A multi-center clinical trial comparing two strategies for control of blood pressure:

Recurrent stroke prevention clinical outcome study

(The RESPECT Study)

STUDY PROTOCOL

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87 Abbreviations

Abbreviation	Expansion
α	Alpha spending function
ACE I	Angiotensin converting enzyme inhibitor
AE	Adverse events
AF	Atrial fibrillation
ALT(GPT)	Alanine transaminase (glutamate pyruvate transaminase)
ARB	Angiotensin II receptor blockers
ARB/HCTZ	combination with ARB and hydrochlorothiazide (HCTZ)
AST(GOT)	Asparagine transferase (glutamate oxaloacetate transaminase)
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CCB	Calcium channel blocker
CH	Cerebral hemorrhage
CHF	Congestive heart failure
CI	Cerebral infarction
CKD	Chronic kidney disease
Cl	Chlorine
Cr	Creatinine
CT	Computed tomography

DBP	Diastolic blood pressure
Diu	Diuretics
DM	Diabetes mellitus
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
HbA1c	Glycosylated hemoglobin A1c
HCTZ	Hydrochlorothiazide
HD	High dose
HDL-C	High-density lipoprotein cholesterol
HR	Heart rate
hsCRP	High sensitivity C-reactive protein
IMT	Intima media thickness
ITT	Intention to treat
K	Potassium
LD	Low dose
LDL-C	Light-density lipoprotein cholesterol
MHLW	the Ministry of Health, labor and Welfare in Japan
MI	Myocardial infarction
MMSE	Mini-mental state examination (A type of investigation of cognitive function)
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale

Na	Sodium
NINDS	National Institute of Neurological Disorders and Stroke
NYHA Classification	New York Heart Association Classification of Heart Failure
QOL	Quality of life
SBP	Systolic blood pressure
SMI	Silent myocardial ischemia
TC	Total cholesterol
TG	Triglyceride
TIA	Transit Ischaemic Attack
TOAST	The trial of Org 10172 in Acute Stroke Treatment
UA	Uric acid

1. PROTOCOL SYNOPSIS

1.1 TITLE

Recurrent Stroke Prevention Clinical Outcome Study (RESPECT Study)

1.2 OBJECTIVE

This study evaluates whether intensive BP management is useful for the prevention of recurrent stroke.

1.3 SUMMARY OF RATIONALE

At one time, stroke was the most common cause of death in the Japanese population: however mortality has gradually decreased with lifestyle changes and treatment development. Currently, stroke is the third most common cause of death, following cancer and myocardial infarction[1)]. The mortality rate of stroke among Japanese declined due to the nationwide spread of anti-hypertensive treatment, and its decreased incidence of stroke. Large-scale epidemiological and clinical studies in Japan and overseas demonstrated that one of the major risk factors for stroke is hypertension. In addition to prevent a stroke, active hypertensive treatment is extremely important in clinical practice.

The incidence of stroke is currently increasing, as the Japanese society is rapidly aging. The nationwide survey by the Ministry of Health, Labor and Welfare in Japan (MHLW) shows that the number of patients admitted to hospitals for stroke was 172/100,000 in 1999, but increased to 178/100,000 in 2002 and to 183/100,000 in 2005[2)]. Considering that the disability from strokes extensively affects the patients' quality of life, and the current health care cost burdens the country, it is important to establish the best preventive treatment for stroke.

The major risk factors for stroke include hypertension, atherosclerosis, cardiovascular events, and smoking. Patients with stroke most frequently have hypertension. In the ACCORD BP trial, the benefit of intensive blood pressure-lowering on stroke prevention in diabetic patients was observed. In a one-year treatment of intensive blood pressure-lowering therapy with the target level of systolic blood pressure (SBP) less than 120 mm Hg, the risk of stroke decreased by up to 47% compared with the standard therapy [3)].

This RESPECT study aimed to evaluate the usefulness of intensive blood pressure (BP)-lowering management in secondary stroke prevention. Study participants will be assigned to the intensive BP control group with a BP target of less than 120/80 mmHg,

and the standard BP control group having a BP target of less than 140/90 mmHg or less than 130/80 mmHg for current diabetes mellitus (DM), chronic kidney disease (CKD), or old myocardial infarction (MI). Both groups are treated with a stepwise multi-drug therapy using an angiotensin-receptor antagonist, diuretic, calcium channel blocker and aldosterone antagonist which have been commonly used in clinical practice in Japan.

1.4 SUMMARY OF STUDY DESIGN (Figure 1)

This trial is a multicenter, prospective, randomised, open-labeled, blinded-endpoint, parallel-group comparison study. The study duration consists of a screening period, a titration period, and a follow-up period. The screening period occurs between written informed consent and authorization of eligibility. Patients who meet all the eligibility criteria will be randomly assigned to two groups; the intensive BP control group or the standard BP control group. The intensive BP control group receives stepwise multi-drug therapy with a BP target of less than 120/80 mmHg, and the standard therapy group receives the same stepwise therapy with a BP target of less than 140/90 mmHg or less than 130/80 mmHg for patients who have current DM, CKD, and/or old MI. The titration period will be 24 weeks at maximum depending on the length required to determine the treatment that produces the target BP for the patient. Once the treatment is established, it will be continued during the follow-up period or until 244 patients experience a recurrent stroke. The expected follow-up period is approximately 3.5 years.

1.5 SAMPLE AND SAMPLE SIZE

Male and female hypertensive patients with a history of stroke, aged 50-85 years old at the time of consent, and those who meet all the other entry criteria will be eligible to enroll.

As an event-driven study, the study will be continued until a total of 244 patients experience their first recurrent stroke. To ensure 244 patients meet this requirement in 3.5 years, approximately, 2,000 patients will be randomised.

An interim analysis will be performed when 50% of the planned stroke events (i.e. 122 events) are observed or at 5 years from the start of the study (i.e. 2015), and the second interim analysis will be performed when 80% of the planned stroke events (i.e. 200 events) are observed.

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN (See Figure1)

The study uses losartan potassium or other Angiotensin II receptor blocker (ARB) tablet, and combination drugs of losartan potassium or other ARB tablets and hydrochlorothiazide (HCTZ), amlodipine besilate tablets and spironolactone tablets to control BP. Any antihypertensive agents can be used for stepwise treatments during the study duration to control BP.

To find a treatment that can achieve the intended BP target, patients will receive stepwise treatments orally every 4 weeks for 24 weeks at maximum during the titration period as follows:

Step 1: Losartan 50 mg or other ARB

Step2: Combination drug containing losartan 50 mg or other ARB and HCTZ 12.5 mg (combination with ARB and HCTZ)

Step 3: combination with ARB and HCTZ + amlodipine besilate 5 mg (Amlodipine LD)

Step 4: ARB alone + combination with ARB and HCTZ + Amlodipine LD

Step 5: ARB alone + combination with ARB and HCTZ + amlodipine besilate 10 mg (Amlodipine HD)

Step 6: ARB alone + combination with ARB and HCTZ + Amlodipine HD + spironolactone 25 mg

1.7 STUDY DURATION

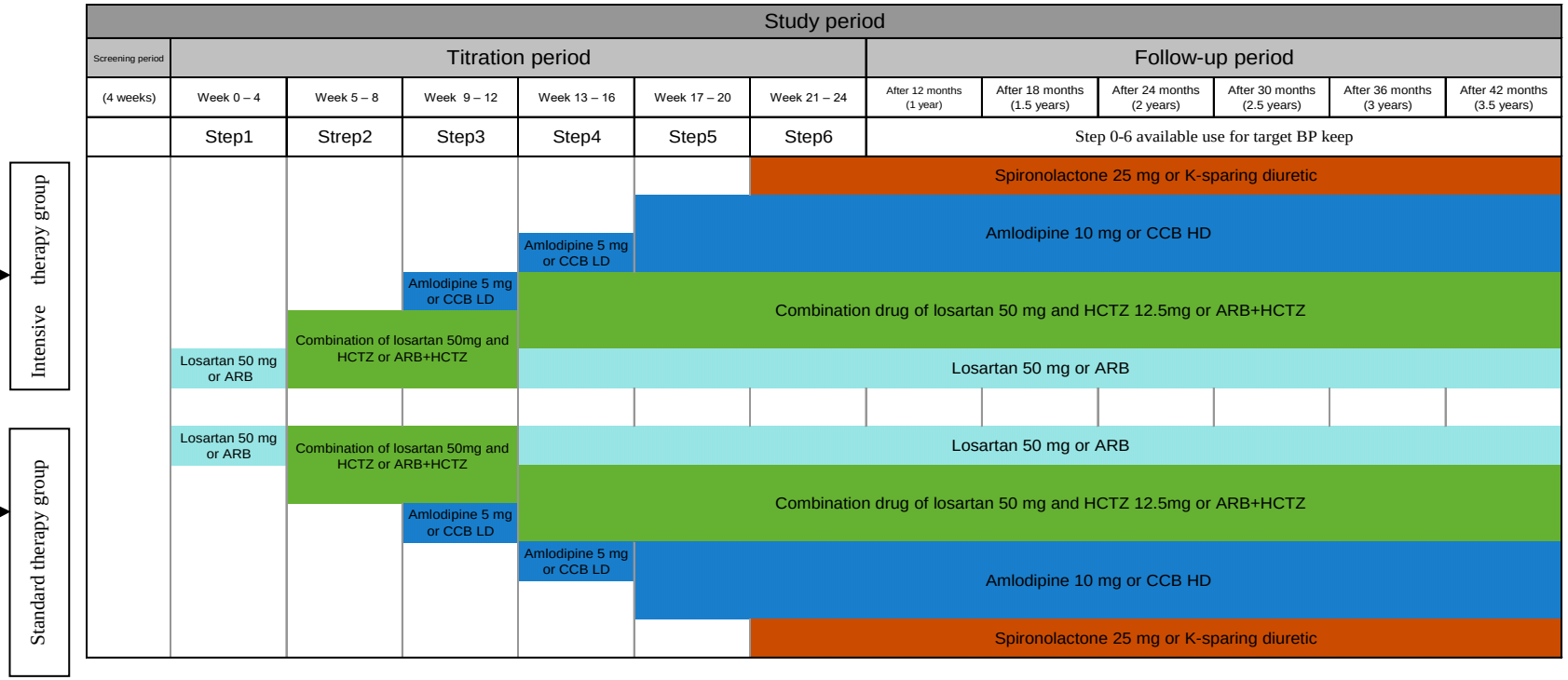
Study duration (Including Data analysis): September 2010 - December 2018

Enrollment: until December 2015.

Figure 1　Schedule of stepwise multi-drug regimen

Patients with history of stroke (cerebral infarction or cerebral hemorrhage) (onset of stroke between 30 days and 3 years)

Informed consent obtained and eligible patients selected.



1) Intensive BP control group: Target BP is less than120/80 mmHg
2) Standard BP control group: Target BP is less than than140/90 mmHg or less than130/80 mmHg with DM, CKD, old MI
3) Patients who have not been treated for hypertension at enrollment will start the multidrug therapy from Step 1.
4) Patients who have been taking one antihypertensive agent at enrollment will discontinue the drug and start from the Step 1.
5) Patients who have been taking two antihypertensive agents at enrollment will discontinue the drugs and start from the Step 2.
6) Because this study will be conducted to investigate recommended therapy regimens, the above schedule must be followed as closely as possible

220

Table 1 Monitoring Schedule and Timing

	Study period														
	Screening period	Titration period						Follow-up period						At onset of event	At discontinuation
	(4 weeks)	Weeks 0 - 4	Weeks 5 - 8	Weeks 9 - 12	Weeks 13 - 16	Weeks 17 - 20	Weeks 21 - 24	After 12 months (1 year)	After 18 months (1.5 years)	After 24 months (2 years)	After 30 months (2.5 years)	After 36 months (3 years)	After 42 months (3.5 years)		
		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 0-6 available use for target BP keep							
Informed consent	○														
Patient background	○														
Randomisation	○														
BP&PR (sitting)	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Laboratory tests	○						○	○	○	○	○	○	○	○	○
ECG	○													○	○
Pregnancy test	○														○
Height	○														
Weight	○							○	○	○	○	○	○		
Use of antihypertensive agents	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Event survey		○	○	○	○	○	○	○	○	○	○	○	○	○	○
Use of concomitant drugs	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Subjective symptoms & objective findings	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○

∗Laboratory values, 12-lead ECG, and status of use of concomitant drugs should be transcribed from medical records.

2 PROTCOL DETAIL

2.1 Title

Recurrent Stroke Prevention Clinical Outcome Study (RESPECT Study)

2.2 Rationale for Study

Strokes were once the most common cause of death in Japan; although currently the mortality has gradually decreased with changes in lifestyle and treatment advances. Currently, strokes are the third most common cause of death following cancer and myocardial infarction[1)].

One major reason for this decline in the mortality rate involves a decrease in the incidence of stroke due to the spread of anti-hypertensive treatment. Large-scale epidemiological and clinical studies conducted in Japan and overseas have suggested that hypertension is the major risk factor for stroke and active antihypertensive therapy is extremely important for the prevention of stroke from the perspective of daily clinical practice.

