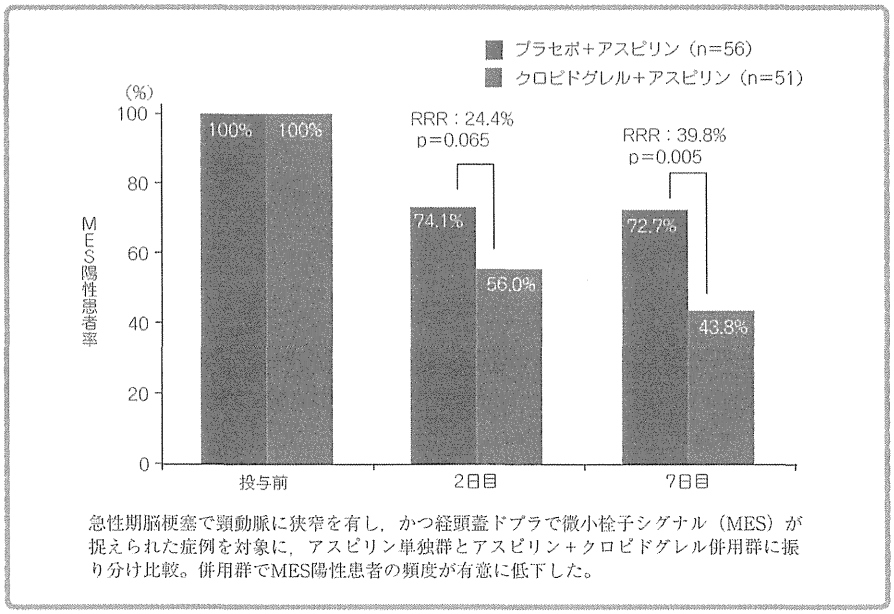

図3　アスピリン単独群とアスピリン+クロピドグレル併用群のMES陽性患者率の比較
〔Markus HS, et al：Circulation, 111：2233-2240, 2005より引用，改変〕

塞の再発予防に用いられる。シロスタゾールはホスホジエステラーゼの阻害薬で，血小板中のサイクリックAMP（cAMP）を上昇させ，抗血小板作用を発揮する。2010年大規模臨床試験CSPS2（Cilostazol Stroke Prevention Study 2）でアスピリンと比較して有意に脳卒中（脳梗塞，脳出血，くも膜下出血）を減少させるという結果が報告され注目を浴びた[4]。頭蓋内狭窄病変の進行抑制・退縮効果もあるとの報告もある[5]。副作用として頭痛や心拍数の上昇があげられている。

抗血栓作用は異なった作用機転の抗血小板薬を併用することで，相乗効果があることがわかっている。特に薬剤溶出性冠動脈ステント後にはアスピリンとクロピドグレルの併用が必須である。アテローム血栓性脳梗塞の場合にも併用療法が有効な場合があるが（図3），脳梗塞では出血のリスクも上がるため，慎重に適応と投与期間について考慮することが必要である。併用療法を考慮すべき症例は，頸動脈の高度狭窄病変で[6]，早期に再発が生じる可能性の高い症例であるが，このような症例は可能であればできるだけ早期の血行再建術の適応も考慮すべきである。

ラクナ梗塞に対する抗血栓療法

ラクナ梗塞に抗血栓薬，特に抗血小板薬が一般的にはよく投与されているが，少なくともアスピリンやチエノピリジン系抗血小板薬には大規模試験によるエビデンスはない。シロスタゾールはラクナ梗塞の再発予防効果がランダム比較化試験により証明されているが[4]（表1），この試験はプラセボとの比較で，アスピリンとの比較を行ったCSPS2のサブ解析では有意差が出ていない。ラクナ梗塞は最近の研究でMRIのT2*画像により検出されるmicrobleedsを合併する頻度も高く，脳出血を起こす血管の多くは穿通枝でありラクナ梗塞と脳出血の発症機序が表裏一体であることを考えれば，抗血小板薬の投与は慎重に行うべきと思われる。

その他の脳梗塞に対する抗血栓療法

検査法の発展により，脳卒中の原因が詳細にわかるようになってきた。大動脈の粥腫を塞栓源とする大動脈原性脳塞栓症は，経食道心エコーの普及により思っていたよりも頻度が多いことがわかってきた。大動脈原性脳塞

