

The Role of Patent Foramen Ovale in Cryptogenic Stroke Kriptojenik İnmede Patent Foramen Ovalenin Rolü

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ABSTRACT

Introduction: Almost one-third of ischemic strokes has an unknown etiology and are classified as cryptogenic stroke. Paradoxical embolism because of a patent foramen ovale (PFO) is detected in 40%–50% of these patients. Recently, PFO has been reported as a risk factor for patients of all age groups.

Methods: In this study, 1080 ischemic stroke patients admitted to our clinic (2011–2013) were retrospectively evaluated. Age, sex, risk factors, complete blood count, vasculitis, biochemical and hypercoagulability tests, magnetic resonance imaging, magnetic resonance angiography, transthoracic echocardiography, transeosophageal echocardiography (TEE) findings, and therapeutic approaches were evaluated.

Results: The age range of the participants (seven male and four female patients) was 20–60 years (mean=43.09±11.13 years). Hemiparesis (n=10), diplopia (n=2), hemianopsia (n=2), and dysarthria (n=2) were the main findings of the neurological examinations. Patient medical history revealed hypertension (n=3), asthma (n=1), deep venous thrombosis (n=1), and smoking (n=4). Diffusion-weighted imaging

showed middle cerebral artery (n=8) and posterior cerebral artery (n=3) infarctions. In one case, symptomatic severe carotid stenosis was detected. In eight cases, TEE showed PFO without any other abnormalities, but PFO was associated with atrial septal aneurysm in two cases, and in one case it was associated with ventricular hypokinesia and pulmonary arterial hypertension. Antiplatelet therapy was applied to nine patients and percutaneous PFO closure operation to two patients. In a 2-year follow-up, no recurrent ischemic stroke was recorded.

Conclusion: PFO, especially in terms of the etiology of cryptogenic stroke in young patients, should not be underestimated. We want to emphasize the importance of TEE in identifying potential cardioembolic sources not only in young but also in all ischemic stroke patients with unknown etiology; we also discuss the controversial management options of PFO.

Keywords: Patent foramen ovale, stroke, transeosophageal echocardiography, atrial septal aneurysm

ÖZ

Amaç: İskemik inmelerin yaklaşık üçte birinde etyolojik sebep bulunamamakta ve bunlar kriptojenik inme olarak sınıflandırılmaktadır. Patent foramen ovaleye (PFO) bağlı paradoksal emboli bu hastalarda %40-50 oranında tespit edilmektedir. Son zamanlarda, PFO tüm yaş gruplarında bir risk faktörü olarak bildirilmektedir.

Yöntem: Bu çalışmada, kliniğimizde 2011-2013 yıllarında takip edilen 1080 iskemik inme hastası retrospektif olarak değerlendirildi. Yaş, cinsiyet, risk faktörleri, hemogram, biyokimya, vaskülit ve hiperkoagülabilité testleri, manyetik rezonans görüntüleme, manyetik rezonans anjiyografi, transtorasik ekokardiyografi ve transözofajal ekokardiyografi (TEE) bulguları ve tedavi yaklaşımları değerlendirildi.

Bulgular: Hastaların yaşları 20-60 yıl arasında olup (ortalama=43,09±11,13 yıl), 7'si erkek, 4'ü kadındı. Nörolojik muayenelerinde hemiparezi (n=10), diplopi (n=2), hemianopsi (n=2) ve dizartri (n=2) mevcuttu. Özgeçmişlerinde hipertansiyon (n=3), astım (n=1), derin ven trombozu (n=1) ve sigara (n=4) vardı. Difüzyon ağırlıklı görüntüleme-

de orta serebral arter (n=8) ve posterior serebral arter (n=3) infarktı görüldü. Bir hastada semptomatik ciddi karotis darlığı tespit edildi. Sekiz hastada, TEE'de başka anormallik olmaksızın PFO mevcutken, 2 olguda, atriyal septal anevrizma ve 1 olguda ise PFO, ventriküler hipokinezi ve pulmoner arteriyel hipertansiyon ile birlikteydi. Dokuz hastaya antiplatelet tedavi, 2 hastaya perkütan PFO kapatma işlemi uygulandı. İki yıllık takiplerinde, tekrarlayan iskemik inme gerçekleşmedi.

