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Considerations When Subtyping Ischemic Stroke in Asian Patients

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Both the incidence and prevalence of stroke in Asia are steadily increasing, and the burden of stroke is particularly high in Asian countries. Although strokes in Asians and Caucasians share many common features, there are some differences that are probably due to differences in lifestyle and genetic background. While there have been advances in the stroke classification system, the assignment of Asian stroke patients to etiological categories has received little attention. The current classification system may not be well suited to Asian patients with ischemic stroke because the proportions and relative importance of stroke subtypes may differ with race and ethnicity. This review addresses concerns about the use of the current stroke classification system in Asian patients with ischemic stroke, and proposes a classification system that is more specific to the Asian population, in conjunction with discussing advances in diagnostic techniques.

Key Words stroke, ischemic stroke, subtype, Asian, classification.

INTRODUCTION

Ischemic stroke is a heterogeneous disease with various cardiac, arterial, hemodynamic, rheological, and other systemic abnormalities. Categorizing patients into classes congruent with their pathophysiology is the key to understanding stroke, providing appropriate treatment, and preventing recurrence.

Various classification systems are applied to the subtypes of ischemic stroke, each of which had its own strengths and weaknesses. The OCSP (Oxfordshire Community Stroke Project classification, Bamford classification) relies primarily on clinical syndromes based on the extent and vascular localization of the stroke: total or partial anterior circulation, lacunar, and posterior circulation syndrome.[1] The following three etiological classifications have been developed due to acute and secondary preventive therapies being developed based on the understanding of the mechanisms underlying the stroke type: the NINDS stroke data bank subtype,[2] the Lausanne Stroke Registry,[3] and the Trial of Org 10172 in Acute Stroke Treatment (TOAST).[4] These classifications are based on both clinical and laboratory data, including neuroimaging and vascular and cardiac workups. The three most common etiologies of stroke are atherosclerotic, cardioembolic, and lacunar. With advances in stroke imaging and diagnostic techniques, and the availability of new epidemiological data, evidence-based algorithms have recently been developed to assign etiological categories in the presence of multiple mechanisms. These new categories include the Stop Stroke Study–TOAST[5] and the A-S-C-O (phenotypic).[6]

While these classification systems have been applied in large studies worldwide, it might be necessary to reassess how Asian stroke patients are assigned to the etiological categories.

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This review addresses concerns about the use of stroke classifications in Asian stroke patients, and proposes a classification system that is more specific to the Asian population, in conjunction with discussing advances in diagnostic techniques.

THE CURRENT CLASSIFICATION SYSTEM MAY NOT BE WELL SUITED TO ASIAN PATIENTS WITH ISCHEMIC STROKE

Both the incidence and prevalence of stroke in Asia are increasing steadily, probably due to lifestyle changes and the aging of the population. Moreover, the burden of stroke is particularly high in Asia,[7] given that almost two-thirds of the deaths worldwide due to stroke occur in Asian countries. The clinical features and epidemiological data related to stroke in Asians are different from those in Caucasians. However, the classification of Asian patients with ischemic stroke has received little attention. The various reasons why a classification system more specific to the Asian population needs to be developed are discussed below.

First, the proportions and relative importance of stroke subtypes are well known to differ with race and ethnicity (Fig. 1).[8-11] While cardioembolism is the most common (25–30%) cause of ischemic stroke in Western countries, atherosclerotic stroke accounts for up to 25–65% of strokes in Asian countries.[10] The prevalence of small-vessel disease is also higher in Asians than in Caucasians; this subtype accounts for up to one-half of ischemic strokes in Asians patients, but only one-fifth of those in Caucasian patients.[10] As a result, the vast majority of Asian patients with ischemic stroke are classified as having disease of large or small cerebral arteries.

