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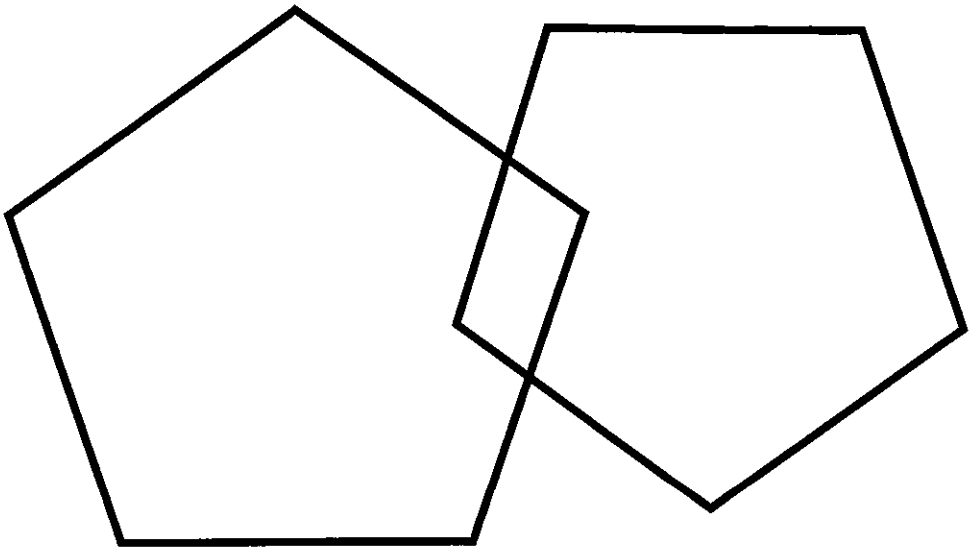

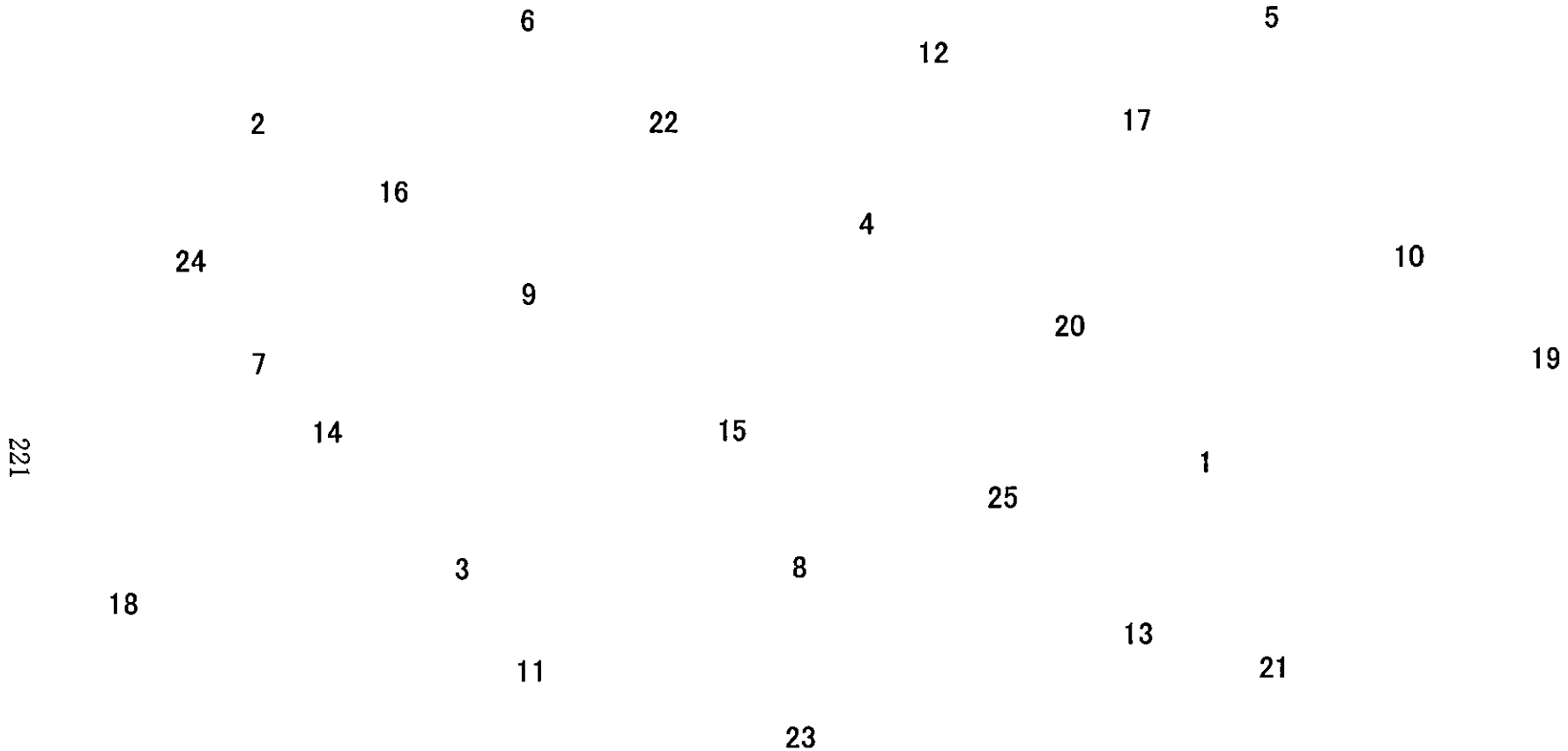
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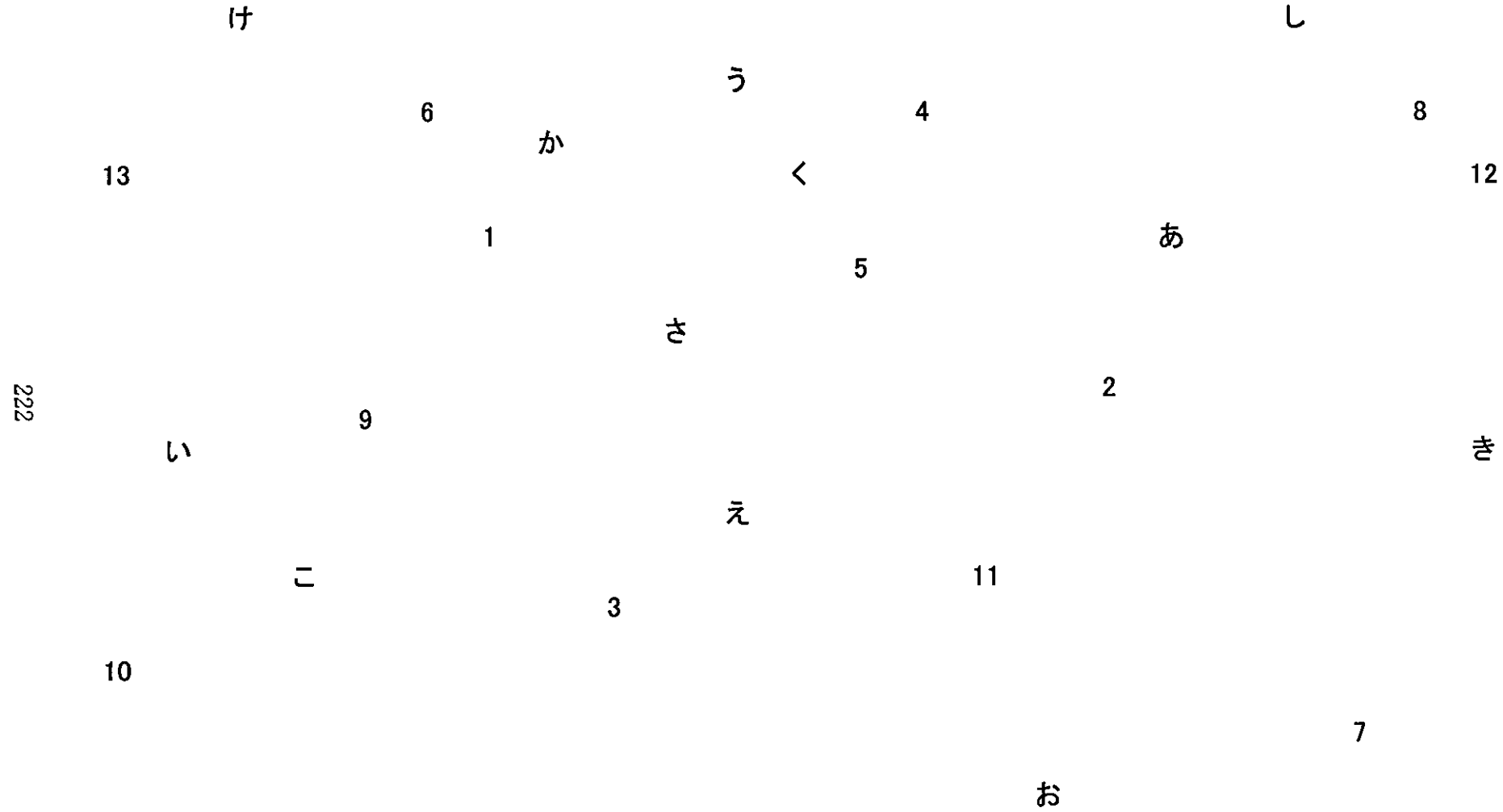
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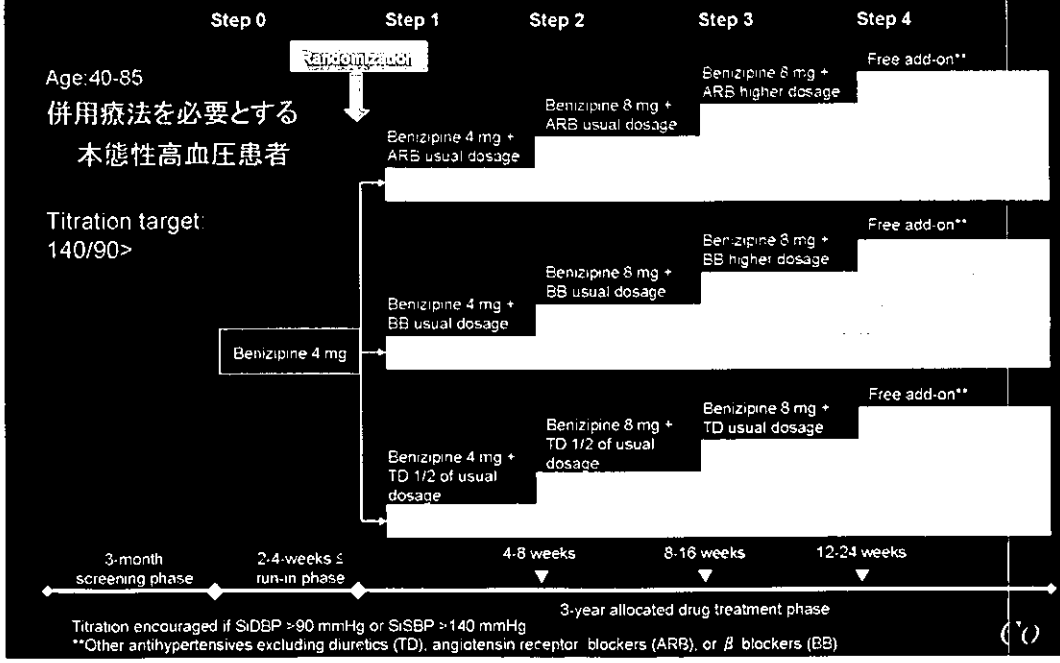
B．降圧剤の組み合わせによる心血管イベント抑制効果の比較

