic attack (TIA) or stroke of known cause, patients with cryptogenic events had a higher prevalence of right-to-left shunt in the overall population (odds ratio [OR] 1.93, 95% CI: 1.32–2.82; $P=0.001$), but remarkably, this was even higher among patients >60 years (OR 2.06, 95% CI: 1.32–3.23; $P=0.001$).¹³ One important limitation was that the PFO prevalence was evaluated by contrast-enhanced transcranial Doppler. The authors extrapolated their results amongst the British population, estimating that every year 8,477 cryptogenic cerebral ischemic events could be attributed to significant right-to-left shunting, with 70% of them occurring in patients older than 60 years.

Pathophysiology of PFO in embolic stroke

Two main potential mechanisms can explain the role of PFO in a systemic arterial embolism. Firstly, paradoxical embolism, meaning the passage of a right-sided venous thrombus to the systemic circulation through the PFO, especially during the transient or persistent elevation of right-heart pressures.³² This mechanism will only need a PFO gap as small as 1–3 mm to cause either severe impairment or a large infarct since 1 mm is the average size of any major cerebral cortical branch and 3 mm is the size of the middle cerebral artery stem.³³ The second mechanism would be *in situ* PFO thrombus formation, which can lead to an embolization into the arterial circulation.³⁴

High-risk anatomical PFO features

Although a PFO can only be a bystander in the settings of an otherwise cryptogenic stroke, several morphologic characteristics have been described as being more prone to a higher risk for paradoxical embolization or *in situ* thrombus formation, thus, with a higher likelihood of causal relationship. These morphologic characteristics include a large PFO (maximum separation of the septum primum from the secundum >2–3 mm),^{35–37} long tunnel (>10 mm),³⁸ atrial septal aneurysm (ASA) (usually defined as hypermobility of the septum with >10 mm excursion),^{14,31,36,39} shunt size,^{14,37,39,40} and prominent Eustachian valve.⁴¹ Identifying these high-risk PFO features is crucial since there is potentially a higher benefit from PFO closure among patients with high-risk anatomical PFO features.⁴²

Moreover, score systems based on these high-risk anatomical

characteristics have been developed to help proper patient selection for closure therapies.^{38,43} Identifying these high-risk PFO features is important, as a recent meta-analysis from randomized trials showed that there is potentially a higher benefit from PFO closure among patients with high-risk anatomical PFO features,⁴⁴ which according to observational studies on PFO closure in younger versus older patients, these high-risk features are more prevalent among the elderly population undergoing PFO closure due to a PFO-related cerebrovascular event.^{17,18,21}

Assessing PFO causality role: limitations of risk scores in the elderly

The risk of paradoxical embolism (RoPE) score allows an evaluation of the potential causal role of a PFO in any given patient with a stroke of unknown cause.⁴⁵ It mainly uses the patient's age, with younger patients having an increased risk of causality, the absence of atherosclerotic risk factors, and infarct topography, to determine the likelihood that a PFO is causally related to stroke in individual patients.⁴⁵ This score has been validated and is used in clinical practice and PFO research.⁴⁶

According to the RoPE score, the higher the score, particularly above 6 points, the stronger the link of causality between a PFO and a cryptogenic stroke. Also, as per RoPE score, younger patients and patients without traditional cardiovascular risk factors have the highest PFO-attributable fraction.⁴⁵ For example, a 29-year-old non-smoker patient with a PFO and a cryptogenic cortical stroke, without hypertension, diabetes, and no history of stroke/TIA, has a RoPE score of 10 points (maximum score) and a PFO-attributable fraction of 88%. However, any patient ≥50 years with a history of hypertension, diabetes, stroke, and smoking, even in the presence of an embolic-like stroke on imaging, has a RoPE score of 3 points, meaning a PFO-attributable fraction of 0%, basically discarding any possible association between a stroke and a PFO,⁴⁵ an estimation that can be misleading in the elderly population. Moreover, in this scoring system, for every 10-year increase in patients' age, there is a decrease in the total RoPE score, and in patients with ≥70 years, the age factor adds 0 points; thus, the possible association between a PFO and an index ischemic stroke is even less likely just by the age. Additionally, based on the RoPE original dataset, Thaler et al.¹⁴ showed that older age was a significant predictor of recurrent stroke among patients with a low (<6) RoPE score (hazard ratio [HR] 1.47, 95% CI: 1.18–1.83).

Trying to overcome some RoPE score limitations, the PFO-Associated Stroke Causal Likelihood (PASCAL) Classification System emerged to further assess the potential causal role²⁵ by combining the RoPE score with the most consistent high-risk PFO anatomical features to provide a more precise causal correlation.

Compared to the conventional RoPE score mainly focused on patient age and other vascular risk factors, PASCAL classification with the addition of the anatomical features of PFO (namely ASA and shunt severity) showed a better performance in distinguishing subgroups who may benefit from PFO closure from those unlikely to benefit from it; thus, selection of patients with ESUS and high-risk PFO features seems to be the first step to expect a significant reduction of recurrent events. However, although the PASCAL classification system is already validated,⁴⁷ it is still limited among older patients since it is based on the RoPE score, which includes age as one of the main variables.