Sonuç: PFO, özellikle genç hastalarda kriptojenik inmenin etiyolojisinde göz ardı edilmemelidir. Bu çalışmada tüm yaş gruplarında nedeni bilinmeyen iskemik inme hastalarında potansiyel kardiyembolik nedenlerin belirlenmesinde TEE'nin önemini vurgulamak ve ayrıca PFO'nun tartışmalı tedavi seçeneklerinden söz etmek istedik.

Anahtar kelimeler: Patent foramen ovale, inme, transözofajal ekokardiyografi, atriyal septal anevrizma

INTRODUCTION

Approximately 40% of ischemic strokes with no clearly definable etiology are classified as cryptogenic stroke (1). The etiology of some cryptogenic strokes may be an embolus from the venous system traversing from the right to left atrium into the systemic circulation through a patent foramen ovale (PFO), a phenomenon known as paradoxical embolism (2). The first description regarding the association of PFO with stroke was in a young woman with cerebral arterial embolism by Cohnheim et al. (3) in 1877. At autopsy series of general population, the prevalence of PFO is 20–26% (4). However, PFO prevalence in cryptogenic strokes changes between 40% and 55.7% (5). A PFO located between the septum primum and septum secundum leads to the passage of fetal blood from the right atrium to the left atrium. In 75% of PFO cases, this



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opening closes after birth, but in 25% of cases, it remains open during the patient's lifetime (4). The presence of a PFO is usually discovered accidentally and has no clinical repercussions. Nevertheless, the possible association of PFOs with clinical signs and symptoms of embolic stroke, platypnea-orthodeoxia syndrome, and decompression sickness in divers and migraine has been reported (6,7,8,9). Atrial septal aneurysm (ASA) is an atrial septal abnormality occurring in the interatrial septum during systole and diastole. ASA is observed in 2% of the normal population, and half of these cases are associated with PFO. First-ever or recurrent stroke risk increases with the presence of ASAs because an ASA may cause thrombosis and is associated with large-sized PFOs (10). Recently, a possible correlation was emphasized between cryptogenic stroke and PFO in young and in elderly patients, and it was stated that PFO may be a risk factor for cryptogenic stroke in patients of every age group (11). In this study, the clinical and radiological features of stroke patients with PFO are assessed.

METHODS

We retrospectively evaluated 1080 ischemic stroke patients admitted to our clinic in 2011–2013, and 11 of the patients diagnosed with PFO were included in the study. Age, sex, risk factors, complete blood count, vasculitis, biochemical and hypercoagulability tests, magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), transthoracic echocardiography (TTE), transeosophageal echocardiography (TEE) findings, and therapeutic approaches were evaluated.

RESULTS

The age range of patients was 20–60 years (mean=43.09±11.13 years), and seven of the patients were males and four were females. Hemiparesis (n=10), diplopia (n=2), hemianopsia (n=2), and dysarthria (n=2) were the main presenting symptoms. The patients' medical history revealed hypertension (n=3), ischemic stroke (n=2), asthma (n=1), deep venous thrombosis (n=1), smoking (n=4), and alcohol use (n=1). Diffusion-weighted MRI showed middle cerebral artery (n=8; right=5, left=3) and posterior cerebral artery (n=3; right=1, left=2) infarctions. In seven patients, cranial MRI - MRA, and cervical MRA showed asymptomatic minor findings such as hypoplasia or small caliber. None of these findings were characterized as the stroke cause; however, only in one patient, severe stenosis/occlusion of the symptomatic side carotid artery was detected. The TTE reports were normal, only two patients revealed suspicious PFO findings. The TEE findings showed PFO in eight cases, PFO associated with ASA

in two cases, and PFO associated with ventricular hypokinesia and pulmonary arterial hypertension in one case. In one patient who had >90% ICA stenosis, further investigations showed total occlusion, and interventional or surgical options were not applied. All the patients were consulted with cardiology, and antiplatelet therapy was administered to nine patients and percutaneous PFO closure operation plus antiplatelet therapy was performed for two patients. In approximately 2-year follow-up, no recurrent ischemic stroke was recorded (Table 1).