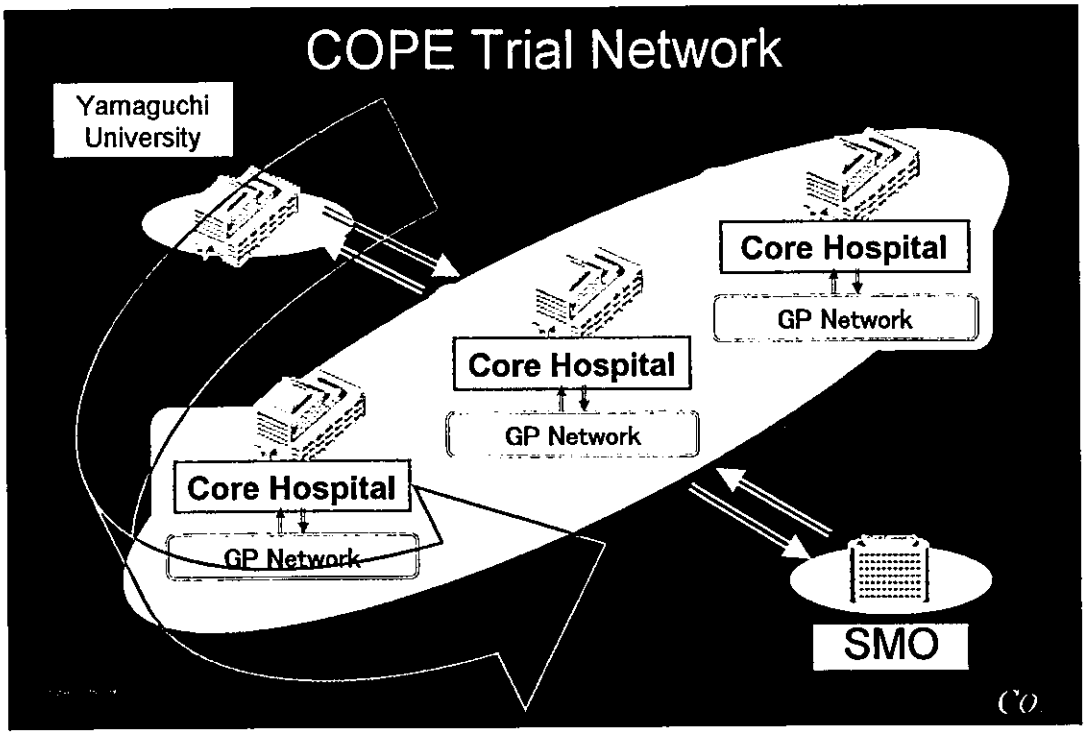
The COmbination Therapy of Hypertension to Prevent Cardiovascular Events Trial the COPE Trial

