10 Atrial Fibrillation and Other Cardiac Dysfunctions Related with Stroke

Woo-Keun Seo

Abstract

Cardioembolic stroke is caused by embolus originating from the heart or aorta. Of all cardioembolic stroke cases, about a quarter are ischemic stroke cases. The clinical features and neuroimaging findings of cardioembolic stroke make differences from other stroke subtypes due to the peculiarity of pathogenesis. Among the causes of cardioembolic stroke, atrial fibrillation is the most frequent and important disease. Stroke patients with atrial fibrillation have severe neurological symptoms and should be managed differently from patients with other types of ischemic stroke. The importance of atrial fibrillation-related stroke has recently been highlighted as the use of newer oral anticoagulants has been introduced. In this chapter, recent trends of diagnosis and treatment for stroke patients with atrial fibrillation, as well as other cardiac dysfunctions related to stroke, will be discussed.

10.1 Introduction

Stroke is a set of clinical syndromes characterized by acute or rapidly progressive focal neurological symptoms originating from diseases of cerebral vessels. Cerebral vascular diseases that cause stroke include atherosclerosis, small vessel occlusion, and cardioembolism. Strokes from different the etiologies have different clinical features, risk factors, and outcomes. In addition, therapeutic strategies also differ according to etiologic mechanism. In that context, cardioembolic stroke has peculiar features from other types of stroke.

Cardioembolic stroke is an ischemic stroke subtype characterized by cortical infarction, sudden onset and rapid regression of symptoms, and simultaneous multiple territorial infarctions [1]. It is responsible for approximately 20% of ischemic stroke cases [2]. The proper diagnosis of cardioembolic etiology in acute stroke patients has become a pressing issue after the introduction of newer oral anticoagulants (NOACs) and with the advancement of reperfusion therapy using endovascular thrombectomy. Unlike other stroke subtypes, the potential source of cardioembolism (PSCE), which is originated from the outside of the brain, is the cause of cerebral arterial occlusion. Among the PSCE, atrial fibrillation (AF) is the most frequent type, and its importance is increasing with the aging of the population [3]. AF accounts for >70% of cardioembolic stroke cases [4], and AF patients with prior stroke or TIA carry even higher stroke

W.-K. Seo (✉)
Department of Neurology, Samsung Medical Center, Sungkyunkwan University, Seoul, Republic of Korea
e-mail: nukseo@skku.edu

S.-H. Lee (ed.), *Stroke Revisited: Pathophysiology of Stroke*, Stroke Revisited,
https://doi.org/10.1007/978-981-10-1430-7_10

risks [2]. Although NOACs are rapidly replacing vitamin K antagonists and reduce the risk of stroke, the risk of stroke in patients with AF is still considerably high.

However, the diagnosis of cardioembolic stroke is still a matter of concern. Approximately one-fourth of those with ischemic stroke is a stroke of an undetermined cause despite thorough investigations, including laboratory tests, brain imaging (cerebral computed tomography [CT]/magnetic resonance imaging [MRI]), MR/CT angiography, and cardiac workup [5]. Considering that the primary etiology of cryptogenic stroke is thromboembolism [6], "embolic strokes of undetermined sources (ESUS)" is a more clinically compatible and suitable definition that imparts a significance to the presence of potential embolic sources [7]. Moreover, AF is considered the major cause of stroke in ESUS. It is important to detect undiagnosed (or paroxysmal) AF in patients with ESUS because patients with AF are recommended to receive oral anticoagulant (OAC) treatment, whereas most patients with other stroke types are usually treated with antiplatelet agents.

Therefore, in this chapter, the clinical importance of AF in stroke prevention will be discussed with an emphasis on the detection of AF in stroke patients. In addition, several other cardiac diseases associated with the incidence of stroke will be discussed.

10.2 Diagnosis and Treatment of Stroke Patients with AF

10.2.1 Stepwise Diagnostic Approach to Detect AF in Stroke Patients

10.2.1.1 Initial Step: History Taking

A stepwise diagnostic approach for cardioembolic stroke was presented in Fig. 10.1. In stroke patients, an essential step is to check for the presence of AF from the early period after the onset of stroke to provide proper management. However, the detailed process for the detection of AF differs according to the clinical situation and pathway in each hospital. In acute stroke patients who are candidates for reperfusion therapy, baseline electrocardiography (ECG) assessment is being recommended [8]. However, the more important step to obtain information about the presence of AF is history taking.

In acute stroke patients who are candidates for reperfusion therapy using intravenous tissue plasminogen activator (t-PA), previous OAC use is an exclusion criterion. Before the era of NOACs, the OAC effect of vitamin K antagonists was estimated with prothrombin time measurement. However, unfortunately, no reliable and clinically applicable measures have been established for the anticoagulant activity of NOACs, until now. Furthermore, about half of patients with AF among those with ischemic stroke have paroxysmal AF, which can be omitted from detection on baseline ECG in the emergency department. Therefore, detailed history taking is crucial to avoid the use of t-PA in orally anticoagulated patients.

