Acute Reperfusion Therapy and Stroke Care in Asia After Successful Endovascular Trials

Kazunori Toyoda, MD; Masatoshi Koga, MD; Mikito Hayakawa, MD; Hiroshi Yamagami, MD

Abstract—The current status of and prospects for acute stroke care in Asia in the situation where both intravenous thrombolysis and endovascular therapies have been recognized as established strategies for acute stroke are reviewed. Of 15 million people annually having stroke worldwide, ≈9 million are Asians. The burdens of both ischemic and hemorrhagic strokes are severe in Asia. The unique features of stroke in Asia include susceptibility to intracranial atherosclerosis, high prevalence of intracerebral hemorrhage, effects of dietary and lifestyle habits, and several disorders with genetic causes. These features affect acute stroke care, such as the dosage of alteplase for thrombolysis and consideration of bleeding complications during antithrombotic therapy. Acute endovascular thrombectomy, as well as intravenous thrombolysis, is relatively prevalent in East Asia, but most of the other Asian countries need to develop their human resources and fundamental medical infrastructure for stroke care. A limitation of endovascular therapy in East Asia is the high prevalence of intracranial atherosclerosis that can cause recanalization failure and require additional angioplasty or permanent stent insertion although intracranial stenting is not an established strategy. Multinational collaboration on stroke research among Asian countries is infrequent. Asians should collaborate to perform their own thrombolytic and endovascular trials and seek the optimal strategy for stroke care specific to Asia. (Stroke. 2015;46:1474-1481. DOI: 10.1161/STROKEAHA.115.008781.)

Key Words: anticoagulants ▪ Asia ▪ cerebral hemorrhage ▪ intracranial atherosclerosis ▪ stroke ▪ thrombectomy ▪ thrombolysis, therapeutic

Diversity, thy name is Asian.

—Anonymous

It is a pity that the 40th G8 summit was not held as it was originally planned in 2014 because the global burden of stroke was a possible topic at that summit. We missed a chance to inform Western developed countries of the current problems of stroke care in Asia.

Of 15 million people annually having stroke worldwide, ≈9 million are Asians (a message from the Asia Pacific Stroke Organization, http://www.theapso.com/message-from-secretary). In 2010, the highest incidences of ischemic stroke were in Central and East Asia, the Mideast, and North Africa (178–238/100 000), as well as in Russia and Eastern Europe, and those of intracerebral hemorrhage (ICH) and subarachnoid hemorrhage combined were in Central and East Asia (101–158/100 000), as well as in east and southern sub-Saharan Africa (Figure 1).1,2 In addition, the mortality:incidence ratio for hemorrhagic strokes was fairly high (≥0.74) in Southeast Asia and the Mideast. Thus, the burdens of both ischemic and hemorrhagic strokes are severe in Asia.

We cannot explain the characteristics of stroke in Asia without considering the heterogeneity of Asian patients with stroke. There are large differences in conditions surrounding stroke among Asian countries. We have tried to discuss the conditions evenly for all of Asia, but some information is unevenly derived from that from East Asia because of the relatively greater number of publications from there.

Unique Aspects of Acute Stroke in Asia

The unique features of stroke in Asia include high prevalence of intracranial atherosclerosis, high prevalence of ICH, effects of dietary and lifestyle habits, and several disorders with genetic etiologies.