the COPE Trial Investigators

Design/Dosing Titration

Hypertens Res 2005:28(4) *in press.*

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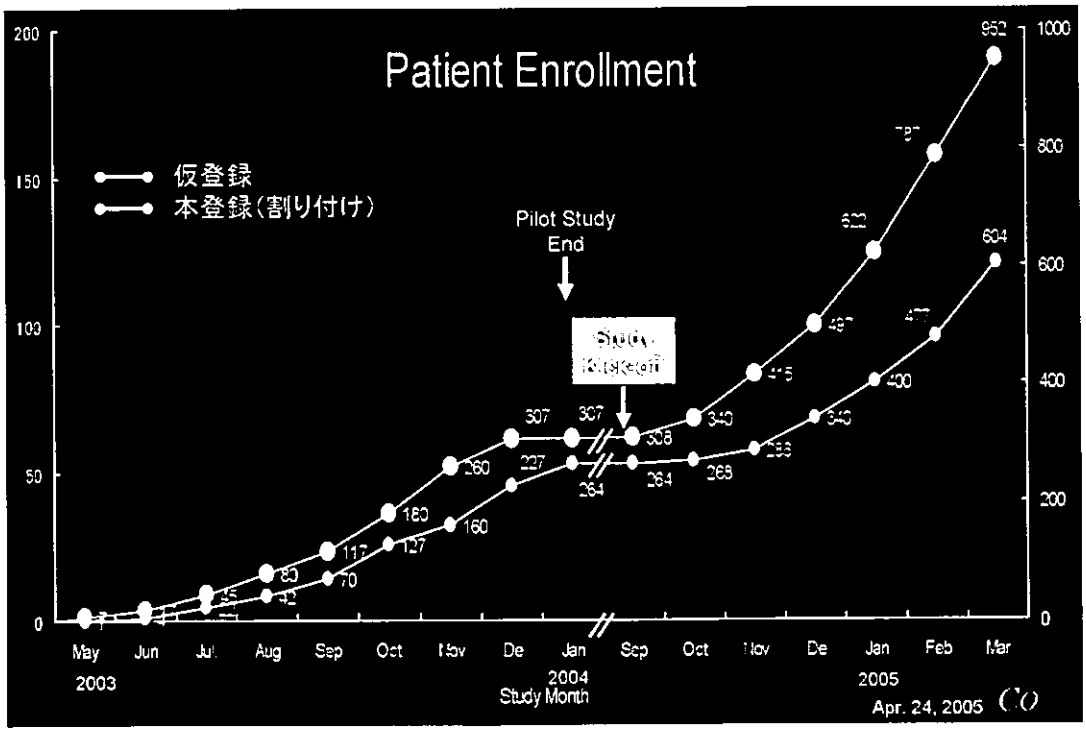
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Ⅳ．研究成果の刊行に関する一覧表

書籍

著者名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
Maekawa T, Hayashi N, Ogino K, Takezawa J, Nagao S, Ohashi Y, Yamashita S, Okabayashi K	A randomized controlled trial of therapeutic hypothermia in severe head-injured patients in Japan : Overview of the protocol.	Hayashi N, Bullock R, Dietrich DW, Maekawa T, Tamura A	Hypothermia for acute brain damage pathomechanism and practical aspects.	Springer-Verlag	Tokyo	2004	246-250

雑誌

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
Toshio Ogihara, Masunori Matsuzaki, Hiroaki Matsuoka, Kazuaki Shimamoto, Kazuyuki Shimada, Hiromi Rakugi, Seiji Umemoto, Akira Kamiya, Norihiro Suzuki, Hiroo Kumagai, Yasuo Ohashi, Shuichi Takishita, Keishi Abe, Takao Saruta, for the COPE Trial Group.	The Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) Trial. Rationale and Design.	Hypertension Research	28(4)	321-338	2005

A Randomized Controlled Trial of Therapeutic Hypothermia in Severe Head-Injured Patients in Japan: Overview of the Protocol

Tsuyoshi Maekawa[1], Nariyuki Hayashi[2], Keiki Ogino[3], Jun Takezawa[4], Seigo Nagao[5], Yasuo Ohashi[6], Susumu Yamashita[1], and Kiyoshi Okabayashi[1]

Summary. Protection against brain insults is one of the most difficult aspects of clinical practice. Recently, mild hypothermia has been applied to cardiopulmonary resuscitated victims and brain-protective effects were proved by two randomized, controlled trials (RCT). Clifton's group applied mild hypothermia therapy in severe head-injured cases (Glasgow Coma Scale; GCS < 8), but failed to prove any effectiveness. Our aim is to apply mild hypothermia therapy as a RCT in 300 traumatic brain injury cases in 40 medical centers in Japan. Inclusion criteria are: (1) GCS 4–8, except best motor response of 6; (2) core body temperature must be reduced to less than 35.5°C at 6 h after head injury in the mild hypothermia group; (3) age ≤ 15 to <70 years old. Patients are randomized into either a control group (35.5°–37.0°C, 100 patients) or a mild hypothermia group (32.0°–34.0°C, 200 patients). Core body temperature must be controlled for at least 72 h in the two groups and may be prolonged, if necessary. Brain-oriented intensive care is required; physiologic parameters are qualified by cardiac index, as well as internal jugular venous oxygen saturation and temperature, which are recorded and stored in a computer in every 1 min. Evaluations of the effect of mild hypothermia therapy are carried out using the Glasgow Outcome Scale at 3 and 6 months, and by biochemical parameters such as cytokines, free radical products, and neurotoxic excitatory amino acids between the two groups. At this point in time, 74 patients have been enrolled.

Key words: Therapeutic hypothermia, Traumatic brain injury, Internal jugular venous oxygen saturation, Glasgow Outcome Scale, Neurochemicals

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Introduction

The pathophysiologic mechanisms responsible for damaging the brain following severe traumatic brain injury (TBI) are multiple, such as glutamate excitotoxicity, intracellular Ca^{2+} overload, free radicals, cytokines and so on, besides the ordinary mechanisms [1]. On the other hand, therapeutic strategies are very poor from the clinical point of view.

Recently, animal experiments have provided persuasive evidence that mild hypothermia confers significant protection against ischemic or traumatic brain insults [2]. In contrast to hypothermia, slight elevation of brain temperature worsened the outcome and very high brain temperature (up to 43.8°C) was actually recorded [3]. Based on these facts, clinical application of therapeutic mild hypothermia has been applied to stroke, severe head-injured, and cardiac arrest-resuscitated victims. The effectiveness of therapeutic mild hypothermia was proven by two randomized controlled trials (RCT) in cardiac arrest-resuscitated patients [4,5].

In severe TBI patients, more than 45 potentially relevant articles have been published [6–8]. Among these clinical trials and their meta-analyses [9], none could prove the effectiveness of mild hypothermia therapy based on neurological outcome. The reasons for failure are not clear, but they seem to the similar to those of brain protection/resuscitation therapy by barbiturate coma. In this report, our RCT of mild hypothermia therapy in severe TBI patients (Glasgow Coma Scale; GCS 4–8) in Japan is introduced.

Brief Overview of the Protocol

Our primary hypothesis is that mild hypothermia for at least 72 h in TBI patients will improve neurological outcome at 3 and 6 months as quantified by the Glasgow Outcome Scale (GOS) score and high brain performance functions at 6 months evaluated by the Mini-Mental Statement, Trial Making Test B, and animal naming test, as compared with antihypothermia (normothermia). It is our secondary hypothesis that mild hypothermia will also improve neuro-pathophysiological events as assessed by cerebrospinal fluid (CSF) excitatory amino acids, free radical-related molecules, and cytokines in a limited number of the patients.