DISCUSSION

The incidence of ischemic stroke is 169/100,000, and the annual incidence of first-ever ischemic stroke is 137–139/100,000. The incidence of ischemic stroke increases with age in both sexes, with a prominent increase in males (12). Because approximately 60% of these events can be attributed to conventional causes, the annual risk attributed to paradoxical embolism has been estimated at 28 per 100,000 persons with PFO per year (13). Mattle et al. (14) found PFO in 24% of healthy adults and in 38% of patients with cryptogenic stroke. In a study involving TTE, Di Tullio et al. (2) reported an increased prevalence of PFO in all age groups with cryptogenic stroke. A meta-analysis by Overell et al. (5) stated that in patients under the age of 55 years, PFO increases the stroke risk. One negative and two positive studies were published regarding the relationship of PFO with stroke in elderly patients after Overell's meta-analysis (11,15,16). Petty et al. suspect the association of PFO with stroke; however, the frequency of PFOs in their stroke group was only 13%, while the average was 32% in other studies (15). Two studies addressing the comparison of PFO in cryptogenic stroke and stroke from known causes indicated an association of PFO with stroke from unknown cause (11,16).

The risk of recurrent stroke in patients with PFO and ASA is greater than that in patients with PFO alone (17). Therefore, the role of TEE in the determination of the morphological structure of PFO and ASA is important and can help to predict the best future treatment protocols. The ASA prevalence in consecutive autopsy series was found to be 1% (18). ASA, a rare isolated irregularity in a majority of cases, is associated with other cardiac abnormalities such as PFO, atrial septal defects, and mitral valve prolapses. These abnormalities are also possible sources of cardiac emboli; thus, it is more difficult to establish the embolic potential of an ASA independently (19). In all age groups, ASA concomitant to PFO is more frequent in patients with cryptogenic stroke than in patients with stroke

Table 1. Distribution of findings and results of treatment options

Patient Number	Sex	Age (years)	Cranial MR	Cranial MRA	Medical treatment	Percutaneous closure	Recurrence of stroke
1	Male	50	PCA	AS	Yes	No	No
2	Male	39	MCA	N	Yes	No	No
3	Male	25	MCA	N	Yes	Yes	No
4	Female	41	MCA	AS	Yes	No	No
5	Male	26	MCA	AS	Yes	No	No
6	Female	60	MCA	N	Yes	No	No
7	Male	56	MCA	AS	Yes	Yes	No
8	Female	39	MCA	N	Yes	No	No
9	Female	52	PCA	AS	Yes	No	No
10	Male	44	PCA	N	Yes	No	No
11	Male	42	MCA	Left ICA severe stenosis (>90%)	Yes	No	No

MR: magnetic resonance; MRA: magnetic resonance angiography; PCA: posterior cerebral artery; MCA: middle cerebral artery; ICA: internal carotid artery; ACA: anterior cerebral artery; AS: asymptomatic minor findings; N: normal

from known cause. The meta-analysis of all case-control studies shows an association with 30% probability in all patients with cryptogenic strokes, 17% in patients younger than 55 years, and 37% in patients older than 55 years (14). In a study by Mas et al. (20) conducted on PFO patients aged 18–55 years with cryptogenic stroke history, the risk of recurrent stroke in a period of 4 years was 2.3%, while in patients with ASA and PFO, the recurrent stroke risk was higher. However, there was no recurrent stroke history in patients with ASA alone. The authors suggested that the association of PFO with ASA has a higher risk of paradoxical embolism. On the contrary, Di Tullio et al. (21) reported a weak correlation between either ASA alone or with PFO and recurrent stroke considering the low ASA incidence (1%–4%) in the general population. Additionally, Meissner et al. (22) emphasized that ASA and PFO association did not increase the risk of stroke recurrence. In our small study group, because there were only two patients with PFO associated with other defects, we postulate that patients with PFO and ASA carry a higher risk of recurrent stroke.