Intracranial atherosclerotic stenosis causes ≤30% to 50% of strokes in East Asia and also seems to be higher in northern India although it causes only 5% to 10% of strokes in whites.3 There seems to be an inherited susceptibility of the intracranial arteries to atherosclerosis. A particular subset of Japanese patients with intracranial atherosclerotic stenosis was reported to have a c.14576G>A variant in ring finger protein 213 (RNF213), which is originally known as a susceptibility gene.
for moyamoya disease. Lifestyle may be another major factor; extracranial carotid stenosis has become more common in Asia these days partly because of westernization of the diet and an increase in hypercholesterolemia. A high proportion of lacunar infarction to total stroke in Asia also indicates susceptibility to intracranial vasculopathy. When compared with the high prevalence of extracranial carotid dissection in Western countries, there is a relatively high percentage of intracranial dissection in Japan. Moyamoya disease, characterized by progressive stenosis of the terminal portion of the internal carotid artery and its main branches, is most common in Asia. Hereditary intracranial disorders causing stroke, including cerebral autosomal dominant and cerebral autosomal recessive arteriopathies with subcortical infarcts and leukoencephalopathy (CADASIL, CARASIL), are often identified in Japan and other Asian countries. The prevalence of ICH in Asia also seems to be associated with susceptibility to intracranial vasculopathy. In addition, high sodium intake in Asia seems to raise blood pressure, increase ICH, and worsen outcomes after ICH (Figure 1).
more common in Asians than in whites.\textsuperscript{11,12} Other than sodium intake, chewing tobacco, water-pipes, Indian clarified butter, and infections are listed as potential risk factors for stroke in South Asia, especially at a younger age.\textsuperscript{13} Differences in socioeconomic and health hygiene status, including a wide difference in lifespan, are various unique features across Asia.

**Current Status and Prospects of Intravenous Thrombolysis in Asia**

The prevalence of intravenous thrombolysis using alteplase, a recombinant tissue-type plasminogen activator, varies among Asian countries. It was performed in \textasciitilde 9\% of patients overall with ischemic stroke in Korea (as of 2011, reports from the Korean Health Insurance Review and Assessment Service), \textasciitilde 1.3\% in China (11th 5-year plan during 2006 and 2010),\textsuperscript{14} \textasciitilde 2\% in Thailand (as of 2012),\textsuperscript{15} and \textasciitilde 3000 patients per year in India (as of 2011).\textsuperscript{16} Only 8 of \textasciitilde 350 hospitals in Saudi Arabia provide thrombolysis.\textsuperscript{17} In a recent Web-survey, no neurologists in Indonesia or Kazakhstan and only one-ninth of those in Bangladesh replied that most of their patients with stroke could undergo thrombolysis.\textsuperscript{18} Thus, the spread of this standard therapy across the whole of Asia is an urgent problem.

Japan was one of the latest to approve the commercial use of alteplase for stroke patients (approval in 2005).\textsuperscript{19} Now, \textasciitilde 12000 patients are estimated to undergo this therapy each year, roughly corresponding to 5\% to 6\% of the overall patients with ischemic stroke. The official dosage of alteplase is 0.6 mg/kg based on the results of a dose comparison study using duteplase\textsuperscript{20} and the multicenter single-dose Japan Alteplase Clinical Trial.\textsuperscript{21} Several hospitals in East Asia and Southeastern Asia have adopted this lower dosage, and it makes comparison of outcomes after thrombolysis in Asia with other regions difficult.\textsuperscript{22} In the Table, the results of observational studies from Europe and Asia are compared.\textsuperscript{23–26} The nationwide Japan Post-Marketing Alteplase Registration Study (J-MARS) and the multicenter Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement (SAMURAI) recombinant tissue-type plasminogen activator Registry, both using alteplase at 0.6 mg/kg, showed similar efficacy and safety when compared with the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) from Europe. The SITS-Non-European Union World (SITS-NEW) across 4 Asian countries had a relatively higher percentage of patients with modified Rankin Scale scores of 0 to 2 and a similar frequency of symptomatic ICH and mortality when compared with others. It is notable that patients in the SITS-NEW were younger and had milder strokes than those in Japanese studies. Actually, the optimal dosage of alteplase has not yet been proven based on highly scientific studies although 0.9 mg/kg is globally approved according to the National Institute of Neurological Disorders and Stroke recombinant tissue-type plasminogen activator stroke study.\textsuperscript{27} Comparisons of outcomes after the same dosage of alteplase between Asians and other populations have not been performed in major trials or their meta-analyses because relatively few Asian patients were included. The Desmoteplase in Acute Ischemic Stroke (DIAS)-3 study seems to be the first international trial to include Asian patients constituting more than half of overall registered patients; analysis by race in the DIAS studies is anticipated. In the Get With The Guidelines-Stroke program, the adjusted odds ratio of symptomatic ICH after alteplase in Asians (1523 patients) to whites (40411 patients) was 1.47 (95\% confidence interval, 1.19–1.82).\textsuperscript{28} To identify the optimal dosage of alteplase, the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTEO; ClinicalTrials.gov NCT01422616) has been recruiting patients from Australia, China, Korea, Vietnam, and others.