Our RCT investigators consist of four clinicians, an epidemiologist, and a biostatistician. Forty centers, mainly university emergency and critical care medical centers, are involved. Three hundred patients who have been admitted with TBI within 6 h following the insults will be enrolled. Inclusion and exclusion criteria are shown in Table 1. Statistical design and sample size calculations are as follows. The RCT is designed to achieve a power of 0.90 and alpha = 0.05 (two-sided) to detect an improvement of 20% in the number of patients with GOS (good outcome plus moderately disabled). Patients are randomized by a 24-h internet allocation system developed by the University Medical Information Network (Tokyo University, Tokyo). The allocation is done by a modified minimization method using each medical center, age (more than 45 or less than or equal to 45 years old), and GCS (4–5 or 6–8) as adjustment variables. The allocation of the patients is shown in Table 2. Neurological outcome evaluated by GOS at 3 and 6 months following TBI will be analyzed when the entry number of the patients reaches 150 (primary research). If a significant effect cannot be obtained, the protocol will be continued with different anesthesia methods, from midazolam and analgesics to neuroleptics. If an effect is then obtained, the protocol will be changed to evaluate the difference between the two anesthesia methods with the effective temperature, either 32.0°–34.0°C or 35.5°–37.0°C (secondary research, Table 2).

TABLE 1. Inclusion and exclusion criteria for therapeutic hypothermia in our protocol

Inclusion criteria

1. Glasgow Coma Scale (GCS) score 4–8, except a case of best motor response = 6
2. Age is ≥15 and <70 years old
3. Either male or female
4. Informed or waiver of consent required

Exclusion criteria

1. Persistent hypotension; systolic blood pressure <90 mmHg
2. Platelet count <50 000/μl
3. Severe liver and/or renal failure
4. Acute myocardial infarction, heart failure, or severe arrhythmia
5. Pregnancy or suspected pregnancy
6. Deep drunkenness
7. Severe penetrating brain injury
8. Suspected good neurological outcome by hematoma evacuation
9. Core body temperature less than 30°C on admission
10. Difficult to adapt to mild hypothermia

TABLE 2. Sample size, grouping, and anesthesia methods

Primary research				
150 cases		Hypothermia M (Midazolam) group	32.0°–34.0°C	100 cases
4 ≤ GCS ≤ 8		Control M (Midazolam) group	35.5°–37.0°C	50 cases
Secondary research				
Primary research	150 cases	Hypothermia NLA group	32.0°–34.0°C	100 cases
is not significant	4 ≤ GCS ≤ 8	Control NLA group	35.5°–37.0°C	50 cases
Primary research	150 cases	Effective temp. M group		75 cases
is significant	4 ≤ GCS ≤ 8	Effective temp. NLA group		75 cases

Registration: 300 cases (24 h applicable using UMIN).
UMIN, University Medical Information Network in Japan; GCS, Glasgow Coma Scale score; NLA, Neurolept analgesia using droperidol and fentanyl.

Midazolam and analgesics with chlorpromazine, or droperidol and fentanyl, are used with nondepolarizing muscle relaxants (pancuronium or vecuronium). In the mild hypothermia and control groups, core body temperature is kept at 32.0°-34.0°C and 35.5°–37.0°C, respectively, for at least 72 h. In the mild hypothermia group, it is preferred that core body temperature be less than 35.5°C at 6 h after TBI, and it is permitted to maintain hypothermia for at least 72 h, if required from a clinical point of view.

In addition to ordinary monitoring, special data are collected such as core body temperature (measured in the brain, internal jugular vein, pulmonary artery, or bladder), internal jugular venous oxygen saturation (Q2 continuous cardiac output/SO2 Computer and a catheter; Abbott Laboratories, North Chicago, IL, USA), cardiac index, and mixed venous oxygen saturation (Vigilance CEDV and a catheter; Edwards Life Sciences, Irvine, CA, USA), which are collected every 1 min and stored in a computer until 72 h following the onset of TBI. Intracranial or cerebrospinal fluid pressure is also monitored, if possible. Brain-oriented intensive care (Table 3) is required. Cessation of the mild hypothermia is very important, this being decided upon by brain computed tomography and/or intracranial pressure. Rewarming in the hypothermia group is allowed 72 h after the onset of TBI. The patients should not be warmed, but the degree of cooling tapered off (less than 0.1°C/h), usually

TABLE 3. Brain-oriented intensive care

Respiration
- PaO_2 > 150 mmHg, or around 100 mmHg (long term)
- Neurogenic pulmonary edema: 3–5 cm PEEP and head-up tilt
- $PaCO_2$ = 35–40 mmHg
  - change by internal jugular venous oxygen saturation or by intracranial pressure
- Prevent fighting against the ventilator and excessive body movements

Circulation
- Cerebral perfusion pressure = 60–100 mmHg
  - relatively low in head-injured patients
  - relatively high in hypertensive patients
- Antiarrhythmia
  - lidocaine: 1–2 mg kg^{-1}, propranolol: 1 mg (total dose ≤10 mg)
- Prevention of hypotension
  - volume load with plasma expanders without glucose
  - dopamine: 2–15 $\mu g\,kg^{-1}\,min^{-1}$, dobutamine: 2–15 $\mu g\,kg^{-1}\,min^{-1}$
  - (avoid persistent peripheral vasoconstriction)
- Prevention of hypertension
  - Ca-blocker (may cause intracranial hyperemia, hence intracranial hypertension)
    - diltiazem: 2 mg i.v., 5–15 $\mu g\,kg^{-1}\,min^{-1}$
    - nicardipine: 10–20 $\mu g\,kg^{-1}$ i.v., 0.3–3.0 $kg\,min^{-1}$
- Prevent intracranial hypertension: <20 mmHg
- Hemodilution
  - Ht = 30%–50%, Hb = 10–12 $g\,dl^{-1}$
- Head-up tilt position
  - 10°–30°
- Prevent excessive neck rotation, flexion, and extension

Metabolism
- Plasma glucose
  - 120–140 $mg\,dl^{-1}$, prevent hyperglycemia and hypoglycemia
- Fluid management
  - electrolyte solution: 30–50 $ml\,kg^{-1}day^{-1}$
  - pH: 7.3–7.5, Na^+: 135–145 $mEq\,l^{-1}$, K^+: 3.5–5.0 $mEq\,l^{-1}$
  - Ca^{2+}: 2.0–2.6 $mEq\,l^{-1}$, Mg^{2+}: 0.98–1.14 $mEq\,l^{-1}$ (Mg: 1.4–2.6 $mg\,l^{-1}$)
  - serum osmolality: 280–320 $mOsm\,l^{-1}$
  - colloid osmotic pressure >15 mmHg, albumin >4 $g\,dl^{-1}$
- Nutrition
  - start nasointestinal tube feeding at early days: 30–50 $kcal\,kg^{-1}\,day^{-1}$
  - prevent stress-induced gastric ulcer
- Body temperature: 35.5°–37.0°C
  - mild hypothermia preferred for severe cases (32.0°–34.0°C)
- Seizure: diazepam 0.2 $mg\,kg^{-1}$, or thiopental 2–5 $mg\,kg^{-1}$

PEEP, positive end-expiratory pressure.

taking a few days. Thereafter, core body temperature is kept below 37.0°C until day 7 after TBI. Brain computed tomography is taken to assess and report on admission and at 7 ± 1 days.

Patients are examined daily for 2 days, on day 3, 1 day before warming, and 1–2 days after rewarming. Glasgow Outcome Scale at days 7 and 30, and at 3 and 6 months, will be assessed. The physician taking part in the RCT cannot be blinded, but the individual responsible for all neurological outcome assessments will be completely blinded. Primary end points will

be evaluated by GOS at 3 and 6 months, and high brain performance functions at 6 months following TBI. Secondary end points will be evaluated by GCS at 7 and 30 days and by physiologic parameters, such as cardiac index, mixed venous oxygen saturation, and internal jugular venous oxygen saturation. Neuropathological molecules, such as excitatory amino acids (glutamate and aspartate), free radical-related molecules (NO_2^-, NO_3^-, nitrotyrosine, 8-hydroxy-2′-deoxyguanosine), and cytokines (tumor necrosis factor-α, interleukin-6, interleukin-10, interleukin-8, granulocyte/monocyte colony-stimulating factor, interferon-γ) in cerebrospinal fluid, blood, or urine will be measured in a limited number of the patients in each group. At this point in time, 74 patients have been enrolled.

