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Pathophysiology of Cardioembolism

Chan-Hyuk Lee

Abstract

Cardioembolism is caused by occlusion of the cerebral artery due to a blood clot created by structural and functional abnormalities of the heart. As the world's population ages, the prevalence of cardiovascular disease is on the rise, as is the rate of cardioembolism. Thrombus formation has two mechanisms: first, fibrinogen mediates activated platelets, which causes platelet aggregation and produces white thrombi; and second, clotting factors in the plasma in which the fibrin clot is finally generated through the contact activation and tissue factor pathways, and red thrombi are formed by interlocking red blood cells. The thrombi formed by cardioembolism are red, produced by plasma coagulation, and structurally unstable. Therefore, red thrombi are prone to degradation, and clinical symptoms of ischemic stroke due to cardioembolism tends to fluctuate. Intracardiac thrombi are most common in the appendages of the left atrium and apex of the left ventricle. Atrial fibrillation, the most common cause of cardioembolism, has a higher incidence in men than in women. However, the proportion of elderly women is higher than that of men, so the absolute prevalence of atrial fibrillation is higher for women. In women, atrial fibrillation increases after menopause. Covert atrial fibrillation has been discussed as a leading cause of embolic stroke of undetermined source. Covert atrial fibrillation is more likely to be detected in a longer measurement period. Therefore, devices for long-term electrocardiography measurements are under development. Although related studies are underway, to date, non-vitamin K antagonist oral anticoagulants do not have an advantage over aspirin for preventing stroke recurrence in patients with embolic stroke of undetermined source.

9.1 Introduction

Cardioembolism (CE) accounts for about 20–30% of all ischemic strokes [1], and its proportion is gradually increasing as the population ages. CE tends to have higher neurological severity in the early stages of stroke compared to stroke caused by other mechanisms. Recovery and prognosis are also poor and recurrence rates are higher than other mechanisms [2]. However, if CE is diagnosed with appropriate tests and treated with anticoagulants, stroke can be effectively prevented. This chapter introduces CE, which is growing in importance in the field of stroke. The first part of the chapter describes the molecular and pathophysiological mechanisms

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C.-H. Lee (✉)
Department of Neurology, Jeonbuk National University Hospital, Jeonju, Republic of Korea

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S.-H. Lee (ed.), *Stroke Revisited: Pathophysiology of Stroke*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1430-7_9

and features of CE, while the second part addresses specific considerations. This chapter is derived in part from the previously published Stroke Revisited series, Volume 1, "Diagnosis and Treatment of Ischemic Stroke." In addition to the previously described contents, the author has provided additional contents that may be helpful.

9.2 Mechanism of Thrombus Formation in CE

Stroke is the second most common cause of death worldwide. Among them, CE accounts for about 20–30% of all stroke patients, and the proportion is increasing over time [1]. Since CE is caused by clotting of the blood vessels generated by various heart diseases, the mechanism may be complicated. However, within that complexity, there is a basic mechanism of thrombus formation that we will summarize here (Fig. 9.1).

9.2.1 Platelet Aggregation

Thrombocytosis is associated with platelets can be classified into two types according to the involved component. First, we describe the process by which platelets participate. Collagen and tissue factors are located below normal vascular endothelial cells. When collagen and tissue factors under the endothelial cells are exposed to the bloodstream due to atherosclerosis, inflammation, and injury, platelet aggregation begins. Collagen exposed to the blood adheres to platelets through two major anchors: Platelet glycoprotein Ib-V-IX and collagen von Willebrand Factor (vWF) bind to each other (anchor 1), while platelet glycoprotein VI interacts with collagen directly (anchor 2). Through this process, collagen and platelets bind tightly. In particular, glycoprotein VI plays an important role in platelet activation and granulation during early thrombus generation. GpIIb/IIIa, located on the membranes of activated platelets, is modified by disulfide

