Endovascular Closure of a Patent Foramen Ovale

Both GLs stated that endovascular closure of a patent foramen ovale can be considered in patients with cryptogenic stroke and either high-risk patent foramen ovale (European GLs, GCP) or recurrent paradoxical cerebral embolism (Japanese GLs, grade C1). It should be noted that the GLs were published before RCTs comparing endovascular closure with medical treatment.

Conclusions

This article summarizes similarities and differences between Japanese and European GLs for the management of ischemic stroke published between 2008 and 2011. Although there are obvious differences between the GLs regarding structure, length and categorization of the level of evidence, the vast majority of recommendations is largely similar. However, there are some interesting differences between the GLs.

For the management of acute ischemic stroke, the most important difference is the dosage of intravenous rt-PA: the approval in Japan envisages a lower dose of 0.6 mg/kg, while in Europe a dose of 0.9 mg/kg is used. The Japanese GLs recommend the selective thrombin inhibitor argatroban for noncardioembolic stroke within 48 h after onset. In Europe, early administration of unfractionated heparin, LMW heparin and heparinoids is generally not recommended. During the acute stage, Japanese GLs propose intravenous infusion of the antiplatelet agent ozagrel sodium for noncardioembolic stroke, a drug not well known and not approved in Europe. In addition, the Japanese GLs recommend the antioxidant edaravone, while in Europe administration of neuroprotective agents are generally not recommended.

For primary and secondary prevention of ischemic stroke, one of the major differences is the dosage of oral anticoagulants for stroke prevention in elderly patients with AF. For patients aged ≥75 years, a target PT-INR of 1.6–2.6 is recommended in Japan instead of 2.0–3.0 for younger patients: In Europe, no specific INR adaptation according to age was provided. For treatment of dyslipidemia in the secondary prevention of stroke, Japanese GLs also allow a combination of eicosapentaenoic acid with low-dose statins as an alternative to the standard treatment with high-dose statins. Finally, the drug cilostazol has been investigated extensively and is approved for the secondary prevention of ischemic stroke in Japan as an alternative to aspirin or clopidogrel.

Some new relevant aspects of stroke management have emerged during the last years, such as interventional thrombectomy, intracranial stenting, extra-/intracranial bypass surgery and stroke prevention with new oral anticoagulants. As the GLs discussed in this article have been announced before publication of trials investigating these treatment strategies, specific recommendations are still lacking. Their inclusion will be a major task for the next upcoming European and Japanese GLs on stroke management.

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Comparison of the European and Japanese Guidelines for the Acute Management of Intracerebral Hemorrhage

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Key Words
Acute stroke treatment · European stroke guidelines · Evidence-based medicine · Hemorrhage · Japanese stroke guidelines · Randomized clinical trials · Review · Stroke prevention

Abstract
Background: Different aspects of acute stroke management and strategies for stroke prevention derive from two viewpoints: specific traditional and historical backgrounds and evidence-based medicine from modern randomized controlled trials (RCTs), meta-analysis and authorized clinical practice guidelines (GLs). Regarding intracerebral hemorrhage (ICH), *Cerebrovascular Diseases* published the 2006 European stroke initiative recommendations for the management of ICH. In 2009, the revised Japanese GLs for the management of stroke, including that of ICH, appeared in Japanese. Whereas GLs for the prevention and treatment of ischemic stroke were presented in detail, recommendations with regard to ICH are relatively rare both in Japan and Europe. ***Methods:*** Since 2011, the authors have met repeatedly and have compared the latest versions of published European and Japanese GLs for ischemic and hemorrhagic strokes. Many aspects have only been addressed in one but left out in the other GLs, which consequently founded the basis for the comparison. Classification of evidence levels and recommendation grades defined by the individual committees differed between both original GLs. ***Results:*** Aspects of major importance were similar and hence did not need extensive interpretation, mostly due to a lack of evidence from appropriate RCTs worldwide. The target level to which systolic blood pressure should be lowered is quite high; <170 mm Hg for patients with known hypertension in Europe and <180 mm Hg in Japan. The results of ongoing clinical trials are awaited for the optimal target level and optimal medications. Concerning ICH associated with oral an-

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ticoagulant therapy, both guidelines give similar recommendations, namely that anticoagulation should be discontinued and the international normalized ratio of prothrombin time should be normalized with prothrombin complex concentrate or fresh-frozen plasma and additional vitamin K. Patients with ICH were treated surgically, often based on individual decisions – more frequently in Japan, depending on the association with hypertension. Patients with large or intraventricular bleedings were only treated if a life-saving performance was considered, irrespective of the neurological outcome. Infra- and supratentorial differences were similarly addressed in both GLs. ***Conclusion:*** This brief survey – when compared with the lengthy original recommendations – provides a stimulating basis for an extended interest among Japanese and European stroke clinicians to learn from their individual experiences and to strengthen efforts for joint cooperation in treating and preventing stroke all around the globe.

Intracerebral hemorrhage (ICH) accounts for 10–17% of all strokes. The incidence of ICH is influenced by racial factors and was found to be higher in Blacks, Hispanics and Asians compared to the white population. In particular, Asian ethnic origin is a possible risk factor for intracranial hemorrhage. In 1965, Japan had the highest mortality of stroke worldwide with the mortality rate of ICH being quite high among all stroke types. A recent meta-analysis indicates that the incidence of ICH in the general Asian population was 2-fold higher than that in the white population [1].

We compared the European Stroke Initiative (EUSI) Recommendations for the management of ICH (2006) [2] and the chapters of ICH in the Japanese guidelines for the management of stroke (2009) [3]. Japanese guidelines are more up to date and thus included trials that were not available when EUSI guidelines were written. In the following, we try to present differences and similarities of both guidelines and worked out which recommendations lacked in both guidelines.

Primary Prevention and Treatment of Risk Factors

The EUSI guidelines give no recommendations for *primary prevention*, but give some evidence concerning different risk factors (table 1). Arterial hypertension is mentioned as the most common risk factor for spontaneous ICH. The EUSI Writing Committee describes that the role of hypertension and the beneficial effect of antihypertensive treatment with regard to the risk of ICH were verified in PROGRESS (Perindopril Protection against Recurrent Stroke Study) [4], which showed that the relative risk of ICH was reduced by 50% in comparison with the placebo-treated group after a 4-year follow-up, but give no recommendation for treatment as primary prevention. In the Japanese guidelines, hypertension is regarded as the greatest risk factor for ICH and ischemic stroke. There is a positive linear correlation between blood pressure levels and the risk of stroke: the higher the blood pressure, the higher the risk of stroke [5]. Thus, medical antihypertensive treatment was strongly recommended as primary prevention [6].

