*Editorial to accompany Leventis, et al.*

**Embolic stroke of undetermined source:**

**The need for an integrated and holistic approach to care**

Yutao Guo1,2, Juqian Zhang2, Gregory Y.H. Lip 1,2, 3

1Medical School of Chinese PLA, Department of Cardiology, Chinese PLA General Hospital, Beijing, China; 2Liverpool Centre for Cardiovascular Sciences, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

The term embolic stroke of undetermined source (ESUS) was first introduced in 2014 to differentiate it from cryptogenic stroke[1]. ESUS was defined as a non-lacunar brain infarct without proximal arterial stenosis or cardiembolic source, with a clear indication for anticoagulation[1]. The condition consists on average 17% of ischaemic strokes[2], and is generally associated with relatively young patients, small emboli, and a high stroke recurrence (>4%), partly due to unclear underlying mechanism(s) which led to inappropriate preventive strategies [2]. Much focus has been directed towards improving our detection and understanding of stroke mechanisms in ESUS.

In a study using machine learning prediction of stroke mechanisms, 44% ESUS were identified as related to cardiac embolism, and each individual’s likelihood of cardiac embolism was associated with eventual detection of AF[3]. Higher probability of cardioembolism for patients with ESUS was associated with older age, vascular disease, heart failure, larger LA size, lower blood pressure and increased creatinine levels[3]. Although various studies have focused on cardiac rhythm monitoring to identify atrial fibrillation (AF)-related cardiac embolism among patients with ESUS[4-6], other evidence points towards atrial cardiopathy, patent foramen ovale (PFO) and arterial disease as potential etiologies of ESUS (see Figure 1).

Cardiopathy was firstly introduced as ‘atrial cardiomyopathy’ to define a familial syndrome affecting mainly the atria and atrioventricular-conducting system in 1972 year.[7] With the accumulation of evidence, the concept of atrial cardiomyopathy has evolved to define any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations[8], which might contribute to stroke risk independently of AF. Nonetheless, the mechanism(s) linking atrial cardiopathy and stroke risk is incompletely elucidated.

The clinical, electrocardiographic, echocardiographic variables and the biochemical markers associated with atrial cardiopathy have been identified among patients with ESUS [9-13], most of which reflected left atrial enlargement, although LA fibrosis and dysfunction were also noted as its features. Various studies in patients with continuous monitoring of atrial rhythm also confirmed that atrial high-rate episodes, atrial tachycardia, and subclinical atrial fibrillation were associated with stroke risk.[14-16] In fact, the anatomical and physiological remodeling of atrial tissue may be the substrate for the thromboembolism associated with stroke[17]. Of note, there are other less pathogenic reasons for atrial cardiomyopathy, e.g. atrial amyloidosis, hereditary muscular dystrophies, gene mutations, genetic repolarization disturbances, drugs, myocarditis, etc. Indeed, assessment of (atrial) substrate is also recommended as part of the overall characterization of conditions that lead to a high risk of stroke, such AF[18]. While it assumed that those patients could possibly benefit from anticoagulant treatment, one ongoing clinical trial will address the issue.[19]

Stroke related to Patent Foramen Ovale (PFO) was primarily thought to be a consequence of paradoxical embolism originating as venous thrombus in 1988 year.[20] Subsequent studies showed that there was a high prevalence of PFO was in patients with ESUS, although at least one third of PFOs discovered were likely to be incidental.[21] More than one in ten patients older than 60 years with a cryptogenic event have PFO combined with a large right-to-left shunt.[22] Besides atrial cardiopathy and PFO, there are other heterogeneous pathologies reported for ESUS, including left ventricular disease, covert atrial fibrillation, atherosclerosis, endothelial dysfunction, valvular heart disease, cancer (Table 1).

In this issue of *Thrombosis & Haemostasis*, Leventis, et al.[23] reported that the presence of atrial cardiopathy was inversely related to the presence of likely PFO in patients with ESUS. The prevalence of atrial cardiopathy was lower in patients with likely pathogenic PFO compared with patients with likely incidental PFO (31.2%) or without PFO, indicating that atrial cardiopathy and likely pathogenic PFO were two competing etiologies for ESUS.

Their findings were in keeping with two recent studies, both used hierarchy clustering analysis, an experimental machine-learning technique. One identified 3 different clusters of clinical phenotypes among 127 patients with ESUS: young age, PFO, posterior circulation infarct, and male sex; hypertension, left atrial cardiopathy, severe stroke, involvement of multiple vascular territories, and diabetes; and dyslipidaemia, ipsilateral vulnerable sub-stenotic carotid atherosclerosis, smoking, anterior territory infarct[24]. The other study noted four distinct clusters of potential embolic sources for ESUS among 800 patients with ESUS: the largest cluster was associated with arterial disease, followed by atrial cardiopathy, PFO, and left ventricular disease in decremental sizes[25]. These studies support the heterogeneity of ESUS where various embolic sources and risk factors play distinct roles[26].