10.2.1.2 Second Step: Suspecting Stroke with AF

As AF is the most important cause of cardioembolic stroke, AF-related stroke shares clinical features and findings on brain imaging with cardioembolic stroke. According to the TOAST (Trial of Org 10,172 in Acute Stroke Treatment) classification, diagnosis of cardioembolic stroke is based on cortical or cerebellar dysfunction with the exclusion of lacunar syndrome, lesions >1.5 cm in size, absence of cerebral arterial stenosis, and presence of a cardiac source of emboli [9]. In detail, cerebral dysfunction in cardioembolic stroke includes sudden onset to the maximal neurological deficit or rapid progression of symptoms; frequently accompanying cerebral cortical symptoms such as visual-field defects, aphasia or neglect, and rapidly improving neurological deficits related to early spontaneous recanalization in some instances; and altered consciousness [1]. Wallenberg's syndrome, cerebellar infarct, and top-of-basilar syndrome are the common clinical features in cardioembolic stroke involving the posterior circulation [1, 10, 11]. Moreover, when the lacunar syndrome is

present, the possibility of cardioembolic origin is low. Besides, seizure or headache at stroke onset, which were suggested as unique features of cardioembolic stroke, are not specific to cardioembolic stroke [1].

More sophisticated approaches to suspect stroke with AF have been made using statistical models. Seo et al. reported that they predicted the presence of AF among acute stroke patients by using a model composed of clinical, neuroimaging, and biomarker variables [12]. The model included age, left atrial size, free fatty acid level, triglyceride level, susceptibility vessel sign, hemorrhagic transformation, and cortical involvement as variables and showed a C-statistic value of 0.908. A similar approach was made to distinguish etiologic mechanisms among patients with ESUS [13]. In this model, clinical and neuroimaging findings were used for the prediction of etiology. Stroke caused by paroxysmal AF had a higher National Institutes of Health Stroke Scale (NIHSS) score at baseline and larger lesion volume.

10.2.1.3 Third Step: Baseline ECG, Telemonitoring, 24-h Holter Monitoring, and Long-Term Monitoring

AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with a resulting deterioration of atrial mechanical function [14]. ECG diagnosis of AF is based on the disappearance of consistent P waves, which are replaced by rapid oscillations or fibrillation waves. The diagnosis of AF is based on the findings from the documented 12-lead ECG, telemetric, or implantable long-term recordings. Current guidelines recommend ECG monitoring for at least 24 h after a stroke [15]. However, the need for the extended periods of monitoring is controversial. In a meta-analysis that assessed the stepwise approach to detect AF in stroke patients, 23.7% of the patients had AF at the final step [16]. In this study, four sequential steps were suggested to improve the detection of AF in stroke patients as follows: baseline ECG, in-hospital ECG monitoring, first ambulatory Holter monitoring, and additional long-term monitoring. Each step improved the detection rate of AF. The first step was admission ECG, which revealed post-stroke AF in 7.7% of the patients. In-hospital ECG tests such as serial ECG, continuous inpatients cardiac telemetry, and in-hospital Holter monitoring can increase the detection rate by 4.2%. If ambulatory Holter monitoring is added to the test, 7.5% of new AF cases can be detected. Finally, additional long-term cardiac monitoring, including outpatient telemetry, external loop recording, and implantable loop recording can detect an additional 4.3% of AF patients. This stepwise approach can improve the detection rate for hidden AF in patients with paroxysmal AF.

As described in the earlier section, a considerable proportion of stroke patients have no confirmatory etiology and are often classified as having a cryptogenic stroke or stroke of undetermined etiology with a negative evaluation result. Recently, ESUS is replacing cryptogenic stroke [17]. In patients with ESUS, the main etiologic disease is speculated to be paroxysmal AF. The most promising method for detecting paroxysmal AF is long-term ECG monitoring using an implantable loop recorder. Its superiority in detecting AF in cryptogenic stroke was validated in the Cryptogenic Stroke and Underlying AF trial [18]. In this randomized controlled trial, 441 stroke patients without AF on 24-h ECG monitoring were divided into an implantable cardiac monitoring group and a conventional evaluation group. The implantable cardiac monitoring group showed a 6.4-fold improvement in AF detection rate as compared with the conventional evaluation group. However, the overall detection rate by 12 months was only 12.4%, which is unexpectedly low. Several case series about long-term ECG monitoring using implantable cardiac monitoring devices showed a similar yield [19].

10.2.2 Neuroimage and Blood Biomarkers of AF-Related Stroke

10.2.2.1 Imaging Biomarkers

Brain images also provide important clues for the diagnosis of cardioembolic stroke. Various imaging modalities are used to assess the etiology of stroke. The most well-known feature of

brain images in cardioembolic stroke is bihemispheric involvement or simultaneous multiple infarcts in multiple territories [1]. In fact, many researchers tried to distinguish embolic stroke from stroke of other causes. However, a simple topographic distribution of infarction was insufficient to differentiate cardioembolic stroke from stroke associated with atherosclerotic occlusion [20]. However, the recent advances in brain imaging technology, such as diffusion-weighted imaging (DWI) are useful to differentiate stroke etiologies. Kang et al. analyzed topographic patterns on DWI in acute stroke patients and reported that a single cortico-subcortical lesion and multiple lesions in multiple territories suggested cardioembolic stroke [21]. However, even with DWI, differentiation between AF-related embolic stroke from the stroke of other embolic sources is not reliable [22].