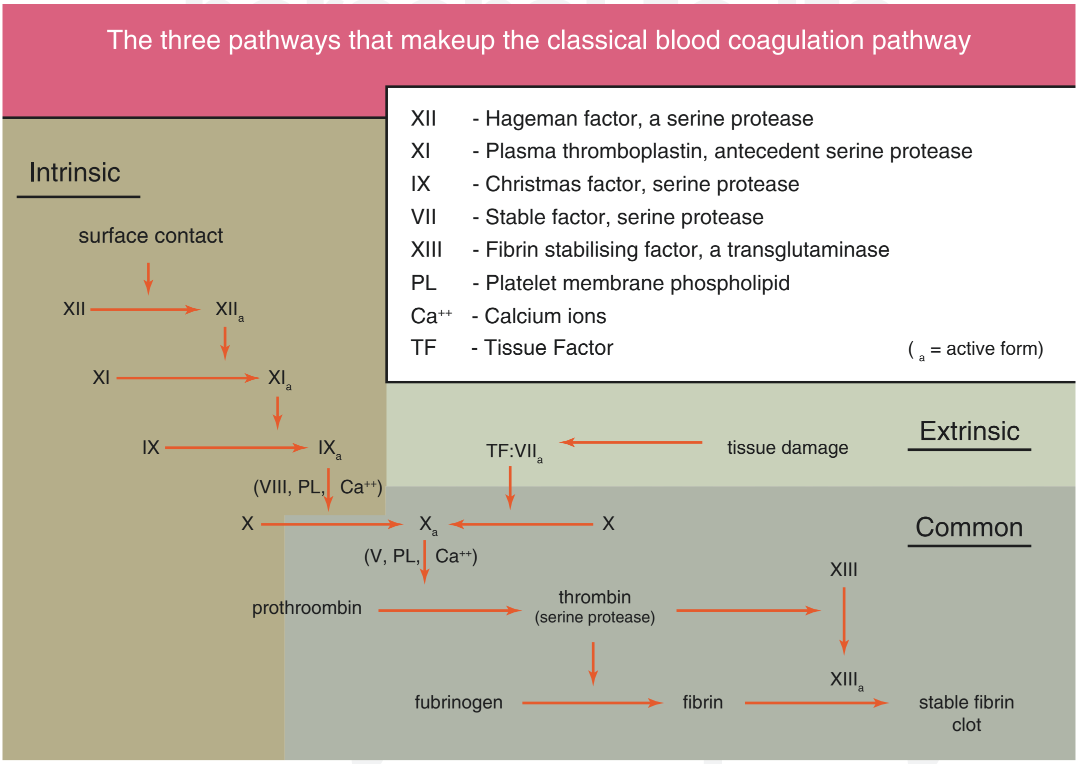
The three pathways that makeup the classical blood coagulation pathway
XII - Hageman factor, a serine protease
XI - Plasma thromboplastin, antecedent serine protease
IX - Christmas factor, serine protease
VII - Stable factor, serine protease
XIII - Fibrin stabilising factor, a transglutaminase
PL - Platelet membrane phospholipid
Ca++ - Calcium ions
TF - Tissue Factor
(a = active form)
Intrinsic
surface contact
XII
XIIa
XI
XIa
IX
IXa
(VIII, PL, Ca++)
Extrinsic
TF:VIIa
tissue damage
Common
X
Xa
X
(V, PL, Ca++)
prothroombin
thrombin
(serine protease)
XIII
XIIIa
fubrinogen
fibrin
stable fibrin clot

Fig. 9.1 Cascade of blood coagulation

isomerase. This increases the affinity for fibrinogen and vWF, allowing platelets to aggregate. On the other hand, the activated granules secrete alpha granules and dense granules to the outside. In particular, dense granules contain adenosine diphosphate (ADP) and calcium ions. ADP is further attached to P2Y1 or P2Y12 receptors on platelets to further promote platelet activation.

