Importance of Finding Embolic Sources for Patients with Embolic Stroke of Undetermined Source

Takeru Umemura, MD, Shigeru Nishizawa, MD, Yoshiteru Nakano, MD, Takeshi Saito, MD, Takehiro Kitagawa, MD, Ryo Miyaoka, MD, Kohei Suzuki, MD, and Junkoh Yamamoto, MD

Objective: The concept of embolic stroke of undetermined source refers to cryptogenic strokes caused by either major or minor risks. Although antiplatelet treatments are most often used for secondary prevention of embolic stroke of undetermined source, optimal strategies remain unclear. To determine the ideal treatment strategy for secondary prevention, we investigated embolic sources among patients with embolic stroke of undetermined source. *Methods*: The study included 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). These 27 patients were examined using contrast-enhanced whole-body computed tomography, transesophageal echocardiography, and Holter electrocardiography. We evaluated whether antiplatelet or anticoagulant treatment was preferred based on the embolic source. *Results*: Embolic sources among patients with embolic stroke of undetermined source included 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%). Embolic sources remained unidentified in 5 patients (18.5%). Our analysis revealed that 21 of the 27 patients (77.8%) with embolic stroke of undetermined source required anticoagulant therapy for secondary prevention. *Conclusion*: Although aspirin is the most commonly used antithrombotic drug for embolic stroke of undetermined source, our results suggest that some patients require anticoagulant therapy. Determining embolic sources is important for selecting the appropriate treatment options for this patient population.

Key Words: ESUS—embolic stroke-–antiplatelet—anticoagulants—cerebral infarction

Introduction

The concept of embolic stroke of undetermined source (ESUS) was first introduced in 2014 and refers to cryptogenic strokes caused by either major or minor risks. Major risks include atrial fibrillation (AF) and left ventricular thrombi, while minor risks include ventricular dysfunction, mitral annular calcification, and patent foramen ovale.[1] Although antiplatelet treatment is used for secondary prevention in the majority of patients with ESUS, optimal strategies for secondary prevention remain unclear.[1-3] According to the literature, a high proportion of cryptogenic ischemic strokes are caused by paroxysmal AF (PAF).[4] Therefore, oral anticoagulants may be more effective than antiplatelet therapy for the prevention of recurrent stroke in patients with ESUS.[1]

From the Department of Neurosurgery, University of Occupational and Environmental Health, Kitakyushu, Japan.

Received March 6, 2019; revision received March 27, 2019; accepted April 17, 2019.

Grant Support: None.

Address correspondence to Takeru Umemura, MD, Department of Neurosurgery, Kyushu Rosai Hospital, Moji Medical Center, 3-1 Higashiminatomachi, Moji-ku, Kitakyushu City, Fukuoka 801-8502, Japan. E-mail address: takeru.u115@gmail.com.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.04.022

The recent ATTICUS randomized trial was designed to investigate the efficacy of aspirin relative to direct oral anticoagulants (DOACs).[5] However, the NAVIGATE and RESPECT ESUS clinical trials recently demonstrated that DOACs are not superior to aspirin for the secondary prevention of ESUS.[6-8]

To determine the most appropriate treatment options (antiplatelets versus anticoagulants) for ESUS, the present study aimed to investigate the sources of embolism and identify stroke mechanisms among this patient population.

Materials and Methods

The present study included 292 consecutive patients (135 men, 157 women; mean age: ± standard deviation 74.3 ± 11.6 years) who had been admitted to the Hospital of the University of Occupational and Environmental Health with cerebral infarction between April 2014 and March 2017. The local Ethics Committee approved the scientific use of the collected data.

Patients were diagnosed with lacunar infarcts (n = 57, 19.5%; 29 men, 28 women), atherosclerotic infarcts (n = 155, 53.1%; 69 men, 86 women), cardiac infarcts (n = 49, 16.8%; 21 men, 28 women), other infarcts (n = 4, 1.4%; ie, dissection of vertebral artery), and ESUS (n = 27, 9.6%; 14 men, 13 women). Mean ages in patients with lacunar, atherosclerotic, and cardiac infarcts were 73.1 ± 10.6 years, 73.8 ± 11.1 years, 81.3 ± 9.6 years, respectively. The mean age in the ESUS group was 70.7 ± 11.5 years.