Noninvasive imaging modalities for evaluating intracranial cerebral arteries improved our understanding of stroke etiology. Early recanalization strongly suggests a cardioembolic stroke.

Another well-known imaging feature of cardioembolic stroke is hemorrhagic transformation [1]. Over 70% of cardioembolic stroke patients experienced hemorrhagic transformation, whereas only 20–40% of all stroke patients did [1]. CT is the first classic modality to identify hemorrhagic transformation. The severity and extent of hemorrhagic transformation in acute stroke are closely related to the clinical outcome and treatment plan for antithrombotics (especially in the case of OAC use). Therefore, quantitative measurement of the severity of hemorrhagic transformation is greatly important, and several grading systems have been developed and used [23]. Gradient echo (GRE) imaging is a new modality that can provide better sensitivity for the detection of hemorrhagic transformation than CT.

Cardioembolic stroke occurs when an arterial embolus originating from the heart or aorta occludes the cerebral artery. Sometimes, the embolus stuck in the cerebral artery can be visualized on brain imaging. The classic "hyperdense middle cerebral artery (MCA) sign" is well known to suggest emboli in the MCA. Red thrombi mainly composed of red blood cells (or hemoglobin) have a higher Hounsfield unit count and appeared as a brighter MCA than the contralateral MCA on cross-sectional non-contrast-enhanced CT imaging [24]. The clinical significance of this sign is that red clots are readily recanalized by thrombolytic agents [25]. GRE imaging is useful for the detection of thrombus as a characteristic dark black signal within the arterial lumen with a blooming artifact [26]. This sign, so-called "susceptibility vessel sign," has a characteristic larger diameter than the contralateral vessel diameter and a tram-like two-layered vessel sign [27]. Figure 10.2 demonstrates the image findings of acute cardioembolic stroke.

In addition, many researchers are investigating the application of artificial intelligence or deep learning technique using clinical and imaging data to predict stroke occurrence, diagnose etiology, and predict outcomes [28]. For example, an artificial intelligence-based approach had been made to distinguish clots of AF and non-AF causes on the basis of dark signals on GRE imaging in acute stroke patients.

10.2.2.2 Blood Biomarkers of Cardioembolic Stroke and AF-Related Stroke

Blood biomarkers are also important targets for investigation in this field. However, most surrogate markers for cardioembolic stroke were nonspecific for cardioembolic or AF-associated stroke [29]. In contrast, biomarkers of AF have specific targets, such as altered hemodynamics, atrial dilatation, myocyte damage, atrial fibrosis, electrical remodeling, prothrombotic state, or impaired cardiac function [30].

The most popular biomarker specific to cardioembolic stroke or AF-associated stroke is brain natriuretic peptide (BNP), an antifibrotic cardiac hormone. BNP derives from the cleavage of inactive NT-proBNP (N-terminal of proBNP) from pro-BNP. Many studies have reported that BNP or NT-proBNP level is predictive of cardioembolic stroke or AF-associated stroke. A recent pooled meta-analysis revealed that the measurement of BNP or NT-proBNP level improved the

accuracy of the diagnosis of cardioembolic stroke or AF-associated stroke [31]. The NT-proBNP level is also predictive of stroke in patients with AF [32]. High-sensitivity troponin, also a marker for myocyte damage, is associated with the cardioembolic stroke subtype or ESUS [33].

GDF-15, a member of the TFG-β cytokine family, is released from macrophages or cardiac myocytes as a stress-inducible cytokine. Plasma levels of GDF-15 is related to increased risk of major bleeding, cardiovascular mortality, and stroke or systemic embolic events in patients with AF [34]. GDF-15 incorporated in a model (ABC score) with age and clinical history, is also validated to predict stroke and other cardiovascular events [35]. The ABC score outperformed the CHA2DS2-VASc score in predicting thromboembolic events and the HAS-BLED score for bleeding complications [34, 36].

Recently, a growing body of evidence shows that FFA is an important biomarker of cardioembolic stroke subtype and outcome in embolic stroke patients [4, 37–39]. The FFA level measured in plasma or cerebrospinal fluid was predictive of the cardioembolic stroke subtype [4, 38]. Moreover, elevated FFA level is a predictive biomarker of recurrent stroke in cardioembolic or AF-associated stroke [37, 39]. All these findings imply that FFA could have a close relationship with cardioembolic stroke.

Currently, several pathogenetic relationships between FFA and cardioembolic stroke have been suggested. Free fatty acids (FFAs), in addition to their role as energy fuel and an important metabolite of lipid metabolism [40], have other important biological activities such as the regulation of platelet activation and thrombosis [41]. The causal relationship between elevated FFA level and thrombogenesis was proved in earlier animal studies [42, 43], and the factors responsible for the thrombogenic effect of FFA appear to be multiple, including oxidative stress, increased inflammation, decreased nitric oxide level with reduced vasodilatation, and platelet activation associated with the arachidonic acid pathway [41]. Another explanation for the association between cardioembolic stroke and FFA level is the arrhythmogenic effect of FFA, which could be supported by the results of the Cardiovascular Health Study [44]. In this population-based cohort study with long-term follow-up, elevated plasma FFA levels at baseline were predictive of future AF development in a dose-dependent manner. Clinical studies have also shown that AF mediates between FFA level and embolic stroke [4, 39]. Finally, elevated FFA levels might be associated with atrial cardiomyopathy. FFAs, through the mitochondrial fatty acid β-oxidation, are the most efficient and predominant substrates for energy production in the normal adult human heart [45]. However, pathological conditions exhibit a "metabolic shift," where the rate of the oxidative metabolism of fatty acids is decreased in favor of increased uptake and metabolism of glucose. Therefore, elevated FFA levels may reflect dysregulated mitochondrial β-oxidation and dysfunctional myocardial disease [45].

