**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 80606

**Manuscript Type:** MINIREVIEWS

**Development and refinement of diagnostic and therapeutic strategies for managing patients with cardiogenic stroke: An arduous journey**

Fan ZX *et al*. Management strategies for cardiogenic stroke

Ze-Xin Fan, Ri-Xia Liu, Guang-Zhi Liu

**Ze-Xin Fan, Ri-Xia Liu, Guang-Zhi Liu,** Department of Neurology, Beijing Anzhen Hospital, Beijing 100029, China

**Author contributions:** Liu GZ conceived the outline and performed the majority of the writing; Fan ZX and Liu RX performed part of writing and prepared the figures and tables.

**Corresponding author: Guang-Zhi Liu, MD, Chief Doctor, Professor,** Department of Neurology, Beijing Anzhen Hospital, No. 2 Anzhen Road, Chaoyang District, Beijing 100029, China. guangzhi2002@hotmail.com

**Received:** October 6, 2022

**Revised:** December 22, 2022

**Accepted:** January 12, 2023

**Published online:** February 6, 2023

**Abstract**

Cardioembolic stroke, referred to as cardiogenic stroke, is a clinical syndrome in which emboli from the heart pass through the circulatory system and cause cerebral artery embolism and corresponding brain dysfunction. Compared to other subtypes of ischemic stroke, cardiogenic stroke presents with more etiologies, greater severity, worse prognosis, and a higher recurrence rate. In this minireview, we provide new insights into the etiological classification, diagnostic methods, and interventions of cardiogenic stroke.

**Key Words:** Cardiogenic stroke; Diagnostic methods; Therapeutic strategies

**©The** **Author(s) 2023.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Fan ZX, Liu RX, Liu GZ. Development and refinement of diagnostic and therapeutic strategies for managing patients with cardiogenic stroke: An arduous journey. *World J Clin Cases* 2023; 11(4): 719-724

**URL**: https://www.wjgnet.com/2307-8960/full/v11/i4/719.htm

**DOI**: https://dx.doi.org/10.12998/wjcc.v11.i4.719

**Core Tip:** There are many reviews focused on the diagnosis and treatment strategies of cardiogenic stroke. However, in clinical practice, there are still many problems such as non-standard diagnosis and large differences in treatment measures. In this minireview, we introduce the latest Chinese expert consensus on cardiogenic stroke-based diagnostic criteria and provide some new insights into the etiological classification and interventions of cardiogenic stroke.

**INTRODUCTION**

Stroke is a disease that can seriously endanger human health. The 2019 Global Burden of Disease study showed that stroke is the second leading cause of death worldwide after ischemic heart disease (11.6% of total deaths), and the third leading cause of death and disability combined (5.7% of total disability-adjusted life years) with ischemic strokes accounting for the majority of strokes (62.4%)[1]. Cardiogenic stroke, also known as cardioembolic stroke, constitutes 20% to 30% of all ischemic strokes. It is a clinical syndrome in which emboli from the heart pass through the circulatory system and cause cerebral artery embolism and corresponding brain dysfunction[2,3]. With the strengthening of community medical management, atherosclerosis risk factors were significantly reduced (*e.g.,* low-density lipoprotein-cholesterol and blood pressure levels were better controlled than before). As a result, stroke/transient ischemic attacks caused by large-artery atherosclerosis (LAA) and small-vessel occlusion were remarkably decreased; conversely, cardiogenic stroke/transient ischemic attack increased significantly[4]. Compared to other subtypes of ischemic stroke, cardiogenic stroke presents with more etiologies, greater severity, worse prognosis, and a higher recurrence rate[5,6]. Although the diagnosis and treatment of cardiogenic stroke has substantially improved worldwide in recent years, there are still plenty of shortcomings, such as insufficient understanding of this disease and significant differences in treatment strategies[3,4]. Therefore, further strengthening the understanding of the etiological classification, diagnostic methods, and intervention measures of cardiogenic stroke, and uniformly improving the diagnosis and treatment of cardiogenic stroke, have become the top priority in the neurology community.

