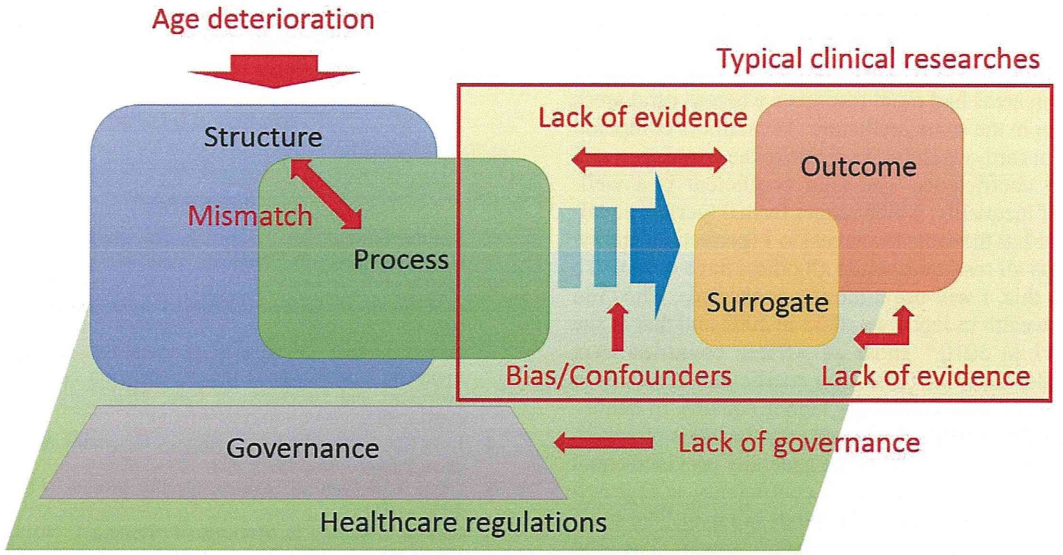

Figure 2. Components of quality of care and their obstacles.

should be considered.

It is not necessarily the case that similar patients received the same care. Some of the reasons are differences in the diseases themselves or patient preferences, but one significant reason is variation, which we term "quality of care".[3] Typically, quality of care is determined and measured by (1) structure, (2) process, and (3) outcome.[3] To clarify the issues in quality of care, I have differentiated surrogates from outcomes, and imputed governance and healthcare regulations (**Figure 2**). The definitions of quality of care and its components are difficult to determine, and several definitions have been reported, but one definition of quality care is "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge".[4] Structure is defined as "the facilities, equipment, services, and manpower available for care and the credentials and qualifications of the health care professionals involved".[5] How is structure determined? Governance and healthcare regulations typically determine the components of structure, such as people and equipment invested. Process is defined as "content of care", in other words, "how the patient is moved into, through, and out of the health care system and the services that are provided during the care episode".[5] Outcomes vary widely from biological changes in disease to physical function or satisfaction of family members, but we should be aware that some of the commonly utilized outcome measures are surrogates, such as the naming of physical conditions or change in blood components (vs. avoidance of cardiovascular events).

Many clinical researchers have tried to provide evidence for the associations between process and outcomes. Relationships between the use of drugs or devices and difference in incidences of diseases are typical examples. For instance, we have explored the association of the unrestricted use of drug-eluting stents (DES) and major cardiovascular events in patients with acute coronary syndrome (ACS).[6] In that study, the process was the unrestricted use of DES in patients with ACS and the outcomes were all-cause death, myocardial infarction, definite stent thrombosis, stroke, any coronary revascularization, and major bleeding. It has been claimed that the unrestricted use of DES for patients with ACS is safe. Thus, can we say that the quality of care of patients with ACS should improve if we used DES rather than other treatment modalities? This phrase may or may not be true. There are many alternative explanations for particular observations, and no one can know the absolute truth. No observation is free from bias and confounders, even in well-conducted randomized controlled trials. There are also many issues with the lack of evidence for associations between process and outcomes, as well as with associations between frequently used surrogates and patient-oriented outcomes (**Figure 2**). We have to recognize the many limitations inherent to any clinical research. Thus, in the future, we should conduct more solid clinical research to confirm previous observed findings and explore new associations to improve the quality of care.