表1　CSPS（Cilostazol Stroke Prevention Study）のサブ解析

		イベント	イベント率/年（%）	相対リスクの減少（%）	p値**
脳梗塞再発（主要評価項目）	シロスタゾール（nyr 889.6*）	30	3.37	41.7	0.015
	プラセボ（nyr 986.0）	57	5.78		
ラクナ梗塞	シロスタゾール（nyr 673.8）	20	2.97	43.4	0.0373
	プラセボ（nyr 743.4）	39	5.25		
アテローム血栓性梗塞	シロスタゾール（nyr 109.8）	7	6.37	39.8	0.2620
	プラセボ（nyr 104.0）	11	10.58		
混合型	シロスタゾール（nyr 90.7）	3	3.31	44.5	0.4361
	プラセボ（nyr 117.5）	7	5.96		

nyr：number of patient-years
＊：Patient-years at risk for outcome
＊＊：Log-rank検定
シロスタゾールとプラセボで脳梗塞再発率を比較。サブ解析でラクナ梗塞の再発が有意に低下していた。
〔Gotoh F, et al：J Stroke Cerebrovasc Dis, 9：147, 2000より引用，一部改変〕

栓症の抗血栓治療は現時点で確立されたエビデンスがまだ存在しない。大規模臨床研究のサブ解析からワルファリンが有効とするデータもあるが，通常はまず抗血小板薬が投与されることが多い。欧米ではARCH（ClinicalTrials.gov Identifier：NCT00235248）というワルファリンと抗血小板薬併用療法との比較を行う大規模臨床試験が進行中であり，その結果が待たれる。

卵円孔開存による奇異性脳塞栓症も経食道心エコー検査により，卵円孔開存の検索が頻繁に行われるようになり，さらに下肢静脈の超音波検査で下腿まで深部静脈血栓の検索が可能になったために注目を集めるようになった。深部静脈血栓が存在すれば，肺塞栓症の危険性もあるために抗凝固療法（現時点ではワルファリン）が適応となるが，深部静脈血栓が確認できない場合には，大規模試験の結果からもアスピリンが第一選択となる[7]。

このほかに，担がん患者での脳塞栓症（Trousseau症候群）では，もちろん原疾患の治療が最も重要であるが，塞栓症の抗血栓療法としてはヘパリンが適応になり，ワルファリンでは十分な再発予防効果が得られないことが知られている。

動脈解離も，思ったより頻度が高いことがわかってきた脳梗塞の原因であるが，抗血栓療法に関しては手探りの状態で，確立したものはない。一般的には，動脈瘤があれば抗血栓療法は行わず，狭窄が高度の場合や再発・進行例に抗血栓療法が施行される。いつまで抗血栓療法を継続すべきかも明らかでないが，狭窄が改善する例もあるので，MRAなどでフォローしながら中止時期を考慮している。

原因不明の脳梗塞に対する抗血栓療法

まず原因となる病変が複数存在する場合であるが，これも確立した治療法はない。心房細動が存在すると，まず抗凝固療法が第一選択となる。心房細動に加えて脳血管の粥状硬化病変があった場合，抗血小板薬を併用するかどうかが問題となるが，試験のデータをみるとワルファリンはLarge vessel diseaseに対してアスピリンと同程度の再発予防効果が期待できることがわかる[8]。この結果を踏まえて，ワルファリン単独投与でよいという意見があるが，エビデンスは明らかではない。大動脈粥腫に関しては検査を行うと高頻度に見つかるが，現時点では心房細動が合併していればワルファリン，脳血管の粥状硬化が合併していれば抗血小板薬が選択されている。

原因となる病変が見つからない場合には，通常は抗血小板療法が選択される。原因不明の脳塞栓症では一過性心房細動が隠れている場合が多いので，外来でのHolter心電図のフォローを繰り返し行う必要がある。また原因不明の一部は悪性腫瘍が背景にある場合もあるので，スクリーニングは必要である。

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EDITORIAL

The cerebro-renal interaction in stroke neurology

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Chronic kidney disease (CKD), defined as a reduced glomerular filtration rate (GFR) or albuminuria, is a known, strong risk factor for stroke. Meta-analyses of cohort studies and trials indicate that proteinuria/albuminuria increases the risk of stroke by 71%–92%, and estimated GFR (eGFR) <60 mL/min/1.73 m^2 increases the risk by 43%.[1,2] CKD is also predictive of poor outcomes after stroke; reduced eGFR is independently associated with increased 1- and 10-year mortalities.[3,4] Since end-stage renal disease (ESRD) is another established predictor of stroke risk and poor stroke outcomes,[5] stroke neurologists should fully understand the interaction between stroke and CKD/ESRD.

