Patent foramen ovale closure in non-lacunar cryptogenic ischemic stroke: where are we now?

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ABSTRACT   Patent foram ovale (PFO) is the most common anatomical cause of an interarterial shunt. It is usually asymptomatic but may cause paradoxical embolism and is a risk factor for non-lacunar cryptogenic cerebral ischemia in young adults. Although the first clinical trials did not show a significant superiority of PFO closure in the secondary prevention of cerebral ischemia as compared with standard antithrombotic treatment, six subsequent randomized clinical trials (CLOSURE I, PC Trial, RESPECT, CLOSE, REDUCE, and DEFENSE-PFO) performed in a sample of cryptogenic stroke in patients aged 60 years or younger provided evidence of a significant reduction of recurrent cerebral ischemia after percutaneous PFO closure. However, the use of percutaneous PFO closure cannot be generalized to the entire population of patients with cerebral ischemia and PFO, but it is indicated in highly selected patients with non-lacunar cryptogenic cerebral infarction with a large right-to-left shunt, an atrial septal aneurysm and no evidence of atrial fibrillation, as well as in association with antithrombotic treatment for an optimal secondary prevention of cerebral ischemia.

Patent foram ovale (PFO) is the most common anatomical cause of an interarterial shunt. It is usually asymptomatic but may cause paradoxical embolism or *in situ* thrombus formation in a PFO niche, which may be the cause of a cryptogenic stroke.[1–4] The prevalence of PFO in the general population across all ages is roughly 25% in autopsy and general adult population on agitated saline transesophageal echocardiography studies.[3] Therefore, the presence of PFO in patients with cerebral infarction is an insufficient evidence to establish PFO as the etiology of cerebral ischemia. However, the prevalence of PFO is remarkably high in patients with cryptogenic ischemic stroke, particularly in young adults, compared to non-cryptogenic ischemic stroke or to healthy population.[5]

Accordingly, it is indispensable to establish an adequate etiological diagnosis of cryptogenic stroke.[6] In different stroke data banks, the rate of cryptogenic stroke ranges between 10% and 40%. In the Sagrat Cor stroke registry of Barcelona, 12% of cerebral infarctions were cryptogenic (Table 1), and

showed a differential cardiovascular risk profile in comparison with the remaining subtypes of cerebral infarction, with a lower frequency of classic risk factors such as hypertension, diabetes or dyslipidemia.

The diagnosis of cryptogenic cerebral infarction, ideally performed by a vascular neurologist, requires a precise clinical evaluation and work-up studies in order to exclude the different etiologies of cerebral infarction. The following subtypes of ischemic stroke should be excluded: large-vessel atherothrombotic infarction, embolic stroke of cardiac origin,[7–9] small-vessel lacunar infarction,[10] and cerebral ischemia of unusual cause including hematological disorders, arterial dissection, inflammatory arteritis, migraine-infarction complex, prothrombotic conditions or malignant diseases among other entities.[11]

CLINICAL TRIALS AND META-ANALYSIS

The initial clinical trials did not show a statistically significant superiority of PFO closure as compared to medical therapy for stroke prevention.[12–14]

Table 1   Cardiovascular risk factors in cryptogenic stroke and other subtypes of ischemic cerebral infarcts in the Sagrat Cor Hospital stroke registry.