Currently, the incidence of stroke has rapidly increased as the aging population increases in the society. According to nationwide surveys by MHLW in Japan, the number of patients admitted to the hospital for stroke was 172/100,000 patients in 1999, but increased to 178/100,000 patients in 2002, and to 183/100,000 patients in 2005[2)]. Since disabilities from stroke markedly decrease patients' QOL and burdens health care cost, establishment of the best preventive measures is crucial.

In a large-scale overseas clinical study on the prevention of recurrent stroke (PROGRESS Study), the combination of perindopril and diuretic reduced BP by 9/4 mmHg compared with a placebo, and the recurrence rate of stroke decreased by 28%. Thus, the combination of an angiotensin converting enzyme inhibitor (ACE I) and diuretic for anti-hypertensive treatment was recommended for secondary stroke prevention[3)].

However, the target blood pressure remains unclear for secondary stroke prevention. Post-hoc analysis of the PROGRESS trial suggested that stroke recurrence was the lowest in patients who achieved a blood pressure of less than 120 mmHg. On the other hands, there are still controversies about on the J-curve phenomenon (a possible increase in the recurrence rate with excessive BP reduction) [4) 5) 6)]. Therefore, it remains unclear whether intensive blood pressure-lowering is more effective for secondary stroke prevention than standard BP-lowering treatment.

Therefore, this study will evaluate the usefulness of intensive antihypertensive therapy

in the prevention of recurrent stroke in hypertensive patients with a history of stroke by assigning patients into two treatment groups: an intensive BP therapy group (BP target: ≤120/80 mmHg) or standard BP therapy group (≤140/90 mmHg; ≤130/80 mmHg in the presence of current DM/CKD/old MI). Our hypothesis was that intensive BP management by a stepwise multi-drug therapy using an angiotensin-receptor antagonist, diuretic, calcium channel blocker and aldosterone antagonist is more effective for the secondary prevention of stroke than standard BP treatment.

2.3 Study objective

This study evaluates whether intensive BP management is useful for the prevention of recurrent stroke. Hypertensive patients with a history of stroke are treated with stepwise multi-drug therapy to achieve a target BP of less than 120/80 mmHg in the intensive BP control group and a target BP of less than 140/90 mmHg or less than 130/80 mmHg for patients with current DM/CKD/old MI in the standard BP control group. The participants receiving antihypertensive drug(s) treatment to achieve their respective BP target will be followed for recurrence of stroke. The study continues until the number of patients with the first recurrent stroke reaches a total of 244 between the two groups.

The occurrence rates of recurrent stroke will be compared between the two groups.

2.4 Study Drugs (See Package Insert)

2.4.1 Angiotensin II receptor antagonist (ARB) (Package Insert: Losartan potassium[7])

Indications
1. Hypertension
2. Diabetic nephropathy in type 2 DM accompanied by hypertension and proteinuria

Adverse reactions [Common adverse reactions]

1) Headache 2) Dizziness 3) Vomiting/sickness 4) Hot flash

[Clinically significant adverse reactions]

1) Anaphylactoid symptoms, 2) Angioedema

3) Hepatitis acute or hepatitis fulminant, 4) Renal failure

5) Shock/syncope/loss of consciousness, 6) Rhabdomyolysis

7) Hyperkalaemia, 8) Arrhythmia

9) Pancytopenia/leukopenia/thrombocytopenia, 10) Hypoglycemia

2.4.2 ARB /antihypertensive diuretic agent

(Package Insert: Losartan potassium /hydrochlorothiazide[8])

Indications
1. Hypertension

Adverse reactions [Most common adverse reactions]

1) Dizziness 2) Pollakiuria 3) Headache

[Severe adverse reactions]

1) Anaphylactoid symptoms, 2) Angioedema

3) Hepatitis acute or hepatitis fulminant, 4) Renal failure acute

5) Shock, syncope, loss of consciousness, 6) Rhabdomyolysis

7) Hyperkalaemia, 8) Arrhythmia,

9) Pancytopenia, leukopenia, thrombocytopenia

10) Aplastic anaemia, haemolytic anaemia

11) Vasculitis necrotizing, 12) Interstitial pneumonia, pulmonary oedema

13) Exacerbation of systemic lupus erythematosus, 14) Hypoglycemia

15) Hyponatraemia

2.4.3 Calcium Channel Blocker (CCB) (Package Insert: Amlodipine besilate[9])

Indications
1. Hyperpiesia
2. Angina pectoris

Adverse reactions [Most common adverse reactions]

1) Hot flush (feeling hot/flushed face etc.) 2) Dizziness/wooziness
3) Headache/ heaviness of head, 4) Palpitations

[Clinically significant adverse reactions]

1) Hepatic function disorder, jaundice, 2) Thrombocytopenia/leukopenia
3) Atrioventricular block

2.4.4 K-sparing diuretic (Package Insert : Spironolactone[10])

Indications
1. Hypertension (essential, renal etc.)
2. Cardiac induced oedema(cardiac failure congestive)
3. Renal induced oedema
4. Hepatic induced oedema
5. Persistent oedema
6. Oedema and ascites accompanied by malignant tumor
7. Trophoedema
8. Diagnosis and improvement of primary hyperaldosteronism

Adverse reactions [Most common adverse reactions]

1) Gynaecomastia, breast swelling 2) Anorexia 3) Nausea/vomiting

[Clinically significant adverse reactions]

1) Electrolyte abnormality (hyperkalaemia, hyponatraemia, metabolic acidosis etc.), 2) Renal failure acute

2.5 Patient Inclusion and Exclusion criteria

2.5.1 Patient inclusion criteria

Participants include those with essential hypertension and a history of stroke* (cerebral infarction (CI) or cerebral hemorrhage (CH)) who satisfy the following criteria:

1. Aged 50-85 years on the day of consent
2. Sex
3. Outpatient
4. Onset of stroke occurred between 30 days and 3 years prior to the date of consent.

5. Drug adherence is ≥80% during the screening period.
6. Mean of 2 BP baseline measurements (measured at outpatient clinic) within 30 days prior to the date of consent is either 180＞SBP≧130 mmHg or 110＞DBP ≧80 mmHg under 0-3 medications of anti-hypertensive drugs. Stroke with severity 3 or less in the modified Rankin scale[11)]

* Definition of stroke: Sudden neurologic symptoms lasting more than 24 hours compatible with brain damage in an arterial territory (shown in CT or MRI). It includes an event that recovers from neurologic symptoms within 24 hours due to specific treatments such as recombinant tissue plasminogen activator.

2.5.2 Patient exclusion criteria

Patients who meet any one of the following criteria are excluded from the study.

1. Women who are pregnant, trying to become pregnant, or are breastfeeding
2. Secondary hypertension
3. Severe hypertension (grade III or greater) with baseline SBP more than 180 mmHg or DBP more than 110 mmHg)[12)]
4. Onset of myocardial infarction or undergoing angioplasty that occurred within 3 months prior to consent
5. Current or previous heart failure with NYHA classification class III or more, or EF ≤35%
6. Severe bilateral carotid stenosis or major cerebral artery occlusion
7. Severe paralysis due to stroke (modified Rankin scale more than 4)
8. Current renal dysfunction (serum creatinine more than 2·0 mg/dL within 1 year prior to consent)
9. Current hepatic dysfunction with AST (GOT) or ALT (GPT) value more than 100 IU/mL within 1 year prior to consent
10. Essential hypertension treated with four or more antihypertensive drugs
11. Hypersensitivity to angiotensin II receptor blockers, thiazide, sulfonamide derivative, dihydropyridine drugs or spironolactone.
12. Major surgery planned during the study period
13. Participants who participated in other clinical studies within the last 30 days
14. Current malignancy (previous malignancy within 5 years after the end of treatment) excluding skin squamous cell carcinoma
15. Current or previous subarachnoid hemorrhage
16. Definitive dementia (based on a clinical diagnosis**)

17. Patients who have difficulty in signing consent or who do not agree to the provided consent
18. Patients who are judged to be unsuitable for participating the study by the primary investigator or sub-investigator.

* Major surgery: laparotomy, thoracotomy, craniotomy and so on under general anesthesia, with respirator mounting or one-day or more hospitalization.

**Definition of Dementia: Screening is done using Mini-mental State Examination[13] (MMSE) (Cut-off less than 24). Diagnosis is determined by the Clinical Dementia Rating (CDR) [14] and Diagnostic criteria from DSM-IV[15].

2.6 Definitions of Stroke Types and Diagnostic Criteria Used in This Study

Diagnosis of stroke types will be made using the TOAST classification[16] (Table 1), and the diagnosis will be termed according to the NINDS classification[17].

1) Atherothrombotic brain infarction

Atherothrombotic brain infarction is a type of cerebral infarction caused by arteriosclerotic stenosis (>50%) or occlusion of a major brain artery or branch cortical artery.

The clinical symptoms of atherothrombotic brain infarction include cerebral cortical impairment (causing conditions such as aphasia, neglect, limited motor function) and brain stem or cerebellar dysfunction. The diagnostic criteria for atherothrombotic brain infarction are (1) presence of infarction(s) of >1.5 cm in the cerebral cortex, cerebellum, brain stem, or subcortical portion of the brain with MRI/CT scans, and (2) presence of a more than 50% stenosis of an intracranial or extracranial artery on ultrasonography or angiography. At the same time, potential sources of cardiogenic embolism should be excluded. Thus, atherothrombotic brain infarction should not be diagnosed if ultra-sonographic or angiographic findings are normal or show only slight abnormality. A history of intermittent claudication or transient ischaemic attacks (TIA) in the same vascular territory, carotid bruit, or disappearance of radial pulse supports the diagnosis of atherothrombotic brain infarction.

2) Cardiogenic embolism

This is a type of cerebral infarction caused by an embolus that occurs in the cardiac chamber. The diagnosis of cardiogenic embolism requires the demonstration of at least one cardiac source of embolus. Cardiac sources of embolus include: left atrial

thrombus, atrial fibrillation-flutter, old myocardial infarction, prosthetic valve, right-to-left cardiac shunt with a venous source of an embolus (Table 2). The clinical symptoms and MRI/CT findings of cardiac embolism are similar to those of atherothrombotic brain infarction; however, no stenotic lesion or occlusion is present in a carotid or major brain artery. Cerebral infarction with a cardiac source of embolism but no other cause of cerebral infarction is classified in this type. A history of TIA, stroke in multiple vascular territories or systemic embolism supports the diagnosis of cardiogenic embolism.

3) Lacunar infarction

This is a type of cerebral infarction associated with symptoms of classical lacunar syndrome (pure motor, pure sensory, sensorimotor, ataxic hemiparesis, or dysarthria-clumsy hand). No cerebral cortical symptoms should be present in patients with lacunar infarction. A diagnosis of lacunar infarction requires the presence of a brain stem or subcortical lesion of less than 1.5 cm. A potential cardiac source of embolism or a stenosis of >50% in ipsilateral extracranial arteries must be excluded. History of DM or hypertension supports the diagnosis of lacunar infarction.

4) Cerebral hemorrhage

A diagnosis of cerebral hemorrhage requires head MRI/CT findings of hematoma(s) or its scar in the cerebrum, cerebellum, or brain stem. The localization of the lesion(s) must be consistent with the patient's neurological symptoms. However, haemorrhagic infarction observed following embolic cerebral infarction is not included in this disease type.

5) Subarachnoid hemorrhage

A diagnosis of subarachnoid hemorrhage requires sudden onset of headache and head MRI/CT findings of hematoma in the subarachnoid space.

6) Stroke of other or undetermined etiology

a) Cerebral infarction of rare etiology

This disease type includes cerebral infarction caused by relatively rare diseases such as vertebral artery dissection, fibromuscular dysplasia, and moyamoya disease, or occurrence from catheterization or surgery.

b) Cerebral infarction of undetermined etiology

This disease type includes cerebral infarction that is explained by two or more causes, or that has no identifiable cause after extensive investigation or due to insufficient investigation.

c) Intracranial hemorrhage associated with cerebral arteriovenous malformation

7) Transient ischaemic attack (TIA)

This disease type is characterized by a sudden onset of focal neurological symptoms that are thought to be caused by a cerebrovascular impairment and disappears within 24 hours. This disease type should further be classified into internal carotid artery TIA or vertebral artery TIA according to the clinical symptoms (Table 3). Identification of responsible lesion(s) by MRI/CT scans is not necessary. Furthermore, TIA must not be diagnosed solely by the symptoms listed in Table 4.

