Small but Steady Steps in Stroke Medicine in Japan

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December 14, 1702, was an unforgettable day for many Japanese, when 47 samurais from Ako Domain launched a raid on their foe's residence in the snowy night of Edo (the former name of Tokyo) and avenged their deceased master, who was illogically forced to commit suicide by self-disembowelment on a sword, after waiting and planning for a year and a half persevering through all sorts of hardships. They have been repeatedly praised by Bunraku (puppet play) and Kabuki plays, novels, and movies. On the same day 316 years later (December 14, 2018), a Stroke and Cardiovascular Disease Control Act was proclaimed by the Japanese government to vanquish these national maladies.[1] Eight basic policies on stroke and cardiovascular diseases are listed in the new law: (1) promotion of education to the general population and prevention by national and local governments; (2) development of a system for transportation using an ambulance and others and acceptance of emergent patients; (3) development of medical institutes where specialized medical care for stroke and cardiovascular diseases can be offered; (4) maintenance and improvement of participation in social activities and other quality of life for patients with subsequent complications; (5) development of a system for collaboration among agencies involved in health, medical care, and welfare, such as hospital ambulance services, social welfare services, and others; (6) human resource development for health, medical support, and welfare; (7) development of a system for collection and provision of information; and (8) promotion of research.

The Japan Stroke Association, a stroke support organization, and other organizations prepared the draft for the basic law on stroke in 2009 and appealed to the government for its enactment but without success. The bill was then expanded to include cardiovascular disease in general and was then finally approved. The Japan Stroke Society, an academic organization, has joined with the Japanese Circulation Society for the 5-year strategy for stroke and cardiovascular diseases (Stop CVD Project) since 2016 in anticipation of the basic law. Although stroke has long been called the Japanese national disease, the government was relatively slow to act to take measures for stroke care compared with cancer care. The new Act is a steady step forward for tomorrow's stroke medicine in Japan.

Epidemiology: Still the National Disease?

Stroke is called *nousocchu* in Japanese; it means "sudden attack of the brain" (Figure 1). In some communities in the Tohoku region, stroke is called *attacking,* and transient ischemic attack is called *grazing*.

From the 1950s through the 1970s, stroke was the leading cause of death in Japan (Figure 2). Afterwards, stroke was replaced by cancer and heart disease and is now the third leading cause. Age-specific incidence rates of stroke decreased consistently, and age- and sex-adjusted survival rates of stroke improved in this half of the century, as shown in the Hisayama study, a well-known population-based prospective cohort study on stroke and cardiovascular disease.[2] However, since the Baby Boomer generation will become septuagenarians in the 2020s and octogenarians in the 2030s, stroke survivors are predicted to increase until the 2020s.

Overall national health expenditure in 2016 was 42.14 trillion JPY and that for medical care was trillion 30.19 JPY. Of the medical care expenditure, 1.77 trillion JPY (≈16 billion USD; 5.9%) was paid for stroke care, 4.16 trillion JPY (13.8%) for other cardiovascular diseases, and 4.25 trillion JPY (14.1%) for neoplasms. Expenditure for stroke care accounted for 6.0% of the medical care expenditure for the young-old population between 65 and 74 years of age and 8.7% of the medical care expenditure for the old-old population 75 years of age or older. Japanese adults are charged 30% of their own medical expenses, and the public pays the remaining 70%; those who are 70 years of age and older are charged 20%, and those 75 years and older are charged 10% according to their income.

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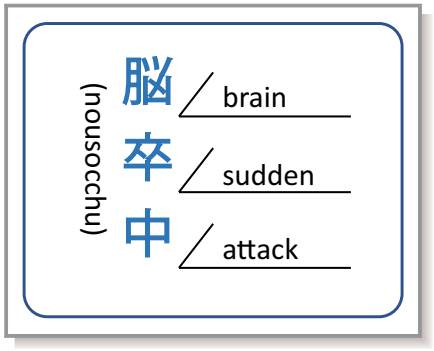

Figure 1. Chinese ideograph (kanji) of stroke.

Figure 3 shows the age distribution of patients with ischemic stroke and those with intracerebral hemorrhage from the Japan Stroke Data Bank, an ongoing prospective hospital-based registry of acute stroke patients.[3] The median age of ischemic stroke onset was 74 years overall, 78 years for women, and 71 years for men, reflecting that Japan is one of the world's top countries for longevity; the average life span was 87.3 years for Japanese women and 81.1 years for Japanese men. The median age of stroke onset became higher with the passing of years. We should be careful to compare crude epidemiologic data on stroke with those in other countries, especially in developing Asian countries, because of the large differences in age distribution.

Pathology: Prevalent Intracranial Vasculopathy

Japan and other Asian countries are known to have a relatively high incidence of hemorrhagic stroke.[4,5] In the1950s, four fifths of fatal strokes reported to public offices in Japan were intracerebral hemorrhages (Figure 2). Foreign researchers criticized the extremely high percentage of intracerebral hemorrhages to be due to simple misdiagnosis. The criticism became a trigger for initiating the Hisayama Study with a high autopsy rate in 1961.[6,7] A drastic decrease in mortality from intracerebral hemorrhage from the 1960s through the 1980s appeared to be mainly due to development of blood pressure management with a decrease in salt intake and powerful antihypertensive agents, as well as improvement of imaging diagnosis of stroke subtypes. Currently, ischemic stroke is the leading stroke subtype, accounting for three fifths of cases according to the official statistics on mortality and three quarters according to the acute stroke registry of the Japan Stroke Data Bank.