Thus far, large clinical trials (NAVIGATE-ESUS and RE-SPECT-ESUS) found that anticoagulation using Rivaroxaban or Dabigatran as non-superior to Aspirin in preventing stroke recurrence following the onset of ESUS, and in the case of rivaroxaban, was associated with more bleeding events[27, 28]. There are two ongoing trials comparing apixaban with aspirin in secondary prevention of stroke, one in cryptogenic stroke and atrial cardiopathy[19] and the other in ESUS with insertable cardiac monitor for AF [29]. Their findings will shed more light on a more individualized stroke prevention strategy for subgroups of ESUS.

The optimal approach for the prevention of recurrent stroke in ESUS relates to age and addressing combined risk factors among those patients with ESUS.[30] An integrated approach to stroke care facilitates a more holistic approach, especially since ESUS management is likely to involve multidisciplinary teams. For example, improved monitoring will aid detection of associated AF, especially if we ‘look harder, look longer and look in more sophisticated ways[31]. Indeed, an integrated approach to AF management is now recommended in guidelines, being associated with good long terms outcomes[32-34]. Older patients with ESUS might possibly benefit from an anticoagulation strategy, given increased comorbidities for thromboembolic risk over aging.[35] Time will provide more evidence, to help guide the optimal approach to investigation and management of AF.

**References**

1. Hart, R.G., et al., *Embolic strokes of undetermined source: the case for a new clinical construct.* Lancet Neurol, 2014. **13**(4): p. 429-38.

2. Hart, R.G., et al., *Embolic Stroke of Undetermined Source: A Systematic Review and Clinical Update.* Stroke, 2017. **48**(4): p. 867-872.

3. Kamel, H., et al., *Machine Learning Prediction of Stroke Mechanism in Embolic Strokes of Undetermined Source.* Stroke, 2020. **51**(9): p. e203-e210.

4. Israel, C., et al., *Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders.* Thromb Haemost, 2017. **117**(10): p. 1962-1969.

5. Schnabel, R.B., et al., *Searching for Atrial Fibrillation Poststroke: A White Paper of the AF-SCREEN International Collaboration.* Circulation, 2019. **140**(22): p. 1834-1850.

6. Tomita, H., et al., *Covert atrial fibrillation and atrial high-rate episodes as a potential cause of embolic strokes of undetermined source: Their detection and possible management strategy.* J Cardiol, 2018. **72**(1): p. 1-9.

7. Nagle, R.E., B. Smith, and D.O. Williams, *Familial atrial cardiomyopathy with heart block.* Br Heart J, 1972. **34**(2): p. 205.

8. Goette, A., et al., *EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication.* Europace, 2016. **18**(10): p. 1455-1490.

9. Arauz, A., et al., *Embolic stroke of undetermined source: Beyond atrial fibrillation.* Neurologia, 2019.

10. Meisel, K., et al., *Embolic Stroke of Undetermined Source: A Population with Left Atrial Dysfunction.* J Stroke Cerebrovasc Dis, 2019. **28**(7): p. 1891-1896.

11. Overvad, T.F., et al., *Left atrial size and risk of stroke in patients in sinus rhythm. A systematic review.* Thromb Haemost, 2016. **116**(2): p. 206-19.

12. Kamran, S., et al., *Left Heart Factors in Embolic Stroke of Undetermined Source in a Multiethnic Asian and North African Cohort.* J Am Heart Assoc, 2020. **9**(15): p. e016534.

13. Gąsiorek, P., et al., *Arterial Stiffness and Indices of Left Ventricular Diastolic Dysfunction in Patients with Embolic Stroke of Undetermined Etiology.* Dis Markers, 2019. **2019**: p. 9636197.

14. Ziegler, P.D., et al., *Detection of previously undiagnosed atrial fibrillation in patients with stroke risk factors and usefulness of continuous monitoring in primary stroke prevention.* Am J Cardiol, 2012. **110**(9): p. 1309-14.

15. Healey, J.S., et al., *Subclinical atrial fibrillation and the risk of stroke.* N Engl J Med, 2012. **366**(2): p. 120-9.

16. Witt, C.T., et al., *Early detection of atrial high rate episodes predicts atrial fibrillation and thromboembolic events in patients with cardiac resynchronization therapy.* Heart Rhythm, 2015. **12**(12): p. 2368-75.