References

1. Siesjo BK (1993) Basic mechanisms of traumatic brain damage. Ann Emerg Med 22:959–966
2. Busto R, Globus MY-T, Dietrich WD, et al (1989) Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 20:904–910
3. Hayashi N, Hirayama T, Udagawa A, et al (1994) Systemic management of cerebral edema based on a new concept in severe head injury patients. Acta Neurochir (suppl) 60:541–543
4. The Hypothermia after Cardiac Arrest Study Group (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346:549–556
5. Bernard SA, Gray TW, Buist MD, et al (2002) Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346:557–563
6. Clifton GL, Allen S, Barrodale P, et al (1993) A phase II study of moderate hypothermia in severe brain injury. J Neurotrauma 10:263–271
7. Marion DW, Penrod LE, Kelsey SF, et al (1997) Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 336:540–546
8. Tateishi A, Soejima Y, Taira Y, et al (1998) Feasibility of the titration method of mild hypothermia in severely head-injured patients with intracranial hypertension. Neurosurgery 42: 1065–1070
9. McIntyre LA, Fergusson DA, Hebert PC, et al (2003) Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review. JAMA 289:2992–2999

Original Article

The Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) Trial: Rationale and Design

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A number of major clinical trials have demonstrated the clinical benefits of lowering blood pressure and have indicated that a majority of patients with hypertension will require more than one drug to achieve optimal blood pressure control. However, there is little data showing which antihypertensive combination best protects patients from cardiovascular events and which best achieves the target blood pressure with the fewest adverse events. The Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trial is the first large-scale investigator-initiated multicenter study with a prospective, randomized, open, blinded endpoint evaluation (PROBE) design to directly compare cardiovascular mortality and morbidity, incidence of adverse drug reaction, and degree of blood pressure reduction in Japanese hypertensive patients for a combination of angiotensin receptor blockers, β-blockers or thiazide diuretics in addition to a calcium antagonist, benidipine hydrochloride, with a response-dependent dose titration scheme. The COPE trial is being conducted with the cooperation of more than 100 centers and clinics in Japan and involves 3,000 patients, who will be followed for 3 years. Eligible patients are being enrolled from May 2003 until May 2006. Results from the COPE trial should provide new evidence for selecting optimal combination therapies for hypertensive patients. (*Hypertens Res* 2005; 28: 331–338)

***Key Words*: hypertension, multicenter clinical trial, PROBE (prospective, randomized, open, blinded endpoint evaluation), combination therapy, benidipine**

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Introduction

Hypertension is an important risk factor for cardiovascular diseases (*1*, *2*). The treatment goal for hypertension is decreasing morbidity and mortality by reducing organ damage and preventing cardiovascular complications. Large-scale clinical trials comparing various antihypertensives have been conducted to investigate their benefits in preventing cardiovascular events due to hypertension. They have shown that treatment with any commonly used regimen reduces the risk of major cardiovascular events and that increased reductions in blood pressure produce a better outcome in decreasing cardiovascular events and mortality (*3–5*). It remains uncertain whether the results obtained in Western countries can be directly applied to the Japanese population because of the differences in intrinsic/extrinsic racial factors between Western countries and Japan, such as the dosage of the drugs, the dietary habits, including higher salt intake (*6*), and the cardiovascular event rates (*7*, *8*). In addition, various combinations of antihypertensive agents are often required to achieve optimal blood pressure control (*9*). Recent clinical guidelines for the treatment of hypertension recommend the combination therapy to achieve optimal blood pressure control (*3*, *10–12*). However, the effects of the combination of antihypertensive drugs have not been well investigated in regard to morbidity and mortality in patients with hypertension. Therefore, it is important to determine which combinations will achieve an optimal outcome with the fewest side effects.

Rationale

It has been reported that all antihypertensive drugs have similar long-term efficacy and safety for the prevention of cardiovascular events in patients with hypertension (*4*), with calcium antagonists being especially effective in stroke prevention (*4*, *13–15*). The Japanese Society of Hypertension Guidelines for Management of Hypertension in 2000 (JSH 2000) recommends calcium antagonists as a first-line drug for the treatment of hypertension (*12*). Prescription rates of the antihypertensive drugs in Japan are reported as follows: calcium antagonists, 73.0%; angiotensin-converting enzyme (ACE) inhibitors, 31.3%; angiotensin receptor blockers, 18.9%; β-blockers, 16.2%; and diuretics, 10.1% (*16*). Recent surveys in Japan revealed that only 50% of the subjects under antihypertensive treatment achieved the targeted blood pressure levels (*17*, *18*). Although selection of some antihypertensive drugs was based on evidence from previous trials on hypertensive patients with diabetes mellitus, chronic heart failure, and renal insufficiency, calcium antagonists were selected for most age groups and in most patients with various complications associated with hypertension. Japanese doctors do not appear to consider age or complications when choosing antihypertensive regimens (*16*). Meta-analysis of 354 randomized double-blind placebo-controlled trials (*19*) demonstrated that the blood pressure reduction effects of different categories of drugs were additive, and symptoms attributable to thiazides, β-blockers, and calcium antagonists were strongly dose-related, whereas angiotensin receptor blockers caused no increase in symptoms. Furthermore, the prevalence of symptoms with two drugs in combination was less than additive, and adverse metabolic effects (such as changes in cholesterol or potassium) were negligible at a half-standard dose, indicating that low-dose combination treatment increases efficacy and reduces adverse drug reactions (*19*). In Japan, Saito *et al.* reported that the most common first-choice drugs by hypertension specialists were a calcium antagonist (69%) or an ACE inhibitor (22%). They further described that 72% selected a calcium antagonist and an ACE inhibitor as a combination therapy, and 17% selected a calcium antagonist and angiotensin receptor blocker as their first-choice drug combination (*20*). Since calcium antagonists are widely and successfully used for the treatment of hypertension in Japan (*21*), it is most likely that combination therapy with a calcium antagonist and some other antihypertensive drug will be chosen as the first-choice combination therapy for the treatment of hypertension. In addition, in Japan, as opposed to Western countries, cerebrovascular events, which are significantly positively related to hypertension, are more frequent than cardiovascular events (*7*). According to the current status of hypertension treatment in Japan, as stated above, the Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trial was designed to investigate, in patients with hypertension, which combination of antihypertensive drugs—angiotensin receptor blockers, β-blockers, or thiazide diuretics in addition to a long-acting calcium antagonist, benidipine hydrochloride—is superior for achieving the targeted blood pressure and preventing cardiovascular events with the fewest adverse drug effects. The COPE trial is conducted as a collaborative research project between Yamaguchi University and Kyowa Hakko Kogyo Co., Ltd. (Tokyo, Japan).

Table 1. Inclusion Criteria for the COPE Trial

1. Outpatients who are required a combination therapy with sitting systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg
2. Outpatients aged over 40 years and less than 85 years (inclusive), regardless of sex
3. Previously untreated patients or patients who are on other therapy, which can be converted to 4 mg of benidipine
4. Patients who can be treated with benidipine, angiotensin receptor blockers, β-blockers, and thiazide diuretics

COPE, Combination Therapy of Hypertension to Prevent Cardiovascular Events.