The prevalence of intracerebral hemorrhage (26.2% of overall stroke by the official statistics on mortality and 18.5% from the Japan Stroke Data Bank) suggests susceptibility to intracranial vasculopathy in Japanese. As other pathologies of intracranial arteriopathies and arteriolopathies, lacunar infarction (31.2% of overall ischemic stroke from the Japan Stroke Data Bank), intracranial atherosclerotic stenosis, moyamoya disease, and hereditary intracranial disorders such as cerebral autosomal dominant and cerebral autosomal recessive arteriopathies with subcortical infarcts and leukoencephalopathy (cerebral autosomal dominant/recessive arteriopathy with subcortical infarcts and leukoencephalopathy) are also relatively common in the Japanese population.[8,9] In a retrospective hospital-based registry by the Spontaneous Cervicocephalic Arterial Dissections Study–Japan, 92% of the inpatients with nontraumatic arterial dissections from 156 institutes in Japan between April 2003 and March 2006 were reported to have intracranial dissections (Figure 4).[10] As a key genetic biomarker, the ring finger protein 213 gene (*RNF 213*) seems to be associated with symptomatic and asymptomatic intracranial atherosclerosis,[11–13] as well as moyamoya disease.[14,15]

Intravenous Thrombolysis: An Overtaken Runner Making a Comeback

Japan was one of the latest countries to approve the commercial use of alteplase for stroke patients (approved in 2005).[8,16] The success of randomized, controlled trials of stroke thrombolysis using duteplase, a 2-chain recombinant tissue plasminogen activator, in the early 1990s was ruined by the lost infringement lawsuit and discontinuance of development of duteplase.[17] The multicenter, 1-arm Japan Alteplase Clinical Trial was performed using 0.6 mg/kg alteplase, which was equivalent to the optimal dose of duteplase based on the results of its dose comparison study (20 MIU) for a patient weighting 60 kg,[18] and the dose was officially approved for commercial use (Table).[18–24]

The 9-year delay in approval of alteplase use as compared with the Unites States (approved in 1996) was a bitter experience. The Japan Stroke Society was so careful to ensure safe and appropriate spread of stroke thrombolysis that it published domestic guidelines for thrombolysis and organized onsite training sessions for proper use using these guidelines as the textbook for all physicians who have chance to perform thrombolysis to stroke patients all over Japan. In 2018, the training sessions were changed into an e-learning system with 60-minute lecture and a certification examination at the end of the lecture. Soon after the publication of the ECASS (European Cooperative Acute Stroke Study)–III,[25] the Japan Stroke Society submitted a proposal to extend the time window from within 3 hours to 4.5 hours of symptom onset to the Ministry of Health, Labour and Welfare, and revised the guidelines concurrently when the health insurance started to cover 3- to 4.5-hour thrombolysis.[26] The guidelines were revised again in March 2019 responding to the results of the WAKE-UP (Efficacy and Safety of MRI-Based Thrombolysis in

