

Characteristics of patients diagnosed for cardiac cause of ischemic neurological events and prescreened with a transcranial Doppler examination

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KEY WORDS

migraine, patent foramen ovale, stroke, transient ischemic attack

ABSTRACT

INTRODUCTION Screening for patent foramen ovale (PFO) in patients with ischemic neurological events is becoming more common.

OBJECTIVES This study aimed to evaluate clinical characteristics and atrial septum anatomy in relation to age and presence of PFO, as well as factors associated with a history of stroke in patients assessed for cardiac causes of ischemic neurological events.

PATIENTS AND METHODS A total of 817 patients with a history of neurological episodes (stroke, transient ischemic attack [TIA], or migraine) were prescreened using transcranial Doppler ultrasound. Transesophageal contrast echocardiography (TEE) was employed to confirm PFO and assess the anatomy of the atrial septum and right atrium.

RESULTS Among the patients, 28% had ischemic stroke, 31% had TIA, and 49% had migraines. PFO was confirmed in 79% of the patients. Regardless of the analyzed age group, PFO was associated with higher prevalence of TIA, migraine and syncope history, atrial septal aneurysm (ASA), and Chiari network. There were fewer women in the PFO group, but only in the population aged 45 years or under. Patient age, male sex, typical cardiovascular risk factors, and the presence of ASA were associated with a history of stroke.

CONCLUSIONS In patients with ischemic neurological events who were prescreened for PFO, confirmation of PFO on TEE was associated with a higher prevalence of TIA, migraine, syncope, Chiari network, and ASA. Advanced age, typical cardiovascular risk factors, and ASA were associated with stroke history in the study population.

INTRODUCTION Patent foramen ovale (PFO) is a remnant of fetal circulation found in about 25% of the general population.^{1,2} Under increased abdominal pressure, PFO may allow communication between the right and left heart chambers, potentially causing paradoxical embolization and ischemic events.^{3,4} Numerous studies have linked PFO to neurological events, especially cryptogenic stroke and transient ischemic attack (TIA).⁵⁻⁷

Additionally, recent discussions have highlighted its potential association with migraine.^{8,9}

However, given the high prevalence of PFO and the considerable heterogeneity among affected individuals, the risk of ischemic neurological events may vary depending on anatomical features, demographic factors, and clinical characteristics. This variability has led to questions about the criteria for interventional closure of PFO.^{10,11}

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WHAT'S NEW?

Patent foramen ovale (PFO), present in approximately 20% to 30% of the general population, is a remnant of fetal circulation that can connect the right and left atria, potentially leading to paradoxical embolism and stroke. The unique aspects of this study include the study population selection and the analysis of demographic and clinical characteristics as well as anatomical features associated with PFO in relation to patient age. The study population included patients with a history of neurological episodes who were prescreened for PFO using transcranial Doppler (TCD) ultrasound. The criteria for this selection were: 1) PFO diagnostic workup is not performed in asymptomatic patients and is limited to those with a history of neurological events; and 2) cardiac assessment with transesophageal echocardiography is usually performed in patients with a positive TCD result. Findings of this study could offer valuable insights for establishing indications for interventional closure of PFO in different age groups.

This study aims to determine patient clinical characteristics and atrial septum anatomy in relation to age and the presence of PFO, as well as to assess the factors associated with a history of stroke in patients evaluated for cardiac causes of neurological events.

PATIENTS AND METHODS **Study population and design** This multicenter study included 817 patients evaluated for cardiological causes of neurological episodes, including stroke, TIA, and migraines, between 2004 and 2013. The study group consisted of patients who had been initially prescreened for PFO using transcranial Doppler ultrasonography (TCD). The inclusion criteria were a history of ischemic stroke, TIA, or migraine. Migraine was defined in accordance with the criteria of the Headache Classification Committee of the International Headache Society.¹² Patients were excluded if they had an identifiable cause of a neurological event, such as a heart cavity mass (eg, tumors, thrombi, vegetations), atherosclerotic plaques in the aorta or cranial arteries, atrial fibrillation, congestive heart failure, severe valvular heart pathology, or a life expectancy of less than 2 years. The assessments included an evaluation of demographic and clinical characteristics as well as a review of history of neurological events. All patients underwent a 12-lead electrocardiogram, transthoracic echocardiography, and transesophageal contrast echocardiography (TEE).