Ethics Committee Procedure and Consent

The study protocol was approved by the ethics committees of

Table 2. Exclusion Criteria for the COPE Trial

1. Seated systolic blood pressure ≥200 mmHg or seated diastolic blood pressure ≥120 mmHg
2. Secondary hypertension
3. Type 1 diabetes mellitus or type 2 diabetes on insulin treatment
4. History of cerebrovascular disorder, myocardial infarction, angina pectoris, coronary angioplasty or coronary artery bypass graft surgery within 6 months prior to enrolment in the study
5. Heart failure (NYHA functional classification II, III or IV)
6. Chronic atrial fibrillation or atrial flutter
7. Congenital heart disease or a history of rheumatic heart disease
8. Severe peripheral arterial disease (Fontaine Class II, III or IV)
9. Serious liver dysfunction (AST or ALT ≥100 IU/l)
10. Serious renal dysfunction (serum creatinine ≥2 mg/dl)
11. History of malignancy 5 years prior to study entry
12. Pregnancy
13. Compliance rate <70% assessed by a patient interview
14. Known hypersensitivity or contraindication to benidipine, angiotensin receptor blockers, β-blockers, and thiazide diuretics
15. Other serious illness or significant abnormalities that the investigator judges inappropriate for the study

COPE, Combination Therapy of Hypertension to Prevent Cardiovascular Events; NYHA, New York Heart Association; AST, alanin aminotransferase; ALT, aspartate aminotransferase.

all institutions involved, and the trial was undertaken in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies in Japan (2003, Ministry of Health Labour Welfare of Japan: http://www.imcj.go.jp/rinri/index.html). All patients gave fully informed written consent.

Study Design

The COPE trial is an investigator-initiated, multi-center study with a prospective, randomized, open, blinded endpoint evaluation (PROBE) design (*22*) with a response-dependent dose titration scheme in Japanese hypertensive patients, who are prescribed a long-acting dihydropyridine calcium antagonist, benidipine, as an initial drug, and then assigned to receive either an angiotensin receptor blocker, β-blocker, or thiazide diuretic as a combination therapy. Benidipine has been widely used and proved beneficial for the treatment of hypertension (*23–25*). The target blood pressure of the COPE trial is less than 140/90 mmHg.

Patient Recruitment

Enrollment of eligible patients began in May 2003 and will continue through May 2006, and follow-up will be continued until May 2009. Inclusion and exclusion criteria are shown in Tables 1 and 2. The design outline of the COPE trial is shown in Fig. 1. Patients already receiving antihypertensive treatment are directly enrolled in the run-in phase of the COPE trial, discontinuing previous drugs and starting at an initial dosage of 4 mg of benidipine (step 0). All patients are required to be treated with benidipine for at least 4 consecutive weeks during the screening and run-in phases. During the run-in phase, blood pressure levels and compliance with benidipine are monitored. If the average blood pressure level at the last baseline visit is equal to or more than 140/90 mmHg and compliance is 70% or more, patients will be randomly assigned to receive an angiotensin receptor blocker, β-blocker, or thiazide diuretic and the initial dosage of benidipine as in step 1. Eligible patients are randomly assigned to one of the three study arms. The randomization is conducted at the COPE Trial Data Center by the dynamic allocation method (the modified minimization method) after stratification by regional block, health center, gender, age, systolic blood pressure (SBP), presence/absence of diabetes, and previous vascular events as adjusting factors in the minimization calculation.

Patient Follow-Up

Following randomization, patients receive follow-up visits over the remaining study period, during which safety parameters are checked annually, any adverse events are noted, and any interim endpoints are recorded. If a blood pressure target of <140/90 mmHg is not obtained, dose-titration is encouraged as shown in Fig. 1. A resting ECG is recorded and carotid bruit is examined at study entry and annually thereafter. During the course of the trial, if for any reason the investigator considers it advisable, the study drug can be withdrawn, but all such patients remain in the study and continue to receive full annual examinations and 6-month interim follow-up visits until the end of the study period. All the information obtained at every 6-month follow-up visit along with the information on cardiovascular events, adverse events, and investigations into discontinuation, if any, will be transmitted to the COPE Trial Data Center. Since patient withdrawal decreases the study's statistical power to detect

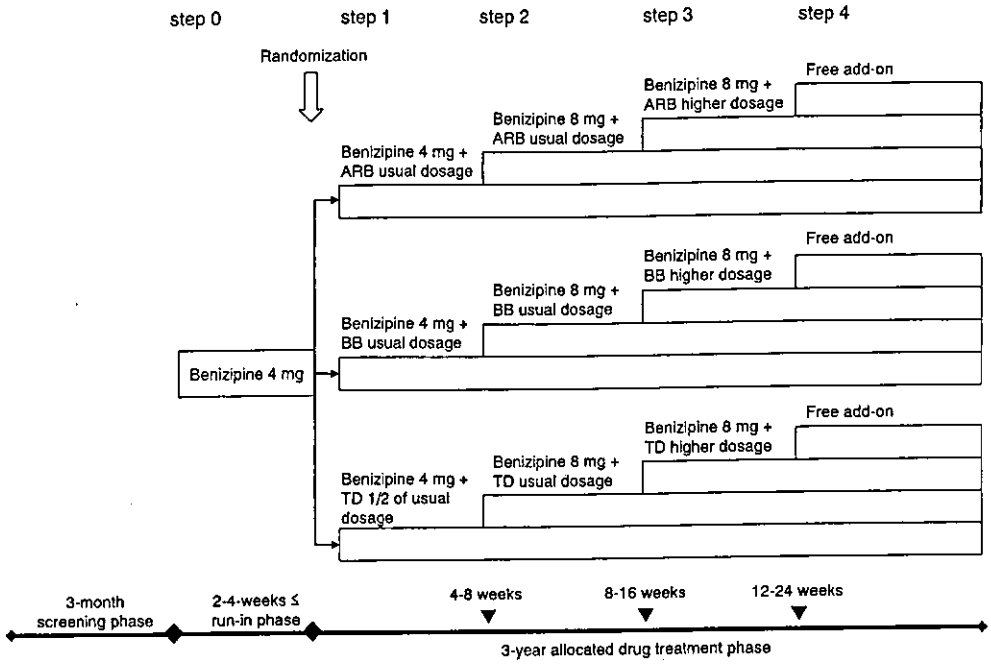

Fig. 1. *Outline of the design of the COPE trial. ARB, angiotensin receptor blockers; BB, β-blockers; TD, thiazide diuretics. "Free add-on" indicates that antihypertensive drugs other than those used for allocation—*i.e., *antihypertensive drugs other than calcium antagonists, angiotensin receptor blockers, β-blockers, or thiazide diuretics—can be added onto the drugs at step 4.*

the true effect of any intervention, all the collaborating investigators counsel their patients regarding the importance of the patients' adherence to the trial. In this way adverse event and clinical endpoint data continue to be collected on all patients. Patients withdrawn from the study drug during the treatment period may be switched to the other drugs or re-prescribed, if possible, at the investigator's discretion. If there is a need to start any therapy for any clinical indication during the study period, the investigator may prescribe additional therapy on top of the study drug. Drugs and dosages can be added at the investigator's discretion.

Endpoint Assessment

An Independent Endpoint Classification Committee will review and adjudicate cardiovascular events and all deaths and classify all potential cases without knowledge of assigned drugs according to criteria specified in the endpoint protocol. The classification of primary and secondary endpoints is shown in Table 3. For the review of the trial, the endpoint reports of the Endpoint Classification Committee will be sent to the Independent Data Monitoring Committee at 6-month intervals.

