Prevalence of left atrial septal pouch among patients with embolic stroke of undetermined source or stroke of known etiology: A retrospective study

Hugo Steyaert¹#, Jose Castro Rodriguez²#, Marie-Dominique Gazagnes³, Marielle Morissens²

¹Université Libre de Bruxelles, Brussels 1050, Belgium; ²Cardiology Department, CHU Brugmann, Université Libre de Bruxelles, Brussels 1020, Belgium; ³Neurology department, CHU Brugmann, Université Libre de Bruxelles, Brussels 1020, Belgium

ABSTRACT

Background and objectives: Cryptogenic strokes can be defined by the criteria established for an embolic stroke of undetermined source (ESUS). Some embolic events might be caused by a left atrial septal pouch (LASP), due to the potential of thrombus formation. In this study we aimed to determine if LASP is a risk factor for ESUS when compared to a population of strokes of known origin, the LASP screening rate in our institution and if LASP dimensions influences the risk of ESUS. Methods: We retrospectively analyzed transesophageal echocardiograms (TEEs) in a large cohort of patients that had experienced ischemic strokes. Two authors performed blinded, independent searches for LASPs by reviewing 1152 TEEs from patients that had experienced a stroke or transient ischemic attack. We excluded 26 TEEs, due to incorrect imaging. Next, we reviewed patient medical files. Results: Among the 1126 included patients, 148 had an ESUS (ESUS+ group) and 978 had strokes of known origin (ESUS– group). A LASP was present in 176 patients, including 32 patients (21.6% of LASPs) in the ESUS+ group and 144 patients (14.7% of LASPs) in the ESUS– group. In multivariate analysis, LASP was independently associated with ESUS (P = 0.019). 61.9% of LASPs that we found were not mentioned in reports from the original TEE operators. Conclusion: This study demonstrated that LASPs were more prevalent in patients with ESUS than in patients with strokes of known origin. Our results gave rise to the question of whether anticoagulation would be appropriate for some patients with ESUS. New large-scale, prospective studies should be conducted to address this issue. Additionally, considering the low rate of LASP descriptions, we concluded that the awareness of operators should be raised to improve their success in identifying LASPs.

Key words: cryptogenic stroke, embolic stroke of undetermined source, left atrial septal pouch, transesophageal echocardiography

INTRODUCTION

Strokes can be divided into two main groups: ischemic, which includes nearly 85% of strokes, and hemorrhagic, which includes the other 15%.² In approximately 40% of cases, no origin is found³ and they are referred to as cryptogenic strokes.

One of the first definitions of cryptogenic stroke was included in the classification of the Trial of Org in Acute Stroke Treatment (TOAST), which was proposed in 1993.⁴ The major concern about the TOAST classification is that a stroke can be classified as cryptogenic, simply because a complete workup was not performed to determine its etiology. For example, the TOAST classification does not consider results from the latest imaging modalities, such as magnetic resonance angiography (MRA) or rhythm monitoring for detecting atrial fibrillation (AF). MRA was first introduced in 1992,⁵ and currently, it has replaced or is used to complement
color-coded Doppler ultrasound. With these advances in diagnostic technology, new classifications have been developed as the causative classification system (CCS) and the Chinese ischemic stroke sub classification (CISS).\cite{6,7} Consequently, in 2014, a strict definition was suggested for strokes without known origins, and this stroke category was called the Embolic Stroke of Undetermined Source (ESUS).\cite{8,9} An ESUS is a non-lacunar cerebral infarct, where a proximal stenosis or major thromboembolism cannot be identified in an extensive workup. The workup should include ECG-Holter monitoring to detect AF, echocardiography to search for cardiac sources of the embolism, and MRA and Doppler ultrasound to exclude intra- and extra-cranial arterial stenosis.\cite{6,9} The criteria for diagnosing embolic stroke of undetermined source (ESUS): (1) Ischemic stroke that is not lacunar detected by computed tomography (CT) or magnetic resonance imaging (MRI). Lacunar stroke is defined as a subcortical infarct ≤1.5 mm (CT) or ≤2 mm (MRI); (2) Absence of extracranial or intracranial atherosclerosis that causes ≥50% lumen stenosis in arteries that supply the region of infarction; (3) No major cardioembolic risk that could indicate the source of the embolism. Examples of risk factors: permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, intracardiac tumor, mitral stenosis, recent myocardial infarction (<4 weeks), left ventricular ejection fraction <30%, valvular vegetation or infective endocarditis, or any condition that requires a minimum diagnostic evaluation that includes rhythm monitoring for more than 24 h; (4) No other specific cause of stroke identified (e.g., arteritis, dissection, vasospasm, drug abuse).\cite{10}