10.2.3 Risk Assessment and Treatment of AF-Associated Stroke

10.2.3.1 Risk Assessment

The mainstay of treatment for stroke patients with AF is focused on anticoagulant use. For stroke patients with AF, treatment with long-term anticoagulation is recommended to prevent thromboembolic events. The current guidelines recommend antithrombotic treatment for AF patients according to their risk of thromboembolism, especially embolic stroke. The risk of thromboembolism or stroke can be easily estimated using risk-estimating schemes such as the $CHADS_2$, CHA_2DS_2-VASc, and ATRIA scores. The $CHADS_2$ score includes congestive heart failure, hypertension, age of ≥75 years, diabetes mellitus, prior stroke, and transient ischemic attack (2 points), with a maximum score of 6 points. The CHA_2DS_2-VASc score includes congestive heart failure, hypertension, age of ≥75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age of 65–74 years, and sex (female), with a maximum score of 9 points. The ATRIA score with the previous stroke includes age of <65 years (8 points), age

65–84 years (7 points), age of ≥85 years (9 points), sex (female), congestive heart failure, hypertension, diabetes mellitus, proteinuria, estimated glomerular filtration rate of <45 mL/(min·1.73 m^2), or end-stage renal disease requiring renal replacement therapy, with a maximum score of 15 points. However, unfortunately, the performances of these risk scoring systems are unsatisfactory with low C-statistic values in recent meta-analyses [46, 47]. In stroke patients with AF, the performances of these scoring systems were not systematically evaluated because all AF patients with a stroke history are considered a high-risk population. Therefore, all stroke patients with AF should be treated with long-term oral anticoagulation. However, these risk-estimating schemes are used as important variables that characterize subjects in clinical studies for AF patients. To compare the results between groups or studies, risk-estimating schemes such as the $CHADS_2$ or CHA_2DS_2-VASc scores are the most useful and reliable explanatory variables that can characterize subjects. However, the performances of these scoring systems are even lower in stroke patients with AF than in non-stroke patients. Therefore, newer risk estimators for stroke patients are needed.

The risk of bleeding in AF patients is assessed using the HAS-BLED score, which is composed of hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), and advanced age (>65 years, frailty). The use of the $HEMORR_2HAGES$ (hepatic or renal disease, ethanol abuse, malignancy, older age [≥75 years], reduced platelet count or function, rebleeding risk, hypertension, anemia, genetic factors, excessive fall risk, and stroke) score, which was suggested previously, is not usually recommended because of its complexity. Instead, the ORBIT and ABC scores are newly suggested as alternatives [48]. The current guidelines recommend the more convenient and practical HAS-BLED score for the assessment of bleeding risk. The predictive value of this score in stroke patients has also been validated.

10.2.3.2 Antithrombotic Treatment for Stroke Patients with Atrial Fibrillation

Vitamin K Antagonist Versus NOACs

Currently, vitamin K antagonists and four NOACs are available for long-term prevention of stroke or embolization in patients with AF. The four NOACs include one direct thrombin inhibitor (dabigatran) and direct factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban). The efficacy and validity of each NOAC in comparison with those of vitamin K antagonists were validated in pivotal clinical trials [49–52]. Subgroup analyses for each trial also verified the efficacy and safety of each NOAC in stroke populations [53–55]. A meta-analysis based on the standard-dose treatment of NOACs in comparison with vitamin K antagonists evaluated the efficacy and safety of each drug in >70,000 patients. As a result, NOACs significantly reduced the risk of stroke by 19% as compared with vitamin K antagonists, and the difference was mainly driven by the reduced risk of hemorrhagic stroke (relative risk, 0.49). Although the risk of gastrointestinal bleeding increased by 1.25-fold with marginal significance, mortality decreased by 10%, and the risk of intracranial hemorrhage decreased by 50% [56]. Furthermore, patients treated with NOACs feel comfortable because of the improved food or drug interaction property and the fact that no regular blood testing is required for INR measurement. This convenience in taking the drug improved drug compliance. Real-world data also showed similar results from those of clinical trials. On the basis of the results of these clinical trials, for stroke patients with AF, the current guidelines favor the use of NOACs over vitamin K antagonists [48]. However, several unsolved issues remain regarding the use of OACs in stroke patients with AF.

Each NOAC class has its own characteristics, and the selection of the appropriate drugs should be individualized according to the patient's condition.