The next consideration is tissue factors, which exist in two main forms and are inactivated in the blood vessel wall but activated in the endothelial cells. Inactive tissue factors in the vessel wall are activated by protein disulfide isomerase. Tissue factors activated by isomerase complex with factor VIIa in the blood, which activates factor IX. Thereafter, various coagulation factor cascade and thrombin are activated. Thrombin plays an important role in fibrin production of the plasma coagulation mechanism described later and breaks down the activated receptor 4 of platelets, thereby activating platelets. Activated platelets secrete ADP, serotonin, and thromboxane A2 to activate other platelets. This series of processes leads to fibrinogen-mediated platelet aggregation. In blood vessels that are narrowed or occluded by arteriosclerosis or damaged, platelets are mainly involved in blood clot formation. Platelet-rich clots produce white thrombi that reflect platelet color.

9.2.2 Coagulation Cascade

The next mechanism to be examined is the plasma coagulation process involving various coagulation factors in the plasma. Here the contact activation and tissue factor pathways are activated, and these two processes converge to factor X via the coagulation factor cascade. After thrombin and fibrin activation, a stable thrombus is formed.

9.2.2.1 Contact Activation Pathway (Intrinsic Pathway)

Initiation of the contact activation pathway begins when high-molecular-weight kininogen and prekallikrein meet factor XII. As they become complexes, prekallikrein is converted to kallikrein, which converts factor XII to factor XIIa. Activated factor XIIa in turn activates factor XI and factor IX. Factor IX activates Factor X as Factor Xa with the help of a complex consisting of Factor VIII, platelet membrane phospholipid, and calcium ions. In this process, Factor XII is the starting point of the contact activation pathway; if it is deficient, the activated partial thromboplastin time becomes prolonged.

9.2.2.2 Tissue Factor Pathway (Extrinsic Pathway)

Tissue factor pathways are important for rapidly generating thrombin through feedback. Tissue factors are involved in the initiation of the pathway and distributed in fibroblasts, pericytes of the epicardium, and smooth muscle cells of blood vessels. The pathway begins when disulfide isomerase secreted from activated endothelial cells or platelets breaks down disulfide bonds of tissue factors. Tissue factors without disulfide bonds are activated and then complexed with factor VII. This complex converts Factor X to Factor Xa. Through this cascade of processes, the tissue factor pathway converges to Factor Xa along with the contact activation pathway described above.

From this point forward, the hemostatic process leads to a common pathway. Activated Factor Xa complexes with Factor V, phospholipids, and calcium ions to convert prothrombin to thrombin. Thrombin then converts the fibrinogen into fibrin, which becomes entangled to form a stable fibrin clot. Thrombin, on the other hand, acts directly on fibrinogen and activates Factor XIII, which also has a bypass pathway that promotes fibrin clot production. Thrombin can independently stimulate Factors V and VIII, causing rapid thrombin production.

9.2.3 Other Factors Involved in Blood Coagulation

The cofactors and modulators involved in the coagulation process participate in a series of processes from the beginning to the end of the coagulation process and play an important role in maintaining overall homeostasis. The first cofactor to mention is calcium and phospholipids, the cell membrane components of platelets. The two cofactors participate in the formation of complexes involving Factors VIII and IX as well as in the complexes of Factors V and X and form thrombin. Vitamin K's role is also essential. Vitamin K acts as a coenzyme of hepatic gamma-glutamyl carboxylase and helps gamma-glutamyl carboxylase attach carboxyl groups to Factors II, VII, IX, and X and proteins C, S, and Z, which participate in the progression and termination of the coagulation process. Vitamin K acts as a coenzyme and oxidizes; vitamin K epoxide reductase is the enzyme that reverses it. Warfarin, which is widely used for its anticoagulant effect, exhibits this effect by inhibiting vitamin K epoxide reductase.

Let us examine the cofactors. Protein C acts as an anticoagulant and is activated by the thrombin and thrombomodulin complexes. Activated protein C degrades factors V and VIII with the help of protein S and phospholipids. Therefore, patients who are naturally deficient in protein C or S are more likely to develop blood clots. Antithrombin acts as a serine protease inhibitor to inhibit thrombin as well as factors IX, X, XI, and XII. Tissue factor pathway inhibitors inhibit tissue factors and interfere with the coagulation mechanisms mediated by tissue factors. Plasmin regulates the coagulation process by breaking down fibrin into a fibrin degradation product. Plasmin is made from plasminogen, which is catalyzed by tissue plasminogen activator (tPA). Artificially synthesized recombinant tPA is useful for thrombolysis in patients with acute ischemic stroke. And finally, prostacyclin inhibits granule secretion associated with platelet activity.

