Liddle症候群原因変異以外のより頻度の多い多型がEHTと関連することも報告されている[11]．Liftonのグループは，高血圧，高カリウム血症，代謝性アシドーシスを呈する常染色体優性遺伝疾患のGordon症候群の原因遺伝子が，腎臓の遠位尿細管に発現し電解質調節に関与する*WNK1*，*WNK4*遺伝子であることを報告した[12]．われわれはこれらの遺伝子多型とEHTとの関連を検討した[13]．両遺伝子にダイレクト・シークエンスを行うことにより*WNK1*に35SNPs，*WNK4*に21SNPsを見出した．この中から頻度，連鎖不平衡を考慮し，*WNK1* 7 SNPs，*WNK4* 2 SNPsを一般住民1,818人に対してタイピングを施行した．結果は，男性のみで*WNK4* C14717T（イントロン14）のCC型（n＝670）保有者の平均収縮期血圧131.3mmHgに比し，Tアレル型（n＝165）では134.4mmHgと有意に高く（p＝0.042），また高血圧患者もTアレル保有者で有意に高頻度に認めた（OR；1.62，95％ CI；1.12～2.33，p＝0.010）．この結果より，*WNK4*は高血圧原因遺伝子の一つと考えられる．さらにわれわれは，Gordon症候群の原因多型が存在する*WNK4*遺伝子のエクソン7と17につき956人の高血圧患者でシークエンスを行い，3つの新規なミスセンスSNPを見出した[14]．これらは頻度が0.1％程度と少なかったが，1,875人の一般住民にこれらの多型は存在しなかったことから高血圧発症に関与している可能性があり，機能の解析が重要と考えている．このような低頻度のSNPsの集積がEHTの発生にかかわっている可能性も否定できず，われわれは積極的にミスセンス変異に関する情報を集積している[15)～17)]．

さらにわれわれは，候補遺伝子アプローチのもう一つのターゲットとして，種々の血圧調節にかかわるホルモンや血管作動性物質の共通の細胞内情報伝達経路に存在するリン酸化蛋白や酵素などが重要な遺伝子と考えている．たとえば，G蛋白結合受容体（G protein-coupled receptor；GPCR）に結合するホルモンやペプチドにはアンジオテンシンIIやエンドセリン-1など代表的な昇圧ペプチドが多いため，GPCRの情報伝達系構成因子や調節因子に注目した．Regulators of G protein signaling（RGS）蛋白は，G蛋白がGDP型からGTP型となり活性化したものを不活性型-GDP型に加水分解により戻す働きをする蛋白であり（図2），Heximerらはこの蛋白に注目し，その遺伝子（*rgs2*）のノックアウトマウスを作製し血圧調節の異常を検討したところ[18]，このマウスはホモ接合対（*rgs2*$^{-/-}$）のみならずヘテロ接合対（*rgs2*$^{+/-}$）でもホモと同等の血圧上昇を示した．この結果より，RGS2遺伝子はヒトにも存在するため，RGS2遺伝子の調節異常がヒトEHTの原因である可能性があり，その遺伝子多型と高血圧の関連性を調べた[19]．953人の高血圧患者の*RGS2*を，プロモーターから全コーディング領域をダイレクト・シークエンスしたところ，5つのミスセンス変異（Gln2Leu，Gln2Arg，Met5Val，Arg44His，Gln78His）ならびに1つのフレームシフト変換（1925-1926 insT）を起こすSNPがおのおのの変異で1～2人みつかった．1,873人の一般住民にもこれらの変異は認められた．まとめると表3のように，高血圧患者で明らかにこれらの機能変化にかかわると考えられるSNPsが多く認められた[20]．この中でもGln2Leuを有する細胞では，アンジオテンシンIIの細胞内情報伝達が2分の1程度抑制されることがほかのグループの報告[20]で示されたことから，機能的な変異であると考えられる．また，イントロン1（1026T>C）と3（1891-1892 delTC）の両アレル頻度が約60％/40％と，頻度の高いSNPsも高血圧に関与しており[19]，この結果は黒人でも同様に1891-1892 delTCが高血圧に関与するとの報告が出され[21]，遺伝子多型研究でもっとも重要と考えられる多型の機能変化の実験的裏づけと再現性が得られたことから，RGS2遺伝子は非常に有力な高血圧原因遺伝子であると考えている．

表2　考えられる高血圧関連候補遺伝子のカテゴリー

1. 水・電解質調節因子
2. RA系，KK系
3. 交感神経系
4. 加齢，酸化ストレス関連
5. 血管作動性物質
6. 糖代謝，脂質代謝，肥満関連因子
7. 細胞内情報伝達因子

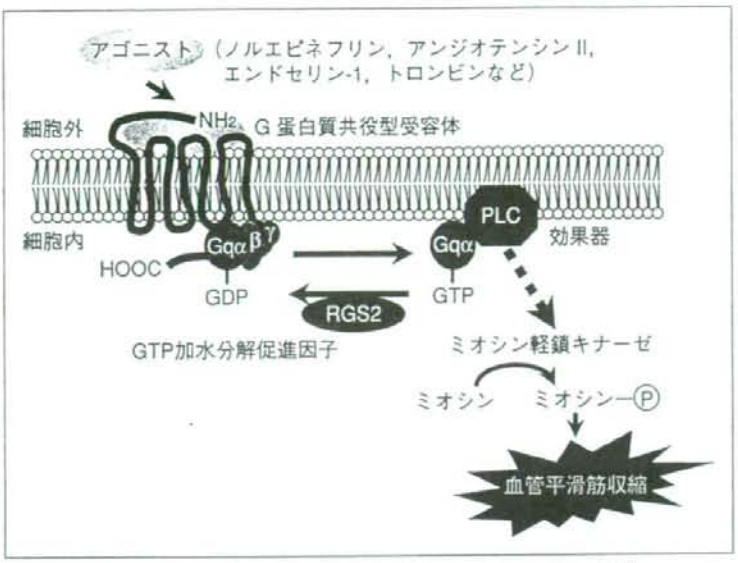

図2　血管平滑筋細胞内情報伝達系におけるRGS2の役割
受容体にアゴニストが結合するとGαがGTP型となり，効果器を活性化し，血管平滑筋の収縮が起こる．RGS2は活性化したGαをGDP型（不活性型）に戻す．

薬剤感受性遺伝子多型

薬剤反応性の個人差には，人種差のような集団として影響を及ぼす因子と各個人の遺伝素因がもたらす因子により20～95％は規定され，これに年齢や薬物代謝にかかわる臓器の機能，併用薬剤や治療，病気の程度などの非遺伝因子が加わると考えられている．冒頭に述べたように高血圧はもっとも頻度の多い生活習慣病で，降圧薬服用者は高血圧治療患者の半数以上を占める．したがって，遺伝的に規定されている降圧薬感受性を薬剤選択する際に考慮できれば，効率のよい高血圧薬物治療を実現することが可能となる．こういった観点から，われわれは降圧薬感受性遺伝子多型を明らかにすることを試みている．これまでにレトロスペクティブな方法で，サイアザイド利尿薬（*TSC* C1784T, *ADRB3* Trp64Arg）[22]，ジヒドロピリジン系カルシウム拮抗薬（*CACNA1C* 527974G>A, *CACNA1D* rs312481G>A）ならびにアンジオテンシンII受容体拮抗薬（*CYP2C9*30*：Ala447Thr）[23]の降圧効果に関与するSNPsの存在を報告してきた．これらの降圧薬関連遺伝子多型は複数存在することが予測され，明らかな薬剤応答性・感受性遺伝子の同定のためには，多数例の無治療高血圧患者に前向きに降圧薬を投与し，正確に降圧の程度を把握し，数多くの薬物代謝酵素や薬理作用機序関連の遺伝子多型との相関を検討する必要がある．これまでわが国にこのような研究はなかったが，国立循環器病センターでは厚生労働科学研究として全国の大学・医療センター計24施設とともに，降圧薬感受性遺伝子多型同定のための多施設共同研究（GEANE研究：Gene Evaluation for ANtihypertensive Effect of drugs）を施行した（図3）．GEANE研究では，同一患者にサイアザ