Lacunar infarcts were defined as subcortical infarcts ≤1.5 cm in the largest dimension in the distribution of perforating cerebral arteries. Atherosclerotic infarcts were defined as a stroke associated with main artery stenosis in the absence of a potential cardiac source. Cardiac embolism was defined as a stroke resulting from a potential cardiac source. According to the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group, ESUS was defined as a visualized nonlacunar brain infarct in the absence of: (1) extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia, (2) major-risk cardioembolic sources, and (3) any other specific cause of stroke (eg, arteritis, dissection, migraine/vasospasm, or drug misuse).

ESUS was differentiated from lacunar infarction via diffusion magnetic resonance imaging (MRI), atherosclerotic infarction via magnetic resonance angiography and carotid ultrasound, cardiac embolism via 24-hour electrocardiography and transthoracic echocardiography, and arteritis via blood examination.

Patients with ESUS underwent contrast-enhanced, whole-body computed tomography (CT) and aortography to determine whether strokes were associated with aortic arch atheroma or cancer. Aortic arch atheroma was defined as the presence of at least 1 calcium deposit or clearly visualized hypodensity of ≥4-mm thickness adjacent to the aortic wall at both transverse and longitudinal projections. If the cause of embolism was not identified, we then performed transesophageal echocardiography to screen for left atrial thrombi, smoke-like echoes in the left ventricle, mitral annular calcification, or patent foramen ovale. If the source of the embolism remained undetermined, we performed Holter electrocardiograms (ECGs) twice to screen for AF or other forms of an irregular pulse. Continuous ECG was performed using an implantable loop recorder (Reveal LINQ). If the source of embolism still remained unidentified following Holter monitoring, we used the strategy that is outlined in Figure 1.

Results

Among the 27 patients diagnosed with ESUS (14 men and 13 women; mean age: 70.7 ± 11.5), the embolic source was identified in 22 individuals (81.5%; Table 1). Contrast-enhanced CT revealed the embolic source in 10 patients (37.0%), 7 of whom were diagnosed with cancer-associated stroke (25.9%). All patients exhibited elevated levels of fibrinogen degradation product and D-dimer, and all cancers were adenocarcinoma. CT identified cancer for the first time in 2 patients, while the remaining 5 patients had been previously diagnosed with cancer. These 7 patients were treated using the anticoagulant warfarin for secondary prevention. Among all 10 patients, 3 (11.1%) were diagnosed with embolic stroke due to aortic arch atherosclerosis via aortography, which confirmed the lack of a cardiac embolic source in all cases.

Nine patients (33.3%) were diagnosed with embolic stroke via transesophageal echocardiogram. Left ventricular diastolic dysfunction (ejection fraction (EF) <30%) caused embolic stroke in 5 patients (18.5%), who also exhibited smoke-like echoes in the left ventricle. Two of these patients were treated with aspirin and warfarin due to coronary artery atherosclerosis, while the remaining 3 were treated with warfarin only. Three patients (11.1%) were diagnosed with valve calcification (aortic valve, n = 1; mitral valve, n = 2) and were subsequently treated using aspirin only. One patient (3.7%) was diagnosed

