*Original Article*

# Design and Baseline Characteristics of an Observational Study in Japanese Patients with Hypertension: Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH)

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**The Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) study is a nationwide, prospective, multicenter observational study that was designed to enroll hypertensive Japanese patients (>30,000 subjects). The patients in this study received treatment with open-label losartan, an angiotensin II receptor antagonist, for a maximum of 5 years. This report summarizes the study protocol and the baseline characteristics of the patients. Between June 2000 and May 2002, patients were screened in all 47 prefectures around Japan. Among the 31,515 patients screened, 31,048 patients were enrolled in this study and treated with losartan at a daily dose of 25–50 mg. These patients were 62.4±12.1 years old (mean±SD) and the mean clinic systolic/diastolic blood pressure (BP) values were 165.3±17.3/94.3±11.7 mmHg (mean±SD). The complications of hyperlipidemia, diabetes mellitus, cardiovascular disease, and cerebrovascular disease were also present in 38.5%, 13.1%, 8.0%, and 4.4% of patients, respectively. Regarding the World Health Organization classification, grade 2 hypertension was most frequent in this patient cohort. Nearly 10,000 patients agreed to perform home BP monitoring and report details regarding their lifestyles at baseline. Among the patients, 4.2% had white coat hypertension at the baseline. The J-HEALTH study is expected to provide valuable information about the significance of clinic and home BP control and home BP monitoring for the management of hypertension in Japanese patients. (*Hypertens Res* 2007; 30: 807–814)**

***Key Words*: hypertension, losartan, blood pressure, cardiovascular disease, home blood pressure monitoring**

## Introduction

Hypertension is one of the most important risk factors for the development of cerebrovascular disease, coronary heart disease, and renal disease (*1*). In Japan, management of hypertension is also one of the major public health issues, since there are approximately 30 million hypertensive patients (*2*).

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The goal of antihypertensive therapy is to reduce the incidence of hypertension-related events. Many large-scale clinical trials have already demonstrated the benefits of antihypertensive treatment with drug therapy (*3*, *4*). Based on these results, guidelines for the clinical management of hypertension such as "Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004)" and the recommendations of the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) have been established and used in the daily management of hypertension (*5*, *6*). According to such guidelines, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are first-line agents for the treatment of hypertension, especially in hypertensive patients with diabetes.

Losartan potassium (losartan), a subtype 1 (AT1) selective angiotensin II (AII) receptor antagonist, has been widely prescribed worldwide. Several reports have suggested that losartan not only lowers the blood pressure (BP) values, but also has target organ protective effects. The Losartan Intervention for Endpoint Reduction (LIFE) study was a double-blind, prospective, parallel group trial that was designed to compare the effects of losartan with those of the β-blocker atenolol on cardiovascular morbidity and mortality in approximately 8,300 hypertensive patients with left ventricular hypertrophy. It demonstrated that losartan had a more favorable effect on cardiovascular events than atenolol (*7*). The Reduction of Endpoints in Non–Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study was a multinational, double-blind, randomized, and placebo-controlled trial that enrolled 1,513 patients with type 2 diabetes and nephropathy. It demonstrated a renoprotective effect of losartan (*8*).

Although studies conducted in Western countries have reported various beneficial effects of losartan therapy (*7*–*11*), the actual therapeutic benefit for Japanese patients has been unclear. Because the genetic and environmental background may differ between Japanese and Western patients (*12*, *13*), an investigation of the effects of losartan in Japanese hypertensive patients would be of value. Accordingly, the Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) study was initiated in 2000 as a large-scale observational study of losartan therapy.

Recently, the significance of home BP monitoring has been an important topic in the management of hypertension (*14*–*16*). Since large-scale analysis of home BP data has not been performed in Japan, direct evidence of the significance of home BP values for future cardiovascular events is still lacking (*17*). Accordingly, the J-HEALTH study was performed to investigate the long-term antihypertensive efficacy and safety of losartan, and the incidence of cardiovascular events and mortality in this population. The study also aimed to investigate whether home BP monitoring would be effective for use in routine antihypertensive treatment.

**Table 1. Exclusion Criteria**

- Pregnant or could become pregnant, or breast-feeding
- Severe hepatic or renal disease
- Diseases of poor prognosis; malignant neoplasm, performing hemodialysis, or virus infections such as HIV
- Taking the study drug prior to the registration
- Recent stroke or myocardial infarction within 1 month
- Other inappropriate conditions judged by each investigator

HIV, human immunodeficiency virus.