Risk factor	Total (n = 2 704)	Cryptogenic (n = 324)	Atherothrombotic (n = 770)	Lacunar (n = 733)	Cardioembolic (n = 763)	Unusual cause (n = 114)
Hypertension	1501 (55.5%)	59 (18.2%)*	509 (66.1%)*	525 (71.6%)*	377 (49.4%)*	31 (27.2%)*
Atrial fibrillation	807 (29.8%)	25 (7.7%)*	120 (15.6%)*	573 (75.1%)*	573 (75.1%)*	8 (7.0%)*
Diabetes mellitus	632 (23.4%)	24 (7.4%)*	242 (31.4%)*	142 (18.6%)†	142 (18.6%)†	6 (5.3%)*
Dyslipidemia	480 (17.8%)	52 (16%)*	164 (21.3%)*	88 (11.5%)*	88 (11.5%)*	10 (8.8%)
Previous cerebral infarction	468 (17.3%)	31 (9.6%)*	164 (21.3%)‡	146 (19.1%)	146 (19.1%)	10 (8.8%)†
Ischemic heart disease	435 (16.1%)	14 (4.3%)*	150 (19.5%)‡	163 (21.4%)*	163 (21.4%)*	4 (3.5%)*
Transient ischemic attack	317 (11.7%)	37 (11.4%)	116 (15.1%)†	73 (9.6%)‡	73 (9.6%)‡	11 (9.6%)
Current smoking (> 20 cigarettes/day)	260 (9.6%)	41 (12.7%)*	87 (11.3%)‡	28 (3.7%)*	28 (3.7%)*	18 (6.9%)
Chronic obstructive pulmonary disease	223 (8.2%)	20 (6.2%)	74 (9.6%)	62 (8.1%)	62 (8.1%)	6 (5.3%)
Peripheral vascular disease	214 (7.9%)	3 (0.9%)†	100 (13%)†	50 (6.6%)	50 (6.6%)	4 (3.5%)†
Valvular heart disease	174 (6.4%)	6 (1.9%)†	11 (1.4%)*	130 (17%)*	130 (17%)*	6 (5.3%)
Congestive heart failure	148 (5.5%)	8 (2.5%)†	43 (5.6%)	72 (9.4%)*	72 (9.4%)*	1 (0.9%)‡
Obesity	118 (4.4%)	13 (4.0%)	36 (4.7%)	17 (2.2%)†	17 (2.2%)†	5 (4.4%)
Oral anticoagulants	94 (3.5%)	2 (0.6%)*	18 (2.3%)‡	63 (8.3%)*	63 (8.3%)*	4 (3.5%)
Alcohol consumption (> 80 g/d)	66 (2.4%)	10 (3.1%)	26 (3.4%)‡	5 (0.7%)‡	5 (0.7%)‡	4 (3.5%)
Chronic liver disease	57 (2.1%)	10 (3.1%)	17 (2.2%)	15 (2.0%)	15 (2.0%)	0
Previous cerebral hemorrhage	32 (1.3%)	6 (1.9%)	9 (1.2%)	9 (1.2%)	7 (0.9%)	1 (0.9%)

Data are presented as n (%). Modified from Arboix, et al.[7] *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$.

The first randomized clinical trial (CLOSURE I)[15] was published in 2012 and significant benefits of PFO closure in patients with cryptogenic stroke after 2 years of follow-up were not observed (5.5% events *vs.* 6.8%, P = NS). In 2013, results of the PC Trial[16] in which the duration of follow-up was prolonged up to 4.1 years, did not show statistically significant differences between PFO closure and optimal antithrombotic pharmacological treatment (3.4% events *vs.* 5.2%, P = NS). It should be noted that the primary end point in the CLOSURE I trial[15] was the presence of stroke, transient ischemic attack (TIA), all-cause deaths within 30 days or neurological deaths, whereas in the PC Trial,[16] primary end points were death, stroke, transient ischemic attack (TIA) or peripheral embolism.

In 2017, the results of the randomized clinical trial RESPECT[17] showed for the first time some benefits of PFO closure in selected patients with cerebral infarction and a more prolonged follow-up period (mean 5.9 years). However, in contrast to these preliminary results, data of three subsequent randomized controlled clinical trials[18–20] demonstrated an adequate efficacy in secondary prevention of cerebral ischemia, with a statistically significant reduction of the risk of recurrent ischemic stroke in patients with cryptogenic stroke undergoing PFO closure (Table 2). In the CLOSE clinical trial,[18] published in 2017, in patients with cryptogenic stroke and PFO associated with aneurysm of the atrial septum or large interarterial shunt, closure of PFO combined with antiplatelet therapy was statistically significant more effective than antiplatelet therapy alone in the prevention of recurrent stroke after a mean follow-up of 5.3 years. In the REDUCE clinical trial[19] also published in 2017, ischemic stroke recurrence and silent cerebral ischemia detected by neuroimaging studies were both assessed, showing an improvement in the group of patients with cryptogenic stroke treated with PFO closure in association with antiplatelet therapy (stroke recurrence rate 1.4%) as compared to patients treated with antiplatelet agents only (stroke recurrence rate 5.4%) at 3.2 years of follow-up. Results of the DEFENSE-

Table 2   Overview of randomized controlled trials of patent foramen ovale (PFO) closure.

