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.

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