Recently, a left atrial septal pouch (LASP) abnormality was suspected to be involved in ESUS. LASPs may be present in up to 25% of patients. A LASP results from an incomplete fusion of the primum and secundum septum, where a pouch is formed on the left side, without an atrial shunt. A LASP is thus defined as the fusion of septum primum and septum secundum at the caudal end of the foramen oval with a flap on the left side creating a pouch that opens towards the left atrium. A pouch may also form on the right side or even bilaterally.\cite{10,11} As reported regularly in case reports,\cite{12-19} a LASP can cause the formation of thrombi, and therefore, it could give rise to embolic events.

Several studies have investigated a potential association between a LASP and cryptogenic stroke, but they have reported contradictory results.

Tugcu et al.,\cite{24} Wayangakar et al.,\cite{21} and Strachinaru et al.\cite{22-23} did not find an association between LASP and cryptogenic stroke. Sun et al.\cite{28} found an association between LASP and stroke. Wong et al.,\cite{24} Yilmaz,\cite{26} Holda et al.\cite{27-28} and more recently Kapoor et al.\cite{29} all found an association between cryptogenic stroke and the presence of a LASP.

Those studies have had several weaknesses, including a small number of patients, a weak definition of cryptogenic stroke, based on the TOAST criteria, and comparisons with a control group without stroke rather than comparing to patients with strokes of known origin.

Here, we undertook a retrospective analysis of transeosophageal echocardiograms (TEEs) in a large, monocentric cohort of patients that presented with an ischemic stroke. This study had three aims: (1) To determine whether a LASP might predispose to an ischemic stroke of undetermined origin. (2) To determine the LASP screening rate in our Cardiology department. (3) To determine whether the pouch dimensions might influence the risk of developing an ESUS.

**MATERIAL AND METHOD**

**Study groups**

Between June 2012 and March 2021, 1714 patients underwent a TEE for a suspected stroke or transient ischemic attack (TIA) in our clinic of Cardiology. For the present study, we retrieved all these TEEs from our existing database. We excluded TEEs of patients with another final diagnosis (e.g., epilepsy, migraine, dizziness, medication, metabolic toxicity etc.). Next, two observers (the first author and an experienced echocardiographist) independently performed blinded reviews (i.e., without knowledge of the stroke classification) of the remaining 1152 patient TEEs to look for inter-atrial septum morphology that indicated a LASP. Due to incorrect imaging of the interatrial septum, 26 TEEs were excluded. The final analyses included 1126 TEEs (Figure 1). The Ethics Committee of Brugmann's Hospital, Brussels, approved this study (CE 2021/23).

Next, we reviewed the medical files of all included patients to collect demographic data, medical histories, and information about the type of ischemic stroke. Strokes were evaluated with the ESUS criteria. An ESUS was defined as a non-lacunar cerebral infarct without proximal stenosis or a major identified thromboembolic cause, based on an extensive workup. The workup included rhythm monitoring for more than 24 h to detect AF, echocardiography to identify the cardiac source of the embolism, and an MRA and Doppler ultrasound to exclude intra- and extra-cranial arterial stenoses.