Table 1. Features of TOAST classification of subtypes of ischaemic stroke

	AI	CE	LI	OT
Clinical				
Cortical or cerebellar dysfunction	+	+	–	+/–
Lacunar syndrome	–	–	+	+/–
Imaging				
Cortical, cerebellar, brain stem, or subcortical infarct $\geq$ 1.5 cm	+	+	–	+/–
Subcortical or brain stem infarct < 1.5 cm	–	–	+/–	+/–
Tests				
Stenosis of extracranial internal carotid artery	+	–	–	–
Cardiac source of emboli	–	+	–	–
Other abnormal findings on tests	–	–	–	+

AI: Large-artery athrosclerosis, CE: Cardioembolism, LI: Small-artery occlusion (lacune), OT: other cause

Table 2. TOAST classification of High- and Medium-Risk sources of cardioembolism

High-risk sources	Mechanical prosthetic valve, Mitral stenosis with atrial fibrillation, Atrial fibrillation (other than lone AF), Left atrial/atrial appendage thrombus, Sick sinus syndrome, Recent myocardial infarction (〈 4 weeks), Left ventricular thrombus, Dilated cardiomyopathy, Akinetic left ventricular segment, Atrial myxoma, and Infective endocarditis
Medium-risk sources	Mitral valve prolapse, Mitral annulus calcification, Mitral stenosis without atrial fibrillation, Left atrial turbulence (smoke), Atrial septal aneurysm, Patent foramen ovale, atrial flutter, lone AF, bioprosthetic valve, nonbacterial thrombotic endocarditis, congestive heart failure, partial reduction of left ventricular wall movement, myocardial infarction (within 6 months but no more recent than 4 weeks)

Table 3. Classification of TIAs (NINDS classification)

Internal carotid artery TIA	1. Motor dysfunction (weakness, paralysis, fine motor dysfunction of upper and lower extremities on either sides and the right and/or left side of the face, or dysarthria). 2. Total or partial loss of vision in one eye (amaurosis fugax) in patients with normal binocular vision. 3. Loss of unilateral visual fields (homonymous hemianopia). 4. Sensory disturbance (numbness and paresthesia in the right or left upper extremity, lower extremity, and/or face) 5. Aphasia (language disturbance)
Vertebral artery TIA	1. Motor dysfunction (weakness, paralysis, impaired fine motor skill) of any combination of upper and lower extremities and face. 2. Unilateral or bilateral sensory disturbance (loss of feeling, numbness or paresthesia). 3. Unilateral or bilateral loss of visual fields 4. Any combination of two or more of the following: ataxia, vertigo, balance disorder, diplopia, dysphagia, and dyslalia.

Table 4. Symptoms that are not characteristics of TIAs or not considered due to TIAs

Symptoms that are not characteristics of TIAs	
• Unconsciousness without vertebrobasilar artery symptoms	• Tonic and/or clonic seizure
• Prolonged march of symptoms over various sites of the body	• Scintillating scotoma
Symptoms that are not considered as TIAs	
• March of sensory disturbance	• Vertigo alone
• Dizziness alone	• Dysphagia alone
• Dysarthia alone	• Diplopia alone
• Urinary/fecal incontinence	• Visual impairment with an altered level of consciousness
• Focal neurological symptoms with migraine	• Confusion alone
• Amnesia alone	• Atonic seizure alone

2.7 Study procedure

2.7.1 Study design

This will be a multi-center, prospective, randomised, open-label, blinded-endpoint, parallel-group comparison trial. The study consists of a screening period, a titration period and a follow-up period.

Hypertensive patients with a history of stroke (CI and/or CH) are randomly assigned to either (1) the intensive therapy group having ⟨120/80 mmHg for BP target or (2) the standard therapy group having ⟨140/90 mmHg or ⟨130/80 mmHg with current DM, CKD or old MI.

2.7.2 Monetary Compensation

Inspection cost for urinary microalbumin and serum high sensitivity C-reactive protein (hsCRP) will be charged by the RESPECT Study group. Otherwise, the cost for daily clinical practice will be covered by health insurance.

2.7.3. Registration of subjects

The screening period is a period between the date of consent and the enrollment and authorization of eligibility. Patients who meet all of the eligibility criteria will be randomly assigned to two groups; the intensive BP control group or the standard BP control group.

2.7.4. Randomisation and Allocation

Participants will be randomly allocated via a web-based randomisation system. Randomisation is stratified by age (≥70 years), presence of DM/CKD/old MI, and atrial fibrillation

(1) The intensive therapy group: BP target is <120/80 mmHg using stepwise multi-drug protocol

(2) The standard therapy group: BP target is <140/90 mmHg (<130/80 mmHg if DM/CKD/old MI is present), using a stepwise multi-drug protocol.

2.7.5. Concomitant Medication/Treatment

1) Prohibited concomitant drugs

The following drugs must not be used throughout study.

(1) BP lowering drugs except for the study drugs (until proceeding step 6)

Other BP lowering drugs will be added for the treatment of refractory hypertensive patients when BP does not reach the target until proceeding to step 6.

Treatment with Ca channel blockers (CCB) and β-blockers for arrhythmia or angina is allowed during the study period.

(2) Drugs contraindicated to the study drugs

<To spironolactone>

- Tacrolimus
- Eplerenone
- Mitotane

2) Partially prohibited drugs

The following drugs may be co-administered with normal dosage and use.

(1) Anti-anxiety agents and hypnotic sedatives
(2) Steroids (external use)
(3) Nonsteroidal anti-inflammatory analgesics
(4) Ephedrine/ephedrine analogs
(5) Sildenafil
(6) Hormone replacement therapy
(7) Calcium channel blockers and β blockers used for anti-arrhythmia or angina
(8) α-blocker for prostate disease

2.7.6. Blood pressure control and treatment schedule

1) Dosage and usage of study drug (Figure 1):

The study uses angiotensin II receptor blocker (ARB) tablets, and combination drugs including ARB and hydrochlorothiazide (HCTZ), calcium channel blocker (CCB, exp. amlodipine besilate etc) and K-sparing diuretics (spironolactone tablet to control BP). Any antihypertensive agents can be used for stepwise treatments during the study duration to control BP.

The method of BP measurement must be consistent with guidelines for management of hypertension[17)]

To find the treatment that can achieve the target BP, patients will receive stepwise treatments orally every 4 weeks for 24 weeks at maximum during the titration period as follows:

Step 1: Losartan potassium 50 mg or another ARB*
Step2: Combination drug containing losartan 50 mg or another ARB and hydrochlorothiazide (HCTZ) 12.5 mg (combination with ARB and HCTZ (ARB/HCTZ))
Step 3: combination with ARB and HCTZ + amlodipine besilate 5 mg (Amlodipine LD)
Step 4: ARB alone + combination with ARB and HCTZ + Amlodipine LD
Step 5: ARB alone + combination with ARB and HCTZ + amlodipine besilate 10 mg (Amlodipine HD)
Step 6: ARB alone + combination with ARB and HCTZ + Amlodipine HD + spironolactone 25 mg

* Other ARBs are available for single use and combination use.

**Dosage and usage of drugs follow the package insert.
***Combination drug with ARB and HCTZ is counted as two drugs.
****Generic drugs are useable.

2) Treatment algorithm

The study period consists of the screening period, stepwise treatment period with study drugs, and follow-up period.

(1) Screening period

The screening period occurs between the written informed consent and authorization of eligibility. Patients who meet all the eligibility criteria will be randomly assigned into one of two groups; the intensive BP control group or the standard BP control group.

(2) Titration period (Week 1-24)

The starting step will be determined following Figure 1.

Blood pressure will be measured in the sitting position at visits outlined in the treatment algorithm.

<u>Up-titrating steps</u>

Regardless of the allocation to either the intensive BP control group (target blood pressure: less than 120/80 mmHg) or the standard BP control group (target blood pressure: less than 140/90 mmHg or less than 130/80 mmHg in the presence of DM, CKD or old MI), patients will receive the stepwise multidrug therapy by adding treatment drugs if no clinical problem is observed. The target blood pressure should be achieved and maintained until 24 weeks after assignment. The treatment must be followed in a direction from Step 1 to Step 6.

If a patient is allocated to the standard BP control group and has new DM or CKD, a target blood pressure is changed to less than 130/80 mmHg.

When a patient experiences new myocardial infarction during study period, the protocol for blood pressure lowering will be ceased, but the patient must be followed up until the end of the study period.

<u>Down titration for standard BP control group</u>

- The titration step will turn back for patients having DM, CKD and/or old MI when the following conditions are observed;

- SBP level goes down to 120 mmHg or lower at least once.
- SBP level goes down to 125 mmHg or lower in two consecutive visits

➢ The titration step will turn back for patients having stroke risk factors when the following conditions are observed;

- SBP level goes down to 130 mmHg or lower at least once
- SBP level goes down to 135 mmHg or lower in two consecutive visits

(3) Follow-up period (After week 25)

The study will continue until the number of patients who experience their first recurrent stroke reaches a total of 244 in the two groups under blood pressure control.

<u>Reporting to specified events (outcomes) and serious adverse events</u>

1. Specified events (outcomes)

When cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, transient ischaemic attack, myocardial infarction, cardiovascular events, and death occur, the physician or CRO will input information required to EDC system as soon as possible. Each event is assessed by the endpoint committee.

2. Within 2 working days from the date informed, a survey form will be sent to the physician. The survey form includes requisite items, and the physician should send it to the RESPECT study office within 2 weeks.

3. The information received by the survey form will be assessed by the endpoint committee.

2.7.7 Measurement items

Information except for blood pressure, hsCRP, and urinary microalbumin will be obtained from clinical records.

1) Screening period

(1) Patient basic information

Birth date (age), sex, height, body weight

(2) Patient characteristic

Medical history/complication diseases, and their severity are obtained from clinical

records.
Cerebral infarction, Cerebral hemorrhage, Transient ischaemic attack, Myocardial infarction*, Angina pectoris*, Atrial fibrillation*, Congestive heart failure*, Asymptomatic ischaemic disease*, Diabetes mellitus**, Renal impairment***, Hepatic abnormality****, Dementia*****, Malignant neoplasm (passed years from the last treatment). Aortic rupture and aortic dissection, Arteriosclerosis obliterans, gout, and others

*Guideline for diagnosis and treatment of cardiovascular disease (2007 edited by the Japanese Circulation Society)[18)]

**Definition of Diabetes mellitus (The Japan Diabetic Society 2010/7/1)[19)]
Diabetes mellitus will be diagnosed with at least one of following lab test value.
1. Fasting blood glucose: more $\geq$126 mg/dL
2. Oral glucose tolerance test: $\geq$200 mg/dL at 2-hour
3. Casual blood glucose: $\geq$200 mg/dL
4. HbA1c: more than 6.5%

***Renal impairment (Evidence based CKD treatment guideline 2009)[20)]
1. Proteinuria (with secretion of urinary microalbumin), GFR <60 mL/min/1.73m^2, Chronic kidney disease, established renal disease (diabetic nephropathy, renal failure etc.)
2. Renal function abnormality (serum creatinine more than 2.0 mg/dL)

****Hepatic function abnormality AST (GOT) of $\geq$100 IU/mL or ALT (GPT) $\geq$100 IU/mL within 1 year from date of informed consent

*****Dementia Screening using MMSE and diagnosis follows DSM-IV and CDR[13-15)]

(3) Pre-usage drugs
Dosage of dose regimen, start and stop date, indication, and drug adherence will be recorded.

- Antihypertensive drugs: CCB, ACEI, ARB, beta-blocker, diuretic, and others
- Antiplatelet drugs: aspirin, ticlopidine, cilostazol, sarpogrelate, dipyridamole, clopidogrel, and others
- Anticoagulant drugs: warfarin, dabigatran, rivaroxaban, apixaban, edoxaban
- Cerebral circulation/metabolic stimulant: meclofenoxate hydrochloride, adenosine triphosphate disodium hydrate, gamma-aminobutyric acid, ifenprodil

tartrate, ibudilast, nicergoline, amantadine hydrochloride, dihydroergotoxine mesylate

- Blood vessel-reinforcing drug: carbazochrome sodium sulfonate hydrate, adrenochrome-monoaminoguanidine mesylate hydrate, carbazochrome sodium sulfonate hydrate
- Anti-plasmin drug: tranexamic acid
- Anti-arrythmia drugs: Na channel blocker, K channel blocker, and others
- Lipid lowering drugs: statin, fibrate, and others
- Anti-diabetic drugs: Oral; Sulfonylurea derivatives, insulin sensitizer (thiazolidine derivatives, biguanide derivative), alpha-glycosidase inhibitor, dipeptidyl peptidase-IV(DPP-4) inhibitor, GLP-1 receptor agonist, and others, Injection; Insulin
- Peptic ulcer agent: protection factor stimulants, proton pump inhibitors, prostaglandin, H2 receptor antagonist, and others
- Others: brain metabolic stimulant, anti-anxiety agent, sedative hypnotics, steroid (external use), nonsteroidal anti-inflammatory drug, ephedrine and its derivative, sildenafil, drug for hormone replacement therapy, and others

(4) Laboratory tests

- BP (sitting position): mean of two times
- HR (sitting position)
- Blood chemistry: hsCRP, urinary microalbumin (stopped on 2014/3/31)
- Pregnancy diagnosis (if necessary)

The following items will be assessed from medical records:

- 12-leads ECG
- NYHA classification
- Modified Rankin Scale
- Blood biochemistry
  Cr, BUN, UA, TC, HDL-C, LDL-C, TG, AST (GOT), ALT (GPT), Na, K, Cl, Ca, HbA1c
- Urinalysis: protein, glucose

2) Titration period (Weeks 1-24) and Follow-up period

(1) Laboratory tests

- BP (sitting position): mean of two times
- HR (sitting position)
- Blood chemistry: hsCRP, urinary microalbumin (Stopped on 2014/3/31)

The following items will be assessed from medical records:

- 12-leads ECG
- NYHA classification
- Modified Rankin Scale
- Blood biochemistry
  Cr, BUN, UA, TC, HDL-C, LDL-C, TG, AST (GOT), ALT (GPT), Na, K, Cl, Ca, HbA1c
- Urinalysis: protein, glucose

(2) Study drugs (antihypertensive agents) and concomitant medication

- A step of the study treatment or its change
- Drug adherence (≥80% or <80% by interview)
- Change or addition of concomitant drug

(3) Occurrence of events

- Cerebral infarction
- Cerebral hemorrhage
- Subarachnoid hemorrhage
- Transient ischaemic attack
- Myocardial infarction
- Cardiovascular event
- Death (Cardiovascular related, others)
- Others

(4) Serious adverse events

- Angina pectoris (Not including silent myocardial ischemia)
- Congestive heart failure
- Atrial fibrillation
- Angioplasty and stent insertion
- Aortic rupture and aortic dissection
- Arteriosclerosis obliterans

- Renal impairment
- Diabetes mellitus
- Gout
- Dementia
- Serum Cr ≥2.0 mg/dL
- Serum Potassium (<3.0 mmol/dL or ≥5.5 mmol/dL)
- Malignant neoplasm
- Others

2.8 Discontinuation/Withdrawal of study

Patient will discontinue the study or treatment if the criteria below occurs.