Second, the relative distribution of intracranial, extracranial, and coronary atherosclerosis may differ between Asians and Caucasians. It was reported that the stroke burden is disproportionately high in East Asia, Africa, and South America, while the ischemic heart burden is higher in the Middle East, North America, Australia, and much of Europe.[12] In addition, the prevalence of intracranial atherosclerosis is high in Asians,[13] causing 30–50% of strokes in Asia,[14] whereas it is the cause of only 8–10% of strokes in North America.[15] Due to this type of stroke receiving little attention in stroke classification systems, and the relatively low frequency of intracranial atherosclerosis in Western countries, patients with intracranial atherosclerosis are often classified as having cryptogenic embolism. However, recent high-resolution MRI and pathological studies have revealed the presence of intracranial arterial plaques in these patients.[16-18] In contrast, patients with a milder degree of intracranial stenosis or large and deep infarcts are likely to be classified as having other cryptogenic causes.

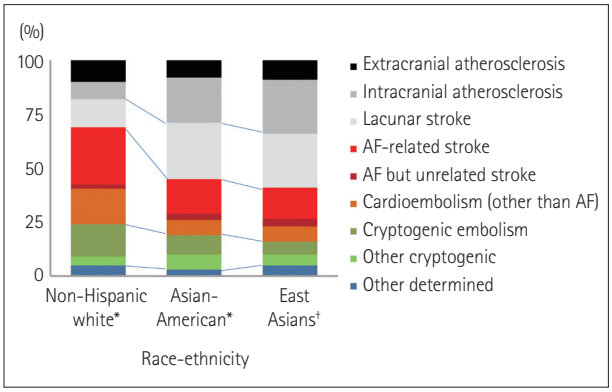

Fig. 1. Stroke subtypes by racial and ethnic groups. *Data from southern Californians (Modified from Bang et al.[8]), †Data from South Koreans. AF: atrial fibrillation.

Third, specific stroke etiologies should be considered in certain stroke populations due to the presence of genetic differences between populations. For example, sickle cell disease can cause stenosis in cerebral vessels, and can result in stroke in blacks but is very rare in East Asians. In contrast, the prevalence of moyamoya disease (MMD) is higher in Asians than in Caucasians. Recent genome-wide linkage and exome analyses identified the *RNF213* mutation as the most important for susceptibility to MMD among East Asian people.[19-21] The number of East Asian patients with MMD has been estimated to be more than 53,800.[22,23]

DETAILED SUBTYPING IS NEEDED TO GUIDE ACUTE TREATMENT AND PREVENT STROKE IN ASIANS

The current classification systems have focused on identifying the atherosclerotic and cardioembolic subtypes. This is because guidelines for stroke prevention emphasize the use of antiplatelet agents and statins for atherosclerotic strokes and anticoagulants for patients with atrial fibrillation (AF) based on the results of large clinical trials. However, from a therapeutic point of view, AF might be more complicated in Asian patients with ischemic stroke.

Atherosclerotic subtype

It might be beneficial to divide the atherosclerotic subtype into isolated intracranial and extracranial (with or without intracranial) atherosclerosis subtypes. Differences in clinical and neuroimaging features and risk factors have been reported between extracranial (e.g., cervical carotid) and intracranial atherosclerosis.[24-26] Previous studies have found atherosclerosis to be frequently localized to either the intra-