In this issue of *Neurology*®, Kumai et al.[6] studied 3,778 patients admitted within 24 hours of onset of their first-ever ischemic stroke from a large-cohort multicenter stroke registry; of these, 1,320 (34.9%) had CKD defined as proteinuria or reduced eGFR on admission. They found that CKD patients had a 49% greater risk of neurologic deterioration, defined as a ≥2-point increase in the NIH Stroke Scale, during hospitalization; a 138% greater risk of in-hospital mortality; and a 25% greater risk of a modified Rankin Scale score (mRS) ≥2 at discharge than non-CKD patients after adjustment for potential confounding factors, including initial stroke severity. As a component of CKD, proteinuria showed a much stronger association with unfavorable outcomes than reduced eGFR; for example, patients with mild proteinuria, with an estimated amount of urine protein of 30–100 mg/mL, had a 69% greater risk of an mRS ≥2 than patients without proteinuria. In contrast, reduced eGFR was not associated with stroke outcomes in the study by Kumai et al.[6] Albuminuria and reduced eGFR may involve separate pathologic processes. Kumai et al. did not measure filtration function prior to stroke onset but only on admission, when it may have been affected by acute stroke damage. Measurement of eGFR and urine protein in the chronic stage of stroke might show different associations.

Other potential limitations include use of semiquantitative measurement of urine protein using dipstick testing, which may result in frequent false-positive and false-negative results. However, it is meaningful that such a handy and economical measurement can predict stroke outcomes. Also, outcomes were measured after only a short interval. Vital and functional outcomes were assessed at hospital discharge (median, 23 days after stroke onset). Because their registry has a plan to perform yearly follow-up for enrolled patients, this limitation will eventually be resolved.

Renal dysfunction is a bystander of stroke, since both conditions are associated with hypertension and several traditional vascular risk factors. Additionally, albuminuria is an indicator of cephalocervical and systemic vascular dysfunction via nontraditional vascular risk factors, including endothelial dysfunction, maladaptive carotid arterial remodeling, homocystinemia, coagulation disorders, impaired endothelial release of tissue plasminogen activator, extravascular coagulation, and higher levels of inflammatory cytokines and oxidative stress. An association between albuminuria and hemorrhagic transformation of infarcts has also been noted.[7] Such factors might cause both initial severity and unfavorable outcomes of stroke in patients with proteinuria.

These data underscore the fact that one can no longer manage and care for stroke patients while disregarding their renal condition. CKD/ESRD is not only predictive of unfavorable outcomes after general stroke, but also of stroke outcomes after specific therapies. In our multicenter observational studies (the SAMURAI rt-PA Registry), reduced eGFR was associated with early symptomatic hemorrhagic conversion, mortality, and an mRS ≥4 at 3 months after IV recombinant tissue plasminogen activator therapy.[8] Although thrombolysis is generally not considered safe for stroke patients undergoing hemodialysis, most experts who responded to an international survey favored its use.[9] Patients with stages 4 and 5 CKD (eGFR <30 mL/min/1.73 m^2) have a high 30-day mortality when

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undergoing carotid endarterectomy or carotid angioplasty and stenting.[10] Dabigatran, a new oral anticoagulant for stroke prevention, is mainly excreted by the kidneys, and should be used cautiously even in patients with moderate renal damage.

Another essential issue that must be resolved is whether active treatment to reduce albuminuria and improve filtration dysfunction can decrease stroke risk and improve stroke outcomes. CKD is also associated with subclinical brain abnormalities, including white matter changes, microbleeds, mild cognitive disorders, and intima-medial thickening of carotid arteries. The cerebro-renal interaction is an understudied and underused concept at present, but it has as great a clinical significance as the cardio-renal interaction and should be studied more extensively and in great detail.