The studies regarding the relationship between PFO and stroke have generally included patients younger than 55 years. In a study conducted by Handke et al., TEE was performed in patients younger and older than 55 years, aiming to determine an etiologic relationship between PFO and cryptogenic stroke. This relationship was stronger in patients with PFO associated with ASA. In addition to these findings, in elderly patients with cryptogenic stroke and PFO, lesser aortic atherosclerosis was found than that in patients with cryptogenic stroke without concomitant PFO, reinforcing the pathogenic role of PFO. It was also shown that the relationship of PFO in cryptogenic stroke in both younger (odds ratio, 3.70; 95% CI, 1.42–9.65; $p=0.008$) and older (odds ratio, 3.00; 95% CI, 1.73–2.3; $p<0.001$) PFO groups was independent of factors such as age, plaque thickness, presence or absence of coronary artery disease, and hypertension (11). Furthermore, Force et al. (16) demonstrated a relationship between cryptogenic stroke and PFO in patients older than 55 years. In our study, only two patients were older than 55 years, and TEE was performed mostly in the group of patients younger in age, which introduces limitations to our contribution to the subject.

Transeosophageal echocardiography is superior to TTE in the diagnosis and evaluation of PFO morphology. Today, TEE is the gold standard technique in diagnosing PFO. For the evaluation of cardiac pathologies in patients with cardiac symptoms, the TTE has a ratio of 25%. This ratio decreases to 10% in asymptomatic patients (23). In a previous study, the specificity of TEE and TTE in diagnosing PFO was 100% for both techniques; however, their sensitivities were 53.8% and 21.4%, respectively (24).

The Valsalva maneuver is an inseparable part of the echocardiography examination. In cryptogenic stroke patients, the presence of the Valsalva maneuver before the appearance of focal neurologic symptoms might be a clue for diagnosing paradoxical embolic events. Increasing right atrial pressure, by weight lifting, coughing, vomiting, sexual activity, straining, or similar maneuvers can cause the formation of right to left shunts or the aggravation of a present one. In a study, among PFO patients with transient ischemic stroke (TIA) or stroke, the presence of the Valsalva maneuver preceding symptoms was detected in 16% of the patients (17). Lynch et al. (25) performed TEE with the saline contrast technique in the resting position in 76 healthy volunteer patients. The right to left shunt prevalence was found to be 5%, meanwhile the prevalence was found to be 18% during the Valsalva maneuver. In the SPARC study, the right to left shunt prevalence during the Valsalva maneuver and coughing-like mechanisms was increased from 14% to 23% (10). The ratio of the presence of the Valsalva maneuver previous to stroke is reported to be 27% (26). In our study, one patient had a history of Valsalva maneuver before stroke episode.

In patients with PFO, different treatment options have been used in preventing the recurrence of ischemic episodes. Although warfarin is the tra-

ditional treatment of choice in preventing secondary stroke episodes, in a study that compared warfarin and aspirin treatment, no significant difference was found during a two year follow-up period (27). According to the 2011 American Heart Association/American Stroke Association criteria, anticoagulant treatment is only suggested in hypercoagulability cases (28). In 2012, the American College of Chest Physicians stated that in cryptogenic stroke and PFO patients, antiplatelet treatment should be used instead of anticoagulant treatment (29). The superiority of medical treatment or percutaneous closure as the secondary prevention of stroke in these patients still is not well established. In a study by STARFLEX, a septal closure system was compared to medical treatment and it was stated that septal closure was superior in preventing mortality because of recurrent stroke (30). Furlan et al. (31) compared percutaneous closure together with antiplatelet treatment to medical treatment alone in 18–60-year-old PFO patients presenting with TIA or stroke episodes. In a two years follow-up, no significant differences were found in the recurrence of stroke or TIA. Although risk factors such as age, hypertension, diabetes mellitus, coronary artery disease, cerebrovascular accident, or enlargement of the left atrium may suggest closure of the PFO, following cardiology consultations only two patients underwent a surgical procedure, and the other nine patients had antiplatelet therapy, similar to the literature.