Extension of the therapeutic time window beyond the 4.5-hour limit is a pressing issue for intravenous thrombolysis. To extend the limit to 9 hours, many institutes in Australasia, Taiwan, and others have participated in the Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial.\textsuperscript{29} Most of the current participants were announced to be the so-called wake-up stroke patients. Observational studies on stroke with unclear time of symptom onset or onset during sleep have been often reported from Korea and Japan.\textsuperscript{30,31} We have started the Thrombolysis for Acute Wake-Up and Unclear-Onset Strokes (THAWS) trial with alteplase at 0.6 mg/kg to determine the efficacy and safety of low-dose alteplase using magnetic resonance imaging-based selection in Japanese patients with unclear-onset stroke.\textsuperscript{32}

**Current Status of Endovascular Thrombectomy in Asia**

Asia is far behind in the development and manufacture of medical devices compared with the United States and the European Union. In addition, some Asian countries, particularly Japan, had a political problem of a slow approval system for such devices, the so-called device lag. The delay became

### Table. Observational Studies of Intravenous Thrombolysis Using Alteplase

<table>
<thead>
<tr>
<th>Area</th>
<th>SITS-MOST</th>
<th>SITS-NEW</th>
<th>J-MARS</th>
<th>SAMURAI r-tPA Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>6483</td>
<td>591</td>
<td>7492</td>
<td>600</td>
</tr>
<tr>
<td>Age, y (median)</td>
<td>68</td>
<td>64</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>Baseline NIHSS (median)</td>
<td>12</td>
<td>12</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Dosage of alteplase, mg/kg</td>
<td>0.9</td>
<td>0.9</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Time window, h</td>
<td>\textless 3</td>
<td>\textless 3</td>
<td>\textless 3</td>
<td>\textless 3</td>
</tr>
<tr>
<td>Symptomatic intracerebral hemorrhage, %*</td>
<td>1.7</td>
<td>1.9</td>
<td>3.5</td>
<td>1.3</td>
</tr>
<tr>
<td>3-mo modified Rankin Scale score 0–2, %†</td>
<td>55</td>
<td>62.5</td>
<td>52</td>
<td>56.1</td>
</tr>
<tr>
<td>3-mo mortality, %†</td>
<td>11.3</td>
<td>12</td>
<td>12</td>
<td>4.0</td>
</tr>
</tbody>
</table>

\*Parenchymal hemorrhage type II combined with an increase of \textasciitilde 4 points from the baseline NIHSS score.

†Restricted to patients between ages 18 and 80 years with NIHSS scores \textasciitilde 25.
shorter for approval of recent thrombectomy devices. The delay for initiating commercial use in Japan when compared with the United States was 6 years (2004 versus 2010) for the Merci Retriever, 3 years (2008 versus 2011) for the Penumbra System, and 2 years (2012 versus 2014) for the Solitaire Flow Restoration device and Trevo Pro Retriever. Introduction of the Solitaire to Korea was much earlier (2011).33 China is unique in that neurologists mainly perform endovascular therapy (EVT); there are >1 to 1.5 interventional neurologists per hospital in major medical centers.34 Japan, China, and India are listed among the 10 major markets for neurovascular interventional devices in 2014. In most other Asian countries, however, acute EVT has spread poorly.

What are the outcomes of acute EVT in real-world settings? The Clinical Research Center for Stroke-Fifth Division (CRCS-5), a prospective registry involving 15 Korean hospitals, showed that 2.0% of patients with acute stroke underwent EVT alone, and 2.6% did EVT combined with intravenous thrombolysis between April 2008 and November 2013.33 Patients with modified Rankin Scale scores of 0 to 1 at 3 months accounted for 32.5% of the overall patients undergoing any acute reperfusion therapy. The proportion of modified Rankin Scale score 0 to 1 was lower in patients with EVT than in those with intravenous thrombolysis alone, partially because the former had higher admission National Institutes of Health Stroke Scale scores. In the Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism (RESCUE)-Japan Registry, patients with acute large artery occlusion were registered from 84 Japanese hospitals between July 2010 and June 2011, when the Merci was an only approved thrombectomy device.35 Acute EVT was performed in 23% of the overall patients, 65% of the alteplase-failed patients, and 35% of the potential candidates for EVT who were ineligible for intravenous thrombolysis. Both clinical and vascular outcomes were relatively better in patients receiving EVT than in those without EVT in both alteplase-failed and alteplase-ineligible patients.