Concerning hypercholesterolemia, the EUSI recommendations mention that hypercholesterolemia is associated with a lower risk of ICH, but treatment with statins did not increase the risk of ICH. The risk of hemorrhagic stroke, including ICH, is higher in smokers, but no recommendation of nonsmoking as a primary prevention is verbalized. An increased body mass index, which was found to be correlated with an increase in intraventricular hemorrhage (IVH) volume, or alcohol consumption are also considered risk factors for ICH. The Japanese guidelines recommend consumption of a moderate amount of vegetables and fruits every day, whereas no dietary advice was found in the EUSI guidelines.

For *secondary prevention* after ICH, EUSI guidelines give recommendations for lowering blood pressure with a diuretic and angiotensin-converting enzyme inhibitor (level A), excessive alcohol should be discouraged (class IV), persons with elevated body mass index should take a weight-reducing diet (despite lack of evidence) and smokers should quit smoking (class IV evidence).

Acute Blood Pressure Management

There is no randomized controlled trial comparing the severity and prognosis of patients with acute hypertension and ICH with/without *blood pressure-lowering treatment* (table 2). Further clinical studies need to be conducted in the future to determine the optimal target level to which blood pressure should be lowered from the perspective of clinical prognosis. The target level in the Japanese guidelines is quite high (systolic blood pressure <180 mm Hg) and differs much from the major expert opinions in the nationwide survey [7], where most experts re-

Table 1. Primary prevention and treatment of risk factors

European guidelines 2006 (EUSI)	Japanese guidelines 2009
Hypertension An important role with regard to the risk of ICH. Treatment of hypertension has a beneficial effect (level A).	Treating hypertension is the most vital step to reduce the risk of ICH (grade A).
Hypercholesterolemia Associated with a lower risk of ICH; however, treatment with statins does not increase the risk of ICH (level B).	It has generally been agreed that its underlying hepatic disease and coexisting hypertension should be treated. Lowering serum cholesterol levels with statins does not increase the incidence of ICH, but some data have implied that intervention for stroke patients may increase the recurrence of ICH (grade B).
Smoking is a risk factor for ICH (level B).	People should be encouraged to take a moderate amount of *vegetables and fruits* every day (grade B).
Alcohol consumption Several studies document an increased risk of ICH in relation to alcohol consumption. Spontaneous ICH can probably also be triggered by binge drinking (level C).	Heavy alcohol consumption leading to abnormal blood γ-GTP levels should be discouraged (grade B).
A variety of *illicit drugs* are known to cause ICH (amphetamines, cocaine and phenylpropanolamine).	We recommend the very careful consideration of an appropriate dose of each *antithrombotic drug* and its dual medications that are required to control concurrent hypertension (grade B).

Table 2. Acute blood pressure (BP) management

European guidelines 2006 (EUSI)	Japanese guidelines 2009
Known hypertension (HPT) If SBP >180 mm Hg or DBP >105 mm Hg → BP <170/100 mm Hg or MAP <125 mm Hg (class IV, level C)	maintain SBP <180 mm Hg or MAP <130 mm Hg (grade C1)
Unknown history of HPT If SBP >160 mm Hg or DBP >95 mm Hg → BP <150/90 mm Hg or MAP <100 mm Hg (class IV, level C)	*when performing surgical treatment:* → more aggressive BP lowering (grade C1)
Decrease pressure not more than 20% of MAP on admission (class IV, level C)	
When ICP elevated (nitroprusside contraindicated) → adapt thresholds to cerebral perfusion pressure >70 (class IV, level C)	
Intravenous drugs recommended for better controllability (GCP)	no special hypotensive drug recommended, careful use of vasodilators (nitrates), because they induce brain HPT (grade C1)

SBP = Systolic blood pressure; DBP = diastolic BP; MAP = mean arterial pressure; HPT = hypertension.

garded <140, <150 or <160 mm Hg as a target systolic blood pressure partly based on results of small domestic studies [8, 9]. The EUSI guidelines recommend target levels and maximum levels of blood pressure for known and unknown hypertension, and recommend an adaptation in case of elevated intracranial pressure (ICP). Routine blood pressure lowering is not recommended.

Furthermore, different medications are mentioned in the EUSI guidelines, especially intravenous drugs due to their better controllability. EUSI guidelines recommend

a careful use of calcium antagonists because of their rapid and excessive hypotensive effect. In the Japanese guidelines, the use of calcium antagonists (e.g. nicardipine) is contraindicated in patients with hyperacute ICH, because of vasodilating effects and possible antiplatelet actions of calcium antagonists; however, direct evidence for this is lacking. In the above-mentioned nationwide survey, nicardipine was the most popular agent for acute ICH management [7]. In 2011, the Japanese government finally ordered the pharmaceutical makers of nicardipine to revise the label. In the new label, description of contraindication for ICH was abolished. In 2012, several Asian nations similarly revised the label of nicardipine.

The EUSI or Japanese guidelines did not consider the results of ATACH (Antihypertensive Treatment of Acute Cerebral Hemorrhage) [10] and INTERACT (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial) [11], although the newer American Heart Association/American Stroke Association guidelines [12] advocate that lowering systolic blood pressure to 140 mm Hg is probably safe based on the results of INTERACT [11]. The results of both INTERACT 2 [13] and ATACH II [14] are awaited, and might further answer the question of whether there are other benefits of early systolic blood pressure reduction in patients with ICH, and provide clearer evidence for the target blood pressure and the choice of drugs. However, it seems reasonable to lower blood pressure cautiously appreciating a slight effect of antihypertensives on hematoma expansion reduction in an overall weak or equivocal context of evidence and considering that autoregulation is often preserved in the acute phase (as opposed to the postacute phase) of ICH and furthermore aggressive lowering of blood pressure theoretically carries the risk of cerebral ischemia in hypertensive patients.

Acute Hemostatic Management

EUSI guidelines do not recommend the *use of hemostatic agents* (as tranexamic acid, e-aminocaproic acid and aprotinin) to control bleeding, because no clinical efficacy has been demonstrated thus far (table 3). Japanese guidelines recommend blood products such as platelets, prothrombin complex concentrate (PCC) or fresh-frozen plasma (FFP) in hypertensive ICH only in case of concurrent abnormal blood coagulation or platelet counts, though such products have been rarely in clinical use as hemostatic agents unless patients were anticoagulant users in Japan.

Concerning *ICH associated with oral anticoagulant therapy*, both guidelines give similar recommendations, whereas Japanese guidelines prefer PCC rather than FFP (although PCC is not covered by the Japanese health insurance). Current questions arise on feasibility, safety and efficacy of prothrombin-dependent coagulation factors in concentrated PCC versus unconcentrated FFP versus single factors like recombinant coagulation factor VIIa. The current information on these questions is inconsistent, and any conclusion drawn towards the preference of one of these coagulants is premature. Time to reversal of the international normalized ratio (INR) seems to be the most important determinant, and minimizing delays in drug administration should have highest priority, as recommended in both guidelines. Initial dosages of PCC for the reversal are different between both guidelines: 10–30 (or 10–50) U/kg in the EUSI recommendation and 500 U regardless of body weight in the Japanese one.