Patients were divided according to the type of stroke, as follows: patients with ESUS (ESUS+ group, N = 148) and patients with strokes of known origin (ESUS− group,
This study design was adopted to avoid a selection bias in the control group, and it allowed a direct comparison with previous studies on the patent foramen oval (PFO).\cite{30,31}

**Population characteristics**

Data were collected from a detailed examination of patient medical files. A smoker was defined as an individual that consumed tobacco currently or at any time in the past. Diabetes was defined as a fasting blood glucose level $\geq 126$ g/L, based on two different samplings; a self-reported history of diabetes; or the use of a medication for diabetes (insulin or an oral anti-diabetic drug). Hypertension was defined as a mean blood pressure $>140/90$ mmHg, based on at least two readings during the hospital stay, or the use of an antihypertensive medication. Hypercholesterolemia was defined as a total serum cholesterol level $>190$ mg/dL; a low-density lipoprotein cholesterol level $>100$ mg/dL, for patients without cardiac risk factors, or $>70$ mg/dL, for patients with cardiac risk factors; or the use of any lipidlowering drug. Obesity was defined according to the body mass index, where values above $30$ kg/m$^2$ were considered diagnostic of obesity. A history of stroke was defined as any mention of a stroke or a TIA in the medical history of the patient. Arteritis was defined as a mention of arteritis in the medical file or signs of arteritis noted during the hospitalization. Coronary artery disease (CAD) was defined as the presence of a known CAD, based on invasive or non-invasive imaging, or a past history of myocardial infarction, stenting, or bypass surgery. AF was defined as a history of documented AF or a new episode detected with Holter-ECG monitoring for one week (or telemetry for more than 24 h).

**Transesophageal echocardiography**

When we examined TEEs, we looked carefully at the interatrial septum from several views. TEEs were performed with the injection of agitated saline at rest and during a Valsalva maneuver. Abnormalities included a PFO (considered present, when bubbles appeared in the left atrium within 3 cardiac cycles following opacification of the right atrium), an atrial septal aneurysm (defined as a septum excursion greater than 10 mm measured in TM mode), and a LASP.

A LASP was defined as a visible, incomplete fusion of the septum primum and septum secundum on the left side, in the absence of shunting across the inter atrial septum, based on a contrast injection (Figure 2). When contrast injection to exclude a PFO was not discriminating we classified the patients as having no LASP. The length and width of the LASP were also recorded.

**Statistical analysis**

Continuous data are presented as the mean and standard deviation; categorical variables are expressed as the proportion ($\%$). Differences between proportions were evaluated with the chi-square test. Differences between mean values were evaluated with the $t$-test. Associations between all factors and the type of stroke were assessed with multivariate binary logistic regression analysis.
All analyses were performed with SPSS software (version 27, IBM 2020, Armonk, NY, USA). P-value < 0.05 were considered significant.

RESULTS

Patient demographics
The study population of 1126 subjects (Table 1) included 148 patients with ESUS+, with a mean age of 62.7 years, and 978 patients with ESUS−, with a mean age of 67.3 years (P = 0.396). As expected, smoking, diabetes, arterial hypertension, hypercholesterolemia, obesity, history of stroke, arteritis, and CAD were less common in the ESUS+ group than in the ESUS− group. No other significant differences in demographics were found between groups.

LASP as a predisposing factor for ESUS
LASP was present in 176 patients. Among these, 32 patients (21.6%) were in the ESUS+ group and 144 patients (14.7%) were in the ESUS− group. Results of univariate and multivariate analysis are shown in Table 2. The prevalence of LASP was higher in the ESUS+ than in the ESUS− group and multivariate analysis shows that LASP is independently associated with ESUS (P = 0.019). Figure 3 shows the odd ratio (OR) for having a cryptogenic stroke, defined with