**AS YET CLARIFIED ETIOLOGICAL CLASSIFICATION OF CARDIOGENIC STROKE**

According to the definite (or potential) cause of cardiogenic stroke in the A-S-C-O (phenotype) classification and its epidemiological characteristics, the relatively common causes are divided into atrial fibrillation (AF), heart failure, acute coronary syndromes, patent foramen ovale (PFO), rheumatic heart disease, artificial heart valve, infectious endocarditis (IE), dilated cardiomyopathy, and cardiac myxoma. In most cases, the intracardiac wall thrombus, tumor surface thrombus/debris, shedding of vegetations on the valve intima or aortic arch plaque, or paradoxical embolism (derived from veins), underlie the pathogenesis, thereby contributing to the obstruction of cerebral blood vessels[7].

To date, the etiological attribution of cardiogenic stroke remains elusive. Firstly, the boundary between cardiogenic stroke and cryptogenic stroke, especially embolic stroke of undetermined source (ESUS), is blurred. Strokes that do not clearly meet the diagnostic criteria of the known ischemic stroke subtypes are classified as cryptogenic strokes[8,9], and cryptogenic stroke is further defined as ESUS when the clinical and neuroimaging features suggest a distant thrombus origin, the absence of lacunar infarcts, a high-risk source of cardiac embolism, or high-degree stenosis of the responsible vessel at the site of the infarction[10,11] (Figure 1). Regarding the etiology of embolism in ESUS, some cases may originate from arterial-arterial embolism caused by large atherosclerotic plaques in the brain, while other cases may result from some cardiac diseases (*e.g.,* paroxysmal AF, PFO, atrial cardiomyopathy, *etc.*)[3,12], strongly suggesting the existence of an overlap between ESUS and cardiogenic stroke. Hence, for ESUS cases, once the above causes are found through adequate standard evaluation, we recommend that, after multi-disciplinary discussion and confirmation of a cardiac cause, cardiogenic stroke should be considered so that treatment can be initiated as soon as possible. Secondly, there is still controversy over whether aortic arch atheroma (AAA)-related stroke should be classified as cardiogenic strokes, as some clinicians have categorized it as an ESUS subgroup of cryptogenic strokes[12]; however, the latest guideline for the prevention of stroke in patients with stroke and transient ischemic attack from the American Heart Association (AHA)/American Stroke Association (ASA) classified it as a subtype of LAA[13]. In view of this, we propose that while the classification of AAA-related strokes as LAA subtypes may reflect its exact pathogenesis, it is still more appropriate to attribute it to cardiogenic strokes. A strong reason for this is that its mechanisms and clinical manifestations are very similar to those of cardiogenic stroke, and studies have shown that attributing it to cardiogenic stroke has no significant impact on the choice of treatment measures and patient prognosis[14].

**URGENCY TO DEVELOP A STANDARDIZED DIAGNOSTIC SYSTEM FOR CARDIOGENIC STROKE**

The diagnosis of cardiogenic stroke is frequently made based on its clinical and neuroimaging features, combined with other elements such as vascular and cardiac evaluation. With improvements in disease awareness and detection methods (*e.g.,* long-term electrocardiogram monitoring, echocardiography), the detection rate of cardiogenic stroke has greatly increased in recent years when compared with other subtypes of ischemic stroke[15]. Nonetheless, several lines of clinical and radiological evidence to support cardiogenic stroke have been proposed in this regard since the 1990s[8,16,17], but there are no well-established diagnostic criteria. Additionally, there is also controversy over the specific examination protocol used to identify the etiology of cardiogenic stroke. Finally, there are many other problems, such as inconsistent diagnosis and treatment levels across different medical institutions, misdiagnosis, and mistreatment.

In an attempt to solve these problems, we first proposed new clinical diagnostic criteria for cardiogenic stroke[7]. According to the Chinese expert consensus on the diagnosis of cardiogenic stroke (2019) (Table 1), cardiogenic stroke is categorized into definite cardiogenic stroke, probable cardiogenic stroke, and possible cardiogenic stroke: Definite cardiogenic stroke = 2 of (A) + at least 1 of (B) + C; probable cardiogenic stroke = 2 of (A), or at least 1 of (A) + at least 1 of (B); possible cardiogenic stroke = at least 1 of (A). Clinical validation of the diagnostic criteria is currently underway.

