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Cryptogenic stroke over 60 years of age: should patent foramen ovale be closed?

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Patent foramen ovale (PFO) is an anatomical communication between the left and the right atrium due to the lack of completed sealing of the fossa ovalis. Epidemiologic data, for the most part derived from young populations studies, suggested that PFO, allowing paradoxical embolization of thrombotic material from the venous to the arterial district, could play a significant role in the pathogenesis of cryptogenic ischaemic cerebral events. Recently, three randomized studies in patients $\leq$60 years of age demonstrated the superiority of percutaneous closure of PFO over medical antithrombotic treatment. Several studies, on the other hand, indicated that also in older patients with cryptogenic cerebral ischaemia, there was an higher prevalence of PFO in patients at low atherosclerosis and cardioembolic risk, and increased incidence of adverse cerebral events (mostly cryptogenic in patients treated medically, but likely due to a new cause in patients who had percutaneous closure of PFO). Advanced age is associated with more risk factors for deep vein thrombosis, and consequent paradoxical embolization through the PFO, so much so that careful consideration should be given to patients over the age of 60 years with cryptogenic stroke, as to not forgo the benefit of percutaneous closure of PFO, merely for anagraphic consideration. This consideration is particularly poignant in light of the more recent technical advances now available, such as direct percutaneous suture, mostly appealing for elderly patients, for its better tolerability and high safety both peri-procedural and during the follow-up, as well as the lack of necessity for antithrombotic treatment.

Introduction

The patent foramen ovale (PFO) is a congenital defect that determines an anatomical communication between the left atrium and the other right due to the failed closure of the oval fossa that normally occurs after birth with the fusion of septum primum and septum secundum. The persistence of PFO affects about one in four people but its prevalence is significantly greater in patients with cryptogenic stroke. This fact obtained essentially in young populations, suggested that PFO, allowing paradoxical embolization of thrombotic material from the venous district to the arterial system, could play a key role in the pathogenesis of cerebral ischaemic syndromes for which there is no obvious cause. It is currently estimated that about a third of the 400 000 transient ischaemic attacks and strokes that occur each year in western Europe are cryptogenic. The best therapeutic strategy for the prevention of cerebral ischaemic recurrences has been the subject of numerous studies in the last 20 years. Recently, three randomized trials have demonstrated the superiority of percutaneous closure compared to antithrombotic medical therapy in the reduction of recurrent cerebral ischaemic events in patients with a history of cryptogenic stroke attributable

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to a PFO.[1-3] In these studies, however, only patients of age less than or equal to 60 years were enrolled.

Association between patent foramen ovale and cryptogenic stroke in patients over 60 years old

In an influential meta-analysis of case-control studies published in 2000, the association between PFO and cryptogenic stroke was significant in patients younger than 55 years but not in older patients.[4] However, the excessive heterogeneity among the studies included in this second group of patients significantly invalidated the reliability of the result.

In 2007, in an analysis of 503 consecutive patients with a history of stroke, the prevalence of PFO was significantly greater in patients with cryptogenic stroke than in patients with stroke due to other causes whether the age was lower (44% vs. 14%, $P < 0.01$) or higher (28% against 12%, $P < 0.001$) than 55 years.[5] This study was markedly different from the previous ones in that all the subjects enrolled had undergone a transoesophageal echocardiogram for the diagnosis of PFO and were evaluated prospectively.

This finding was recently confirmed in a population-based analysis conducted in the Oxford Vascular Study in which consecutive patients with recent transient ischaemic attack or non-invalidating stroke were studied with transcranial Doppler, demonstrating a significantly higher right-to-left shunt prevalence in patients with cryptogenic cerebral ischaemia (36% vs. 21%, $P < 0.001$).[6] The clinical characteristics of the patients, very similar to those of the subjects enrolled in the studies on percutaneous PFO closure, constitute a distinctive and relevant aspect of this study. Furthermore, in an extrapolation of their results to the British population, the authors calculated that every year 8477 cryptogenic cerebral ischaemic events could occur, attributable to a significant right-to-left shunt, of which 70% in patients older than 60 years.