There is a considerable dilemma concerning when to restart anticoagulant therapy following ICH. The *optimum timing of the resumption of anticoagulation* is a crucial issue with conflicting evidence. EUSI recommended to restart not earlier than 10–14 days after the index bleeding but to check indication first. The Japanese guidelines recommend use of heparin after normalization of INR in patients with an elevated risk for embolism, but do not mention the timing of heparinization. Among the respondents in the nationwide survey, the timing to restart anticoagulation varied greatly: within 4 days in 7%, 5–7 days in 21%, 8–14 days in 25%, 15–28 days in 28% and 29 days or later in 18% [15].

The *new direct oral anticoagulants (DOAC)* as dabigatran, rivaroxaban and apixaban seem to be a safer and more convenient replacement for warfarin. Due to fewer drug and food interaction, easier handling and a more favorable risk-benefit profile compared with warfarin, it is conceivable that the number of patients treated with DOAC will increase. The optimal management of DOAC-associated ICH is unknown and no specific antidote is available. For this reason, physicians are faced with new challenges, especially in emergency situations, and questions arise on how to manage emergency situations like the indication for thrombolysis in acute stroke, and the management of intracranial or gastrointestinal bleedings. In the future, guidelines have to give recommendations how to manage DOAC-associated hemorrhages, but data are still limited.

Table 3. Acute hemostatic management

European guidelines 2006 (EUSI)	Japanese guidelines 2009
For non-antithrombotic users Pending further data on efficacy and safety, recombinant factor VIIa should not be used outside of a phase III trial. A phase III trial is needed to confirm the beneficial effect of recombinant factor VIIa in ICH (class IV, level B, obsolete).	Hypertensive ICH + normal coagulation → Blood products are not recommendable (grade C2). Hypertensive ICH + abnormal platelets or blood coagulation system + bleeding tendency → consider blood products such as platelets, PCC and FFP (grade C1). There is no adequate scientific evidence to support the use of capillary stabilizers or antiplasmin agents for the treatment of acute ICH (grade C1).
ICH during oral anticoagulant treatment (OAT) such as warfarin INR >1.4 → OAT should be discontinued and the INR should be normalized with PCC or FFP. Intravenous vitamin K should be added (class IV).	Stop warfarin and normalize the prothrombin time (PT) INR to ≤1.35 using vitamin K and blood products as soon as possible (grade B). Use of PCC (not covered by Japanese health insurance) is recommended rather than FFP (grade B). With high risk or recurrent cerebral embolism → activated partial thromboplastin time should be 1.5- to 2-fold higher using heparin after normalizing PT-INR (grade C1).
After ICH, *antiplatelet treatment* has to be individualized, depending on the presence of ischemic vascular diseases or their perceived risk on the one hand and the anticipated risk of ICH recurrence on the other (class IV).	
	In patients who develop *ICH during thrombolytic therapy*, thrombolytic drugs and antithrombotic drugs should be immediately stopped, and it is recommended to correct the low levels of coagulation factors such as fibrinogen and prolonged PT and activated partial thromboplastin time using blood products and protamine (grade C1). Indication for surgical evacuation of the hematoma should be carefully examined while taking account of the functional prognosis after correcting the bleeding tendency (grade C1).
After having rechecked the indication for anticoagulation (following the EUSI recommendations on ischemic stroke), OAT may be continued after 10–14 days, depending on the perceived risk of thromboembolic occlusion and ICH recurrence (class IV).	

Table 4. Respiratory management

European guidelines 2006 (EUSI)	Japanese guidelines 2009
Included in the general management and as part of ICP management (see text).	Airway management and/or artificial respiratory management should be considered when disturbance of consciousness has progressed and a respiratory disorder is present during the acute phase (grade C1). Routine oxygen administration to patients with mild-to-moderate stroke is not recommended (grade C2).
	Hyperbaric oxygen therapy for treatment or determination of surgical indication is not recommended (grade C2).

Table 5. Management of brain edema and intracranial hypertension

European guidelines 2006 (EUSI)	Japanese guidelines 2009
The following measurements might be considered in patients with ICH if ICP increases beyond 20 mm Hg:	(ICP level is not defined)
Body position Elevation of body position with respect to CPP (CPP >60 mm Hg; class IV, level C).	Raising the upper part of the bed to put the body at a 30° angle has been reported to be beneficial for patients with intracranial hypertension (grade C1); however, attention should be given to lowering blood pressure.
Osmotic therapy Glycerol (500 ml 10% per day). Mannitol (100 ml 20%; every 3–6 h; serum osmolality <320 mmol/l). Hyper-HAES (NaCl 7.5%, HES 6%, serum sodium <150 mmol/l). THAM buffer (central line because of tissue necrosis) 1 mmol/kg bolus, 0.25 mmol/kg as permanent infusion (pH <7.5–7.55; class IV, level C).	Intravenous administration of hypertonic glycerol is recommended for major acute ICH accompanying intracranial hypertension (grade B). There is no specific rationale supporting the idea that mannitol treatment is effective for acute ICH (grade C2), but this treatment can be considered when intracranial pressure progressively increases or clinical findings deteriorate in relation to mass effect (grade C1).
Hyperventilation Intermittent hyperventilation (pCO_2 level of 30–35 mm Hg), most useful in the first hours (class IV, GCP).	In patients using a respirator, a mild hyperventilation (pCO_2 adjusted to 30–35 mm Hg) is recommended (level IIb).
Analgosedation with barbiturates (pentobarbital or thiopental).	
Corticosteroids At the current stage, corticosteroids are not recommended (class IV, level C).	There is no concrete scientific evidence demonstrating that corticosteroids are effective in reducing acute ICH (grade C2).
Hematoma evacuation with/without craniectomy.	
External ventricular drainage in case of hydrocephalus or clinical deterioration and neuroradiological evidence of brainstem compression (GCP).	

Table 6. Management of seizures

European guidelines 2006 (EUSI)	Japanese guidelines 2009
Early prophylactic treatment of seizures is not recommended for all patients, but may be considered for selected patients with lobar ICH. In all other cases, seizures should only be treated if they occur (level C).	Antiepileptics should be used for seizure attacks in patients with acute stroke. Thereafter, the dosage should be carefully reduced while taking into account the possibility of developing late-onset epilepsy (grade C1).
If seizures occur, a stepwise administration of antiepileptic drugs is generally recommended. Antiepileptic treatment should be continued for 30 days. After this time, treatment should be reduced and eventually discontinued. If seizures reoccur, patients should receive chronic treatment with anticonvulsants (level C).	Seizure occurs frequently in patients with ICH involving the cerebral cortex. In ICH limited to the putamen, thalamus or infratentorium, concurrent seizure is rare. The prophylactic use of antiepileptics is not recommended except for patients who have undergone brain surgery (grade C2).
	In ICH patients who developed late-onset seizures (>2 weeks after onset), recurrent seizures often occur; thus, administration of anti-epileptics is advisable (grade C1).