**URGENT NEED FOR THE DEVELOPMENT OF A STANDARDIZED AND REFINED INTERVENTION STRATEGY FOR CARDIOGENIC STROKE**

Even though the treatment principles of cardiogenic stroke are generally similar to other subtypes of ischemic stroke, more emphasis is placed on anticoagulation therapy. However, when to start or restart anticoagulation therapy and the choice of anticoagulants are mostly based on personal experience, mainly due to the lack of clinical evidence or clinical guidelines. Although the principle of using intravenous thrombolysis in the acute phase is similar of all subtypes, cardiogenic stroke also has its own specificity. In light of the above issues, the standardization of treating cardiogenic stroke has become an urgent issue which needs to be addressed.

For most stroke patients with AF, the guidelines for the early management of acute ischemic stroke from the 2018 AHA/ASA recommend that oral anticoagulation therapy should be initiated within 4 to 14 d after onset[17]. Nevertheless, in a recent multicenter real-world cohort study, initiation of oral anticoagulation within 4 to 14 d did not significantly reduce the incidence of ischemic and hemorrhagic stroke compared to that initiated within zero to three days[18]. Additionally, regarding the best time to restart oral anticoagulation after acute stroke, Hindricks *et al*[19] suggests that anticoagulation be restarted as soon as possible within 2 wk of onset under the guidance of a multi-disciplinary team (neurologist and cardiologist), in combination with the patient’s willingness to treat; however, so far there are no reliable data to support this viewpoint. Regarding the anticoagulant choice, results from four randomized controlled trials involving anticoagulation for stroke or systemic embolism in AF showed that, novel oral anticoagulants (NOACs) are noninferior to warfarin in reducing the risk of stroke or systemic embolism in patients with AF but are safer in terms of adverse reactions, such as risk of intracranial hemorrhage[20-23]. Due to this, we recommend that the risk of hemorrhagic transformation in cardiogenic stroke be taken into account, regardless of indications for anticoagulation (*e.g.,* AF, valvular disease), and treatment should be started or restarted several days to several weeks after the onset of the disease, in consideration of the severity of the disease, the size of the acute cerebral infarction, and the risk of bleeding. It is also necessary to fully consider the faster effect and higher safety characteristics of NOACs compared with warfarin.

With regard to intravenous thrombolysis in cardiogenic stroke, to date, most studies were observational or small sample studies[24-26]; in addition, the consensus on efficacy and adverse reactions such as bleeding were different, mainly owing to differences in inclusion criteria and patient characteristics. It should be kept in mind that the use of intravenous thrombolysis is also limited or complicated under special circumstances, such as with prior anticoagulation therapy[27-32], recent valve surgery or percutaneous coronary intervention[33,34], and IE-related stroke[35]. Accordingly, a variety of guidelines and expert consensus have provided corresponding individualized treatment advice or recommendations[18,36-38]. Chinese neurologists have also recently reported a case of cardiogenic stroke successfully treated by intravenous thrombolysis with alteplase after reversal of dabigatran by idacilizumab[39]. Hence, for patients with acute cardiogenic stroke, especially those who received anticoagulation before disease onset, we recommend the treatment strategy should be individualized according to the specific situation, and intravenous thrombolytic therapy can be performed after multi-disciplinary consultation to improve patient outcomes.

**CONCLUSION**

In summary, three major issues are raised in this review: The etiology classification; the boundary between cardiogenic stroke, cryptogenic stroke and ESUS; as well as the attribution of AAA-related stroke all need to be clarified. Regarding the diagnosis, given the fact that currently no well-established diagnostic standard is available, we hence developed a new diagnostic system for cardiogenic stroke. Additionally, we recommend that anticoagulant therapy should be initiated or restarted several days to weeks after the onset of stroke, based on the patients’ specific situation, and treatment for acute phase and prevention of recurrent stroke should be actively carried out after multidisciplinary consultation. Despite substantial progress in the diagnosis and treatment of cardiogenic stroke worldwide, there is still a long way to go to address all issues. In particular, the development of a standard protocol for management of the acute phase and recovery phase should be determined as soon as possible. Thus, we look forward to seeing additional evidence-based research, real-world research, and health economics evidence in the future in order for clinicians to gain a more comprehensive understanding of cardiogenic stroke and precise prevention and treatment measures, thereby maximizing the clinical benefit and improving the prognosis of patients.