## Methods

### Objectives

This study was designed to enroll 30,000 patients with hypertension throughout Japan, and the patients were treated with losartan on an open-label basis at a daily dose at 25–50 mg with standard clinical management for a maximum of 5 years. The aims of this study were to investigate the efficacy and safety profile of losartan during actual clinical use in the 5-year post-marketing period, the incidence of cardiovascular events and mortality, the value of lifestyle modification as antihypertensive therapy, and the relationship between the clinic BP and the home BP values in Japanese hypertensive patients primarily treated with losartan.

### Patients Recruitment

The eligible patients were men or women ≥20 years of age who were diagnosed as having hypertension by their physicians and had not taken any antihypertensive agents within the previous 1 month. Patients who had previously take losartan were excluded. The other exclusion criteria are shown in Table 1. Each patient was informed of the purpose and methods of the study, as well as the effects and possible risks of losartan therapy, the right to withdraw from the study at any time, and the measures for privacy protection before they were enrolled. Patients provided their verbal informed consent and then underwent a complete medical history review, physical examination, and laboratory evaluation.

### Drug Treatment and Study Procedure

The patients were initially treated with losartan at a dose of 25–50 mg once daily (usually in the morning), which is the approved dosage in Japan. The dose was increased up to a dose of 100 mg once daily, if necessary. Addition of other antihypertensive agents was allowed from 3 months after the start of losartan treatment, if required. No restrictions were placed on the treatment of complications.

The enrolled patients were registered in a central study registry that included the following information at baseline:

**Table 2. Patients' Characteristics at Baseline**

| | Men | Women | Total |
|---|---|---|---|
| Number of patients (*n* (%)) | 13,737 | 17,311 | 31,048 |
| Age (years old) | 60.0±12.0 | 64.3±11.8 | 62.4±12.1 |
| SBP (mmHg) | 164.4±17.0 | 165.9±17.4 | 165.3±17.3 |
| DBP (mmHg) | 96.2±11.6 | 92.8±11.6 | 94.3±11.7 |
| BMI (kg/m$^2$) | 24.3±3.3 | 23.9±3.8 | 24.1±3.6 |
| Alcohol drinkers (*n* (%)) | 9,147 (66.6) | 2,674 (15.4) | 11,821 (38.1) |
| Current smokers (*n* (%)) | 6,085 (44.3) | 1,664 (9.6) | 7,749 (25.0) |
| Complications | | | |
| Hyperlipidemia (*n* (%)) | 4,935 (35.9) | 7,005 (40.5) | 11,940 (38.5) |
| Diabetes mellitus (*n* (%)) | 2,170 (15.8) | 1,883 (10.9) | 4,053 (13.1) |
| Cardiovascular disease (*n* (%)) | 1,097 (8.0) | 1,400 (8.1) | 2,497 (8.0) |
| Cerebrovascular disease (*n* (%)) | 616 (4.5) | 745 (4.3) | 1,361 (4.4) |
| Hepatic disease (*n* (%)) | 1,901 (13.8) | 1,069 (6.2) | 2,970 (9.6) |
| Renal disease (*n* (%)) | 509 (3.7) | 496 (2.9) | 1,005 (3.2) |
| ECG abnormality (*n* (%)) | 2,119 (15.4) | 2,234 (12.9) | 4,353 (14.0) |
| Concomitant drugs | | | |
| Lipid-lowering drugs (*n* (%)) | 2,632 (19.2) | 5,033 (29.1) | 7,665 (24.7) |
| Antidiabetics (*n* (%)) | 1,452 (10.6) | 1,336 (7.7) | 2,788 (9.0) |
| UA lowering drugs (*n* (%)) | 1,371 (10.0) | 239 (1.4) | 1,610 (5.2) |
| Aspirin or antiplatelets (*n* (%)) | 1,102 (8.0) | 1,188 (6.9) | 2,290 (7.4) |

Mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; UA, uric acid.

demographic data, physical data (height and body weight), history of hypertension, and use of antihypertensive drugs; BP values and pulse rate; complications and medical history (renal disease, hepatic disease, cerebrovascular disease, coronary heart disease, endocrine/metabolic disease, and other diseases); laboratory test results (complete blood count, biochemistry tests, and urinalysis); lifestyle modification if performed (physical exercise, restriction of alcohol consumption or salt intake, ceasing smoking, weight loss, *etc*.); and electrocardiograph findings.