Expanding the scope from the typical clinical research (red-bordered square in **Figure 2**), we should be aware of other important components in the quality of care, namely structure and its determinants (governance and healthcare regulations). If the findings that suggest the unrestricted use of DES improved the long-term outcomes in patients with ACS are true, does the quality of care for such patients improve? The answer is no. If DES use were not approved for ACS patients? If the charge was not reimbursed by the insurance? If the ACS patient was not diagnosed correctly? If such patients cannot meet capable interventional cardiologists within the appropriate time? If radiology technicians are not available when such patients arrived? If, if, if... We are now aware of the importance of structure, governance, and healthcare systems to achieve state-of-the-art medical excellence in real-world medicine.

In this issue of the Journal, Tomoike and colleagues[7] provide an excellent view on the geographical distribution of medical resources in cardiovascular medicine as part of a Japanese Circulation Society project. Readers should keep in

mind that this report was based on a limited number of hospitals that responded to the survey, which the authors note as a limitation. However, the authors did their best to compare their data with the national census. It is also vital to keep in mind that urban areas had more resources whereas rural areas had fewer even in the same prefecture. The authors compared the resources in cardiovascular medicine to the population and obtained Gini coefficients. The Gini coefficient is a well-known scale of inequality, which ranges from 0 (perfect equality, ie, everyone has the same resources) to 1 (perfect inequality, ie, only one has all resources while all others have none).[8] To better explain this, I will use a monetary example. The Gini coefficient of wealth in Japan was 0.32 in 2008 and that of the USA was 0.41 in 2010.[9] Those of African countries were generally greater than 0.5.[9] The Gini coefficient of wealth in Finland, a country well known for higher equality in healthcare, was still 0.28 in 2010. Compared with the index of wealth distribution, cardiovascular medicine generally provided equal practice, by comparison of the Gini coefficients, at approximately 0.15 among the surveyed hospitals in Japan. The study also sheds light on an area that needs improvement. The Gini coefficients of pediatric care were greater than 0.25.

These data represent one aspect of the structure of cardiovascular medicine in Japan. To improve the structure, good governance and good healthcare regulations are needed. As shown in the article, the equality of healthcare is generally good in Japan, but we still need the support of healthcare regulations. The breakdown of structure occurs if governance is poor or if age deterioration is allowed to occur. We frequently encounter a mismatch between structure and process in many aspects of reality. This article does not demonstrate the association between structure and process or outcomes. Therefore, well-designed clinical research studies to confirm the relationship between structure and true outcomes are strongly needed.

Conflict of Interest

Nothing to declare.

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Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of stroke recurrence and longitudinal progression of white matter lesions and silent brain infarcts on MRI (CEREBRAL study): rationale, design, and methodology

Shigeru Yamano[1,2], Manabu Horii[1,3], Takeshi Takami[4], Mio Sakuma[5], Takeshi Morimoto[5], Sadanori Okada[1], Toshiaki Taoka[6], Kimihiko Kichikawa[6], Hiroyuki Sasamura[7], Hiroshi Itoh[7], Yoshiko Furuya[8], Satoshi Ueno[8], Tomoaki Imamura[9], Seigo Sugiyama[10], Hisao Ogawa[10], and Yoshihiko Saito[1,11]*

Correspondence: Yoshihiko Saito*, First Department of Internal Medicine, Nara Medical University, 840 Shijyo-cho, Kashihara, Nara 634-8522, Japan.
E-mail: yssaito@naramed-u.ac.jp
[1]First Department of Internal Medicine, Nara Medical University, Kashihara, Japan
[2]Department of Internal Medicine, Nara Prefectural General Rehabilitation Center, Shiki, Japan
[3]Department of Internal Medicine, Nara City Hospital, Nara, Japan
[4]Department of Internal Medicine, Clinic Jingumae, Kashihara, Japan
[5]Center for General Internal Medicine and Emergency Care, Kinki University, Sayama, Japan
[6]Department of Radiology, Nara Medical University, Kashihara, Japan
[7]Department of Internal Medicine, Graduate School of Medical Sciences, Keio University, Tokyo, Japan
[8]Department of Neurology, Nara Medical University, Kashihara, Japan
[9]Department of Public Health, Health Management and Policy, Nara Medical University, Kashihara,Japan
[10]Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
[11]Department of Regulatory Medicine for Blood Pressure, Nara Medical University, Kashihara, Japan