cranial or the extracranial arterial system, rather than occurring in both systems.[24,27] More importantly, intracranial stenosis can be caused by diverse conditions, including MMD, dissection, vasculitis, and reversible cerebral vasoconstriction syndrome (Fig. 2). In contrast, atherosclerosis is the main cause of cervical carotid stenosis, with only rare exceptions of carotid dissection, fibromuscular dysplasia, Takayasu arteritis, and radiation arteritis being differentiated clinically. In addition, intracranial atherosclerotic stroke can be caused by branch occlusive disease as well as artery-to-artery embolism or hemodynamic impairment.[28,29] The risk factors, vessel wall pathology, and treatment strategies may differ between these two subtypes of intracranial atherosclerotic stroke.[28,30-33] Patients with branch occlusive disease often show a mild degree of stenosis and are misclassified as having lacunar stroke or other cryptogenic stroke (Fig. 3). However, high-resolution MRI studies have demonstrated intracranial plaques occluding perforating arteries, which suggests that statin plays a role in these patients. Our ongoing serial follow-up high-resolution MRI study in patients with intracranial atherosclerotic stroke is currently addressing this issue (clinicaltrial.gov identifier NCT02458755). Asian investigators are concerned about the definition of stroke subtypes in these patients, and have suggested that lesion size limitations should not be strictly applied to cases of small-vessel occlusions, and that the degree of stenosis in atherosclerotic vessels should not be limiting in determining the presence of intracranial atherosclerotic stroke.[10]

Lacunar subtype

The pathogenic mechanisms of lacunar stroke are similar to those of hypertensive intracranial hemorrhage, and patients with lacunar stroke often experience hemorrhagic stroke.[34] The two subclinical subtypes of lacunar stroke are cerebral deep microbleeds (red type) and leukoaraiosis (white type).[35] Cerebral microbleeds are more common in Asians than in Caucasians and are associated with intracranial hemorrhage as well as ischemic stroke (Fig. 4),[36] while leukoaraiosis may be caused by silent, acute lacunar infarcts.[37,38] Thus, the optimal treatment strategies may differ between the two condi-