9.2.4 Blood Coagulation and CE

Several cardiovascular diseases can cause CE, but the underlying cause is stagnant blood flow caused by heart disease [3]. When blood flow is slowed by cardiovascular disease, a core of red blood cells is temporarily formed in the heart. Once the erythrocyte core is created, various coagulation factors are involved to activate the blood coagulation process. This process causes fibrin to bind to red blood cells, which rarely involves platelets, producing a red blood cell-rich "fibrin meshwork (red thrombi)" [4]. As such, intracardiac thrombi are produced by coagulation cascades rather than platelet aggregation. However, as described earlier, coagulation factors, including tissue factors, are also involved in the process of inducing platelet aggregation. Although not as effective as anticoagulants, this means that antiplatelet agents may also have some ability to prevent CE.

Another consideration in CE is the fact that the distribution of coagulation factors in the stroke of stroke patients due to atrial fibrillation (AF) is abnormal. Related studies reported increased fibrin turnover in patients with acute or chronic AF [5, 6]. Patients with AF have prothrombotic index abnormalities, and some prothrombotic indexes have been identified only in AF or paroxysmal AF [7, 8]. However, past studies were sporadic, and the rationale for supporting such studies remain insufficient. The authors reviewed the relevant reports and summarized the mechanism by which coagulation factor distribution differs from normal in AF patients. First, long-term AF causes endocardial damage and structural remodeling. Structural changes in the endocardium cause dysfunction of the various coagulation factors that work in association with it, which promotes blood clot production [2]. As mentioned earlier, cardiac dysfunction, such as AF, interferes with normal blood flow, which leads to abnormal distribution of coagulation factors such as D-dimer, thereby promoting thrombus formation. Blood clotting factor abnormalities in cardiovascular disease, including AF, are an essential topic for elucidating the key mechanisms of CE, which should be clarified through ongoing research.

9.3 Features of CE

CE differs from stroke due to atherosclerotic thrombosis, with the most severe neurologic deficits at the time of stroke and often a dramatic improvement in symptoms. This property is closely related to the thrombus component produced in the heart. Intracardiac thrombi are red thrombi containing few platelets. In contrast, the thrombi produced by atherosclerotic vessels are platelet-rich and white. Unlike white thrombi, red thrombi are unstable and easily decomposed because few platelets play a role in structural stabilization. That is, even if the intracardiac thrombus occludes the cerebral artery, the blood vessels are often reopened due to high blood pressure and proximal blood flow. At this time, if the blood vessels are quickly reopened before ischemic tissue damage is caused by the thrombus, the patient's symptoms may be rapidly improved. However, if a vessel is opened after a period of time after the tissue is damaged, hemorrhage or hemorrhagic transformation may occur in the damaged tissue, which may worsen the patient's symptoms. Therefore, it is reasonable to suspect CE if the patient's symptoms improve sharply after a stroke or if hemorrhagic or hemorrhagic transformation is identified by brain computed tomography (brain CT) or magnetic resonance imaging (MRI).

Intracardiac blood clots tend to affect specific areas (atria and ventricles) depending on their location. First, in the atrium, it is likely to occur in the left atrial appendage, a tissue attached to the atrium with a narrow entrance and a long internal structure. This structure slows the internal circulating blood flow, increasing the chance of thrombus formation [9]. In the ventricles, thrombus is often produced in the apex of the left ventricle. In particular, left ventricular (LV) aneurysm or acute myocardial infarction are associated with further blood flow impediments, increasing the chance of blood clots. The risk of thrombosis is highest at the time of acute myocardial infarction and then gradually decreases.

