ORIGINAL RESEARCH PAPER

Cardiology

KEY WORDS: PFO=Patent foramen ovale, SIA=Interatrial septal aneurysm, TIA=transient ischemic attack, TTE=transthoracic echocardiography, TEE=transesophageal echocardiography, DAPT=dual antiplatelet therapy

LONG TERM FOLLOW-UP IN PEOPLE WITH PATENT FORAMEN OVALE (PFO)

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ABSTRACT

OBJECTIVE 8 years follow-up (6.8 ± 2.2 years) of subjects with PFO. The evaluation of the incidence of cryptogenetic Stroke/TIA and/or migraine and/or platypnea-orthodoxy in subjects with PFO with and without closure.

METHODS: 74 subjects were studied (17M, 57F), all originating from Latina and surrounding areas, with an average age of 50.3 ± 11.2 years; 56 patient were subjected to percutaneous closure for TIA/cryptogenetic stroke between the years 2008 and 2016. All patients under the same control protocol during the mean follow-up of 6.8 ± 2.2 years;

RESULTS: there was no evidence of cerebrovascular recurrences in patients who had undergoing closure and in patients with medical prophylaxis. In 30/74 patients with migraine (with or without aurea), 13 sujects remained symptomatic after closure: 8 patients reported migraine with platypnea-orthodoxy, 2 patients symptoms free after closure. Two patients died > 12 months after the procedure from non-cardiovascular disease.

CONCLUSION: Long-term follow-up, in a "selected" population for specific delivery from other medical centers, highlighted a high reduction ($p< 0.01$) in events associated with PFO with its closure. In the group undergoing percutaneous closure of the PFO, a significant reduction ($p <0.001$) of the incidence of cerebrovascular events (stroke / TIA) and ($p <0.001$) was observed in the reduction of other associations (migraine and / or platypse-orthodoxy).

INTRODUCTION

Patent foramen ovale (PFO) is a residue of fetal development, resulting from the melting of septum primum and septum secundum at the level of fossa ovalis, which under certain hemodynamic conditions may allow a shunt paradox dx vs sx emodynamically not significant (Qp/Qs < 1,2). The incidence of PFO was estimated around 27% by autopsy studies[1], while epidemiological clinical estimates seem to rise to 44%[2-4]. The PFO has been associated with several clinical cases: A) Cryptogenetic stroke represents about 30-40% of ischemic stroke[2,3]**;** this is an argument of current interest for the definition of a correct diagnosis[4] and for the best therapeutic strategy to be adopted in the presence of PFO. Therapeutic recommendations have been proposed considering clinical and anatomical risk factors[5]. Over time, controlled randomized trials were conducted to compare medical and interventional therapy, which did not demonstrate the superiority of one with respect the other[6]. Recently, based on the results of the long-term follow-up of the RESPECT study[7,8], the FDA has approved the use of the Amplatzer device in USA[9], for the long-term superiority of interventional therapy compared to medical therapy, in the occurrence of cerebrovascular events. B) The PFO-migraine association is a new topic of great debate[10,12]. Although AA has observed, in patients with PFO and TAO / ASA therapy a positive trend in reducing duration, intensity and auricemia of migraine, currently there is no indication of PFO closure in migraine subjects only, if associated with cerebrovascular events of cryptogenetic nature[13,14].

C) Platypnea-orthodoxy presence in patients with PFO does not represent a clinical aspect of real interest, while it remains a highly debated topic in the scientific world, are the attribute an manifestation of the PFO, especially when the shunt is minimal and not relevant[10-13].

Aim of study:

- Look at the incidence of PFO and what correlation there is to TIA / STROKE , Headache / Migraine and Platipnea-Orthodoxy
- Does percutanous closer of PFO reduce the incidnece TIA / STROKE , Headache / Migraine and Platipnea-Orthodoxy

MATERIAS AND METHODS

The patients were observed and studied over a period of over 8 years (6,8±2,2 aa) at the Department of Cardiology Polo Pontino "LaSapienza" in Rome; 74 patients with PFO were included (17 M e 57 F) the mean age 50.3 ± 11.2 years, all originating in the province of Latina. The 17 M had an average age of 52.6 ± 9.2 and the 57 F had an average age of 49.5 ± 10.5 years.