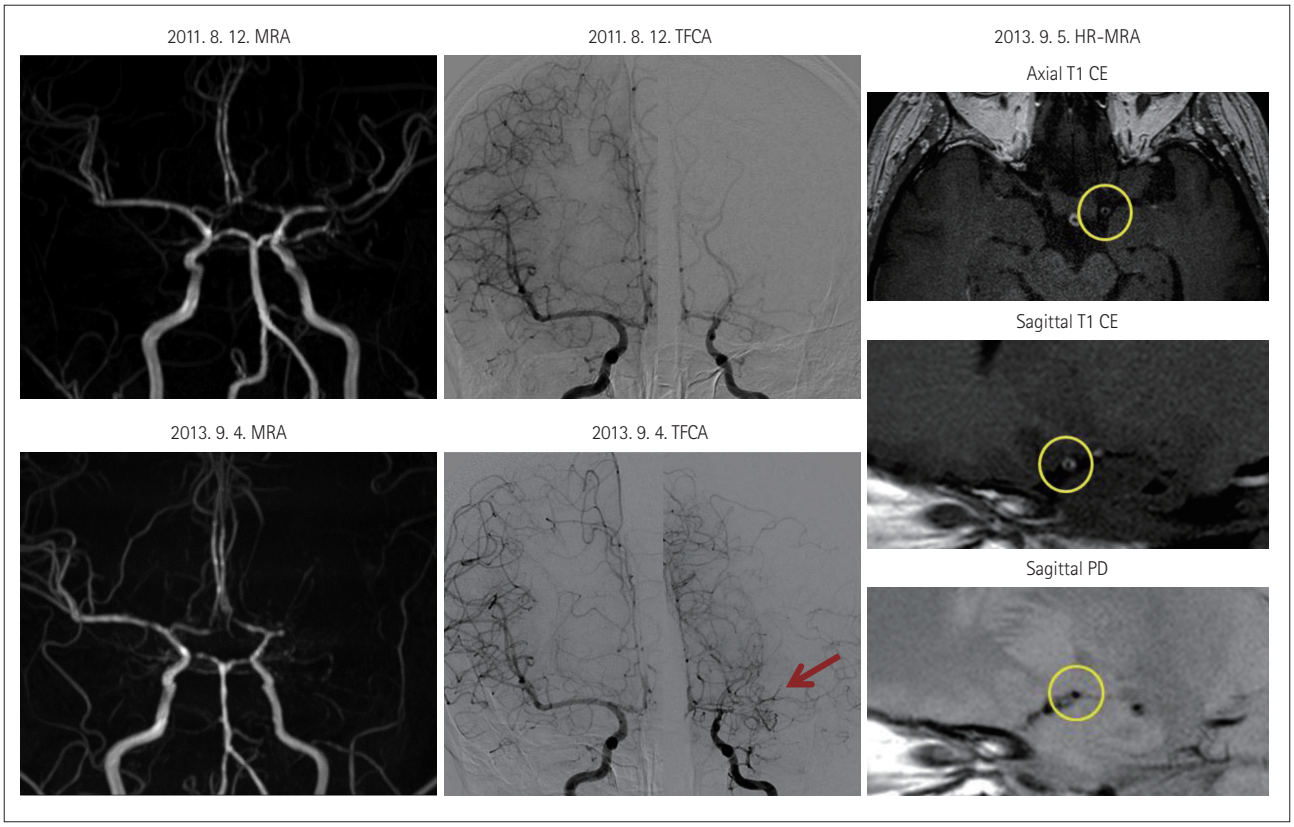

Fig. 2. Recurrent infarcts with progression of intracranial stenosis. A 32-year-old female experienced recurrent left middle cerebral artery (MCA) infarcts (three times) within 2 years. Serial time-of-flight magnetic resonance angiography (MRA) showed the progression of stenosis in the left MCA. Transfemoral cerebral angiography (TFCA) showed no stenosis in the distal internal carotid artery or basal collaterals suggestive of moyamoya disease (MMD) (arrow). However, high-resolution (HR) MRI revealed a smaller outer diameter, concentric enhancement, and the absence of focal plaques in the stenotic segment (circle). A genetic investigation revealed that the *RNF213* mutation was associated with MMD (p.Arg4810Lys). CE: contrast enhanced.