A necessary follow-up must be made after discontinuation

1） When a patient requests discontinuation, treatment under assignment to each group must be terminated regardless of the reason. Detailed information on the discontinuation should be documented in eCRF.

2） Others

The data on the patient must be handled as follows;

(1) If the patient withdraws the consent, the data are unusable.

(2) If the patient refuses to continue the study, the data are usable.

2.9 Discontinuation of the study drug treatment

If continuation of the treatment is not feasible according to the reasons below, the treatment must be discontinued immediately. However, the follow-up of the patient must be continued as long as possible:

(1) On the recurrence of stroke

(2) When the primary investigator or sub-investigator judges the discontinuation of the study drug treatment necessary due to other reasons (Occurrence of myocardial infarction and so on).

2.10 Central assessment of Efficacy and Safety

All adverse events will be reported to the endpoint committee by an investigator. The endpoint committee will review events reported, and then determine validity as a primary outcome, secondary outcomes, or adverse events, individually. If the report needs further information, feedback will be provided to the investigator.

2.11 Efficacy and safety measurements

1) Efficacy Endpoint

Primary outcome

The frequency of recurrent stroke in both groups will be compared among various aspects, and whether intensive BP management is useful for the prevention of recurrent stroke will be assessed.

Secondary outcome

- Onset of cerebral infarction*
  Subclassified into: lacunar infarction, atherothrombotic infarction, cardio-embolic infarction, and other/unclassified/unknown
- Onset of cerebral hemorrhage
- Onset of subarachnoid hemorrhage
- Onset of transient ischaemic attack
- Onset of myocardial infarction**
- Composite cardiovascular outcomes (cardiovascular death ***+ nonfatal stroke**** + nonfatal myocardial infarction)
- All death
- All death + nonfatal stroke + nonfatal myocardial infarction

* Definition of acute ischaemic stroke subtype and Diagnostic criteria

Subtypes of acute ischaemic stroke type are categorized using the TOAST classification[16] and depend on the NINDS classification[17] .

** Myocardial infarction

Q wave myocardial infarction, non-Q wave myocardial infarction, asymptomatic myocardial infarction, suspected non-Q wave myocardial infarction, myocardial infarction that occurred after invasive cardiovascular intervention, myocardial infarction that occurred postoperatively for non-cardiovascular regions

*** Death attributed to cardiovascular events

(1) Sudden death: death within 24 hours attributed to a cardiovascular event
(2) Fatal myocardial infarction: death attributed to acute myocardial infarction (definitive diagnosis and in the hospital)
(3) Fatal congestive heart failure: acute ischaemic event (including

cardiogenic shock) is ruled out and death attributed to congestive heart failure diagnosed based on clinical condition, radiological diagnosis, and post-mortal phenomena

(4) Fatal stroke: Death due to attack, specific symptoms, and sign of stroke

(5) Others deaths attributed to cardiovascular events: Death attributed to other cardiovascular disease including pulmonary embolism

(6) Suspected deaths attributed to cardiovascular events: Death attributed to cardiovascular events speculated from clinical symptoms

(7) Death attributed to post performance of invasive intervention for cardiovascular diseases.

(8) Death attributed to bradyarrhythmia or supraventricular tachyarrhythmia not caused by ischaemic heart disease

(9) Death attributed to operation for non-cardiovascular disease (DIC, intestinal obstruction etc.)

****Definition of stroke in secondary endpoint: Cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, stroke (unspecified), Stroke that occurs after invasive cardiovascular intervention, cerebral infarction after any surgical operation.

2) Rationale for Safety Endpoint

The frequency of serious adverse experiences in both groups will be compared to evaluate the tolerability of the treatment.

- Angina (not include asymptomatic)
- Congestive heart failure (onset or exacerbation)
- Atrial fibrillation (onset or exacerbation: conversion from paroxysmal to sustained one)
- Angioplasty and stent insertion
- Aortic rupture and aortic dissection
- Renal dysfunction (serum creatinine ≥ 2.0 mg/dL, hemodialysis therapy)
- Arteriosclerosis obliterans (onset or exacerbation)
- Diabetes mellitus
- Goat
- Serum potassium (<3.0 mg/dL or ≥ 5.5 mg/dL)
- Dementia (onset or exacerbation)
- Malignant neoplasm

- Others

*****A serious adverse event (experience)[21)] is any untoward medical incident that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapability. A serious adverse event also includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the daily activity or may require intervention to prevent one of the other outcomes listed in the definition above.

ICH E2A Guideline Clinical Safety Data management: Definition and standards for expected reporting on 27 Oct 1994[21)]

2.12 Statistical analysis, sample size, and power consideration

2.12.1 Sample size

Intensive blood pressure control group	1,000 cases
Standard blood pressure control group	1,000 cases

According to the number of patients with stroke registered in Akita prefecture, 6,469 patients (12%) experienced recurrent stroke among 55,003 patients. Some patients experienced up to 7 more strokes, the highest during the period. Patients who experienced recurrent stroke, mostly cerebral infarction, had a relatively younger age and concurrent risk factors for recurrent stroke such as hypertension, diabetes, and atrial fibrillation (as analyzed with Cox's proportional hazards model). Analysis for recurrent stroke revealed that the cumulative recurrent rate was 21% for cerebral infarction, 17% for intracerebral hemorrhage, and 9% for subarachnoid hemorrhage. The rate of recurrent stroke was 2.5% during the first two years, which was 5 times higher in comparison with the rate of the first occurrence of stroke. The rates were 2% in the third year and 1.6% in the 10th year. At 10th year, the rate of recurrent stroke was still 2 times higher than that of the first occurrence of stroke (0.81%). [22)]
In the ACCORD study, the mean SBP of the intensive therapy group was 139.0 mmHg at baseline, and decreased to 119.3 mmHg after one year, while that of the standard therapy group decreased from 139.4 mmHg at baseline to 133.5 mmHg after one year. The BP difference between treatment groups was 14.2 mmHg (95% CI 13.7-14.7 mmHg). The intensive therapy produced a 41% reduction in relative risk for occurrence of stroke.[23)]

Based on the information above, our original sample size was 5000. In 2014, a blinded analysis with 1,192 person-years of observation showed an annual recurrence rate of stroke as 4·6%. Therefore, a recurrence rate of stroke was revised to 4·5%/year. Assuming that a cumulative recurrence rate of stroke is 15·6% in the standard group during 3·5 years of follow-up, a revised sample size of 2000 patients will have 80% power (at an overall alpha level of 0·05) to detect a 30% reduction in relative risk of the recurrent stroke in the intensive BP control group, with a drop-out rate of 10%. As an event driven study, this study will be continued until 244 events of recurrent stroke are reported.

An independent Data Monitoring Committee (DMC) will review unblinded data during the trial. A formal interim analysis will be performed when 50% of the planned stroke events (i.e. 122 events) are observed or at 5 years from the start of the study (i.e. 2015), and the second formal interim analysis will be performed when 80% of the planned stroke events (i.e. 200 events) are observed. Based on the Lan- DeMets's alpha spending function approach, a significance level of a two-sided α will be 0.0015 in the first interim analysis and 0·0118 at the second. The final last level of significance with three will be 0·0487.

The DMC will serve as the primary reviewer of unblinded results of the interim analyses and will recommend discontinuation or protocol modification to the Steering Committee.

2.12.2 Analysis outcomes

1) Primary outcome

Time from the randomisation to onset of the first recurrent stroke (cerebral infarction and intracerebral hemorrhage) will be compared between the intensive BP control group and the standard BP control group using a log-rank test in the principle of intension-to-treat (ITT) with a significance level of $p<0·0478$ (two-sided).

2) Secondary outcomes

Time from randomisation to the first event of each outcome will be compared between randomised groups using a log-rank test in the principle of intension-to-treat (ITT).

- cerebral infarction and each subtype
- intracerebral hemorrhage
- subarachnoid hemorrhage
- transient ischaemic attack

- myocardial infarction**
- composite cardiovascular outcomes (cardiovascular death ***+ nonfatal stroke**** + nonfatal myocardial infarction)
- All death
- All death + nonfatal stroke + nonfatal myocardial infarction

1) Safety Endpoints

Frequency of serious adverse events will be compared between randomised groups.

- Angina (not including silent myocardial ischemia)
- Congestive heart failure (new-onset or exacerbation)
- Atrial fibrillation (new-onset or exacerbation defined as conversion from paroxysmal to sustained)
- Vascular surgery or endovascular intervention
- Ruptured aortic aneurysm or aortic dissection
- Peripheral arterial disease (new-onset or exacerbation)
- Renal dysfunction (increase of serum creatine ≥2·0mg/dL or hemodialysis treatment)
- Diabetes mellitus (new-onset)
- Gout (new-onset)
- Abnormal serum potassium (<3·0 mg/dL or ≥5·5 mg/dL)
- Dementia (new-onset or exacerbation)
- Malignant neoplasm
- Others

See Section 2.11.2 for a list of safety measurements. For laboratory tests, vital signs and ECG parameters, baseline data is defined as the randomisation visit (Table 5 Survey items and their timing).

2) Analysis Populations

In accordance with the intention to treat (ITT) principle, all patients, except for (1) those who immediately withdrew their consent and (2) those that did not have any information after randomisation, will be included in the analysis.

2.12.3 Statistical analysis:

2.12.3.1 Statistical hypotheses

The risk for stroke recurrence is not equal between the intensive BP control group and the standard BP control group.

2.12.3.2 Statistical significance for interim analyses and early termination

Two interim analyses and the final analysis will be performed based on Lan-DeMets's alpha spending function approach. The study will be terminated early if the two-sided p-value is <0·0015 at the first interim analysis with 122 events or if <0·0118 at the second interim analysis with 200 events. The same two-sided p-value of <0·0015 will be used when the first interim analysis is conducted at 5 years from the start of the study (i.e. 2015) without reaching 122 events. For safety purposes, a composite outcome of the primary outcome and serious adverse events will be used for the interim analyses only.

2.12.3.3 Statistical significance for the final analysis

A log-rank test will be used to compare time between the intensive BP control group and the standard BP control group using the intension-to-treat principle. The final level of significance after three looks will consequently be 0·0478 (two-sided).

If the significance level is satisfied for the primary outcome, the same level of significance (0·0478) will be used for secondary outcomes without considerations of the multiple comparison issue. If the significance level is not satisfied for the primary outcome, the significance level of p<0·006 (two-sided) (1/8 of p=0·0478) will be used for secondary outcomes.

2.13 Study duration

This study will be continued until a defined number of recurrent strokes are observed. An expected observation period will be from September 2010 to December 2018. The recruitment period may be postponed until 244 recurrence strokes are expected to be observed.

2.14 Expected Drug-related Adverse Experiences and Their Countermeasures

Because this study uses dosage and administration of drugs in which their safety is confirmed, only adverse experiences that are described in the package inserts are expected to occur in the study period. When drug-related adverse experiences occur, the countermeasure will be taken according to the document as specified in the package inserts. When serious drug-related adverse experiences occur when dosage and administration are followed according to the instructor as determined by an investigator, compensation will be paid according to the Relief System for Sufferers from Drug-related Adverse Experiences. Treatment for other drug-related adverse

experiences will be covered by health insurance.
When unexpected drug-related adverse responses or adverse experiences occur, the investigator must promptly take appropriate actions by placing ensuring safety, and then immediately report the incident to the head of the study institution. The investigator must also notify the drug maker (medical representative,) according to the specified procedure.
The RESPECT study Safety Monitoring Committee will review adverse experiences reported.