Recurrent cerebrovascular events after an index PFO-related stroke in the elderly

According to meta-analyses, patients with a PFO-related stroke, the annual recurrence rate on medical therapy ranges from 0% to 5.8% for stroke and from 0% to 14% for stroke or TIA.^{48,49} Several factors have been associated with a higher risk of recurrent events, such as older age, presence of ASA, use of acetylsalicylic acid (compared to oral anticoagulation), thrombophilia, stroke as index event, and PFO size.⁷

Remarkably, compared to younger patients, elderly patients are at higher risk of recurrent cryptogenic stroke after an index PFO-related event. According to the latest European guidelines on the management of patients with PFO, based on four studies with a total of 2,171 patients,^{12,14-16} older patients are at an increased risk of recurrent cerebrovascular events after an index PFO-related cryptogenic stroke; among other factors, older age has an HR of 1.47 (95% CI 1.2–1.8) for cryptogenic stroke recurrence in the presence of PFO.⁷ In an analysis of the CLOSE (Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence) and DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale) trials, one of the variables associated with time to recurrent stroke was age, with a crude HR of 1.52 (95% CI 1.17–1.97, $P=0.001$) per 10-year increase.³⁹ Interestingly, another study in patients with ESUS showed that older patients had twice recurrent embolic strokes after a median follow-up of 3 years, and, when analyzed by potential embolic sources, this difference was mainly driven by PFO-related strokes among the older population (recurrent embolic stroke 12.5% vs. 5.6% in young patients with PFO-related stroke).⁵⁰

The most recent evidence on recurrent events was reported by Mazzucco et al.⁵¹ The authors showed that the absolute risk of recurrent ischemic stroke in the overall population was 2.0 per 100 patient-years (95% CI, 1.57–2.55), based on 268 recurrent events during 15,058 patient-years. After analyzing by age groups, the pooled ischemic stroke risk in patients of 60 years or older

was 3.27 per 100 patient-years (95% CI, 2.59–4.13). Remarkably, the authors performed another pooled analysis of four studies reporting ischemic stroke risk stratified by age in patients with cryptogenic TIA/stroke with PFO versus patients without PFO, finding that the association between PFO and stroke risk also increased with age (<65 years: OR, 0.8; 95% CI, 0.4–1.5; ≥65 years: OR, 2.5; 95% CI, 1.4–4.2; $P=0.001$).

The cause behind the recurrent strokes in older patients with PFO left under medical treatment remain unclear since the data on this subject is very limited. In the DEFENSE PFO trial, all recurrent strokes were considered as PFO-related.⁵² Additionally, observational data shows recurrent strokes being cryptogenic even with negative AF after prolonged cardiac monitoring.²⁰ In observational PFO closure studies, recurrent stroke rates are lower and importantly, the main causes are atherothrombotic, AF-related, vertebral dissection and small vessel disease, among others, with the most strongly associated factors being diabetes and chronic renal disease.^{18,21} Ongoing trials will provide further details on the cause of recurrent stroke in these patients.

Special considerations in elderly patients with a PFO-related stroke

The causal relationship between a PFO and a stroke among elderly patients was once thought to be lower as the incidence of stroke due to other causes increased. Nevertheless, this causal association may be higher than expected. Autopsy studies including healthy hearts showed that PFO size is larger in the last decades of life²⁶ with an increase in mean PFO size from 3.4 mm in the first decade to 5.8 mm in the 10th decade of life,²⁶ and the larger the PFO, the higher the risk of having a PFO-related stroke.³⁸

Another special consideration is the increased risk of venous thromboembolism. The risk of deep venous thrombosis (DVT) is strongly associated with age,⁵³ and its overall incidence has been increasing over time, particularly among elderly patients,⁵⁴ also including those cases with silent thrombus formation.⁵⁵ When a DVT develops, it can serve as the nidus for a barrage of thromboemboli directed at the right atria, with 300 to 50,000 emboli per hour.⁵⁶ Both DVT and pulmonary embolism are essential considerations since, in these patients, the presence of PFO is associated with ischemic brain lesions, both at baseline and at follow-up.⁵⁷

It is known that right ventricular systolic and diastolic function, as evaluated by transthoracic echocardiogram, decreases gradually among the healthy elderly population,⁵⁸ data that has been recently refined by cardiac magnetic resonance imaging.⁵⁹ Although not directly proven, having increased filling pressures in the right ventricle could increase the risk of a right-sided thrombus migrating to the systemic circulation through an interatrial

shunt, especially during transitory pressure elevation in the right side of the heart observed in the Valsalva maneuver.

PFO Closure in Young Patients and Current Clinical Guidelines Recommendations

Transcatheter PFO closure has been established as an ambulatory (same-day discharge), straightforward interventional procedure.⁷ The intervention has a very high safety profile, with <1% of major periprocedural complications and a 2%–6% rate of AF episodes (usually transient) within the days to weeks following the procedure.⁶⁰

In patients with cryptogenic stroke, up to four randomized trials have shown a significant reduction in recurrent ischemic stroke events following transcatheter PFO closure.^{1–5} All randomized trials in the PFO-stroke field excluded patients older than 60 years, except one,³ meaning that most patients randomized in these trials were younger than 60 years. Therefore, compelling scientific evidence exists for transcatheter PFO closure in man-

aging younger patients with cryptogenic stroke. Table 1 summarizes the randomized clinical trials on PFO closure versus medical therapy, including their age inclusion criteria and the mean age for each treatment group.

Every major clinical guideline on the management of patients with a PFO-related event recommends performing transcatheter PFO closure over medical therapy alone for patients aged 18 and ≤60–65 years with a PFO-related stroke. However, some discrepancies are observed regarding the recommendations in patients older than 60–65 years. While some guidelines are stringent and do not recommend (class III) the closure for patients >60–65 years old, others emit limited or reserved recommendations, with the possibility of a case-by-case clinical decision strategy in such cases. Table 2 summarizes the most recent and important clinical guidelines on PFO-related stroke management, emphasizing age-related recommendations and transcatheter PFO closure in younger versus older patients.^{6–11}

Table 1. Randomized clinical trials on patent foramen ovale closure versus medical treatment in patients with cryptogenic stroke