Timing of OAC Therapy Initiation

The timing of initiating OAC therapy is one of the practical issues. Hemorrhagic transformation and intracranial hemorrhage complicated by acute stroke are important causes of neurological deterioration in acute stroke patients. Especially cardioembolic stroke due to AF tends to change into the hemorrhagic stroke, and the occluded cerebral artery in cardioembolic stroke easily recanalizes without reperfusion therapy. Therefore, identification of the optimal timing of OAC therapy initiation is an important issue. The TRIPLE-AXEL trial compared the early use of rivaroxaban and warfarin in mild AF-related stroke and showed comparable efficacy and safety [57]. However, a limitation of this study was that the patients enrolled only had a substantially minor stroke. A recent guideline suggested a practical recommendation in that the start of (N)OAC can be determined according to stroke severity (NIHSS score) and additional factors. This recommendation could be the best way to individualize the timing for initiating OAC therapy according to the patient's condition based on the clinical decision of the physician.

In addition, hemorrhagic stroke patients with AF is another clinical vignette. Several observational studies have reported that OAC uses 4–8 weeks after the onset of hemorrhagic stroke is acceptable considering the composite risks of ischemic and hemorrhagic stroke [58].

Optimal Dose or Intensity of Anticoagulants

When a vitamin K antagonist is used for the prevention of thromboembolic events in AF patients, the dose of the drug or intensity of the treatment can be estimated by measuring prothrombin time (with INR). In AF patients, the recommended optimal INR was between 2.0 and 3.0 [48]. On the other hand, the anticoagulant effect of NOACs is challenging to measure. The recommended doses of NOACs on packaging labels were decided based on early-phase clinical trials performed in small numbers of subjects. Thus, the validity of the dose should be reconfirmed. Recently, several real-world data about this issue have been reported. However, the results were inconsistent and needed to be validated, especially in Asian populations.

A significant proportion of stroke patients with AF have comorbid arterial thrombotic diseases and frequently need to be treated with interventions such as percutaneous coronary intervention or carotid artery stenting. In these cases, the decision for the simultaneous use of OACs and antiplatelets is complex. The patients underwent percutaneous coronary intervention and triple antithrombotic therapy for one month, followed by dual therapy (OAC plus aspirin or clopidogrel) for 1 year. However, no controlled studies have been conducted, and no guidelines have been established about stroke patients with atherosclerotic disease or patients who had undergone cerebral artery intervention. Many neurologists or neurosurgeons apply the guideline for PCI in stroke patients after the cerebral vascular intervention, but separate studies are needed.

10.2.3.3 Non-OAC Treatment for Stroke with AF

Some patients with AF irrespective of a previous stroke are contraindicated for long-term OAC use, although NOAC use has become popular. These patients include those with cerebral amyloid angiopathy, those with esophageal varix, or those who need specific drugs that interact with (N)OACs. In these cases, exclusion of cardiac atrial appendage can be one of the options for the prevention of thromboembolic events. Surgical occlusion or exclusion of the left atrial appendage may be considered for stroke prevention in patients with AF if long-term OAC use is contraindicated. Two clinical trials were conducted to compare the efficacy of percutaneous closure of the left atrial appendage with that of vitamin K antagonist therapy and showed non-inferiority of the former, implying that left atrial occlusion could be an alternative to vitamin K antagonists. The relative efficacy and safety of left atrial appendage occlusion in comparison with those of NOAC therapy are well studied and should be investigated with controlled clinical trials.

In terms of non-OAC treatment, rhythm or rate control for AF is usually indicated for symptom improvement in patients with AF, but its efficacy has

not been validated for stroke patients with AF, especially for the prevention of thromboembolic events.

10.3 Patent Foramen Ovale and Other Stroke-Related Cardiac Diseases

Various cardiac or aortic diseases can produce embolus, resulting in cardioembolic stroke. Because the moment when emboli block the cerebral arteries is difficult to determine, etiologic conditions, which are presumed to cause cardioembolic stroke are called PSCE. Several lists of cardiac or cardio-aortic sources of embolisms exist, with subtle differences among the lists. However, recent myocardial infarction, mitral valve disease, severe congestive heart failure, infective endocarditis, intracardiac mass, and nonbacterial thrombotic endocarditis are commonly considered sources of cardioembolic stroke. On the other hand, the thrombogenic properties of patent foramen ovale (PFO), mitral annular calcification, and aortic arch atheroma are controversial. Thus, these conditions are considered sources of embolism when no cardiac source is apparent in patients with a suspected embolic stroke.

Among these conditions, PFO is a common condition even in the general population and has been associated with non-stroke neurological diseases such as migraine. A long-lasting controversy surrounds the usefulness of PFO closure in stroke patients. Recently, three clinical trials that compared percutaneous closure of PFO with the conventional treatment showed the beneficial effect of PFO closure in terms of reducing the risk of recurrent stroke among cryptogenic stroke patients [59–61]. In light of these results, a recent guideline recommends percutaneous PFO closure for cryptogenic stroke patients aged 18–65 years [62]. Further investigations are needed to specify the target population who would significantly benefit from the treatment and reassess the concern about the new AF development (Figs. 10.1 and 10.2).