表3　高血圧患者ならびに一般住民におけるRGS2遺伝子ミスセンス多型，フレームシフト変換を有する人のまとめ

Mutations	高血圧患者集団（n＝953）	一般住民	
		高血圧（n＝771）	正常血圧（n＝1,102）
Gln2Leu	2	0	0
Gln2Arg	1	2	1
Met5Val	1	0	0
Arg44His	2	4	1
Gln78His	1	0	2
1925-1926insT	1	1	0
計	8	7	4

（文献[19]より改変引用）

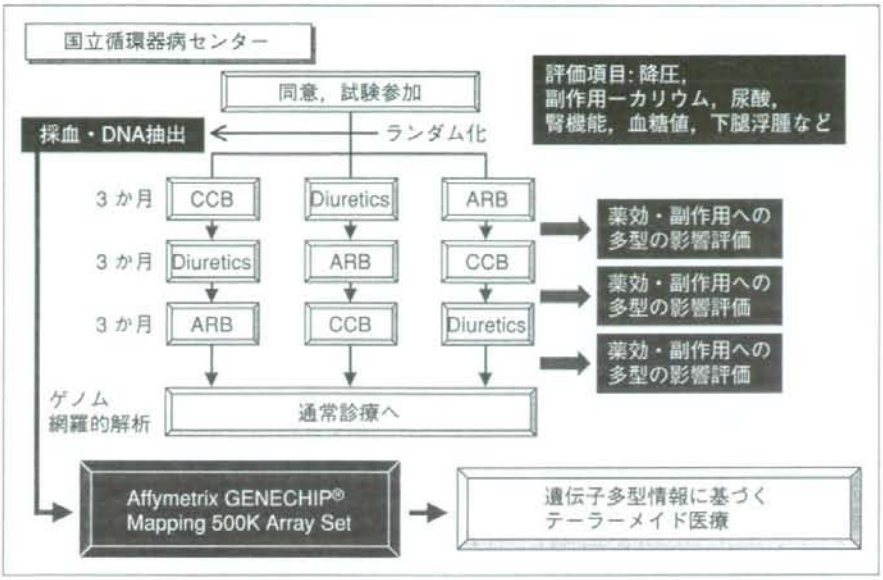

図3　GEANE研究(Gene Evaluation for ANtihypertensive Effect of drugs)

イド利尿薬，ジヒドロピリジン系カルシウム拮抗薬，アンジオテンシンII受容体拮抗薬をクロスオーバー法で服用させて降圧効果を調べ，遺伝子多型はゲノム網羅的に50万SNPsを検討している．現在，症例登録や遺伝子解析は終了し，最終の解析を行っている段階であり，この研究によりこれら3種類の薬剤関連SNPsが数多く明らかになることが期待される．

テーラーメード医療の実現に向けて

高血圧のテーラーメード医療実現には適確な研究成果の集積と出てきた遺伝子多型を用いた迅速遺伝子診断システムの開発，このような遺伝子診断システムを導入した場合の有用性を確かめる前向き試験，遺伝子多型診断を考慮した新しい高血圧診療ガイドラインの策定などが必要である．世界的にも活発に研究が続けられているので，確実な研究成果の集積により新しいパラダイムによる医療の実現が期待される．無駄が少なく，より安全で，合併症を減少させることができるような高血圧診療を患者に提供することを目標に研究を進めている．

謝辞：本稿中の研究成果は，独立行政法人医薬品医療機器総合機構の「保健医療分野における基礎研究推進事業」より助成金を得たミレニアムゲノムプロジェクト(高血圧等循環器疾患における遺伝子解析，創薬推進事業：研究代表者ー国立循環器病センター病院長・友池仁暢)ならびに医薬基盤研究所による研究課題(高血圧等循環器疾患のゲノム情報多元的意義付けと画期的診断・治療法の開発：研究代表者ー国立循環器病センター研究所部長・森崎隆幸)によるものである．また，降圧薬関連遺伝子多型の前向き臨床試験は平成17～20年度の厚生労働科学研究費(研究代表者ー国立循環器病センター病院部長・河野雄平)のサポートを受けている．本研究に御指導をいただいた研究所病因部・宮田敏行部長，御協力をいただいた内科高血圧腎臓部門および循環器予防検診部のスタッフの皆様に深謝いたします．

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Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease in a Japanese Urban Cohort

The Suita Study

Yoshihiro Kokubo, Kei Kamide, Tomonori Okamura, Makoto Watanabe, Aya Higashiyama, Katsuyuki Kawanishi, Akira Okayama, Yuhei Kawano

Abstract—Few prospective studies have examined the association between high-normal blood pressure and cardiovascular disease (CVD) in Asia. We examined the impact of high-normal blood pressure on the incidence of CVD in a general urban population cohort in Japan. We studied 5494 Japanese individuals (ages 30 to 79 years without CVD at baseline) after completing a baseline survey who received follow-up through December 2005. Blood pressure categories were defined on the basis of the ESH-ESC 2007 criteria. In 64 391 person-years of follow-up, we documented the incidence of 346 CVD events. The frequencies of high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 18.0%, 20.1%, and 10.1% for men and 15.9%, 15.6%, and 8.8% for women, respectively. Antihypertensive drug users were also classified into the baseline blood pressure categories. Compared with the optimal blood pressure group, the multivariable hazard ratios (95% confidence intervals) of CVD for normal and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 2.04 (1.19 to 3.48), 2.46 (1.46 to 4.14), 2.62 (1.59 to 4.32), and 3.95 (2.37 to 6.58) in men and 1.12 (0.59 to 2.13), 1.54 (0.85 to 2.78), 1.35 (0.75 to 2.43), and 2.86 (1.60 to 5.12) in women, respectively. The risks of myocardial infarction and stroke for each blood pressure category were similar to those of CVD. Population-attributable fractions of high-normal blood pressure and hypertension for CVD were 12.2% and 35.3% in men and 7.1% and 23.4% in women, respectively. In conclusion, high-normal blood pressure is a risk factor for the incidence of stroke and myocardial infarction in a general urban population of Japanese men. (***Hypertension.*** **2008; 52:652-659.)**

Key Words: cardiovascular diseases ■ epidemiology ■ general population ■ high-normal blood pressure ■ myocardial infarction ■ prospective studies ■ stroke

Many cohort studies have demonstrated that hypertension is a strong risk factor for total mortality and cardiovascular disease (CVD)[1–5] in both developing and developed countries.[2,6,7] The guidelines of the Joint National Committee 7 from the United States has recently introduced a category, designated "prehypertension," for people with blood pressures ranging from 120 to 139 mm Hg for systolic pressure or 80 to 89 mm Hg for diastolic pressure.[8] The European Guidelines[9] and Japanese Society of Hypertension Guidelines,[10] however, divide this population into 2 groups: those with systolic blood pressures between 120 and 129 mm Hg or diastolic blood pressures between 80 and 84 mm Hg are classified as normal, whereas those with systolic blood pressures between 130 and 139 mm Hg or diastolic blood pressures between 85 and 89 mm Hg are classified as high-normal. Although the association of cardiovascular risk with elevated blood pressure is well accepted,[1–4,6] only a few studies have addressed the absolute and relative risks of CVD for the population with blood pressure values in the high-normal range. The Framingham Heart Study revealed an association of high-normal blood pressure with increased risk of CVD.[11] The Framingham coronary heart disease prediction functions perform well for whites and blacks in different settings; these findings can be applied to other ethnic groups, like in the ARIC study, after recalibration for differing prevalence of risk factors for coronary heart disease events.[12] Few studies have investigated the association between blood pressure category and the incidence of CVD in Japan,[5,13] where there is a higher incidence of stroke and lower incidence of myocardial infarction (MI) than those in Western countries.[7] We performed a prospective examination of the risk of stroke and MI in men and women according to blood pressure category comparing normal and high-normal blood pressures in a general urban Japanese population.