2.15 Investigator's Responsibility to Report Adverse Experiences

All adverse experiences will be reported to the steering committee of the RESPECT study group, the regulatory agency, and IRB/IEC, according to all applicable laws and regulations.

2.16 Ethical consideration

1) Ethical review board

Prior to securing a contract agreement with the study site, the study protocol and informed consent forms with relative materials must be deliberated, and then must be approved by the study site's ethical review board.

The investigator must obtain the signed informed consent form from each potential patient and give a copy of the signed and dated consent form and a document used for study explanation to the patient before study participation.

2) Preparation of Informed consent

The informed consent form includes the items below.

(1) Title of the research and approval of the chief executive of the research implementing that entity has been given concerning its implementation

(2) Names of the research implementing entity and the principal investigator (including names of the collaborative research implementing entity(s) and principal investigators of such collaborative research implementing entity(s), when the research is conducted collaborator with other research implementing entity(s)

(3) Objective and significance of the research

(4) Method of time periods of the research

(5) Reasons why the patients were asked to be enrolled in the research

(6) Burdens that the research subjects might experience and predictable risks and benefits

(7) Information that the research subjects may withdraw their consent at any time even after they have provided consent

(8) Means to make information on the research public

(9) The fact that research subjects can request and obtain or read the research protocol and documents to the extent, which does not interfere with the personal information protection, the originality of the research, and Handling of personal information.

(10) Means for storage and disposable of specimens and information

(11) Status of research-related conflict of interest of the research implementing entity, such as research fund resources, as well as research-related conflicts of interest of each investigator

(12) Response to consultation made by research subject and other individuals concerned

(13) When the research involves any financial expenditure on or remuneration for the research subject, a statement to that effect and detail of such

(14) When the research involves any medical technique beyond usual medical practice, description of alternative procedure(s) or course(s) of treatment.

(15) When any significant finding that concerns the subject's health or genetic characteristics which may be inherited by his/her offspring, may be obtained through implementing the research, handling of the research results related to the research subject (including incidental findings)

(16) When the research involves any invasive, whether or not compensation will be offered for research-related injury and details of such compensation.

(17) With respect to specimens and information acquired from the research subject, when any of those may be utilized or provided to other research implementing entity(s) for the research in future that is not identified at the time of obtaining consent.

(18) When the research involves any invasiveness (not including minor invasiveness) and intervention (not including minor invasiveness), the fact that the monitor(s), the auditor(s) and the ethical review committee will be granted direct access to the specimens and information acquired from the research, without violating confidentiality of the research subjects, to the extent necessary.

3) Informed Consent

The investigator must obtain the signed informed consent form from each potential patient and give a copy of the signed and dated consent form and a document used for study explanation to the patient before study participation.

2.17 Necessary procedure prior to patient enrollment

1) Investigator qualifications and agreements for the study site

In general, the investigators should be thoroughly familiar with neurology, neurosurgery, and cardiology. Measurement and clinical assessments in this study should be performed by a physician. Under a physician's review, co-medical workers may enter the data into the EDC system.

2) Registration of investigators and co-medical workers who will participate in the study

3) Communication with the Institution Review Board (IRB) and Contract agreement for The RESPECT study group.

4) Notification for the approval by the site's IRB

5) Issuance of Researcher's ID and password for accessing the EDC system

2.18 Web-based study management

Each investigator enters information directly into web-based forms and saves it in the database. The web-data-bases system checks the data immediately after data entry, including verification of eligibility prior to randomisation. The data are immediately available for dynamic reports for study management. The website is also used to manage the outcome adjudication process. Information associated with data management procedures are referred to

in the eCRF entry guidelines provided by the RESPECT study data center.

2.19 Study Costs

Study expenses for patient registration, follow-up and CRC support will be provided by the RESPECT Study Group. The expense required for special laboratory values including highly sensitive CRP and microalbumin will be covered by the RESPECT Study Group.

2.20 Compensation for Health Injury

For patient health injury related to the study, the investigator should discuss the relationship of the study with the study institution. When the relationship between the health injury and the study cannot be denied, the indemnification and compensation must be discussed. Prior to study initiation, the RESPECT Study group must purchase insurance for the study to guarantee the compensation.

2.21 Protocol Amendment

If modification, addition, or deletion of the study protocol is required, the monitoring committee will discuss the feasibility. Based on the monitoring committee recommendation, the representative of the study group and the study steering committee will make the decision for the protocol change. The details of the changes will be notified to study investigators at all study sites.

After receiving such notification, an independent Ethics Committee of each study institution will review the protocol amendment, and the head of the institution must approve the change.

2.22 Publication of Study Results

1) All the information and data obtained from the study belong to the incorporated nonprofit organization of the RESPECT Study Group (the representative: Kazuyuki Shimada; Local incorporated administrative agency (LIAA) Shin-Oyama City Hospital Chief director and Head of hospital).
2) A researcher appointed by the study representative or the Study Steering Committee will promptly summarize the results, and publish them in an appropriate journal published in English or at scientific conferences. The names of all the participating study sites and physicians responsible for the study in each site will be published in the publication.
3) When presenting information from the study to external parties such as medical conferences, the investigators must obtain prior written approval

from the RESPECT Study Group.

4) Location and duration of data storage

Study data will be stored in a designated server (located somewhere in Tokyo; a large server will be installed in the center) during the study period. After study completion, the Study Group will permanently store study data in recorded media.

After study completion, the data in the designated server will be destroyed and disposed after approval of the RESPECT Study Group.

2.23 RESPECT Study Committee

2.23.1 Principal Investigator

Kazuyuki Shimada (Shin-Oyama City Hospital)

2.23.2 The steering committee

Kazuyuki Shimada (Chair)	(Shin-Oyama City Hospital)
Satoshi Umemura	(Yokohama Rousai Hospital)
Yasushi Okada	(National Kyushu Medical Center)
Genjiro Kimura	(Cardio-renal and health research institute)
Kazuaki Shimamoto	(Japan Health Care College)
Norio Tanahashi	(Saitama Medical University International Medical Center)
Jitsuo Higaki	(Ehime University Graduate School of Medicine)
Masayasu Matsumoto	(Sakai City Medical Center)

2.23.3 The protocol committee

Masayasu Matsumoto (Chair)	(Sakai City Medical Center)
Sadayoshi Ito	(Tohoku University School of Medicine)
Shinichiro Ueda	(University of the Ryukyu)
Yusuke Ohya	(University of the Ryukyu)
Kazuo Kitagawa	(Tokyo Women’s Medical University)
Yasumasa Yamamoto	(Kyoto Katsura Hospital)
Hiromi Rakugi	(Graduate School of Medicine, Osaka University)

2.23.4 The endpoint committee

Kazuo Minematsu (Chair)	(National Cerebral and Cardiovascular Center)
Kazuomi Kario	(Jichi Medical University)

Yoshihiko Saito (Nara Medical University)
Yasuo Terayama (Iwate Medical University)
Kazunori Toyoda (National Cerebral and Cardiovascular Center)
Takafumi Okura (Ehime University Graduate School of Medicine)
Haruhiko Hoshino (Tokyo Saiseikai Central Hospital)
Kazuo Eguchi (Jichi Medical University)
Hirofumi Makino (Okayama University)
Haruhito Uchida (Okayama University Graduate School of Medicine)

2.23.5 The independent data monitoring committee

Shinichiro Uchiyama (Chair) (International University of Health and welfare)
Hideki Etani (OBP Clinic)
Tatsuo Kohriyama (Brain Attack Center Ota Memorial Hospital)
Hidekazu Tomimoto (Mie University Graduate School of Medicine)
Taku Yoshio (Jichi Medical University)
Takao Saruta (Keio University School of Medicine)
Shotai Kobayashi (Shimane University)

2.23.6 The statistical analysis team

Hisatomi Arima (Chair) (Fukuoka University Faculty of Medicine)
Takahide Khoro (Jichi Medical University)
Koji Yonemoto (University of the Ryukyu)

2.23.7 Data Management Center

Hiroko Usami (Chair) (NPO RESPECT Study Group)
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APPENDICES

1. Definitions of Stroke Types and Diagnostic Criteria Used in This Study

Diagnosis of stroke types will be made using the TOAST classification[13] (Table 1), and the diagnosis will be termed according to the NINDS classification[14].

1) Atherothrombotic brain infarction

Atherothrombotic brain infarction is a type of cerebral infarction caused by arteriosclerotic stenosis (>50%) or occlusion of a major brain artery or branch cortical artery.

The clinical symptoms of atherothrombotic brain infarction include cerebral cortical impairment (causing the conditions such as aphasia, neglect, limited motor function motor) and brain stem or cerebellar dysfunction. The diagnostic criteria for atherothrombotic brain infarction are (1) presence of infarction(s) of >1.5 cm in the cerebral cortex, cerebellum, brain stem, or subcortical portion of the brain with MRI/CT scans, and (2) presence of a more than 50% stenosis of a intracranial or extracranial artery on ultrasonography or angiography. At the same time, potential sources of cardiogenic embolism should be excluded. Thus, atherothrombotic brain infarction should not be diagnosed if ultra-sonographic or angiographic findings are normal or show only slight abnormality. A history of intermittent claudication or transient ischaemic attacks (TIA) in the same vascular territory, carotid bruit, or disappearance of radial pulse supports the diagnosis of atherothrombotic brain infarction.

2) Cardiogenic embolism

This is a type of cerebral infarction caused by an embolus that occurs in the cardiac chamber. A diagnosis of cardiogenic embolism requires the demonstration of at least one cardiac source of embolus. Cardiac sources of embolus include: left atrial thrombus, continuous/acute atrial fibrillation-flutter, old myocardial infarction, prosthetic valve, and a right-to-left cardiac shunt with a venous source of an embolus (Table 2). The clinical symptoms and MRI/CT findings of cardiac embolism are similar to those of atherothrombotic brain infarction; however, no lesion, that can be a cause of thrombus or embolus, must be present in a carotid or major brain artery. Cerebral infarction with a cardiac source of embolism but no other cause of cerebral infarction is classified in this

disease type. A history of TIA, stroke in multiple vascular territories or systemic embolism supports the diagnosis of cardiogenic embolism.

3) Lacunar infarction

This is a type of cerebral infarction associated with symptoms of classical lacunar syndrome (pure motor, pure sensory, sensorimotor, ataxic hemiparesis, or dysarthria-clumsy hand). No cerebral cortical symptoms should be present in patients with lacunar infarction. A diagnosis of lacunar infarction requires normal MRI/CT findings, or presence of a brain stem or subcortical lesion of <1.5 cm that is consistent with the symptoms. However, a potential cardiac source of embolism or a stenosis of >50% in ipsilateral extracranial arteries must be excluded. History of DM or hypertension supports the diagnosis of lacunar infarction.

4) Cerebral hemorrhage

The diagnosis of a cerebral hemorrhage requires head MRI/CT findings of hematoma(s) or a scar in the cerebrum, cerebellum, or brain stem. The localization of the lesion(s) must be consistent with the patient's neurological symptoms. However, haemorrhagic infarction following embolic cerebral infarction is not included in this disease type.

5) Subarachnoid hemorrhage

A diagnosis of subarachnoid hemorrhage requires sudden onset of headache, and head MRI/CT findings of hematoma in the subarachnoid space.

6) Stroke of other or undetermined etiology.

a) Cerebral infarction of rare etiology

This disease type includes cerebral infarction caused by relatively rare diseases such as vertebral artery dissection, fibromuscular dysplasia, and moyamoya disease, and cerebral infarction occurred during catheterization or surgery.

b) Cerebral infarction of undetermined etiology

This disease type includes cerebral infarction that is explained by two or more causes, or that has no identifiable cause after extensive investigation or due to insufficient investigation.

c) Intracranial hemorrhage associated with cerebral arteriovenous malformation

7) Transient ischaemic attack (TIA)

This disease type is characterized by a sudden onset of focal neurological symptoms that are thought to be caused by a cerebrovascular impairment, and the following the disappearance of the symptoms within 24 hours. This disease type should further be classified into internal carotid artery TIA or vertebral artery TIA according to the clinical symptoms (Table 3). Identification of responsible lesion(s) by MRI/CT scans is not necessary. Furthermore, TIA must not be diagnosed solely by the symptoms listed in Table 4.