Study, year[reference]	Patients number	Follow-up years	Control arm	Primary end point	Control group	Closure group	Conclusion
CLOSURE I, 2012[15]	909	2	Aspirin and/or warfarin	Composite of stroke, TIA, death from any cause during the first 30 days or death from neurological causes	6.8%	5.5%	No statistically significant differences
PC Trial, 2013[16]	414	4.1	Antiplatelet agents or oral anticoagulants	Composite of death, non-fatal stroke, TIA or peripheral embolism	5.2%	3.4%	No statistically significant differences
RESPECT, 2017[17]	980	5.9	Aspirin or warfarin or clopidogrel or aspirin with dipyridamole	Composite recurrent non-fatal cerebral infarct, fatal cerebral infarct or early death	ITT 1.07 events per 100 patients/year (28 patients)*	ITT 0.58 Events per 100 patients/year (18 patients)†	Closure better to medical therapy in ITT analysis during extended follow-up
CLOSE, 2017[18]	663	5.3	a) Aspirin or clopidogrel or aspirin with dipyridamole b) Oral anticoagulant group (vitamin K, novel anticoagulants)	Recurrent fatal or non-fatal stroke	6% (14/235) 5-year estimate anticoagulants vs. antiplatelet therapy 1.5% vs. 3.8%	No stroke occurred	Closure combined with antiplatelet therapy better than antiplatelet therapy alone in PFO associated with atrial septal aneurysm or large shunt Anticoagulation equivalent to antiplatelet (but increased risk of atrial fibrillation)
REDUCE, 2017[19]	664	3.2	Aspirin or clopidogrel or aspirin with dipyridamole	Recurrent stroke. New brain infarct inclusive of silent brain infarct detected on imaging	Ischemic stroke 5.4% New brain infarct 11.3%	Ischemic stroke 1.4% New brain infarct 5.7%	Closure combined with antiplatelet therapy better to antiplatelet therapy alone (but higher rates of device complications and atrial fibrillation)
DEFENSE-PFO, 2018[20]	120	2.8	Aspirin or aspirin and clopidogrel or aspirin and cilostazol or warfarin	Composite stroke, vascular death or thrombolysis in myocardial infarction (TIMI) - defined major bleeding	Brain infarct 10.5% 2-year event rate 12.9%	Brain infarct 0 2-year event rate 0	Closure better in the presence of high risk PFO with lower rate of primary endpoint as well as stroke recurrence vs medical therapy

ITT: intention-to-treat; PFO: patent foramen ovale. *new stroke of unknown mechanism 0.86 events per 100 patients/year (23 patients); †new stroke of unknown mechanism 0.31 events per 100 patients/year (10 patients).

PFO clinical trial[18] published in 2018 were consistent with data of the CLOSURE I trial. Patients undergoing transesophagic echocardiography with neurosonographic characteristics of high risk embolism due to the anatomical morphology of the PFO (presence of atrial septal aneurysm and/or hypermobility of the interatrial septum and/or large size of the interatrial shunt), ischemic stroke recurrences in patients undergoing PFO closure were not observed, with a statistically significant higher efficacy as compared with the control group.

Safouris and co-workers[21] reported data providing information based on meta-analysis of these six major randomized controlled clinical trials (CLOS-URE I, PC Trial, RESPECT, CLOSE, REDUCE, and DEFENSE-PFO trials) showing a statistically significant superiority of percutaneous closure of PFO with a right-to-left interatrial shunt compared to antithrombotic therapy alone in secondary stroke prevention by reducing recurrent non-lacunar cryptogenic ischemic stroke. A total of 37 recurrent ischemic strokes occurring among 1,889 patients randomized to PFO closure compared to 79 strokes among 1,671patients randomized to antithrombotic therapy (pooled risk ratio [RR] 0.36, 95% confidence interval [CI]: 0.17−0.79, *P* = 0.01), corresponding to a number needed to treat (NNT) of 131 to prevent one recurrent stroke during one person-

year of follow-up. Risk reduction was more pronounced in patients with high-risk atrial PFO (atrial septal aneurysm or large shunt). In these patients the pooled RR for PFO closure was 0.27 (P = 0.01), whereas there was a moderate non-significant trend for RR at 0.80 (P = 0.41) in patients with low risk anatomical features.

CHARACTERISTICS OF STUDY POPULATIONS

Of note, the study populations included in randomized controlled clinical trials were highly selected patients, that is, patients with non-lacunar cryptogenic stroke and younger than 60 years of age. These patients had no presented TIA and PFO was the only potential source of embolism with no other evident source of stroke despite a comprehensive vascular, cardiac and serological evaluation.[22,23] It was noted, however, that the patients most likely to benefit were those with an associated atrial septal aneurysm (Figure 1) and/or a large right-to-left interatrial shunt (Figure 2).[24] Therefore, it is important to emphasize that benefits from PFO closure are extended to a small percentage of patients, being transesophagic echography the diagnostic technique of choice. Transcranial Doppler imaging may be used as an initial diagnostic screening modality.