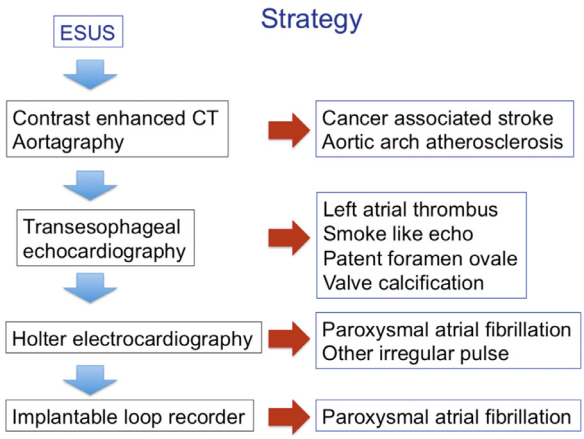

Figure 1. *Strategy for determining the source of embolism.*

Table 1. *Source of embolism and second prevention*

Embolic source		Second prevention	
Cancer associated stroke	7 (25.9%)	Warfarin	7
Aortic arch atherosclerosis	3 (11.1%)	Aspirin	3
Left ventricle diastolic dysfunction	5 (18.5%)	Aspirin and warfarin	2
		Warfarin	3
Valve calcification (aortic valve 1, mitral valve 2)	3 (11.1%)	Aspirin	3
Patent foramen ovale	1 (3.7%)	DOAC	1
Paroxysmal atrial fibrillation	2 (7.4%)	DOAC	2
Sick sinus syndrome	1 (3.7%)	Warfarin	1
Unknown	5 (18.5%)	Warfarin	5

with paradoxical cerebral embolism. This patient exhibited a thrombus in the lower limbs, as well as a patent foramen ovale on transesophageal echocardiography, and was treated using DOACs.

The embolic source was identified via Holter monitoring in 3 patients (11.1%). Two of these patients (7.4%) were diagnosed with PAF and were treated using DOACs. The 1 remaining patient (3.7%) was diagnosed with sick sinus syndrome and treated with warfarin.

The embolic source could not be identified in 5 patients (18.5%), even after continuous monitoring using an implant loop recorder, which revealed a normal pulse in all patients. Furthermore, they did not have any plaque that could cause embolic infarction observed in magnetic resonance angiography, carotid ultrasound, and aortography. These patients were still thought to have a possible cardiogenic infarction caused by covert AF and, thus, were treated with warfarin for secondary prevention.

Nineteen patients (70.4%) with ESUS were treated using anticoagulant therapy for secondary prevention, 6 (22.2%) were treated with antiplatelet therapy, and 2 (7.4%) were treated with both anticoagulant and antiplatelet therapies.

Illustrative Cases

Left Ventricle Dysfunction

A 59-year-old man with hypertension and a history of smoking was admitted to our hospital due to aphasia and right, severe hemiparesis. Diffusion-weighted MRI revealed a left infarction induced by a middle cerebral artery embolism (Fig 2, A). He was treated with a tissue plasminogen activator (tPA) and underwent endovascular mechanical thrombectomy. Recanalization resulted in improvements in aphasia and hemiparalysis. ECG (>24 hours) and transthoracic ECG were performed to identify the source of stroke, although the patient did not exhibit AF or thrombi in the left atrium. Following a diagnosis of ESUS, he underwent transesophageal ECG, which revealed smoke-like echoes induced by left ventricular dysfunction (Fig 2, B). These findings suggested a state of hypercoagulation in the left ventricle. Thus, the patient was treated with heparin, although he also required antiplatelet treatment due to atherosclerotic changes in the coronary artery; therefore, the heparin was switched to warfarin. In this case, warfarin and aspirin were used for secondary prevention.

Paroxysmal Atrial Fibrillation

A 70-year-old man with diabetes mellitus was admitted to our hospital with left visual field defect, left hemiparalysis, and nausea. CT revealed right occipital hemorrhagic infarction (Fig 3, A), and he was treated with heparin and maintained on warfarin. The following year, he presented with poor coordination on the left side, and diffusion-weighted MRI revealed a pontine infarction (Fig 3, B). This second infarction was diagnosed as a lacunar infarction, and the patient was switched from warfarin to antiplatelet therapy. Approximately 18 months later, he presented with sensory aphasia, and diffusion-weighted MRI revealed a left parietal infarction (Fig 3, C). Following a diagnosis of atherosclerotic infarction, statin therapy was added to his treatment regimen. The next year, he presented with sensory aphasia, and diffusion-weighted MRI revealed a left temporal lobe infarction (Fig 3, D). He was diagnosed with embolic infarction and treated using heparin. Although a >24-hour ECG, transthoracic ECG, and carotid ultrasound were performed to identify the source of the stroke, he exhibited no AF or indicative abnormalities and was thus diagnosed with ESUS. Neither whole-body CT nor transesophageal ECG suggested an embolic source. However, Holter monitoring revealed PAF as the embolic source and the patient was subsequently treated with DOACs. No recurrence has been observed to date.