Imaging In this study, imaging was performed to confirm PFO and conduct a detailed analysis of the atrial septum anatomy using TEE. Midesophageal 4-chamber, midesophageal short axis, aortic, and midesophageal 4-chamber views were used on echocardiography. To detect right-to-left atrial leakage, echocardiographic contrast was injected into the basilic vein while the patient performed the Valsalva maneuver. The results, that is, the amount of contrast bubbles passing into the left atrium, were graded on a scale from 0 to 3, with 0 indicating no passage, 1 indicating a few

bubbles, 3 indicating a cloud of bubbles, and 2 indicating an intermediate amount of bubbles between grade 1 and 3.¹³⁻¹⁷

The diagnosis of atrial septal aneurysm (ASA) was based on the following specific criteria: a deviation of a portion of the septum of at least 10 mm into either the right or left atrium with an amplitude of at least 10 mm towards either atrium or a combined deviation exceeding 15 mm into both atria.¹⁸

Statistical analysis Quantitative variables were summarized using the first and third quartiles for non-normally distributed data. Categorical variables were presented as percentages. The Shapiro–Wilk test determined data normality. The Mann–Whitney test (for non-normally distributed data) was applied for continuous variable comparisons. Statistical analysis of data expressed on a binary scale was performed using the χ^2 test. The Fisher exact test was used for binary variables with expected numbers of less than 5. A univariable logistic regression model was constructed to identify factors associated with stroke history. Variables including demography, clinical characteristics, and atrial septum anatomical details were assessed. Statistical significance was set at a *P* value of less than 0.05. All statistical analyses were performed using SPSS Statistics 29 (IBM Inc., Armonk, New York, United States).

RESULTS In the study population, the distribution of neurological events was as follows: history of ischemic stroke was reported in 228 (28%), TIA in 253 (31%), and migraines in 402 (49%) patients. PFO was confirmed in 644 patients (79%) and 173 patients (21%) did not have PFO.

The patients with PFO demonstrated higher rates of TIA, syncope, and migraine history, as compared with those without PFO (TABLE 1). With regard to the atrial septum anatomy, those with PFO more frequently had Chiari network and ASA (TABLE 1).

A comparison of patients based on age is presented in TABLE 2. There were fewer women in the group of patients older than 45 years. Additionally, this group showed higher rates of stroke and typical cardiovascular risk factors, including arterial hypertension, diabetes mellitus, hypercholesterolemia, and varicose veins of the lower limbs. Analysis of patients based on their history of stroke is presented in TABLE 3. The group of patients with a history of stroke had a lower proportion of women. Furthermore, the patients in this group were older and had a higher prevalence of ASA and higher rates of arterial hypertension, hypercholesterolemia, and smoking. In TABLE 4, we present patient characteristics in relation to the presence of migraines. Those with a history of migraines were younger, more commonly female, and had higher rates of PFO and Chiari network.

In Supplementary material, we present analysis focused on patients 45 years old or younger in

TABLE 1 Patient characteristics in relation to the presence of patent foramen ovale

Parameter	Patients without PFO (n = 173)	Patients with PFO (n = 644)	P value
Age, y, median (IQR)	40 (32–49)	37 (28–49)	0.06
Women	72	68	0.16
Stroke	32	27	0.1
TIA	25	32	0.04
>1 TIA	6	13	0.01
Syncope	14	22	0.01
Arterial hypertension	28	25	0.25
Diabetes mellitus	2	1	0.72
Smoking	21	21	0.4
Hypercholesterolemia	28	26	0.36
Hormonal contraception	12	16	0.13
Varicose veins of lower limbs	10	12	0.26
Migraine	33	54	<0.001
Migraine without aura	13	17	0.07
Migraine with visual aura	20	36	<0.001
Chiari network	3	9	0.003
Atrial septal aneurysm	8	36	<0.001
PFO grade 1	–	21	–
PFO grade 2	–	23	–
PFO grade 3	–	45	–

Data are presented as percentage unless otherwise indicated.

