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Special Review

Medical Treatment of Intracranial Atherosclerosis: An Update

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For patients with symptomatic intracranial atherosclerosis (ICAS), antithrombotic agents are the mainstay of therapy. Anticoagulation (warfarin) is not widely used since it is not more effective than aspirin and carries a high risk of bleeding. New oral anticoagulants are showing promise, but their use has not been investigated in appropriate clinical trials. Since the recurrent stroke risk is high with aspirin monotherapy, dual antiplatelets are considered in the early stage of symptomatic ICAS. Based on the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) and Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) results, aspirin plus clopidogrel has been recommended. However, this combination was not superior to aspirin monotherapy in patients with ICAS in the CHANCE substudy. Progression of ICAS is common, and it is associated with recurrent strokes. In the Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis (TOSS) study, aspirin plus cilostazol was more effective than aspirin monotherapy in preventing progression. The TOSS II trial showed that the overall change in stenosis was better with aspirin plus cilostazol than with aspirin plus clopidogrel. Aside from antithrombotic therapy, risk factor management is critical for secondary prevention, and high blood pressure is clearly linked to recurrent stroke. However, blood pressure may have to be cautiously managed in the early stage of stroke. Considering that ICAS is the major cause of stroke worldwide, further investigations are needed to establish optimal management strategies for patients with ICAS.

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Introduction

Intracranial atherosclerotic disease (ICAS) is more prevalent in Asians and Blacks than in Caucasians.[1] The stroke recurrence rate in patients with ICAS is approximately 4–19% annually,[2-5] which is comparable with that of symptomatic severe carotid stenosis.[6] Angioplasty and stenting, or bypass surgery, are only occasionally performed, and antithrombotic medications continue to be the mainstay of therapy. Risk factor management is another important factor in the prevention of stroke in patients with ICAS.

Although there have been a few general reviews on ICAS,[7-9] those that focused specifically on medical management were published approximately 10 years ago.[10,11] Moreover, they did not consider risk factor control[10] nor focused sufficiently on ICAS.[11] Thus, it is necessary to update the current knowledge on the medical management of patients with ICAS. In this narrative review, we will describe the current status on the medical treatment of ICAS, focusing on antithrombotic therapy and risk factor control. We will also discuss future directions for the

optimization of management strategies. Although intravenous t-PA with or without endovascular therapy is warranted in patients with acute thrombotic occlusion associated with ICAS, this issue will not be discussed here since it was already described in a previous paper.[12]

Antithrombotic therapy

Anticoagulants

There is much contention as to the role of anticoagulation in the management of patients with ICAS. Anticoagulation with warfarin has been empirically used for patients with severe occlusive disease in the vertebrobasilar artery and recurrent ischemic stroke despite antiplatelet treatment according to the favorable results of clinical trials performed in 1960s.[13] However, a large, double-blind, randomized controlled trial called Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) that compared the efficacy of warfarin and aspirin was conducted recently.[6] Investigators planned to recruit 806 patients with transient ischemic attacks (TIAs) or non-disabling stroke caused by angiographically verified 50–99% stenosis of the major intracranial artery within 90 days after the events. During the study period, the safety monitoring committee recommended discontinuation of the trial after the enrollment of 569 patients due to safety concerns regarding the patients assigned to warfarin. During a mean follow-up period of 1.8 years, the primary endpoint, defined as ischemic stroke, brain hemorrhage, or vascular death, occurred at a rate of 22.1% in the aspirin group and 21.8% in the warfarin group (hazard ratio [HR] 1.04; P=0.83). The occurrence of major hemorrhage was significantly lower in the aspirin group (aspirin group: 3.2%; warfarin group: 8.3%; HR 0.39; 95% confidence interval [CI] 0.18–0.84; P=0.01), while the mortality rate was lower in the aspirin group (aspirin group: 2.4%/year, warfarin group: 5.2%/year; HR 0.46; 95% CI 0.23–0.90; P=0.02). Based on these results, oral anticoagulation is now rarely used in patients with ICAS.