Adverse Events

All patients are questioned about adverse events at each follow-up visit. If a serious adverse event occurs, the investigators, at their discretion, may interrupt or discontinue the study drug. Both serious and non-serious adverse events are recorded, and the Safety Committee will review the data. The reports of the Safety Committee will be sent for review to the Independent Data Monitoring Committee at 6-month intervals.

Safety Considerations

The Independent Data Monitoring Committee, not involved in the administration of the trial, monitors all endpoints and medically serious and non-serious adverse events, and will perform interim analyses on the primary efficacy parameters at intervals throughout the study. The Independent Data Monitoring Committee receives safety reports from the Safety Committee and endpoint reports from the Endpoint Classification Committee at 6-month intervals, and will convene to review the trial. This Committee will have sole access to unblinded data and will inform the Steering Committee if there is a recommendation to discontinue the trial.

Statistical Considerations

Sample-Size Determination

The planned sample size (total 3,000, each arm 1,000) was determined mainly by considerations of feasibility. Regarding the proportion of patients attaining the target blood pressure levels, which is one of the primary endpoints, the

Table 3. Primary and Secondary Endpoints

1. Primary endpoints
1) A composite of fatal and non-fatal cardiovascular events
(1) Sudden death (acute onset and intrinsic death within 24 h)
(2) Fatal or nonfatal stroke (new onset or recurrence)
(3) Fatal or nonfatal myocardial infarction (new onset or recurrence), hospitalization due to unstable angina, new onset of heart failure (Class II, III, or IV), sudden cardiac death
(4) New onset or worsening of peripheral arterial disease
(5) New onset or worsening of renal failure (as indicated by a serum creatinine level that is at least doubled to over 2 mg/dl), serum creatinine ≥4.0 mg/dl, renal dialysis or renal transplantation
2) Achievement of target blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)
2. Secondary endpoints
(1) All-cause mortality
(2) Death from cardiovascular events
(3) Fatal and non-fatal cardiovascular events
(4) Hospitalization due to heart failure
(5) New onset of diabetes mellitus
(6) Safety (adverse events and adverse drug reaction)

required sample size for detecting a 5% difference among treatment arms around the average proportion 50% (type I error, two sided $\alpha=0.10$ with multiplicity adjustments; power $1-\beta=0.90$) is about 620 for each arm, and thus the planned sample size is expected to have high statistical power. The required sample size for detecting a clinically significant difference in one of the primary endpoints, the incidence of cardiovascular events, with a high statistical power is huge (5,000–10,000 for each arm in the current situation), as will be illustrated later. Therefore, the objective of this trial is to identify the optimal combination of drugs based on the achievement of target blood pressure level, incidence of cardiovascular events, profile of major adverse drug reactions, and incidence of newly diagnosed diabetes. For three endpoints, besides incidence of cardiovascular events, sufficient statistical power is expected with a sample size greater than 600 per arm, and the current sample size (total 3,000) was selected to assure a high probability of selecting a better combination (if there are differences among arms in the incidence of vascular events), as described later. The results of this trial will be submitted to future meta-analyses of similar trials with the objective of comparing anti-hypertensive drug combinations, and the sample size used will protect against interactions between trial and treatment arms.

Based on recent Japanese clinical trials (*14*, *26*), the incidence of cardiovascular events in the patient population of this trial is expected to be around 20/1,000 person-years or around 15/1,000 person-years if the combination therapy is effective. The expected person-years and the expected number of events from the planned follow-up of 3,000 patients are approximately 11,000 and 165–220, respectively. On the other hand, the necessary number of events for detecting a clinically significant risk ratio of 1.2 (two sided $\alpha=0.05$; $1-\beta=0.90$) is 633 in an inferior arm. The necessary numbers of events for assuring the non-inferiority of the diuretic arm against the other two arms combined are 475 and 380 in each arm if the clinically acceptable limit of risk ratios are 1.2 and 1.25, respectively (under the assumption of the diuretic arm being similarly effective). These numbers are far from those expected from the current settings of this trial. Therefore, we calculated the number of events necessary to assure the high probability in such a way that the results of a truly better arm will not be overtaken by those of a truly inferior arm; the necessary number is calculated as 70–80 in each arm if the clinically significant risk ratio is defined as 1.2 and the probability is set to 0.95 (taking account of a multiplicity of 3 comparisons). This number is attainable by the current settings of this trial.

Statistical Analysis

The incidence of cardiovascular events, which is one of the two primary endpoints, is analyzed using the methods of time-to-event analysis (*27*). The cumulative incidence rates are calculated using the Kaplan-Meier method defining the random allocation date as the starting point. The comparison among treatment arms is conducted using the log-rank test. If the overall p-value is less than 0.10, then a pair-wise comparison is calculated for the interpretation. The logarithm of hazard ratio and its 95% confidence interval are calculated from the log-rank scores and the Cox regression with adjustment of important prognostic factors for each comparison of drug combinations. Based on these statistics, Bayesian posterior probabilities for superiority and non-inferiority among treatment arms are calculated; the limit of clinical equivalence is set as 1/1.2–1.2.

The other primary endpoint, the cumulative proportion of patients attaining the target blood pressure levels, is summarized using the Kaplan-Meier method and compared by the generalized Wilcoxon test. All statistical tests will be two-sided with values of $p<0.05$ indicating statistical significance unless otherwise stated.

Organizational Structure

The organization and the members of the various committees of the COPE trial are given in Appendix. The Principal Study Coordinators and the Steering Committee have responsibility for the general design and administration of the study. This includes the responsibility for reviewing and implementing recommendations from the Independent Data Monitoring Committee, for protocol changes, and for premature termination of the study because of lack of treatment efficacy or early demonstration of benefit. Together, these activities will ensure that the trial is progressing properly, efficiently, and in accordance with protocol. The Protocol Committee has responsibility for the study design and protocol changes. The Safety Committee is responsible for the evaluation of adverse events and for recommendations to the Steering Committee if a serious adverse event occurs. The Endpoint Classification Committee is responsible for evaluation of the primary and secondary endpoints. This committee consists of a chair, 2 cardiologists, 2 nephrologists, and 2 neurologists. The Independent Data Monitoring Committee is responsible for overseeing the welfare of the patients enrolled in the trial, reviewing the compliance and trial progress at specified intervals as requested by the Executive Committee, and making recommendations to the Executive Committee should any problems arise. The Study Statistician is responsible for designing the statistical analysis plan and determining the validity of the analysis results. The Coordinating Center is responsible for organizing the Committees and will analyze the study data. The Coordinating Center liaises with the COPE Trial Data Center, which is responsible for patient registry and data management.

Discussion

Hypertension is a major risk factor for cardiovascular diseases. It is evident that most patients with moderate or severe hypertension require two or more antihypertensive agents to achieve appropriate blood pressure control (*3*, *10*, *11*). The recent guidelines for hypertension in the USA and Europe recommend using a combination of two agents as an initial therapy in patients with moderate or severe hypertension (*3*, *10*). An obvious disadvantage of initiating with two drugs, even if at a low dose, is the potential for exposing the patient to an unnecessary agent, but the advantages of combination therapies are: 1) by using two drugs with different mechanisms of action, it is more likely that the blood pressure will be controlled and complications prevented; 2) by using combinations, both the first and second drugs can be given in the low-dose range, which is more likely to be free of side-effects, thus optimizing compliance (*10*). It is likely that some combinations of antihypertensive agents are more clinically effective than others; however, despite the recommendation of the major hypertension treatment guidelines that combination therapy be used as a first-line treatment, only a limited number of reports have attempted to identify which combinations are best for antihypertensive treatments and for the prevention of cardiovascular disease (*3*, *10*). Thus, it is clear that the next challenge will be to determine which combination regimens will provide the greatest cardiovascular benefits for patients with hypertension.