17. Kamel, H., et al., *Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation.* Future Cardiol, 2015. **11**(3): p. 323-31.

18. Potpara, T.S., et al., *The 4S-AF Scheme (Stroke Risk; Symptoms; Severity of Burden; Substrate): A Novel Approach to In-Depth Characterization (Rather than Classification) of Atrial Fibrillation.* Thromb Haemost, 2020.

19. Kamel, H., et al., *The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: Rationale and methods.* Int J Stroke, 2019. **14**(2): p. 207-214.

20. Lechat, P., et al., *Prevalence of patent foramen ovale in patients with stroke.* N Engl J Med, 1988. **318**(18): p. 1148-52.

21. Alsheikh-Ali, A.A., D.E. Thaler, and D.M. Kent, *Patent foramen ovale in cryptogenic stroke: incidental or pathogenic?* Stroke, 2009. **40**(7): p. 2349-55.

22. Mazzucco, S., et al., *Prevalence of patent foramen ovale in cryptogenic transient ischaemic attack and non-disabling stroke at older ages: a population-based study, systematic review, and meta-analysis.* Lancet Neurol, 2018. **17**(7): p. 609-617.

23. Leventis, I.A., et al., *Atrial Cardiopathy and Likely Pathogenic Patent Foramen Ovale in Embolic Stroke of Undetermined Source.* Thromb Haemost, 2020.

24. Lattanzi, S., et al., *Clinical phenotypes of embolic strokes of undetermined source.* Neurol Sci, 2020.

25. Ntaios, G., et al., *Data-driven machine-learning analysis of potential embolic sources in embolic stroke of undetermined source.* Eur J Neurol, 2020.

26. Ntaios, G., *Embolic Stroke of Undetermined Source: JACC Review Topic of the Week.* J Am Coll Cardiol, 2020. **75**(3): p. 333-340.

27. Hart, R.G., et al., *Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source.* N Engl J Med, 2018. **378**(23): p. 2191-2201.

28. Diener, H.C., et al., *Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source.* N Engl J Med, 2019. **380**(20): p. 1906-1917.

29. Geisler, T., et al., *Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): Rationale and study design.* Int J Stroke, 2017. **12**(9): p. 985-990.

30. Hviid, C.V.B., C.Z. Simonsen, and A.M. Hvas, *Recurrence Risk in Patients with Cryptogenic Stroke, Patent Foramen Ovale, and Thrombophilia: A Systematic Review and Meta-Analysis.* Thromb Haemost, 2019. **119**(11): p. 1839-1848.

31. Gue, Y.X., T.S. Potpara, and G.Y.H. Lip, *Detection of Atrial Fibrillation on Stroke Units: Look Harder, Look Longer, Look in More Sophisticated Ways.* Cerebrovasc Dis, 2020. **49**(6): p. 656-658.

32. Lip, G.Y.H., *The ABC pathway: an integrated approach to improve AF management.* Nat Rev Cardiol, 2017. **14**(11): p. 627-628.

33. Guo, Y., et al., *Mobile health technology-supported atrial fibrillation screening and integrated care: A report from the mAFA-II trial Long-term Extension Cohort.* Eur J Intern Med, 2020.

34. Hindricks, G., et al., *2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS).* Eur Heart J, 2020.

35. Kasner, S.E., et al., *Rivaroxaban or aspirin for patent foramen ovale and embolic stroke of undetermined source: a prespecified subgroup analysis from the NAVIGATE ESUS trial.* Lancet Neurol, 2018. **17**(12): p. 1053-1060.

36. Kamel, H., et al., *Electrocardiographic left atrial abnormality and stroke subtype in the atherosclerosis risk in communities study.* Ann Neurol, 2015. **78**(5): p. 670-8.

37. Kamel, H., et al., *Electrocardiographic Left Atrial Abnormality and Risk of Stroke: Northern Manhattan Study.* Stroke, 2015. **46**(11): p. 3208-12.

38. Kim, J.W., et al., *Association between the amount of right-to-left shunt and infarct patterns in patients with cryptogenic embolic stroke: a transcranial Doppler study.* Int J Stroke, 2013. **8**(8): p. 657-62.

39. Ntaios, G., et al., *Embolic strokes of undetermined source in the athens stroke registry: a descriptive analysis.* Stroke, 2015. **46**(1): p. 176-81.

40. Umemura, T., et al., *Importance of Finding Embolic Sources for Patients with Embolic Stroke of Undetermined Source.* J Stroke Cerebrovasc Dis, 2019. **28**(7): p. 1810-1815.