The following patient information was recorded in the worksheets and collected every year after the start of losartan-based antihypertensive treatment: adverse events, clinic BP values, pulse rate, heart rate, weight, daily dose of losartan, concomitant drugs, laboratory tests, and ECG (if performed).

The clinic BP was measured by the routine method at each institution. At each time of measurement, one clinic BP value was reported at the discretion of the physician. The clinic BP data measured at a maximum of 3 different visits prior to starting losartan therapy was used for calculation of the mean baseline clinic BP. After starting losartan therapy, the clinic BP value was measured every 3 months. The clinic BP data thus obtained were used for analysis of the clinic BP values during treatment.

The home BP was measured during the study by patients who voluntarily agreed to monitor their BP themselves. Home BP was measured with an electronic automated sphygmomanometer based on the cuff-oscillometric principal (HEM-740A; Omron Healthcare Co., Ltd., Kyoto, Japan). Patients who had already been using another device and insisted on continuing its use were permitted to do so. Patients were asked to measure the home BP at rest in the sitting position once every morning just after waking and urinating, and before medication. Home BP was measured once at one opportunity of measurement. If the patient measured home BP twice or more at one opportunity, the first measured value was reported. Home BP values obtained prior to the start of losartan therapy were used to calculate the mean baseline home BP. As a rule, morning home BP values measured each month, usually on the day of attending hospital, were used for analysis of the mean home BP value during treatment.

Standard laboratory tests (including ECG recording) were performed with the routine methods used at each institution, so standardization of measuring methods and reference values was not carried out. A maximum of 2 results of standard laboratory tests measured prior to losartan therapy were used to calculate the baseline values. After the start of losartan therapy, standard laboratory tests were performed every 6 months.

To assess the complications and the medical history, physicians judged the existence of diseases indicated in the registration form prior to the start of the study at their discretion.

In addition, the patients who were receiving drug treatment for hyperlipidemia or diabetes mellitus and met the definition of either disease indicated in the relevant guidelines were defined as having hyperlipidemia or diabetes.

All adverse events were recorded by the investigators and were classified as definitely related, possibly related, or defi-

**Table 3. Distribution of Age and WHO Hypertension Grade, and Mean Blood Pressure at Baseline**

| | Men ($N$=12,698) | | Women ($N$=16,250) | | Total ($N$=28,948) | |
|---|---|---|---|---|---|---|
| | *n* (%) | SBP/DBP (mmHg) | *n* (%) | SBP/DBP (mmHg) | *n* (%) | SBP/DBP (mmHg) |
| Age (years old) | | | | | | |
| 20–39 | 556 (4.4) | 160.1±16.0/102.2±11.3 | 261 (1.6) | 163.5±16.7/101.9±10.6 | 817 (2.8) | 161.2±16.3/102.1±11.1 |
| 40–59 | 5,518 (43.5) | 163.5±16.7/100.1±10.4 | 5,494 (33.8) | 167.1±18.2/97.9±10.5 | 11,012 (38.0) | 165.3±17.6/99.0±10.5 |
| 60–79 | 6,029 (47.5) | 165.5±17.0/92.9±11.1 | 8,963 (55.2) | 165.3±16.8/90.6±10.7 | 14,992 (51.8) | 165.4±16.9/91.5±10.9 |
| ≥80 | 595 (4.7) | 165.4±18.9/87.0±11.5 | 1,532 (9.4) | 166.0±18.4/85.7±12.1 | 2,127 (7.4) | 165.9±18.5/86.0±12.0 |
| BP classification | | | | | | |
| Optimal to High-normal | 349 (2.7) | 130.2±8.4/77.0±8.2 | 499 (3.1) | 130.3±8.3/75.7±8.6 | 848 (2.9) | 130.3±8.3/76.2±8.5 |
| Grade 1 | 3,282 (25.9) | 149.9±6.7/89.1±7.5 | 4,349 (26.8) | 150.6±6.1/86.7±8.1 | 7,631 (26.4) | 150.3±6.4/87.7±7.9 |
| Grade 2 | 6,027 (47.5) | 164.2±8.6/95.9±8.5 | 7,619 (46.9) | 165.9±7.2/92.8±9.1 | 13,646 (47.1) | 165.2±7.9/94.1±8.9 |
| Grade 3 | 3,040 (23.9) | 184.3±15.7/106.6±12.0 | 3,783 (23.3) | 188.3±14.5/102.0±12.6 | 6,823 (23.6) | 186.5±15.2/104.1±12.5 |

Mean±SD. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

nitely unrelated to losartan, or as unknown. All losartan-related adverse events were pooled and classified as adverse drug reactions (ADRs).