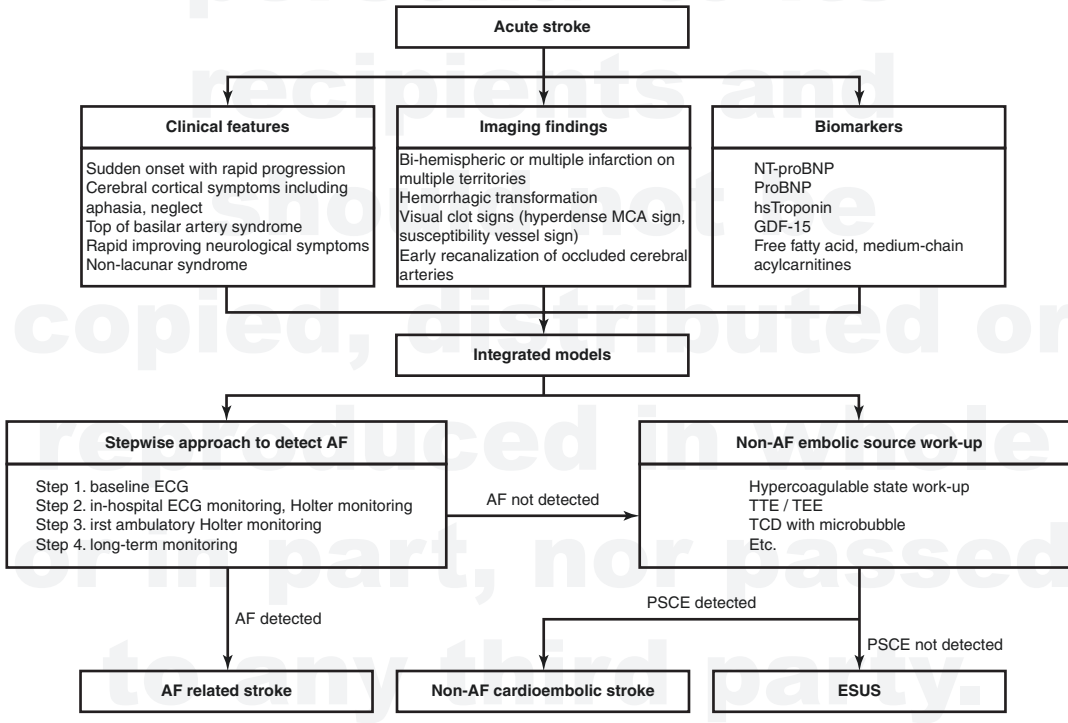

Fig. 10.1 The flow of diagnosis in patients with embolic stroke

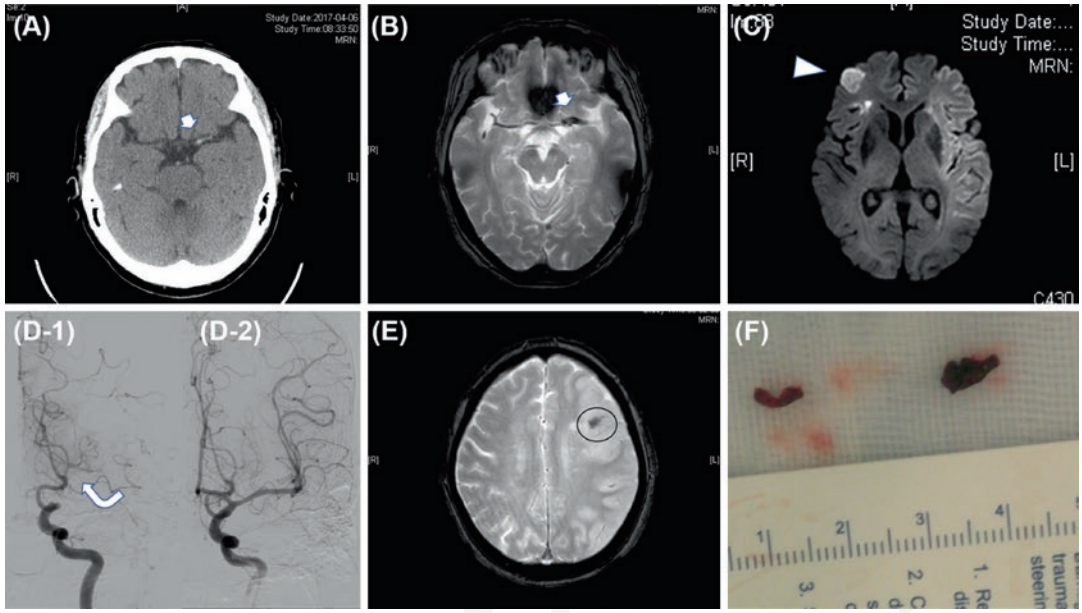

Fig. 10.2 Illustrated case of cardioembolic stroke. A 66-year-old female with a history of atrial fibrillation presented sudden aphasia and right hemiparesis. (**a**) Non-contrast brain CT at the emergency department revealed a hyperdense MCA sign (white arrow). (**b**) At the same lesion, enlarged dart signal intensity with blooming artifact on the GRE image is shown (susceptibility vessel sign). (**c**) The diffusion-weighted image of the patient revealed multiple acute infarctions with different stages involving both cerebral hemispheres. (**d**) Transfemoral catheter angiography before (D-1) and after (D-2). The left middle cerebral artery was recanalized after the endovascular thrombectomy procedure was performed. (**e**) On the GRE image obtained just after the thrombectomy procedure, the small cortical hemorrhagic transformation was found. (**f**) The thrombus extracted from the occluded cerebral artery by endovascular thrombectomy