All patients were had a clinical follow-up every 6 months, which included medical history and examination, hematochemicaltest, neurological test (headache / migraine) ECG examination, trans-thoracic echocardiography with microbubble test. The histroy included questions on the absence of events or recurrences of cerebrovascular events, the presence or absence of headache, and the presence of symptoms related to platypnea-orthodoxy.

Patients were divided into two groups:

Group A (Gr A) 56 patients (pz) undergoing percutaneous closure for TIA / cryptogenetic stroke; 49 pz completed the long-term follow up.

Group B (Gr B) 18 patients did not undergo percutaneous closure, for absence of indication according to LG, but with migraine with or without aura. There are no patients with platypnea-orthodoxy in this group.

pre closure	**Grp A** Gr B	**Grp B** Gr A Gr B
Total pz	56 pz GrA2 GrA3 GrA4	18 pz 8 2 % 50 Num %

Absence	23	0 3,5 0 -
Migraine	22	18 71 6 33
Migraine + P.O.	8	0 89 0 -
P.O.	3	0 89 0 -

Tab.2 Absence = asymptomatic migraine and platypne-orthodoxy; P.O. = platypnea-orthodoxy;

All the patients woh had PFO closure, presented with a history of repeated TIA / stroke cryptogenetic episodes and they were also subjected to neurological and cardiological screening for percutaneous closure. All patients performed a cerebral Nuclear Magnetic Resonance (RMN) positive, and Carotid ecografy (ECO-TSA) negative for atheroma. The presence of shunt dx sx was highlighted in some patients with TTE with microbubbles (29/56), meanwhile in all patients the presence of PFO was confirmed by TEE and completed the study (collar, shunt, spontaneous contrast). All patients were subjected to thrombophilic screening. Clinical and anatomical risk factors have been identified for each patient. The criteria for percutaneous closure were the following: TIA / cryptogenetic stroke with or without recurrent events; PFO with significant shunt (3rd grade); age <65 years.

An hour before the procedure, endovene antibiotic prophylaxis was administered to all patients. With local lidocaine anesthesia, the right femoral vein was canulated: 10 or 12 F, F introducer was used, then diagnostic catheter Mpa1 or Jr4 and Aqwire guide 180 cm / 260 cm Ptfe guide. Amplatzer System (kit + device); introducer 8F (2,8mm) 90 cm for the study with Acunav probe for intracardiac echo. Once in the right atrium, heparin was administered depending on the patient's weight and flectadol 250/300 mg after the device was released. For the first six months, double antiaggregation was administered with acetylsalicylic acid (ASA) + clopidogrel and then only ASA based on the opinion of the clinician. Concerning migraine symptoms, at each control, all patients were evaluated with questionnaires15-16 (MSQoL, HIT-6 and MIDAS) and clinical diary, particularly in patients who were closed, the test was repeated pre and post-closure of PFO.

Regarding platypnea-orthodoxy symptomatology, at each control, all patients were questioned on lifestyle and re-evaluated the clinical diary and subjected to observational clinical evaluation by varying posture from orthostatic to genuflessa

Statistic analysis

Statistical analysis were processed through Microsoft Excel 2010 spreadsheets. Continuous variables were analyzed with mean ± standard deviation; the discrete variables as percentages. The evaluated parameters were considered statistically significant for p-values $p<0.05$ using the McNemar's test (test used on paired nominal data). and Student's test

RESULTS

The were 74 patients (pz): 56 have been undergoing percutaneous closure, while 18 patients had no indication of closure; On 56 pazienti (GrA); 7 subjects were lost in followup The risk factors and demographic data were reported in Table 1.

