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Review

Intracranial Atherosclerosis: Current Understanding and Perspectives

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The importance of intracranial atherosclerotic disease (ICAD) as a cause of stroke is underscored as compared to that of extracranial carotid stenosis and nonvalvular atrial fibrillation. Recent large clinical trials of ICAD, which evaluated the effectiveness of anticoagulation and stenting to prevent thromboembolism and restore hemodynamic compromise, failed to reduce major vascular events in patients with ICAD. These trials showed the importance of optimal control of risk factors to reduce major vascular events in these patients. Recent advances in risk factors for ICAD are summarized, together with possible reasons for race-ethnic differences in the prevalence of ICAD. In addition, the failure of the major clinical trials of ICAD may be caused by limitations in the understanding of ICAD. Unlike in patients with extracranial carotid stenosis or atrial fibrillation, stroke associated with ICAD occurs in association with various stroke mechanisms such as *in situ* thrombotic occlusion, artery-to-artery embolism, hemodynamic insufficiency, and branch occlusion. In clinical trials of ICAD, patients with all these types of ICAD were included. However, treatment effects may differ among the different types of ICAD. Treatment strategies might be selected based on clinical features (including the time after onset) and serologic and neuroimaging biomarkers (including diffusion-weighted image pattern and plaque images). Additional clinical trials considering these features are needed.

Keywords Atherosclerosis; Stroke; Intracranial; Plaque

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Introduction

The importance of intracranial atherosclerotic disease (ICAD) as a cause of stroke is underscored as compared to that of extracranial carotid stenosis and nonvalvular atrial fibrillation. There have been several studies with long-term follow-up data and randomized clinical trials in extracranial carotid stenosis and nonvalvular atrial fibrillation; the risk of stroke and treatment effects were evaluated separately in both asymptomatic (stroke-free) and symptomatic patients. On the contrary, ICAD was not considered or was lumped with extracranial carotid stenosis as an atherosclerotic stroke subtype in most clinical trials[1] and current stroke guidelines.[2] However, ICAD differs from extracranial atherosclerotic stroke in many aspects, including risk factors and stroke patterns.[3-5]

Large clinical trials of ICAD have recently evaluated the effectiveness of anticoagulation (the Warfarin Aspirin Symptomatic Intracranial Disease [WASID] trial) and stenting (the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis [SAMMPRIS] trial) to prevent thromboembolism and restore hemodynamic compromise, but failed to reduce major vascular events in patients with ICAD.[6,7] The failure of these trials may be caused by limitations in the current understanding of ICAD. In this review, the vari-

ous mechanisms of stroke will be discussed because treatment effects may differ among the different types of ICAD. In addition, recent advances in risk factors for ICAD are summarized because the trials drew attention to the importance of recognition and adequate control of risk factors for ICAD.

Epidemiology and natural course of ICAD

Knowledge of the epidemiology of ICAD is limited.[8] There have been no data on the prevalence of ICAD in large clinical trials, and data are limited regarding the prevalence of asymptomatic ICAD in the general population. ICAD may be as prevalent as extracranial carotid artery disease. The population-based Rotterdam study has evaluated the prevalence of intracranial internal carotid artery calcification, a marker of intracranial atherosclerosis which was observed in over 80% of older, white subjects.[9] In addition, a transcranial Doppler study showed that the prevalence of asymptomatic middle cerebral artery (MCA) stenosis ranged from 7.2%-30% among Asian patients who had vascular risk factors without a history of stroke or TIA.[10] ICAD causes 30%-50% of strokes in Asia,[11] and 8%-10% of strokes in North America,[12] making it one of the most common causes of stroke worldwide.[13]