References

1. Ferro JM. Cardioembolic stroke: an update. Lancet Neurol. 2003;2:177–88.
2. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American heart association/American stroke association council on stroke: co-sponsored by the council on cardiovascular radiology and intervention: the American academy of neurology affirms the value of this guideline. Stroke. 2006;37:577–617.
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (atria) study. JAMA. 2001;285:2370–5.
4. Seo WK, Kim J, Kim YH, Kim JH, Oh K, Koh SB, et al. Elevated free fatty acid is associated with cardioembolic stroke subtype. J Can Sci Neurol. 2011;38:874–9.
5. Fonseca AC, Ferro JM. Cryptogenic stroke. Eur J Neurol. 2015;22(4):618–23.
6. Nouh A, Hussain M, Mehta T, Yaghi S. Embolic strokes of unknown source and cryptogenic stroke: implications in clinical practice. Front Neurol. 2016;7:37.
7. Cantu-Brito C, Sampaio Silva G, Ameriso SF. Embolic stroke of undetermined source in latin America: a review. Neurologist. 2017;22(5):171–81.
8. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 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.
9. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. Stroke. 1993;24:35–41.
10. Timsit SG, Sacco RL, Mohr JP, Foulkes MA, Tatemichi TK, Wolf PA, et al. Early clinical differentiation of cerebral infarction from severe atherosclerotic stenosis and cardioembolism. Stroke. 1992;23:486–91.

11. Arboix A, Alio J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. Curr Cardiol Rev. 2010;6:150–61.
12. Seo WK, Kang SH, Jung JM, Choi JY, Oh K. Novel composite score to predict atrial fibrillation in acute stroke patients: Af predicting score in acute stroke. Int J Cardiol. 2016;209:184–9.
13. Ryoo S, Chung JW, Lee MJ, Kim SJ, Lee JS, Kim GM, et al. An approach to working up cases of embolic stroke of undetermined source. J Am Heart Assoc. 2016;5:e002975.
14. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. 2011 accf/aha/hrs focused updates incorporated into the acc/aha/esc 2006 guidelines for the management of patients with atrial fibrillation: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. Circulation. 2011;123:e269–367.
15. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. 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. 2013;44:870–947.
16. Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2015;14:377–87.
17. 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;13:429–38.
18. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370:2478–86.
19. Ziegler PD, Rogers JD, Ferreira SW, Nichols AJ, Richards M, Koehler JL, et al. Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population. Int J Cardiol. 2017;244:175–9.
20. Hennerici M, Daffertshofer M, Jakobs L. Failure to identify cerebral infarct mechanisms from topography of vascular territory lesions. AJNR Am J Neuroradiol. 1998;19:1067–74.
21. Kang DW, Chalela JA, Ezzeddine MA, Warach S. Association of ischemic lesion patterns on early diffusion-weighted imaging with toast stroke subtypes. Arch Neurol. 2003;60:1730–4.
22. Kim YD, Hong HJ, Cha MJ, Nam CM, Nam HS, Heo JH. Determinants of infarction patterns in cardioembolic stroke. Eur Neurol. 2011;66:145–50.
23. Neuberger U, Möhlenbruch Markus A, Herweh C, Ulfert C, Bendszus M, Pfaff J. Classification of bleeding events. Stroke. 2017;48:1983–5.
24. Kirchhof K, Welzel T, Mecke C, Zoubaa S, Sartor K. Differentiation of white, mixed, and red thrombi: value of ct in estimation of the prognosis of thrombolysis phantom study. Radiology. 2003;228:126–30.
25. Puig J, Pedraza S, Demchuk A, Daunis IEJ, Termes H, Blasco G, et al. Quantification of thrombus hounsfield units on noncontrast ct predicts stroke subtype and early recanalization after intravenous recombinant tissue plasminogen activator. AJNR Am J Neuroradiol. 2012;33:90–6.
26. Cho KH, Kim JS, Kwon SU, Cho AH, Kang DW. Significance of susceptibility vessel sign on t2∗-weighted gradient echo imaging for identification of stroke subtypes. Stroke. 2005;36:2379–83.
27. Yamamoto N, Satomi J, Tada Y, Harada M, Izumi Y, Nagahiro S, et al. Two-layered susceptibility vessel sign on 3-tesla t2∗-weighted imaging is a predictive biomarker of stroke subtype. Stroke. 2015;46:269–71.
28. Lee EJ, Kim YH, Kim N, Kang DW. Deep into the brain: artificial intelligence in stroke imaging. J Stroke. 2017;19:277–85.
29. Llombart V, Garcia-Berrocoso T, Bustamante A, Fernandez-Cadenas I, Montaner J. Cardioembolic stroke diagnosis using blood biomarkers. Curr Cardiol Rev. 2013;9:340–52.
30. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a clinical review. Eur Heart J. 2013;34:1475–80.
31. Llombart V, Antolin-Fontes A, Bustamante A, Giralt D, Rost NS, Furie K, et al. B-type natriuretic peptides help in cardioembolic stroke diagnosis: pooled data meta-analysis. Stroke. 2015;46:1187–95.
32. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Christersson C, Ezekowitz J, et al. N-terminal pro-b-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the aristotle trial (apixaban for the prevention of stroke in subjects with atrial fibrillation). J Am Coll Cardiol. 2013;61:2274–84.
33. Yaghi S, Chang AD, Ricci BA, Jayaraman MV, McTaggart RA, Hemendinger M, et al. Early elevated troponin levels after ischemic stroke suggests a cardioembolic source. Stroke. 2018;49:121–6.
34. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD, et al. Growth-differentiation factor 15 and risk of major bleeding in atrial fibrillation: insights from the randomized evaluation of long-term anticoagulation therapy (re-ly) trial. Am Heart J. 2017;190:94–103.
35. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM, et al. The abc (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. Eur Heart J. 2016;37:1582–90.
36. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, et al. The novel biomarker-based abc (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. Lancet. 2016;387:2302–11.
37. Choi JY, Kim JS, Kim JH, Oh K, Koh SB, Seo WK. High free fatty acid level is associated with recurrent stroke in cardioembolic stroke patients. Neurology. 2014;82:1142–8.