Table 1. Features of TOAST classification of subtypes of ischaemic stroke Harold P. et al Classification of subtype of acute ischaemic stroke Definition for use in a multicenter clinical trial Stroke 1993;24:35-41

	AI	CE	LI	OT
Clinical				
Cortical or cerebellar dysfunction	+	+	–	+/–
Lacunar syndrome	–	–	+	+/–
Imaging				
Cortical, cerebellar, brain stem, or subcortical infarct >1.5 cm	+	+	–	+/–
Subcortical or brain stem infarct less than 1.5 cm	–	–	+/–	+/–
Tests				
Stenosis of extracranial internal carotid artery	+	–	–	–
Cardiac source of emboli	–	+	–	–
Other abnormal findings on tests	–	–	–	+

AI: Large-artery atherosclerosis, CE: Cardioembolism, LI: Small-artery occlusion (lacune), OT: other cause

Table 2. TOAST classification of High- and Medium-Risk sources of cardioembolism

High-risk sources	Mechanical prosthetic valve, Mitral stenosis with atrial fibrillation, Atrial fibrillation (other than lone AF), Left atrial/atrial appendage thrombus, Sick sinus syndrome, Recent myocardial infarction (〈 4 weeks), Left ventricular thrombus, Dilated cardiomyopathy, Akinetic left ventricular segment, Atrial myxoma, and Infective endocarditis
Medium-risk sources	Mitral valve prolapse, Mitral annulus calcification, Mitral stenosis without atrial fibrillation, Left atrial turbulence (smoke), Atrial septal aneurysm, Patent foramen ovale, atrial flutter, lone AF, bioprosthetic valve, nonbacterial thrombotic endocarditis, congestive heart failure, partial reduction of left ventricular wall movement, myocardial infarction (within 6 months but no more recent than 4 weeks)

Table 3. Classification of TIAs (NINDS classification)

Internal carotid artery TIA	1. Motor dysfunction (weakness, paralysis, fine motor dysfunction of upper and lower extremities on either sides and the right and/or left side of the face, or dysarthria). 2. Total or partial loss of vision in one eye (amaurosis fugax) in patients with normal binocular vision. 3. Loss of unilateral visual fields (homonymous hemianopia). 4. Sensory disturbance (numbness and paresthesia in the right or left upper extremity, lower extremity, and/or face) 5. Aphasia (language disturbance)
Vertebral artery TIA	1. Motor dysfunction (weakness, paralysis, impaired fine motor skill) of any combination of upper and lower extremities and face. 2. Unilateral or bilateral sensory disturbance (loss of feeling, numbness or paresthesia). 3. Unilateral or bilateral loss of visual fields 4. Any combination of two or more of the following: ataxia, vertigo, balance disorder, diplopia, dysphagia, and dyslalia.

Table 4. Symptoms that are not characteristics of TIAs or not considered due to TIAs

Symptoms that are not characteristics of TIAs	
• Unconsciousness without vertebrobasilar artery symptoms	• Tonic and/or clonic seizure
• Prolonged march of symptoms over various sites of the body	• Scintillating scotoma
Symptoms that are not considered as TIAs	
• March of sensory disturbance	• Vertigo alone
• Dizziness alone	• Dysphagia alone
• Dysarthia alone	• Diplopia alone
• Urinary/fecal incontinence	• Visual impairment with an altered level of consciousness
• Focal neurological symptoms with migraine	• Confusion alone
• Amnesia alone	• Atonic seizure alone

∗Degree of independence in daily activities: Modified Rankin Scale

2. Japanese modified Rankin Scale Criteria

Score 0: No symptoms
Score 1: No significant disability: Capable to carry out all usual activities without assistance.
Score 2: Slight disability: Capable to look after own affairs without assistance, but incapable to carry out all daily activities.
Score 3: Moderate disability: Requires some assistance, but capable to walk unassisted.
Score 4: Moderate to severe disability: Incapable to attend to own bodily needs without assistance, and incapable to walk unassisted.
Score 5: Severe disability: Requires constant nursing care and attention, and bedridden and incontinent.

3. Office blood pressure monitoring - from the 2009 Guidelines for Treatment of Hypertension[12)]

1) Equipment

a. The auscultation method is adopted using a properly calibrated mercury/aneroid manometer. Use of a properly calibrated electronic manometer is also allowed[*1].
b. A cuff of 13 cm wide and 22-24 cm long must be used with a rubber bag.
[For children, use a pediatric cuff if the upper arm circumference if <27 cm, and an adult cuff if ≥34 cm]

2) Measurement conditions

a. Quiet environment at an appropriate room temperature
b. After taking a rest for several minutes in a sitting position on a chair with backrest with the legs uncovered
c. No talking
d. No smoking, drinking alcohol, or caffeine intake prior to measurement

3) Measurement method

a. Location of the cuff should be maintained at the height of the heart
b. Pressure to the cuff should be rapidly increased
c. The exhaust velocity of the cuff should be 2-3 mm Hg per pulse or per second

d. With this auscultation method, Korotkoff Phase I is regarded as the systolic blood pressure and Korotkoff Phase V as the diastolic blood pressure.

4) Measurement frequency

Blood pressure should be taken at least twice, allowing a 1 to 2- minute interval. If the blood pressure levels from these two measurements are extremely different from each other, a third blood pressure reading must be taken.

5) Assessment

a. The mean of two stable values[*2] should be used as the blood pressure level.
b. Hypertension must be diagnosed based on blood pressure levels measured from at least two different occasions.

6) Other cautions

a. Difference in blood pressure in both upper arms should be checked at the first visit.
b. The cuff should not be applied over a thick shirt/jacket or a shirt/jacket rolled-up that may compress the arm.
c. In patients who may have orthostatic hypotension such as patients with DM or elderly, the blood pressure should be checked at 1 and 3 minutes in a standing position for the presence of orthostatic hypotension.
d. The person who performs auscultation should have sufficient hearing ability and should have received appropriate training for the method.
e. Pulse rate should also be measured and recorded.

[*1] Recently, the use of electronic manometers is recommended in consideration of the mercury effect regarding the environment, accuracy control of mercury columns, and accuracy problems of aneroid manometers. Hybrid manometers with an electronic analog column instead of a mercury column are also available. The use of an automatic cuff winding device in the waiting room should be carefully supervised to prevent errors.

[*2] A stable value refers to measured values with a difference of <5 mm Hg.

4. Diagnostic criteria for dementia

●Imaging finding: CT or MRI

●Cognitive function survey: Mini-Mental State Examination (MMSE)[13)]

●DMS-IV Diagnostic criteria for dementia (a summary)

A. Memory impairment (long-term/short-term)
B. Presence of at least one of the followings
    1. Abstract thinking impairment
    2. Judgment impairment
    3. High cortical function impairment
    (aphasia/apraxia/agnosia/constructional apraxia)
    4. Character change
C. Failure to carry on work/social life/ human relationships due to A/B
D. Diagnosis may not be made when patients have impaired consciousness (excluding delirium)
E. Presence of organic brain factors is inferable from medical history and test results.

1994 American Psychiatric Association DSM-IV (Diagnostic and Statistical Manual of Mental Disorders. 3rd Ed. Revised Ed.)[15)]

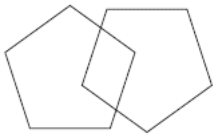
●ICD-10 Diagnostic criteria for dementia (summary)

A. Presence of the following two conditions
    1）Memory impairment that can affect daily life
    2）Cognitive impairment
B. Above conditions in A can be identified for a sufficient duration
    Ability to recognize the surrounding is maintained (clouding of consciousness is not detected)
C. One of the following conditions is detected.
    1）Emotionally unstable
    2）Irritable
    3）Indifferent
    4）Roughness in social behavior
D. Definite diagnosis is made after symptoms in above A are identified for more than 6 months.

1994 World Health Organization ICH-10
(International Classification of Disease 10th revision)

1389 [Cognitive function survey: Mini-Mental State Examination (MMSE)]

Question	Content	Response	Score
1	What year are we in now?	Year	01
	What season is it now?		01
	What day of the week is it today?	Day	01
	What is today's date and month?	Month	01
		Date	01
2	What is the name of this hospital?	Hospital	01
	What prefecture are we in?	Prefecture	01
	What city are we in?	City	01
	What floor are we on?	Floor	01
	What region are we in?	Region	01
3	Please memorize the three words that I say now. «The examiner names three objects that are not related to one another (one second to say each), and asks the patient to repeat them; one point for each correct answer. Repeat until the patient can say all three words (up to six attempts).» e.g., cherry, cat, train; ball, flag, tree.		01 01 01
4	Please subtract 7 from 100, and then 7 from the result. «Ask the patient to count backwards from 100 by subtracting 7 each time (up to five times).»	93 86 79 72 65	01 01 01 01 01

5	Please repeat the three words you memorized before. «Ask the patient to say the words shown in the Question 3; order irrelevant. Clues such as an "animal", "plant" and "vehicle" may be given.»		01 01 01
6	(Showing a watch) What is this? (Showing a pencil) What is this?		01 01
7	Please repeat the sentence, "we unite everyone's strength to pull a rope."		01
8	(3-stage commands) "Take this piece of paper in your right hand." "Fold it in half." "Give it to me."		01 01 01
9	Please follow the written command. "Raise your right hand."		01
10	Please write a sentence.		01
11	Please draw the following figure. 		01
		Total	/30

5. Guidelines for diagnosis of DM –from the Guidelines 2007 compiled by the Japan Diabetes Society–[19)]

1） Diagnosis of DM

Diabetes mellitus is diagnosed based on symptoms, clinical findings, family history, and body weight history in addition to chronic hyperglycemia,.

2） Diagnostic criteria of hyperglycemia

As shown in Table 1, blood glucose condition are classified into three types; diabetic type, normal type, and borderline type based on the combination of

fasting glucose level and glucose level at 2 hours after 75 g oral glucose tolerance test (OGTT). A casual glucose level ≥200 mg/dL is also considered as the diabetic type.

Table 1 Criteria for assessment of fasting glucose level and 2-hour OGTT
(Venous plasma level, mg/dL; figures in parentheses, mmol/L)

	Normal range	Diabetic range
Fasting glucose level glucose 2 hours after 75 g OGTT	<110 mg/dL (6.1 mmol/L) <140 mg/dL (7.8 mmol/L)	≥ 126 mg/dL (7.0 mmol/L) ≥ 200 mg/dL (11.1 mmol/L)
Assessment of 75 g OGTT	Glucose level meets both above criteria is defined as normal type.	Glucose level meets both above criteria is defined as diabetic type.
	Glucose level that belongs to neither the normal type nor diabetic type is defined as the borderline type.	

A casual glucose level ≥200 mg/dL (≥11.1 mmol/L) is also considered as the diabetic type.

Among people with the normal type, those with a 1-hour value ≥180 mg/dL (10.0 mmol/L) have higher risk of developing DM than those with a 1-hour value <180 mg/dL. Therefore, the former case needs to be handled in the same way as people with the borderline type (e.g., requiring extended observation).

3） Diagnosis criteria of DM and diabetic type

Diabetes mellitus is diagnosed when the blood glucose criteria for the diabetic type are recognized on more than two occasions examined on separate dates.

However, the diagnosis can be also made by the criteria for the diabetic type, and one of the following conditions.

(1) Presence of typical symptoms of DM (e.g., thirst, polydipsia, polyuria, weight loss).
(2) HbAlc ≥6.5%
(3) Unequivocal diabetic retinopathy

In an epidemiological study to determine the prevalence of DM, the case is

regarded as DM if hyperglycemia of a diabetic type is observed once.

The presence of diabetes in the patient's medical records

The patient can be considered as having diabetes when past medical records show a diagnosis of diabetes above the diagnostic criteria in section 3, even if the present glucose level is below the standard.

4) Diabetes mellitus that cannot be re-confirmed by repeated tests

If repeated tests of the glucose level and OGTT with several months in between does not confirm the presence of diabetes, further observation with repeated tests is recommended.

5) Normal type and borderline type

Less than 1% of people with the normal type annually progress to the diabetic type. People with the borderline type have a higher rate of the progression to the diabetic type and have a higher frequency of developing arteriosclerotic complications. Lifestyle guidance (regarding diet, exercise, and the correction of obesity if present) and periodic examination must be provided to those with the borderline type. For those with the borderline type and metabolic syndrome, "Appendix: Metabolic Syndrome" should be referred.

6) OGTT Procedures

After fasting for 10 hours or longer, the subject is instructed to take a solution containing 75 g of glucose before breakfast. Blood glucose level is measured by collecting samples at fasting and 30 to 60-minute intervals after glucose administration. While measurement at fasting and two hours after is essential, measurements at the time points in-between are preferable in the clinical practice. Measurements of insulin levels at fasting and at 30 minutes after glucose administration are desirable to investigate the early phase insulin response for following reasons;

(1) Even among people with the normal type, those with a high level of 1-hour glucose tend to progress to the diabetic type.

(2) People with the normal type or borderline type tend to progress to the diabetic type if their insulinogenic index is 0·4 or lower. The insulinogenic index is defined as the ratio between the increase in insulin level (μU/mL) and the

increase in glucose level (mg/dL) measured at 0 to 30 minutes after glucose administration (ΔIRI/ΔPG).

7） Classification of DM and causes of abnormal glucose metabolism

Classification of DM related to the metabolic abnormality is shown in Table 2. Diabetes is roughly classified into four categories; type 1 diabetes, type 2 diabetes, diabetes caused by other mechanisms or diseases, and gestational diabetes. The relationship between the diabetes classification and the progressive severity in metabolic abnormality is shown in Figure 1.