**Essential Issues for Acute EVT in Asia**

February 2015 may be a historical turning point for stroke medicine. Of the landmark articles in that month, the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanulation Times (ESCAPE) trial included a small number of patients from Korea,36 and the EXTEND-Intra-Arterial (EXTEND-IA) study was an Australasian trial.37 Their results will undoubtedly affect the conditions of acute stroke care in Asia.

The levels of stroke care differ among Asian countries. Public awareness, training for physicians and medical staff, and development of medical infrastructure including stroke care units and neurointerventional units are necessary in many countries in Southeast Asia, South Asia, Central Asia and the Mideast before establishing strategies for EVT. On the contrary, infrastructure for EVT is relatively well maintained in East Asia.

A large limitation of EVT in East Asia is the high prevalence of intracranial atherosclerosis. Patients with milder stroke may be widely regarded as eligible for EVT because the ESCAPE trial included patients with baseline National Institutes of Health Stroke Scale scores ≥26, and the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) included those with National Institutes of Health Stroke Scale scores ≥2.38 Patients with atherothrombotic stroke, whose initial neurological deficits are generally milder than those of cardioembolic patients, may accordingly have more chance to receive EVT. Because symptoms of atherothrombotic stroke often gradually deteriorate, it may be difficult to judge when and how to choose EVT for such cases. Intracranial atheromata do not seem to fit the properties of stent retrievers. They can resist sufficient expansion of devices at the occlusive lesion or retrieval of devices and cause inadvertent detachment, arterial dissection, and vasospasm. Recanalization failure and mortality after thrombectomy using stent retrievers were reported to be high in patients having atherothrombotic lesions (Figure 2).39,40 In addition, intracranial atherosclerosis may cause artery tortuosity and small arterial size, a Japanese report demonstrated a relatively sharp curve angle of the horizontal middle cerebral artery segment (115°±30°).41 Excessive tortuosity constrains effective delivery of the device and exertion of retraction force.41,42 Similar anatomic problems have been seen with aortoiliac stent grafting for Hawaiian patients of Asian ancestry.43 In brief, one should keep in mind that performance of thrombectomy without careful consideration of the cause of arterial occlusion may be harmful to patients with atherothrombotic occlusion.

Additional angioplasty or stenting may be needed to obtain sufficient recanalization when thrombectomy alone is not successful. Figure 3 demonstrates a case having a basilar arterial atheroma for which balloon angioplasty right after thrombectomy brought sufficient recanalization. Two single-center reports on Solitaire-based thrombectomy from Korea showed diametrically opposite results; permanent stent insertion with balloon angioplasty was emergently added in 6 of 23 patients after thrombectomy in one,44 and successful recanalization without balloon angioplasty was achieved in 8 of 11 patients with the probably atherothrombotic occlusion at the middle...
cerebral artery occlusion in the other. An essential limitation of such a strategy is lack of evidence for angioplasty or stenting in acute atherothrombotic stroke. In particular, angioplasty without stenting may be ineffective because of recoil or cause further endothelial denudation and dissection leading to rapid rethrombosis despite apparent favorable immediate angiographic results. Stenting may be promising to sustain vessel patency in intracranial large artery occlusion from rupture of high-grade stenotic atherosclerosis; that is relatively common in Asians.

Although the self-expanding Wingspan stent system was not promising for patients with recent mild stroke (median time from qualifying events of 7 days) when compared with aggressive medical therapy in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, clinical outcomes after the Wingspan were generally favorable in reports from China (including 100 patients; median, 29.5 days) and Korea (77 patients; median, 15 days). In Japan, the Wingspan was approved for commercial use in 2013 after a small domestic trial involving 20 patients with symptomatic intracranial stenosis. The use of the Wingspan as rescue from dissection and elastic recoil after balloon angioplasty was recommended without limitation of the timing after stroke onset in the Japanese guideline. However, most Japanese interventionists voluntarily refrain from Wingspan use for patients with hyperacute stroke because of its failure in the SAMMPRIS trial and particularly the lack of data on its use for acute atherothrombotic occlusion.