Finally, the Fukuoka Stroke Registry that Kumai et al.[6] used as a study cohort merits specific comment. This multicenter registry for acute stroke patients in the Fukuoka metropolitan area, in western Japan, has several strengths, since the database includes extensive underlying patient information, image data principally from MRI/magnetic resonance angiography, long-term follow-up of vital and functional conditions for many years, and the results of serologic and genome genetic analyses for most participants. This systematic stroke registry will help resolve several problems in stroke neurology, in particular in relation to stroke in the Asian population, in whom the stroke burden is increasing.

DISCLOSURE

The author reports no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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Run-up to participation in ATACH II in Japan

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Abstract

Intracerebral hemorrhage (ICH) is a major cause of morbidity and mortality in Japan. Seventeen Japanese institutions are participating in the Antihypertensive Treatment for Acute Cerebral Hemorrhage (ATACH) II Trial (ClinicalTrials.gov no. NCT01176565; UMIN 000006526). This phase III trial is designed to determine the therapeutic benefit of early intensive systolic blood pressure (BP) lowering for acute hypertension in ICH patients. This report explains the long run-up to reach the start of patient registration in ATACH II in Japan, including our preliminary study, a nationwide survey on antihypertensive treatment for acute ICH patients, a multicenter study for hyperacute BP lowering (the SAMURAI-ICH study), revision of the official Japanese label for intravenous nicardipine, and construction of the infrastructure for the trial.

Keywords

acute stroke; antihypertensive treatment; blood pressure; clinical trial; hypertension; intracerebral hemorrhage; nicardipine

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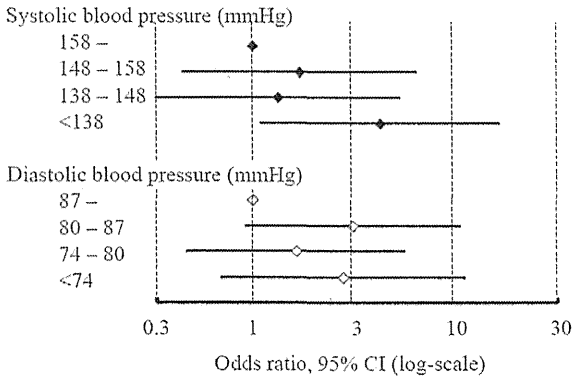

Figure 1. Average of blood pressure levels during the initial 24 h and an mRS of 1 or less at 3 weeks after intracerebral hemorrhage from a Japanese dual-center observational study.
Compared with patients with the average of systolic blood pressure at least 158 mmHg, patients with the level <138 mmHg more frequently had an mRS of 1 or less after multivariate adjustment (OR 4.36, 95% CI 1.10–17.22). The frequency did not differ among the patient quartiles based on diastolic blood pressure.
See Itabashi *et al* [3] for more information.

Introduction

Asian ethnic origin is an important risk factor for intracerebral hemorrhage (ICH). A recent meta-analysis reported that the incidence of ICH per 100,000 person-years was 51.8% in Asian people as compared to 24.2% in Caucasians [1]. The high prevalence of small-artery cerebrovascular lesions in Asians may be responsible for the high prevalence of ICH. In Japan, acute ICH patients account for 17–30% of overall acute stroke patients [2]. Undoubtedly, ICH is a burden for the Japanese population that needs to be overcome, though the meta-analysis also provided some good news: the median case fatality at 1 month after ICH was lower in Japan than anywhere else in the world (16.7 vs. 42.3%) [1].

A problem in acute ICH management is the lack of a therapeutic strategy that brings dramatic symptomatic improvement like that seen with thrombolysis for ischemic stroke. Blood pressure (BP) lowering during the hyperacute stage may prevent hematoma expansion and improve outcomes after ICH. We reported an observational study involving 244 patients who were admitted to the National Cerebral and Cardiovascular Center, Osaka, or the National Hospital Organization Kyushu Medical Center, Fukuoka, within 24 h after ICH onset [3]. Lowering the systolic BP (SBP) to less than 138 mmHg during the initial 24 h immediately after identification of ICH on emergency computed tomography was predictive of independent activity corresponding to a modified Rankin Scale (mRS) score of 1 or less at 3 weeks (Figure 1). Although this result is promising, a prospective interventional trial is required to ascertain the clinical significance of the cutoff level (138 mmHg or roughly 140 mmHg) as an emergent antihypertensive goal.