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Objectives **Patients with a history of ischemic stroke are known to develop new ischemic stroke. While asymptomatic, the presence and progression of silent brain infarcts and white matter lesions on magnetic resonance imaging are associated with an increased risk of future strokes. Both angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are recommended for the primary and secondary prevention of stroke, but there are no direct comparisons of angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers regarding their cerebroprotective effects, including their effect on asymptomatic cerebral lesions detected by magnetic resonance imaging.**

Methods **Elderly (65 years or older) patients with essential hypertension who underwent cerebral magnetic resonance imaging and were found to have any cerebral ischemic lesions, such as cerebral infarction, silent brain infarct, or white matter lesion, were enrolled in this CEREBRAL study. Patients who agreed to participate were enrolled in the randomized controlled trial portion. Patients who did not agree to participate in the randomized controlled trial were enrolled in the cohort study portion. After two-years of angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers treatment, follow-up magnetic resonance imaging examination will be performed. The primary end-point is the composite of (1) occurrence of a fatal or nonfatal cerebrovascular event or (2) progression of cerebrovascular lesions as evaluated by magnetic resonance imaging, including white matter lesions or silent brain infarcts. After enrollment, cognitive function was evaluated, if possible, using the Mini-Mental State Examination.**

Conclusions **Our study will clarify whether angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are more effective for preventing primary and recurrence of ischemic stroke, including the progression of asymptomatic cerebral lesions on magnetic resonance imaging, in elderly hypertensive patients.**

Key words: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, asymptomatic cerebral lesion, hypertension, magnetic resonance imaging, stroke recurrence

Introduction and rationale

Hypertension has a highly specific and close relationship with stroke. As average blood pressure levels increase, so do morbidity and mortality rates due to stroke. In Japan, the morbidity and mortality rates due to stroke are higher than those of ischemic heart disease or myocardial infarction (1). According to clinical studies conducted abroad, the relative risk of stroke decreases by 30–40% with a 10–20 mmHg reduction in systolic blood pressure and a 5–10 mmHg reduction in diastolic blood pressure (2).

Patients with a history of cerebrovascular disease are known to develop new cerebrovascular lesions, and the control of hypertension, which is its greatest risk factor, is extremely important for the treatment of patients with chronic cerebrovascular disease.

Antihypertensive drug therapy significantly reduces the recurrence of all types of cerebrovascular disease, as well as nonfatal cerebral infarction (3). Calcium (Ca) channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and diuretics are recommended in patients with chronic cerebrovascular diseases (3). ACEIs lower levels of angiotensin II (AII), elevate levels of bradykinin, and reduce cardiovascular disease risk in high-risk individuals, resulting in effective prevention of myocardial infarction, stroke, heart failure, and nephropathy, as well as improvements in survival rate (4). In the Perindopril Protection Against Recurrent Stroke Study (5), the combination of an ACEI and a diuretic seemed to reduce the recurrence rate of cerebrovascular disease compared with placebo. However, ACEIs do not completely block the renin-angiotensin system because AII is also produced via non-ACE-mediated pathways. ARBs are well tolerated and effective blood pressure-lowering agents, and have many of the benefits of ACEIs, with fewer side effects (6). In the Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention study (MOSES) (7), a significantly lower percentage of patients in the ARB group reached the primary end-points (all death, all cardiovascular and cerebrovascular events) and, among secondary end-points, cerebrovascular events at a similar reduction in blood pressure as patients in the Ca channel blocker group. Thus, both ACEIs and ARBs are essential to blood pressure management, because they could have cerebroprotective effects beyond blood pressure lowering (5,7). However, a head-to-head comparison of the cerebroprotective effects of ACEIs versus ARBs has not been performed.

At least two subtypes of angiotensin receptors have been defined on the basis of their different pharmacological and biochemical properties and have been designated as type 1 (AT1) and type 2 (AT2) receptors (8). Blockade of the AT1 receptor by ARBs may also reduce the deleterious effects of AII, along with a reflex increase in AII levels and activation of AT2. The latter may lead to important antigrowth and antitissue proliferation effects (9). In the brain, AT2 receptors are expressed not only in the vascular wall but also in the thalamus, hypothalamus, and specific brainstem nuclei (10). When the AT1 receptor is blocked by an ARB, unbound AII acts preferentially on the AT2 receptor. Iwai *et al.* (11) reported that the ischemic area induced by middle cerebral artery occlusion was significantly larger in AT2 receptor-deficient mice than wild-type mice. This result suggests that AT2 receptor stimulation has a protective effect on ischemic brain lesions.