ICAD is more prevalent in Asians than in Westerners; the reason for this is unknown. Possible explanations include inherited susceptibility of intracranial vessels to atherosclerosis,[14] acquired differences in the prevalence of risk factors,[15,16] and differential responses to the same risk factors.[17,18] Lifestyle may play a role in the racial-ethnic differences: the pattern of ischemic stroke is changing in Asian patients. With the westernized lifestyle, the number of extracranial cervical disease is rising.[19,20] Lastly, it is also possible that patients with adult-onset moyamoya disease (MMD) are misclassified as having ICAD, which may partly explain the high prevalence of intracranial atherosclerosis in Asians. Ring finger 213 (RNF213) was recently identified as the strongest susceptibility gene for MMD in East Asian people by a genome-wide linkage analysis and an exome analysis.[21,22] The number of patients with MMD was estimated to be more than 53,800 in East Asian populations.[23,24] The prevalence of MMD has recently increased with more careful consideration of the disease and better diagnostic techniques;[25] many patients may have been misclassified as having ICAD.

The natural history of asymptomatic vs. symptomatic ICAD differs from that of extracranial carotid disease. Compared to asymptomatic extracranial carotid disease, asymptomatic ICAD has a low risk of stroke in the stenotic arterial territory, while the risk is very high in patients with symptomatic ICAD, especially in patients with clinically significant hemodynamic stenosis, early after stroke.[6,26] Several clinical and laboratory findings reportedly predict stroke in patients with ICAD. The WASID trial showed that a shorter time from stroke ($\leq$ 17 days), severe stenosis ($\geq$ 70%), baseline severe neurological deficits, poorly controlled hypertension, and elevated low-density lipoprotein cholesterol (LDL) levels are independent predictors for recurrence after stroke due to ICAD.[27] Regardless, progression in stenosis[28,29] and DWI lesion pattern (subcortico-cortical lesion and multiple lesions)[30] are also associated with recurrent stroke in ICAD.

Phenotypes and high-resolution MRI findings of ICAD

From single, small subcortical perforator infarctions to multiple cortical infarctions, various radiologic stroke patterns are associated with ICAD.[31,32] Stroke associated with ICAD occurs in association with various stroke mechanisms such as in situ thrombotic occlusion, artery-to-artery embolism, hemodynamic insufficiency, and branch occlusion (Figure 1). Patients with unstable intracranial plaque may show large territorial lesions via sudden thrombotic occlusion. Artery-to-artery embolism, which commonly causes multiple cortico-subcortical infarcts, can be detected by performing transcranial duplex monitoring. Branch occlusive disease (BOD) is one of the main stroke mechanisms of ICAD, which can be characterized by a milder degree of stenosis[33] and comma-shaped infarcts extending to the basal surface of the parent artery.[34]

Two major features of intracranial atherosclerosis include: (a) atherosis caused by cholesterol deposition and inflammation, and (b) sclerosis secondary to endothelial dysfunction, leading to arterial stiffness.[35] Risk factors and vessel wall pathology may differ between the two. An autopsy study showed that risk factors differed between those with intracranial-plaque vs. plaque-negative stenosis.[36] Older age, male gender, and diabetes were commonly associated with the presence of intracranial plaques and stenoses. Interestingly, history of myocardial infarct was an independent risk factor for intracranial plaque but not for plaque-negative stenosis, whereas stroke history was associated with stenosis but not plaque.

Recently, high-resolution MR techniques have been used to evaluate the frequency and role of intracranial artery plaques in living patients with stroke. Patients with symptomatic (vs. asymptomatic) and non-BOD type (vs. BOD) ICAD had characteristic changes in (a) the wall area (larger plaques), (b) plaque signals (eccentric enhancement and heterogeneous signal intensity suggesting unstable plaque), and (c) remodeling patterns (positive remodeling suggesting outward expansion of the