However, the failure of warfarin therapy was mainly derived from the high incidence of bleeding rather than the lack of efficacy. Since the new oral anticoagulants (NOACs) have comparable efficacy and are associated with significantly fewer bleeding complications than warfarin, NOACs may be used in patients with ICAS. Indeed, the WASID study showed that in patients whose international normalized ratio (INR) was maintained within the ideal therapeutic window (2.0–3.0), the risk of stroke reduced to 5.1% per year (95% CI 2.7–8.7%) from 24.9% per year (95% CI 15.8–37.3%) among those whose INR was <2.0, and the risk of major hemorrhage was 3.5% per year (95% CI 1.6–6.6%) compared with 15.2% (95% CI 6.6–30.0%) for those whose INR ranged from 3.1 to 4.4.[6] These results suggest that the benefits of warfarin can be maximized when the ideal therapeutic window is maintained. Unfortunately, NOACs have yet to be tried in patients with non-cardiogenic stroke. Considering the relatively high risk of recurrent stroke in symptomatic patients with ICAS, future studies that compare the efficacy of NOACs and antiplatelets should be performed in patients with ICAS.

Antiplatelets

Aspirin and aspirin plus clopidogrel

Aspirin is the most widely used antiplatelet in the world. However, when aspirin alone is used in symptomatic patients with ICAS, patients were reported to develop recurrent stroke at an annual rate of 4–19%.[2-5] Therefore, the use of combined antiplatelets has been deemed a better strategy for symptomatic ICAS, especially in the early stage of stroke when the risk of recurrent stroke is particularly high. Theoretically, the addition of antiplatelet agents with different mechanisms may block the diverse pathways of platelet activation and result in the more complete inhibition of platelet activation. By contrast, dual antiplatelet therapy is likely to increase the risk of bleeding, which must be seriously considered.

The combined use of aspirin and clopidogrel seems to have benefits over aspirin monotherapy for the management of acute coronary syndrome, as demonstrated by 2 large clinical trials: the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial[14] and the Clopidogrel for the Reduction of Events During Observation (CREDO) trial.[15] Combination therapy may also be beneficial in the management of stroke patients. Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) showed that combination therapy more significantly reduced microemboli detected on transcranial Doppler than when aspirin monotherapy was used in patients with symptomatic carotid stenosis.[16]

Subsequently, treatment with the combined use of aspirin and clopidogrel was examined in patients at high risk of secondary ischemic events. Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) investigators randomly assigned 5,170 patients to combination therapy (clopidogrel and aspirin) or aspirin monotherapy treatment groups within 24 hours after the onset of minor ischemic stroke or high-risk TIA.[17] Results showed that the primary endpoint (any type of stroke within 90 days) occurred in 8.2% of patients in the clopidogrel plus aspirin group as compared with

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11.7% of those in the aspirin monotherapy group (HR 0.68; 95% CI 0.57–0.81; *P*<0.001). There was no difference in the rate of severe hemorrhage between the 2 groups. Therefore, the combination of clopidogrel and aspirin appears to be superior to aspirin monotherapy for reducing the risk of stroke in the early stage in patients with TIA or minor stroke without an increased risk of hemorrhage.

Aspirin plus clopidogrel may also improve the outcome of ICAS patients. In the Stenting and Aggressive Medical Therapy for Intracranial Stenosis (SAMMPRIS) trial,[4] symptomatic patients with ICAS of 70–99% of the diameter of a major intracranial artery were enrolled. The main purpose of the study was to compare aggressive medical management using aspirin plus clopidogrel and angioplasty/stenting. The primary endpoint was stroke or death within 30 days after enrollment or stroke in the territory of the qualifying artery beyond 30 days. The outcome in the medical-management group, 12.2% in one year, was far more favorable than those in the aspirin monotherapy group in the WASID trial. For this reason, aspirin plus clopidogrel combination therapy is currently widely used in symptomatic ICAS patients in many parts of the world. However, risk factor management was stricter in the SAMMPRIS study than in the WASID cohorts (see below). Moreover, since statin therapy was considered imperative for atherosclerotic stroke following publication of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial in 2006,[18] the aggressive use of statins may have improved the outcome of SAMMPRIS patients. Therefore, interpretations should be made carefully when comparing the efficacy of antithrombotics between the SAMMPRIS and WASID cohorts.