**REFERENCES**

1 **GBD 2019 Stroke Collaborators**. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021; **20**: 795-820 [PMID: 34487721 DOI: 10.1016/S1474-4422(21)00252-0]

2 **Bogiatzi C**, Hackam DG, McLeod AI, Spence JD. Secular trends in ischemic stroke subtypes and stroke risk factors. *Stroke* 2014; **45**: 3208-3213 [PMID: 25213343 DOI: 10.1161/STROKEAHA.114.006536]

3 **Kamel H**, Healey JS. Cardioembolic Stroke. *Circ Res* 2017; **120**: 514-526 [PMID: 28154101 DOI: 10.1161/CIRCRESAHA.116.308407]

4 **Spence JD**. Cardioembolic stroke: everything has changed. *Stroke Vasc Neurol* 2018; **3**: 76-83 [PMID: 30022801 DOI: 10.1136/svn-2018-000143]

5 **Lin HJ**, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke* 1996; **27**: 1760-1764 [PMID: 8841325 DOI: 10.1161/01.str.27.10.1760]

6 **Bjerkreim AT**, Khanevski AN, Thomassen L, Selvik HA, Waje-Andreassen U, Naess H, Logallo N. Five-year readmission and mortality differ by ischemic stroke subtype. *J Neurol Sci* 2019; **403**: 31-37 [PMID: 31185434 DOI: 10.1016/j.jns.2019.06.007]

7 **Liu GZ**, Hu R, Peng DT; Geriatric Neurology Group, Geriatric Branch of Chinese Medical Association; Writing Group of Chinese expert consensus on diagnosis of cardiogenic stroke. Chinese expert consensus on the diagnosis of cardiogenic stroke (2019). *Chin Med J (Engl)* 2021; **134**: 505-507 [PMID: 33652457 DOI: 10.1097/CM9.0000000000001217]

8 **Adams HP Jr**, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. 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 [PMID: 7678184 DOI: 10.1161/01.str.24.1.35]

9 **Ay H**, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, Ayata C, Towfighi A, Smith EE, Chong JY, Koroshetz WJ, Sorensen AG. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. *Stroke* 2007; **38**: 2979-2984 [PMID: 17901381 DOI: 10.1161/STROKEAHA.107.490896]

10 **Hart RG**, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ; Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014; **13**: 429-438 [PMID: 24646875 DOI: 10.1016/S1474-4422(13)70310-7]

11 **Hart RG**, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic Stroke of Undetermined Source: A Systematic Review and Clinical Update. *Stroke* 2017; **48**: 867-872 [PMID: 28265016 DOI: 10.1161/STROKEAHA.116.016414]

12 **Ntaios G**. Embolic Stroke of Undetermined Source: JACC Review Topic of the Week. *J Am Coll Cardiol* 2020; **75**: 333-340 [PMID: 31976872 DOI: 10.1016/j.jacc.2019.11.024]

13 **Kleindorfer DO**, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, Kamel H, Kernan WN, Kittner SJ, Leira EC, Lennon O, Meschia JF, Nguyen TN, Pollak PM, Santangeli P, Sharrief AZ, Smith SC Jr, Turan TN, Williams LS. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke* 2021; **52**: e364-e467 [PMID: 34024117 DOI: 10.1161/STR.0000000000000375]

14 **Amarenco P**, Davis S, Jones EF, Cohen AA, Heiss WD, Kaste M, Laouénan C, Young D, Macleod M, Donnan GA; Aortic Arch Related Cerebral Hazard Trial Investigators. Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. *Stroke* 2014; **45**: 1248-1257 [PMID: 24699050 DOI: 10.1161/STROKEAHA.113.004251]

15 **Pepi M**, Evangelista A, Nihoyannopoulos P, Flachskampf FA, Athanassopoulos G, Colonna P, Habib G, Ringelstein EB, Sicari R, Zamorano JL, Sitges M, Caso P; European Association of Echocardiography. Recommendations for echocardiography use in the diagnosis and management of cardiac sources of embolism: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr* 2010; **11**: 461-476 [PMID: 20702884 DOI: 10.1093/ejechocard/jeq045]

16 **Kelley RE**, Kelley BP. Heart-Brain Relationship in Stroke. *Biomedicines* 2021; **9** [PMID: 34944651 DOI: 10.3390/biomedicines9121835]

17 **Powers WJ**, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018; **49**: e46-e110 [PMID: 29367334 DOI: 10.1161/STR.0000000000000158]