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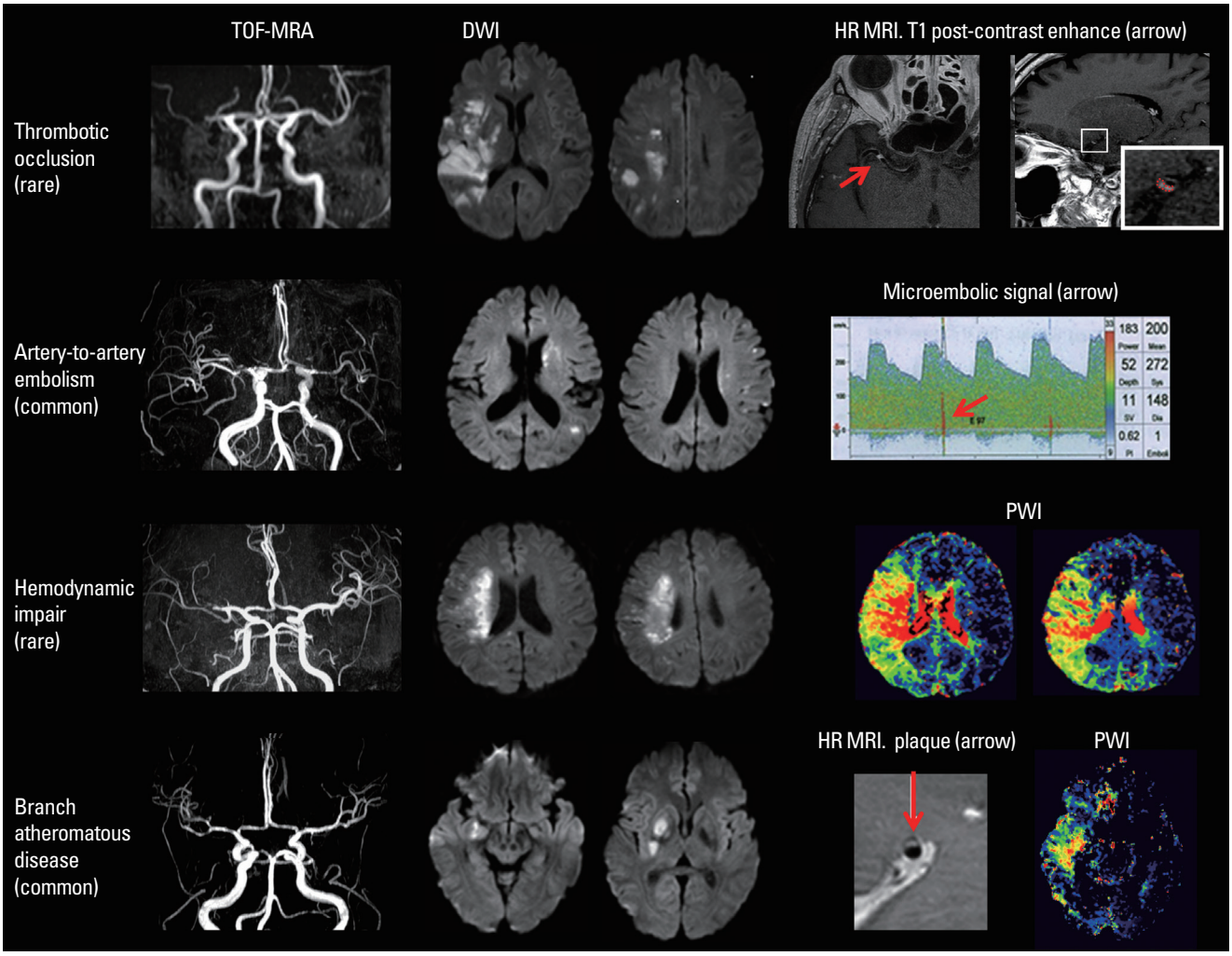

Figure 1. Mechanisms of stroke in patients with ICAD. (A) Thrombotic occlusion is a rare phenotype of ICAD. Magnetic resonance angiography (MRA) shows *in situ* thrombotic occlusion at the site of stenotic plaque. DWI shows territorial infarcts by severe hemodynamic compromise and embolic infarcts on the cortex. High-resolution MRI can show vulnerable plaque on intracranial vessels. (B) Artery-to-artery embolism is one of common phenotypes of ICAD. Artery-to-artery embolism is usually associated with a severe degree of intracranial stenosis, and transcranial Doppler ultrasonography can detect symptomatic or asymptomatic embolism during microembolic signal monitoring. DWI shows small, scattered, cortical embolic infarcts. (C) Hemodynamic impairment is another phenotype of ICAD. This phenotype is usually associated with a severe stenosis and a marked hemodynamic compromise, as seen on a perfusion-weighted image (PWI). DWI typically shows border-zone-type infarcts, and infarct growth is common with clinical deterioration. (D) Branch occlusive disease is a common phenotype of ICAD. This phenotype is often misclassified as small arterial disease due to a mild degree of stenosis on MRA, small deep infarcts on DWI, and relatively small perfusion defects. High-resolution MRI can reveal plaque without stenosis near the orifices of penetrating arteries.