On the basis of large clinical trials and experimental data, we hypothesized that the cerebroprotective effects of ARBs may be greater than those of ACEIs in the secondary prevention of stroke. Furthermore, in the asymptomatic phase, silent brain infarctions (SBIs) and white matter lesions (WMLs) are frequently observed on cerebral magnetic resonance imaging (MRI) of elderly hypertensive patients (12).They are considered to be the main MRI findings of cerebral small-vessel disease, and are frequently observed in the elderly (13). Their presence and progression are independent risk factors for cerebrovascular disease and impairment of cognitive function (12). Antihypertensive treatments for hypertensive patients with asymptomatic cerebrovascular disease are as useful as during the chronic phase of ischemic stroke. To our knowledge, a direct comparison of ACEIs versus ARBs has not been designed with regard to pressure-independent cerebroprotective effects. As asymptomatic MRI findings are more sensitive in detecting ischemic brain changes than clinical symptoms and often occur prior to clinical symptoms, they are suitable for comparing the cerebroprotective effects of ACEIs and ARBs. Therefore, we sought to longitudinally evaluate whether ARBs are superior to ACEIs as a class in preventing the recurrence of ischemic stroke, including the progression of asymptomatic cerebral lesions on MRI.

Furthermore, cognitive function was evaluated, if possible, by the Mini-Mental State Examination (MMSE) (14) in our CEREBRAL study. The large-scale ONTARGET/TRANSCEND studies (15) evaluated single versus dual angiotensin receptor blockade (ACEI and/or ARB) and have already showed no differences in MMSE end-points over nearly five-years of follow-up. The CEREBRAL study will be underpowered in comparison with ONTARGET/TRANSCEND studies. But it would be possible that our study would report the relationship between progressions of WMLs or SBIs on MRI and a decline in MMSE score, which is few reported (16), in addition to the effects of long-term blood pressure lowering treatment with ACEI and ARB on cognitive function in elderly hypertensive patients.

Participants and methods

Study design and participants

The CEREBRAL study consists of a randomized open-label controlled trial with blinded end-point assessment (RCT) and a prospective cohort study (Cohort study). Patient enrollment began in October 2004 and concluded in January 2011. Follow-up will continue until 2013. Study centers include Nara Medical University, Kumamoto University, Keio University, and their associated hospitals.

RCT

Patients who satisfied all inclusion criteria (Table 1) were enrolled in the RCT after written informed consent was obtained. Patients stopped taking all antihypertensive drugs, including ACEIs or ARBs, prescribed before enrollment, and were then randomly allocated to receive either an ACEI or ARB. We used a list of random numbers to assign patients to receive ACEI or ARB. We used minimization method to adjust for baseline characteristics. Physicians in charge administered the allocated drug immediately after randomization without a placebo run-in period, and patients will continue taking the allocated drug for two-years when end-points will be evaluated by MRI, or when certain end-points occur, including primary or secondary end-points, adverse drug events, or discontinued participation in the study. Patients who met any of the exclusion criteria (Table 2) or who declined to participate were not enrolled. Physicians in charge were asked to manage clinic blood pressure with a target of less than 140/90

Table 1 Inclusion criteria

- Patients who voluntarily give written informed consent
- Patients who are 65 years or older at entry
- Patients with essential hypertension as defined by either of the following criteria: (1) a systolic pressure of at least 140 mmHg, a diastolic pressure of at least 90 mmHg during clinic blood pressure measurements, or both; and (2) patients who are currently receiving antihypertensive treatment regardless of blood pressure control
- Patients with previous cerebrovascular events, asymptomatic cerebrovascular lesions as evaluated by MRI examined within six-months prior to enrollment, or both

MRI, magnetic resonance imaging.