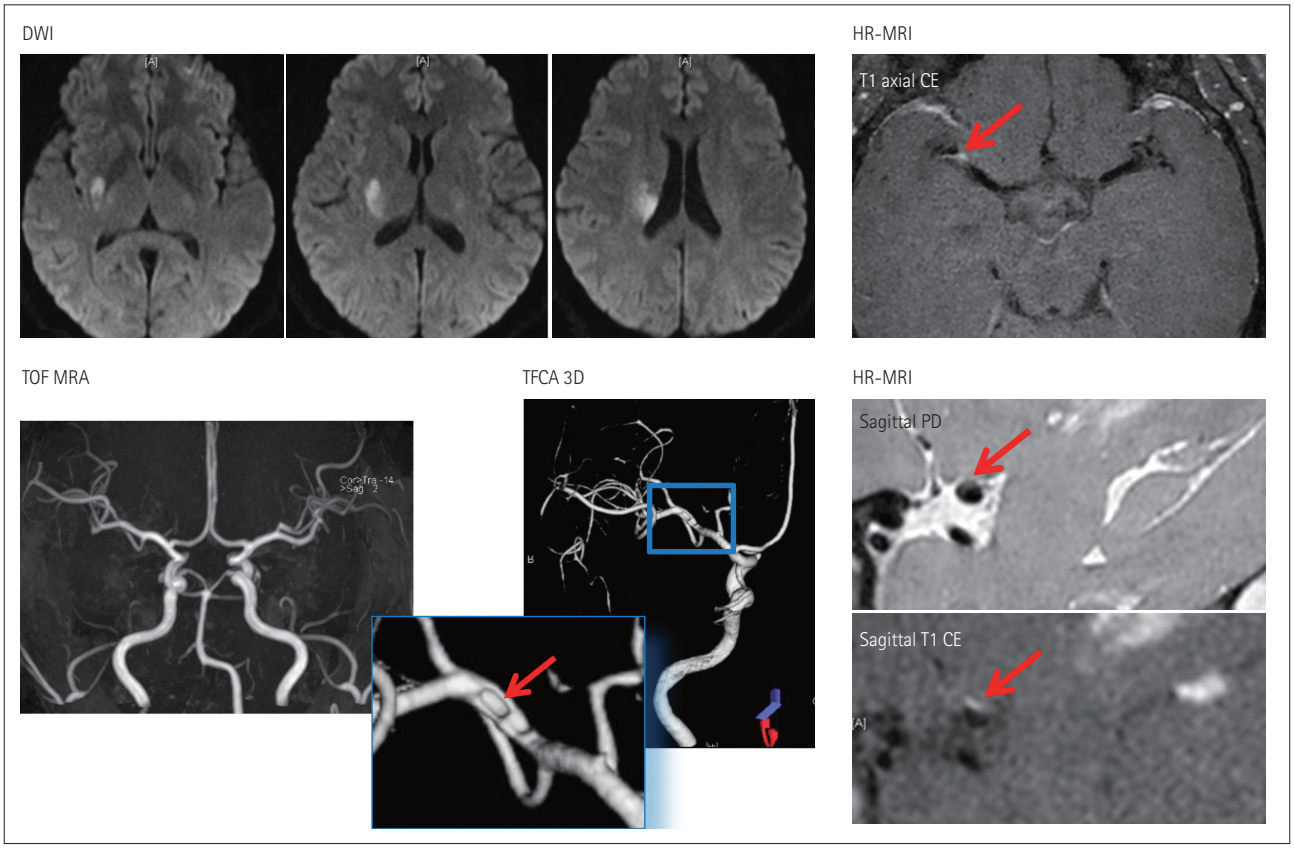

Fig. 3. Subcortical infarction but no significant stenosis. A 48-year-old female experienced left hemiparesis. Diffusion-weighted imaging (DWI) shows a deep infarct in the right basal ganglia and corona radiata. MRA shows no significant stenosis in the relevant vessels. TFCA and high-resolution (HR) MRA show a small plaque in the superior half of the middle cerebral artery (arrow). CE: contrast enhanced, MRA: magnetic resonance angiography, PD: proton density, TFCA: transfemoral cerebral angiography, TOF: time of flight, 3D: three dimensional.

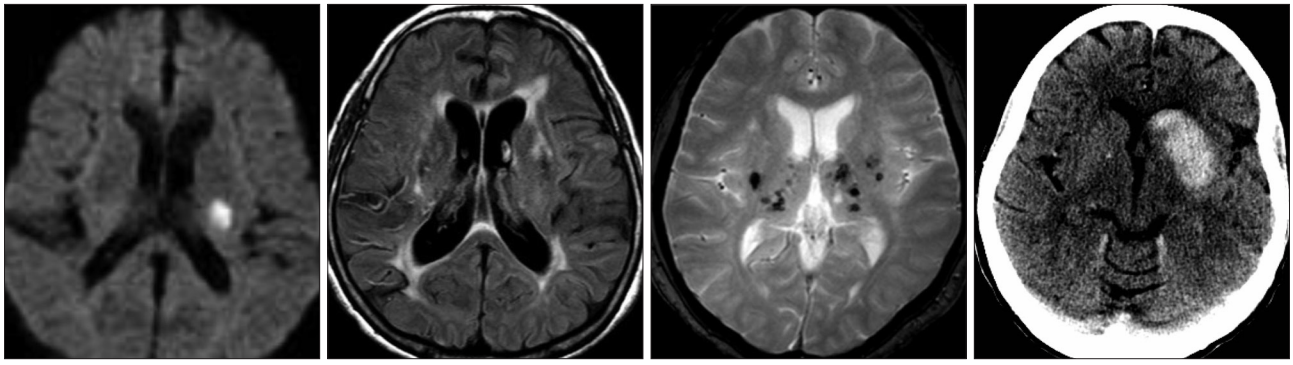

Fig. 4. A 59-year-old male presented with right hemiparesis. Diffusion-weighted imaging shows a small acute lacunar infarct in the left corona radiata. The magnetic resonance angiography findings were normal. Gradient-echo imaging shows multiple cerebral microbleeds in deep regions bilaterally. Two years later he was readmitted to the Department of Neurosurgery due to intracranial bleeding while taking dual antiplatelet agents.