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From the Department of Preventive Cardiology (Y. Kokubo, T.O., M.W., A.H., A.O.) and the Division of Hypertension and Nephrology (K. Kamide, Y. Kawano), National Cardiovascular Center, Osaka, Japan; The Suita Medical Association (K. Kawanishi), Osaka, Japan; and the Japan Anti-Tuberculosis Association (A.O.), Tokyo, Japan.

Correspondence to Yoshihiro Kokubo, MD, PhD, Department of Preventive Cardiology, National Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka, 565-8565 Japan. E-mail ykokubo@hsp.ncvc.go.jp

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Methods

Study Subjects

The Suita Study,[5,14,15] an epidemiological study of cerebrovascular and cardiovascular disease, was based on a random sampling of 12 200 Japanese residents of Suita. As a baseline, participants between the ages of 30 and 79 years were randomly selected from the municipality population registry and stratified into groups by sex and age in 10-year increments in 1989. Of these, 6485 men and women underwent regular health checkups between September 1989 and March 1994. Subjects have continued to visit the National Cardiovascular Center every 2 years since that time for regular health checkups.

Cohort members in the study population were excluded from these analyses if they had a past or present history of CVD at baseline (n=208), were missing data (n=170), attended health checkups after April 1994 (n=79), or failed to complete the follow-up health surveys or questionnaires after baseline examination (n=534). After applying these exclusions, 5494 individuals were included in the analysis.

Measurement of Blood Pressure and Covariates

Well-trained physicians measured blood pressure 3 times in a seated position with a mercury column sphygmomanometer and an appropriately sized cuff according to standard protocol after at least 5 minutes of rest before the initial blood pressure reading was obtained. Systolic blood pressure was measured first to obtain approximate systolic blood pressure levels. Systolic (SBP) and diastolic (DBP) blood pressures were the average of the second and third measurements recorded more than 1 minute apart.

At baseline examination, subjects were classified into one of the 5 blood pressure categories based on the criteria of ESH-ESC 2007: optimal (SBP <120 mm Hg and DBP <80 mm Hg), normal (SBP 120 to 129 mm Hg or DBP 80 to 84 mm Hg), high-normal blood pressure (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg), hypertension Stage 1 (SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg), or hypertension Stage ≥2 (SBP ≥160 mm Hg or DBP ≥100 mm Hg).[9,10] Antihypertensive drug users were classified according to their blood pressure levels at baseline survey. Due to the small sample size for Grade 3 hypertension, both Grades 2 and 3 were combined. Therefore, we compared optimal blood pressure with Grade 1 and Grades 2 plus 3 hypertension in this study. In addition, after antihypertensive drug users were classified into the hypertension Stage ≥1 group, subjects were classified into one of the 4 blood pressure categories: optimal, normal, and high-normal blood pressure and hypertension Stage ≥1 group. If the SBP and DBP readings for a subject were in different categories, the subjects were categorized into the higher of the 2 blood pressure categories.

At the baseline examination, we performed routine blood tests, including serum total cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose levels. Physicians or nurses administered questionnaires regarding individual personal habits and present illnesses. Subjects were classified as current smokers, nonsmokers, and past smokers. We also measured height and body weight in a fasting state. Body mass index was calculated as weight (kg) divided by the square of the height (m^2). Hyperlipidemia was defined as total serum cholesterol levels ≥5.7 mmol/L (220 mg/dL) and/or current use of antihyperlipidemic medications. Diabetes was defined as fasting plasma glucose levels ≥7.0 mmol/L (126 mg/dL) and/or current use of antidiabetic medications. We obtained informed consent from all participants. This study was approved by the Institutional Review Board of the National Cardiovascular Center.

Confirmation of Strokes and Myocardial Infarctions

Five hospitals in the Suita area were capable of performing CT scans and/or MRI, all of which were the major hospitals to which patients with acute stroke and those with MI were admitted. Medical records were reviewed by registered hospital or research physicians who were blinded to the baseline data. Stroke and MI events were registered if they occurred between the date on which the baseline health examination was performed and December 31, 2005. Strokes were defined according to the US National Survey of Stroke criteria,[16] which require rapid onset neurological deficits lasting at least 24 hours or until death. For each stroke subtype (cerebral infarction [thrombotic or embolic infarction], intracerebral hemorrhage, and subarachnoid hemorrhage), a definitive diagnosis was established based on CT, MRI or autopsy. Definitive and probable MIs were defined according to the criteria set by the MONICA project,[17] which requires electrocardiographic evidence, cardiac enzyme elevations, and/or autopsy. Sudden death was defined as death of unknown origin occurred within 24 hours from onset.

To complete our surveillance for fatal strokes and MIs, we conducted a systematic search for death certificates. We identified possible strokes or MIs using data from (1) the health examination and questionnaires from the stroke and MI registries without informed consent for medical records survey; and (2) death certificates without registration of CVD incidence, which were defined as probable stroke or MI. CVD was defined as stroke and MI in this study.

End Point Determination

The end points of the current follow-up study were (1) date of the first MI or stroke event; (2) date of death; (3) date of leaving Suita; and (4) December 31, 2005 (censored). To detect MI and stroke occurrences, each participant's health status was checked at clinical visits to the National Cardiovascular Center every 2 years. Yearly questionnaires by mail or telephone were also completed for all participants. We also obtained informed consent to review in-hospital medical records for 86.2% participants who were suspected to have signs or symptoms related to stroke or MI events.

Statistical Analysis

Analysis of variance and χ^2 tests were used to compare the mean values and frequencies by sex according to blood pressure category. For each subject, person-years of follow-up were calculated from the date of baseline survey, to the first end point, CVD event, death, emigration, or December 31, 2005. The Cox proportional hazard ratios (HRs) were fit for each blood pressure category after adjusting for age and other potential confounding factors, including age, present illness of hypercholesterolemia or diabetes, smoking status (nonsmoker, past smoker, and current smoker), and drinking status (nondrinker, past drinker, and current drinker) at baseline survey.

To express the impact of blood pressure categories on CVD occurrence in the participants, we estimated the population-attributable fraction (%). Population-attributable fraction was estimated as $Pe \times (HR-1)/HR$, in which Pe is the proportion of incident cases in the blood pressure category and HR is the multiple-adjusted hazard ratio.[18] All statistical analyses were conducted using SAS statistical package software (release version 8.2; SAS Institute Inc, Cary, NC).

Results

At baseline, we observed several differences in the distribution of CVD risk factors according to blood pressure categories (Table 1). The percentages of subjects with optimal, normal, and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 31%, 20%, 18%, 20%, and 11% for men and 42%, 17%, 16%, 16%, and 9% for women, respectively. On average, both men and women with higher blood pressure were older and had higher serum total cholesterol levels, higher body mass index, and higher incidences of hyperlipidemia and diabetes than those with optimal blood pressure. The percentages of antihypertensive drug users classified as having hypertension Stages 1 and ≥2 at baseline were 21.3% and 37.7% for men and 24.2% and 40.6% for women, respectively.