In the more recent CHANCE substudy on 481 patients with ICAS,[19] there was a trend for more favorable outcomes (recurrent strokes at 90 days) in the clopidogrel plus aspirin group than in the aspirin monotherapy group (11.3% vs. 13.6%). However, the difference was not statistically significant. Therefore, further studies are required that include a larger number of patients with ICAS. In addition, a concern was raised over so-called "clopidogrel resistance" that might explain the failure in the CHANCE substudy.

An important issue for clopidogrel is that it is an inactive pro-drug that requires conversion to the active metabolite via CYP2C19. It has been suggested that clopidogrel resistance is more prevalent in Asians than in whites. In another CHANCE substudy,[20] the authors examined whether the presence of carriers of a loss-of-function allele contributes to the lack of efficacy of clopidogrel. Among 2,933 patients, 1,726 (59%) were carriers of loss-of-function alleles. After 90 days of follow-up, clopidogrel plus aspirin reduced the rate of new stroke in the non-carriers, but not in the carriers of the loss-of-function alleles (*P*=0.02 for interaction; events among non-carriers, 41 [6.7%] with clopidogrel plus aspirin vs. 74 [12.4%] with aspirin; HR 0.51; 95% CI 0.35–0.75; events among carriers, 80 [9.4%] with clopidogrel plus aspirin vs. 94 [10.8%] with aspirin; HR 0.93; 95% CI 0.69–1.26).

Cilostazol

Cilostazol has vasodilating, anti-inflammatory, and anti-atherogenic effects in addition to its antiplatelet effect, and it has been shown to be effective in the symptomatic improvement of intermittent claudication,[21,22] the prevention of restenosis after coronary stenting, and for decreasing the progression of carotid intima medial thickness in diabetic patients.[23] Moreover, because the risk of bleeding complications is significantly lower compared to that of other antiplatelets, it can be safely used in stroke patients. A meta-analysis of 13 clinical trials with a total of 6,165 patients showed that cilostazol reduced the incidence of vascular events by 16%, compared with placebo. Moreover, cilostazol did not increase the incidence of serious bleeding complications, compared with placebo (1.4% vs. 1.5%).[24]

Therefore, trial of cilostazol in symptomatic intracranial stenosis (TOSS) investigators attempted to examine the efficacy of cilostazol in the management of ICAS. The TOSS I study[25] randomized 135 Korean patients with acute symptomatic ICAS (middle cerebral artery or basilar artery) into either a cilostazol or placebo group. Aspirin (100 mg/day) was additionally administered to all patients. The degree of stenosis was assessed at the time of enrollment and at 6 months after treatment using magnetic resonance angiography (MRA) and the transcranial Doppler test. Progression of ICAS occurred in 6.7% of the cilostazol plus aspirin group and in 28.8% of the aspirin monotherapy group. Furthermore, the regression rate was higher in the cilostazol (24.4%) group than in the placebo (15.4%) group. The differences were significant both for the progression (*P*=0.008) and overall changes in stenosis (*P*=0.018). The subsequent study, TOSS II, compared the efficacy of dual antiplatelet therapies (aspirin plus cilostazol vs. aspirin plus clopidogrel) in the management of symptomatic ICAS.[26] Medication was administered for 7 months, and the progression of intracranial stenosis was assessed. Progression occurred in 20 patients in the cilostazol group (9.3%) and 32 patients in the clopidogrel group (15.5%), but the difference was not statistically significant (*P*=0.092). However, the overall change in the stenosis was more favorable (i.e., less progression and more regression) in the cilostazol group (*P*=0.049).