Trial	Age inclusion criteria (yr)	Number of patient per group (PFOc/MT)	Mean age by treatment group (yr) (PFOc/MT)	Closure device	Medical treatment arm	Mean follow-up (yr)	Primary end-point	Main results (PFOc vs. MT)
CLOSURE I (2012) ⁶⁸	18–60	447 462	46.3±9.6 45.7±9.1	STARFlex	Warfarin, aspirin, or both	2	Composite of stroke or TIA, death, death from neurologic causes	5.5% vs. 6.8% (HR 0.78, 95% CI 0.45–1.35; P=0.37)
PC (2013) ⁶⁹	<60	204 210	44.3±10.2 44.6±10.1	Amplatzer PFO occluder	Antiplatelet therapy or oral anticoagulation	4.1	Composite of death, non-fatal stroke, TIA, or peripheral embolism	3.4% vs. 5.2% (HR 0.63, 95% CI 0.25–1.62; P=0.34)
RESPECT LTF (2017) ¹	18–60	499 481	45.7±9.7 46.2±10	Amplatzer PFO occluder	Aspirin, warfarin, clopidogrel, or aspirin+dipyridamole	5.9	Composite of stroke or early death	0.58 events per 100 patient-years vs. 1.07 (HR 0.55, 95% CI 0.31–0.999; P=0.046)
CLOSE (2017) ⁴	16–60	238 235	42.9±10.1 43.8±10.5	Any approved device	Aspirin, clopidogrel or aspirin+dipyridamole; warfarin or DOAC	5.3	Composite of fatal or non-fatal stroke	0% vs. 4.9% cumulative estimated probability in the antiplatelet only group (HR 0.03, 95% CI 0–0.26; P<0.001)
Gore REDUCE LTF (2021) ^{2,5}	18–59	441 223	45.4±9.3 44.8±9.6	Helex or Cardioform septal occluder	Aspirin, clopidogrel or aspirin+dipyridamole	5	Composite of clinical stroke or silent infarct detected on imaging	1.8% vs. 5.4% (HR 0.31, 95% CI 0.13–0.76; P=0.007)
DEFENSE-PFO (2018) ³	18–80	60 60	49±15 54±12	Amplatzer PFO occluder	Aspirin, aspirin+clopidogrel, aspirin+cilostazol, or warfarin	2.8	Composite of stroke, vascular death, or major bleeding	0% vs. 12.9% (P=0.013)

PFOc, patent foramen ovale closure; MT, medical treatment; TIA, transient ischemic attack; HR, hazard ratio; CI, confidence interval; PFO, patent foramen ovale; LTF, long-term follow-up; DOAC, direct oral anticoagulant; CLOSURE I, Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale; PC, Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism; RESPECT LTF, Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke; CLOSE, Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke; Gore REDUCE LTF, GORE® Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients; DEFENSE-PFO, Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale.

Table 2. Clinical guideline recommendations on transcatheter management of patients with PFO-related thromboembolic events according to age

Guideline	Young patients (18 to ≤60–65 years)	Older patients (>60–65 years)
American Heart Association/ American Stroke Association ⁸	In patients 18 to 60 years of age with a non-lacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO with high-risk anatomic features, it is reasonable to choose closure with a transcatheter device and long-term antiplatelet therapy over anti-platelet therapy alone for preventing recurrent stroke.	None
American Academy of Neurology ⁶	In patients younger than 60 years with a PFO and embolic-appearing infarct and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits (absolute recurrent stroke risk reduction of 3.4% at 5 years) and risks (periprocedural complication rate of 3.9% and increased absolute rate of non-periprocedural atrial fibrillation of 0.33% per year).	PFO closure may be offered in other populations, such as for a patient who is aged 60–65 years with a very limited degree of traditional vascular risk factors (i.e., hypertension, diabetes, hyperlipidemia, or smoking) and no other mechanism of stroke detected following a thorough evaluation, including prolonged monitoring for atrial fibrillation (level C).
Society for Cardiovascular Angiography & Interventions ¹⁰	<ul style="list-style-type: none"> - In patients between the ages of 18 and 60 with a prior PFO-associated stroke, the SCAI guideline panel recommends PFO closure rather than antiplatelet therapy alone (strong recommendation, moderate certainty of evidence). - In patients between the ages of 18 and 60 with a prior PFO-associated stroke and no other indication for treatment with anticoagulation, the SCAI guideline panel suggests PFO closure plus antiplatelet therapy rather than anticoagulation therapy alone (conditional recommendation, low certainty of evidence). - This recommendation is independent of patient anatomy (i.e., presence of ASA, size of shunt) due to limited clinical data on these sub-populations. A RoPE score ≥ 7 may identify patients who are likely to receive greater benefit from PFO closure. 	<ul style="list-style-type: none"> - In patients 60 years or older with a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure rather than long-term antiplatelet therapy alone (conditional recommendation, very low certainty of evidence). - In patients 60 years or older with a prior PFO-associated stroke and no other indications for treatment with anticoagulation, the SCAI guideline panel suggests PFO closure plus antiplatelet therapy rather than long-term anticoagulation therapy alone (conditional recommendation, very low certainty of evidence). - Patients in this age group who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure-related risks may reasonably decline PFO closure.
Canadian Stroke Best Practice Recommendations ⁹	For carefully selected patients with a recent ischemic stroke attributed to a PFO, PFO device closure plus long-term antiplatelet therapy is recommended over long-term antithrombotic therapy alone, provided all the following criteria are met [Evidence Level A]: a. Age 18–60 years, b. The diagnosis of the index stroke event is confirmed by imaging as a non-lacunar embolic ischemic stroke, c. The patient has been evaluated by a neurologist or healthcare professional with stroke expertise, and the PFO is felt to be the most likely cause for the index stroke event following a thorough etiological evaluation that has excluded alternate likely etiologies.	None
European position paper on the management of patients with patent foramen ovale ⁷	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.	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.
Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference ¹¹	In patients aged 18–60 years old with cryptogenic stroke/TIA and with high risk PFO features (moderate or severe shunt, ASA, atrial septal hypermobility) we recommend percutaneous closure plus medical therapy instead of antiplatelet therapy alone (Grade A).	<ul style="list-style-type: none"> - In patients between 60 and 65 years, percutaneous closure plus medical therapy instead of antiplatelet therapy alone can be offered (Grade B). - Percutaneous closure plus medical therapy can be considered in place of antiplatelet therapy alone also for patients aged <18 and >65 years old on an individual basis (Grade C).