## Endpoint Evaluation

The primary endpoint of the study was a composite of cardiovascular events, including fatal or non-fatal stroke (new occurrence or recurrence of cerebral hemorrhage, cerebral infarction, or subarachnoid hemorrhage diagnosed on the basis of typical clinical symptoms persisting for more than 24 h and/or computerized tomography/magnetic resonance imaging findings), transient ischemic attack defined as a focal neurological deficit presumed to be vascular in origin persisting for less than 24 h, fatal or non-fatal myocardial infarction (new occurrence or recurrence) diagnosed on the basis of typical clinical symptoms, ECG changes and elevation of cardiac enzymes, or sudden cardiac death. In addition, the independent event classification committee reviewed adjudicated endpoint events on the basis of all available information documented in the case report form by the physicians.

## Statistical Considerations

### *Determination of the Sample Size*

When performing life-table analysis combined with the log-rank test, a 30% difference in the incidence of the primary endpoint (stroke, transient ischemic attack, acute myocardial infarction, or sudden cardiac death) was assumed between a subgroup of patients that represented 60% of the total population with higher BP and the remaining patients with lower BP. The incidence of stroke, myocardial infarction and sudden cardiac death in the Japanese population is 6.8/1,000 patient-years in men and 4.8/1,000 patient-years in women according to the Hisayama study (*18*), and the mean follow-up period for the J-HEALTH was 2.7 years. Thus, a total of 28,000 patients were required to detect the assumed between-group difference with a 90% power at $\alpha$=0.05 (2-sided). Therefore, the target sample size was set at 30,000 patients.

### *Statistical Analysis*

For the present interim analysis, variables were compared using the *t*-test, the $\chi^2$ test, or analysis of variance (ANOVA). Results were expressed as the mean±SD, and differences were considered statistically significant at $p<0.05$.

Statistical analysis of the overall results was based on survival analysis. Subgroups were classified by the BP values at baseline or during treatment. Differences between subgroups were assessed by the log-rank test or the $\chi^2$ test. Relationships between the endpoints and the BP values, as well as prognostic factors, were assessed by using the Cox proportional hazards model with adjustment for gender, age, alcohol drinker, current smoker, coexisting of cardiovascular disease, cerebrovascular disease, diabetes mellitus, and hyperlipidemia. For analysis of safety data, the number of ADRs, drug-related ADRs and other ADRs were calculated. For efficacy analysis, the antihypertensive effect of losartan with respect to both clinic BP and home BP values was assessed, and subgroup analyses were performed as described for the safety analysis. Comparison of safety and efficacy among the subgroups was performed with the $\chi^2$ test, *t*-test, or ANOVA. Results were expressed as the mean±SD and a 2-sided $p<0.05$ was considered statistically significant. Statistical analysis was conducted with the SAS package (version 8.02; SAS Institute Inc., Cary, USA).

## Organization

The organization and the members of the committees of the J-HEALTH study are given in the Appendix. These committees were responsible for performing the study or analyzing the data. The Monitoring Committee determined the validity of continuing the study based on the safety and effectiveness of losartan therapy from an ethical point of view. The Event Assessment Committee reviewed the events of cerebrovascular disease and coronary heart disease reported during the

**Table 4. Lipid Profiles at Baseline**

| | Men (*N*=13,737) | Women (*N*=17,311) | Total (*N*=31,048) |
|---|---|---|---|
| Hyperlipidemia (*n*) | 4,935 | 7,005 | 11,940 |
| TC (mg/dL) | 216.4±37.2 | 230.2±35.3 | 224.4±36.7 |
| HDL-C (mg/dL) | 51.5±15.5 | 59.2±16.3 | 56.0±16.4 |
| TG (mg/dL) | 214.2±142.9 | 159.9±96.3 | 182.8±121.3 |
| Without hyperlipidemia (*n*) | 8,802 | 10,306 | 19,108 |
| TC (mg/dL) | 189.3±29.0 | 199.5±29.6 | 194.7±29.8 |
| HDL-C (mg/dL) | 56.5±14.5 | 61.1±15.0 | 58.9±14.9 |
| TG (mg/dL) | 126.8±89.1 | 110.0±58.4 | 117.8±74.7 |