Balloon-expandable stents are another option for intracranial atherosclerosis, being superior to self-expanding stents in expanding power, but inferior in the rigidity of the device and high inflation pressures. The use of balloon-expandable intracranial stents for high-grade symptomatic atherosclerotic stenosis was successful and relatively safe in a report from India. A randomized clinical trial on balloon-expandable stent for symptomatic intracranial stenosis was unsuccessful; the stent use increased stroke risk compared with medical therapy.

The efficacy of intracranial stenting in reopening acute local thrombo-occlusion because of underlying atherosclerosis needs further investigation. In addition, dual antiplatelet medication required for patients treated with stent replacement may increase the risk for hemorrhagic transformation especially just after receiving a full systemic dose of alteplase. Now, trials of acute EVT for Asian patients including those with intracranial atherosclerosis are required.

### Other Problems of Acute Stroke

#### Care Awaiting Solution

Neuroprotective medication is essential for acute stroke care, but it has not been in global use. The therapy is theoretically effective for expansion of the time window of reperfusion therapy and improvement of clinical outcomes when combined with reperfusion therapy. Edaravone, a free radical scavenger, is approved for commercial use for acute ischemic stroke in Japan. It seems to attenuate edema and hemorrhagic transformation after stroke partly because of cerebrovascular protection from ischemic damage. The efficacy of edaravone should be ascertained in the other Asian and ex-Asian countries.

Dual antiplatelet medication for 3 weeks, principally the combination of aspirin and clopidogrel, may be recommended for patients within 24 hours of minor stroke based on the results of the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trial from China. Frequent bleeding complications during antithrombotic therapy should be noted. ICH is more common in Asians than in whites, while taking a single antiplatelet agent, dual antiplatelet agents, and vitamin K antagonists.

The Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com) has been recruiting patients from Japan to determine the efficacy and safety of dual antiplatelet therapy involving cilostazol because the bleeding risk with cilostazol is relatively low.

Early initiation of oral anticoagulation after stroke is not strongly recommended globally in current guidelines. However, recent studies indicate the safety of early non–vitamin K antagonist oral anticoagulant (NOAC) use. Major trials comparing NOACs with warfarin in nonvalvular atrial fibrillation showed interesting racial differences (Figure 4). Both ischemic and hemorrhagic events occurred often in Asians. However, the racial difference in the risk of intracranial hemorrhage was more subtle in NOAC users than in warfarin users. The presence of genetic differences in
metabolizing warfarin is a potential reason for the high risk of ICH during warfarin in Asians,\textsuperscript{65} but genetic differences in metabolizing NOACs have not been clarified. NOACs may be an ideal option for acute stroke therapies in Asians.

The proportion of acute ICH care to total acute stroke care is high in Asia. The second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) recruited patients mainly from China and showed a marginally significant reduction in the rate of death or disability after ICH by rapid lowering of systemic blood pressure to <140 mm Hg.\textsuperscript{66}

In the ongoing Antihypertensive Treatment for Acute Cerebral Hemorrhage (ATACH) II Trial, more than one half of the participants were from Japan, China, Taiwan, and Korea.\textsuperscript{67} Finally, multinational collaboration on clinical stroke research among Asian countries is gradually increasing, but it remains infrequent.\textsuperscript{68} Asians should collaborate more often to seek the optimal strategy for stroke care specific to Asia. As an example, we found interesting differences in emergent stroke transfer to our hospital and to the Severance Hospital, Seoul.\textsuperscript{69} Onset-to-arrival time was relatively short in our hospital, mainly because of more frequent use of emergency medical services. In contrast, many patients arrived at the Severance hospital by private cars with their families. Emergency medical services may be more developed in Osaka, but the other side of the coin is that Seoul citizens may have more chance to live together with their younger families. It is difficult to judge which situation is better as a medical environment. To know one another is essential for Asians to proceed to an Asia-oriented stroke care system.

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**Disclosures**

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