![Figure 2: Plane view of a left atrial septal pouch (arrow) during an injection of agitated saline in the right atrium. LA: left atrium; RA: injected right atrium.](image_url)

| Table 1. Determinants of embolic stroke of undetermined source |
|---------------------------------------------------------------|
| **Factors** | **ESUS+ (N = 148)** | **ESUS− (N = 978)** | **P-value (Univariate)** | **P-value (Multivariate)** |
| LASP (%) | 22 | 15 | 0.031 | 0.019 |
| Age (mean) | 62.7 | 67.3 | <0.001 | 0.023 |
| Female sex (%) | 48 | 43 | 0.29 | - |
| Smoker (%) | 20 | 46 | <0.001 | <0.001 |
| Diabetes (%) | 10 | 39 | <0.001 | <0.001 |
| Hypertension (%) | 56 | 81 | <0.001 | 0.004 |
| Dyslipidemia (%) | 63 | 83 | <0.001 | 0.035 |
| Obesity (%) | 11 | 41 | <0.001 | <0.001 |
| Antecedent stroke (%) | 13 | 19 | 0.07 | - |
| Arteriopathy (%) | 1 | 6 | 0.007 | 0.367 |
| Coronaropathy (%) | 3 | 15 | <0.001 | 0.024 |

LASP: left atrial septal pouch; ESUS: embolic stroke of undetermined source.
ESUS criteria.

**Evolution of the LASP screening rate**
Descriptions of LASP detected by the original TEE operators slowly increased over time ($P = 0.015$). Among the LASPs reported in our population, only 16.66% were reported in 2012, and more than 50% were reported in the last 4 years (2018 to 2021; Figure 4).

**Association between LASP dimensions and ESUS**
The mean LASP length and width were 11.72 mm and 2.80 mm, respectively. The mean LASP dimensions were almost the same between the ESUS$^-$ group (length: 11.59 mm and width: 2.82 mm) and in the ESUS$^+$ group (length: 12.33 mm and width: 2.74 mm). No significant difference was observed between groups ($P = 0.398$ for the length and $P = 0.681$ for the width). No thrombi were found in any of the LASPs.

Figure 3: Graphic representation of odd ratio (OR). LASP: left atrial septal pouch; ESUS: embolic stroke of undetermined source; HTA: Hypertension.

Figure 4: Evolution of the rate of detecting a left atrial septal pouch, from 2012 to 2021.
DISCUSSION

Left atrial septal pouch was first described on autopsied hearts and its prevalence is high, reaching almost 50%. Holda et al. proposed that the fusion of septum primum with septum secundum is a lifelong continuous process leading to a spectrum of incomplete fusions (PFO, LASP and right atrial septal pouch) where the most incomplete fusion, represented by the PFO, is more prevalent at a younger age. These authors analyzed the anatomical features of these pouches on autopsied hearts and found that LASP has a complex shape with secondary diverticula that promote stasis and can lead to thrombi formation.

In addition to the pouch morphology, other factors have been proposed to favor thrombus formation. One essential factor is circulatory stasis, which is of course the case in atrial fibrillation but also in situations where left atrial pressure rises, like in mitral stenosis or heart failure. Another possible mechanism could be endothelial injury with inflammatory, as described in a histopathology of a resected thrombus.

As a consequence of this thrombogenic potential it is logical to think that LASP is not only an innocent structure but could be a cause of stroke. However, the clinical importance of LASP is still debated.

Previous studies that investigated the potential impact of a LASP on stroke risk have presented divergent results. Holda et al. performed a retrospective study to compare patients with stroke to controls without stroke. They found an association between the presence of a LASP and the development of a cryptogenic stroke. Wong et al. showed similar results in comparing patients with cryptogenic strokes, defined with the TOAST criteria, and patients with strokes of known origin.

Recently, a retrospective study by Kappor et al. demonstrated that patients with LASP had a significantly increased risk of cryptogenic stroke. However, they also used the modified TOAST criteria and compared a stroke group to a control group without stroke.