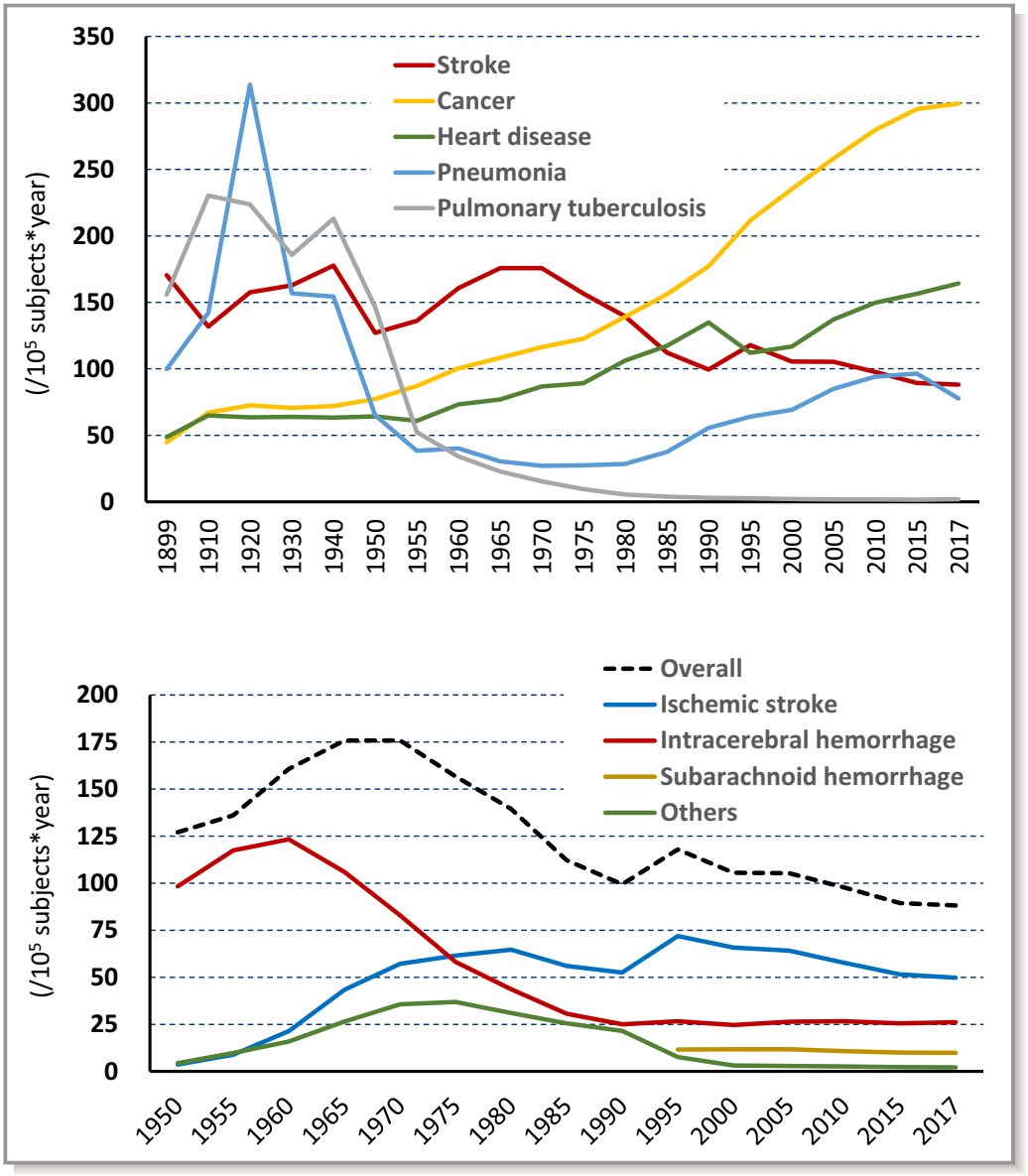

Figure 2. Trends in the crude death rate in Japan. Constructed based on the Vital Statistics in Japan by the Ministry of Health, Labour and Welfare. Top panel: by causes of death; Bottom panel: by stroke subtypes.

Wake-up Stroke) trial,[27] the development of direct oral anticoagulants and their antidotes, rapidly improved mechanical thrombectomy, and others. Its full English version will be published soon. Major points of revision are briefly illustrated in Figure 5. Intravenous alteplase (0.6 mg/kg) is recommended for selected stroke patients with >4.5 hours from last known well who can be treated within 4.5 hours of symptom recognition (eg, awakening) when diffusion-weighted imaging and fluid-attenuated inversion recovery show a pattern of diffusion-weighted imaging–fluid-attenuated inversion recovery mismatch (in other words, fluid-attenuated inversion recovery–negative finding). Because the evidence for thrombolysis of unclear-onset stroke patients was derived only based on the WAKE-UP trial with concern for the safety results where 0.6 mg/kg alteplase was not tested, the current strength of the recommendation for the therapy is weak. We completed the THAWS (Thrombolysis for Acute Wake-up and Unclear-Onset Strokes with Alteplase at 0.6 mg/kg) trial and will publish the results soon to address the limitations.[28] Regarding thrombolysis for stroke patients who were taking direct oral anticoagulants, relatively active recommendations were described in the revised guidelines, which followed recommendations in consensus guides on stroke thrombolysis for anticoagulated patients in Japan published in 2018.[29] For example, intravenous thrombolysis is not recommended if international normalized ratio of