PFO, patent foramen ovale; SCAI, Society for Cardiovascular Angiography & Interventions; ASA, atrial septal aneurysm; RoPE, risk of paradoxical embolism; TIA, transient ischemic attack.

Evidence of PFO Closure in Older Patients

Clinical trial sub-analysis

The DEFENSE PFO trial is the only randomized clinical trial in the PFO closure field which included a small proportion of patients older than 60 years. This trial included 120 patients between 18 to 80 years (mean age of 50 years).³ In a recent sub-analysis comparing younger (<60 years) versus older (≥60 years) patients, the 2-year event rate difference between medical treatment versus PFO closure was 24.6% (HR, 7.36; 95% CI, 0.28–195.81; log-rank $P=0.07$) in patients >60 years after a median follow-up of 3 years, and it was even higher (80%) in patients ≥70 years (HR, 11.64; 95% CI, 0.43–318.81; log-rank $P=0.03$).⁵²

Observational studies

Besides the aforementioned sub-analysis, all the evidence available on PFO closure among older patients with PFO-related thromboembolic events comes from observational studies.

Not surprisingly, all studies showed that older patients had a higher prevalence of traditional age-related cardiovascular risk factors.^{17,18,20,21} Most importantly, most studies showed a higher prevalence of high-risk anatomical PFO features among older patients^{17,18,21} compared to younger patients. Transcatheter PFO closure was safe in all studies, with a very low complication rate between groups, except for one study that reported a higher incidence of vascular complications in the elderly population.¹⁷

Overall, the mean incidence of recurrent stroke events following PFO closure in older patients (excluding ancient studies with discontinued PFO closure devices) has been about 1.38 per 100 patients-years (from 0.55 to 2.67 per 100 patients-years),^{17–21} which appears to be lower than 3.27 per 100 patient-years, which is the reported incidence of recurrent cerebrovascular events in studies of older patients with PFO treated medically.⁵¹

One important confounder in studies involving older patients with ischemic cerebrovascular events is the role of AF (frequently silent episodes) as the primary source of thromboembolism and the risk of PFO closure procedure-related AF. As a consequence, the workup of any cryptogenic ischemic cerebrovascular event includes prolonged cardiac monitoring for the detection of episodes of symptomatic or silent AF;⁸ however, the optimal duration of post-stroke cardiac monitoring remains unknown.⁶¹ A recent meta-analysis⁶¹ including 8 studies (5 randomized clinical trials) showed that prolonged post-stroke cardiac rhythm monitoring after an ischemic stroke or TIA could lead to higher rates of AF detection and anticoagulant initiation. Nevertheless, the authors concluded that there was no solid evidence from randomized trials supporting prolonged cardiac rhythm monitor-

ing for the prevention of recurrent stroke events.

The next clinically challenging question is how often occult AF is causally related to cryptogenic ischemic stroke. Chaisinanunkul et al.⁶² identified, in a systematic review, all case-control and cohort studies on patients with identical long-term monitoring techniques in patients with cryptogenic and know-source strokes. After performing a random-effects meta-analysis applying Bayes' theorem to determine the probability of silent AF being causal or incidental, they concluded that in patients with cryptogenic stroke, when occult AF is found, it is causal in about 38.2% of patients. Remarkably, after age stratification, occult AF detected in patients with cryptogenic stroke was considered causal in 62.3% (95 CI, 0%–87.1%) of patients under the age of 65 years and only in 28.5% (95 CI, 0%–63.7%) of patients aged 65 years and older.

In a recent meta-analysis in the younger population undergoing PFO closure, the incidence of AF after PFO closure was 3.7 per 100 patient-years (95% CI: 2.6–4.9), which was higher than the incidence of 0.1 per 100 patient-years (95% CI: 0.0–0.4) observed in patients treated medically (HR: 5.3, 95% CI: 2.5–11.41), $P<0.001$.⁶⁰ Interestingly, the increased risk of AF development occurred mainly in the first 45 days post-procedure, and according to a meta-regression analysis, a higher risk was observed in older patients ($P=0.001$).

Observational studies on PFO closure in the elderly population have reported a rate of *de novo* symptomatic AF ranging from 2% to 9.2% versus 0.7% to 8.4% among their younger counterparts.^{17–21} While seven studies reported no impact of age in the incidence of AF after PFO closure, two studies showed a higher rate of post-procedural AF among older patients.^{21,63} Overall, before PFO closure, only one study excluded patients with prior evidence of AF,¹⁷ while the others did not exclude or mention the rate of patients with a history of AF before the procedure. Several limitations on detection methods of AF before and after the procedure and the unknown rates of asymptomatic AF would preclude drawing definite conclusions from these studies in terms of AF before and after PFO closure in older patients with a PFO-related stroke.

A potential approach for PFO closure candidates older than 55–65 years with no history of AF could be an implantable loop recorder 6 months before the procedure and systematic mid-term monitoring for arrhythmia detection and its corresponding treatment. Ongoing clinical trials addressing the recurrence of AF among older patients undergoing PFO closure will provide definitive insights on this important confounder among the elderly population with PFO and a cryptogenic stroke (Figure 1).