In contrast, Tugcu et al., in 2010, and Wayangankar et al., in 2012, did not find any association between LASP and stroke, when they compared patients with stroke to controls without stroke. However, both studies included a small number of patients with cryptogenic stroke (respectively, 69 and 44 patients), defined with the TOAST criteria. Similarly, Strachinaru et al., in 2016, could not find an association between LASP and cryptogenic stroke, when they compared a cryptogenic stroke group, defined with the TOAST criteria, to a control group without stroke.

Our study included a large number of patients, and we found a strong association between the presence of a LASP and ESUS. Unlike most previous studies, we defined a cryptogenic stroke with precise criteria (ESUS criteria). Our definition included a more complete workup and updated tools for investigating the origin of the ischemic stroke. Furthermore, we compared two groups of patients with different types of strokes, which prevented a selection bias and reinforced our results.

Our overall LASP prevalence was 15.6%. Based on a review of the TEEs, we found that 61.9% of LASPs were not mentioned by the original TEE operators. However, we noted that this discordance progressively declined over time (P = 0.015); in 2012, 83.4% of LASPs were not mentioned in the original reports; but in 2021, only 40% of LASPs were not mentioned in the original reports. This increase in the rate of LASP descriptions indicated an increased awareness among cardiologists to this newly described structure.

Nevertheless, the prevalence of LASPs was far lower than the LASP prevalence reported previously for autopsied patients. Krishnan and Salazar reported a 39% prevalence in their series, Holda et al. a 47% prevalence and Klimek-Piotrowska et al. reported a 50% prevalence. This difference in prevalence observed between autopsy studies and in vivo studies could likely be explained by the pressure regimen on the foramen oval membrane in a living heart, which is very different from the pressure in a bloodless heart. Some of the pouches observed during autopsies probably did not display any signs in vivo.

Although previous reports have shown that thrombi can occur in these pouches, we did not find any thrombi in the 176 LASPs that we reviewed (although we have already seen thrombus in a LASP in a patient not included in the present study because stroke was not the indication for TEE, Figure 5). One explanation could be that the LASP is a small, non-trabeculated pouch, and thus, thrombi are not retained for long times. Two recent studies compared anticoagulation to antiplatelet therapy in patients with ESUS, but neither study could show superiority. A third study is still ongoing. These negative results could be explained by the heterogeneity of embolic source in ESUS patients. Nevertheless, the thrombus observations and our results have given rise to the question of whether it might be appropriate to prescribe anticoagulation therapy to some patients with a LASP that experienced an ESUS.

Our study was designed to evaluate cryptogenic stroke, which, by definition, excludes atrial fibrillation. This was done with a quite strong workup, even stronger than it was done in other studies, as in CLOSE study for example.

The role of AF and other factors (as coagulation abnormalities for example) in thrombus formation in a LASP could be an
interesting subject to study.

Our study also demonstrated that the anatomical dimensions of the LASP were not associated with an ESUS. Therefore, special attention should be given to even small pouches during routine examinations. Future studies should confirm this result with larger patient cohorts.

STUDY LIMITATIONS

The main limitation of this single-center study was its retrospective design. Thus, the TEE procedure was not designed to search for LASPs, in particular. However, all the TEEs in both groups were reviewed blindly by two independent observers, which prevented potential biases in data collection. Contrast injection to exclude a PFO was sometimes not discriminating and these patients where therefore classified as having no LASP, this could induce an underestimation of LASPs. Another potential limitation was the relatively small number of patients in the ESUS+ group (148 patients). However, to our knowledge, this was the largest ESUS+ cohort studied to date.

CONCLUSION

To our knowledge this is the first study on LASP, to date, to use ESUS definition for classifying a cryptogenic stroke. We found a higher prevalence of LASP in patients with ESUS compared to patients with strokes of known origin. Given this result, we recommend that patients with a cryptogenic stroke should be routinely screened for the presence of a LASP. Moreover, our results gave rise to the question of whether anticoagulation might be an appropriate treatment for some patients with a LASP that presented an ESUS. Future, large-scale, prospective studies should be conducted to address this issue.