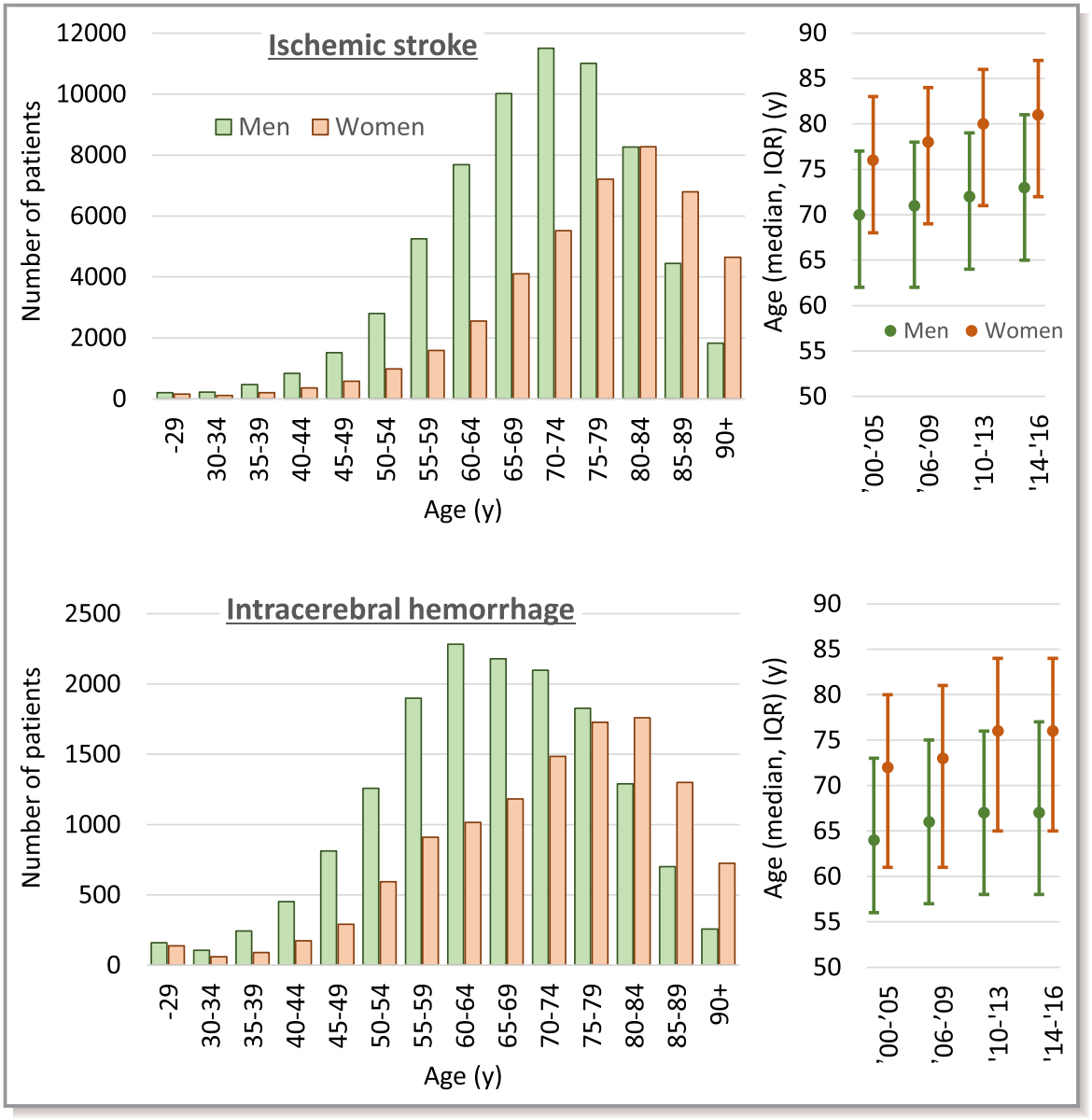

Figure 3. Age distribution of patients with ischemic stroke and those with intracerebral hemorrhage: the Japan Stroke Data Bank. Based on data from 109 135 patients with ischemic stroke (top panel, 43 086 women) and 15 564 patients with intracerebral hemorrhage (bottom panel, 11 448 women) registered from 2000 and through 2016.

prothrombin time exceeds 1.7, activated partial thromboplastin time exceeds 1.5 times the baseline value (>≈40 seconds only as a guide), or the time of the last dose for direct oral anticoagulants is <4 hours; this timing roughly corresponds to time to maximum concentration of direct oral anticoagulants in the nonfasting condition. Otherwise, patients are eligible for thrombolysis with caution.

Approximately 17 000 patients were estimated to receive thrombolysis in 2018 based on the amount prepared by Japanese pharmaceutical makers, estimated to correspond to ≈7% to 8% of overall ischemic stroke patients. The rate is lower than that in Germany (13.5% in 2016) and other Western countries, slightly lower than that in South Korea, and generally higher than other Asian countries.[8,30] Poor human resources for acute stroke care and poor public awareness of stroke warning signs and calling an ambulance on recognizing strokelike symptoms, especially in rural areas, seem to cause the low rate. The new Act is a good trigger for resolving such problems.

Mechanical Thrombectomy and Emergent Care Systems Responding to Thrombectomy Era

The device lag for mechanical thrombectomy has been less severe than the drug lag for alteplase. The improvement

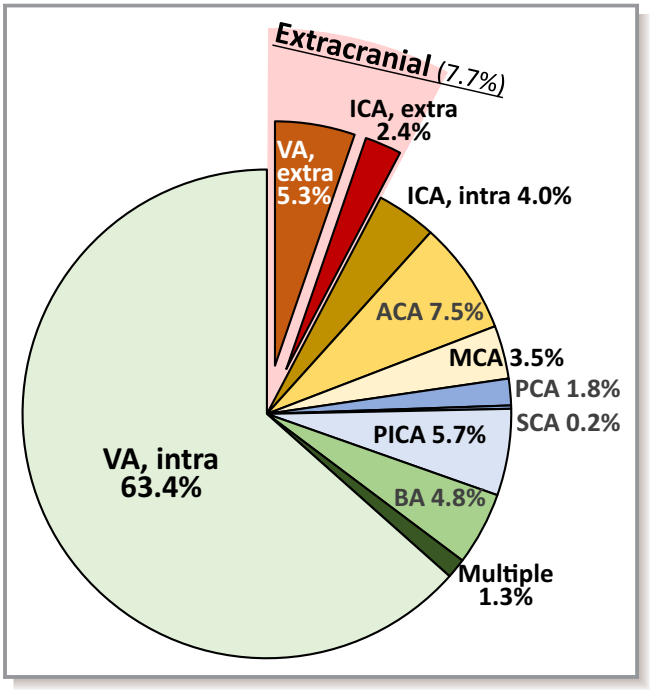

Figure 4. Sites of dissection in Japanese patients with cerebral artery dissection. Of 454 patients (median 54 years old, 134 women), 229 developed ischemic stroke or transient ischemic attack, 126 developed hemorrhagic stroke, and 24 developed both. Constructed on the basis of results from Minematsu et al.[10] ACA indicates anterior cerebral artery; BA, basilar artery; extra, extracranial; ICA, internal carotid artery; intra, intracranial; MCA, middle cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery; VA, vertebral artery.