Abbreviations: IQR, interquartile range; PFO, patent foramen ovale; TIA, transient ischemic attack

TABLE 2 Patient characteristics in relation to age

Parameter	Patients ≤45 years old (n = 547)	Patients >45 years old (n = 270)	P value
PFO	79	78	0.65
Age, y, median (IQR)	32 (25–38)	52 (49–56)	<0.001
Women	71	64	0.04
Stroke	20	44	<0.001
TIA	35	22	<0.001
>1 TIA	14	7	0.002
Syncope	22	18	0.2
Arterial hypertension	16	46	<0.001
Diabetes mellitus	0.7	3	0.02
Smoking	19	23	0.2
Hypercholesterolemia	18	45	<0.001
Hormonal contraception	17	11	0.02
Varicose veins of lower limbs	10	16	0.02
Migraine	54	38	<0.001
Migraine without aura	18	13	0.04
Migraine with visual aura	36	25	0.001
Chiari network	8	8	1
Atrial septal aneurysm	28	34	0.051
PFO grade 1	17	14	0.36
PFO grade 2	18	17	0.56
PFO grade 3	36	34	0.75

Data are presented as percentage unless otherwise indicated.

Abbreviations: see [TABLE 1](#)

relation to the presence of PFO. Generally, the results were similar to the previous calculations presented in [TABLE 1](#), which included all age groups. We reported a lower proportion of women in the PFO population, but only in patients 45 years old or younger (Supplementary material, [Table S1](#)).

Logistic regression analysis was conducted to identify predictors of past stroke episodes (Supplementary material, [Table S2](#)). Factors associated with a higher prevalence of stroke corresponded with findings presented in [TABLE 3](#), and included age, male sex, arterial hypertension, hypercholesterolemia, smoking, and ASA.

DISCUSSION The key findings from the present study, conducted in a cohort of patients with a history of neurological ischemic events who were initially screened for PFO, are as follows: 1) individuals with confirmed PFO, regardless of age group, more frequently had a history of TIA, migraines, and syncope as well as higher rates of Chiari network and ASA; 2) there were fewer women among the patients with confirmed PFO, but only in the population of patients 45 years old or younger; 3) advanced age, male sex, typical cardiovascular risk factors, and ASA were associated with more common history of stroke.

A substantial body of evidence from numerous trials has demonstrated a significant association between PFO and ischemic neurological events.^{19–24} A review of retrospective studies identified key contributors to an elevated risk of stroke in patients with PFO, including a large foramen ovale, an extensive right-to-left shunt, shunt at rest, increased mobility of the PFO valve, and coexisting ASA.^{25,26} Furthermore, in line with findings from our study and previous research, demographic characteristics, such as older age, male sex, and typical cardiovascular risk factors also contributed to an increased risk of stroke in that patient population.^{25,26}

Despite the high prevalence of PFO, its exact role in the pathogenesis of stroke remains unclear. It may involve paradoxical embolization or thrombus formation within the PFO itself, which adds complexity to the understanding of its implications in stroke pathology.²⁴

In a clinical setting, identifying the source of embolic material in patients with PFO and ASA is often challenging. Despite thorough examination of the deep veins of the lower limbs and pelvis, the precise source might remain unknown.²⁷ In our study, there was no difference in the number of subjects with varicose veins between the patients with and without PFO (we only noted a trend toward a higher occurrence of this factor in the PFO cohort). Notably, varicose veins were more prevalent in the patients over 45 years of age. This suggests that in the absence of deep vein thrombosis, emboli might originate from thrombi formed at the PFO edges or on the ASA surface.²⁸ Another hypothesis is that small fibrin-platelet fragments in the venous system may represent a potential source of paradoxical embolism,

TABLE 3 Patients characteristics in relation to the history of stroke

Parameter	Patients without stroke history (n = 589)	Patients with stroke history (n = 228)	P value
PFO	80	76	0.21
Age, y, median (IQR)	35 (27–46)	46 (37–52)	<0.001
Women	74	56	<0.001
TIA	37	14	<0.001
>1 TIA	14	5	<0.001
Syncope	23	13	<0.001
Arterial hypertension	18	45	<0.001
Diabetes mellitus	1.4	1.7	0.75
Smoking	17	31	<0.001
Hypercholesterolemia	19	47	<0.001
Hormonal contraception	15	15	1
Varicose veins of lower limbs	11	14	0.23
Migraine	56	32	<0.001
Migraine without aura	17	14	0.21
Migraine with visual aura	38	18	<0.001
Chiari network	8	8	1
Atrial septal aneurysm	25	41	<0.001
PFO grade 1	17	14	0.21
PFO grade 2	17	20	0.42
PFO grade 3	35	35	1

Data are presented as percentage unless otherwise indicated.