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) cites 30 combination drugs for hypertension (*3*). Most of these combination drugs consist of an antihypertensive and a diuretic. In Japan, however, calcium antagonists are the most widely prescribed antihypertensives (*21*). When a questionnaire survey was administered to Japanese clinical specialists in hypertension to gauge their opinions on the 1999 revised version of the Guidelines for Hypertension in the Elderly, 65% of the respondents selected long-acting calcium antagonists, ACE inhibitors, and low-dose diuretics as first-line agents for the treatment of hypertension without complications in the elderly (*28*). In addition, it was reported that the combination of a calcium antagonist with an ACE inhibitor or angiotensin receptor blocker was their first-choice drug combination (*20*). It is generally considered that the most rational combinations consist of a calcium antagonist and either an ACE inhibitor, an angiotensin receptor blocker, a β-blocker, or a thiazide diuretic (*10*). Therefore, it is very useful and important to compare the efficacy of each calcium antagonist-based combination in Japan.

In the COPE trial, the calcium antagonist benidipine was selected as the initial drug for combination therapy for the treatment of essential hypertension in Japan. Several mega-trials and meta-analyses have confirmed that calcium antagonists are as effective as other agents in reducing overall morbidity and mortality in hypertensive patients, and that they also lower blood pressure (*4*, *28*, *29*). It has also been demonstrated that calcium antagonists decrease the risk of stroke more effectively than other treatments in patients with essential hypertension (*30*). Benidipine is well tolerated at a dose of 4–8 mg/day and is an effective treatment for patients with mild to moderate hypertension (*24*). In addition, it is suggested that combination therapy with benidipine and an angiotensin receptor blocker decreases blood pressure more effectively than either drug alone and may be expected to add benefits to the treatment of hypertension (*31*, *32*).

To ensure data quality, efficiently enroll a sufficient number of patients, and improve administration of the trial, clinical research coordinators from the site management organization will provide the collaborating investigators with technical assistance in data collection and report preparation, thereby reducing their workload.

In conclusion, the COPE trial is an important study that will help to clarify the questions of which antihypertensive combination confers the best protection against cardiovascular mortality and morbidity, and which antihypertensive combination best achieves the target blood pressure.

Appendix

The Combination Therapy of Hypertension to Prevent Cardiovascular Events Trial Group

Principal Study Coordinators: T. Ogihara, T. Saruta.

Steering Committee: M. Matsuzaki (Chairman), K. Kikuchi, S. Itoh, H. Matsuoka, H. Suzuki, T. Fujita, J. Higaki, T. Etoh, C. Tei, A. Kamiya.

Protocol Committee: H. Matsuoka (Chairman), K. Shimamoto, H. Kumagai, H. Rakugi, S. Takishita, Y. Ohashi, S. Umemoto.

Safety Committee: N. Suzuki (Chairman), S. Nogawa, T. Yoshikawa, K. Yumura, K. Utsunomiya.

Endpoint Classification Committee: K. Shimada (Chairman), K. Kario, K. Kitagawa, H. Makino, M. Matsumoto, K. Hayashi, M. Kawana.

Independent Data Monitoring Committee: K. Abe (Chairman), M. Fujishima, K. Otsuka, Y. Ohashi, K. Tanabe.

Study Statistician: Y. Ohashi.

Coordinating Center: EBM Office, Pharmaceutical Clinical Research Center, Yamaguchi University Hospital.

References

1. Kannel WB: Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA* 1996; **275**: 1571–1576.
2. Gorelick PB, Sacco RL, Smith DB, *et al*: Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA* 1999; **281**: 1112–1120.
3. Chobanian AV, Bakris GL, Black HR, *et al*: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**: 1206–1252.
4. Staessen JA, Wang JG, Thijs L: Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001; **358**: 1305–1315.
5. Turnbull F: Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; **362**: 1527–1535.
6. Yamori Y, Nara Y, Mizushima S, Sawamura M, Horie R: Nutritional factors for stroke and major cardiovascular diseases: international epidemiological comparison of dietary prevention. *Health Rep* 1994; **6**: 22–27.
7. Levi F, Lucchini F, Negri E, La Vecchia C: Trends in mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world. *Heart* 2002; **88**: 119–124.
8. Ueshima H, Zhang XH, Choudhury SR: Epidemiology of hypertension in China and Japan. *J Hum Hypertens* 2000; **14**: 765–769.
9. Koshy S, Bakris GL: Therapeutic approaches to achieve desired blood pressure goals: focus on calcium channel blockers. *Cardiovasc Drugs Ther* 2000; **14**: 295–301.
10. European Society of Hypertension–European Society of Cardiology Guidelines Committee: 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**: 1011–1053.
11. Whitworth JA, World Health Organization, International Society of Hypertension Writing Group: 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003; **21**: 1983–1992.
12. Japanese Society of Hypertension Guidelines Subcommittee for the Management of Hypertension: Guidelines for the management of hypertension for general practitioners. *Hypertens Res* 2001; **24**: 613–634.
13. Gong L, Zhang W, Zhu Y, *et al*: Shanghai trial of nifedipine in the elderly (STONE). *J Hypertens* 1996; **14**: 1237–1245.
14. National Intervention Cooperative Study in Elderly Hypertensives Study Group: Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. *Hypertension* 1999; **34**: 1129–1133.
15. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker *vs* diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**: 2981–2997.
16. Yamamoto Y, Sonoyama K, Matsubara K, *et al*: The status of hypertension management in Japan in 2000. *Hypertens Res* 2002; **25**: 717–725.
17. Japanese Society of Hypertension Guidelines Subcommittee for the Management of Hypertension: Guidelines for the Management of Hypertension 2004. Tokyo, Life Science Publishing Co., Ltd., 2004, pp 4–6.
18. Hozawa A, Ohkubo T, Kikuya M, *et al*: Blood pressure control assessed by home, ambulatory and conventional blood pressure measurements in the Japanese general population: the Ohasama study. *Hypertens Res* 2002; **25**: 57–63.
19. Law MR, Wald NJ, Morris JK, Jordan RE: Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003; **326**: 1427.
20. Saito I, Kawabe H, Tsujioka M, Hirose H, Shibata H: Trends in pharmacologic management of hypertension in Japan one year after the publication of the JSH 2000 guidelines. *Hypertens Res* 2002; **25**: 175–178.
21. Saruta T: Current status of calcium antagonists in Japan. *Am J Cardiol* 1998; **82**: 32R–34R.
22. Hansson L, Hedner T, Dahlof B: Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. *Blood Press* 1992; **1**: 113–119.
23. Kalke S, Shah BV, Nair KG, Gala D, Sood OP, Bagati A: Clinical trial of benidipine in mild to moderate hypertension. *J Assoc Physicians India* 1999; **47**: 195–197.
24. Hoshide S, Kario K, Mitsuhashi T, Ikeda U, Shimada K: Is there any difference between intermediate-acting and long-acting calcium antagonists in diurnal blood pressure and autonomic nervous activity in hypertensive coronary artery disease patients? *Hypertens Res* 2000; **23**: 7–14.
25. Nomura M, Nakaya Y, Uemura E, *et al*: Effects of benidipine hydrochloride on autonomic nervous activity in hypertensive patients with high- and low-salt diets. *Arzneimittelforschung* 2003; **53**: 314–320.