would be partly because of the positive action by the Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency to accelerate the approval process of medical devices. A joint committee from the Japan Stroke Society, the Japanese Society for Neuroendovascular Therapy, and the Japan Neurosurgical Society published the domestic guidelines for thrombectomy and revised them every couple of years to capture drastic improvements of the therapy. It is highly recommendable that thrombectomy was performed by specialists certified by the Japanese Society for Neuroendovascular Therapy (1343 physicians had been certified by May 2019) or semispecialists who had sufficient therapeutic experience. Organized onsite training sessions for proper performance of thrombectomy are held on a regular basis using these guidelines as the textbook for neurointerventionists who work in remote areas where there are no certified specialists. The training session by specialists certified by the Japanese Society for Neuroendovascular Therapy was held twice in fiscal 2018 at the time of the annual meeting of the Japan Stroke Society and that of the Japan Neurosurgical Society with a 60-minute lecture. The number of patients receiving mechanical thrombectomy in Japan jumped from 7702 in 2016, 10 360 in 2017, to 12 482 in 2018 on the basis of the survey by the Japanese Society for Neuroendovascular Therapy (RESCUE-Japan Project Team, personal communication, 3 June 2019), estimated to correspond to ≈6% of overall ischemic stroke patients in 2018. Tron FX (JIMRO, Takasaki, Japan), the first domestic thrombectomy device, has been in commercial use since April 2019. The narrowest size of this new device, 2 mm in diameter, seems to be easy to manipulate for elderly Japanese patients with narrow and tortuous intracranial branch arteries.

To accelerate the development of an efficient emergent care system for stroke, the Japan Stroke Society has a plan to regroup acute stroke hospitals into primary stroke centers, thrombectomy-capable stroke centers, and comprehensive stroke centers. As the first step, necessary conditions for primary stroke centers were published in March 2017, where 24/7 emergent care including stroke thrombolysis should be available on demand with one or more physicians certified by the Japan Stroke Society. Application of primary stroke centers will be started in July 2019. The number, distribution, and mutual relationship of each center will be settled within a couple of years.

For emergent contact among stroke medical teams and drip-and-ship interhospital communication, smartphone

Table. Major Trials and Multicenter Observational Studies on Intravenous Thrombolysis in Japan Using 0.6 mg/kg Alteplase

	Outline	Patient Number	Time Window	mRS 0 to 1 at 3 mo	Early Symptomatic Intracranial Hemorrhage*
J-ACT (2006)[18]	Phase III 1-arm trial before the official approval	103	≤3	36.9%	5.8%
J-ACT II (2010)[19,20]	Phase IV 1-arm trial for patients with the MCA occlusion on MRA	58	≤3	46.6%	0
J-MARS (2010)[21]	2-year postmarket national survey	7492	≤3	33.1%	3.5%
SAMURAI (2009)[22,23]	Multicenter observational registry with several substudies	600	≤3	33.2%	1.3%
YAMATO (2017) [24]	Trial with comparison between early and late injection of edaravone	165	Partly ≤4.5	55%	3.6%

J-ACT indicates Japan Alteplase Clinical Trial; J-MARS, Japan Post-Marketing Alteplase Registration Study; MCA, middle cerebral artery; MRA, magnetic resonance angiography; mRS, modified Rankin Scale; SAMURAI, Stroke Acute Management with Urgent Risk-factor Assessment and Improvement; YAMATO, Tissue-Type Plasminogen Activator and Edaravone Combination Therapy.
*With an increase of ≥4 points from the baseline National Institutes of Health Stroke Scale score.