However, optimal patient selection criteria for percutaneous closure of PFO are still under investigation. PFO closure may be more effective in younger age groups. In a systematic review on long-term efficacy after closure of PFO for ischemic neurological events in young adults, Xu, et al.[5] concluded that younger patients under the age of 55 years with ischemic stroke/TIA benefit significantly from PFO closure.

Despite a thorough investigation the etiology of ischemic stroke remains undetermined in almost 10-40% of cases.[2] There is accumulating evidence that occult atrial fibrillation is still the most common cause of cryptogenic stroke and should be excluded by ambulatory electrocardiographic monitoring for at least three consecutive weeks before planning closure of PFO.[25–27] Hematological disorders[11] with ischemic stroke as the presenting manifestation should also be discarded and biochemical testing would exclude arterial hypercoagulable states (e.g.,

antiphospholipid syndrome and hyperhomocysteinemia), which are other causes of cerebral ischemia of unusual etiology. Accordingly, to rule out atrial fibrillation, underlying hematological disorders or even complex atheromatous aortic arch disease in ascending aorta or proximal arch (protruding with < 4 mm thickness, or mobile debris, or plaque ulceration) are mandatory for optimal patient selection criteria prior to PFO closure. Thus, it is advisable to establish multidisciplinary team discussion (consisting of a stroke neurologist, a cardiologist and a hematologist) to make decisions on PFO closure.[28]

The presence of neuroimaging findings of lacunar ischemia (typically involving a cerebral perforating artery with an infarction of < 1.5 in diameter) responsible for the cerebral infarction, is a criterion largely used for excluding the indication of PFO closure, since small-vessel disease is caused by microatheromatosis or lipohyalinosis related to hypertension and/or diabetes in most of the cases.[29,30] Thus, the cumulative evidence indicates that there may be little or no benefit of PFO closure in patients with small deep infarcts (Figure 3).