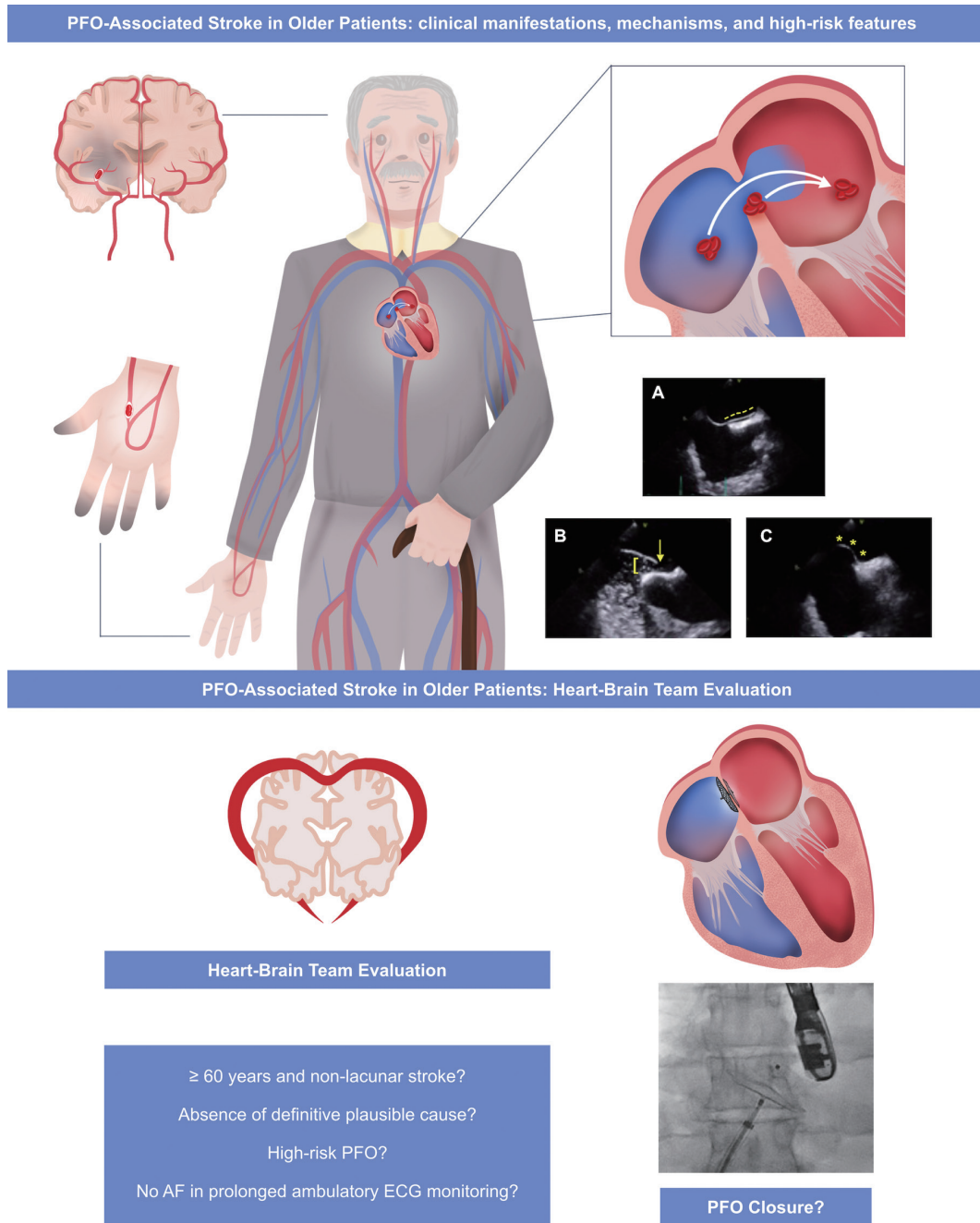


Figure 1. Patent foramen ovale (PFO)-associated stroke in the elderly population. The main clinical manifestations are stroke, transient ischemic attack (TIA), or peripheral embolism. This can be caused by two mechanisms: paradoxical embolism or *in situ* thrombus formation. The main high-risk anatomical PFO features are (A) long tunnel (dashed yellow line), (B) large PFO, >2–3 mm (yellow square bracket; yellow arrow depicting a large free passage of bubbles from the right atrium to the left atrium), and (C) atrial septal aneurysm (yellow asterisks). A heart-brain team should carefully evaluate case-by-case to assess the potential causal association between a non-lacunar stroke without any definitive plausible cause in the presence of a high-risk PFO to consider transcatheter PFO closure, ideally after discarding occult atrial fibrillation (AF) with a reasonable approach, perhaps requiring a long-term monitoring system.

Ongoing Trials on PFO Closure in Older Patients

Although some data suggest that transcatheter PFO closure is effective in older patients with a PFO-associated stroke, there are still several gaps in the evidence, namely the absence of specific

randomized clinical trials in such patients. Nevertheless, there are several important ongoing studies in this field (Table 3). The CLOSE-2 trial (PFO Closure, Oral Anticoagulants or Antiplatelet Therapy After PFO-associated Stroke in Patients Aged 60 to 80 Years; NCT05387954)⁶⁴ will assess whether PFO closure plus antiplatelet therapy is superior to antiplatelet therapy alone and

Table 3. Ongoing studies on older (≥60 years) patients with PFO-related cerebrovascular events

Study name	Study locations	Study type	Estimated enrollment	Age-related considerations	Design model	Study population or groups	Primary outcome	Estimated completion date
CLOSE-2 ⁶⁴	31 Centers in France	Clinical trial	792	Patients aged 60 to 80 years	Randomized	- PFO closure plus antiplatelet therapy vs. antiplatelet therapy alone - Oral anticoagulation vs. antiplatelet therapy	Time to recurrent stroke (ischemic or hemorrhagic fatal or non-fatal)	June 1, 2030
COACH ESUS ⁶⁵	Multicentric; Korea	Observational	1,200	60 years and older	Case-control	- PFO closure plus standard antiplatelet treatment vs. standard antiplatelet only	Ischemic stroke recurrence	May 31, 2027
DefenseElderly ⁶⁶	Multicentric; Korea	Observational	300	60 years and older	Cohort	- ESUS and PFO that is likely to have causative role (high-risk anatomical feature) - ESUS without PFO, or with non-high risk PFO	Paroxysmal AF episodes >30 seconds detected with intermittent recordings or ≥2 minutes during ICM within 6 months	October 2, 2024
International PFO Consortium ⁶⁷	19 Centers, international	Observational	1,500	18 years and older	Cohort	- PFO closure vs. antithrombotic therapy alone	Proportion of patients free of any stroke (including fatal stroke) or TIA *Etiological role of PFO for stroke/TIA in patients aged >55 years	December 2021

PFO, patent foramen ovale; ESUS, embolic stroke of undetermined source; AF, atrial fibrillation; ICM, insertable cardiac monitoring.