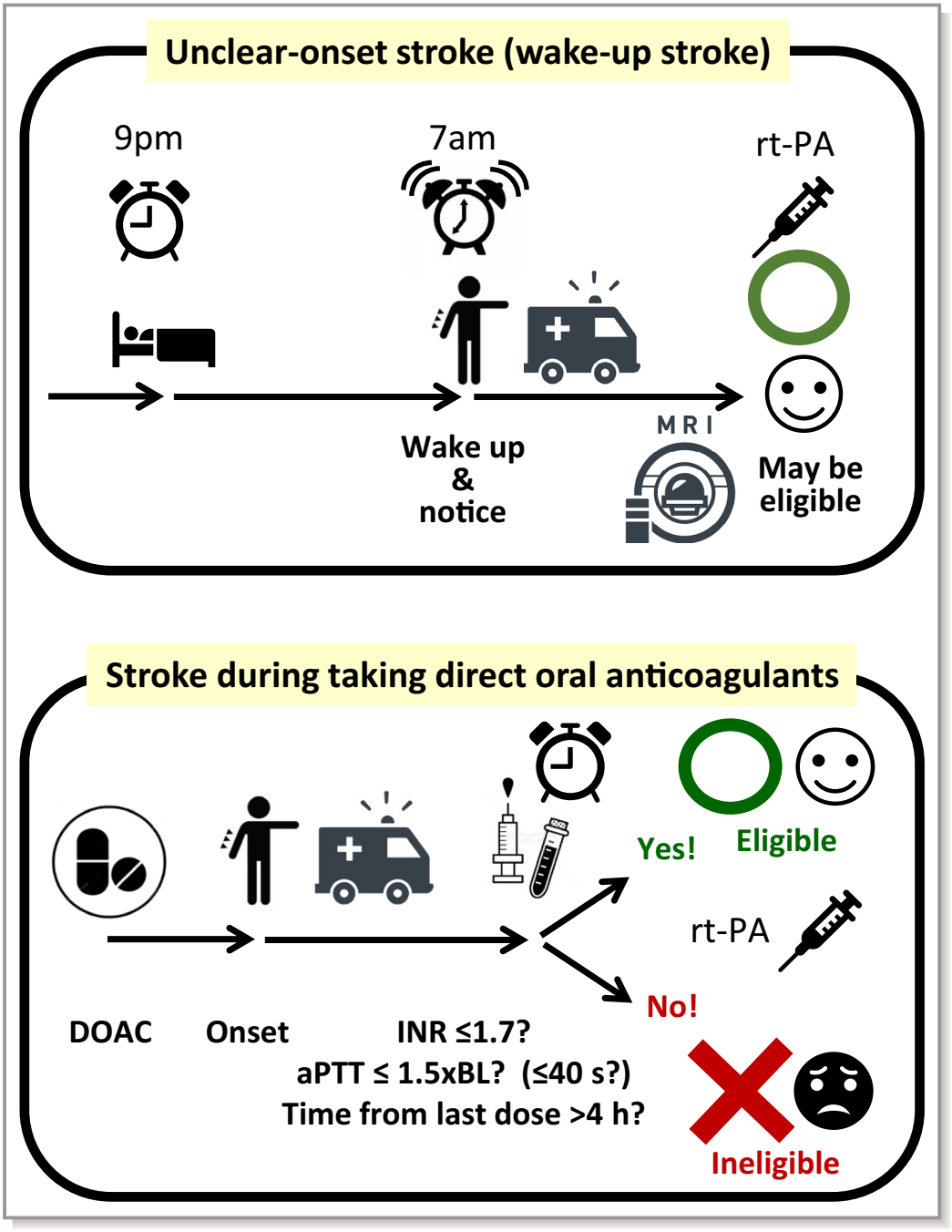

Figure 5. Illustration of major revised points of Japanese guidelines for stroke thrombolysis. Constructed on the basis of the third version of Japanese guidelines for stroke thrombolysis (March 2019) Top panel: illustration of thrombolysis for patients with unclear-onset stroke; Bottom panel: illustration of thrombolysis for stroke patients who were taking direct oral anticoagulants. aPTT indicates activated partial thromboplastin time; DOAC, direct oral anticoagulant; MRI magnetic resonance imaging; rt-PA, recombinant tissue plasminogen activator.

technology seems to be useful. Join (Allm Group, Tokyo, Japan), a smartphone application program providing general imaging diagnostics workstations, has been in commercial use since 2016 (Figure 6). Join allows all registered members to share emergent call messages and group chat, still images of radiologic examinations, and video. The device was also listed as a class I medical device by the Food and Drug Administration in the United States and as the CE declaration of conformity in 2015. As a successful example, calculation software of the Field Assessment Stroke Triage for Emergency Destination scale, a prehospital 9-point scale to identify large vessel occlusion strokes based on the following items of the