In conclusion, PFO, especially in terms of the etiology of cryptogenic stroke in young patients should not be underestimated. TTE examination is important in this regard, however, especially in cases of suspected TTE, TEE is strictly suggested. We want to emphasize the importance of TEE in identifying PFO, potential cardioembolic sources, not only in young but all ischemic stroke patients with unknown etiology. Most of our patients had medical therapy, so we could not compare the results of percutaneous closure or antiplatelet treatments accurately, however, recent studies have shown no differences in superiority between them.

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REFERENCES

1. 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; 25:382-390. [\[CrossRef\]](#)
2. Di Tullio M, Sacco R, Gopal A, Mohr JP, Homma S. Patent foramen ovale as a risk factor for cryptogenic stroke. *Ann Intern Med* 1992; 117:461-465. [\[CrossRef\]](#)
3. Cohnheim J. *Trombose und Embolie* In: *Vorlesung über Allgemeine Pathologie*. Berlin, Germany: Hirschwald, 1877; 134.
4. 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. [\[CrossRef\]](#)
5. Overall JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000; 55:1172-1179. [\[CrossRef\]](#)
6. Medina A, de Lezo JS, Caballero E, Ortega JR. Platypnea-orthodeoxia due to aortic elongation. *Circulation* 2001; 104:741. [\[CrossRef\]](#)
7. Torti SR, Billinger M, Schwerzmann M, Vogel R, Zbinden R, Windecker S, Seiler C. Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. *Eur Heart J* 2004; 25:1014-1020. [\[CrossRef\]](#)
8. Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla Volta G. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. *Neurology* 1999; 52:1622-1625. [\[CrossRef\]](#)