*Listed as one of the main study objectives; CLOSE-2, PFO Closure, Oral Anticoagulants or Antiplatelet Therapy After PFO-associated Stroke in Patients Aged 60 to 80 Years; COACH ESUS, Prospective Registry of Elderly ESUS With PFO; DefenseElderly, Evaluation of Prevalence and Clinical Impact of Atrial Fibrillation in Elderly Patients With Cryptogenic Stroke and High-Risk Patent Foramen Ovale.

whether oral anticoagulant therapy is superior to antiplatelet therapy to prevent stroke recurrence in patients aged 60 to 80 years. The COACH ESUS (Prospective Registry of Elderly ESUS With PFO; NCT05238610)⁶⁵ study is a multicenter registry of elderly cryptogenic stroke patients undergoing PFO closure. The DefenseElderly study (Evaluation of Prevalence and Clinical Impact of Atrial Fibrillation in Elderly Patients With Cryptogenic Stroke and High-Risk Patent Foramen Ovale; NCT04285918)⁶⁶ will determine the incidence and clinical impact of AF and evaluate the clinical impact of AF in elderly ESUS patients (≥60 years) with no other known sources of stroke besides a high-risk PFO. Finally, one of the International PFO Consortium (NCT00859885)⁶⁷ objectives is to assess the etiological role of PFO for stroke/TIA.

Conclusions

Similar to younger patients, older (>55–65 years) patients with cryptogenic stroke present a higher prevalence of PFO than their stroke of known cause counterparts. Additionally, older patients exhibit a higher prevalence of high-risk anatomical PFO features, present inherent age-related risk factors that might increase the risk of paradoxical embolism, and have higher rates of recurrent ischemic events after an index PFO-related thromboembolic event compared to their younger counterparts. Several observational studies suggest that transcatheter PFO closure is as safe and effective for preventing recurrent ischemic thromboembolic events in older patients as in younger patients. However, ischemic stroke classification and PFO-causality score systems have significant restraints, particularly in the elderly population, and age-related recommendations by the clinical guidelines on the management of PFO are limited. Therefore, a thorough multidisciplinary case-by-case evaluation is warranted to define the best treatment option for older patients with high-risk PFO-related stroke. Treatment options for these patients could safely include transcatheter PFO closure. Nevertheless, known stroke causes, including other cardioembolic ischemic sources, should always be taken into account since they are highly prevalent in this group. Ongoing trials will provide important insights into the role of transcatheter PFO closure in the elderly population.

Funding statement

None

Conflicts of interest

Dr. Rodés-Cabau has received institutional research grants from Abbott Vascular Canada. The other authors have nothing to declare.

Author contribution

Conceptualization: JRC, JIFP. Investigation: all authors. Writing—original draft: JIFP, JRC, MR. Writing—review & editing: all authors. Approval of final manuscript: all authors.

Acknowledgments

Dr. Rodés-Cabau holds the Research Chair "Fondation Famille Jacques Larivière" for the Development of Structural Heart Disease Interventions (Laval University, Quebec City, Canada).

References

1. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017; 377:1022-1032.
2. Søndergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017; 377:1033-1042.
3. Lee PH, Song JK, Kim JS, Heo R, Lee S, Kim DH, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. *J Am Coll Cardiol* 2018;71:2335-2342.
4. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017;377: 1011-1021.
5. Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, et al. Five-year outcomes of PFO closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2021; 384:970-971.
6. Messé SR, Gronseth GS, Kent DM, Kizer JR, Homma S, Rosterman L, et al. Practice advisory update summary: patent foramen ovale and secondary stroke prevention: report of the guideline subcommittee of the American Academy of Neurology. *Neurology* 2020;94:876-885.
7. Pristipino C, Sievert H, D'Ascenzo F, Louis Mas J, Meier B, Scacciatella P, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *Eur Heart J* 2019;40:3182-3195.
8. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke* 2021;52:e364-e467.
9. Gladstone DJ, Lindsay MP, Douketis J, Smith EE, Dowlatshahi D, Wein T, et al. Canadian stroke best practice recommendations: secondary prevention of stroke update 2020. *Can J Neurol Sci* 2022;49:315-337.
10. Kavinsky CJ, Szerlip M, Goldsweig AM, Amin Z, Boudoulas KD, Carroll JD, et al. SCAI guidelines for the management of patent foramen ovale. *J Soc Cardiovasc Angiogr Interv* 2022; 1:100039.
11. Ahmed N, Audebert H, Turc G, Cordonnier C, Christensen H, Sacco S, et al. Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 11-13 November 2018. *Eur Stroke J* 2019;4:307-317.
12. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med* 2007;357:2262-2268.
13. Mazzucco S, Li L, Binney L, Rothwell PM; Oxford Vascular Study Phenotyped Cohort. Prevalence of patent foramen ovale in cryptogenic transient ischaemic attack and non-disabling stroke at older ages: a population-based study, systematic review, and meta-analysis. *Lancet Neurol* 2018;17:609-617.
14. Thaler DE, Ruthazer R, Weimar C, Mas JL, Serena J, Di Angelantonio E, et al. Recurrent stroke predictors differ in medically treated patients with pathogenic vs. other PFOs. *Neurology* 2014;83:221-226.
15. Tobe J, Bogiatzi C, Munoz C, Tamayo A, Spence JD. Transcranial Doppler is complementary to echocardiography for detection and risk stratification of patent foramen ovale. *Can J Cardiol* 2016;32:986.e9-986.e16.
16. Homma S, DiTullio MR, Sacco RL, Sciacca RR, Mohr JP. Age as a determinant of adverse events in medically treated cryptogenic stroke patients with patent foramen ovale. *Stroke* 2004; 35:2145-2149.
17. Scacciatella P, Meynet I, Presbitero P, Giorgi M, Lucarelli C, Zavalloni Parenti D, et al. Recurrent cerebral ischemia after patent foramen ovale percutaneous closure in older patients: a two-center registry study. *Catheter Cardiovasc Interv* 2016; 87:508-514.
18. Wintzer-Wehekind J, Alperi A, Houde C, Côté JM, Del Val D, Côté M, et al. Transcatheter closure of patent foramen ovale in patients older than 60 years of age with cryptogenic embolism. *Rev Esp Cardiol (Engl Ed)* 2020;73:219-224.
19. Nachoski D, Schroeder J, Almalla M, Kubini R, Tchaikovski V, Kosinski C, et al. Dual-center experiences with interventional closure of patent foramen ovale: a medium-term follow-up study comparing two patient groups aged under and over 60 years. *Clin Cardiol* 2021;44:386-391.
20. Poli S, Siebert E, Mbroh J, Poli K, Krumbholz M, Mengel A, et al. Closure or medical therapy of patent foramen ovale in