Table 7. Prevention of deep venous thrombosis and pulmonary embolism

European guidelines 2006 (EUSI)	Japanese guidelines 2009
Compression stockings and intermittent pneumatic compression are recommended for the prevention of thromboembolism in patients with disabling limb weakness from the beginning of treatment (class IV).	When paralysis is noted in patients with acute ICH, deep venous thrombosis and pulmonary embolisms should be prevented using compression stockings or intermittent pneumatic compression, or the combination of these (grade B).
Low-dose subcutaneous heparin or low-molecular-weight heparin should be considered after 24 h, especially in patients who are at high risk of thromboembolism (class IV).	Administration of low-dose heparin can be considered for ICH patients with concurrent hemiplegia without rebleeding 3–4 days after onset (level IIa).

Respiratory Management

There is no special recommendation concerning *respiratory management* for patients with ICH in the EUSI guidelines (table 4). Oxygenation should be monitored continuously; in addition, respiratory care and prophylactic measures concerning aspiration pneumonia should be part of the general treatment of all stroke patients, including those with ICH. Japanese guidelines give special recommendations for respiratory management.

Management of Brain Edema and Intracranial Hypertension

EUSI guidelines concerning *ICP management* give more detailed recommendations, especially for drug dosage and an escalation scheme for treatment (table 5). Both guidelines recommend a mild therapeutic hyperventilation to achieve arterial pCO_2 levels of 30–35 mm Hg, and both recommend elevation of body position at a 30° angle to decrease ICP. Intravenous administration of hypertonic glycerol is a frequent choice for major acute ICH in Japan. Concerning the application of mannitol, Japanese guidelines recommend the use only in cases of severe mass effect. Barbiturates are not recommended in Japanese guidelines as ultimate treatment option. Both guidelines do not mention hypothermia as therapeutic option to reduce ICP. Japanese guidelines do not recommend hypothermia because of lacking evidence (grade C2). Both guidelines recommend lowering of body temperature in case of fever, using even methods such as cooling.

Management of Seizures

In Japanese guidelines, the management of early and late-onset seizures is separately recommended. EUSI guidelines are more detailed and recommend a stepwise treatment with recommendations including drug dosages for seizure or status epilepticus treatment (table 6).

Prevention of Deep Venous Thrombosis and Pulmonary Embolism

Concerning *prevention of deep venous thrombosis and pulmonary embolism,* both guidelines have similar recommendations (table 7).

Surgical Indication for Acute ICH

Concerning *surgical indication* for acute ICH, Japanese guidelines distinguish between treatment in patients with hypertensive ICH and ICH not associated with hypertension. For hypertensive ICH, detailed recommendations according to different locations are provided. EUSI guidelines discern only between supratentorial or infratentorial ICH (tables 8, 9). Supratentorial ICH is divided into superficial (mostly) lobar and deep (mostly basal ganglion) locations, which mainly goes back to the results of STICH (International Surgical Trial in Intracerebral Hemorrhage) [16]. They give no general recommendations for surgical treatment. For infratentorial hemorrhages, good results are mentioned for surgical evacuation of cerebellar hematomas, but optimal timing for surgery is not provided. EUSI guidelines do not give recommendations for brain stem hemorrhage, but they

Table 8. Surgical indication for supratentorial ICH

European guidelines 2006 (EUSI)	Japanese guidelines 2009
No evidence for a general recommendation (class IV, level C).	General recommendation: If ICH <10 ml or mild neurological deficit regardless of the site if ICH → no surgery (grade D). No rationale for recommending evacuation for patients with deep coma (Japan Coma Scale III-300) (grade C2).
If ICH is superficial (the clot is subcortical ≤1 cm from the surface and does not reach the deep basal ganglia) or if there is deterioration in consciousness (from GCS level of between 12 and 9 to ≤8) → Consider craniotomy (level C).	Putaminal hemorrhage: – Consider evacuation if hematoma volume >31 ml in patients with moderate neurological findings and evidence of severe mass effect (grade C1). – Particularly stereotactic evacuation is recommended for patients with disturbed consciousness (Japan Coma Scale II-20 to 30) (grade B).
Deep-seated hematomas do not benefit from craniotomy. Stereotactic aspiration may be considered (class IV), especially if mass effect is present.	Thalamic hemorrhage: No rationale for hematoma evacuation in the acute stage (grade C2). Ventricular drainage can be considered when accompanied with intraventricular hematoma or marked ventricular dilatation (grade C1).
	Lobar (subcortical) hemorrhage: – Consider surgery if hematoma is <1 cm of the surface (grade C1). – Craniotomy recommended as surgical procedure (grade C1).

Table 9. Surgical indication for infratentorial ICH

European guidelines 2006 (EUSI)	Japanese guidelines 2009
Cerebellar hemorrhage If cerebellar ICH >2–3 cm in diameter, deterioration or brain stem compression and/or hydrocephalus occurs consider surgical evacuation and ventricular drainage as soon as possible (class IV, level C).	Surgery can be considered if cerebellar hemorrhage is >3 cm, if patients deteriorate neurologically, or patients have brain stem compression and hydrocephalus from ventricular obstruction (grade C1).
Intraventricular hemorrhage Intraventricular thrombolysis trials may be considered if an external ventricular drainage becomes necessary (class IV, level C), but not in infants. An intraventricular thrombolysis with urokinase or recombinant tissue plasminogen activator seems to be effective.	Because it is quite likely to be associated with vascular disease it is desirable to perform angiography to detect the bleeding source (grade C1). Ventricular drainage should be considered for acute hydrocephalus (grade C1).
Brainstem hemorrhage No recommendation.	There is no rationale for hematoma evacuation (grade C2). Ventricular drainage can be considered when most of the hematoma is in the ventricle and the ventricle is highly dilated (grade C1).
In case of hydrocephalus External drainage can be ventricular or via the lumbar route if it is a communicating type of hydrocephalus (class IV). Lumbar drainage is definitely contraindicated with all types of obstructive hydrocephalus or if the etiology is in doubt.	Consider external ventricular drainage (grade C1).

are more detailed concerning treatment of hydrocephalus compared with the Japanese guidelines. Both guidelines recommend the use of external ventricular drainage in case of hydrocephalus.

Organized studies on the selection of treatment procedures are rare. Some trials showed a trend in favor of early surgery in supratentorial nonaneurysmal ICH. The international STICH trial was conducted to demonstrate clinical efficacy of surgery in ICH but was not designed to look at the ideal surgical technique. It suggested a small nonsignificant advantage for surgery. A subgroup analysis showed that patients with superficial hematomas and without IVH presented a more encouraging picture of surgery [16]. Thus we are still unable to specify potential candidates for the optimum surgical technique in current guidelines. The ongoing STICH II trial [17] investigates the hypothesis that patients with superficial lobar hematomas and no IVH might benefit from early hematoma evacuation (<12 h after randomization) [17]. A previously published meta-analysis of 2,186 cases concluded that in particular early surgery (<8 h of ictus) is beneficial [18].