Therefore, cilostazol appears to be effective in the prevention of stenosis progression in patients with symptomatic ICAS. However, both the TOSS I and TOSS II trials have limitations in that the numbers of patients were small, all patients were Korean, and, most importantly, the main endpoint was the progression of ICAS and not clinical outcome. Despite those limitations, cilostazol is currently widely used in some parts of the world (mostly Asia). It has been previously shown that the stenosis of intracranial arteries frequently progresses,[27,28] which may represent a more serious event than the stenosis of extracranial arteries; unlike extracranial arteries, hemodynamic disturbances caused by ICAS cannot be compensated by collateral circulation via the Circle of Willis. Hence, there is a close association between the progression of ICAS and clinical stroke recurrence.[27,28]

Other potentially useful antiplatelets

As discussed above, the presence of loss of function alleles may exert an effect during treatment with clopidogrel. One drug that has the potential to resolve this resistance issue is ticagrelor, an antiplatelet agent that acts by the same mechanism as clopidogrel (inhibition of the platelet ADP receptor P2Y12). Since ticagrelor is an active agent, the resistance issue can be avoided,[29] and it may even replace clopidogrel in our clinical practice in the future.[30] In the main trial of the Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) study,[31] 13,199 patients with non-cardiogenic, non-severe ischemic stroke or high-risk TIA were randomly assigned to receive either ticagrelor or aspirin within 24 hours of the event. The primary endpoint was the time to the occurrence of stroke, myocardial infarction, or death. During 90 days of treatment, a primary endpoint event occurred in 442 of the 6,589 patients (6.7%) who were treated with ticagrelor vs. 497 of the 6,610 patients (7.5%) who were treated with aspirin (HR 0.89; 95% CI 0.78–1.01; *P*=0.07). Ischemic stroke occurred in 385 patients (5.8%) treated with ticagrelor and 441 patients (6.7%) treated with aspirin (HR 0.87; 95% CI 0.76–1.00). Thus, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death at 90 days.

However, ticagrelor may be effective in certain groups of stroke patients, especially those with atherosclerotic stroke. In a substudy of SOCRATES, investigators examined the efficacy of ticagrelor in patients with ipsilateral atherothromobotic stroke.[32] Among 3,081 such patients, stroke, myocardial infarction, or death occurred within 90 days in 103 (6.7%) of 1,542 patients with ipsilateral stenosis in the ticagrelor group and 147 (9.6%) of 1,539 patients with ipsilateral stenosis in the aspirin group (HR 0.68; 95% CI 0.53–0.88; *P*=0.003). Thus, ticagrelor may be superior to aspirin in preventing stroke, myocardial infarction, or death at 90 days specifically in patients with ipsilateral symptomatic atherosclerotic stenosis. Unfortunately, the location of cerebral atherosclerosis was not carefully examined in this study, and information regarding its efficacy in patients with ICAS is lacking. Among the SOCRATES cohort, 29% of patients were Asians, and in a SOCRATES substudy analyzing these patients, there was no definite evidence that ticagrelor is more effective in Asians than in whites.[33] Thus, the overall effectiveness of ticagrelor in patients with ICAS remains to be established.

Vorapaxar, a selective antagonist of protease activator receptor-1 (PAR-1), is a new class of antiplatelet agent.[34] In one study of 26,449 patients with a history of myocardial infarction, ischemic stroke, or peripheral arterial disease, vorapaxar, as compared to a matching placebo, significantly reduced the occurrence of the composite of death from cardiovascular causes, myocardial infarction, or stroke at 3 years.[35] However, in a subsequent substudy involving patients with a history of ischemic stroke (n=4,883), the benefit of vorapaxar over placebo could not be documented.[36] Further studies are required to examine the possible effects of this drug in patients with symptomatic ICAS.