Abbreviations: see [TABLE 1](#)

as they are too small to be detected by current diagnostic techniques. A key factor supporting this mechanism is the observed association between cerebral strokes and activities involving the Valsalva maneuver.²⁹

Previous research has indicated an association between the risk of ischemic stroke and both the size of the foramen ovale canal and the magnitude of the right-to-left shunt. However, standardized guidelines for quantitatively assessing contrast leakage through the PFO canal are currently lacking.³⁰ Some researchers recommend counting the number of bubbles passing through the septum as an indicator, but this modality has its limitations, including inconsistent leakage relative to PFO size and subjective bubble counting.³¹

In our study, we encountered challenges in definitively correlating PFO size with a history of ischemic stroke, primarily due to the inherent limitations in measuring PFO size during TEE. A key challenge lies in synchronizing the Valsalva maneuver with contrast administration, a procedure that rarely yields comparable images for accurate determination of PFO size between patients. Consequently, our study did not prioritize PFO dimensions. More invasive measurement techniques (eg, using a low-pressure balloon) exist but are not routinely employed due to their complexity and extended duration of the procedure.³² Instead, we focused on evaluating shunt intensity

during TEE with the Valsalva maneuver, finding that nearly half of our patients exhibited a shunt intensity corresponding to the highest degree on our semiquantitative scale.

In our study, the group with PFO exhibited a higher prevalence of ASA and other anomalies, such as the Chiari network, both of which are recognized contributors to paradoxical embolism. ASA can affect the opening and size of the PFO, thereby increasing the risk of embolism.³³ Another potential source of embolism may be fibrin-platelet thrombi that are formed on the left atrial surface of the ASA.²⁸ Additionally, ASA is associated with paroxysmal supraventricular arrhythmias, including atrial fibrillation, which further elevates the risk of cerebral embolism.³⁴ The Chiari network, a remnant of the sinus venosus valve, also presents an increased risk of paradoxical embolism and was found to be more common in the patients with PFO in our study.^{35,36}

Our findings demonstrated that patients older than 45 years had a more frequent history of stroke, as compared with their younger counterparts. This contrasts with previous studies, which typically report a higher prevalence of PFO-associated cryptogenic stroke in younger individuals.²⁴ It remains unclear whether the increased stroke incidence in the group of older patients with PFO is attributable to more frequent cardiovascular risk factors or the prolonged presence of PFO. Notably, this population also exhibited a higher prevalence of ASA, an additional recognized risk factor for stroke.

Our study observed higher rates of migraine, particularly migraine with visual aura, in the patients with PFO, consistent with previous findings.³⁷ The precise mechanism linking migraines and PFO remains unclear. One possible explanation is paradoxical microembolization, a phenomenon similar to that proposed in the pathogenesis of ischemic stroke.³⁷

Limitations A notable limitation of our study is the exceptionally high prevalence of PFO, observed in nearly 80% of the study population. This unusually high rate can be attributed to our initial selection criteria of patients with prior neurological diagnoses, in whom TCD examinations with echocardiographic contrast via the antecubital vein were routinely conducted. In the Silesian Voivodeship, young patients who have experienced ischemic neurological events frequently undergo TCD testing, likely leading to a predominance of individuals with positive TCD results in our cardiac assessment. This may have resulted in an overrepresentation of PFO cases compared with the general population and those with cryptogenic neurological events.