In Japan, a nationwide survey on 7,010 patients with putaminal hemorrhage was conducted, and mortality and functional prognosis 3 months after its onset were compared in 1990 [19]. The survey indicated that surgical therapy for putaminal hemorrhage was beneficial only when it was performed to save the lives of patients in very poor condition. A randomized comparative trial on stereotactic evacuation of putaminal hemorrhage in patients with moderately disturbed consciousness on admission showed a better functional outcome than in those with medical treatment [20].

It has been shown that patients with smaller hemorrhage have a better clinical outcome and a lower mortality, which led to the hypothesis that methods of removing ICH in stable patients could result in a lowered risk of mortality and improved outcome [21, 22]. The ongoing MISTIE (Minimally Invasive Surgery plus rt-PA for ICH Evacuation) trial [22] (NCT00224770) has the purpose to determine the efficacy of using a combination of minimally invasive surgery and clot lysis with recombinant tissue plasminogen activator to remove ICH using image-based surgery (MRI or CT) to provide catheter access to ICH for the intervention for clot aspiration followed by instillation of up to 9 doses of recombinant tissue plasminogen activator compared to conventional medical management. The specific objective of MISTIE is to test the efficacy and safety of this intervention and assess its ability to remove blood clots from brain tissue. The treatment of spontaneous supratentorial ICH will remain controversial until a definitive prospective randomized controlled trial shows evidence in favor of a particular treatment. At present, the recommendations for or against surgery are based on conflicting evidence.

Also, for IVH, recommendations are difficult due to the lack of evidence. The EUSI recommend intraventricular thrombolysis only within clinical trials, and Japanese recommendations discuss different randomized comparative trials on urokinase treatment, concluding that intraventricular urokinase is effective at least for life-saving treatment for patients with severe IVH [23], but give no recommendation for this therapy. It needs to be mentioned that urokinase might not be available in many countries.

Concerning ICH caused by cerebral *arteriovenous malformation, dural arteriovenous fistulas, cavernous angiomas or venous angiomas,* Japanese guidelines give very detailed information and recommendations concerning risk factors for bleeding, surgery, embolization, stereotactic radiotherapy, epilepsy and pediatric patients. EUSI guidelines give only a short recommendation for ICH caused by arteriovenous malformations. Japanese recommendations also cover ICH due a to *brain tumor* ['Surgical treatment is recommended for patients with massive hemorrhage from a brain tumor accompanied by the mass effect (grade C1). Acute deterioration of visual acuity and the visual field due to pituitary apoplexy are indications for emergency surgery (grade C1)'].

Recommendations Mentioned Only in One of the Guidelines

In the EUSI guidelines, recommendation for brain imaging for ICH diagnosis was described. CT and MRI are equally sensitive, however CT may be faster. ICH in a typical location but at young age or without a history of hypertension needs further diagnostic workup, including MR angiography, CT angiography or digital subtraction angiography to investigate the underlying vascular pathology. However, Japanese guidelines do not refer to imaging strategies.

Japanese guidelines give special recommendations concerning *upper gastrointestinal bleeding* in patients with hypertensive ICH. Special caution should be exercised to concurrent gastrointestinal bleeding, and prophylactic administration of an antiulcer agent is recommended (C1). EUSI guidelines do not mention upper

gastrointestinal bleedings. Furthermore, special recommendations for *ICH in patients with renal failure* are covered only in the Japanese guidelines.

Concerning secondary prevention of *depression,* European guidelines did not mention this complication, whereas Japanese guidelines recommend the following: Depression frequently occurs after stroke including ICH. It should be assiduously examined for because depression is a factor interfering with cognitive and physical function and activities of daily living (grade B). Drug therapy for a poststroke depressive state is recommended because it is expected to improve depressive symptoms and physical function (grade B).

Both guidelines recommend *treatment in specialized care units* (in the chapter of Stroke in General in the Japanese guidelines). All patients with acute ICH should preferably be treated in stroke units or in intensive care units if the patient condition requires this, because stroke unit care reduces mortality and increases the likelihood of good functional outcome of stroke in general. Due to a variety of similarities between acute ischemic stroke and ICH, it seems to be plausible that the specialized treatment might also be beneficial for patients with ICH (level C). Early *mobilization and rehabilitation* unless intracranial hypertension is present is recommended only in EUSI guidelines (class IV evidence).

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Effects of Intensive and Moderate Public Education on Knowledge of Early Stroke Symptoms Among a Japanese Population: The Acquisition of Stroke Knowledge Study

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Effects of Intensive and Moderate Public Education on Knowledge of Early Stroke Symptoms Among a Japanese Population

The Acquisition of Stroke Knowledge Study

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Background and Purpose—To assess the effects of intensive and moderate public education on knowledge of early stroke symptoms among a general Japanese population.

Methods—Information on early stroke symptoms was distributed by leaflet 12× and by booklet twice in an intensive intervention area >22 months, and by leaflet and booklet once each in a moderate intervention area. No distribution occurred in the control area. Before and after the intervention, a mailed survey was conducted in the 3 areas. A total of 2734 individuals, aged 40 to 74 years, who did not select all 5 correct symptoms of stroke in the preintervention survey were eligible for our analysis.

Results—The numbers of correct answers selected about stroke symptoms did not differ significantly among the 3 areas in the preintervention survey (P=0.156). In the postintervention survey, the proportions of participants who selected sudden 1-sided numbness or weakness (94.2% in the intensive intervention area, 88.3% in the moderate intervention area, and 89.2% in the control area; P<0.001) and sudden severe headache (76.8%, 70.1%, and 70.4%, respectively; P<0.001) differed significantly among the 3 areas. After adjustment for confounding factors, the multivariable-adjusted odds ratios (95% confidence intervals) for correctly choosing all 5 symptoms were 1.35 (1.07–1.71) in the intensive intervention area and 0.96 (0.74–1.24) in the moderate intervention area compared with the control area.

Conclusions—Our findings suggest that frequent distribution of leaflets and booklets significantly improved the short-term knowledge of community residents about early symptoms of stroke. **(*Stroke*. 2013;44:2829-2834.)**

Key Words: early stroke symptoms ■ knowledge ■ leaflet/booklet distribution ■ public education

Reducing the time between stroke onset and hospital arrival offers the greatest opportunity for effective acute stroke therapy.[1] Previous studies have demonstrated that alteplase treatment within 4.5 hours of onset improved functional outcome.[2–4] However, it has also been reported that there often remain substantial delays in hospital presentation of patients with acute stroke.[5–7] The major reason for the delay was attributed to a lack of knowledge of stroke symptoms.[7,8] Therefore, it would seem that knowledge of the early stroke symptoms should be disseminated more widely in the general population.