- cryptogenic stroke: prospective case series. *Neurol Res Pract* 2021;3:16.
21. Alperi A, Guedeney P, Horlick E, Nombela-Franco L, Freixa X, Pascual I, et al. Transcatheter closure of patent foramen ovale in older patients with cryptogenic thromboembolic events. *Circ Cardiovasc Interv* 2022;15:e011652.
 22. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bitencourt MS, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation* 2022;145:e153–e639.
 23. Ding Q, Liu S, Yao Y, Liu H, Cai T, Han L. Global, regional, and national burden of ischemic stroke, 1990–2019. *Neurology* 2022;98:e279–e290.
 24. Ntaios G. Embolic stroke of undetermined source: JACC review topic of the week. *J Am Coll Cardiol* 2020;75:333–340.
 25. Elgendy AY, Saver JL, Amin Z, Boudoulas KD, Carroll JD, Elgendy IY, et al. Proposal for updated nomenclature and classification of potential causative mechanism in patent foramen ovale-associated stroke. *JAMA Neurol* 2020;77:878–886.
 26. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984;59:17–20.
 27. Koutroulou I, Tsvigoulis G, Tsalikakis D, Karacostas D, Grigoriadis N, Karapanayiotides T. Epidemiology of patent foramen ovale in general population and in stroke patients: a narrative review. *Front Neurol* 2020;11:281.
 28. Mac Grory B, Ohman EM, Feng W, Xian Y, Yaghi S, Kamel H, et al. Advances in the management of cardioembolic stroke associated with patent foramen ovale. *BMJ* 2022;376:e063161.
 29. Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? *Stroke* 2009;40:2349–2355.
 30. Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988;318:1148–1152.
 31. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;55:1172–1179.
 32. Anderson RG. Paradoxical embolism. *Br Med J* 1946;1:836.
 33. Saver JL, Mattle HP, Thaler D. Patent foramen ovale closure versus medical therapy for cryptogenic ischemic stroke: a topical review. *Stroke* 2018;49:1541–1548.
 34. Yan C, Li H. Preliminary investigation of in situ thrombus within patent foramen ovale in patients with and without stroke. *JAMA* 2021;325:2116–2118.
 35. Nakayama R, Takaya Y, Akagi T, Watanabe N, Ikeda M, Nakagawa K, et al. Identification of high-risk patent foramen ovale associated with cryptogenic stroke: development of a scoring system. *J Am Soc Echocardiogr* 2019;32:811–816.
 36. Lee JY, Song JK, Song JM, Kang DH, Yun SC, Kang DW, et al. Association between anatomic features of atrial septal abnormalities obtained by omni-plane transesophageal echocardiography and stroke recurrence in cryptogenic stroke patients with patent foramen ovale. *Am J Cardiol* 2010;106:129–134.
 37. Fukuoka T, Dembo T, Nagoya H, Kato Y, Yasuko O, Deguchi I, et al. Factors related to recurrence of paradoxical cerebral embolism due to patent foramen ovale. *J Neurol* 2012;259:1051–1055.
 38. Vizzari G, Pizzino F, Zwicke D, Tajik AJ, Carerj S, Di Bella G, et al. Patent foramen ovale: anatomical complexity and long-tunnel morphology related issues. *Am J Cardiovasc Dis* 2021;11:316–329.
 39. Turc G, Lee JY, Brochet E, Kim JS, Song JK, Mas JL. Atrial septal aneurysm, shunt size, and recurrent stroke risk in patients with patent foramen ovale. *J Am Coll Cardiol* 2020;75:2312–2320.
 40. Benvenuti F, Meucci F, Vuolo L, Nistri R, Pracucci G, Picchioni A, et al. Relation between the size of patent foramen ovale and the volume of acute cerebral ischemic lesion in young patients with cryptogenic ischemic stroke. *Neurol Sci* 2022;43:453–458.
 41. Cai Q, Ahmad M. Eustachian valve, interatrial shunt, and paradoxical embolism. *Echocardiography* 2020;37:939–944.
 42. Mas JL, Saver JL, Kasner SE, Nelson J, Carroll JD, Chatellier G, et al. Association of atrial septal aneurysm and shunt size with stroke recurrence and benefit from patent foramen ovale closure. *JAMA Neurol* 2022;79:1175–1179.
 43. Hołda MK, Krawczyk-Ożóg A, Koziej M, Kołodziejczyk J, Sorysz D, Szczepanek E, et al. Patent foramen ovale channel morphometric characteristics associated with cryptogenic stroke: the MorPFO score. *J Am Soc Echocardiogr* 2021;34:1285–1293.e3.
 44. Garg A, Thawabi M, Rout A, Sossou C, Cohen M, Kostis JB. Recurrent stroke reduction with patent foramen ovale closure versus medical therapy based on patent foramen ovale characteristics: a meta-analysis of randomized controlled trials. *Cardiology* 2019;144:40–49.
 45. Kent DM, Ruthazer R, Weimar C, Mas JL, Serena J, Homma S, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology* 2013;81:619–625.
 46. Kent DM, Saver JL, Ruthazer R, Furlan AJ, Reisman M, Carroll JD, et al. Risk of paradoxical embolism (RoPE)—estimated attributable fraction correlates with the benefit of patent foramen