tions, and differential risk factors have been reported.[39-41] The Rotterdam Scan study showed that use of antiplatelet agents is related to the presence of cerebral microbleeds.[42] One prospective study found that the risk of subsequent intracranial bleeding increased with the number of cerebral microbleeds, and that the high risk and mortality of intracranial bleeding outweighed the modest benefit of antithrombotic agents in patients with at least five cerebral microbleeds.[43]

Cardioembolic subtype

While the use of anticoagulants is the standard treatment applied to prevent stroke in patients with AF, AF may not always be the cause of stroke in AF patients. In fact, one-sixth of strokes in AF patients were reported to be unrelated to AF

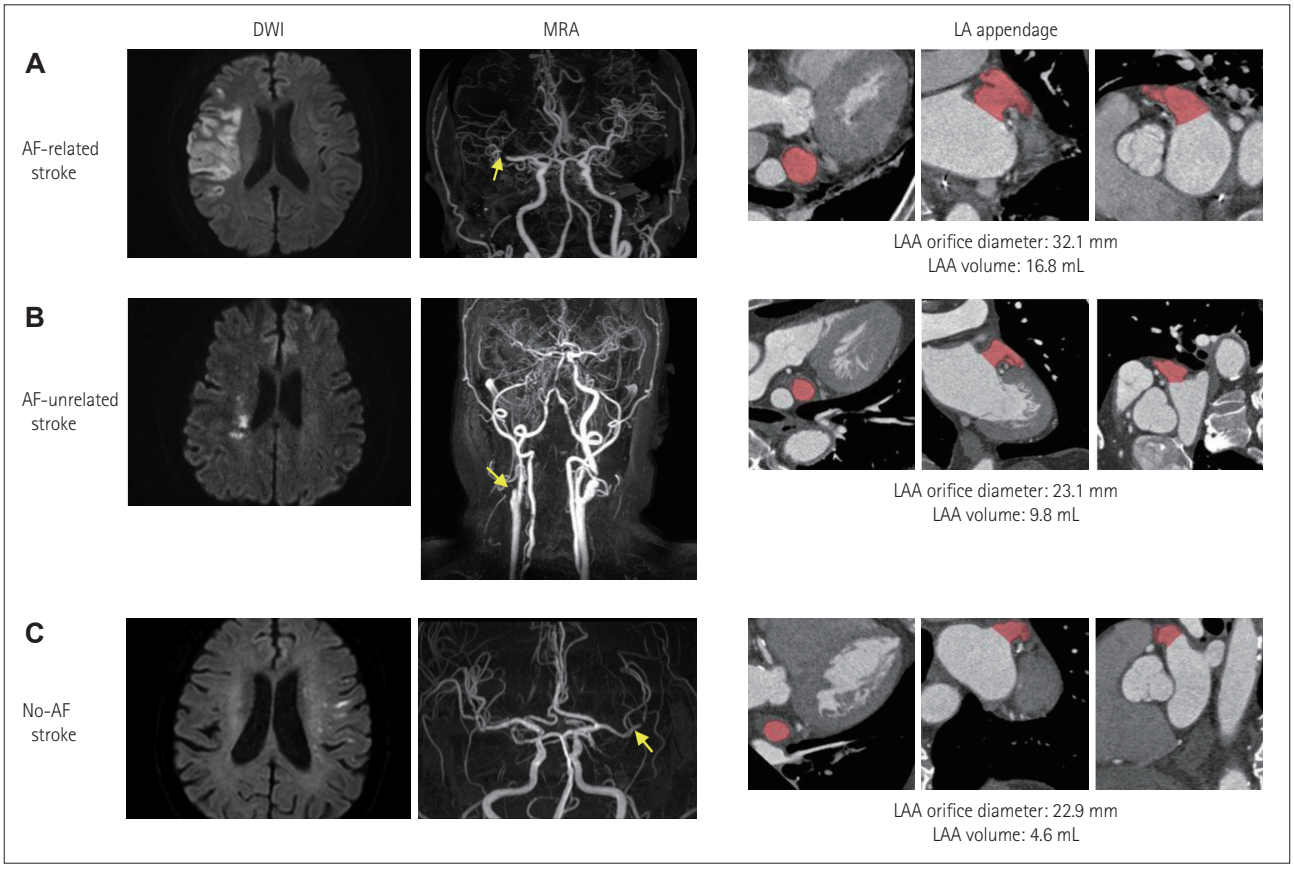

Fig. 5. Typical cases of atrial fibrillation (AF)-related stroke (A), AF-unrelated stroke (B), and no-AF stroke (C). Left panel, DWI. Middle panel, MRA. Right panel, multidetector cardiac computed tomography. A: AF-related stroke with a larger left atrial appendage (LAA) orifice diameter (32.1 mm) and larger LAA volume (16.8 mL). This patient had an infarction and occlusion in the right MCA territory, but no stenosis or occlusion in other intra- and extracranial vessels was noted. B: AF-unrelated stroke with a smaller LAA diameter (23.1 mm) and smaller LAA volume (9.8 mL). This patient had a right-sided border zone infarction with severe right cervical carotid occlusion. C: No-AF stroke with a smaller LAA orifice diameter (22.9 mm) and smaller LAA volume (4.6 mL). This patient had left cortical small infarcts with left MCA stenosis. DWI: diffusion-weighted imaging, MCA: middle cerebral artery, MRA: magnetic resonance angiography.

and showed clinical and echocardiographic characteristics distinct from those with AF-related stroke.[44] Most patients with AF-unrelated stroke experienced recurrent strokes despite receiving adequate anticoagulation treatment with warfarin (Fig. 5). Because the prevalence of micro- and macroangiopathy is higher in Asians than in Caucasians, more Asian patients with AF are classified as having undetermined etiology with two or more causes, and differentiation of AF-related vs. -unrelated stroke may be more important in Asians than in Caucasians.