However, such selection reflects a real-world scenario. Firstly, PFO diagnostic workup is typically limited to patients with neurological episodes and is not performed in asymptomatic individuals. Secondly, TCD is recommended as the first-choice diagnostic tool, with subsequent

TABLE 4 Patient characteristics in relation to the history of migraine

Parameter	Patients without migraine history (n = 415)	Patients with migraine history (n = 402)	P value
PFO	72	86	<0.001
Age, y, median (IQR)	41 (31–51)	35 (27–46)	<0.001
Women	58	80	<0.001
Stroke	37	18	<0.001
TIA	22	40	<0.001
>1 TIA	7	16	<0.001
Syncope	12	29	<0.001
Arterial hypertension	28	23	0.09
Diabetes mellitus	1.2	1.7	0.57
Smoking	21	21	1
Hypercholesterolemia	28	25	0.34
Hormonal contraception	7	22	<0.001
Varicose veins of lower limbs	8	15	0.002
Migraine without aura	–	33	–
Migraine with visual aura	–	66	–
Chiari network	6	10	0.03
Atrial septal aneurysm	29	31	0.7
PFO grade 1	13	19	0.02
PFO grade 2	14	21	0.01
PFO grade 3	28	43	<0.001

Data are presented as percentage unless otherwise indicated.

Abbreviations: see [TABLE 1](#)

cardiac evaluation using TEE to confirm a right-to-left shunt through the PFO and assess its anatomy.

Conclusions In patients with ischemic neurological events who were prescreened for PFO, confirmed PFO was associated with a higher frequency of TIA, migraines, syncope, Chiari network, and ASA as well as lower prevalence of female sex but only in those 45 years old or younger. In contrast, advanced age, male sex, traditional cardiovascular risk factors, and ASA were associated with a history of ischemic stroke.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT PW and MW contributed equally to this work. PW conceived the concept of the study. MW analyzed the data and prepared the draft of the manuscript. PK, EK-K, and MS collected the data. KM-S supervised the study and approved the final version of the manuscript. AD corrected the final version of the manuscript. TR supervised the study and corrected the final version of the manuscript. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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REFERENCES

- Mojadidi MK, Christia P, Salamon J, et al. Patent foramen ovale: unanswered questions. *Eur J Intern Med.* 2015; 26: 743-751. [↗](#)
- Węglarz P, Węgiel M, Konarska-Kuszevska E, et al. Experience in patent foramen ovale closure with the CERA Lifetech occluder in patients with cryptogenic stroke. *Postepy Kardiol Interwencyjne.* 2023; 19: 257-261. [↗](#)
- Kheiwia A, Hari P, Madabhushi P, Varadarajan P. Patent foramen ovale and atrial septal defect. *Echocardiography.* 2020; 37: 2172-2184. [↗](#)
- Mac Grory B, Ohman EM, Feng W, et al. Advances in the management of cardioembolic stroke associated with patent foramen ovale. *BMJ.* 2022; 376: e063161. [↗](#)
- Miranda B, Fonseca AC, Ferro JM. Patent foramen ovale and stroke. *J Neurol.* 2018; 265: 1943-1949. [↗](#)
- Alkhouli M, Sievert H, Holmes DR. Patent foramen ovale closure for secondary stroke prevention. *Eur Heart J.* 2019; 40: 2339-2350. [↗](#)
- Maloku A, Hamadanchi A, Franz M, et al. Patent foramen ovale – When to close and how? *Herz.* 2021; 46: 445-451. [↗](#)
- Lip PZ, Lip GY. Patent foramen ovale and migraine attacks: a systematic review. *Am J Med.* 2014; 127: 411-420. [↗](#)
- Kumar P, Kijima Y, West BH, Tobis JM. The connection between patent foramen ovale and migraine. *Neuroimaging Clin N Am.* 2019; 29: 261-270. [↗](#)
- Sun YP, Homma S. Patent foramen ovale and stroke. *Circ J.* 2016; 80: 1665-1673. [↗](#)
- Jasper R, Blankenship JC. Patent foramen ovale closure to prevent secondary neurologic events. *Eur J Intern Med.* 2017; 44: 1-11. [↗](#)
- Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia.* 2004; 24: 9-160.
- Seiler C. Wow should we assess patent foramen ovale?. *Heart.* 2004; 90: 1245-1247. [↗](#)
- Hausmann D, Mügge A, Becht I, Daniel WG. Diagnosis of patent foramen ovale by transesophageal echocardiography and association with cerebral and peripheral embolic events. *Am J Cardiol.* 1992; 70: 668-672. [↗](#)
- Stoddard MF, Keedy DL, Dawkins PR. The cough test is superior to the Valsalva maneuver in the delineation of right-to-left shunting through a patent foramen ovale during contrast transesophageal echocardiography. *Am Heart J.* 1993; 125: 185-189. [↗](#)
- Ha JW, Shin MS, Kang S, et al. Enhanced detection of right-to-left shunt through patent foramen ovale by transthoracic contrast echocardiography using harmonic imaging. *Am J Cardiol.* 2001; 87: 669-671. [↗](#)
- Berkompas DC, Sagar KB. Accuracy of color Doppler transesophageal echocardiography for diagnosis of patent foramen ovale. *J Am Soc Echo.* 1994; 7: 253-256. [↗](#)
- Mügge A, Daniel WG, Angermann C, et al. Atrial septal aneurysm in adult patients: a multicenter study using transthoracic and transesophageal echocardiography. *Circulation.* 1995; 91: 2785-2792. [↗](#)
- Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med.* 1988; 318: 1148-1152. [↗](#)
- Webster M, Chancellor A, Smith H, et al. Patent foramen ovale in young stroke patients. *Lancet.* 1988; 2: 11-12. [↗](#)
- Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. *Stroke.* 1993; 24: 1865-1873. [↗](#)
- Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology.* 2000; 55: 1172-1179. [↗](#)
- Handke M, Harloff A, Bode C, Geibel A. Patent foramen ovale and cryptogenic stroke: a matter of age? *Semin Thromb Hemost.* 2009; 35: 505-514. [↗](#)
- Pristipino C, Sievert H, D'Ascenzo F, 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.
- Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. *J Am Coll Cardiol.* 2018; 71: 2335-2342. [↗](#)
- Cabanes L, Coste J, Derumeaux G, et al. Interobserver and intraobserver variability in detection of patent foramen ovale and atrial septal aneurysm with transesophageal echocardiography. *J Am Soc Echocardiogr.* 2002; 15: 441-446. [↗](#)
- Lapergue B, Decroix JP, Evrard S, et al. Diagnostic yield of venous thrombosis and pulmonary embolism by combined CT venography and pulmonary angiography in patients with cryptogenic stroke and patent foramen ovale. *Eur Neurol.* 2015; 74: 69-72. [↗](#)