We also found that the rate of describing LASPs was low among TEE operators. Therefore, we strongly recommend that TEE operators should be made aware of the importance of searching for LASPs in TEEs.

Ethics Approval

The Ethics Committee of Brugmann’s Hospital, Brussels, approved this study (CE 2021/23).

Conflict of Interest

None declared.

REFERENCES

1. Thrift A, Cadilhac D, Thayabaranathan T, Howard G, Howard V, Rothwell P, et al. Global stroke statistics. Int J Stroke 2013;9:6–18.
2. Mozaffarian D, Benjamin E, Go A, Arnett D, Blaha M, Cushman M, et al. Executive summary: Heart disease and stroke statistics-2016 Update. Circulation 2016;133:447–54.
3. Sacco RL, Ellenberg JH, Mohr JP, Tatemichi TK, Hier DB, Price TR, et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. Ann
Steyaert et al.: Left atrial septal pouch as a risk factor for embolic stroke of undetermined source

4. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. 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.

5. Anderson CM, Saloner D, Lee RE, et al. Assessment of carotid artery stenosis by MR angiography: comparison with x-ray angiography and color-coded Doppler ultrasound. Am J Neuroradiol 1992;13:989–1003.

6. Chen P, Gao S, Wang Y, Xu A, Li Y, Wang D. Classifying ischemic stroke, from TOAST to CISS. CNS Neurosci Ther 2012;18:452–6.

7. Yaghi S, Bernstein R, Passman R, Okin P, Furie K. Cryptogenic stroke: Research and Practice. Cir Res 2017;120:527–40.

8. Hart R, Diener H, Coutts S, Easton J, Granger C, O’Donnell M, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13:429–38.

9. Hart R, Catenese I, Perera K, Ntaios G, Connolly S. Embolic stroke of undetermined source: A Systematic Review and Clinical Update. Stroke 2017;48:867–72.

10. Holda M, Koziej M, Wszołek K, Pawlik W, Krawczyk-Ożog A, Sorysz D, et al. Left atrial accessory appendages, diverticula, and left-sided septal pouch in multi-slice computed tomography. Association with atrial fibrillation and cerebrovascular accidents. Int J Cardiol 2017;244:163–8.

11. Holda M, Koziej M, Holda J, Piattek K, Tyraż K, Cholopiak W, et al. Atrial septal pouch-Morphological features and clinical considerations. Int J Cardiol 2016;220:337–42.

12. Gurudevan SV, Shah H, Tolstrup K, Siegel R, Krishnan SC. Septal thrombus in the left atrium: is the left atrial septal pouch the culprit? JACC Cardiovasc Imaging 2010;3:1284–6.

13. Kuwaki H, Takeuchi M, Kaku K, Haruki N, Yoshitani H, Tamura M, et al. Thrombus attached to the left atrial septal pouch assessed on 3-dimensional transesophageal echocardiography. Circ J 2011;75:2280–1.

14. Strachinaru M, Morissens M, Latifiyan S, Costescu I. Left atrial septal pouch thrombus assessed on three-dimensional transoesophageal echocardiography. Eur Heart J Cardiovasc Imaging 2012;13:967.

15. Shimamoto K, Kawagoe T, Dai K, Inoue I. Thrombus in the left atrial septal pouch mimicking myxoma. J Clin Ultrasound. Wiley 2014;42:185–8.

16. Bandypadhyay S, Mandal R. Left atrial septal pouch: a potential source of systemic thromboembolism: incidental transesophageal echocardiogram findings. Anesth Analg 2015;121:59–61.

17. Aggarwal S, Kalavakunta J, Gupta V. Left atrial septal pouch thrombus: a common pathology in an uncommon location. Int J Cardiol 2016;212:369–70.