Table 2 Etiology of Diabetes Mellitus Categories in Relation to Decreased Glucose Tolerance*

I. Type 1 (characterized by β-cell apoptosis; usually progresses to absolute insulin deficiency)
   A. Autoimmune
   B. Idiopathic

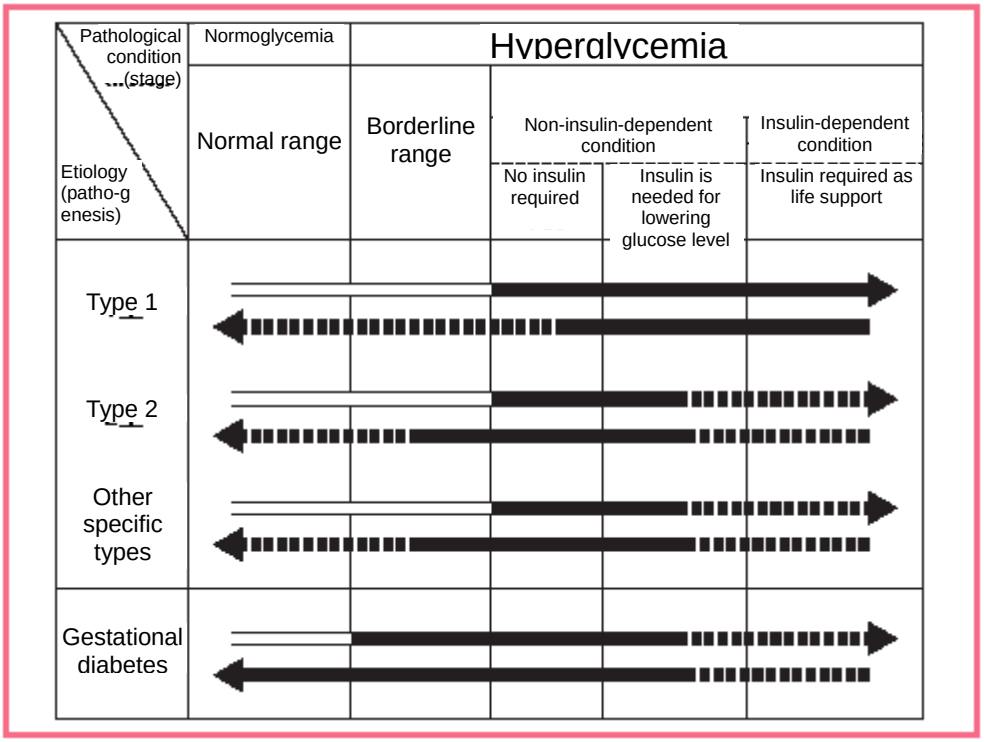
II. Type 2 (caused by decreased insulin secretion or by insulin resistance with relative insulin deficiency)

III. Diabetes caused by other mechanisms or diseases
   A. Genetic abnormality identified as genetic factor for diabetes
      1) Genetic abnormality involving pancreatic β cell function
      2) Genetic abnormality involving in cascade of insulin action
   B. Other diseases or conditions
      1) Pancreatic exocrine disease
      2) Endocrine disease
      3) Hepatic disease
      4) Conditions caused by drugs or chemical substances
      5) Infection
      6) Rare pathological conditions caused by immunological mechanism
      7) Other genetic syndromes that are often accompanied by DM

VI. Gestational diabetes

*: Decreased glucose tolerance which contribution to the development of a diabetic complication may not be verified

Figure 1 Etiology (Pathogenesis) and Pathological Condition (Stage) of Diabetes Mellitus



The arrows pointing to right indicate exacerbation of abnormality in glucose metabolism (including onset of diabetes). Of those, this section, ▪▪▪▪, indicates a condition, "DM." The arrows pointing to the left indicate alleviation of abnormalities in glucose metabolism. Of those, the broken line indicates events with low incidence. For example, some cases of type 2 diabetes may progress to ketoacidosis at the time of infection and may temporarily require insulin therapy for life support. People who once developed diabetes are regarded as patients with diabetes even after the glucose metabolism alleviate. This is presented with the left-pointing arrows of solid black lines. Glucose metabolism rarely becomes completely normal, which is presented by the broken lines in left-pointing arrows.

In range of the glucose level, a non-insulin-dependent condition corresponds to the so-called NIDDM and an insulin-dependent condition to the so-called IDDM.

1473

1474

1475

Confirmation of types of DM and presence of complications

A diagnosis should be made after a thorough investigation of not only the presence of DM but also the types, severity of metabolic abnormality, presence of any complication and its severity.

6. Diagnosis and risk assessment of acute coronary syndrome

– According to the Guidelines for Diagnosis and Treatment of Cardiovascular Diseases (2007 Joint Research Group Report) [18)]

Medical history and physical findings

It is important to take a detailed history of a patient who complains of chest pain. You should pay attention to the nature, site, duration, trigger, temporal change, and concomitant symptoms of the chest pain. There are no specific physical findings for acute coronary syndrome, and they are not necessarily useful in confirming the diagnosis. However, physical findings are often helpful in diagnosing complications of ischaemic heart diseases such as cardiac insufficiency and distinguishing it from other diseases that cause chest pain such as acute aortic dissection. The new classification of the types of unstable angina proposed by Braunwald includes the severity, clinical presentation and treatment circumstance (Table 1). It has been demonstrated that this classification is not only useful to predict a prognosis but is also consistent with coronary arteriographic findings.

Table 1. Classification of unstable angina (Braunwald, 1989)

<Severity>

Class I: New onset of severe or accelerated angina

- Patients with new onset within the last two months
- Patients who develop accelerated angina with three or more episodes/day or precipitated by mild exertion

No angina at rest

Class II: Subacute angina at rest

- Patients who experienced one or more episodes of angina at rest within the last one month but not within the preceding 48 hours

Class III: Acute angina at rest

- Patients who experienced one or more episodes of angina at rest within the preceding 48 hours

<Clinical circumstances>

Class A: Secondary unstable angina (which develops in the presence of extracardiac conditions such as anemia, pyrexia, hypotension, and tachycardia)

Class B: Primary unstable angina (which develops in the absence of extracardiac conditions mentioned for Class A)

Class C: Postinfarction unstable angina (which develops within two weeks after onset of myocardial infarction)

<Treatment circumstances>

1) Unstable angina occurring in the absence of or with minimal antianginal therapy
2) Unstable angina occurring in the presence of the general therapy for stable angina (the administration of conventional doses of β inhibitors, long-acting nitrates and calcium antagonists)
3) Unstable angina occurring in the presence of optimal therapy with antianginal drugs including intravenous nitroglycerin.

1）Diseases that should be distinguished

Diseases that are needed to be distinguished from acute coronary syndrome are shown in Table 2.

Table 2. Diseases that should be distinguished

1. Coronary artery disease:	Angina of effort
2. Myocardial disease:	Acute myocarditis, hypertrophic cardiomyopathy, dilated cardiomyopathy
3. Pericardial disease:	Acute pericarditis
4. Aortic disease:	Acute aortic dissection
5. Valvular disease:	Aortic valve stenosis
6. Pulmonary disease:	Pulmonary embolism, pleurisy, pneumothorax, pneumonia
7. Digestive disease:	Acute abdomen
8. Cerebrovascular disorder:	Subarachnoid hemorrhage

2）Nonoperative examination

2-1) Chest X-ray test and electrocardiography

In the diagnosis of acute coronary syndrome, the chest X-ray test is important to determine a differential diagnosis and severity assessment. For acute coronary syndrome, a precise diagnosis in the early phase is important, and simple electrocardiography occupies an important place even today, though the examination methods have advanced. The temporal change of electrocardiograms is vital, as well as the findings discovered during follow-up visits (ST-T wave change, the presence or absence of Q wave or negative U wave). An exercise stress test should be conducted after the acute coronary syndrome has been stabilized.

Chest X-ray test

Class I

The Chest X-ray test is conducted in patients with the signs and symptoms of cardiac diseases (congestive cardiac failure, valvular heart disease, and ischaemic heart disease) and pericardial diseases, or aortic diseases (dissecting aortic aneurysm).

Class IIa

The Chest X-ray test is conducted in patients with the signs and symptoms of pulmonary/ pleural diseases and mediastinal diseases.

Class IIb

The Chest X-ray test is conducted in all patients with chest pain.

Class III

Not necessary

Resting electrocardiography

Class I

For patients with continued chest discomfort, a 12-lead electrocardiogram should be recorded immediately (within 10 minutes). For patients with a history of chest discomfort that is consistent with acute coronary syndrome but has been resolved at the time of assessment, a 12-lead electrocardiogram should be recorded as soon as possible.

Class IIa

(1) Resting electrocardiogram is recorded for all patients with chest pain.

(2) For patients with suspected ischaemic chest pain, 12-lead electrocardiogram is recorded in an ambulance before admission.

Class IIb

Not necessary

Class III

Not necessary

Exercise electrocardiography

Class I

An exercise electrocardiography is conducted for patients whose symptoms are stabilized by treatment and who can tolerate exercise stress (except for patients with ST change before exercise stress, left bundle branch block, left ventricular hypertrophy, preexcitation syndrome, digitalis therapy or cardiac pacing).

Class II

Not necessary

Class III

Exercise electrocardiography is conducted during the period when the disease condition is not stabilized.

2-2) Echocardiography

Bedside echocardiography is useful for the diagnosis of patients who complain of chest pains and stratification of risks at an emergency outpatient unit. It can also be used to assess heart function and the presence of other organic cardiac diseases.

Class I

(1) Echocardiography is conducted for patients with acute coronary syndrome.

(2) For patients with acute coronary syndrome stabilized by treatment, exercise or drug stress echocardiography is conducted if the assessment with electrocardiography is difficult.

Class IIa

Not necessary

Class IIb

(1) When patient develops a chest symptom, echocardiography is conducted for those with suspected acute coronary syndrome for those who show no obvious abnormality in echocardiography.

(2) For patients with obvious acute coronary syndrome who are not scheduled to undergo coronary angiography and left cardiac ventriculography, echocardiography is conducted to assess left ventricular function.

Class III

Not necessary

2-3) Nuclear medicine study

(1) Nuclear medicine study in an unstable phase

Myocardial perfusion image at rest

When a patient visits the hospital due to chest pain and is not likely to have acute coronary syndrome based on electrocardiography and blood tests that are conducted immediately after the visit or repeatedly, it is beneficial to determine a subsequent therapeutic strategy to take a myocardial perfusion image at rest and assess the presence of acute myocardial ischemia and the site and range of related risk areas.

(2) Nuclear medicine study in stable phase

Exercise or drug stress myocardial perfusion image

When a patient visits the hospital due to chest pain and is not likely to

have acute coronary syndrome based on the follow-up with a 12- to 24-h electrocardiography and blood test, an exercise stress myocardial perfusion image is useful to assess the presence of coronary diseases (related risk areas and the range) and chronic prognosis.

3） Blood biochemistry

The measurement of troponin T and troponin I that are specific to the cardiac muscle can detect very minor myocardial damage with the non-ST-elevation acute coronary syndrome. The elevation is useful to determine the therapeutic strategy and predict cardiac events.

Class I

(1) Biochemical markers of myocardial damage are used for the stratification of early risks of patients with chest pain or discomfort.

(2) A biochemical marker, creatinine kinase (CK and CK-MB), and myocardial troponins (troponin T and troponin I) with high myocardial specificity are measured in all patients with suspected acute coronary syndrome.

(3) Even if the biochemical markers are negative in the measurement within 6 hours after the onset of chest pain, they are measured again 6-12 hours after the onset.

Class IIa

Myoglobin is measured in addition to myocardial troponins within 6 hours after the onset of chest symptoms.

Class IIb

C-reactive protein (CRP) and other inflammatory markers are measured to aid diagnosis.

Class III

Not necessary

4）Invasive examination

4-1) Coronary angiography and left cardiac ventriculography

In general, when acute coronary syndrome is suspected, the patient should be

hospitalized in a facility where coronary angiography can be conducted if possible. The benefits of coronary angiography are as follows: (1) Important information to predict the prognosis and select appropriate treatment can be obtained based on the severity of coronary lesion, (2) we can expect an improved prognosis, decreased doses of antianginal drugs, and shortened hospitalization because of revascularization. The disadvantages of coronary angiography include the occurrence of complications due to an invasive procedure, increased unnecessary PCI, and increased medical costs involved. Left cardiac ventriculography has been conducted as the gold standard of the left ventricular systolic performance assessment. This can record good and highly reproducible images in almost all patients, and it is useful when only unclear echocardiographic images are obtained. The indications for coronary angiography are shown in Table 3, and the indications for left cardiac ventriculography are shown in Table 4.