Some reports have maintained that multimedia campaigns using television and newspapers are optimal for improving public knowledge of stroke.[9–12] However, multimedia campaigns are very expensive and usually run on a commercial basis.[9,10] Therefore, it is also necessary to present sustainable methods that can be conducted by local governments, patient associations, nonprofit organizations, academic societies, and volunteer groups. In the present study, we set out to determine the effects of intensive or moderate public education initiatives by the Japan Stroke Association among a general Japanese population, which involved home distribution of leaflets and booklets giving information on the early stroke symptoms.

Methods

Study Setting

The Acquisition of Stroke Knowledge study was a nonrandomized community intervention trial, which aimed to improve public knowledge about the early stroke symptoms and the appropriate

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response to stroke onset, in 3 cities of Japan (ie, Akita [Akita, Japan], Kure [Hiroshima, Japan], and Shizuoka [Shizuoka, Japan]).[13] Characteristics of the 3 cities are shown in Table I in the online-only Data Supplement. In the present study, 2 districts of Akita, namely Kawabe and Yuwa, were selected as the intensive intervention area. Kure was selected as a moderate intervention area, and Shizuoka was selected as a control area. A 3-month preintervention survey (April 2006 to June 2006) was followed by 22 months of community intervention (July 2006 to April 2008). After the community intervention, a 2-month postintervention survey (May 2008 to June 2008) was performed. This study was approved by the ethics committee of Shiga University of Medical Science (17–97).

Participants

From the 3 areas, 11306 (3776 in the intensive intervention area, 3695 in the moderate intervention area, and 3835 in the control area) community residents, aged 40 to 74 years, were randomly selected by an age-stratified random sampling method from the Basic Resident Register, and 5540 individuals (49.0%) responded to the preintervention mailed survey.[13] Of 5509 individuals who agreed to participate in the postintervention survey, 3926 individuals responded to the postintervention mailed survey. In consequence, a response rate was 71.3% in total, 73.8% (1719/2329) in the intensive intervention area, 71.4% (1116/1562) in the moderate intervention area, and 67.4% (1091/1618) in the control area ($P<0.001$ for χ^2 test). Of these respondents, we excluded 915 (378 in the intensive intervention area, 279 in the moderate intervention area, and 258 in the control area) individuals who selected all 5 correct symptoms of stroke in the preintervention survey, 30 individuals who did not complete the self-administered questionnaire by themselves, 6 individuals who selected all 10 items (including 5 decoys) as early stroke symptoms, and 241 individuals who had missing data. A total of 2734 individuals (1140 in the intensive intervention area, 804 in the moderate intervention area, and 790 in the control area) were included in the analysis.

Community Intervention

The community intervention was conducted by distribution of leaflets and booklets and by holding lectures. Leaflets and booklets were distributed to all homes in the intensive and moderate intervention areas. Contents of the leaflets and booklets are shown in Table 1. In the intensive intervention area, we distributed leaflets 12× and booklets twice, and presented lectures 13× not only about the early symptoms of stroke, but also about the risk factors for stroke. In the moderate intervention area, we distributed leaflets and booklets once each, and presented lectures 5×. The control area did not receive any of these interventions.

Main Outcome Measures

In both pre- and postintervention surveys, a self-administered questionnaire was mailed to each participant. A closed-ended questionnaire included demographic information, social factors, history of disease, presence or absence of patients with stroke living close to the participants, and early symptoms of stroke. The questions on early symptoms of stroke consisted of 5 correct answers (sudden confusion or trouble speaking or understanding speech, sudden 1-sided numbness or weakness of the face, arms, or legs, sudden severe headache with no known cause, sudden trouble with walking, dizziness, or loss of balance or coordination, and sudden visual disturbances in 1 or both eyes)[14,15] and 5 decoy answers (sudden nasal bleeding, sudden increase in body temperature, sudden pain on left shoulder, numbness of both hands and fingers, and sudden difficulty in breathing) as multiple-choice items. Participants were asked to choose which of 10 listed symptoms were early stroke symptoms. The main outcome was the choice of all 5 correct symptoms of stroke in the postintervention survey among individuals who did not select all 5 correct symptoms of stroke in the preintervention survey.

A nationwide stroke campaign with newspaper advertisements about the early stroke symptoms by Advertising Council (AC) Japan was also conducted in the intervention period after the introduction of thrombolytic therapy with tissue-type plasminogen activator for cerebral infarction. In the postintervention survey, therefore, we asked participants whether they had seen the newspaper advertisements by AC Japan and adjusted for this as a confounding factor.

Table 1. Contents of Leaflets and Booklets Distributed to All Homes in Intensive and Moderate Intervention Areas

Intervention Area	Time	Leaflet or Booklet	Content
Intensive	April 2007	Booklet 1	A+B
	May 2007	Leaflet 1	A
	May 2007	Leaflet 2	C
	June 2007	Leaflet 3	A
	July 2007	Leaflet 4	A
	August 2007	Leaflet 5	A+D (hypertension)
	September 2007	Leaflet 6	A+D (arrhythmia)
	October 2007	Leaflet 7	A+D (diabetes mellitus)
	November 2007	Leaflet 8	A+D (smoking)
	December 2007	Leaflet 9	A+D (alcohol consumption)
	January 2008	Booklet 2	A+B
	February 2008	Leaflet 10	A+D (dyslipidemia)
	March 2008	Leaflet 11	A+D (salt and fat intake)
	April 2008	Leaflet 12	A+D (obesity)
Moderate	May 2007	Leaflet 1	A
	January 2008	Booklet 1	A+B

A indicates early stroke symptoms and appropriate response to stroke onset; B, prevention, treatment, and rehabilitation of stroke; C, intravenous thrombolytic therapy; and D, risk factors of stroke.

Statistical Analysis

Differences in demographic characteristics and knowledge of the early stroke symptoms among the 3 areas were determined using ANOVA for age and the χ^2 test for dichotomous and categorical data. Logistic regression analysis was used to estimate the multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the correct choice of all 5 symptoms of stroke in the intensive intervention area and the moderate intervention area compared with the control area. Data were adjusted for age, sex, education (≤12 or >12 years), living alone (yes or no), history of stroke (yes or no), history of transient ischemic attack (yes or no), and presence or absence of patients with stroke living close to the participants in the pre- and postintervention surveys, and exposure to newspaper advertisements by AC Japan (presence or absence) in the postintervention survey. All data were analyzed using SPSS statistical software (version 19.0J; SPSS Japan Inc, Tokyo, Japan).