AF, an important cause of CE, differs between the sexes. In a study of North American and European populations, males showed a 1.5–2 times higher incidence of AF than females; the incidence increases with age in both sexes. Prevalence was also reported to be higher in males than females [10]. Nevertheless, women have a longer life expectancy than men, so the absolute figure is higher for them. This trend is evident in North America and Europe but not in Asia (0.78% for males and 0.76% for females) [11]. The prevalence of AF has increased more than in the past. According to the Minnesota study, the incidence of AF has increased in both men and women since the 1980s at rates that were similar in men and women [12]. Although there is a difference according to the study, the actual frequency of CE was higher in women. This is because the prevalence of AF in women after menopause is higher than that in men. The effects of AF on stroke incidence also vary by sex. If a woman has AF, the risk of stroke is higher than that for men [13].

9.4 Noteworthy CE Points

CE is caused by clogging of the cerebral artery due to structural and functional abnormalities of the heart. CE has various causes that are classified into high risk and medium to low risk according to the degree of contribution. High risks include AF, mechanical prosthetic valve, left atrial thrombus, left ventricular thrombus, and dilated cardiomyopathy. Medium to low risks include patent foramen ovale, atrial septal aneurysm, mitral valve prolapse, and congestive heart failure. Although CE usually comes to mind only AF, as mentioned above, AF is one of its several causes.

The ESUS (embolic stroke of undetermined source) is a new concept proposed in 2014 that refers to non-lacunar strokes among cryptogenic strokes where the specific cause of stroke is unknown [14]. As the term suggests, the cause is unknown but suggests an embolic source. ESUS accounts for about 17% of all ischemic strokes [15], but the cause is unknown and there has been disagreement among researchers regarding its diagnosis and treatment. Recently, covert AF, one of the causes of CE, has attracted attention as the underlying cause of ESUS. Covert AF is a condition in which AF occurs shortly, but it was not confirmed by cardiac rhythm examination, but in reality, AF occurs intermittently. Past studies reported that intermittent AF occurs at the same level of thromboembolic complications as sustained AF [16]. This suggests that the presence of AF is more important than duration. If a patient has covert AF but the doctor has not diagnosed it, the patient may not be adequately treated, which may increase the likelihood of stroke recurrence. On the other hand, if covert AF is found, appropriate treatment may effectively prevent secondary stroke. However, 24-h Holter monitoring, which is commonly used to monitor heart rhythm in stroke patients, has difficulty identifying covert AF. Instead, a study of 149 patients with ischemic stroke or TIA reported a higher probability of finding covert AF as the test duration increased. Electrocardiography at admission (2.7%), echocardiography (4.1%) within 5 days, 24-h Holter monitoring (5%), and recorder (5.7%) for 7 days [17]. Studies such as the CRYSTAL AF and EMBRACE have also shown that long-term electrocardiographic monitoring is useful for covert AF detection. Recently, a device for monitoring the heart rate by attaching it to a mobile phone or a smart watch has been developed, and an implantable loop recorder that can be monitored for several years by implanting the device in the body has also been developed (Figs. 9.2 and 9.3).

As the importance of covert AF emerges and related research continues, the American Heart Association guideline recommends prolonged rhythm monitoring for up to 30 days. A recent large-scale study compared the secondary prevention effect of NOAC and aspirin in patients with ischemic stroke classified as ESUS [18, 19]. Two studies of dabigatran and rivaroxaban showed no advantage over aspirin, and apixaban studies are ongoing. We should wait for one more study, but we can estimate that ESUS is temporarily overcoagulated by other causes than AF, including covert AF, and that NOAC may not effectively suppress it.