Discussion

The present study marks the first investigation of embolic sources in patients with ESUS. While it remains to be determined whether antiplatelet or anticoagulant therapy should be used for secondary prevention among patients with ESUS, embolic sources were confirmed in 22 of the 27 patients (81.5%), most of whom required anticoagulant therapy (16/27, 59.3%). Seven of these 27 patients (25.9%) were diagnosed with cancer-associated stroke, for which anticoagulant therapy is currently recommended.[9] Another 5 patients (18.5%) were diagnosed with left ventricle dysfunction. As

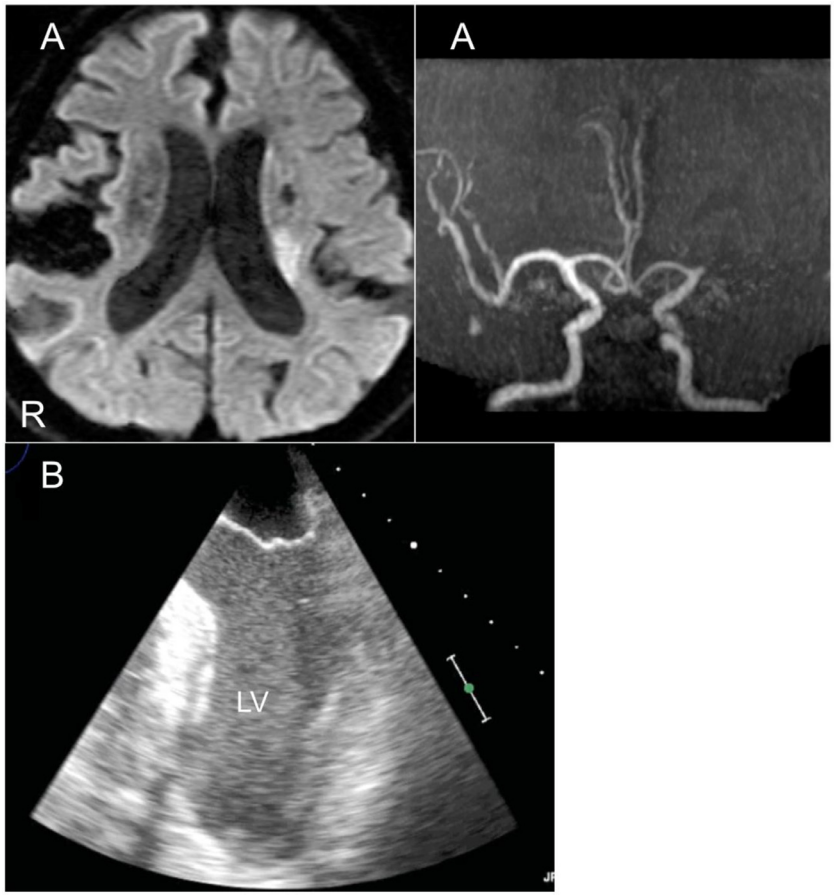

Figure 2. *Illustrative case 1. Diffusion-weighted MRI revealed left infarction induced by middle cerebral artery embolism (A). Transesophageal echocardiography revealed smoke-like echoes in the left ventricle (LV) (B).*

this causes hypercoagulability in the left ventricle, these patients should also be treated with anticoagulant agents. Furthermore, anticoagulant treatment is recommended for patients with paradoxical cerebral embolism, as well as those with PAF and sick sinus syndrome, as these also induce hypercoagulability in the heart.

Embolic sources remained unidentified in 5 patients following our examinations. These patients did not have any plaque which could have caused the embolic infarction, and embolic sources were ruled out with continuous monitoring using an implant recorder. It is difficult to choose between antiplatelet and anticoagulant for prevention. Anticoagulants are known to increase the risk for hemorrhage when compared with antiplatelet.[10] However, this is suggestive of covert AF, which accounts for most cases of ESUS.[1,4] These patients should be treated with anticoagulant therapy to prevent cardiogenic infarction. Overall, 21 of the 27 patients with ESUS (77.8%) required treatment with anticoagulant agents. Cardioembolic stroke was considered to include left ventricle dysfunction, PAF, paradoxical stroke, and sick sinus syndrome (n = 9, 33.3%). Cardioembolic stroke is the most severe type of stroke[11,12] and should be treated with anticoagulant therapy rather than aspirin.[13-16] Considering that both these patients and those with cancer-associated stroke should be treated using anticoagulant therapy,[9] our results suggest that most patients with ESUS require treatment with anticoagulant agents. Six patients with aortic arch atherosclerosis and valve calcification required treatment with antiplatelet agents. These represent rare causes of embolism for which secondary prevention measures remain unclear.[17,18]