Cryptogenic stroke risk in patients with patent foramen ovale and over 60 years

In a different analysis of the Oxford Vascular Study, patients with recent cryptogenic stroke (average age 70 years) showed a significantly lower prevalence of single atherosclerotic risk factors. Consistently their overall number, the presence of symptomatic atherosclerosis in another arterial district, and the risk of experiencing an acute coronary event were lower compared to stroke patients due to large and small cerebral blood vessel disease.[7] Similarly, patients with cryptogenic stroke had the lowest prevalence and lowest incidence of subclinical episodes of long-term paroxysmal atrial fibrillation, the lowest prevalence of cardiac abnormalities detectable in a standard echocardiogram and the lowest risk of systemic embolic events compared with patients with other types of stroke. Overall, these data indicate that patients with cryptogenic stroke have a low atherosclerotic and cardioembolic risk.

On the other hand, with age advancing some relevant factors, such as changes in endothelial and platelet function, comorbidity and reduced physical activity, increase the risk of thrombosis in the veins of the pelvis and lower limbs. Furthermore, in older patients, the diameter of the PFO is larger and the filling pressure of the right ventricle is greater.[8] Thus, the higher probability of thrombotic material in the venous district and of haemodynamic conditions favouring a right-to-left shunt increase the risk of paradoxical embolism in elderly patients.

Risk of recurrent events in patients with advanced age with patent foramen ovale and cryptogenic stroke

In a retrospective analysis of the PICSS study (PFO In Cryptogenic Stroke Study), 250 patients treated with medical therapy were divided by age into three categories: <55 years, 55-64 years, 65 years or older.[9] Of these patients, 98 (39%) had a PFO. Recurrent death and stroke have a significantly greater risk in patients aged 65 years and over (hazard ratio 3.21; 95% confidence interval 1.33-7.75; $P = 0.01$) but not in the two younger patient's groups (hazard ratio 0.21; 95% confidence interval 0.02-1.78; $P = 0.15$ in patients under 55 years and hazard ratio 0.72, 95% confidence interval 0.14-3.73; $P = 0.70$ in patients aged 55-64 years).

In a British study of 2555 patients with a mean age of 74 years and recent strokes, a large percentage of recurrences (63%) were cryptogenic.[7] In turn, these data suggest that the exclusion of patients over 60 years may have affected the outcome of clinical trials comparing medical therapy with percutaneous PFO closure.

Risk of recurrent events in patients of advanced age subjected to percutaneous patent foramen ovale closure

Several series have been published of patients over 55 years of age undergoing percutaneous PFO closure with device implantation following a cryptogenic stroke.[10-13] Table 1 summarizes the salient features. Studies differ in methodological rigour, presentation of data, and results. When available, the prevalence of atherosclerotic risk factors, in particular, systemic arterial hypertension, hypercholesterolaemia, diabetes mellitus, is significantly greater in patients aged over 50 years, while the percentage of residual shunt does not appear different between the two groups.

The first two published studies refer to American registries and do not demonstrate a significant difference in recurrent neurological events in patients older than 55 years.[10,11] The next two European studies both show a markedly longer follow-up, and a significantly increased incidence of ischaemic neurological events in patients over 55 years.[12,13] For the latter two studies the Kaplan-Meier curves begin to separate late suggesting an evolution of the general clinical picture and the intervention of a new cause in patients with new cerebral ischaemic event. This data appears in agreement with the demonstration, in patients

Table 1 Studies reporting percutaneous closure of patent foramen ovale in patients older than 55 years

Author	Year	Number of 'young' patients	Number of 'old' patients	Follow-up	Recurrence 'young'	Recurrence ' old'	*P*
Kiblawi *et al.*[10]	2006	272 ≤55 years	184 >55 years	1–45 months (mean 18 mesi)	1.5%	1.6%	0.80
Spies *et al.*[11]	2008	632 ≤55 years	423 >55 years	0–162 months (median 18 mesi)	1.3%	1.8%	0.60
Luermans *et al.*[12]	2011	215 <55 years	120 >55 years	Media 4 years	0.6%	2.4%	0.005
Scacciatella *et al.*[13]	2016	307 <55 years	151 ≥55 years	19–5217 days (mean 4.5 anni)	0.3%	4.0%	0.002