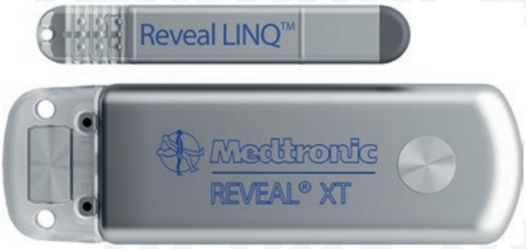

Fig. 9.2 REVEAL XT and Reveal LINQ, Medtronics' implantable loop recorder

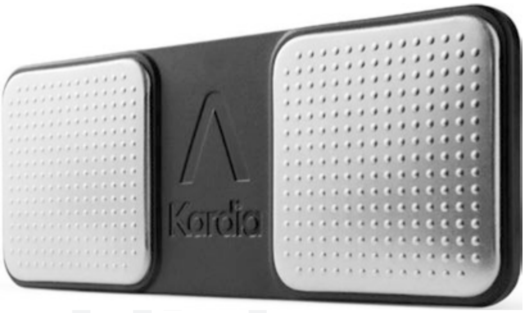

Fig. 9.3 KardiaMobile EKG Monitor from AliveCor, capable of measuring heart rhythm in conjunction with a smartphone

9.5 Conclusions

CE has a poor prognosis compared to stroke due to other mechanisms, and the prevalence of CE is increasing due to the global aging trend. The social interest in CE is ever higher. There are also more opportunities for neurologists to confront CE patients. In recent years, the CE treatment paradigm has also shifted rapidly from warfarin to NOAC. To keep pace with these increased social concerns and rapid changes in care practices, it is time for neurologists to pay more attention to CE and consider it carefully to ensure proper diagnosis and treatment.

References

1. Font MA, Krupinski J, Arboix A. Antithrombotic medication for cardioembolic stroke prevention. Stroke Res Treat. 2011;2011:607852.
2. Arboix A, Alio J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. Curr Cardiol Rev. 2010;6(3):150–61.

3. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. Lancet. 2009;373(9658):155–66.
4. Spence JD. Cardioembolic stroke: everything has changed. Stroke Vasc Neurol. 2018;3(2):76–83.
5. Marin F, Roldan V, Climent VE, Ibanez A, Garcia A, Marco P, et al. Plasma von Willebrand factor, soluble thrombomodulin, and fibrin D-dimer concentrations in acute onset non-rheumatic atrial fibrillation. Heart. 2004;90(10):1162–6.
6. Mahe I, Drouet L, Chassany O, Mazoyer E, Simoneau G, Knellwolf AL, et al. D-dimer: a characteristic of the coagulation state of each patient with chronic atrial fibrillation. Thromb Res. 2002;107(1–2):1–6.
7. Mondillo S, Sabatini L, Agricola E, Ammaturo T, Guerrini F, Barbati R, et al. Correlation between left atrial size, prothrombotic state and markers of endothelial dysfunction in patients with lone chronic nonrheumatic atrial fibrillation. Int J Cardiol. 2000;75(2–3):227–32.
8. Kamath S, Blann AD, Chin BS, Lip GY. A prospective randomized trial of aspirin-clopidogrel combination therapy and dose-adjusted warfarin on indices of thrombogenesis and platelet activation in atrial fibrillation. J Am Coll Cardiol. 2002;40(3):484–90.
9. Cianciulli TF, Saccheri MC, Lax JA, Bermann AM, Ferreiro DE. Two-dimensional speckle tracking echocardiography for the assessment of atrial function. World J Cardiol. 2010;2(7):163–70.
10. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. Nat Rev Cardiol. 2016;13(6):321–32.
11. Li Y, Wu YF, Chen KP, Li X, Zhang X, Xie GQ, et al. Prevalence of atrial fibrillation in China and its risk factors. Biomed Environ Sci. 2013;26(9):709–16.
12. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114(2):119–25.
13. Cove CL, Albert CM, Andreotti F, Badimon L, Van Gelder IC, Hylek EM. Female sex as an independent risk factor for stroke in atrial fibrillation: possible mechanisms. Thromb Haemost. 2014;111(3):385–91.
14. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13(4):429–38.
15. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. Stroke. 2017;48(4):867–72.
16. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, et al. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W substudy. J Am Coll Cardiol. 2007;50(22):2156–61.
17. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. Stroke. 2004;35(7):1647–51.
18. Hart RG, Sharma M, Mundl 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(23):2191–201.
19. Diener HC, Easton JD, Granger CB, Cronin L, Duffy C, Cotton D, 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(8):1309–12.