Our findings should be interpreted with caution, as our sample size was too small to determine the ideal treatment for ESUS. However, due to the likelihood of cardioembolic stroke, our findings indicate that some patients with ESUS require anticoagulant treatment. Based on embolic sources and prognoses observed in the present study, it remains unclear whether antiplatelet or anticoagulant treatments should be utilized in these patients with ESUS. Previous studies have recommended antiplatelet therapy for these patients.[19,20] Therefore, determining the embolic source is critical for selecting the ideal treatment strategy, particularly among patients with cardioembolic stroke who should be treated with anticoagulant therapy. However, it is difficult to perform enhanced CT and transesophageal ECG for all patients with ESUS. In our study, cancer-associated stroke and

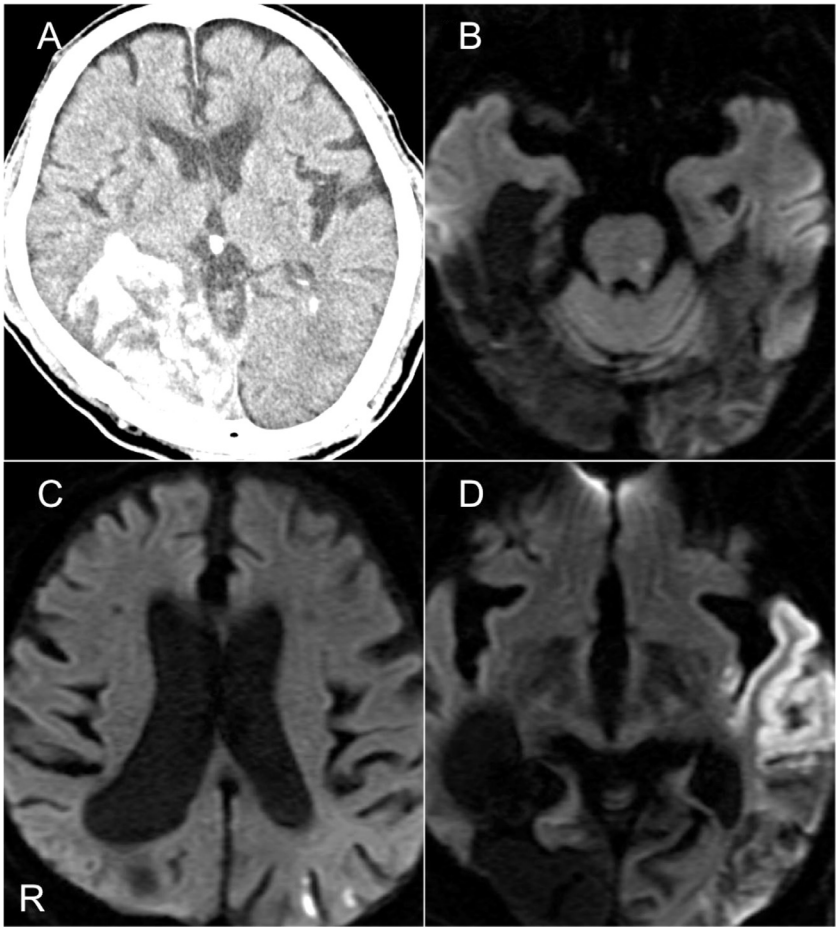

Figure 3. *Illustrative case 2. CT revealed right occipital hemorrhagic infarction (A). Diffusion-weighted MRI revealed pontine infarction (B), left parietal infarction (C), and left temporal lobe infarction (D).*

stroke induced by left ventricle dysfunction accounted for the majority of ESUS cases. Research suggests that cancer-associated stroke can be easily diagnosed based on MRI features, such as bilateral cerebral embolism.[21] Stroke induced by left ventricular dysfunction is considered to occur when the EF is less than 40%.[22,23] Therefore, these 2 causes of stroke may be easy to diagnose without contrast-enhanced CT and transesophageal ECG, ultimately aiding in the selection of appropriate treatment strategies.