Palesch and Qureshi offered us the chance to be involved in such a trial by inviting us to join the NIH-funded trial, the Antihypertensive Treatment for Acute Cerebral Hemorrhage (ATACH) II [4], and they visited Tokyo for our first domestic meeting on this trial in October, 2008. However, to facilitate trial participation in Japan, some problems needed to be resolved, including reassessment of the official label for nicardipine, a trial drug. This is a report of the long run-up to reach the start of patient registration in ATACH II in Japan.

Nationwide survey of acute BP control in Japan

As the first step, it was necessary to ascertain the current status of antihypertensive treatment for acute ICH patients in Japan. Thus, a nationwide survey was conducted in 2008 [5]. Web questionnaires regarding acute ICH management and antihypertensive treatment strategies were sent to 1,424 hospitals, and 600 (42%) responded. Most respondents answered that the goal of lowering SBP was to reach a maximum of 140, 150, or 160 mmHg (82%). The results indicated that aggressive BP lowering was common in Japan as compared to the recommendations of domestic and Western guidelines.

In addition, nicardipine was the major first choice of intravenous antihypertensive drug (57%) and the second choice (27%) in the survey. However, 26% of the respondents thought that nicardipine was inappropriate mainly due to contraindications included on the official Japanese label for this drug. According to the official label, nicardipine was contraindicated for ICH patients with a suspicion of ongoing intracranial bleeding, since the drug may enhance bleeding, and it was also contraindicated for acute stroke patients with elevated intracranial pressure, since the drug may accelerate intracranial pressure elevation.

SAMURAI-ICH study: a multicenter study of hyperacute antihypertensive therapy

The next step was to elucidate the safety and feasibility of SBP lowering to 160 mmHg or less in acute ICH using nicardipine, the standard strategy in most Japanese hospitals according to the Web survey. A prospective, multicenter study was conducted in Japan from July 2009 through July 2011 by the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) study investigators; this multicenter group was funded by the Ministry of Health, Labour and Welfare (MHLW), Japan, and dealt with themes related to acute stroke management.

Most protocols for patient selection and nicardipine injection were similar to those of ATACH or ATACH II [4,6]. Patients with supratentorial ICH within 3 h of onset, admission SBP ≥180 mmHg, Glasgow Coma Scale (GCS) score ≥5, and hematoma volume ≤60 ml were initially treated with intravenous nicardipine to maintain SBP between 120 and 160 mmHg with 24-h frequent BP monitoring. The primary endpoints were neurological deterioration within 72 h (GCS decrement ≥2 points or NIHSS increment ≥4 points) and serious adverse effects resulting in stopping intravenous nicardipine within 24 h. The secondary endpoints included hematoma expansion >33% at 24 h and an mRS score of 4 or more and death at 3 months. The endpoints were compared with predicted proportions based on the weighted average of previous studies.

A total of 211 patients were enrolled. The main results and a substudy on conjugate eye deviation in the cohort were described in our previous articles [7,8]. Briefly, all the endpoints were close to or below the estimated level. Thus, SBP lowering to ≤160 mmHg using nicardipine appeared to be safe and feasible for Japanese ICH patients. The interim and final results of the study were presented at domestic and international conferences in 2011, including the 20th European Stroke Conference, where the necessity for the reassessment of the official label for nicardipine was stressed.

Revision of the official label for intravenous nicardipine

As far as we could determine, the contraindication of the use of nicardipine for patients with ongoing intracranial bleeding or high-intracranial pressure was suggested only by a few experimental or clinical studies reported a couple decades ago. The detailed situations related to the label were described in our previous article [5]. The nationwide survey clarified the prevalence of nicardipine administration to acute ICH patients without reports of any significant adverse events despite the contraindications. Based on the results of the survey and other considerations, a formal request for reassessment of the official label for nicardipine was submitted to the MHLW by the Japan Stroke Society, the Japan Neurosurgical Society, and the Japanese Society of Hypertension in October 2008. After several discussions, the MHLW finally ordered the pharmaceutical manufacturers of nicardipine to revise the label in June 2011, deleting the ICH-related contraindications.

Advance creation of the research network for ATACH II in Japan

After the above-mentioned steps, we formed a Japanese study group for ATACH II, which consists of 17 Japanese stroke institutes, involving the SAMURAI study investigators (Table 1). We recently introduced this network elsewhere in the Japanese language [2]. Briefly, we ensured independent relationships among clinical sites, data coordination, and financial management by managing the three parts independently by the Departments of Cerebrovascular Medicine (Toyoda) and Advanced Medical Technology Development (Yamamoto), the National Cerebral and Cardiovascular Center, and the Japan Cardiovascular Research Foundation (Yamaguchi), respectively. We registered the trial design in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) in Japan as trial number 000006526.