Table 2 Exclusion criteria

- Patients with atrial fibrillation on electrocardiography or a past history of atrial fibrillation
- Patients with any of the following conditions: cancer, cerebral hemorrhage, subarachnoid hemorrhage, chronic renal failure, congestive heart failure, bilateral renal artery stenosis, unilateral kidney, hyperkalemia, secondary or malignant hypertension
- Patients with any allergies to either ARBs or ACEIs
- Patients who are ineligible in the opinion of the investigators

ARB, angiotensin II receptor antagonist; ACEI, angiotensin-converting enzyme inhibitor.

mmHg according to the guidelines established by the Japanese Society of Hypertension (17). Clinic blood pressure readings were taken by a physician after 5–10 min rest at the sitting position by using an appropriately sized arm cuff and mercury sphygmomanometer. Clinic blood pressure was determined by multiple measurements on one visit, and two values within 5 mmHg were averaged. Participants were seen on at least six occasions per one-year. If the blood pressure was not controlled with the allocated drug within this range (less than 140/90 mmHg), physicians in charge could increase the dosage of the allocated drug or administer additional antihypertensive drugs to control blood pressure, although the simultaneous use of ACEI and ARB was prohibited.

Cohort study

Patients who gave informed consent that showed that they took part in not RCT but prospective cohort study were enrolled in the Cohort study. They also met the inclusion and exclusion criteria. Patients who were taking ACEI or ARB at entry continued taking the same medication. Patients not already on an ACEI or ARB were given ACEI or ARB according to physician discretion (Fig. 1).

Primary outcome variables

The primary end-point is the composite of (1) fatal or nonfatal cerebrovascular event and (2) progression of cerebrovascular lesions including WMLs or SBIs as evaluated by MRI.

MRI is performed at baseline and at year 2 using the same protocol, with a 1·5T clinical MR unit with an 8-channel phased array coil. All examinations include axial sections of conventional spin-echo T1-weighted (TR = 560 ms, TE = 12 ms), spin-echo T2-weighted (TR = 4000 ms, TE = 94 ms), and fluid attenuated inversion recovery (FLAIR: TR = 10000 ms, TI = 2600 ms, TE = 110 ms) sequences. Slices were oriented in the axial plane perpendicular to the posterior margin of the pons with a slice thickness of 5 mm and a 2-mm gap. Images were obtained using

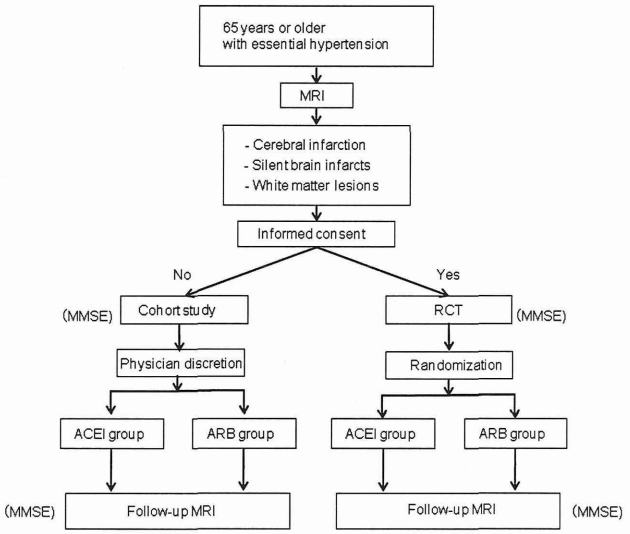

Fig. 1 Study design of the CEREBRAL study. MRI, magnetic resonance imaging; RCT, randomized controlled trial; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; MMSE, Mini-Mental State Examination.

a 256 × 256 matrix and a 230-mm field of view. Central independent raters evaluated all MRI images without knowledge of the clinical status of each patient.

WMLs were classified into white matter hyperintensities (WMH) in the subcortical area and periventricular hyperintensities (PVH). WMH severity was rated visually on the axial FLAIR images using the Fazekas scale (18) (absent, grade 0; punctate, grade 1; early-confluent, grade 2; confluent, grade 3) and the Scheltens rating scale (19)(range 0 to 30), in which scores of 0 to 6 can be given in four subcortical white matter. PVH severity was rated as 0 to 3 using the Fazekas scale and 0 to 2 for three periventricular regions using the Scheltens rating scale. Ratings of basal ganglia and infratentorial hyperintensities were not included in this study.