Consideration of the above characteristics leads to the conclusion that the optimal treatment strategies may differ among patients with the same stroke subtype. Owing to the paucity of evidence, current guidelines do not provide detailed treatment strategies according to the subclassification of stroke subtype. Future studies should investigate different treatment strategies for the various subclassifications, such the optimal dose of statins for intracranial vs. extracranial atherosclerosis, the use of antithrombotics for white vs. red phenotypes of lacunar stroke, and the addition of antiplatelet agents to anticoagulation for AF-related vs. -unrelated stroke (Table 1). In the meantime, continuous efforts are needed to individualize the treatments provided to Asian patients with ischemic stroke.

ADVANCES IN DIAGNOSTIC TECHNIQUES MAY BE PARTICULARLY HELPFUL IN ASIAN PATIENTS

The application of advanced diagnostic technologies may reduce the proportion of patients diagnosed with cryptogenic stroke.[45] These techniques could also play a role in diagnosing patients with known vascular and cardiac abnormalities.

High-resolution MRI can visualize wall pathology (i.e., plaque, dissection, or vasculitis), and it has been shown to be effective in differentiating MMD and intracranial atheroscle-

Table 1. Stroke subtyping and related issues in Asians

Traditional subtype	Detailed subtypes		Relevant issues
Atherosclerotic	Extracranial (with or without intracranial)		
	Intracranial *	BOD	Degree of significant stenosis
			Role of statins
		Non-BOD	Prevalence of mimicking conditions (dissection, MMD, vasculitis, or RCVS)*
Lacunar	Isolated lacunar		Lesion size
	Red (multiple CMBs)*		Role of antithrombotics in patients with multiple CMBs
	White (leukoaraiosis)*		
Cardioembolic	AF	Related to AF	
		Unrelated to AF (2 or more causes)*	Role of additional antiplatelet agents in AF plus other mechanisms
	Other than AF		