Risk factor management

Hypertension, diabetes, dyslipidemia, and cigarette smoking are risk factors associated with cerebral artery atherosclerosis including ICAS. The differences in risk factors between ICAS and extracranial atherosclerosis (ECAS) have been subject to debate; dyslipidemia seems to be more closely associated with ECAS, while advanced hypertension, metabolic syndrome, or diabetes may be more closely associated with ICAS.[37] The presence of risk factors may also be linked to the severity of ICAS. According to one study that used WASID data, dyslipidemia, metabolic syndrome, and diabetes were more common in severe ICAS than in mild/moderate ICAS.[38] Thus, these risk factors should be aggressively managed for the primary and secondary prevention of stroke in patients with ICAS.

Previously, risk factor management has not been seriously considered in the clinical research on ICAS. However, in the recent SAMMPRIS trial, investigators attempted to use a multimodal aggressive risk factor approach for stroke prevention: targeting systolic blood pressure (SBP) ≤140 mm Hg (≤130 mm Hg if diabetic) and low-density lipoprotein (LDL) cholesterol <70

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mg/dL. The study neurologists and coordinators at each site implemented risk factor management for both primary (SBP and LDL cholesterol) and secondary (non-high density lipoprotein cholesterol, hemoglobin A1c (HbA1c), smoking, weight management, physical activity) targets and were assisted by an evidence-based, educational, lifestyle modification program (INTERxVENT) that was administered at regularly scheduled times to all patients throughout the study.

Compared to similar patients treated with usual management approach in the WASID trial, patients enrolled in SAMMPRIS had substantially better risk factor control: within the first 30 days, mean SBP decreased by >5 mm Hg and mean LDL cholesterol decreased by >20 mg/dL. Among WASID patients who met the SAMMPRIS entry criteria, the stroke and death rate was 10.7% at 30 days and the primary endpoint was 25% at 1 year. These rates were much higher than those of the SAMMPRIS patients who were assigned to the medication-only group whose 30-day rate of stroke or death was 5.8% and whose 1-year rate of primary endpoint occurrence was 12.2%. Since the antithrombotics that were used differed between the 2 studies (aspirin plus clopidogrel in SAMMPRIS vs. aspirin or warfarin in WASID), the 2 groups cannot be directly compared, but it is likely that the improved risk factor control contributed to better outcomes in the medical management arm of SAMMPRIS.

In a recent prospective observational study involving 50 acute stroke patients with symptomatic ICAS (≥70%), intensive medical therapy for 12 months with the therapeutic targets of LDL cholesterol <70 mg/dL, HbA1c <6.5%, and SBP <140 mm Hg resulted in relatively good outcomes in terms of ICAS progression: regression occurred in 49% of patients, quiescence in 43%, and progression in 8%.[39] These results appear to be superior to those of TOSS, in which regression occurred in 15% and progression in 29% of the aspirin arm, with regression occurring in 24% and progression in 7% in the aspirin plus cilostazol arm over 6 months.[25] These outcomes once again suggest that strict risk factor control is important in the management of ICAS.

However, the intensity of the control of blood pressure and cholesterol levels remains subject to debate. In the following section, we present a detailed discussion of the management of those 2 important risk factors, i.e., blood pressure and cholesterol, for secondary prevention in patients with ICAS.

Blood pressure control

Hypertension is an important risk factor for ICAS, and may be a factor more closely associated with ICAS than ECAS,[37] making the strict control of blood pressure an important strategy for the management of ICAS. However, the intensity of blood pressure reduction for the secondary prevention of stroke remains unclear in ICAS patients. Although strict blood pressure control is generally recommended, some physicians believe that maintaining blood pressure may be necessary in these patients to protect against hypoperfusion.

Using 567 patients from the WASID trial, investigators analyzed the frequency of ischemic stroke according to the mean SBP and mean diastolic blood pressure (DBP) during the study period.[40] Increased mean SBP and DBP both significantly increased the risk of stroke in general as well as strokes occurring in the territory of the stenosed artery. The increased risk of stroke with increasing SBP was driven largely by the highest SBP (≥160 mm Hg) in patients who had significantly increased risk of stroke in the territory of the ICAS (HR 3.9; 95% CI 1.1–14.1). The increased risk of stroke in the relevant territory was observed with increased SBP and DBP in the patients with both moderate (<70%) and severe (≥70%) stenosis. Therefore, the authors argued that in patients with ICAS, strict blood pressure control is important and there is no need to maintain elevated blood pressure in any of these patients.