Table 1. Baseline Characteristics of Study Subjects According to Blood Pressure Category

Groups and Variables	Blood Pressure Category*					*P* Values
	Optimal	Normal	High-Normal	Stage 1	Stage ≥2	
Men						
No. of subjects	803	502	463	516	286	
Age, years	50.8±13.2	54.0±12.9	57.5±12.2	60.1±11.7	62.0±11.1	<0.001
SBP, mm Hg	107.8±7.5	121.7±5.4	131.4±5.8	143.9±8.5	167.0±17.4	<0.001
DBP, mm Hg	68.2±6.7	76.6±6.3	81.2±6.9	87.5±8.2	97.0±11.7	<0.001
Total cholesterol, mmol/L†	5.1±0.8	5.2±0.9	5.3±0.9	5.3±0.9	5.3±0.9	<0.001
High-density lipoprotein cholesterol, mmol/L†	1.3±0.3	1.3±0.4	1.3±0.3	1.3±0.3	1.3±0.3	0.332
Body mass index, kg/m^2	22.0±2.7	22.7±2.6	23.2±2.7	23.3±3.0	23.6±3.2	<0.001
Antihypertensive medication, %	0.6	3.9	7.7	21.3	37.7	<0.001
Hyperlipidemia, %	23.7	27.4	30.6	34.4	31.4	<0.001
Diabetes, %	3.8	5.3	5.6	8.9	9.7	<0.001
Current smokers, %	59.7	49.6	46.3	44.3	40.9	<0.001
Current drinkers, %	71.7	77.0	75.0	76.8	79.6	0.045
Women						
No. of subjects	1240	504	465	457	258	
Age, years	47.8±11.9	54.0±11.5	58.9±11.5	61.6±9.4	62.9±9.6	<0.001
SBP, mm Hg	105.5±7.9	122.4±4.8	132.4±4.9	145.7±7.8	169.9±14.0	<0.001
DBP, mm Hg	66.4±6.6	75.5±7.1	79.7±6.9	85.0±9.0	92.3±13.9	<0.001
Total cholesterol, mmol/L†	5.2±0.9	5.6±1.0	5.7±0.9	5.9±0.9	5.8±1.0	<0.001
High-density lipoprotein cholesterol, mmol/L†	1.5±0.3	1.4±0.3	1.4±0.3	1.4±0.3	1.4±0.3	<0.001
Body mass index, kg/m^2	21.1±2.7	22.5±3.0	22.8±3.2	23.2±3.3	23.7±3.7	<0.001
Antihypertensive medication, %	0.9	4.3	11.3	24.2	40.6	<0.001
Hyperlipidemia, %	28.8	44.2	50.9	58.6	58.1	<0.001
Diabetes, %	1.5	3.3	4.0	6.7	5.8	<0.001
Current smokers, %	15.6	11.7	9.2	6.9	8.9	<0.001
Current drinkers, %	37.0	32.5	27.9	29.8	25.4	<0.001

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Plus–minus values are means±SD.

†To convert cholesterol values to mg/dL, multiply ×38.67.

During an average 11.7-year follow-up period, we documented 213 strokes (155 definitive strokes and 58 probable strokes) consisting of 141 cerebral infarctions, 32 intracerebral hemorrhages, 22 subarachnoid hemorrhages, and 18 unclassified strokes. We also documented 133 MIs (64 definitive MIs and 69 probable MIs or sudden cardiac deaths). Subjects who moved from Suita (16.8% of the total participants) were censored at that time.

We determined the age- and multivariable-adjusted hazard ratios for CVD, MI, and stroke according to blood pressure categories in the presence or absence of antihypertensive medication (Table 2). In men, the multivariable HRs (95% CIs) of CVD incidence were 2.04 (1.19 to 3.48), 2.46 (1.46 to 4.14), 2.62 (1.59 to 4.32), and 3.95 (2.37 to 6.58) for men and 1.12 (0.59 to 2.13), 1.54 (0.85 to 2.78), 1.35 (0.75 to 2.43), and 2.86 (1.60 to 5.12) for women with the normal and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 groups, respectively. The risks of MI and stroke for each blood pressure category were similar to the risk of CVD. In a combined analysis of men and women, the multivariable HR of CVD incidence were 1.62 (1.08 to 2.43), 2.08 (1.42 to 3.05), 2.06 (1.42 to 2.98), and 3.53 (2.43 to 5.13) for the normal and high-normal blood pressure and hypertension Stages 1 and ≥2 groups, respectively (data not shown). In addition, the multivariable HR of CVD incidence in men and women younger than 60 years old were similar to those seen in men and women older than 60 years of age (data not shown).

In a second analysis in which all antihypertensive drug users were categorized to the Stage ≥1 group, we determined the age- and multivariable-adjusted HRs for CVD, MI, and stroke according to blood pressure category (Table 3). In men, the multivariable HRs (95% CIs) of CVD incidence were 1.83 (1.05 to 3.20), 2.11 (1.22 to 3.64), and 3.20 (2.01

Table 2. Age- and Multivariable-Adjusted HRs for CVD According to Blood Pressure Category With and Without Antihypertensive Medications

	Blood Pressure Category*				
Groups and Variables	Optimal	Normal	High-Normal	Stage 1	Stage ≥2
Men					
Person-years	9724	5889	5127	5611	3025
Cardiovascular disease					
Case	23	34	43	57	52
Age-adjusted	1	2.03 (1.19–3.46)	2.42 (1.45–4.03)	2.44 (1.49–3.99)	3.71 (2.25–6.16)
Multivariable-adjusted	1	2.04 (1.19–3.48)	2.46 (1.46–4.14)	2.62 (1.59–4.32)	3.95 (2.37–6.58)
MI					
Case	10	14	19	25	20
Age-adjusted	1	2.07 (0.92–4.68)	2.56 (1.18–5.53)	2.45 (1.16–5.17)	3.47 (1.60–7.51)
Multivariable-adjusted	1	2.14 (0.94–4.86)	2.65 (1.20–5.85)	2.72 (1.26–5.84)	3.89 (1.76–8.56)
Stroke					
Case	13	20	24	32	32
Age-adjusted	1	2.13 (1.06–4.30)	2.39 (1.21–4.71)	2.49 (1.30–4.78)	4.17 (2.17–8.01)
Multivariable-adjusted	1	2.12 (1.04–4.30)	2.43 (1.21–4.86)	2.62 (1.35–5.09)	4.38 (2.24–8.56)
Women					
Person-years	15 438	6100	5391	5272	2812
Cardiovascular disease					
Case	25	17	28	29	38
Age-adjusted	1	1.05 (0.56–1.95)	1.48 (0.85–2.59)	1.32 (0.75–2.30)	3.00 (1.77–5.09)
Multivariable-adjusted	1	1.12 (0.59–2.13)	1.54 (0.85–2.78)	1.35 (0.75–2.43)	2.86 (1.60–5.12)
MI					
Case	7	5	10	9	14
Age-adjusted	1	1.09 (0.34–3.48)	1.71 (0.63–4.59)	1.38 (0.50–3.80)	3.56 (1.39–9.08)
Multivariable-adjusted	1	1.44 (0.42–4.90)	2.27 (0.78–6.57)	1.69 (0.56–5.10)	5.24 (1.85–14.85)
Stroke					
Case	18	12	18	20	24
Age-adjusted	1	1.05 (0.50–2.19)	1.39 (0.71–2.75)	1.29 (0.66–2.52)	2.83 (1.49–5.39)
Multivariable-adjusted	1	1.05 (0.49–2.24)	1.29 (0.63–2.67)	1.21 (0.61–2.45)	2.20 (1.07–4.50)

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Multivariate analyses were adjusted for age, body mass index, hyperlipidemia, diabetes, and smoking and drinking status. Antihypertensive drug users were classified according to their blood pressure levels at baseline survey.

to 5.09) for normal and high-normal blood pressure subjects without antihypertensive medication and subjects with hypertension Stage ≥1 with or without antihypertensive medication, respectively. In women, the multivariable HR of CVD incidence was 2.13 (1.25 to 3.62) for the hypertension Stage ≥1 group with or without antihypertensive medications. The risks of MI and stroke for high-normal blood pressure and hypertension Stage ≥1 group were observed in men (HR=2.32, 95% CI: 1.02 to 5.27 and HR=3.35, 95% CI: 1.64 to 6.80 for MI; HR=2.04, 95% CI: 1.00 to 4.22 and HR=3.33, 95% CI: 1.80 to 6.15 for stroke, respectively). HRs for CVD according to prehypertensive category excluding subjects taking antihypertensive drugs (Table 3) were similar but slightly lower than that category including subjects taking antihypertensive drugs (Table 2).

Using the HRs, we estimated the positive fraction of CVD attributable to exposure for each blood pressure category at baseline by sex (Figure). For men, 8.3%, 12.2%, 16.8%, and 18.5% of CVD incidence were excessive incidence due to normal and high-normal blood pressures and hypertension Stages 1 and ≥2 with values of 1.3%, 7.1%, 5.4%, and 18.0%.