Table 3 Indications for coronary angiography

Usually indicated	• Patients with recurrent episodes resistant to drug therapy (emergency coronary angiography) • Patients with relapsing symptoms after being stabilized by initial therapy (emergency coronary angiography) • Patients who are considered to be high-risk [Table 6] based on medical history, physical findings, electrocardiogram and biochemical test (quasi-emergency coronary angiography) • High-to moderate-risk [Table 6] patients who are stabilized by initial therapy • Patients with severe ischaemic findings and reduced left ventricular function based on noninvasive test • Patients who underwent PCI within 6 months • Patients with prior coronary artery bypass grafting • Patients with suspected vasospastic angina
Usually not indicated	• Patients with poor objective findings of ischemia • Patients whom coronary revascularization is not indicated for • Patients at high risk from coronary angiography due to comorbidities

Table 4 Indications for left cardiac ventriculography

Usually indicated	Patients who need assessment of left ventricular systolic performance and viable mass and cannot be adequately evaluated with nonoperative examination (it is generally conducted in addition to coronary angiography)
Usually not indicated	Patients with comorbidities such as reduced renal function, who are expected to have risks which overweigh benefit of obtained information

5) Risk assessment and in-hospital and short-term prognoses

We can evaluate risks and predict in-hospital and short-term prognoses using medical history, physical findings and various test findings. The risks of short-term prognosis are stratified into three stages summing up these factors

(Table 5). In addition, the TIMI risk score that uses multiple risk factors has been reported (Table 6). It has been demonstrated that the prognosis worsens synergistically as the number of risk factors increases.

Table 5 Classification of short-term risk

	High risk	Moderate risk	Low risk
Medical history			
Chest pain	At rest Exacerbation within 48 hours	At rest and at night CCS class III° or IV° within 2 weeks	Exertional It started 2 weeks or more ago and the threshold lowers gradually.
Duration	Chest pain lasting not less than 20 minutes Continuous	History of chest pain lasting not less than or not more than 20 minutes	Within 20 minutes
Efficacy of nitrite	Ineffective	Resolved	Effective
Concomitant symptom	Cold sweat, retching, dyspnea	Effective	
Physical findings	New third heart sound Rales in the lung field Holosystolic murmur (mitral regurgitation) Decreased blood pressure, bradycardia, tachycardia		Normal
Electrocardiogram change	ST depression ≥ 0.5 mm Sustained ventricular tachycardia New onset of left bundle branch block	T wave inversion ≥ 3 mm Occurrence of Q wave	Normal
Biochemical findings	Elevated troponin T (qualitative positive, > 0.1 ng/mL)	Elevated troponin T (qualitative positive, less than 0.1 ng/mL)	No elevated troponin T (qualitative negative)

If a patient has one or more of the following histories and conditions, an increase to the next step should be considered.

1. Old myocardial infarction
2. Cerebrovascular and peripheral vascular disorders
3. Coronary artery bypass grafting and percutaneous transluminal coronary angioplasty
4. Administration of aspirin
5. Diabetes mellitus
6. Age ≥75 years old

Table 6 TIMI risk score

(1) Age ≥ 65 years old
(2) Three or more coronary risk factors (family history, hypertension, dyslipidemia [hyperlipidemia], DM and smoking)
(3) Known significant coronary stenosis (> 50%)
(4) Presence of ST deviation ≥ 0.5 mm in electrocardiogram
(5) Presence of two or more angina episodes within 24 hours
(6) Administration of aspirin within 7 days
(7) Elevated markers of myocardial damage
(8) Risk is assessed with the number of risk factors.

Statistical Analysis Plans
(SAP)

Version 1.1

Author The RESPECT study research group

Title A multi-center clinical trial comparing two strategies for control of blood pressure in the patients having had previous strokes: Recurrent Stroke Prevention Clinical Outcome Study (RESPECT Study)

Date 28 Aug 2015 (Translated on 3 September 2018)

Contents

Abbreviations

Abbreviation	Spell out
α	Alpha spending function
ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse events
ALT	Alanine transaminase
ARB	Angiotensin II receptor blocker
AST	Asparagine transferase
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CCB	Calcium channel blocker
CH	Cerebral hemorrhage
CHF	Congestive heart failure
CI	Cerebral infarction
CKD	Chronic kidney disease
Cl	Chlorine
Cr	Creatinine
DBP	Diastolic blood pressure
Diu	Diuretics
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
$HbA1_c$	Hemoglobin $A1_c$
HDL-C	High-density lipoprotein cholesterol
HR	Heart rate
hsCRP	High sensitivity C-reactive protein
ITT	Intention to treat
K	Potassium
LDL-C	Light-density lipoprotein cholesterol
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
mRS	Modified Rankin Scale
Na	Sodium
SBP	Systolic blood pressure
SMI	Silent myocardial ischemia

TC	Total cholesterol
TG	Triglycerides
UA	Uric Acid

I Revision process

This is the 1st version (Ver1.0).

II Objective

This study evaluates whether strict BP management is useful for the prevention of recurrent stroke.

Hypertensive patients with a history of stroke are treated with a stepwise multi-drug therapy to achieve a intensive BP target (≤120/80 mmHg) in an intensive BP treatment group and a standard BP target (≤140/90 mmHg or ≤130/80 mmHg for patients with DM/CKD/old MI) in the standard BP control group. The primary outcome is stroke recurrence. The study will continue until the number of patients who experienced a recurrent stroke reaches a total of 224 in both groups. The incidence rates of recurrent stroke will be compared between the two groups.

III Study Design

The RESPECT study is a multi-center, prospective, randomized, open-label, blinded-endpoint, parallel-group comparison trial

3.1 Participants

Two thousand subjects (1,000 in each group) with essential hypertension and a history of stroke will be included. The detailed inclusion criteria are:

(1) Aged 50-85 years on the day of consent
(2) Any sex
(3) Ability to visit an outpatient clinic
(4) Thirty days to 3 years since the onset of index stroke (cerebral infarction and/or intracerebral cerebral hemorrhage)
(5) Drug adherence rate ≥80 % during the screening period
(6) Untreated hypertension or hypertensive patients on 1-3 BP lowering medications with a mean of 2 office BP measurements within 30 days prior to the date of consent is 130-179/80-109 mmHg
(7) Modified Rankin scale of 3 or less

3.2 Randomization

Participants will be randomly allocated to the intensive BP control group or the standard

BP control group via a web-based randomization system. Randomization will be stratified by age (≥70 years), the presence of DM/CKD/old MI, and atrial fibrillation

(1) The intensive therapy group: BP target is <120/80 mmHg) using stepwise multi-drug protocol;

(2) The standard therapy group: BP target is <140/90 mmHg (<130/80 mmHg if there is DM/CKD/old MI), using stepwise multi-drug protocol.

IV Interim analysis and last statistical evaluation

Two interim analyses and one final analysis are planned.

4.1 Date for last evaluation

The study will be closed when 244 recurrent stroke events are observed.

4.2 Interim analysis

An interim analysis will be performed when 50% of the planned stroke events (i.e. 122 events) are observed or at 5 years from the start of the study (i.e. 2015), and the second interim analysis will be performed when 80% of the planned stroke events (i.e. 200 events) are observed.

V Statistical analysis

5.1 Statistical hypotheses

The risk for stroke recurrence is not equal between the intensive BP control group and the standard BP control group.

5.2 Statistical significance

Two interim analyses and the final analysis will be performed based on Lan-DeMets's Alpha Spending functions.

5.2.1 Statistical significance for the final analysis

A log-rank test will be used to compare time to the primary outcome between the intensive BP control group and the standard BP control group using the intension-to-treat principle. The final level of significance consisting of three looks will consequently be 0.0478 (two-sided).

If the significance level is satisfied for the primary outcome, the same level of significance

(0·0478) will be used for secondary outcomes without considerations of issues among multiple comparisons. If the significance level is not satisfied for the primary outcome, the significance level of p<0·006 (two-sided) (1/8 of p=0·0478) will be used for the secondary outcomes.

5.2.2 Statistical significance for the interim analysis and early termination of the trial

The study will be terminated early if the two-sided p-value is <0·0015 at the first interim analysis with 122 events or if <0·0118 at the second interim analysis with 200 events. The same two-sided p-value of <0·0015 will be used when the first interim analysis is conducted at 5 years from the start of the study (i.e. 2015) without reaching 122 events. For the safety purposes, the composite outcome of the primary outcome and serious adverse events will be used for the interim analyses only.

VI Analysis population

In accordance with the intention to treat (ITT) principle, all patients except for (1) those who immediately withdraw their consent and (2) those who do not have any information after randomization, will be included in the analysis.

VII Outcomes

7.1 Primarily outcome

The time from randomization to onset of the first recurrent stroke (cerebral infarction and intracerebral hemorrhage) will be compared between the intensive BP control group and the standard BP control group using a log-rank test in the principle of intension-to-treat (ITT) with a significance level of p<0·0478 (two-sided).

7.2 Secondary outcomes

The time from randomization to the first event of each outcome will be compared between the groups using a log-rank test in the principle of intension-to-treat (ITT).

- Cerebral infarction
  Subclassified into: lacunar infarction, atherothrombotic infarction, cardio-embolic infarction and other/unclassified/unknown
- Intracerebral hemorrhage
- Subarachnoid hemorrhage
- Transient ischemic attack
- Myocardial infarction

- Composite cardiovascular outcomes (cardiovascular death, nonfatal stroke, nonfatal myocardial infarction)
- All death
- All death + nonfatal stroke + nonfatal myocardial infarction

7.3 Safety outcomes

The frequency of serious adverse events will be compared between the randomized groups.

- Angina (not including silent myocardial ischemia)
- Congestive heart failure (new-onset or exacerbation)
- Atrial fibrillation (new-onset or exacerbation defined as change from paroxysmal to sustained)
- Vascular surgery or endovascular intervention
- Ruptured aortic aneurysm or aortic dissection
- Peripheral arterial disease (new-onset or exacerbation)
- Renal dysfunction (increase of serum creatine ≥2·0mg/dL or dialysis)
- Diabetes mellitus (new-onset)
- Gout (new-onset)
- Abnormal serum potassium (<3·0 mg/dL or ≥5·5 mg/dL)
- Dementia (new-onset or exacerbation)
- Malignant neoplasm
- Others

VIII Missing values

In principle, missing values will not be imputed.

IX Statistical analysis

In accordance with the intention to treat (ITT) principle, all patients except for (1) those who withdraw their consent and (2) those who do not have any information after randomization, will be included in the analysis.

Statistical analysis will be conducted using SAS and STATA software.

9.1 Baseline characteristics of the study population

A categorical variable will be summarized as the number of cases (percentage) in each group. A continuous variable will be summarized as a mean (SD) in each group.

Continuous variables that do not follow a normal distribution, will be summarized as a median (interquartile range). In addition, unknown values of each variable will be treated as missing values.

9.2 Primary and secondary outcomes

The incidence rate of each outcome in each group will be estimated using the person-year approach according to the intension-to-treat principle. The cumulative incidence for each group at each time point will also be estimated using the Kaplan-Meier method. If a patient is lost to follow-up, the patient will be censored at the last visit. The difference in incidence of outcomes between the randomized groups will be compared using a log-rank test with the level of statistical significance as described in 5.2.2. The difference will also be compared using a Cox's proportional hazards model and a hazard ratio; 95% confidence interval will be reported. If there is significant imbalance among important factors in the baseline characteristics, a multivariable-adjusted Cox's proportional hazards model will be used as a sensitivity analysis.

9.3 Safety outcomes

Frequencies of each safety outcome will be estimated both in the intensive BP control group and in the standard BP control group.

X Outline of the tables/figures

	Table or figure	Grouping	Variables
Baseline Characteristics	Table	Randomized groups	Age, gender, height, weight, BMI, SBP, DBP, HR, history of cerebral infarction, history of intracerebral hemorrhage, mRS, history of myocardial infarction, angina, atrial fibrillation, Silent myocardial ischemia, DM, CKD, liver dysfunction, dementia, malignant neoplasm, pre-trial BP lowering therapy, pre-trial antithrombotic therapy
Blood pressure	Table and Figure	Randomized groups and visits	SBP, DBP, H R

BP lowering medications	Table	Randomized groups and visits	Number of medications, drug class
Lab tests	Table	Randomized groups and visits	Cr, BUN, UA, TC, HDL-C, LDL-C, TG, AST, ALT, Na, K, Cl, Ca, HbA1c, urinary albumin, body weight
Incidence of outcomes	Table	Randomized groups	* Primary outcome * Cerebral infarction and its subtypes * Intracerebral hemorrhage * Subarachnoid hemorrhage * Transient ischemic attack * Myocardial infarction * Composite cardiovascular outcome * Total death * Total death + nonfatal stroke + nonfatal myocardial infarction
Cumulative incidence	Figure	Randomized groups	* Primary outcome

Safety outcomes	Table	Randomized groups	*Angina pectoris *Congestive heart failure *Atrial fibrillation *Vascular surgery or endovascular intervention *Ruptured aortic aneurysm or aortic dissection *Peripheral arterial disease *Renal dysfunction *Diabetes mellitus *Gout *Abnormal serum potassium *Dementia *Malignant neoplasm *Others

Continuous variables will be summarized as mean (SD), median (interquartile range), or mean (95%CI). Categorical variables will be summarized by percentages.