More recently, using the data set of 402 patients with symptomatic ICAS who were enrolled in the TOSS II study, investigators attempted to examine the relationship between mean SBP and the progression of ICAS, which was defined as a worsening by 1 grade or more at the 7-month follow-up MRA.[41] ICAS progression was observed in 52 (12.9%) subjects. Percentages of ICAS progression by mean SBP category showed a J-shape pattern: low-normal (<120 mm Hg, 21.4%), normal to high-normal (120–139 mm Hg, 10.7%), high (140–159 mm Hg, 11.4%), and very high (≥160 mm Hg, 38.9%). Multivariable analysis showed that, as compared to the odds ratio (OR) for the normal to high-normal SBP group, the OR (95% CI) for ICAS progression was 1.88 (0.62–5.67) for low-normal SBP, 1.06 (0.47–2.37) for high SBP, and 8.75 (2.57–29.86) for very high SBP.

Thus, both the WASID and TOSS II substudies indicate that very high mean SBP (≥160 mm Hg) is closely associated with a high risk of recurrent stroke and ICAS progression. However, the findings regarding the low-normal blood pressure appear contradictory. This discrepancy may be attributable to the fact that the patients in the TOSS II trial were enrolled sooner following their stroke events than those in the WASID trial. In other words, the hazard of excessive blood pressure reduction, if it exists, may be more apparent in the early stage of stroke. Moreover, the 2 data sets are not comparable because the pri-

mary endpoints were different (recurrent stroke in WASID vs. ICAS progression in TOSS II). It remains unclear why the progression rate tended to be higher in the low-normal (<120 mm Hg) SBP group in the TOSS II substudy.

The potential danger of excessive blood pressure reduction in patients with ICAS can be attributed primarily to early neurological progression (END), which could not be captured in studies where outcomes were defined as recurrent stroke or mortality. In a recent multicenter study,[42] investigators examined whether administration of an antihypertensive drug (valsartan) for the first 7 days after stroke influences the rate of END. END occurred more frequently (17% [31 of 187]) in the valsartan group than in the placebo group (6% [14 of 185]) (OR 2.43; 95% CI 1.25–4.73; *P*=0.008). Investigators also found that the difference in the frequency of END was most pronounced in patients with symptomatic large artery stenotic disease. Since this study was conducted in Korea where ICAS is a predominant type of large artery disease, the result suggests that early blood pressure reduction may increase the risk of END in ICAS patients.

The occurrence of END in patients with ICAS is likely to be caused by a perfusion defect in the territory of the stenosed artery. According to a study that enrolled 95 patients with ICAS,[43] 14 (15%) developed END defined by worsening of ≥4 points on the National Institutes of Health Stroke Scale from baseline during the 1st week. Independent predictors of END were the presence of borderzone infarcts on baseline diffusion-weighted MRI (OR 7.21; 95% CI 1.88–27.66; *P*=0.004). Another study enrolling 211 patients with MCA territory stroke[44] also found that borderzone infarction on early MRI was an independent factor associated with END (OR 2.50; 95% CI 1.09–5.74; *P*=0.031).

This observation suggests that an increase rather than a decrease in blood pressure may be beneficial in patients with END, which is presumably due to unstable cerebral perfusion in the early stage of stroke. Although the benefit of so-called 'induced hypertension' has not been fully documented, some small studies have demonstrated improved outcomes in cerebral perfusion,[45] language function,[46] or neurological function[47] after induced hypertension therapy. Thus, many centers are currently using induced hypertension in patients who show END. In one recent study, among the 121 patients with END who received induced hypertension therapy, large artery disease accounted for 41% and cardiogenic infarction accounted for only 4%, whereas among the age/sex-matched controls (patients admitted on the nearest day to that of the index patient), large artery disease accounted for 31% and cardiogenic embolism for 35%. Thus, END is more common and induced hypertension is more often performed in patients with large artery diseases, most likely associated with hypoperfusion, than in patients with cardiac embolism. In patients with large artery disease who received induced hypertension therapy, approximately 80% had ICAS (unpublished data), which suggests that END due to cerebral hypoperfusion often occurs in patients with ICAS for whom early, excessive blood pressure reduction might be hazardous.