Discussion

In this cohort study of a general Japanese urban population, we determined that high-normal blood pressure was a risk factor for the incidence of stroke and MI in men in comparison to subjects with optimal blood pressure. In this study, 20.5% and 8.4% of CVD incidence may derive from prehypertension cases in men and women, respectively. This is the

Table 3. Age- and Multivariable-Adjusted HRs for CVD According to Blood Pressure Category

	Blood Pressure Category*			
Groups and Variables	Optimal	Normal	High-Normal	Stage ≥1
Men				
Person-years	9670	5662	4805	9243
Cardiovascular disease				
Case	23	28	35	123
Age-adjusted	1	1.80 (1.03–3.13)	2.09 (1.23–3.55)	3.00 (1.91–4.72)
Multivariable-adjusted	1	1.83 (1.05–3.20)	2.11 (1.22–3.64)	3.20 (2.01–5.09)
MI				
Case	10	11	16	51
Age-adjusted	1	1.71 (0.72–4.03)	2.27 (1.02–5.03)	2.98 (1.49–5.93)
Multivariable-adjusted	1	1.78 (0.75–4.22)	2.32 (1.02–5.27)	3.35 (1.64–6.80)
Stroke				
Case	13	17	19	72
Age-adjusted	1	1.93 (0.93–3.98)	2.01 (1.00–4.08)	3.18 (1.75–5.79)
Multivariable-adjusted	1	1.92 (0.92–3.97)	2.04 (1.00–4.22)	3.33 (1.80–6.15)
Women				
Person-years	15 293	5890	4834	9002
Cardiovascular disease				
Case	24	12	20	81
Age-adjusted	1	0.80 (0.39–1.61)	1.28 (0.69–2.36)	2.12 (1.30–3.44)
Multivariable-adjusted	1	0.86 (0.42–1.72)	1.32 (0.69–2.53)	2.13 (1.25–3.62)
MI				
Case	7	4	7	27
Age-adjusted	1	0.91 (0.26–3.14)	1.38 (0.47–4.01)	2.23 (0.94–5.28)
Multivariable-adjusted	1	1.17 (0.31–4.34)	1.83 (0.58–5.75)	2.97 (1.11–7.91)
Stroke				
Case	17	8	13	54
Age-adjusted	1	0.76 (0.32–1.79)	1.22 (0.58–2.58)	2.12 (1.17–3.83)
Multivariable-adjusted	1	0.77 (0.32–1.83)	1.11 (0.50–2.49)	1.89 (1.00–3.58)

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Multivariate analyses were adjusted for age, body mass index, hyperlipidemia, diabetes, and smoking and drinking status. Antihypertensive drug users were classified into the hypertension Stage ≥1 group.

first cohort study to examine the impact of high-normal blood pressure on the risks of stroke and MI incidence in a general Japanese urban population, who have a relatively higher incidence of stroke and lower incidence of MI than those seen in Western countries.[7]

Compared with the previous studies, this study has several methodological strengths. First, we evaluated a large prospective cohort of people selected randomly from a general population in Japan, which allowed us to perform subanalyses by age and CVD subtype. Second, our cohort population was selected from an urban population in contrast to the majority of other cohorts in Japan, which have been selected from rural populations. Because approximately 66% of the Japanese population lives in urban areas, this is an important strength of our analysis. The health status of each participant was examined every 2 years during a clinical visit at the National Cardiovascular Center. In addition, a health questionnaire was administered to each participant yearly by mail or telephone. In combination with frequent evaluation of the CVD registry, we could effectively examine the incidence of CVD events in this population. Finally, we examined the risk of CVD incidence, which is a more direct measure of CVD risk than risk of CVD mortality, because mortality from CVD is significantly influenced by treatment.

This study revealed that normal and high-normal blood pressures were risk factors for CVD in Japanese urban men. The results of a multiple ethnic groups investigation has demonstrated that high-normal blood pressure is a risk factor for incidence of coronary heart disease in both men and women.[11] Compared with optimal blood pressure, the relative risk of CVD was 2.33 (1.85 to 2.92) for high-normal blood pressure and was 1.81 (1.47 to 2.22) for normal blood pressure among blacks.[19] An inverse association of optimal blood pressure and a positive association of Stage 1 hyper-

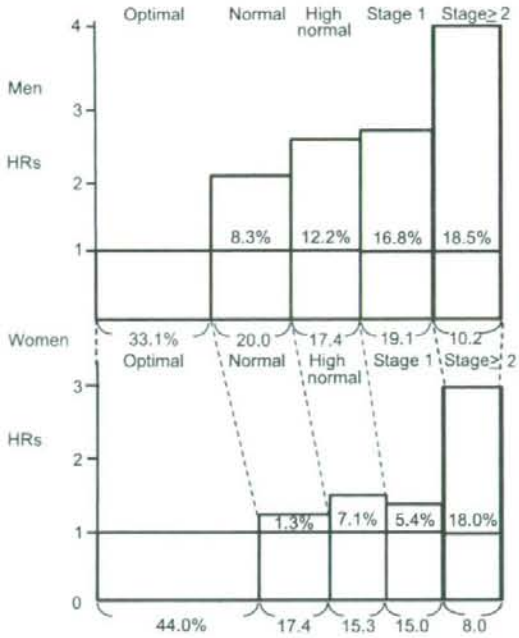

Figure. The HRs and positive fraction attributable to exposure to each blood pressure category (optimal, normal, and high-normal blood pressures and hypertension Stages 1 and ≥2) at baseline for CVD were estimated by sex. The gray area displays excessive incidence of CVD due to normal and high-normal blood pressures and hypertension Stages 1 and ≥2.

tension with coronary heart disease were observed in men compared with normal blood pressure.[12] The Framingham Heart Study revealed that 17.6% and 37.3% of subjects with baseline normal and high-normal blood pressure, respectively, were diagnosed with hypertension within 4 years. High-normal blood pressure has also been associated with increased risk of carotid atherosclerosis,[20] altered cardiac morphological features,[21] and diastolic ventricular dysfunction,[22] all of which may be precursors of incidence of CVD.

Some prospective studies have looked at mortality from CVD in Japanese populations. Murakami et al demonstrated a relationship between prehypertension and overall mortality by performing a meta-analysis of data from 13 population-based cohort studies conducted in Japan.[5] Sairenchi et al revealed that high-normal blood pressure was associated with an increased risk of CVD mortality in Japanese men.[23] The NIPPON DATA 80 also indicated that high blood pressure was a risk factor for mortality from all causes as well as death from CVD among Japanese.[24] All of these studies used end points of mortality. The risk of CVD incidence, like used in this study, is a more direct measure of CVD risk than is the risk of CVD mortality, which is heavily influenced by treatment.

In prospective studies examining the incidence of CVD in Japanese populations, the Ohasama study demonstrated that high-normal blood pressure was a risk factor for stroke by using homed blood pressure, but not by using causal blood pressure.[13] The Hisayama study, which observed the natural course of untreated hypertension in a general Japanese elderly population over a 32-year period, indicated that high-normal blood pressure was not a risk factor for cerebral infarction.[4] This cohort was approximately half the size of our cohort, and the subjects were older and observed for longer periods of time. Hypertensive risk for CVD decreased with advancing age.[25] Over very long periods, confounding factors, including advancing aging, menopause, lifestyle modifications, and medication, will affect blood pressure classification. The Tanno-Sobetu study determined that high-normal blood pressure, determined according to the 1999 World Health Organization/International Society of Hypertension criteria, was not a risk factor for CVD in comparison to optimal and normal blood pressures.[26]

In this study, we did not find an association between high-normal blood pressure and CVD incidence in women. The association between blood pressure category and coronary heart disease is well documented to be weaker in women than in men.[12] For each racial/ethnic group, the mean SBP and DBP values in men were 6 to 7 and 3 to 5 mm Hg higher, respectively, than the values in women.[27] Postmenopausal effects have been associated with elevated blood pressure.[28] Therefore, the period of hypertension exposure tends to be shorter in women than in men. The incidence of CVD was lower in women (3.9 per 1000 person-year) than in men (7.1 per 1000 person-years) in this study. The percentages of those with hypertension who were aware, treated, and controlled were higher for women than men.[27]Because the frequency of white coat hypertension is higher in women than in men,[29,30] blood pressure at baseline examination may be overestimated in women, which may result in the absence of an association between high-normal blood pressure and CVD incidence in women.