Table 2 Results of NobleStitch EL Italian Registry in prospective

Study	Shunt right-left Grade 0–1 (%)	Adverse events (%)
CLOSURE I	86.7	16.9
PC Trial	91.1	21.1
Gore Helix	94.5	12.8
RESPECT	93.5	4.2
NobleStich EL Italian Registry	89	0

with PFO and cryptogenic stroke, of an identifiable cause other than paradoxical embolism in more than one-third of recurrent neurological events.[14]

Finally, no study showed a different incidence of peri-procedural complications between the two groups of patients following percutaneous closure of PFO with an implantable device.

Current events and future developments in the treatment of patients with patent foramen ovale

After a long debate in the scientific community on the best treatment of patients with PFO, in 2017, the results of three important randomized clinical studies were published—the extended follow-up of the RESPECT study, the REDUCE study and the CLOSE study—which demonstrate a reduction of ischaemic neurological events following percutaneous PFO closure with an implantable device compared to medical therapy with acetylsalicylic acid in patients aged up to 60 years and history of cryptogenic stroke.[1-3] However, in patients undergoing percutaneous PFO closure, the incidence of adverse events was higher, in particular, episodes of atrial fibrillation. This occurrence appears to be associated with the presence and size of the double-disc implanted device for the closure of the PFO with an umbrella mechanism. Furthermore, the presence of a metal device in the heart is associated with a vast spectrum of complications which, although rare, can also be very serious. Finally, the antithrombotic therapy necessary to avoid the risk of thrombosis of the device during the period preceding its complete endothelization is itself a possible source of iatrogenic complications.

New approaches have, therefore, been developed to avoid implantation of a metal device in the heart. On the one hand, a more potent pharmacological treatment with the new oral anticoagulants does not seem to offer advantages compared to the antiplatelet therapy with acetylsalicylic acid.[15] On the other hand, the closure of the PFO by percutaneous suture with the NobleStitch EL system appears absolutely promising. This technology involves the use of two distinct catheters for the polypropylene suture of the septum secundum and of the septum primum and of a third catheter to guarantee a closure of the fossa ovalis implemented through the bending of the septum primum towards the right atrium so as to determine the coaptation with the septum secundum stabilized by suture fixation (*Figure 1*). The advantages of this approach include an increased patient comfort and a higher procedural safety due to the absence of transoesophageal echocardiographic guidance and the necessary sedation, the absence of a device implanted in the heart and of any foreign material in the left side of the interatrial septum, the predictable absence of complications typically attributable to the presence of the device and, in particular, the non-necessity of antithrombotic therapy.

The NobleStitch EL Italian Registry showed at an average follow-up of 206 ± 130 days the presence of a right-to-left shunt of Grade 0–1 in the vast majority of patients (89%) and no complication related to the suture of atrial septa were observed, with no episodes of atrial fibrillation.[16]

Conclusions

Although the prevalence of clinical features associated with stroke from known causes increases with age, the same happens with factors favouring paradoxical embolism through a PFO. Furthermore, the inclusion of subjects aged <60 years in randomized clinical trials that have demonstrated the advantage of percutaneous PFO closure should not be a preclusion to the treatment of older patients who are at greater risk of recurrence of cerebral ischaemia. In a patient over 60 years, a careful evaluation of the temporal and topographical characteristics of the stroke, atherosclerotic risk factors, cardiac rhythm, inter-ventricular septum anatomy, lower limb veins, degree of autonomy, of co-morbidities and haemo-coagulative balance help to assess the relative risk of a cryptogenic stroke compared to an ischaemic event from other causes. Furthermore, the recent introduction in the clinical field of PFO closure by percutaneous suture appears particularly favourable for