A NEUROLOGICAL APPROACH

A classic but infrequent clinical cardioembolic presentation[8,13] in PFO include the onset of symptoms after a Valsalva provoking activity (coughing, bending, etc.) suggesting paradoxical embolism facilitated by a transient rise in right atrial pressure and the co-occurrence of cerebral and systemic emboli. Also, other very uncommon cases that allow establishing a cause-effect relationship between PFO and cerebral infarction include stroke related to air travel or the "economy class syndrome" (paradoxical embolism due to deep vein thrombosis in long-haul flights) or cerebral infarction associated with venous thromboembolic disease.[9] However, in most patients with cryptogenic stroke and PFO without classic clinical manifestations, to determine whether PFO is the cause of stroke or whether it is an incidental finding remains unclear. The RoPe scale (Risk of Paradoxical Embolism score),[24] designed in 2013, may help clinicians to predict the risk of PFO in the presence of cryptogenic stroke. In contrast, low RoPE scores suggest an incidental PFO.[24]
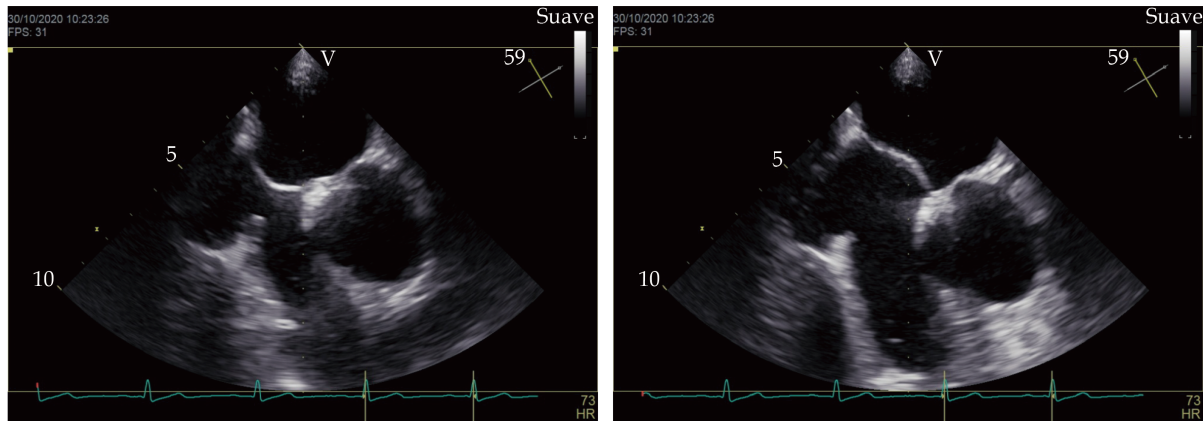
Figure 1   Transesophageal echocardiography showing an atrial septal aneurysm with wide mobility; one of the anatomical features associated with a high embolic risk in PFO. PFO: patent foram ovale.
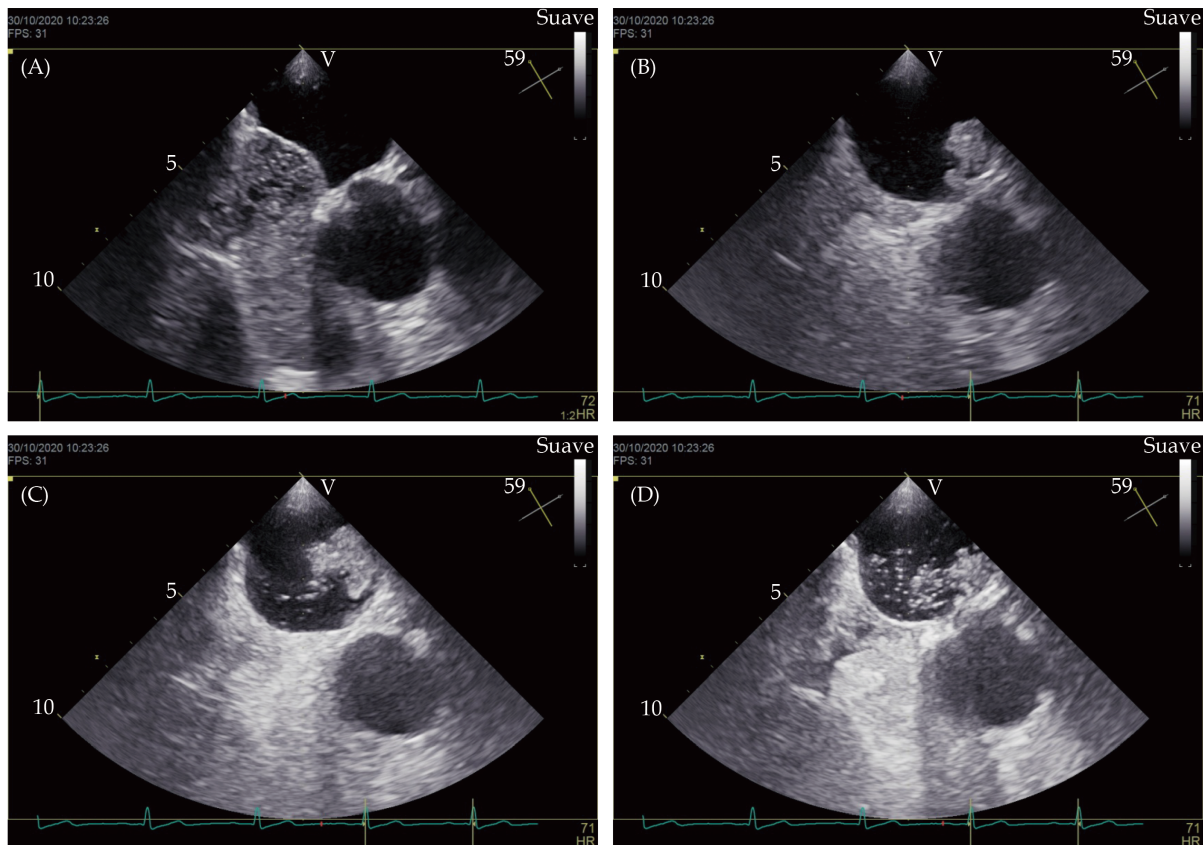
Figure 2   Transesophageal echocardiography showing permeability of the oval foramen. After intravenous injection of a contrast (agitated saline) (A), there is early passage (1st-3rd beat) of the contrast from the right atrium (B) with gradual filing and opacification of the left atrium (C, D).