A problem for the smooth start of this trial is the lack of experienced and well-funded support systems and human resources for investigator-initiated clinical trials in Japan [9], although they are gradually forming in

Table 1.
List of Japanese institutions participating in the ATACH-II trial.

Institution	Department	Location	Responsible investigator
Clinical sites			
National Cerebral and Cardiovascular Center	Cerebrovascular Medicine Neurology	Suita, Osaka	Kazunori Toyoda (Clinical PI) Kazuyuki Nagatsuka
Nakamura Memorial Hospital	Neurosurgery and Stroke Center	Sapporo, Hokkaido	Jyoji Nakagawara
Kohnan Hospital	Stroke Neurology	Sendai, Miyagi	Eisuke Furui
Kyorin University Hospital	Neurosurgery and Stroke Center	Mitaka, Tokyo	Yoshiaki Shiokawa
St. Marianna University Hospital	Neurology	Kawasaki, Kanagawa	Yasuhiro Hasegawa
NHO Nagoya Medical Center	Neurology	Nagoya, Aichi	Satoshi Okuda
Kobe City Medical Center General Hospital	Stroke Center	Kobe, Hyogo	Nobuyuki Sakai
Kawasaki Medical School Hospital	Stroke Medicine	Kurashiki, Okayama	Kazumi Kimura
NHO Kyushu Medical Center	Cerebrovascular Medicine	Fukuoka, Fukuoka	Yasushi Okada
Gifu University Hospital	Neurosurgery	Gifu, Gifu	Shin-Ichi Yoshimura
Tokyo Saiseikai Central Hospital	Neurology	Minato-ku, Tokyo	Haruhiko Hoshino
Toranomon Hospital	Neurology	Minato-ku, Tokyo	Yoshikazu Uesaka
NHO Kagoshima Medical Center	Neurology	Kagoshima, Kagoshima	Takahiro Nakashima
Keio University Hospital	Neurology	Shinjuku-ku, Tokyo	Yoshiaki Itoh
St. Marianna University Toyoko Hospital	Strokology	Kawasaki, Kanagawa	Toshihiro Ueda
Saiseikai Kumamoto Hospital	Neurosurgery	Kumamoto, Kumamoto	Tohru Nishi
Saiseikai Yokohamashi Tobu Hospital	Neurology	Yokohama, Kanagawa	Jun Gotoh
Data Coordination Unit (DCU)			
National Cerebral and Cardiovascular Center	Advanced Medical Technology Development	Suita, Osaka	Haruko Yamamoto (DCU PI)
Management of subcontract			
Japan Cardiovascular Research Foundation		Suita, Osaka	Takenori Yamaguchi
Supervisory adviser			
National Cerebral and Cardiovascular Center		Suita, Osaka	Kazuo Minematsu

NHO National Hospital Organization

other medical fields such as oncology [10]. Government-funded clinical trial support systems like those in the United States are necessary to enable us to plan and conduct clinical trials effectively and reliably, cooperating with other clinical research professionals including biostatisticians. This time, two projects are available for maintaining the trial infrastructure: a study funded by an Intramural Research Fund of the National Cerebral and Cardiovascular Center and another funded by a Health and Labor Sciences Research Grant of the MHLW. There is a substantial need to encourage Japanese stroke researchers to join in the international, investigator-initiated, multicenter trials to obtain universal clinical evidence that is also common to Japanese. We are learning much about how to support several stroke institutes in Japan academically and financially through the experience of preparing for ATACH II.

The ATACH-II trial could be the seminal research project for stroke researchers in Japan to demonstrate themselves as effective contributors to investigator-initiated, international clinical trials. The first Japanese patient was enrolled in ATACH-II on March 1, 2012.

List of abbreviations

ATACH, Antihypertensive Treatment for Acute Cerebral Hemorrhage; BP, Blood pressure; GCS, Glasgow Coma Scale; ICH, Intracerebral hemorrhage; MHLW, Ministry of Health, Labour and Welfare; mRS, Modified Rankin Scale; SAMURAI, Stroke Acute Management with Urgent Risk-factor Assessment and Improvement; SBP, Systolic blood pressure.

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