18 **Yaghi S**, Trivedi T, Henninger N, Giles J, Liu A, Nagy M, Kaushal A, Azher I, Mac Grory B, Fakhri H, Brown Espaillat K, Asad SD, Pasupuleti H, Martin H, Tan J, Veerasamy M, Liberman AL, Esenwa C, Cheng N, Moncrieffe K, Moeini-Naghani I, Siddu M, Scher E, Leon Guerrero CR, Khan M, Nouh A, Mistry E, Keyrouz S, Furie K. Anticoagulation Timing in Cardioembolic Stroke and Recurrent Event Risk. *Ann Neurol* 2020; **88**: 807-816 [PMID: 32656768 DOI: 10.1002/ana.25844]

19 **Hindricks G**, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; **42**: 373-498 [PMID: 32860505 DOI: 10.1093/eurheartj/ehaa612]

20 **Connolly SJ**, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139-1151 [PMID: 19717844 DOI: 10.1056/NEJMoa0905561]

21 **Patel MR**, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883-891 [PMID: 21830957 DOI: 10.1056/NEJMoa1009638]

22 **Granger CB**, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**: 981-992 [PMID: 21870978 DOI: 10.1056/NEJMoa1107039]

23 **Giugliano RP**, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**: 2093-2104 [PMID: 24251359 DOI: 10.1056/NEJMoa1310907]

24 **Vaclavik D**, Vilionskis A, Jatuzis D, Karlinski MA, Gdovinova Z, Kõrv J, Tsivgoulis G, Mikulik R. Clinical outcome of cardioembolic stroke treated by intravenous thrombolysis. *Acta Neurol Scand* 2018; **137**: 347-355 [PMID: 29218699 DOI: 10.1111/ane.12880]

25 **Anticoli S**, Bravi MC, Perillo G, Siniscalchi A, Pozzessere C, Pezzella FR, Tanzi P, Gallelli L, Cartoni D. Effect of Cardioembolic Etiology on Intravenous Thrombolysis Efficacy for Acute Ischemic Stroke. *Curr Neurovasc Res* 2016; **13**: 193-198 [PMID: 27149937 DOI: 10.2174/1567202613666160506125426]

26 **Wang XG**, Zhang LQ, Liao XL, Pan YS, Shi YZ, Wang CJ, Wang YL, Liu LP, Zhao XQ, Wang YJ, Li D, Wang CX; Thrombolysis Implementation and Monitoring of acute ischemic Stroke in China (TIMS-China) Investigators. Unfavorable Outcome of Thrombolysis in Chinese Patients with Cardioembolic Stroke: a Prospective Cohort Study. *CNS Neurosci Ther* 2015; **21**: 657-661 [PMID: 26096605 DOI: 10.1111/cns.12421]

27 **Xian Y**, Liang L, Smith EE, Schwamm LH, Reeves MJ, Olson DM, Hernandez AF, Fonarow GC, Peterson ED. Risks of intracranial hemorrhage among patients with acute ischemic stroke receiving warfarin and treated with intravenous tissue plasminogen activator. *JAMA* 2012; **307**: 2600-2608 [PMID: 22735429 DOI: 10.1001/jama.2012.6756]

28 **Toyoda K**, Yamagami H, Koga M. Consensus Guides on Stroke Thrombolysis for Anticoagulated Patients from Japan: Application to Other Populations. *J Stroke* 2018; **20**: 321-331 [PMID: 30309227 DOI: 10.5853/jos.2018.01788]

29 **Agosti S**, Casalino L, Rocci E, Zaccone G, Rota E. Successful intravenous thrombolysis for ischemic stroke after reversal of dabigatran anticoagulation with idarucizumab: a case report. *J Med Case Rep* 2017; **11**: 224 [PMID: 28806993 DOI: 10.1186/s13256-017-1404-2]

30 **Barber PA**, Wu TY, Ranta A. Stroke reperfusion therapy following dabigatran reversal with idarucizumab in a national cohort. *Neurology* 2020; **94**: e1968-e1972 [PMID: 32079737 DOI: 10.1212/WNL.0000000000009155]

31 **Mazya MV**, Lees KR, Markus R, Roine RO, Seet RC, Wahlgren N, Ahmed N; Safe Implementation of Thrombolysis in Stroke Investigators. Safety of intravenous thrombolysis for ischemic stroke in patients treated with warfarin. *Ann Neurol* 2013; **74**: 266-274 [PMID: 23744571 DOI: 10.1002/ana.23924]