9. Domitrz I, Mieszkowski J, Kwiecieński H. The prevalence of patent foramen ovale in patients with migraine. *Neural Neurochir Pol* 2004; 38:89-92.
10. Meissner I, Whisnant JP, Khandheria BK, Spittell PC, O'Fallon WM, Pascoe RD, Enriquez-Sarano M, Seward JB, Covalt JL, Sicks JD, Wiebers DO. Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study: Stroke Prevention: Assessment of Risk in a Community. *Mayo Clin Proc* 1999; 74:862-869. [\[CrossRef\]](#)
11. 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. [\[CrossRef\]](#)
12. Alzamora MT, Sorribes M, Heras A, Vila N, Vicheto M, Forés R, Sánchez-Ojanguren J, Sancho A; "ISISCOG Study Group"; Pera G. Ischemic stroke incidence in Santa Coloma de Gramenet (ISISCOG), Spain. A community-based study. *BMC Neurol* 2008; 8:5.
13. Kraywinkel K, Jauss M, Diener HC, Weimar C. Patent foramen ovale, atrial septum aneurysm, and stroke. An examination of the status of recent evidence. *Nervenarzt* 2005; 76:935-942. [\[CrossRef\]](#)
14. Mattle HP, Meier B, Nedeltchev K. Prevention of stroke in patients with patent foramen ovale. *Int J Stroke* 2010; 5:92-102. [\[CrossRef\]](#)
15. Petty GW, Khandheria BK, Meissner I, Whisnant JP, Rocca WA, Christianson TJ, Sicks JD, O'Fallon WM, McClelland RL, Wiebers DO. Population-based study of the relationship between patent foramen ovale and cerebrovascular ischemic events. *Mayo Clin Proc* 2006; 81:602-608. [\[CrossRef\]](#)
16. Force M, Massabuau P, Larrue V. Prevalence of atrial septal abnormalities in older patients with cryptogenic ischemic stroke or transient ischemic attack. *Clin Neurol Neurosurg* 2008; 110:779-783. [\[CrossRef\]](#)
17. Lamy C, Giannesini C, Zuber M, Arquizan C, Meder JF, Trystram D, Coste J, Mas JL. Clinical and imaging findings in cryptogenic stroke patients with or without patent foramen ovale. The PFO-ASA Study.
18. Silver MD, Dorsey JS. Aneurysms of the septum primum in adults. *Arch Pathol Lab Med* 1978; 102:62-65.
19. Ghosh S, Ghosh AK, Ghosh SK. Patent foramen ovale and atrial septal aneurysm in cryptogenic stroke. *Postgrad Med J* 2007; 83:173-177. [\[CrossRef\]](#)
20. Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeaux G, Coste J; Patent Foramen Ovale and Atrial Septal Aneurysm Study Group. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med* 2001; 345:1740-1746. [\[CrossRef\]](#)
21. Di Tullio MR, Sacco RL, Sciacca RR, Jin Z, Homma S. Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. *J Am Coll Cardiol* 2007; 49:797-802. [\[CrossRef\]](#)
22. Meissner I, Khandheria BK, Heit JA, Petty GW, Sheps SG, Schwartz GL, Whisnant JP, Wiebers DO, Covalt JL, Petterson TM, Christianson TJ, Agmon Y. Patent foramen ovale: innocent or guilty? Evidence from a prospective population-based study. *J Am Coll Cardiol* 2006; 47:440-445. [\[CrossRef\]](#)
23. Rahmatullah AF, Rahko PS, Stein JH. Transesophageal echocardiography for the evaluation and management of patients with cerebral ischemia. *Clin Cardiol* 1999; 22:391-396. [\[CrossRef\]](#)
24. Clarke NR, Timperley J, Kelion AD, Banning AP. Transthoracic echocardiography using second harmonic imaging with Valsalva manoeuvre for the detection of right to left shunts. *Eur J Echocardiogr* 2004; 5:176-181. [\[CrossRef\]](#)
25. Lynch JJ, Schuchard GH, Gross CM, Wann LS. Prevalence of right-to-left atrial shunting in a healthy population: detection by Valsalva maneuver contrast echocardiography. *Am J Cardiol* 1984; 53:1478-1480. [\[CrossRef\]](#)
26. Kitsios GD, Lasker A, Singh J, Thaler DE. Recurrent stroke on imaging and presumed paradoxical embolism: A cross-sectional analysis. *Neurology* 2012; 78:993-997. [\[CrossRef\]](#)
27. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP; PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: Patent Foramen Ovale in Cryptogenic Stroke Study. *Circulation* 2002; 105:2625-2631. [\[CrossRef\]](#)
28. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke* 2011; 42:227-276. [\[CrossRef\]](#)
29. Lansberg MG, O'Donnell MJ, Khatri P, Lang ES, Nguyen-Huynh MN, Schwartz NE, Sonnenberg FA, Schulman S, Vandvik PO, Spencer FA, Alonso-Coello P, Guyatt GH, Akl EA; American College of Chest Physicians. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141:e601S-365.
30. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, Felberg R, Herrmann H, Kar S, Landzberg M, Raizner A, Wechsler L; CLOSURE I Investigators. Study design of the CLOSURE I trial: a prospective, multicenter, randomized, controlled trial to evaluate the safety and efficacy of the STARFlex septal closure system versus best medical therapy in patients with a stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramen ovale. *Stroke* 2010; 41:2872-2883. [\[CrossRef\]](#)
31. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, Felberg R, Herrmann H, Kar S, Landzberg M, Raizner A, Wechsler L; CLOSURE I Investigators. Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale. *N Engl J Med* 2012; 366:991-999. [\[CrossRef\]](#)