Baseline demographics	**Gr A**		**Gr B**	
Number of patients	56		18	
Mean age in years	51,7± 10,8 ys		46±9,1 ys	
	Number	percentage	Number	percentage
Male	16	28%	1	5%
Female	40	72%	17	95%
Coronary risk factors				
Diabetes	3	5%	0	-
Current smoker	6	10%	5	27%
Hypercholesterolaemia	8	14%	5	27%
Family history	3	5%	6	39%
Age>60	15	26%	2	11%
Coagulation disorder	5	9%	2	11%
Arterial hypertension	25	44%	6	33%

Tab 1 Anagraphic distribution and risk factors in relation to subgroups

In Table 2 are reported the clinical and anatomical risk factors observed from the history and the hematochemical examinations, RMN, ecocardium both TTE and TTE

Clinical Risk Factors	**Gr A**		**Gr B**		**Anatomical Risk Factors**	**Gr A**		**Gr B**	
	Num 56 7	% 3	Num	% 5,3 %		Num 8 2	% 50	Num	%
Multiple lesions on CT/MR	56	100	4	22	Eustachian valve>10	8	14	0	-
Recurrent clinical events	7	12,5	0	-	Chiari network	2	3,5	0	-
Thrombophilia	5	9	2	11	SIA	40	71	6	33
DVT/PE	3	5,3	0	-	Basal R-L shunt	50	89	0	-

Tab.2 thromboembolic risk study in relation to morphology

In Group A patients, echocardiography showed interatrial septum aneurysm (SIA) in 71% of cases, of which 61% of type IB cases.

During the follow-up of 6.8 ± 2.2 years, none of the GrA patients had an recurrence of cerebrovascular events. NO short-term and long-term complications was observed. Of the 56 patients who had the procedure, only 49 patients (86%, 36 F-13 M, mean age of 48.8 ± 10.8 years) completed periodic clinical and instrumental controls, while 7 patients (20%, 3 F-4 M, of an average age of 50.8 ± 6.6 years) have voluntarily interrupted the follow up, in the last year.

In 55/56 patients (99%) was verified the correct positioning of the device and the absence of residual shunt at TTE and contrast TEE.

Only one patient, after 12 months of control, had a low residual shunt but no indication of re-intervention.

In GrA 54% of the pts (30/56 pts of which 7 M, 23 F) were affected by recurrent episodes of migraine before the PFO closure, of 30 pts, only 22 had only migraine; 8 pts only migraine and platypnea-orthodoxy; 3 pts exclusively platypnea-orthodoxy; After closure (tab.3) in 13/30 (23%) pts (all women) persisted migraine but with lower index (MSQoL, HIT-6 and MIDAS) and no one reported gold (McNemar' test = 4,3 of p<0,05)

Only migraine	PFO Post closure		PFO Pre closure	
	NO	SI	Tot. pre	
positive	17	13	30	N° pz
negative	26	0	26	N° pz
total	43	13	56	N° pz

Tab.3: GrA → McNemar' test

46% of the GrA pts were asymptomatic for headache and platypnea-orthodoxy both before and after the procedure (26 pcs on 56 pcs of which 11M, 15 F) (Tab2).

56% of GPs with or without headache with mean age 49.3 ± 9.9 years with TTE + positive contrast for shunt with number of bubbles> 10 were cerebrovascular imaging injury (19 of 30 of 63% of TIA, 2 of 30 of 7% of stroke, 7 of 30 of 23% of silent ischemia).

Based on data from the TEE study, we compared the PFO size and tunnel lenght in the patient of GrA1 and GrA2, without pointing to any statistically significant difference, confirming the absence of correlation between PFO size and migraine symptomatology (tab.3)

TEE	Gr A1	Gr A2	Student's T.	
Size PFO (mmq)	2,6±0,6	3,7±2	0,2	NS
Tunnel Length (mm)	11,5±3,1	13±5,7	0,6	NS

Tab.3: TEE study → Morphology of the PFO in the Gr with or without

As regards the typing of the muscle, all the pcs of the Gr A were evaluated by MSQoL, HIT-6 and MIDAS questionnaires and the collection of the pre-and post-closure clinical diary of PFO. 13 out of 30 patients had migraine with aura (41% prevalence).