Therefore, not all cases of PFO needed to be closed in the setting of cryptogenic ischemic stroke. Echocardiographic features that increase the risk of stroke include large PFO size, large right-to-left shunt, spontaneous right-to-left shunt, greater PFO flap mobility, prominent Eustachian valve or Chiari network, and the presence of an atrial septal an-eurysm. Patients who are candidates for PFO closure should have a transesophageal echocardiography to confirm that the intracardiac shunt is caused by a PFO, to define atrial septal anatomy and suitability for device closure, and to exclude other causes of embolic stroke or shunt.[24,31]Exclusions to percutaneous device closure include the
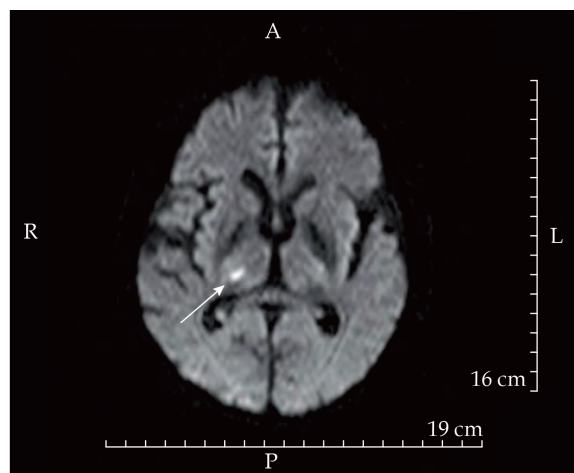
Figure 3 Diffusion-weighted magnetic resonance imaging showing a right thalamic lacunar cerebral infarction (arrow). Small-vessel cerebral vascular disease is by definition unrelated to PFO and initially excludes the diagnosis of cryptogenic cerebral infarction. PFO: patent foramen ovale.

presence of an inferior vena cava filter, elevated bleeding risk or coagulopathy, and vascular, cardiac, or PFO anatomy that is unsuitable for device placement.[28] Surgical closure is an alternative that is rarely required instead of percutaneous PFO closure, and it is only indicated when there is a need of concomitant heart surgery (e.g., valve repair) or when for technical reasons, percutaneous PFO closure is not feasible.[28]

LIMITATIONS OF PFO CLOSURE

In patients under 60 years of age, the treatment of choice is the use of antiplatelet agents only, except for cases with evidence of paradoxical embolism with deep vein thrombosis, pulmonary embolism or other thromboembolism, or in patients with a meaningful thrombophilia who are generally treated with anticoagulant agents.[32–34]

Other limitations of PFO closure are associated with the risk of closure, such as: (1) 5% increase in the risk of new-onset atrial fibrillation in the device closure group (the most common adverse effect); (2) there are rare procedural complications including hematoma at the puncture site, device migration, device embolization, development of scar tissue, device erosion, atrial perforation with tamponade requiring surgical removal of the device or fistula formation or rarely create an atrial septal defect; and (3) rare potential long-term risk of aortic root

dilatation and subsequent erosions caused by the implanted device; and d) rare potential formation of thrombi on the device with possible and recurrent ischemic stroke.[24,28]

FUTURE PERSPECTIVES

Optimal candidates for PFO closure are still not precisely defined. Trials only investigated patients of less than 60 years of age, so that it cannot be generalized to the entire population of patients with PFO. Future research lines should consider the conflicting evidence in older age groups (> 60 years), and there are currently no recommendations for the management of these patients as this segment of the population has been excluded from clinical trials. There is a lack of experience in very old patients (85 years old or more) or in the age group of 60–75 years which account for the highest prevalence of cerebral infarction in stroke registries.[34]

All recent successful PFO closure trial did not include patients with TIAs to prevent "stroke mimics". Studies focused on patients with lacunar cerebral infarction have not been carried out because this subtype of ischemic stroke is usually due to occlusion of a single penetrating artery as a result of microatheromatosis or lipohyaliosis. However, cryptogenic lacunar strokes account for 5–10% of lacunar infarctions and, in these cases, an embolic occlusion of perforating arteries could be another possible although unusual pathogenetic mechanism. Future studies may also focused on younger patients (e.g., < 30 years of age) with a single, small, deep infarct, a large shunt and absence of any vascular risk factors related to intrinsic small-vessel disease, such as hypertension, diabetes or hyperlipidemia.[10] Consequently, studies of PFO and PFO closure in pediatric stroke populations and in selected patients over 60 years of age are also needed. Moreover, long-term term and large-scale safety registries for patients who have received PFO closure are required.

CONCLUSIONS

Percutaneous closure of PFO is indicated in highly selected patients with non-lacunar cryptogenic ischemic stroke in association with antithrombotic therapy. It is indispensable to emphas-

ize the adoption of healthy lifestyle habits, including smoking cessation, increase of physical exercise, and healthy diet) and strict control of blood pressure, low-density lipoprotein cholesterol levels, and serum glucose levels.[35]

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