Mean±SD. TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol; TG, triglycerides.

study. The Safety Assessment Committee assessed the causal relationship between the ADRs that are reported and the drugs that are administered during the study. The Medical Expert Advisory and Publication Committee was responsible for reviewing the results and writing the paper.

## Results

### Baseline Patients' Characteristics

Between June 2000 and December 2001, patients were screened in all 47 prefectures throughout Japan. The number of patients enrolled in this study per prefecture ranged from 165 in Okinawa to 2,667 in Tokyo. The distribution of patient enrollment was similar to the recent Japanese population statistics (*19*), and there were no major regional differences of BP values among the prefectures (data not shown).

A total of 31,515 patients were screened at 3,755 institutions by 4,149 investigators. Among them, 31,048 patients were enrolled in this study and 467 patients were excluded according to the exclusion criteria shown in Table 1 or withdrew their consent before actual enrollment. The baseline characteristics of the 31,048 enrolled patients (13,737 men [44.2%] and 17,311 women [55.8%]) are summarized in Table 2. The mean age of the patients was 62.4±12.1 years and the mean clinic systolic/diastolic BP (SBP/DBP) values were 165.3±17.3/94.3±11.7 mmHg.

Concomitant medications and complications are also listed in Table 2. All complications and ECG abnormality were diagnosed by the study investigators. The prevalences of hyperlipidemia, diabetes mellitus, cardiovascular disease, cerebrovascular disease, and ECG abnormality were 38.5%, 13.1%, 8.0%, 4.4%, and 14.0% respectively. Subjects taking anti-diabetic agents or lipid-lowering drugs were defined as having diabetes or hyperlipidemia, respectively.

Table 3 shows distributions of age groups and grade in the World Health Organization (WHO), and the mean BP values at baseline. Young patients (20–39 years) accounted for 2.8%, middle-aged patients (40–59 years) accounted for 38.0%, and elderly patients (60–79 years) made up 51.8% of the total patients. It is worth noting that there were 2,127 (7.4%) very elderly patients (≥80 years). The age distribution was generally similar between men and women. Then we analyzed the BP values of each age group. As shown in Table 3, the SBP values increased with age, but the difference was relatively small. On the other hand, the DBP values decreased markedly with age. Grade 2 hypertensive patients (based on the WHO classification) were most frequent in our cohort (*n*=13,646, 47.1%), while the numbers of grade 1 and 3 patients were almost equal (*n*=7,631, 26.4% *vs*. *n*=6,823, 23.6%, respectively).

The mean total cholesterol (TC) level of all patients was 209.6 mg/dL, while the mean TC levels of hyperlipidemic patients (*n*=11,940) and non-hyperlipidemic patients (*n*=19,108) were 224.4 mg/dL and 194.7 mg/dL, respectively. Details of the lipid profile are given in Table 4.

A total of 11,135 patients agreed to measure their BP values at home. Although data were limited at the time of enrollment (*n*=9,182), the scatter plot (Fig. 1) demonstrates the relationship between clinic BP and home BP for both the SBP and DBP values. The Pearson's correlation coefficients were 0.62 and 0.69, respectively. "White-coat hypertension" (WCHT) was defined by the following criteria: clinic SBP ≥140 or clinic DBP ≥90 mmHg and home SBP <135 and home DBP <85 mmHg. Based on these criteria, 4.2% of our patient cohort had so-called WCHT.