Results

A comparison of demographic characteristics among the 3 areas in the preintervention survey is shown in Table 2. Education level ($P<0.001$), living alone ($P=0.005$), and presence of patients with stroke living close to the participants ($P<0.001$) differed significantly among the 3 areas. Age, sex, history of stroke, and history of transient ischemic attack did not differ significantly among the 3 areas. The knowledge of early symptoms of stroke among individuals in the preintervention survey is also shown in Table 2. The numbers of correct answers selected did not differ significantly among the 3 areas. The numbers of incorrect answers selected differed significantly among the 3 areas ($P=0.039$).

Table 2. Demographic Characteristics and Knowledge of Early Stroke Symptoms in the Preintervention Survey of 3 Areas

	Control Area (n=790)	Intervention Areas		P Value
		Moderate (n=804)	Intensive (n=1140)	
Age*, y	58.9±9.5	59.4±9.7	58.8±9.8	0.390
Men	358 (45.3)	381 (47.4)	523 (45.9)	0.687
Education, y				<0.001
≤12	554 (70.1)	538 (66.9)	983 (86.2)	...
>12	236 (29.9)	266 (33.1)	157 (13.8)	...
Living alone	54 (6.8)	81 (10.1)	71 (6.2)	0.005
History of stroke	20 (2.5)	21 (2.6)	28 (2.5)	0.977
History of transient ischemic attack	5 (0.6)	5 (0.6)	5 (0.4)	0.805
Presence of patients with stroke living close to the participants	392 (49.6)	332 (41.3)	728 (63.9)	<0.001
Correct answer about stroke symptoms				
Sudden confusion or trouble speaking or understanding speech	679 (85.9)	685 (85.2)	926 (81.2)	0.009
Sudden 1-sided numbness or weakness of the face, arms, or legs	655 (82.9)	652 (81.1)	977 (85.7)	0.022
Sudden severe headache with no known cause	524 (66.3)	515 (64.1)	767 (67.3)	0.329
Sudden trouble with walking, dizziness, or loss of balance or coordination	401 (50.8)	406 (50.5)	651 (57.1)	0.004
Sudden visual disturbances in 1 or both eyes	135 (17.1)	137 (17.0)	157 (13.8)	0.066
Numbers of correct answers selected				0.156
None	24 (3.0)	46 (5.7)	40 (3.5)	...
1	48 (6.1)	51 (6.3)	74 (6.5)	...
2	125 (15.8)	116 (14.4)	165 (14.5)	...
3	276 (34.9)	252 (31.3)	370 (32.5)	...
4	317 (40.1)	339 (42.2)	491 (43.1)	...
Incorrect answer about stroke symptoms				
Numbness of both hands and fingers	280 (35.4)	304 (37.8)	470 (41.2)	0.032
Sudden difficulty in breathing	117 (14.8)	113 (14.1)	188 (16.5)	0.308
Sudden nasal bleeding	44 (5.6)	24 (3.0)	85 (7.5)	0.001
Sudden pain on left shoulder	24 (3.0)	22 (2.7)	29 (2.5)	0.808
Sudden increase in body temperature	12 (1.5)	7 (0.9)	17 (1.5)	0.417
Numbers of incorrect answers selected				0.039
None	423 (53.5)	428 (53.2)	538 (47.2)	...
1	270 (34.2)	298 (37.1)	453 (39.7)	...
2	85 (10.8)	65 (8.1)	118 (10.4)	...
3	11 (1.4)	10 (1.2)	25 (2.2)	...
4	1 (0.1)	3 (0.4)	5 (0.4)	...
5	0 (0.0)	0 (0.0)	1 (0.1)	...

*Age was analyzed using ANOVA, and is shown in the mean and SD. Dichotomous and categorical data were analyzed using the χ^2 test, and are shown as number (%).

In the postintervention survey (Table 3), ≈90% of participants correctly selected sudden speech problems and sudden 1-sided numbness or weakness as early symptoms, followed by sudden severe headache (72.8%) and sudden dizziness or loss of balance (63.8%). Furthermore, 33.3% of participants selected sudden visual problems. The symptoms sudden 1-sided numbness or weakness (P<0.001) and sudden severe headache (P<0.001) differed significantly among the 3 areas. The proportions of participants who selected all 5 correct symptoms were 22.8% in the intensive intervention area, 18.5% in the moderate intervention area, and 18.6% in the control area, with a significantly higher proportion in the intensive intervention area (P=0.011). The numbers of incorrect answers selected did not differ significantly among the 3 areas. In addition, in the postintervention survey, the proportions of participants who reported that they had participated in the lectures were only 3.3% in the intensive intervention area and only 2.4% in the moderate intervention area. The proportions of participants who reported that they had read newspaper advertisements about early symptoms of stroke

Table 3. Knowledge of Early Stroke Symptoms in the Postintervention Survey of Areas

	Control Area (n=790)	Intervention Areas		*P* Value
		Moderate (n=804)	Intensive (n=1140)	
Correct answer about stroke symptoms in preintervention survey				
Sudden confusion or trouble speaking or understanding speech	725 (91.8)	733 (91.2)	1055 (92.5)	0.430
Sudden 1-sided numbness or weakness of the face, arms, or legs	705 (89.2)	710 (88.3)	1074 (94.2)	<0.001
Sudden severe headache with no known cause	556 (70.4)	564 (70.1)	876 (76.8)	<0.001
Sudden trouble with walking, dizziness, or loss of balance or coordination	486 (61.5)	511 (63.6)	752 (66.0)	0.065
Sudden visual disturbances in 1 or both eyes	252 (31.9)	270 (33.6)	395 (34.6)	0.210
Numbers of correct answers selected				0.011
None	15 (1.9)	18 (2.2)	6 (0.5)	...
1	25 (3.2)	27 (3.4)	45 (3.9)	...
2	97 (12.3)	95 (11.8)	118 (10.4)	...
3	240 (30.4)	238 (29.6)	305 (26.8)	...
4	266 (33.7)	277 (34.5)	406 (35.6)	...
5	147 (18.6)	149 (18.5)	260 (22.8)	...
Incorrect answer about stroke symptoms				
Numbness of both hands and fingers	341 (43.2)	341 (42.4)	523 (45.9)	0.263
Sudden difficulty in breathing	115 (14.6)	118 (14.7)	193 (16.9)	0.258
Sudden nasal bleeding	30 (3.8)	29 (3.6)	50 (4.4)	0.589
Sudden pain on left shoulder	26 (3.3)	29 (3.6)	47 (4.1)	0.623
Sudden increase in body temperature	10 (1.3)	9 (1.1)	16 (1.4)	0.859
Numbers of incorrect answers selected				0.272
None	387 (49.0)	396 (49.3)	533 (46.8)	...
1	300 (38.0)	310 (38.6)	441 (38.7)	...
2	88 (11.1)	82 (10.2)	128 (11.2)	...
3	14 (1.8)	12 (1.5)	31 (2.7)	...
4	1 (0.1)	4 (0.5)	7 (0.6)	...
5	0 (0.0)	0 (0.0)	0 (0.0)	

Dichotomous and categorical data were analyzed using the χ^2 test, and are shown as number (%).

by AC Japan were 42.5% in the intensive intervention area, 41.9% in the moderate intervention area, and 36.2% in the control area.