In the tab. 4 post-closure results

Migraine characteristics	PRE-CLOSURE	POST-CLOSURE	P value
Aura yes/no	16/14	0/13	-
Monthly diary (days)	13,6±9,3	2,8±6,4	<0,01
MIDAS points	23,4±22,6	3,7±5,9	<0,01
MIDAS degrees	3,7±0,9	1,3±0,9	<0,01
HIT 6	57,4±10,3	25±24	<0,01
MSQoL	44,9±16,6	13,2±15,3	<0,01

Tab.4 Gr A Changes in pre-and post-closure migraine characteristics; P value = t Student

In GrA, 6.8 ± 2.2 years after surgery: 17 patients were asymptomatic (57% of cases), 10 patients (33%) were symptomatic but lower in class, and 3 patients (10%) did not significant change.

In Gr.B only 5/18 patients had migraine with aura (28%); while 13/18 patients (72%) had headaches without aura. There was no significant (p> 0.05) difference in migraine characteristics between GrB and GrA

Migraine characteristics	Gr B
Aura yes/no	5/13
Monthly diary (days)	2,8±6,4
MIDAS points	3,7±5,9
MIDAS degrees	1,3±0,9
HIT 6	25±24
MSQoL	13,2±15,3

Tab.5 Gr B characteristics of the aura and absence of it

Differences have been made on the magnitude of the number of past microbubbles (low <10 and high> 10) in patients with headache without aura and with aura. The Fisher test was found to be insignificant (p> 0.05) so the presence of aura does not depend on the size of microbubbles in the first three heart cycles (fig 1)

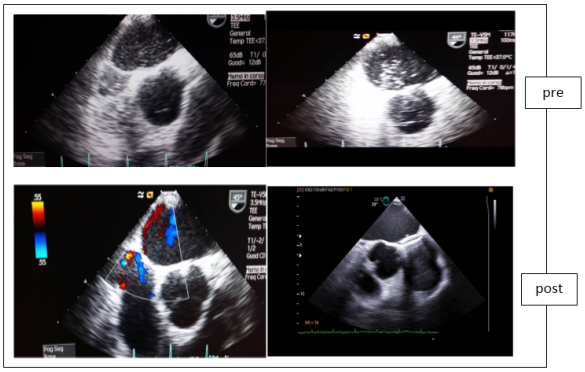

Fig 1 TTE image with microbolle and dopplercolor test; positiveand negative for PFO; pre-after closure

All patients were followed every 6 months with a re-evaluation of migraine symptoms, which was unchanged in the total of Gr B, in constant therapy.

Two patients died at distance > 12 months for non-cardiovascular disease

DISCUSSION

This long-term follow-up study was aimed to evaluate the incidence and frequency of symptoms / pathology (embolic thromboembolic events, migraine, and platypnea-orthodoxy) in isolation or association with PFO documented[10-12]. Ourt study demonstarted majoirty of our cohort had cerbral event, 56 out of 74 (76%) these indivudals who then went on to have PFO closure, as indicated by LG.

This is one of the limitation of this study as our population was predominantly selected based on closure. The main observation in the patient who had closure were that they were asymptomatic.

Another limitation of this study is represented by the small cohort (18 pz) who were only undergoing medical therapy who had no indication of the closure device e.g. stroke. In the AHA guidelines of 2014 [17], the percutaneous closure indication was recognized in class II B only for pz with PFO and stroke / TIA cryptogenetic evidence with deep venous thrombosis (TVP), based on the recurrent TVP risk.