Finally, long-term treatment with ACE inhibitors was reported to prevent the progression of atherosclerotic processes detected by carotid duplex scan.[48] Although it remains unclear whether this reflects a class effect of antihypertensive drugs, the potential advantages of certain classes of antihypertensives remain to be investigated in patients with ICAS.

Lipid management and statin use

Current guidelines emphasize lipid-lowering (statin) therapy to reduce the risk of atherosclerotic strokes.[49] In the WASID study, a history of a lipid disorder was independently associated with severe stenosis (OR 1.62; 95% CI 1.09–2.42; *P*=0.02),[38] which illustrates the importance of lipid-lowering therapy in patients with ICAS. The guidelines also recommend the use of high-intensity statins in patients with ICAS, based on the indirect evidence of the effects of statin therapy, comparing the historical control of the WASID and SAMMPRIS trials.[4,50] However, the role of high-intensity statins in patients with ICAS still remains unclear, partly because dyslipidemia has been considered a relatively less important risk factor in ICAS than in ECAS.[51] Unfortunately, there have been no reliable, randomized trials that revealed the beneficial effects of high-intensity statins in patients with ICAS.

Nevertheless, there is some evidence that statin therapy is important in the secondary prevention of stroke in ICAS patients. In one study,[52] 55 Korean patients with symptomatic ICAS who underwent initial and follow-up MRA at 1 year after the index stroke were studied. Patients were divided into a statins group (treated with statins for more than 75% of the follow-up period) and a non-statins group. At a median follow-up time of 22 months, the ICAS progressed in 11%, regressed in 26%, and remained stationary in 64%. After adjustment for other variables, statin treatment was significantly associated with non-progression of ICAS (*P*=0.024). Another single-center, randomized, single-blind clinical trial[53] enrolled 120 Chinese patients with symptomatic ICAS identified by computed tomography angiography (CTA) and CT perfusion. Patients were randomly divided into the low-dose (10 mg/day), stan-

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dard-dose (20 mg/day), and intensive-dose atorvastatin therapy (40 mg/day) groups in a 1:1:1 ratio. After 52 weeks of treatment, improvement in serum lipid profiles, degree of stenosis, and perfusion-related parameters was significantly better in the intensive-dose group. In addition, the cumulative probability of cerebrovascular events was significantly lower in the intensive group than in the low-dose group. The statin therapy was well tolerated, and there was no difference in side effects according to different dosages. These results suggest that high-intensity statin treatment may be safe and effective in Asian ICAS patients. However, the intensive dose (40 mg/day) in this study was still smaller than the one used in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial (80 mg/day),[18] and it is still unclear whether a high-intensity therapy is effective and safe in ICAS patients.

Currently, the Treat-Stroke-To-Target (TST) trial is ongoing (clinicalTrials.gov identifier, NCT01252875). In this study, patients with ischemic stroke (within 3 months) or TIA (within 15 days) and evidence of atherosclerotic vascular diseases were randomized to maintain an LDL cholesterol level of either 100±10 mg/dL or <70 mg/dL. The number of target patients was 3,760, and they will be followed up for at least 12 months. The primary endpoint was the composite of nonfatal ischemic stroke, nonfatal myocardial infarction, and any vascular death. Partly because both Caucasian (French) and Asian (Koreans) patients are enrolled, and partly because the location of atherosclerosis is mandatorily documented in the protocol, it is expected that the study result may provide an answer as to whether the therapeutic target of LDL cholesterol should vary according to different ethnicities (whites vs. Asians) and different locations of atherosclerosis (ICAS vs. ECAS).