The Figure presents the multivariable-adjusted ORs for the correct choice of all 5 symptoms in the postintervention survey among the 3 areas. After adjustment for age, sex, education, living alone, history of stroke, history of transient ischemic attack, presence or absence of patients with stroke living close to the participants, and exposure to newspaper advertisements by AC Japan, the multivariable-adjusted ORs and 95% CIs for correctly choosing all 5 symptoms were 1.35 (1.07–1.71) in the intensive intervention area and 0.96 (0.74–1.24) in the moderate intervention area compared with the control area. In the covariates used for the adjustment, education (OR for >12/≤12 years, 1.46 [95% CI, 1.16–1.83]), presence of patients with stroke living close to the participants (OR for presence/absence, 1.28 [95% CI, 1.05–1.57]), and exposure to newspaper advertisements by AC Japan (OR for presence/absence, 1.52 [95% CI, 1.26–1.85]) were significantly associated with the correct choice of all 5 symptoms of stroke. Age, sex, living alone, history of stroke, and history of transient ischemic attack were not significantly associated with the correct choice of all 5 symptoms of stroke.

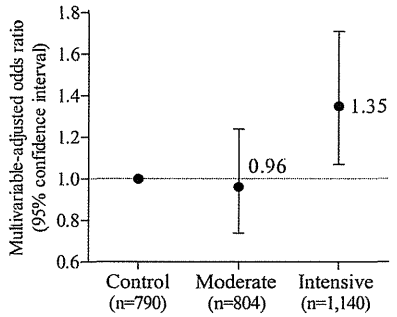

Figure. Multivariable-adjusted odds ratios for the correct choice of all 5 stroke symptoms in the postintervention survey by the 3 areas. Adjusted for age, sex, education, living alone, history of stroke, history of transient ischemic attack, and presence or absence of patients with stroke living close to the participants in the pre- and postintervention surveys, and exposure to newspaper advertisements by Advertising Council Japan in the postintervention survey.

Discussion

Ours is the first community-based study to survey not any household member but individuals, and to show an improvement in the knowledge of early stroke symptoms by public education, consisting of repeated distribution of leaflets and booklets to all homes among a general Japanese population. The intensive intervention area was 1.35× more likely to correctly choose all 5 stroke symptoms compared with the control area, with no difference seen in the moderate intervention area. Accordingly, frequent distribution of leaflets and booklets significantly improved the short-term knowledge of community residents about early stroke symptoms. Furthermore, the intensive intervention area had the highest response rate in the postintervention survey, although proportion of participants with education >12 years in the intensive intervention area was lower than in other areas. We think our intervention may also affect response rate in the intervention area irrespective of their education level.

It has been reported that intermittent long-term intervention was effective in increasing the knowledge about early symptoms of stroke, but short-term intervention was less effective.[16] Multimedia campaigns are powerful for improving the knowledge about stroke,[9–13] and nowadays there are many healthcare programs and news bulletins of recent medical breakthroughs on television. It can be possible to negotiate with the producers of these programs, but many television campaigns usually require content to be produced on a commercial basis, and are bound by audience ratings. In addition, the cost of educational multimedia campaigns using television and newspapers is expensive,[9,10] so that it might be difficult to continue a multimedia campaign over a long time. However, the costs of leaflets and booklets can be reduced when they are distributed through monthly or weekly free official gazette of local municipalities, which often have space for health education for community residents. Therefore, the present study shows the usefulness of a practical long-term strategy to educate the population. In performing a long-term strategy, effective frequency and timing of distribution of leaflets and booklets should be considered. This study suggested that such community intervention should be performed more frequently than that in the moderate intervention area. Community residents, however, may skip the information of leaflets and booklets in the long-term intervention, and we should present these in a way that is not boring. Alternatively, it may be more feasible to conduct such intensive interventions according to seasonal increases of stroke incidence.

In previous studies, it was reported that 35% to 70% of participants had knowledge about the early stroke symptoms.[9,11,17] The discrepancy in the proportion of people with stroke knowledge between previous studies and the present study may be because of the difference in the definitions of having knowledge of stroke symptoms. In the present study, individuals with the knowledge were defined as those who selected all 5 stroke symptoms from 10 symptoms. However, in previous studies, the effectiveness of campaigns was assessed by the ability to name 2 early symptoms of stroke without being shown multiple-choice items.[9,17] However, patients with stroke are unable to choose their own symptoms at the time of onset, and people should be aware of all the typical early symptoms of stroke. In addition, it has been reported that British people poorly recognized symptoms not included in the Face, Arm, Speech Test Time to call 999 campaign (leg weakness and visual symptoms) and indicated that this lack of the knowledge might lead to delays in hospital presentation.[18] Accordingly, the present study assessed improvements in knowledge on the basis of increase of the proportions of participants who correctly chose all 5 early symptoms from preintervention to postintervention surveys. Less severe symptoms, such as sudden dizziness or loss of balance and sudden visual problems, which were poorly recognized as in the British survey, should be emphasized in any long-term strategy to educate the population about early stroke symptoms.

There are several limitations in the present study. First, we only evaluated the effectiveness of the intervention by the improvement in short-term knowledge about early symptoms of stroke by intensive and moderate interventions; therefore, further study is necessary to assess the effectiveness by the behavioral changes of patients with stroke. For example, time from symptom onset to hospital presentation, the number of patients with stroke calling an ambulance, how soon bystanders called the emergency center after having noticed early symptoms, and the number of patients able to undergo intravenous thrombolytic therapy should be evaluated. Second, we did not evaluate exposure to mass media, such as television programs or newspaper articles about stroke. However, we surveyed participants who had read newspaper advertisements by AC Japan and adjusted for its effect in our multivariable model. We think that this represented a surrogate marker for exposure to mass media because those participants would likely be exposed to information by other mass media. Third, respondents may have been community residents who were relatively interested in stroke, such that the effects of intervention on knowledge of early stroke symptoms in a group not interested in stroke could not be determined. Fourth, closed-ended questions may provide the respondent with some prompt as to what the correct answer should be,[15] and, therefore, may have been likely to produce substantially higher identification of early stroke symptoms. Finally, the nationwide stroke campaign with newspaper advertisements by AC Japan may have influenced the knowledge of early stroke symptoms in the control area.

In conclusion, our findings suggest that intensive intervention comprising distribution of leaflets and booklets to all homes was effective in improving the short-term knowledge about early stroke symptoms, and was more effective than moderate intervention. The costs of leaflet and booklet distribution can be reduced by delivery in free official gazette issued by local municipalities. The findings of this study indicate that this would be an effective and practical long-term strategy to educate the general population.

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