- 28 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. [↗](#)
- 29 Ozcan Ozdemir A, Tamayo A, Munoz C, et al. Cryptogenic stroke and patent foramen ovale: Clinical clues to paradoxical embolism. *J Neurol Sci*. 2008; 275: 121-127. [↗](#)
- 30 Van der Giessen H, Wilson LC, Coffey S, Whalley GA. Review: detection of patent foramen ovale using transcranial Doppler or standard echocardiography. *Australas J Ultrasound Med*. 2020; 23: 210-219. [↗](#)
- 31 González-Alujás T, Evangelista A, Santamarina E, et al. Diagnosis and quantification of patent foramen ovale. Which is the reference technique? Simultaneous study with transcranial Doppler, transthoracic and transesophageal echocardiography. *Rev Esp Cardiol*. 2011; 64: 133-139. [↗](#)
- 32 Kumar P, Mojadidi MK, Tobis JM. Proper sizing of patent foramen ovale and grading of residual right-to-left shunt. *JACC Cardiovasc Interv*. 2021; 14: 106. [↗](#)
- 33 Turc G, Lee JY, Brochet E, et al. Atrial septal aneurysm, shunt size, and recurrent stroke risk in patients with patent foramen ovale. *J Am Coll Cardiol*. 2020 May; 75: 2312-2320. [↗](#)
- 34 Yetkin E, Ileri M, Korkmaz A, Ozturk S. Association between atrial septal aneurysm and arrhythmias. *Scand Cardiovasc J*. 2020; 54: 169-173. [↗](#)
- 35 Schuchlenz HW, Saurer G, Weihs W, Rehak P. Persisting eustachian valve in adults: relation to patent foramen ovale and cerebrovascular events. *J Am Soc Echocardiogr*. 2004; 17: 231-233. [↗](#)
- 36 Goel SS, Tuzcu EM, Shishehbor MH, et al. Morphology of the patent foramen ovale in asymptomatic versus symptomatic (stroke or transient ischemic attack) patients. *Am J Cardiol*. 2009; 103: 124-129. [↗](#)
- 37 Zhang Y, Wang H, Liu L. Patent foramen ovale closure for treating migraine: a meta-analysis. *J Interv Cardiol*. 2022; 2022: 6456272. [↗](#)