In the literature, the natural observation of patients with PFO shows low incidence of events[4] with paradoxical thromboembolism; That is why long-term follow-up studies, specific and detailed protocol on disorders in the PFO, have a particular value in quantifying the incidence of this and other events. The "IPSYS registry" study did not highlight superiority of interventional therapy compared to medical therapy, but suggested that percutaneous closure could represent a better therapeutic strategy especially in younger subjects <37 years , with significant shunt dx-sx[20]. In the study of Eeckhout et al. [18] Which had the primary endpoint to evaluate the occurrence of cerebrovascular events on 238 patients undergoing percutaneous PFO closure, up to 10 years of follow-up (mean 7.6 ± 2.4 years), a recurrence of cerebrovascular events was reported in 5 patients, representing an annual risk of 0.28%. In the study of Taggart et al[19] (730 patients) with an average follow-up of 6 years, recurrent stroke / TIA was observed in 6.1% (45 patients). RESPECT[8] follow-

up results showed a significant reduction of recurrent ischemic stroke in favor of the closure of the PFO.

Over the period of our study of 8 years, no TIA recurrence was observed in the 56 patients undergoing PFO closure, although there was an abnormal case locally. This excellent result may also be due to life style changes (diet, walking and elastic stockings) and recommended therapy; while it is very interesting to see a statistically significant ($p < 0.01$) association between migraine and PFO, which is even more relevant if we take into account the type of migraine with aura. In the GrB we observed a prevalence of 100% PFO, specifically 28% in patients with headache with aura and 72% in those with headaches without aura In Gr A (56 pts), prior to PFO closure, a prevalence of migraine was observed in 56% of pts while in 44% were asymptomatic. In GrA, pts with headache with aura were 41% while the remaining 59% by migraine without aura Some studies[21-25] suggested that there is a relationship between headache with aura and high shunt PFO. In our study, we have tried to evaluate the existence of statistically significant differences about the magnitude of shunt (low: < 10 microbubble; high: > 10 microbubble) between the group of patients with non-migraine headaches and those with migraine-related patients aura in Gr B. The Fisher test provided a $p > 0.05$, meaning not significant, showing that the association does not depend either on the size of the shunt or by the presence or absence of aura. Also in the 2010 study of Rigatelli[26], performed on 40 patients with PFO closure and with headache with an aura (an average follow-up of 29.2 ± 14.8 months), showed a significant regression of symptomatology with the disappearance of the headache after PFO closure.

At a distance of 6.8 ± 2.2 years after surgery, in our study we observed in GrA the following results: 13 patients remained symptomatic (43%, all females), of which 10 patients (33%) were symptomatic but lower in the class, while the remaining 3 patients (10%) had no significant changes before and after surgery. We also observed the disappearance of the aura in all patients in post-closure Gr A.

Migraine remains a multifactorial pathology, where the pathophysiological substrate of the relationship with the PFO is not exactly known; it is also unclear if there is correlation between the entity of paradox shunt (through PFO) and induction of migraine attacks, both in terms of frequency and severity[27-30].

There is currently no scientific evidence to support percutaneous closure in the patient's migraine patient, but a tendency to improve symptoms after closure has been emphasises many times by retrospective studies.

CONCLUSION

The study compared two groups (GrA vs GrB) of a PFO carrying population of which GrA was subjected to PFO closure and GrB for lack of criteria according to L.G. the PFO has not been closed;

The whole poppulation (GrA + GrB) was observed for about 8 aa by studying the presence of cerebral vascular disease (TIA / StrocK) or headache / migraine or platypnea-orthodoxy symptom representing the predominant clinic in pts with PFO .

The results of our long-term follow-up with semi-annual controls showed a no recurrence of TIA / Strock, a statistically significant reduction in number and quality of migraine / headache episodes and platypnea-orthodoxy symptom ($p < 0.001$) in the GrA after the closure of the PFO.

This study confirms the effectiveness of percutaneous intervention therapy in secondary prevention of ischemic cerebrovascular events, and also a reduction headache / migraine episodes.