38. Sun GJ, Ding SC, Ling WY, Wang F, Yang XP. Cerebrospinal fluid free fatty acid levels are associated with stroke subtypes and severity in Chinese patients with acute ischemic stroke. World Neurosurg. 2015;84:1299–304.
39. Choi JY, Jung JM, Kwon DY, Park MH, Kim JH, Oh K, et al. Free fatty acid as an outcome predictor of atrial fibrillation-associated stroke. Ann Neurol. 2016;79:317–25.
40. Pilz S, Marz W. Free fatty acids as a cardiovascular risk factor. Clin Chem Lab Med. 2008;46:429–34.
41. Dhindsa S, Ghanim H, Dandona P. Nonesterified fatty acids, albumin, and platelet aggregation. Diabetes. 2015;64:703–5.
42. Connor WE. The acceleration of thrombus formation by certain fatty acids. J Clin Invest. 1962;41:1199–205.
43. Connor WE, Hoak JC, Warner ED. Massive thrombosis produced by fatty acid infusion. J Clin Investig. 1963;42:860.
44. Khawaja O, Bartz TM, Ix JH, Heckbert SR, Kizer JR, Zieman SJ, et al. Plasma free fatty acids and risk of atrial fibrillation (from the cardiovascular health study). Am J Cardiol. 2012;110:212–6.
45. Murphy E, Ardehali H, Balaban RS, DiLisa F, Dorn GW 2nd, Kitsis RN, et al. Mitochondrial function, biology, and role in disease: a scientific statement from the American heart association. Circ Res. 2016;118:1960–91.
46. Zhu W, Fu L, Ding Y, Huang L, Xu Z, Hu J, et al. Meta-analysis of atria versus cha2ds2-vasc for predicting stroke and thromboembolism in patients with atrial fibrillation. Int J Cardiol. 2017;227:436–42.
47. Xiong Q, Chen S, Senoo K, Proietti M, Hong K, Lip GY. The chads2 and cha2ds2-vasc scores for predicting ischemic stroke among east Asian patients with atrial fibrillation: a systemic review and meta-analysis. Int J Cardiol. 2015;195:237–42.
48. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 esc guidelines for the management of atrial fibrillation developed in collaboration with eacts. Eur Heart J. 2016;37:2893–962.
49. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
50. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
51. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
52. Ruff CT, Giugliano RP, Braunwald E, Morrow DA, Murphy SA, Kuder JF, et al. Association between edoxaban dose, concentration, anti-factor xa activity, and outcomes: an analysis of data from the randomised, double-blind engage af-timi 48 trial. Lancet. 2015;385:2288–95.
53. Easton JD, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L, et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the aristotle trial. Lancet Neuro. 2012;11:503–11.
54. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the re-ly trial. Lancet Neurol. 2010;9:1157–63.
55. Hankey GJ, Patel MR, Stevens SR, Becker RC, Breithardt G, Carolei A, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of rocket af. Lancet Neurol. 2012;11:315–22.
56. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955–62.
57. Hong KS, Kwon SU, Lee SH, Lee JS, Kim YJ, Song TJ, et al. Rivaroxaban vs warfarin sodium in the ultra-early period after atrial fibrillation-related mild ischemic stroke: a randomized clinical trial. JAMA Neurol. 2017;74:1206–15.
58. Pennlert J, Overholser R, Asplund K, Carlberg B, Van Rompaye B, Wiklund PG, et al. Optimal timing of anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation. Stroke. 2017;48:314–20.
59. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med. 2017;377:1022–32.
60. Sondergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med. 2017;377:1033–42.
61. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med. 2017;377:1011–21.
62. Pristipino C, Sievert H, D'Ascenzo F, Louis Mas J, Meier B, Scacciatella P, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. Eur Heart J. 2018;40(38):3182–95.