## Discussion

The JSH 2004 have been published and updated periodically based on mainly Western epidemiological and clinical results (*5*). Although many large-scale investigational studies have been conducted worldwide to explore the management of hypertension (*3*, *4*), it is difficult to determine which studies are best applicable to each individual case in clinical practice. Therefore, it is very important to clarify the characteristics, clinical effects, and safety profiles of various drugs in clinical practice. Many studies with Japanese hypertensives have been conducted, but these have usually employed small cohorts in rural areas. Practical information from large-scale investigational studies in clinical practice is limited in Japan (*20*). The J-HEALTH is a large-scale (30,000 patients)

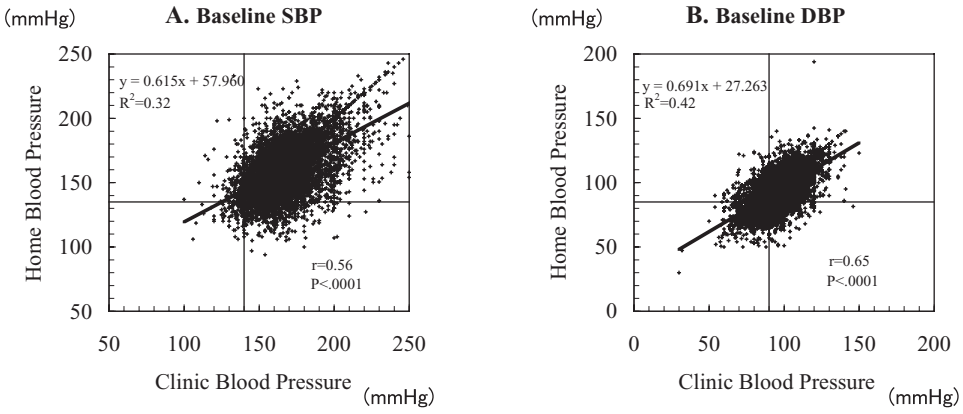


**Fig. 1.** *Scattered diagrams of clinic and home blood pressure at baseline (n=9,182). Each patient's clinic and home blood pressure was plotted for SBP (A) and DBP (B) with regression equations. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

nationwide multicenter observational study, which may provide us valuable epidemiological information on Japanese patients with hypertension.

The distribution of the hypertensive patients enrolled in the J-HEALTH study was similar to that of the recent Japanese population statistics (*19*). Thus, the patients in this study can be regarded as being representative of the overall Japanese population. Geographical differences in the prevalence of hypertension have previously been noted in Japan (*21*), with a higher incidence in the primarily rural northern part of Japan and a lower rate in the Western region (*5*). One of the reasons for the higher BP values in rural northern Japan is the high salt intake of the local population. However, no major regional differences of the mean clinic BP values were observed among the prefectures in the J-HEALTH study. This may reflect recent lifestyle changes and/or the widespread acceptance of antihypertensive therapy in Japan.

It is well known that vascular mortality increases with age, but the contribution of BP values to vascular mortality differs between age groups. The Prospective Studies Collaboration has published a meta-analysis of individual data for one million adults in 61 prospective observational studies of BP values and mortality (*22*). Although the proportional difference in the risk of vascular death is associated with an absolute difference in BP values, the proportional difference in vascular mortality is only about half as large at 80–89 years compared with that at 40–49 years. Therefore, the age of the subjects is an essential factor when analyzing study endpoints. The mean age of the J-HEALTH cohort is 62.4±12.1 years. On the other hand, the mean age was 67 years in the LIFE study (*7*). This age difference between randomized trials and actual clinical practice should be taken into consideration when applying the results of randomized trials.

The risks and benefits of treatment with antihypertensive agents are uncertain in patients older than 80 years (*23*). Gueyffier *et al*. suggested that antihypertensive treatment could prevent stroke, major cardiovascular events, and heart failure, but not cardiovascular death based on a meta-analysis of data from 1,670 patients aged 80 years or older (*24*). The Hisayama study suggested that the Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-6) recommendations were not applicable to elderly Japanese persons over 80 years of age (*25*). Many very elderly hypertensive patients (≥80 years) were enrolled (595 men and 1,532 women) in the J-HEALTH study. Such a large number of elderly Japanese has not been studied before, so the results of the J-HEALTH study should be informative for this age group.

Of course, the BP is the most important characteristic of the patients in this study. The mean clinic SBP/DBP values of the J-HEALTH cohort were 165.3/94.3 mmHg. In contrast, the mean SBP/DBP values were 174.4/97.8 mmHg in the LIFE study. Based on their age and mean BP values, the J-HEALTH cohort is younger and has milder hypertension compared with the subjects of the LIFE study (*7*). Therefore, the J-HEALTH study may be able to assess the beneficial effects of ARB-based treatment for relatively low-risk hypertensive patients, who are the most common type encountered in clinical practice in Japan.