Our study supports an association between PFO and migraine, although the causality / casuality remains to be defined.

REFERENCES

1. 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.
2. Adams HP.JR, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24: 35-41
3. Sacco RL, Ellenberg JH, Mohr JP, Tatemichi TK, Hier DB, Price TR, Wolf PA. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. Ann Neurol 1989; 25: 382-90
4. Kent DM, Ruthazer R, Weimar C, Mas JL, Serena J, Homma S, Di Angelantonio E, Di Tullio MR, Lutz JS, Elkind MSV, Griffith J, Jaigobin C, Mono ML, Nedeltchev K, Papetti F, David E and Thaler DE. Index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. Neurology 2013; 81: 619–625.
5. Ferrarini G, Malferrari G, Zucco R, Gaddi O, Norina M, Pini LA. High prevalence of patent foramen ovale in migraine with aura. J Headache Pain. 2005; 6:71-76.
6. Pristipino C, Anzola GP, Ballerini L, Bartorelli A, Cecconi M, Chessa M, Donti A, Gaspardone A, Neri G, Onorato E, Palareti G, Rakar S, Rigatelli G, Santoro G, Toni D, Ussia GP, Violini R. Management of Patients with Patent Foramen Ovale and Cryptogenic Stroke: A Collaborative, Multidisciplinary, Position Paper. Catheterization and Cardiovascular Interventions 2013;82:38-51.
7. O'Gara PT, Messe SR, Tuzcu EM, Catha G, Ring JC. Percutaneous Device Closure of Patent Foramen Ovale for Secondary Stroke Prevention A Call for Completion of Randomized Clinical Trials A Science Advisory From the American Heart Association/American Stroke Association and the American College of Cardiology Foundation Circulation. 2009; 119: 2743-2747
8. Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, Marks DS and Tirschwell DL. Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke N Engl J Med 2013; 368: 1092-1100
9. Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, Andersen G, Ibrahim R, Schuler G, Walton AS, Wahl A, Windecker S, Jüni P. Percutaneous Closure Of Patent Foramen Ovale In Cryptogenic Embolism. N Engl J Med. 2013; 368:1083-1091.
10. Maxwell GL. Respect: Final Long-term Outcomes From a Prospective, Randomized Trial of PFO Closure in Patients With Cryptogenic Stroke presented at the Transcatheter Cardiovascular Therapeutics meeting. Washington DC, 2016; 132: 45-55.
11. Hornung M, Bertog SC, Franke J, Taaffe M, Wunderlich N, Vaskelyte L, Hofmann I, Sievert H. Long-term results of a randomized trial comparing three different devices for percutaneous closure of a patent foramen ovale. Eur Heart J. 2013; 34: 3362-3369.
12. Balbi M, Canepa M, Cheli M, Brunelli C. Forame ovale pervio ed emicrania: relazione causale o casuale? Ital Cardiol. 2010; 10: 25-29
13. Mattle HP, Evers S, Hildick-Smith D. Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial. European Heart Journal 2016; 37: 2029–2036
14. Dowson A, Mullen MJ, Peatfield R, Muir K, Khan AA, Wells C, Lipscombe SL, Rees T, De Giovanni JV, Morrison WL, Hildick-Smith D, Elrington G, Hillis WS, Malik IS, Rickards A. Migraine Intervention With STARFlex Technology (MIST) Trial A Prospective, Multicenter, Double-Blind, Sham-Controlled Trial to Evaluate the Effectiveness of Patent Foramen Ovale Closure With STARFlex Septal Repair Implant to Resolve Refractory Migraine Headache Circulation 2008; 117: 1397-1404
15. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33: 629–808.
16. Sauro KM, Rose MS, Becker J, Christie SN, Giammarco R, Mackie GF, Eloff AG, Gawel MJ.