A SBI was defined exclusively as a low-signal-intensity area ≥3 mm in size (but all were <15 mm in size) on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images (20). Enlargement of periventricular spaces (Virchow-Robin spaces) was defined as a lesion with a maximum diameter of <3 mm which was seen as a spotty high spinal intensity on T2-weighted images (20). SBIs were scored in five brain lesions (frontal, parietooccipital, temporal, basal ganglia, and infratentorial). At follow-up, visual rating of WMH progression and new lacunae was performed in side-by-side fashion with blinding of the patient's clinical information. WMH and PVH progression were rated on FLAIR images according to the Rotterdam Progression Scale (21)(range −7 to 7) that denotes decrease, no change, or increase (−1, 0, or 1, respectively) in WMHs in four subcortical regions and in PVHs in three periventricular regions. Primary and secondary clinical outcomes are assessed by central independent raters.

Secondary outcome variables

Secondary outcome valuables include: (1) fatal or nonfatal acute coronary syndrome; (2) hospitalization due to congestive heart failure; and (3) death from any cause. Primary and secondary outcome variables reported will be reviewed and settled by the independent steering committee that consists of outside members.

Measurements

Baseline clinical factors were recorded at the time of enrollment. These include age, sex, height, body weight, duration of hypertension, current medications, and risk factors (smoking, dyslipidemia, alcohol consumption, and diabetes mellitus). Past medical conditions of the participants recorded include stroke, myocardial infarction, angina pectoris, congestive heart failure, dyslipidemia, hyperuricemia, diabetes mellitus, and large or peripheral artery disease. Duration of hypertension was based mainly on information from self-reports and medical records. Family history of hypertension was also recorded. General clinical laboratory tests included urinalysis (to evaluate for proteinuria), blood chemistry tests (creatinine, total cholesterol, triglycerides, high- density lipoprotein, low-density lipoprotein, uric acid, plasma glucose).

After enrollment, cognitive function was evaluated, if possible, by the MMSE (14), which is widely used as a screening tool for the assessment of cognitive function. Cognitive impairment and cognitive decline were evaluated (15). Cognitive impairment was defined by investigator-reported diagnosis of dementia or significant cognitive dysfunction, or a score of ≤23 on the MMSE during follow-up in patients without dementia or cognitive impairment at baseline. Cognitive decline was defined as a decrease of ≥3 points on the MMSE from baseline during follow-up (15).

Safety monitoring

Safety is evaluated by regular examinations and laboratory tests after enrollment until the end of the study. The safety committee consists of outside members to evaluate adverse drug events and to review effectiveness and safety of our data.

Sample size calculation

As a direct comparison of ARB with ACEI in terms of reducing WMLs and SBIs has not been previously reported, we assumed that the incidence of the primary end-point would be 58·6% based on the following data: (1) the progression rate of WMLs or SBI was 30% per year in 80 patients who have undergone MRI scanning at a two-year interval in our hospital; (2) the incidence of clinical stroke onset in Japanese subjects with WMLs or SBIs was 8·6 % per two-years (22); and (3) the incidence of stroke recurrence was 20% per two-years in the Japanese general population (23). We assumed that the ARB group would achieve a 15% reduction of risk compared with the ACEI group, giving our study 80% statistical power and an alpha error of less than 5%. The required sample size was 173 in each group for a total of 346.

Patients who did not agree to participate in the RCT were enrolled in prospective Cohort study. We will compare the results of RCT with those of cohort study.

Data management and statistical analysis

Study statisticians (M. S., T. M.) with full access to the data will conduct all statistical analyses, independent of the principal investigators and collaborators. Efficacy comparisons will be performed on the basis of time to end-point according to the intention-to-treat principle. Cumulative incidences of primary and secondary end-points will be estimated by the Kaplan–Meier method and differences between groups will be assessed with the log-rank test. We will also assess the number of adverse events and perform chi-square tests to determine the safety profile. A two-sided P level of less than0·05 will be considered to indicate statistical significance. All statistical analyses will be performed using JMP 9.0 (SAS Institute Inc., Cary, NC, USA) and STATA version 10 software (StataCorpLP, College Station, TX, USA).

Ethical considerations and resister

We used good clinical practice guidelines in accordance with the Declaration of Helsinki. Institutional review boards at every participating hospital approved the protocol and subsequent amendments. We carefully explained the trial objectives and study design, and the risks and benefits of participation to all patients and obtained informed consent. This study has been registered at ClinicalTrials.gov (NCT00126516).

Conclusions

We believe that our study will provide useful information on whether an ACEI or ARB is more effective for the secondary and tertiary prevention of ischemic stroke, including the progression of SBIs or cerebral WMLs on MRI, in elderly hypertensive patients.

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