The multivariable HR of CVD incidence for normal blood pressure was 2-fold higher than that for optimal blood pressure. In the Honolulu heart program and the Puerto Rico heart health program, the multivariable HRs of CVD incidence for normal blood pressure were approximately 2-fold higher than those for optimal blood pressure.[12] Thus, lower blood pressure appears to prevent the incidence of CVD.

The crude 10-year cumulative incidences of CVD in this subjects who had optimal, normal, and high-normal blood pressure were approximately 2%, 6%, and 8% for men and 2%, 3%, and 5% for women, respectively (data not shown). In the Framingham Heart Study, those were 5%, 8%, and 10% for men and 1%, 3%, and 6% for women, respectively.[12] Compared with the Framingham Heart Study, the incidences of CVD for optimal blood pressure in the Suita study tend to be lower in men and similar in women.

Our study has several limitations. The primary limitation is a dilution bias[31]; this study was based on a single-day measurement of blood pressure, which may lead to a misclassification of blood pressure levels. Previous epidemiological evidence has suggested, however, that blood pressure measurements taken on a single day are accurate.[32] Second, approximately 10% of subjects who underwent baseline survey did not respond to our questionnaires thereafter. However, we found no clinical background difference be-

tween participants and nonparticipants, because the main denial reason for participation in this study was not a health problem. Age- and sex-adjusted systolic blood pressures were 127 mm Hg for participants and 128 mm Hg for nonparticipants ($P=0.08$). To achieve a minimum of failure study subjects, we performed close follow-up with health questionnaires annually and health checkups every 2 years.

In conclusion, high-normal blood pressure is a risk factor for MI and stroke in general Japanese urban men. Approximately 20% and 8% of CVD incidences can be attributed to normal and high-normal blood pressure in both men and women, respectively. To prevent the incidence of CVD, it is necessary for subjects with high-normal blood pressure to attempt to control these values through lifestyle modifications.

Perspectives

Although it is well accepted that hypertension is a strong risk factor for total mortality and CVD all over the world, only a few studies have addressed the absolute and relative risks of CVD for the population with blood pressure values in the high-normal range. In this study, the impact of high-normal blood pressure on the incidence of CVD was examined in a general urban population cohort in Japan. Blood pressure categories were defined on the basis of the ESH-ESC 2007 criteria. In 64 391 person-years of follow-up, 346 CVD events were identified. Compared with the optimal blood pressure group, the multivariable HR of CVD for high-normal blood pressure was 2.5 times in men but was not statistically significant in women. This might be due to a postmenopausal effect, higher frequency of controlled or medication for hypertension, and white coat hypertension in women compared with those in men, but it should be researched further whether these reasons can be applied in women. The risks of MI and stroke for each blood pressure category were similar to those of CVD. Approximately 20% and 8% of CVD incidences can be attributed to prehypertension in men and women, respectively. It is a remarkable finding that one fifth of CVD incidence is derived from prehypertension in men. Our results suggest that it is necessary for subjects with high-normal blood pressure to attempt to control blood pressure through lifestyle modifications to prevent the incidence of CVD.

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Disclosures

None.

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Original Article

A Randomized Trial of the Effect of an Angiotensin II Receptor Blocker SR47436 (Irbesartan) on 24-Hour Blood Pressure in Patients with Essential Hypertension

Yuhei KAWANO[1], Yoichi SATO[2], and Kaoru YOSHINAGA[3]

The aim of this placebo-controlled, double-blind randomized study was to evaluate the duration of the effect of once-daily administration of irbesartan in patients with essential hypertension. After a placebo run-in baseline period (of 2–4 weeks), 79 patients were randomized to either irbesartan (one 100 mg tablet per day) or placebo, for 6 weeks. The primary outcome was the reduction in the mean 24-h blood pressure (BP) as assessed by ambulatory BP monitoring under standardized conditions. Seventy-six patients completed the study protocol. In the irbesartan group, the average reductions in 24-h systolic and diastolic BPs were 5.8 and 3.4 mmHg, respectively (95% confidence interval: 3.2–8.4/1.6–5.1 mmHg), and in the placebo group, they were −1.7 and −0.5 mmHg, respectively (95% confidence interval: −4.3 to 1.0/−1.8 to 0.7 mmHg). There were statistically significant differences in the average reductions of 24-h BP (7.5/3.9 mmHg, $p<0.001$), daytime BP (8.6/4.0 mmHg, $p<0.001$) and nighttime BP (6.1/3.4 mmHg, $p<0.05$) as well as casual BP (9.0/5.0 mmHg, $p<0.001$). The trough/peak (*T/P*) ratios for the systolic and diastolic BPs were 0.84 and 0.78, respectively, in the irbesartan group. The incidence of adverse events was similar in both groups. The results showed that irbesartan administered 100 mg once daily was well tolerated in the treatment of essential hypertension and was effective in producing sustained 24-h BP control. (*Hypertens Res* 2008; 31: 1753–1763)

Key Words: **SR47436, irbesartan, double-blind randomized study, ambulatory blood pressure monitoring, essential hypertension**

Introduction

Hypertension is a major risk factor for cardiovascular diseases (*1*). The aim of antihypertensive therapy is to lower the morbidity and mortality from cardiovascular diseases, and a number of intervention studies have shown that such therapy is effective (*2*). Given the long-term objectives of antihypertensive treatment aimed at cardiovascular disease prevention, it is desirable to use an antihypertensive agent which reliably controls blood pressure (BP) with few adverse drug reactions when administered once daily.

Blood pressure can now be measured non-invasively for 24 consecutive hours (*3–5*). Several studies have shown that the average BP measured by ambulatory BP monitoring (ABPM) correlates more strongly with the severity of hypertensive organ damage than the values measured during outpatient visits (*6*). In addition, the guidelines for clinical assessment of antihypertensive drugs in Japan recommend the use of trough/peak (*T/P*) ratios based on ABPM measurements to investigate the duration of therapeutic effects (*7*).

SR47436 (irbesartan) is a non-peptide angiotensin II (AII) receptor blocker that can be administered orally. Irbesartan selectively binds to a type 1 AII receptor and lowers BP by

From the [1]Division of Hypertension and Nephrology, National Cardiovascular Center, Suita, Japan; [2]Strategic Development Department, Shionogi & Co., Ltd., Osaka, Japan; and [3]Miyagi Foundation for the Prevention of Adult Diseases, Sendai, Japan.