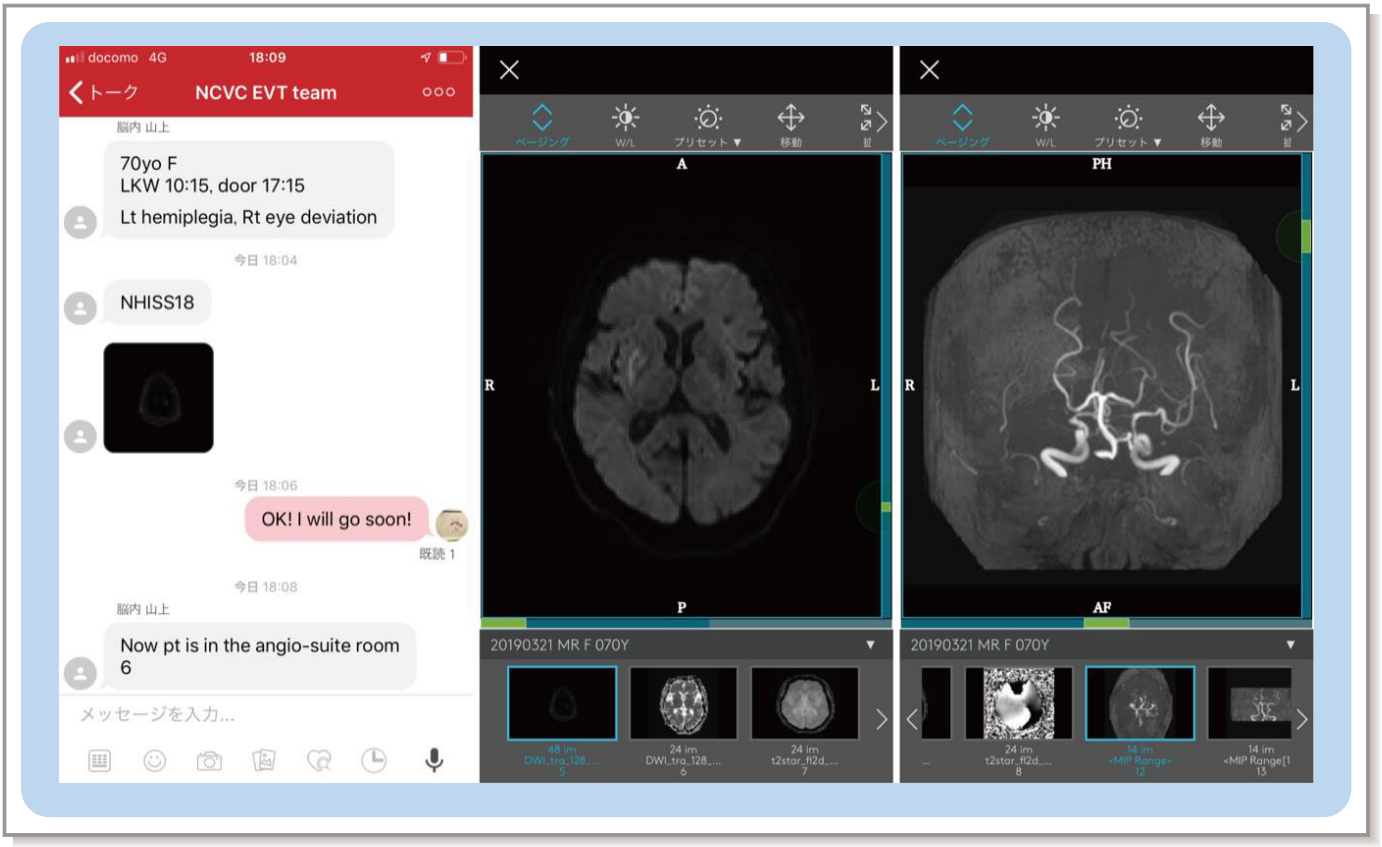

Figure 6. Display on Join. Left panel: emergent call messages among the stroke team; Middle panel: emergent diffusion-weighted image showing a fresh infarct in the right hemisphere; Right panel: emergent magnetic resonance angiography showing occlusion at the horizontal portion of the middle cerebral artery.

National Institutes of Health Stroke Scale: facial palsy (scored 0–1), arm weakness (0–2), speech changes (0–2), time (documentation for decision making but no points), eye deviation (0–2), and denial/neglect (0–2),[31] was inserted in Join and was used for field triage of acute patients to stroke centers by the Emergency Medical Services.[32] It has a great potential to a reduction in hospital arrival times and increased performance of both intravenous thrombolysis and mechanical thrombectomy.

Secondary Prevention: Are Made-in-Japan Antithrombotics Effective for Stroke?

Cilostazol, a phosphodiesterase 3 inhibitor also developed in Japan in the late 20th century, has antiplatelet and vasodilatory properties, as well as anti-inflammatory and antiproliferative effects, and it causes bleeding complications less frequently than other antiplatelet agents.[33] In 2 randomized, controlled trials in Japan, the CSPS (Cilostazol Stroke Prevention Study) and the CSPS 2, cilostazol decreased recurrent stroke in patients with noncardioembolic ischemic stroke, with a similar risk of serious bleeding compared with placebo and with half the risk of serious bleeding compared with aspirin (Figure 7).[34,35] In the recent third CSPS trial named the CSPS.com (CSPS for Antiplatelet Combination), the combination of cilostazol with a classical antiplatelet agent (aspirin or clopidogrel) had a lower risk of ischemic stroke recurrence and a similar risk of severe or life-threatening bleeding compared with aspirin or clopidogrel alone in patients with noncardioembolic ischemic stroke having stenosis of a major intracranial or extracranial artery or 2 or more of the vascular risk factors.[36] Addition of cilostazol to aspirin or clopidogrel seems to be a pharmacotherapeutic regimen that could be recommended in the chronic stage of ischemic stroke.

Prasugrel, a P2Y12 receptor antagonist, was another antiplatelet agent developed in Japan. It has the potential to inhibit platelet aggregation more rapidly, more consistently, and to a greater extent than clopidogrel, and independently of CYP2C19 genetic polymorphism status. However, the agent is contraindicated in patients with acute coronary syndrome with a history of stroke or transient ischemic attack in Western countries because of relatively higher incidences of major adverse cardiovascular events and bleeding events with