18. Strachinaru M, Wauthy P, Sanoussi A, Morissens M, Costescu I, Catez E. The left atrial septal pouch as a possible location for thrombus formation. Journal of Cardiovascular Medicine 2017;18:713–4.

19. Ohanany A, Cuminetti G, Morissens M. Beware of the LASPI! A structure with thrombogenic potential. Echocardiography 2019;37:152–3.

20. Tugcu A, Okajima K, Jin Z, Rundek T, Homma S, Sacco R, et al. Septal pouch in the left atrium and risk of ischemic stroke. JACC: Cardiovasc Imaging 2010;3:1276–83.

21. Wayangankar SA, Patel JH, Patel B, Stavrakis S, Sivaram CA. Clinical and echocardiographic variables associated with LA septal pouch. JACC: Cardiovasc Imaging 2013;6:833–5.

22. Strachinaru M, Catez E, Jousten I, Pavel O, Janssen C, Morissens M, et al. The left atrial septal pouch as a possible risk factor for stroke. Echocardiography 2016;33:1016–23.

23. Strachinaru M, Castro-Rodriguez J, Verbeet T, Gazagnes M. The left atrial septal pouch as a risk factor for stroke: A systematic review. Arch Cardiovasc Dis 2017;110:250–8.

24. Wong J, Lombardo D, Barseghian A, Dhoot J, Hundal H, Salcedo J, et al. Left atrial septal pouch in cryptogenic stroke. Front Neurol 2015;6:57.

25. Sun JP, Meng F, Yang XS, Lee AP-W, Chen M, Zhang R, et al. Prevalence of atrial septal pouch and risk of ischemic stroke. Int J Cardiol 2016;214:37–40.

26. Yilmaz M, Vural MG, Karcaaltincaba M, Yoldas TK, Yilmaz MS, Kavalcı C. Left-sided atrial septal pouch and risk of cryptogenic stroke. Acta Medica Mediterranea 2016;32:785–9.

27. Holda M, Koziej M. Left-sided atrial septal pouch as a risk factor of cryptogenic stroke: A systematic review and meta-analysis. Cerebrovasc Dis 2018;46:223–9.

28. Holda M, Krawczyk-Ożog A, Koziej M, Sorysz D, Holda J, Dudek D, et al. Left-sided atrial septal pouch is a risk factor for cryptogenic stroke. J Am Soc Echocardiogr 2018;31:771–6.

29. Kapoor R, Wadi L, Becerra B, Eskander M, Razmara A, Lombardo D, et al. The left atrial septal pouch: A new stroke risk factor?. Transl Stroke Res 2021;12:205–11.

30. Di Tulio M, Sacco RL, Gopal A, Mohr JP, Homma S. Patent foramen ovale as a risk factor for cryptogenic stroke. Ann Intern Med 1992;117:461–5.

31. Handke M, Harloff A, Olscheswski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med 2007;357:2262–8.

32. Krishnan SC, Salazar M. Septal pouch in the left atrium: a new anatomical entity with potential for embolic complications. JACC Cardiovasc Inter 2010;3:98–104.

33. Klimek-Piotrowska W, Holda MK, Koziej M, Piattek K, Holda J. Anatomy of the true interatrial septum for transseptal access to the left atrium. Ann Anat 2016;205:205–60.

34. Hart RG, Sharma M, Mundh H, Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med 2018;378:2191–201.

35. Dinter HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, et al. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. N Engl J Med 2019;380:1906–17.

36. Geisler T, Poli S, Meissner C, Schreieck J, Zaern CS, Nägele T, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): Rationale and study design. Int J Stroke 2017;12:985–90.

37. Geisler T, Mengel A, Ziemann U, Poli S. Management of embolic stroke of undetermined source (ESUS). Drugs. 2018;78:823–31.

38. Mas JL, Derumaux G, Guillon B, Massardier E, Hossini H, et al. Patent foramen ovale and cryptogenic stroke: A retrospective study. J Transl Intern Med 2021;10: 48–55.