41. Ntaios, G., et al., *Aortic Arch Atherosclerosis in Patients With Embolic Stroke of Undetermined Source: An Exploratory Analysis of the NAVIGATE ESUS Trial.* Stroke, 2019. **50**(11): p. 3184-3190.

42. Ikonomidis, I., et al., *Impaired Arterial Elastic Properties and Endothelial Glycocalyx in Patients with Embolic Stroke of Undetermined Source.* Thromb Haemost, 2019. **119**(11): p. 1860-1868.

**Table 1 The potential etiologies of patients with embolic stroke of undetermined source**

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| **Authors** | **Studies** | **Main finding** |
| **Atrial cardiomyopathy** |
| Kamel H, et al. Ann Neurol 2015[36] | 14,542 participants 45 to 64 years904 participants (6.2%) with a definite or probable ischemic stroke | Left atrial abnormality was associated with nonlacunar stroke (HR, 1.49; 95% CI: 1.07-2.07) |
| Kamel H, et al. Stroke 2015[37] | Patients in sinus rhythm who subsequently had ischemic stroke (n=241) and a randomly selected subcohort without stroke (n=798) | ECG-defined left atrial abnormality was associated with incident cryptogenic or cardioembolic stroke independently of the presence of AF |
| Meisel K, et al. J Stroke Cerebrovasc Dis. 2019[10] | 18 ESUS patients, average age was 58 years old and 44% were female | ESUS subjects have LA dysfunction and remodeling at rest and exercise |
| **Patent foramen ovale** |
| Lechat P, et al. N Engl J Med 1988[21] | 60 adults with ischaemic stroke under 55 years old ,a control group of 100 patients | The prevalence of patent foramen ovale was significantly higher in the patients with stroke than in the control group  |
| Kim BJ, et al. Int J Stroke. 2013[38] | 157 patients with presumed cryptogenic embolismRight-to-left shunt was observed in 96 (61·1%) patients | Right-to-left shunt was more frequently observed in patients with small (<1 cm) infarcts than in those with a large infarct (66·7% vs. 45·9%)The mechanisms of stroke other than paradoxical mechanism may play an important role in patients with large cryptogenic embolic stroke |
| **Other potential embolic sources** |
| Ntaios G, et al. Stroke. 2015[39] | 2735 patients with ESUS | Covert paroxysmal atrial fibrillation:43.2%;%; Left ventricle :20.2%; Arteriogenic emboli : 13.9%; Non-atrial fibrillation atrial dysrhythmias and stasis :5.9%; Paradoxical embolism: 5.1%; Mitral valve:4.7%; Aortic valve: 5.5%; Atrial structural abnormalities :3.6Cancer-associated :1.2%  |
| Perera KS, et al. Eur Stroke J. 2018 [35] | 2144 patients with ischaemic stroke-24% (n = 78) of young vs. 15% (n = 273) of older patients with embolic stroke of undetermined source criteria. | Fewer young embolic stroke of undetermined source patients (63%) had potential minor risk embolic sources identified vs. older embolic stroke of undetermined source patients (77%)  |
| Umemura T, et al. J Stroke Cerebrovasc Dis. 2019[40] | 292 consecutive patients (135 men, 157 women; mean age: 74.3 ± 11.6 years) diagnosed with cerebral infarction-27 of whom were diagnosed with embolic stroke of undetermined source (9.2%; 14 men, 13 women; mean age: 70.7 ± 11.5 years). | Valve calcification (11.1%), left ventricle diastolic dysfunction (18.5%), cancer-associated stroke (25.9%), covert atrial fibrillation (7.4%), aortic arch atherosclerotic plaques (11.1%), paradoxical embolism (3.7%), and sick sinus syndrome (3.7%). |
| Ntaios G, et al. Stroke. 2019[41] | 1382 patients with ESUS | 397 (29%) had aortic arch atherosclerosis and 112 (8%) had complex aortic arch atherosclerosis |
| Ikonomidis, et al. Thromb Haemost. 2019 [42] | 90 patients with ESUS vs 90 controls with similar risk factors | Compared with control, ESUS patients had significantly higher arterial stiffness, endothelial glycocalyx damage, and oxidative stress, as well as higher LA volume, and reduced reservoir LA strain (P<0.05). In ESUS, glycocalyx damage was related with increased pulse wave velocity which was linked with LA reservoir strain.  |

\* HR: hazard ratio. CI: confidential interval. AF: atrial fibrillation. LA: left atrium. ESUS： embolic stroke of undetermined source.

**Figure-1. Main etiologies of ESUS apart from atrial fibrillation.**

Legend: A. Arterial disease/atherosclerosis. B. Atrial cardiopathy. C. Patent foramen ovale.