- men ovale closure: an analysis of 3 trials. *Stroke* 2020;51:3119–3123.
47. Kent DM, Saver JL, Kasner SE, Nelson J, Carroll JD, Chatellier G, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke. *JAMA* 2021; 326:2277–2286.
 48. Abo-Salem E, Chaitman B, Helmy T, Boakye EA, Alkhwam H, Lim M. Patent foramen ovale closure versus medical therapy in cases with cryptogenic stroke, meta-analysis of randomized controlled trials. *J Neurol* 2018;265:578–585.
 49. Almekhlafi MA, Wilton SB, Rabi DM, Ghali WA, Lorenzetti DL, Hill MD. Recurrent cerebral ischemia in medically treated patent foramen ovale: a meta-analysis. *Neurology* 2009;73: 89–97.
 50. Hou Y, Elmashad A, Staff I, Alberts M, Nouh A. Potential embolic sources differ in patients with embolic stroke of undetermined source according to age: a 15-year study. *Front Neurol* 2022;13:860827.
 51. Mazzucco S, Li L, Rothwell PM. Prognosis of cryptogenic stroke with patent foramen ovale at older ages and implications for trials: a population-based study and systematic review. *JAMA Neurol* 2020;77:1279–1287.
 52. Kwon H, Lee PH, Song JK, Kwon SU, Kang DW, Kim JS. Patent foramen ovale closure in old stroke patients: a subgroup analysis of the DEFENSE-PFO trial. *J Stroke* 2021;23:289–292.
 53. Kniffin WD Jr, Baron JA, Barrett J, Birkmeyer JD, Anderson FA Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. *Arch Intern Med* 1994; 154:861–866.
 54. Stein PD, Hull RD, Kayali F, Ghali WA, Alshab AK, Olson RE. Venous thromboembolism according to age: the impact of an aging population. *Arch Intern Med* 2004;164:2260–2265.
 55. Scurr JH, Machin SJ, Bailey-King S, Mackie IJ, McDonald S, Smith PD. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. *Lancet* 2001;357:1485–1489.
 56. Nicholls SC, O'Brian JK, Sutton MG. Venous thromboembolism: detection by duplex scanning. *J Vasc Surg* 1996;23:511–516.
 57. Zietz A, Sutter R, De Marchis GM. Deep vein thrombosis and pulmonary embolism among patients with a cryptogenic stroke linked to patent foramen ovale—a review of the literature. *Front Neurol* 2020;11:336.
 58. Henein M, Waldenström A, Mörner S, Lindqvist P. The normal impact of age and gender on right heart structure and function. *Echocardiography* 2014;31:5–11.
 59. Luu JM, Gebhard C, Ramasundarahettige C, Desai D, Schulze K, Marcotte F, et al. Normal sex and age-specific parameters in a multi-ethnic population: a cardiovascular magnetic resonance study of the Canadian alliance for healthy hearts and minds cohort. *J Cardiovasc Magn Reson* 2022;24:2.
 60. Chen JZ, Thijs VN. Atrial fibrillation following patent foramen ovale closure: systematic review and meta-analysis of observational studies and clinical trials. *Stroke* 2021;52:1653–1661.
 61. Tsvigoulis G, Triantafyllou S, Palaiodimou L, Grory BM, Deftereos S, Köhrmann M, et al. Prolonged cardiac monitoring and stroke recurrence: a meta-analysis. *Neurology* 2022;98:e1942–e1952.
 62. Chaisinanunkul N, Khurshid S, Buck BH, Rabinstein AA, Anderson CD, Hill MD, et al. How often is occult atrial fibrillation in cryptogenic stroke causal vs. incidental? A meta-analysis. *Front Neurol* 2023;14:1103664.
 63. Kiblawi FM, Sommer RJ, Levchuck SG. Transcatheter closure of patent foramen ovale in older adults. *Catheter Cardiovasc Interv* 2006;68:136–142; discussion 143–144.
 64. Mas JL, Chatellier G. PFO closure, oral anticoagulants or antiplatelet therapy after PFO-associated stroke in patients aged 60 to 80 years (CLOSE-2) [Internet]. Bethesda, MD: US National Library of Medicine; 2022 [accessed May 15, 2023]. Available from: <https://ClinicalTrials.gov/show/NCT05387954>.
 65. National Evidence-Based Healthcare Collaborating Agency. Prospective registry of elderly ESUS with PFO (COACH_ESUS) [Internet]. Bethesda, MD: US National Library of Medicine; 2022 [accessed May 15, 2023]. Available from: <https://ClinicalTrials.gov/show/NCT05238610>.
 66. Medtronic. Evaluation of prevalence and clinical impact of atrial fibrillation in elderly patients with cryptogenic stroke and high-risk patent foramen ovale (DefenseElderly) [Internet]. Bethesda, MD: US National Library of Medicine; 2020 [accessed May 15, 2023]. Available from: <https://ClinicalTrials.gov/show/NCT04285918>.
 67. Nedeltchev K, Mono ML, Arnold M. Secondary stroke prevention in patients with patent foramen ovale: international PFO consortium [Internet]. Bethesda, MD: US National Library of Medicine; 2017 [accessed May 15, 2023]. Available from: <https://clinicaltrials.gov/study/NCT00859885>.
 68. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012;366:991–999.
 69. Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med* 2013;368:1083–1091.