vessel wall).[37-39] On the contrary, superiorly located MCA plaques (near to the orifices of penetrating arteries) are associated with BOD-type ICAD.[40,41]

Results of major clinical trials of ICAD

There are three therapeutic strategies for ICAD: (a) antithrombotics, (b) intervention to prevent thromboembolism and restore blood flow, and (c) identification and control of risk factors. Most studies have focused on the prevention of thromboembolism, including the WASID trial[6] and the FISS-tris trial,[42] which compared the benefit of anticoagulants vs. aspirin, and the recent SAMMPRIS wingspan stenting trial.[7] However, no studies have been conducted to evaluate the effect of risk factor control in preventing stroke recurrence in ICAD patients.

Both oral and parenteral anticoagulation failed to show beneficial effects in preventing recurrent stroke in patients with ICAD.[6,43] The WASID trial has shown that warfarin and aspirin were equally effective for preventing stroke or vascular death.[6] In fact, both warfarin and aspirin were ineffective, given the high event rates in both arms. Risk factors were poorly controlled in the WASID trial. The most important findings in the WASID trial were related to the importance of controlling risk factors to reduce major vascular events in ICAD patients. Patients were

poorly controlled in terms of mean systolic blood pressure and LDL level. Although this study did not examine the effect of risk factor control in symptomatic ICAD patients, the post hoc analyses suggest that lowering blood pressure and LDL may reduce major vascular events in ICAD patients.[44]

Thus, in the following SAMMPRIS trial, aggressive risk factor management was performed, targeting LDL below 70 mg/dL, systolic blood pressure below 140 mmHg, and a comprehensive lifestyle modification program.[7] In the SAMMPRIS trial, the rate of stroke or death within the first 30 days was 14% in the Wingspan stenting arm vs. 5.8% in the aggressive medical management arm. The SAMMPRIS investigators stopped enrollment prematurely due to futility; the trend was not changed until 1 year. The higher stroke rate in the stenting arm than in aggressive medical management arm in SAMMPRIS was driven by several factors such as (a) inclusion of patients with perforator syndrome, a smaller vessel size, diffuse stenoses (oversizing of devices) in patients with high peri-procedural stroke risk (ischemic or hemorrhagic), (b) procedural considerations of stringent blood pressure control, general anesthesia, operator experience, etc., and (c) most importantly, improved medical treatment including high-dose statin therapy.[45,46] It is interesting that the rate of stroke or death in the aggressive medical management arm was substantially lower than in historical (WASID) controls. This highlights the importance of aggressive control of risk factors. As shown in Table 1, the recurrence rate of stroke decreased in the recent clinical trials of ICAD. This is in line with the carotid intervention (endarterectomy) trials, which showed that in patients with asymptomatic carotid stenosis the stroke risk in the control group has lowered during the last 30 years with aggressive medical treatment including risk factor control.[47] The annual risk rate of stroke in the control group of the recent trials has lowered even more than that in the carotid intervention group. Just as carotid endarterectomy is indicated only for high risk (annual stroke risk > 1%) patients with asymptomatic carotid stenosis, intracranial stenting should be reserved for high risk patients/lesions to prevent disabling stroke refractory to a comprehensive regimen of medical therapy.