Address for Reprints: Yuhei Kawano, M.D., Division of Hypertension and Nephrology, National Cardiovascular Center, 5–7–1 Fujishirodai, Suita 565–8565, Japan. E-mail: ykawano@hsp.ncvc.go.jp

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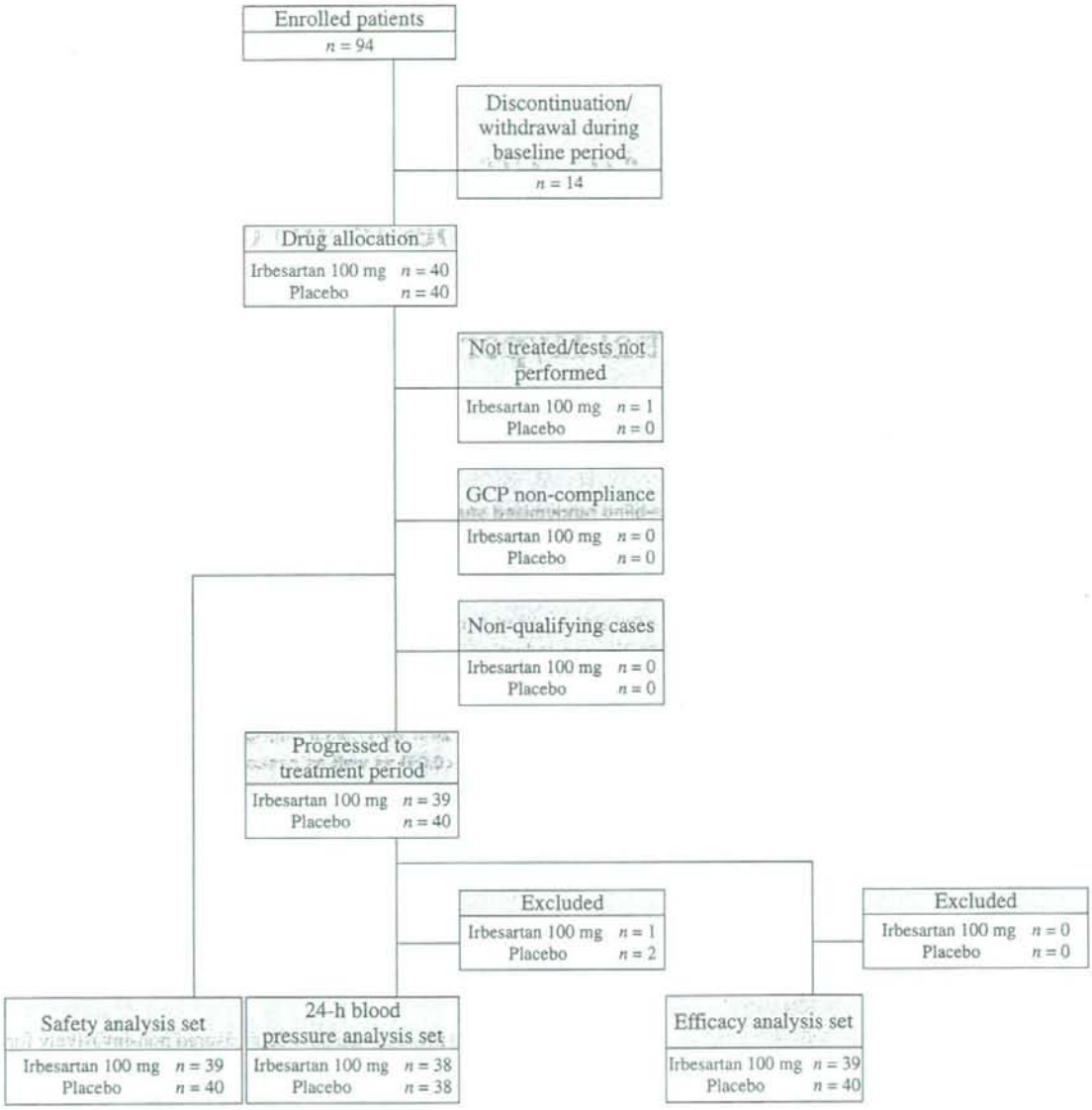

Fig. 1. *Flowchart depicting the inclusion and exclusion of study subjects.*

competing with AII to bind to the receptor. In Japan, single-dose and repeated-dose studies have been conducted among healthy male volunteers. Among those with mild to moderate essential hypertension, two studies of irbesartan have been conducted: a pilot study and a late phase II clinical study (*8*). The results of these studies showed that irbesartan could safely and effectively lower BP when administered once daily, and the optimal clinical doses were estimated at 50–100 mg/d.

The present study investigated the duration of the antihypertensive effect of irbesartan using ABPM. The effect of once-daily administration of 100 mg of irbesartan was evaluated in a placebo-controlled, double-blind randomized study.

Methods

The present study was conducted according to the "Good Clinical Practice for Trials on Drugs (GCP)" ordinance of Japan (Pharmaceutical Affairs Law, Article 14, Section 3 and Article 80, Sections 2-1, 4 and 5) established in accordance with the Declaration of Helsinki. The study was also approved by the institutional review board of each participat-

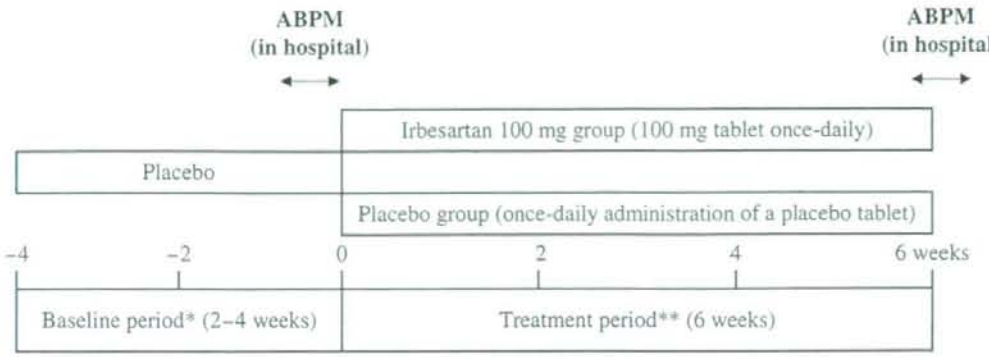

Fig. 2. *Study timeline. *Lengthened by up to 2 weeks depending on patient circumstances. **Shortened or lengthened by 1 week depending on patient circumstances.*

ing medical institution.

Subjects

Eligible subjects were patients with essential hypertension who visited one of the ten medical institutions listed in the Appendix between August 2001 and June 2002. Prior to the start of the baseline period, the investigators used a GCP-compliant consent form to explain the details of the present study to the subjects, and informed consent was obtained in writing from all subjects.

Inclusion criteria at the start of the recruitment were as follows: 1) age from 25 to 79 years, 2) men or postmenopausal women, 3) outpatients with essential hypertension, 4) untreated with antihypertensive agents or, if treated, willing to forgo current medication during the 4-week placebo run-in baseline period and the 6-week main study period. Inclusion criteria at the start of the study period were as follows: 1) stable sitting BP in the last two measurements during the baseline period, 2) sitting systolic BP of 150 mmHg or above and diastolic BP of 95 mmHg or above, or systolic BP of 160 mmHg or above and diastolic BP of 90 mmHg or above, 3) sitting diastolic BP of less than 120 mmHg, 4) mean 24-h systolic BP of 130 mmHg or above, or diastolic BP of 80 mmHg or above. The reason we used several criteria for casual BP was that we wanted to include only patients with definite systolic-diastolic hypertension. Patients with secondary or malignant hypertension, cardiovascular diseases such as stroke, myocardial infarction and heart failure, renal failure or liver dysfunction, and patients judged unsuitable for participation by the investigator were excluded from the present study.

A total of 94 subjects were enrolled in the present study (Fig. 1). Of these patients, 14 discontinued or withdrew during the baseline period. Hence, drug allocation was performed in 80 patients (irbesartan group: $n=40$; placebo group: $n=40$). One patient in the irbesartan group was excluded from the study because the proper allocated drug was not administered. Consequently, 79 patients (irbesartan group: $n=39$; placebo group: $n=40$) progressed to the treatment period, and their data were used for the evaluation of safety and efficacy. During the treatment period, GCP compliance guidelines were upheld for all 79 patients. Ambulatory BP monitoring was not properly performed in three patients (irbesartan group: $n=1$; placebo group: $n=2$); therefore, for the analysis of 24-h BP, we used data from the remaining 76 patients (irbesartan group: $n=38$; placebo group: $n=38$).

Based on the findings of another ABPM study of irbesartan (*9*), it was estimated that the mean difference in the reduction in mean 24-h BP between the irbesartan group and placebo group would be 5.0 mmHg with a SD of 6.0 mmHg. Using these values, the required number of subjects to detect a difference between the two groups was estimated to be 23 per group (power of test: 80%, $\alpha=0.05$, two-sided). Therefore, the target number of cases was set at 30 subjects per group (total number of subjects: 60), allowing for dropouts and withdrawals.