HIT-6 and MIDAS as measures of headache disability in a headache referral population. Headache. 2010; 50: 383-95.
17. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson DJ, Schwamm LH, Wilson JA. Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2014; 45: 100-109.
18. Eckhout E, Martin S, Delabays A, Michel P, Girod G. Very long-term follow-up after percutaneous closure of patent foramen ovale. EuroIntervention 2015; 10: 1474-1479
19. Taggart NW, Reeder GS, Lennon RJ, Slusser JP, Freund MA, Cabalka AK, Cetta F, Hagler DJJ. Long-term Follow-up After PFO Device Closure: Outcomes and Complications in a Single-center Experience Catheterization and Cardiovascular Interventions. 2016; 89: 124–133
20. Pezzini A, Grassi M, Lodigiani C, Patella R, Gandolfo C, Zini A, Delodovici ML, Paciaroni M, Del Sette M, Toriello A, Musolino R, Calabrń RS, Bovi P, Adami A, Silvestrelli G, Sessa M, Cavallini A, Marcheselli S, Bonifati DM, Checcarelli N, Tancredi L, Chiti A, Del Zotto E, Tomelleri G, Spalloni A, Giorli E, Costa P, Giacalone G, Ferrazzi P, Poli L, Morotti A, Piras V, Rasura M, Simone AM, Gamba M, Cerrato P, Zedde ML, Micieli G, Melis M, Massucco D, Guido D, DeGiuli V, Bonaiti S, D'Amore C, LaStarza S, Iacoviello L, Padovan A. On behalf of the Italian Project on Stroke in Young Adults (IPSYS) Investigators. Propensity Score–Based Analysis of Percutaneous Closure Versus Medical Therapy in Patients With Cryptogenic Stroke and Patent Foramen Ovale The IPSYS Registry (Italian Project on Stroke in Young Adults) Circ Cardiovasc Interv. 2016; 9: 1034 1047
21. Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. Clin Sci (Lond). 2001; 100: 215-220.
22. Anzola GP, Morandi E, Casilli F, Onorato E. Different degrees of right-to-left shunting predict migraine and stroke: data from 420 patients. Neurology. 2006; 66: 765-777
23. Snijder RJ1, Luermans JG2, de Heij AH3, Thijs V4,5, Schonewille WJ6, Van De Bruaene A7, Swaans MJ8, Budts WI9, Post MC8. Patent Foramen Ovale With Atrial Septal Aneurysm Is Strongly Associated With Migraine With Aura: A Large Observational Study. J Am Heart Assoc. 2016 Dec 1;5(12).
24. Wilmshurst P, Pearson M, Nightingale S. Re-evaluation of the relationship between migraine and persistent foramen ovale and other right-to-left shunts.Clin.Sci (Lond) 2005; 108: 365- 377.
25. Schwerzmann M, Nedeltchev K, Lagger F. Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology. 2005; 65: 1415-1418.
26. Rigatelli G, Dell'Avvocata F, Ronco F, Cardaioli P, Giordan M, Braggion G, Aggio S, Chinaglia M, Rigatelli G, Chen JP. Primary transcatheter patent foramen ovale closure is effective in improving migraine in patients with high-risk anatomic and functional characteristics for paradoxical embolism. JACC Cardiovasc Interv. 2010; 3: 282-287.

27. Shi YJ, Lv J, Han XT, Luo GG. Migraine and percutaneous patent foramen ovale closure: a systematic review and meta-analysisBMC Cardiovasc Disord. 2017 Jul 26;17(1):203.
28. Hildick-Smith D, Williams TM. Patent Foramen Ovale and Migraine Headache. Interv Cardiol Clin. 2017 Oct;6(4):539-545.
29. Tobis JM, Charles A, Silberstein SD, Sorensen S, Maini B, Horwitz PA, Gurley JC. Percutaneous Closure of Patent Foramen Ovale in Patients With Migraine: The PREMIUM Trial. J Am Coll Cardiol. 2017 Dec 5;70(22):2766-2774.
30. Wilmshurst PT. Migraine with aura and persistent foramen ovale. Eye (Lond). 2017 Dec 8,: 10.1038