Control of risk factors for ICAD

Therefore, it is important to control vascular risk factors aggressively, and to find out risk factors more specific to ICAD. Until now, risk factors for ICAD of various conditions have been reported, from risk factors associated with asymptomatic ICAD to risk factors for stroke recurrence (Table 2). Classic risk factors for stroke such as hypertension, diabetes, and lipid disorders, are commonly associated with these conditions. However, many studies showed that these classic risk factors are not major determinants of the location of extracranial or intracranial ath-

Table 1. Low rate of stroke in the recent clinical trials of ICAD

	WASID, 2005 (Anticoagulation)	SAMMPRIS, 2011 (Stenting)	TOSS-2, 2011 (Antiplatelet)
Treatment arms	Warfarin (n=289) vs. ASA (n=280)	AMM (n=227) vs. Stenting (n=224)	ASA+Clopiodogrel (n=225) vs. ASA+Cilostazol (n=232)
Patients	50%-99% stenosis	70%-99% stenosis	Focal stenosis on MRA
Randomization after stroke	<90 days (median, 17 days)	<30 days (median, 7 days)	<14 days
Duration of F/U	1.8 years	1 year	7 months
Primary end point	21.8% vs. 22.1%	12.2% vs. 20.0%	4.4% vs. 6.5% (clinical events)
Risk factor control (baseline → follow up)			
Systolic BP	<140 mmHg, 55 → 53%	Mean, 147 → 135 mmHg	
LDL-C	<100 mg/dL, 29 → 56% <70 mg/dL, 9 → 10%	Mean, 98 → 73 mg/dL	Mean, 121 → 95 mg/dL
HDL-C	>40 mg/dL, 64 → 63%	Mean, 39 → 42 mg/dL	Mean, 43 → 49 mg/dL
HbA1C	≤7%, 32 → 52%	Mean, 8.3 → 7.5%	Mean, 6.7 → 6.2%

ASA, aspirin; AMM, aggressive medical management; MRA. Magnetic resonance angiography.

Table 2. Risk factors associated with ICAD

Asymptomatic ICAD in stroke-free	Severity of ICAD	Progression of stenosis	Stroke recurrence among symptomatic ICAD
Hypertension[66-71]	Diabetes[54]	Diabetes[73]	Systolic BP ≥ 140 mmHg[75]
Diabetes[66,67,68,71]	Lipid disorder[54]	Smoking[73]	Cholesterol ≥ 200 mg/dL[75]
Lipid disorder[66,71]	Metabolic syndrome[54,49,51]	Absence of carotid disease[74]	Metabolic syndrome[76]
Metabolic syndrome[53]	Smoking[72]	Apolipoprotein B/A1 ratio[62]	Severe stenosis ≥ 70%[27]
Age[66,67,68,70,71]			Race (black)[77]
Male[67,69]			Poor collaterals[78]
Race (Asian and black)[69]			

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erosclerosis.[48-50] Because ICAD risk could not be fully explained by conventional risk factors, there have been efforts to find risk factors specific to ICAD.

Controversial results regarding risk factors for ICAD could be caused by the following reasons. First, the current stroke classification system may have limitations in defining ICAD. We have recently reported that BOD-type ICAD patients were frequently misclassified as having SAD or cryptogenic stroke under the TOAST or revised (SSS) TOAST classification.[33] Second, as mentioned earlier, various mechanisms of stroke exist related to ICAD (Figure 1), and the risk factors may differ depending on the stroke mechanisms. Lastly, there may be non-conventional risk factors for ICAD. Metabolic syndrome is a cluster of cardiovascular disease risk factors and metabolic alterations associated with excess fat. We have previously reported an association between metabolic syndrome and ICAD.[48] Patients with more severe metabolic abnormalities were more likely to have severe intracranial atherosclerosis but not extracranial atherosclerosis, suggesting a dose-dependent relationship.[49,51] These results were confirmed by other studies from different cohorts of asymptomatic multi-ethnic populations[52,53] and symptomatic ICAD patients in a multi-center trial.[54] A recent genetic study also supported this association.[55] Risk factors, components of metabolic SD, elevated serum insulin, and adipokines secreted from adipocytes, all cause oxidative stress and endothelial dysfunction.[56,51,18] Adults with the metabolic syndrome have suboptimal concentrations of several antioxidants, and intracranial arteries may become susceptible to oxidative stress. Oxidative stress leads to the attenuation of endothelial function through decreased production of nitric oxide (NO) and increased destruction of NO by superoxide.[57] The Asymptomatic Intracranial Atherosclerosis (AsIA) study showed that asymmetric-dimethylarginine (ADMA, an endogenous inhibitor of endothelial NO) was associated with ICAD.[53] In addition, a recent report evaluating the circulating endothelial microparticle pattern in stroke patients showed that ICAD and ECAS may have different pathophysiologies.[58] It was speculated that the endothelial activation is related to plaque instability in patients with extracranial arterial stenosis, and endothelial apoptosis is related to vascular narrowing in patients with ICAD.[58]