Not only the mean BP value itself, but also the grade of hypertension, is an important factor to be taken into consideration when evaluating a large-scale study. Grade 2 hypertension is the most frequent type in the J-HEALTH study population (47.1%). In their sub-analysis of the Hisayama study, Arima *et al*. excluded treated hypertensive patients and followed up 588 cardiovascular disease-free residents who were at least 60 years of age for about 30 years (from 1961 to 1993) to evaluate their cardiovascular risk. Among these patients, BP grade 1, 2, and 3 accounted for 27.2%, 18.6%, and 14.1%, respectively (they included normal BP and high normal BP subjects). Since the Hisayama study was an observational investigation of the general population, the hyperten-

sion stage distribution of the Hisayama population is different from that of the J-HEALTH cohort (*25*).

Complications represent another important background factor. The prevalences of ECG abnormality, cardiovascular disease, and cerebrovascular disease are 14.0%, 8.0%, and 4.4%, respectively, in the J-HEALTH cohort. These rates are lower than those in the LIFE study, again indicating that the J-HEALTH enrolled healthier subjects than the LIFE (*7*). The J-HEALTH cohort includes a high percentage of hyperlipidemic patients (38.5%). However, as shown in Table 4, the mean TC level of these hyperlipidemic patients is not extremely high, possibly because 24.7% of all the patients were taking lipid-lowering drugs (Table 3).

It has been emphasized that home BP values measured by ambulatory blood pressure (ABP) monitoring or self-measurement can be an important tool for the optimal management of hypertension with respect to cardiovascular risk (*26*). In the Pressioni Alteriose Monitorate e Loro Associazioni (PAMELA) study of 2,051 subjects who were representative of the general population, the clinic BP, home BP, and 24-h ABP values were measured. This study demonstrated that the risk of death increased more with a given increase in home BP or ABP than clinic BP values (*27*). Den Hond *et al*. investigated the diagnostic values of self-measured BP *vs*. ABP, and concluded that the specificity and sensitivity of ABP values for detecting WCHT were better than those of home BP values (*28*). While ABP values have better prognostic accuracy, the American Society of Hypertension Ad Hoc Panel recommends the use of home BP values for screening. Self-measurement of the BP is easy to repeat and is useful for patients to assess their own control (*29*). Hozawa *et al*. investigated the BP measured by home, ambulatory, and conventional methods in 1,174 Japanese subjects (150 with untreated hypertension, 399 with treated hypertension, and 625 normotensives). They also concluded that it was useful to measure the non-clinic BP values (*30*). We therefore determined the distribution and relation between clinic BP and home BP values at enrollment (Fig. 1).

WCHT is diagnosed by comparing the clinic BP and non-clinic BP values, and whether it causes target organ damage and cardiovascular events is one of the most important issues in the treatment of hypertension (*31*). The Ohasama study examined the prognostic significance of WCHT based on ABP monitoring, and concluded that the predictive power of the ABP values for subsequent mortality was stronger than that of the clinic BP values (*28*). The prevalence of WCHT is 4.2% in the J-HEALTH cohort, but the reported prevalence of WCHT in other studies varies widely because of differences in the definition of WCHT, method of BP measurement (self-measurement *vs*. ABP monitoring), and characteristics of the study population (untreated hypertension *vs*. treated hypertension). Masked hypertension (MHT) is also a topic of interest for antihypertensive therapy. The Self-Measurement of Blood Pressure at Home in the Elderly; Assessment and Follow-up (SHEAF) study demonstrated that about 9% of treated elderly patients had MHT and that the cardiovascular risk associated with MHT is significantly high (*32*).

A total of 9,182 patients measured their home BP values at the baseline in the J-HEALTH cohort. Therefore, we will use their data to identify WCHT and MHT and investigate the effect of home BP data on cardiovascular events. The home BP data obtained by self-measurement will display the time course effect of antihypertensive management and provide prognostic information for the hypertensive population.

The J-HEALTH study began in June 2000, and follow-up was completed in December 2005. The J-HEALTH study will clarify the long-term antihypertensive efficacy and safety of losartan-based therapy, and assess its preventive effect on hypertension-related diseases. It may provide new insights into therapeutic strategies for Japanese hypertensive patients.

## Appendix

### J-HEALTH Committees

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