Several recent studies have investigated the use of DOACs for ESUS.[5-7] Cerebral embolism induced by PAF (7.4%) and paradoxical embolism (3.7%) were treated using DOACs in some patients of our study, and most required treatment with anticoagulant agents. We considered that patients with ESUS included those with cardioembolic stroke induced by left ventricle dysfunction, paroxysmal arterial fibrillation, paradoxical stroke, or sick sinus syndrome. Taken together, our findings highlight the need to investigate embolic sources in patients with ESUS in order to determine the ideal treatment strategy.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.04.022.

References

1. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13:429-438.
2. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444-1451.
3. ESPRIT Study GroupHalkes PH, van Gijn J, et al. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurol 2007;6:115-124.
4. Ntaios G, Vemmos GK. Response to letter regarding article, "Embolic stroke of undetermined source in the Athens stroke registry: a descriptive analysis." Stroke 2015;46:e70.
5. Geisler T, Poli S, Meisner C, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS

randomized trial): rationale and study design. Int J Stroke 2017;12:985-990.
6. Diener HC, Easton JD, Granger CB, et al. Design of randomized, double-blind, evaluation in secondary stroke prevention comparing the efficacy and safety of the oral thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with embolic stroke of undetermined source (RE-SPECT ESUS). Int J Stroke 2015;10:1309-1312.
7. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med 2018;378:2191-2201.
8. Diener HC, Sacco RL, Easton JD, et al. RE-SPECT ESUS: Dabigatran versus acetylsalicyclic acid for stroke prevention in patients with embolic stroke of undetermined source. Int J Stroke [published online October 18, 2018]. (Abstr).
9. Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. Blood 2007;110:1723-1729.
10. Toyoda K, Yasaka M, Iwade K, et al. Bleeding with Antithrombotic Therapy (BAT) Study Group. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. Stroke 2008;39:1740-1745.
11. Michel P, Odier C, Rutgers M, et al. The Acute SToke Registry and Analysis of Lausanne (ASTRAL): design and baseline analysis of an ischemic stroke registry including acute multimodal imaging. Stroke 2010;41:2491-2498.
12. Ntaios G, Papavasileiou V, Makaritsis K, et al. Association of ischaemic stroke subtype with long-term cardiovascular events. Eur J Neurol 2014;21:1108-1114.
13. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993;342:1255-1262.
14. Hart RG, Sherman DG, Easton JD, et al. Prevention of stroke in patients with nonvalvular atrial fibrillation. Neurology 1998;51:674-681.
15. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. JAMA 2002; 288:2441-2448.
16. Diener HC, Eikelboom J, Connolly SJ, et al. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. Lancet Neurol 2012;11:225-231.
17. Amarenco P, Davis S, Jones EF, et al. Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. Stroke 2014;45:1248-1257.
18. Mahajan N, Khetarpal V, Afonso L. Stroke secondary to calcific bicuspid aortic valve: case report and literature review. J Cardiol 2009;54:158-161.
19. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86. Erratum in: BMJ 2002;324:141.
20. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308:81-106. Erratum in: BMJ 1994; 308:1540.
21. Umemura T, Yamamoto J, Akiba D, et al. Bilateral cerebral embolism as a characteristic feature of patients with Trousseau syndrome. J Clin Neurosci 2017;42:155-159.
22. Takasugi J, Yamagami H, Noguchi T, et al. Detection of left ventricular thrombus by cardiac magnetic resonance in embolic stroke of undetermined source. Stroke 2017;48:2434-2440.
23. Hays AG, Sacco RL, Rundek T, et al. Left ventricular systolic dysfunction and the risk of ischemic stroke in a multiethnic population. Stroke 2006;37:1715-1719.