Treatment strategies in ICAD: endothelium, plaque, and platelet

Several treatments could improve endothelial function. The most consistently reported treatment strategies that have restored endothelial function are statins, angiotensin converting enzyme inhibitors, phosphodiesterase inhibitors to enhance NO signaling (e.g. cilostazol and sildenafil), control of vascular risk factors, and lifestyle modification (exercise and smoking cessation). Several active clinical trials are currently seeking to restore the endothelial dysfunction. In particular, because the use of a high-dose statin reportedly improved arterial elasticity and reduced the plaque burden of carotid and coronary arteries (anti-atherogenic effects),[59] several clinical trials of statins are ongoing in patients with ICAD. In addition, cilostazol reportedly protects endothelial function[60] and prevents progression of intracranial stenosis.[61] A recent multicenter clinical trial (the Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis [TOSS]-2 trial) found no significant difference in the vascular events between cilostazol and clopidogrel therapies in patients with symptomatic ICAD.[62] In this study, the cilostazol group had a trend toward decreased progression of symptomatic intracranial stenosis and more regression of asymptomatic intracranial stenosis with a reduction in the level of apolipoprotein B, whereas the clopidogrel group showed a tendency toward fewer new lesions. A randomized clinical trial showed that combination therapy with clopidogrel and aspirin is more effective than aspirin alone in reducing microembolic signals in patients with acute symptomatic ICAD.[63]

Therefore, it is possible that therapeutic target differs between hyperacute (platelet) vs. subacute/chronic stages (endothelium and plaque) after stroke in ICAD patients. In addition, treatment effects may differ among the different types of ICAD. For example, the use of aggressive antiplatelet agents and stenting (in selected patients) can be considered in patients with a higher degree of stenosis and non-BOD type infarcts, whereas stenting may be harmful (perforator stroke due to snowplowing effect) in patients with BOD. Strategies targeting anti-atherogenic effects and restoration of endothelial function may be more efficacious in the latter patients.

Last but not least, public health measures may be particularly important in this subtype of stroke. The very recently reported Chinese IntraCranial AtheroSclerosis (CICAS) study showed a geographic and sex difference in the distribution of symptomatic ICAD in China, which may be explained by differences in risk factors such as obesity, alcohol/smoking habit, and diabetes.[64] In addition, since the Asian population is known to be preferentially affected, focused trials need to be performed to establish treatment modalities that are most effective in this population.[65]

Summary

The failure of the major clinical trials of ICAD may be caused by limitations in the current understanding of ICAD. Various

mechanisms are associated with stroke in patients with ICAD, as compared to those with extracranial carotid stenosis or atrial fibrillation. It is unlikely that one therapeutic strategy (such as stenting of a new device) will succeed in the near future because endothelium/plaque and platelets both play an important role in the development of stroke in patients with ICAD. Treatment strategies might be selected based on clinical features (including the time after onset) and serologic and neuroimaging biomarkers (including DWI pattern, plaque images, and microembolic signals). Although treatment effects may differ among the different types of ICAD, patients with all of these types of ICAD were included together in clinical trials of ICAD. Selection of target patients based on the ICAD types is needed in clinical trials of ICAD. In addition, recently developed MRI techniques (e.g. plaque image) and results of novel biomarkers (e.g. endothelial dysfunction) may extend our understanding of pathophysiological mechanisms of stroke in patients with ICAD. Further clinical trials using serologic and neuroimaging biomarkers as surrogate biomarkers would save time and money.

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