32 **Frank B**, Grotta JC, Alexandrov AV, Bluhmki E, Lyden P, Meretoja A, Mishra NK, Shuaib A, Wahlgren NG, Weimar C, Lees KR; VISTA Collaborators. Thrombolysis in stroke despite contraindications or warnings? *Stroke* 2013; **44**: 727-733 [PMID: 23391774 DOI: 10.1161/STROKEAHA.112.674622]

33 **Manoukian SV**, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, Dangas GD, Lincoff AM, White HD, Moses JW, King SB 3rd, Ohman EM, Stone GW. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. *J Am Coll Cardiol* 2007; **49**: 1362-1368 [PMID: 17394970 DOI: 10.1016/j.jacc.2007.02.027]

34 **Kamel H**, Johnston SC, Kirkham JC, Turner CG, Kizer JR, Devereux RB, Iadecola C. Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. *Circulation* 2012; **126**: 207-212 [PMID: 22679143 DOI: 10.1161/CIRCULATIONAHA.112.094326]

35 **Brownlee WJ**, Anderson NE, Barber PA. Intravenous thrombolysis is unsafe in stroke due to infective endocarditis. *Intern Med J* 2014; **44**: 195-197 [PMID: 24528816 DOI: 10.1111/imj.12343]

36 **Demaerschalk BM**, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, Palesch YY, Prabhakaran S, Saposnik G, Saver JL, Smith EE; American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2016; **47**: 581-641 [PMID: 26696642 DOI: 10.1161/STR.0000000000000086]

37 **Diener HC**, Bernstein R, Butcher K, Campbell B, Cloud G, Davalos A, Davis S, Ferro JM, Grond M, Krieger D, Ntaios G, Slowik A, Touzé E. Thrombolysis and thrombectomy in patients treated with dabigatran with acute ischemic stroke: Expert opinion. *Int J Stroke* 2017; **12**: 9-12 [PMID: 27694315 DOI: 10.1177/1747493016669849]

38 **Berge E**, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, de la Ossa NP, Strbian D, Tsivgoulis G, Turc G. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J* 2021; **6**: I-LXII [PMID: 33817340 DOI: 10.1177/2396987321989865]

39 **Xie D**, Wang X, Li Y, Chen R, Zhao Y, Xu C, Zhang Q, Zhang Y. Intravenous Thrombolysis After Reversal of Dabigatran With Idarucizumab in Acute Ischemic Stroke: A Case Report. *Front Aging Neurosci* 2021; **13**: 765037 [PMID: 34970137 DOI: 10.3389/fnagi.2021.765037]

**Footnotes**

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed

**Peer-review model:** Single blind

**Peer-review started:** October 6, 2022

**First decision:** December 13, 2022

**Article in press:** January 12, 2023

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Alkhatib AJ, Jordan; Teramoto-Matsubara OT, Mexico **S-Editor:** Wang JJ **L-Editor:** A **P-Editor:** Wang JJ

**Figure Legends**



**Figure 1 Relationship between cryptogenic stroke, embolic stroke of undetermined source, and cardiogenic stroke.** AF: Atrial fibrillation; ESUS: Embolic stroke of undetermined source.

**Table 1 Diagnostic criteria for cardiogenic stroke[7]**

|  |  |
| --- | --- |
| **Criteria** | **Element** |
| A: Essential criteria | Typical clinical manifestations |
| Characteristic neuroimaging (brain CT/MRI) findings |
| B: Supportive criteria | Cardiogenic embolus on echocardiography1 |
| Arrhythmia on electrocardiogram, especially atrial fibrillation |
| Characteristic vascular neuroimaging/cerebral angiography findings2 |
| C: Exclusion of other diseases |  |

1Intracardiac thrombus, intracardiac vegetation, intracardiac tumor and right-to-left intracardiac shunt.

2An abrupt cut-off of the main trunk or branch of an intracranial large-vessel, in the absence of significant atherosclerotic plaques which cause narrowing of the upstream vessels (*e.g.,* internal carotid artery).

CT: Computed tomography; MRI: Magnetic resonance imaging.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2023 Baishideng Publishing Group Inc. All rights reserved.**