Finally, it has been suggested that the statin therapy strategy may have be modified according to the pathologic nature of ICAS. With recent advances in high-resolution MRI techniques, intracranial arterial plaque can be visualized. It has been shown that ICAS has heterogeneous features in terms of plaque instability and vascular remodeling.[54] Atherosclerosis is a systemic disease, and there may be an echo of plaque activity between coronary and intracranial vessels as measured by high-resolution MRI.[55] Therefore, information on the characteristics of intracranial plaques may guide the treatment and work-up (e.g., search for hidden coronary diseases) strategies. High-resolution MRI findings can also be used as a surrogate marker in patients with ICAS; statin therapy may induce plaque regression and improve plaque vulnerability. Prior use of statins was found to be associated with plaque characteristics in patients with ICAS.[56] A prospective study of serial high-resolution MRI after intensive statin therapy in statin-naïve, symptomatic patients with ICAS is currently ongoing (STAMINA-MRI study, clinicalTrials.gov identifier, NCT02458755).

Future direction

New trials and new antithrombotics

Despite the high prevalence of ICAS throughout the world, clinical trials focusing on ICAS have been rare, and further active clinical studies are needed. As previously discussed, NOACs should be examined for their efficacy in secondary stroke prevention in ICAS patients since they offer effective anticoagulation with decreased occurrence of bleeding complications compared to warfarin. Although cilostazol has been found to be efficacious in preventing the progression of ICAS, its effect on clinical outcomes still needs to be tested through larger studies. The efficacy of clopidogrel should also be re-examined, possibly with concomitant tests on genetic polymorphisms such as the loss of function gene. Ticagrelor is one of the promising drugs that should be tested in symptomatic patients with ICAS. Testing various combinations of antiplatelets with different basic mechanisms (e.g., cilostazol plus clopidogrel) may provide valuable information as well. Finally, studies on the duration of dual antiplatelets should be performed given that the benefit of long-term dual antiplatelet therapy may be counteracted by the potentially increased incidence of bleeding complications.

Improved assessment of etiology and stroke mechanisms

Imaging techniques such as MRA, CTA, and catheter angiography can examine luminal stenosis, but not vascular wall pathology. Therefore, non-atherosclerotic etiologies such as moyamoya disease (MMD), dissection, and vasculitis may be erroneously categorized as ICAS. One diagnostic tool that can be used to examine the vessel wall is high-resolution vessel wall MRI.[57] A recent study from Korea assessed high-resolution MRI findings in patients who were initially diagnosed as presumable ICAS, but were young (age ≤55 years) and had minimal (0 or 1) risk factors. Of the 95 patients analyzed, only 26 (27.4%) had vessel wall findings consistent with atherosclerosis, whereas the others showed findings consistent with non-atherosclerotic diseases.[58] Since MMD,[59] arterial dissection,[60] and vasculitis[61] affecting the intracranial arteries occur more frequently in Asians than in whites, the problem of contamination of non-atherosclerotic diseases is likely to be greater in Asian patients.[62] Since the natural courses, mechanisms of stroke, and

therapeutic response vary among the different causes of arterial disease, this contamination seems to be one of the reasons for the inconsistent results of the ICAS studies. From the therapeutic point of view, it is likely that the life-long use of high-intensity statins is not helpful in patients with non-atherosclerotic diseases. Thus, future studies should be performed based on more accurate diagnoses of intracranial arterial pathologies.

In addition, ICAS leads to stroke or TIA via diverse mechanisms including artery-to-artery embolism, in-situ thrombotic occlusion, branch occlusion, and hemodynamic impairment.[63] Since artery-to-artery embolism is closely related with platelet aggregation and thrombus formation in the diseased artery, strong antiplatelets (e.g., dual antiplatelets) may be advantageous, especially in the early stage of stroke. On the other hand, in patients with progressive narrowing of the intracranial artery, drugs with the potential to inhibit atherosclerosis progression, e.g., cilostazol, statin, may have to be considered. Further studies are needed to elucidate whether this tailored therapeutic approach is scientifically reasonable.

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