*Prevalence higher in Asians than in Caucasians.
AF: atrial fibrillation, BOD: branch occlusive disease, CMBs: cerebral microbleeds, MMD: moyamoya disease, RCVS: reversible cerebral vasoconstriction syndrome.

rosis.[46,47] A recent high-resolution MRI study found that plaques were present in only 26 of 95 Korean patients with isolated stenotic lesions in the middle cerebral artery with no or minimal atherosclerotic risk factors, while the remaining 69 patients had nonatherosclerotic high-resolution MRI features, such as MMD, dissection, or vasculitis, suggesting a role for nonatherosclerotic pathologies in this population.[48] Therefore, patients should not be classified as having atherosclerotic subtype simply because they have stenotic lesions on relevant proximal vessels. This is especially true in patients with a relatively healthy risk-factor profile and in Asian populations whose intracranial arteries are prone to dissection and carriers of the *RNF213* mutation are more common. Although intracranial artery dissection is less common than cervical artery dissection in adults of European ethnicity, intracranial artery dissection is reportedly more common in Asian populations.[49] Unlike pediatric MMD, it is often difficult to angiographically differentiate adult MMD from intracranial atherosclerosis. In adult patients with intracranial stenosis and the *RNF213* mutation, typical angiographic findings of MMD (i.e., basal collaterals) are not necessarily prominent, and some patients develop typical angiographic findings of MMD on follow-up angiography.[50] Therefore, high-resolution MRI or a follow-up vascular study might be valuable for demonstrating interval changes of basal collaterals and luminal stenosis in these patients.

Efforts have been made to find and validate possible biomarkers that can reliably predict the risk of stroke in patients with AF, including risk schemes[51] and serological[52,53] and genetic[54] biomarkers. The use of cardiac imaging biomarkers is another approach for differentiating between cardiogenic and noncardiogenic stroke. For example, AF patients with the "chicken wing" type of left atrial appendage (LAA) morphology on multidetector cardiac computed tomography are reportedly less likely to have an embolic event after controlling for comorbidities and $CHADS_2$ score.[55] Both other[56] and our studies[57] have shown that the LAA volume and LAA orifice diameter are both greater in patients with AF-related stroke than in those with AF-unrelated stroke and those without AF (Fig. 5). Therefore, physicians should consider the possibility of an AF-unrelated mechanism if multidetector cardiac computed tomography shows such findings and no thrombus.

Targeted selection and judicious use of the appropriate tests in the workup of stroke are crucial. An extensive pathogenic workup may paradoxically increase the prevalence of cause-undetermined cases (i.e., cases with ≥2 determined causes). Thus, advanced vascular techniques should be applied to patients with milder stenosis for demonstrating vulnerable plaques, and to those with a relatively healthy risk-factor profile in order to preclude nonatherosclerotic stenosis in which specific treatment may be needed. In addition, antithrombotic usage could be guided by the findings of cardiac imaging (the use of antiplatelet agents in addition to oral anticoagulants to prevent AF-unrelated stroke) or gradient-echo imaging (while avoiding the use of aggressive antithrombotics in patients with lacunar stroke and multiple cerebral microbleeds).

CONCLUSIONS

This review of the literature has addressed the need for a more-detailed stroke classification system and the systematic application of advanced diagnostic tests in the evaluation of

stroke etiology in Asian patients. The continuing advances in technology mean that more diagnostic tests will become available, but this does not mean that it will be possible to apply these advanced techniques in routine clinical practice. Continuous efforts are needed to refine the approach applied for the workup of Asian patients with ischemic stroke.

Conflicts of Interest

The author has no financial conflicts of interest.

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