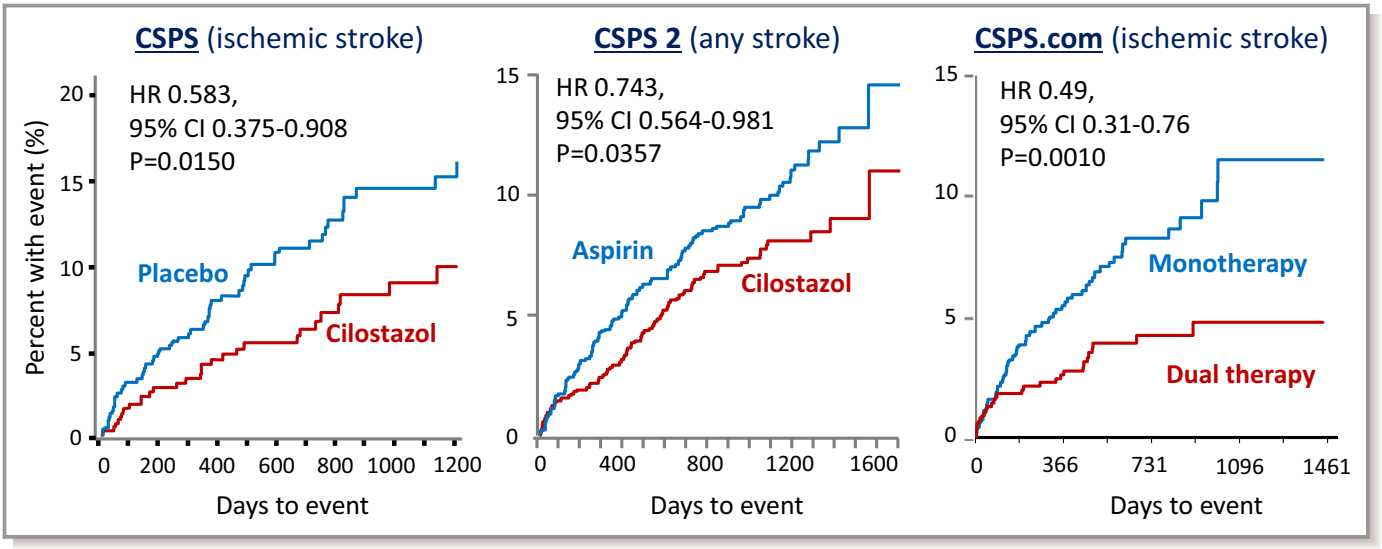

Figure 7. Kaplan–Meier analysis of primary efficacy outcomes: the CSPS trials. Noncardioembolic ischemic stroke within 6 months (26 weeks) were included in the CSPS (Cilostazol Stroke Prevention Study) and CSPS 2. Those additionally with ≥50% stenosis of a major intracranial or extracranial artery or 2 or more of the vascular risk factors were included in the CSPS.com trial Monotherapy in the CSPS.com trial means either aspirin or clopidogrel, and dual therapy means a combination of cilostazol with aspirin or clopidogrel. Data derived from Gotoh et al,[34] Shinohara et al,[35] and Toyoda et al.[36]

the combination of prasugrel (10 mg once daily as a maintenance dose) with aspirin in such a subgroup of patients in the TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38).[37] In a randomized, double-blind, controlled trial involving 3747 patients aged 74 years or younger with a noncardioembolic stroke in the previous 1 to 26 weeks from 224 institutes over Japan (the PRASTRO-I [Comparison of Prasugrel and Clopidogrel in Japanese Patients With Ischemic Stroke] trial), the noninferiority of low-dose prasugrel (3.75 mg once daily) to clopidogrel for prevention of ischemic stroke, myocardial infarction, and death from other vascular cause was not confirmed.[38] However, there was no significant difference in the incidence of bleeding events between the 2 groups. A smaller trial for comparison of these 2 P2Y12 receptor antagonists, again with revised inclusion criteria where the upper age limitation was removed, is currently ongoing.

The median age of cardioembolic stroke onset was 4 years older (78 years) than that of any ischemic stroke onset, 82 years for women and 74 years for men, from the Japan Stroke Data Bank (Japan Stroke Data Bank Investigators, unpublished data, 2019). Edoxaban, a direct oral factor Xa inhibitor, was named after Edo. In the ENGAGE AF–TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction Study 48), edoxaban provided an even greater absolute reduction in major bleeding and in intracranial hemorrhage over warfarin for patients aged 75 years or older compared with treatment with edoxaban versus warfarin in younger patients.[39] As a unique multicenter, prospective, observational study, 33 213 patients with nonvalvular atrial fibrillation aged 75 years or older were enrolled in Japan, as elderly patients with multiple morbidities were often excluded from major clinical trials, and the generalizability of trial results to them remains uncertain.[40] We have been continuing 2-year follow-up for this large population.

Research, Registry, and Drug Development

Stroke is categorized as a cardiovascular disease as a matter of health policy in Japan. The Japan Agency for Medical Research and Development acts as a control tower that directs and assists integrated medical research, from basic research to practical application, and the National Cerebral and Cardiovascular Center contributes to provision of advanced and specialized medical care and conduct of research on stroke and cardiovascular system diseases as one of the 6 National Research Centers for Advanced and Specialized Medical Care (the other 5 centers are in charge of cancer, neurology/psychiatry, child health, etc). The National Cerebral and Cardiovascular Center, where we are working, embodies basic and practical collaboration among specialists who major in stroke, heart disease, kidney disease, vascular disease, and others. The new Act on stroke and cardiovascular disease measures declares that central and local governments must develop medical institutes and collect and provide information on stroke and cardiovascular disease with the cooperation of the National Cerebral and Cardiovascular Center.

The National Cerebral and Cardiovascular Center currently operates and manages the above-stated Japan Stroke Data Bank, as well as the JROAD (Japanese Registry of All Cardiac and Vascular Diseases), a nationwide database of patients with cardiovascular diseases derived from a Japanese Circulation Society national survey.[41]

Some intravenous drugs for acute ischemic stroke were developed in the late 20th century and approved for clinical use for acute ischemic stroke only in Japan after the domestic phase III trials, including ozagrel, a thromboxane A2 synthesis inhibitor; argatroban, a direct thrombin inhibitor; and edaravone, a free radical scavenger.[24] These drugs are beneficial for expansion of therapeutic options but are problematic from the perspective of global comparisons and generalization of stroke medicine. It is a problem that Japanese pharmaceutical makers seem to be content with commercial approval of new drugs only in Japan partly because Japan is a relatively large market. They should try global markets.

In conclusion, stroke care in Japan has been stepping forward clearing targets about reperfusion therapy, systems of care, research collaboration, legislation, and others. Each step is small but distinct. The accumulation of these small steps will result in a giant leap for tomorrow's stroke medicine in Japan.

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