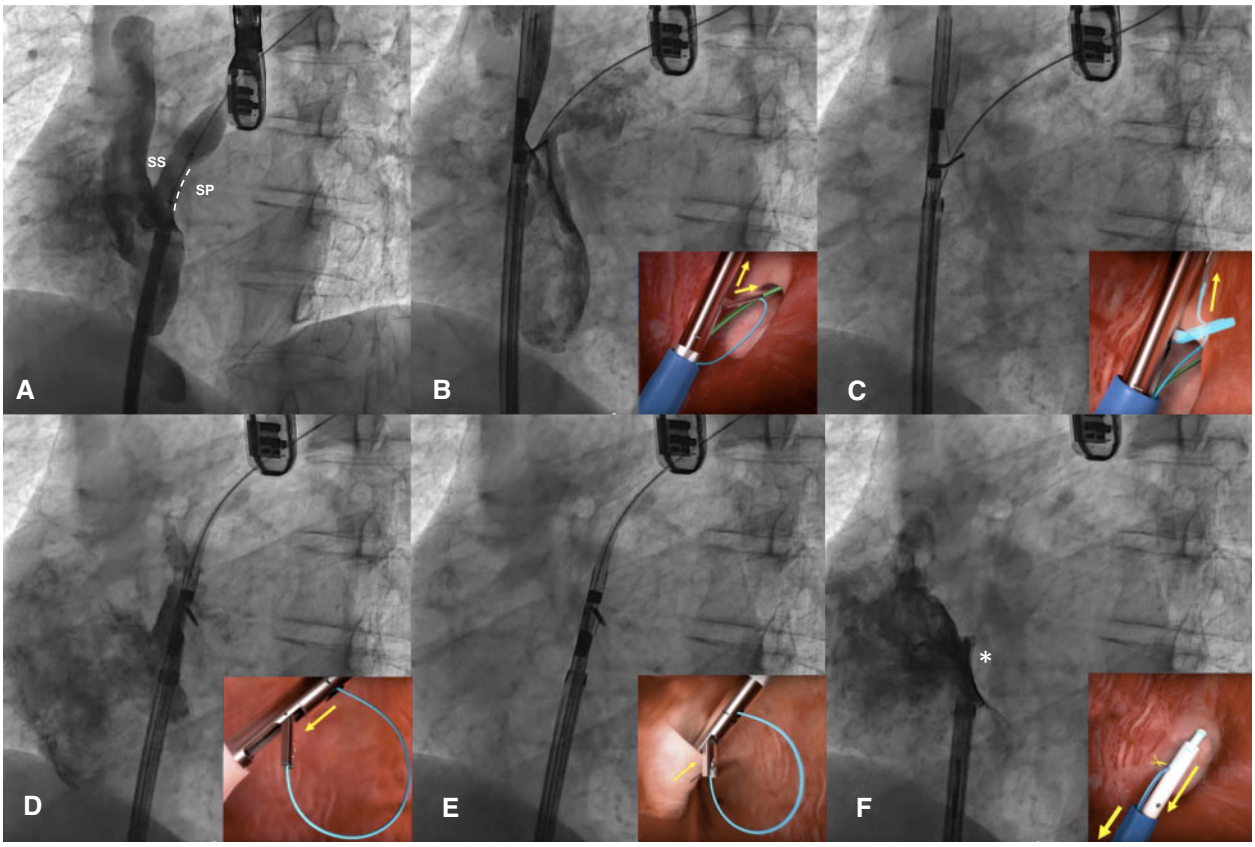

Figure 1 Percutaneous closure of the patent foramen ovale with the NobleStitch EL system. (*A*) Evaluation of patent foramen ovale with sizing balloon to determine the anatomy of the septum secundum and the septum primum during contrast medium injection. (*B-E*) Sequential advancement of the two catheters for the septum secundum and septum primum suturing. (*F*) Subsequently, following the application of a moderate tension on the suture threads, the septum primum is overturned towards the right atrium so as to coaplate with the septum secundum and determine the closure of the oval fossa. This configuration is stabilized with a polypropylene point released by a third catheter on the right side of the interatrial septum (asterisk). The same catheter is used to cut the excess suture threads which are then removed along with it. SP, septum primum; SS, septum secundum.

use in older patients for better tolerability and safety of the procedure.

Conflict of interest: none declared.

References

1. Sondergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, Sjostrand C, Roine RO, Hildick-Smith D, Spence JD, Thomassen L, Gore R. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017;**377**: 1033–1042.
2. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, Tirschwell DL; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017;**377**:1022–1032.
3. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, Arquizan C, Bejot Y, Vuillier F, Detante O, Guidoux C, Canaple S, Vaduva C, Dequatre-Ponchelle N, Sibon I, Garnier P, Ferrier A, Timsit S, Robinet-Borgomano E, Sablot D, Lacour JC, Zuber M, Favrole P, Pinel JF, Apoil M, Reiner P, Lefebvre C, Guerin P, Piot C, Rossi R, Dubois-Rande JL, Eicher JC, Meneveau N, Lusson JR, Bertrand B, Schleich JM, Godart F, Thambo JB, Leborgne L, Michel P, Pierard L, Turc G, Barthelet M, Charles-Nelson A, Weimar C, Moulin T, Juliard JM, Chatellier G; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017; **377**:1011–1021.
4. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;**55**: 1172–1179.
5. 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.
6. Mazzucco S, Li L, Binney L, Rothwell PM; Oxford Vascular Study Phenotyped Cohort. Pevalence 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.
7. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, Rothwell PM, Oxford VS. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol* 2015;**14**:903–913.
8. Mattle HP, Saver JL. Patent foramen ovale increases stroke risk in older people. *Nat Rev Neurol* 2018;**14**:573–574.
9. Homma S, DiTullio MR, Sacco RL, Sciacca RR, Mohr JP; PICSS Investigators. Age as a determinant of adverse events in medically treated cryptogenic stroke patients with patent foramen ovale. *Stroke* 2004;**35**:2145–2149.
10. Kiblawi FM, Sommer RJ, Levchuck SG. Transcatheter closure of patent foramen ovale in older adults. *Catheter Cardiovasc Interv* 2006; **68**:136–142; discussion 143–4.
11. Spies C, Khandelwal A, Timmemanns I, Kavinsky CJ, Schrader R, Hijazi ZM. Recurrent events following patent foramen ovale closure in patients above 55 years of age with presumed paradoxical embolism. *Catheter Cardiovasc Interv* 2008;**72**:966–970.

12. Luermans JG, Budts W, Ten Berg JM, Plokker HW, Suttorp MJ, Post MC. Comparison of outcome after patent foramen ovale closure in older versus younger patients. *EuroIntervention* 2011;**7**:209–215.
13. Scacciatella P, Meynet I, Presbitero P, Giorgi M, Lucarelli C, Zavalloni Parenti D, Biava LM, Marra S. Recurrent cerebral ischemia after patent foramen ovale percutaneous closure in older patients: a two-center registry study. *Catheter Cardiovasc Interv* 2016;**87**:508–514.
14. Mono ML, Geister L, Galimanis A, Jung S, Praz F, Arnold M, Fischer U, Wolff S, Findling O, Windecker S, Wahl A, Meier B, Mattle HP, Nedeltchev K. Patent foramen ovale may be causal for the first stroke but unrelated to subsequent ischemic events. *Stroke* 2011; **42**:2891–2895.
15. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, Swaminathan B, Lavados P, Wang Y, Wang Y, Davalos A, Shamalov N, Mikulik R, Cunha L, Lindgren A, Arauz A, Lang W, Czlonkowska A, Eckstein J, Gagliardi RJ, Amarenco P, Ameriso SF, Tatlisumak T, Veltkamp R, Hankey GJ, Toni D, Bereczki D, Uchiyama S, Ntaios G, Yoon BW, Brouns R, Endres M, Muir KW, Bornstein N, Ozturk S, O'Donnell MJ, De Vries Basson MM, Pare G, Pater C, Kirsch B, Sheridan P, Peters G, Weitz JI, Peacock WF, Shoamanesh A, Benavente OR, Joyner C, Themeles E, Connolly SJ; NAVIGATE ESUS Investigators. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;**378**:2191–2201.
16. Gaspardone A, De Marco F, Sgueglia GA, De Santis A, Iamele M, D'Ascoli E, Tusa M, Corciu A, Mullen M, Nobles A, Carminati M, Bedogni F. Novel percutaneous suture-mediated patent foramen ovale closure technique: early results of the NobleStitch EL Italian Registry. *EuroIntervention* 2018;**14**:e272–e279.