Investigational Drugs

Irbesartan (100 mg) tablets and placebo tablets, indistinguishable in appearance, were used. The tablets were randomly distributed within each of the 30 blocks used; each block consisted of four patients (two in the irbesartan group and two in the placebo group).

Administration of the Drugs

During the baseline run-in period, one placebo tablet was administered once daily after breakfast for 2 weeks to patients with untreated essential hypertension and for 4 weeks to patients who stopped antihypertensive therapy before enrolling (Fig. 2). During the treatment period, one tablet (either 100 mg of irbesartan or placebo) was administered once daily after breakfast for 6 weeks.

Table 1. Characteristics of the Study Population

Item	Irbesartan 100 mg group	Placebo group	Total
Total number of subjects	38 (100.0)	38 (100.0)	76 (100.0)
Gender			
Male	28 (73.7)	25 (65.8)	53 (69.7)
Female	10 (26.3)	13 (34.2)	23 (30.3)
Age (years)	58.9±8.3	58.8±9.4	58.9±8.8
Body weight (kg)	66.5±13.4	64.6±10.9	65.5±12.2
Height (cm)	162.1±7.6	161.0±8.3	161.5±7.9
Complications			
No	9 (23.7)	7 (18.4)	16 (21.1)
Yes	29 (76.3)	31 (81.6)	60 (78.9)
WHO-ISH 1993 Guidelines			
Stage I	13 (34.2)	15 (39.5)	28 (36.8)
Stage II	25 (65.8)	22 (57.9)	47 (61.8)
Stage III	0 (0.0)	1 (2.6)	1 (1.3)
History of antihypertensive therapy			
No past history	8 (21.1)	11 (28.9)	19 (25.0)
Drug taken in the past	9 (23.7)	9 (23.7)	18 (23.7)
Drug taken until just before the study	21 (55.3)	18 (47.4)	39 (51.3)

Data are mean±SD or *n* (%).

Table 2. Distribution of Baseline Values

Item	Irbesartan 100 mg group (n=38)	Placebo group (n=38)	Total (n=76)
Mean 24-h BP during baseline period (mmHg)			
Systolic BP	145.0±10.9	142.9±10.6	143.9±10.7
Diastolic BP	95.0±8.8	92.0±7.8	93.5±8.4
Casual BP during baseline period (mmHg)			
Systolic BP	163.4±11.3	163.7±9.1	163.6±10.2
Diastolic BP	100.0±5.4	99.2±5.7	99.6±5.5
Casual pulse rate during baseline period (beats/min)	73.2±13.1	72.2±11.4	72.7±12.2

Data are mean±SD. BP, blood pressure.

Use of other antihypertensive drugs was prohibited during the baseline and treatment periods. Use of the following drugs was also prohibited unless necessary: psychotropic agents, anti-anxiety drugs, sedatives, hypnotic agents, analgesics, central acting muscle relaxants, phenothiazine antihistamines, or phosphodiesterase-5 inhibitors.

Measurements

Casual BP and pulse rate were measured at 2-week intervals in a sitting position after sufficient rest. A tablet of irbesartan or placebo was taken before the measurement. Casual BP was measured twice, and the average values were used for analysis. At the end of the baseline period and at the end of the treatment period, casual BP was also measured in the supine, and standing positions.

At the end of the baseline period and at the end of the treatment period, ABPM was carried out for 26 consecutive hours in the hospital using a portable automatic sphygmomanometer (TM-2421; A&D Co., Ltd., Tokyo, Japan) at 15-min intervals during the day (6:00–21:00) and at 30-min intervals at night (21:00–6:00). The same sphygmomanometer was used for each patient. During ABPM, the investigational drug was administered at 10 AM. The patients were instructed to relax the upper arm as a cuff was fastened in place and to remain in a sitting position while BP was monitored at peak (3–6 h after administration) and trough (23–24 h after administration) hours. The patients were also instructed to record daily activities, such as the times of meals, sleeping and getting up.

At the end of the baseline period and at the end of the treatment period (or at discontinuation of treatment), the following tests were conducted: hematology, blood chemistry, urinalysis, chest X-ray, electrocardiography, and funduscopy (if possible).

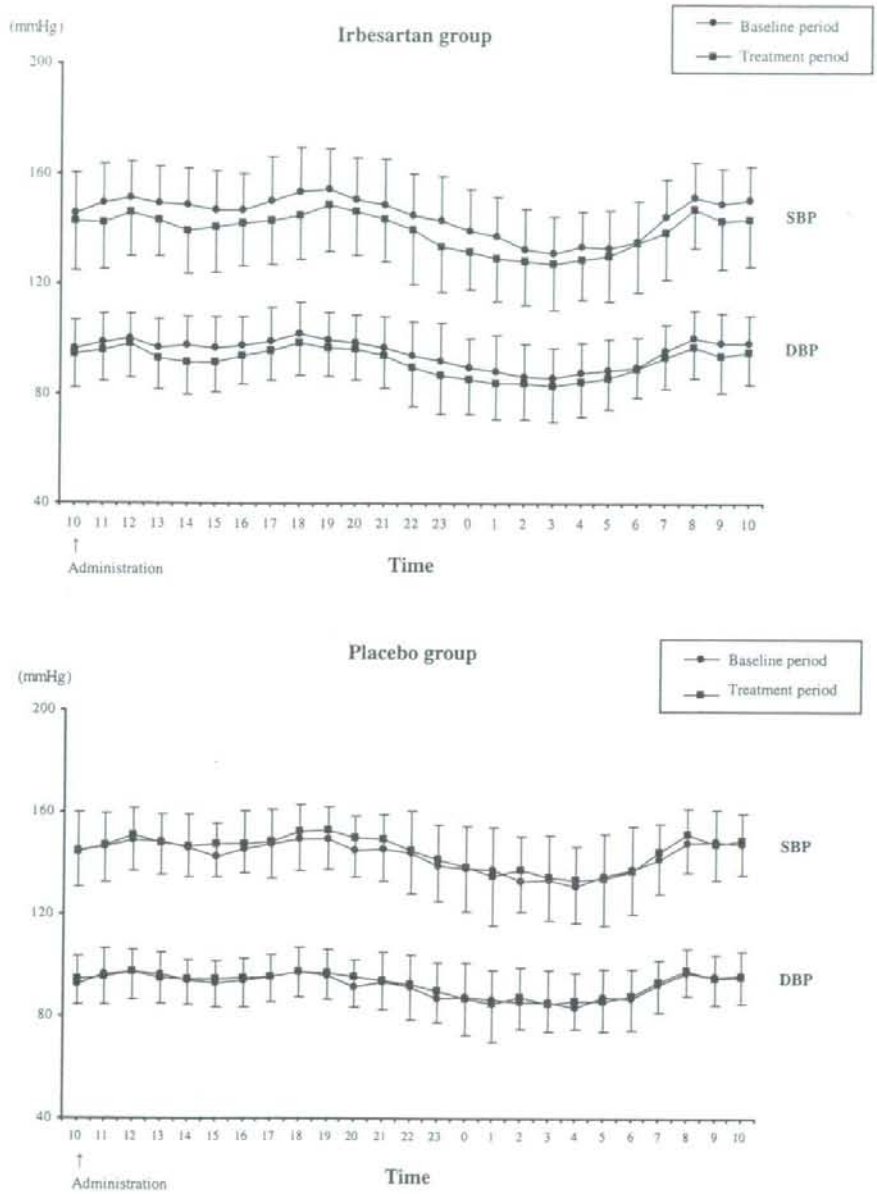

Fig. 3. *Twenty-four-hour blood pressure in the irbesartan and placebo groups. Mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

Adverse Events

All subjective symptoms and objective findings or diseases which newly appeared or which were exacerbated during the study were noted and the details were recorded. Any abnormal changes in laboratory data were evaluated based on a comparison of observed values in the baseline and treatment periods. If possible, follow-up investigations were performed until recovery.

Overall Safety

To investigate the severity of adverse drug reactions, overall safety of use was rated on a scale of 1–5: 1, safe (no safety

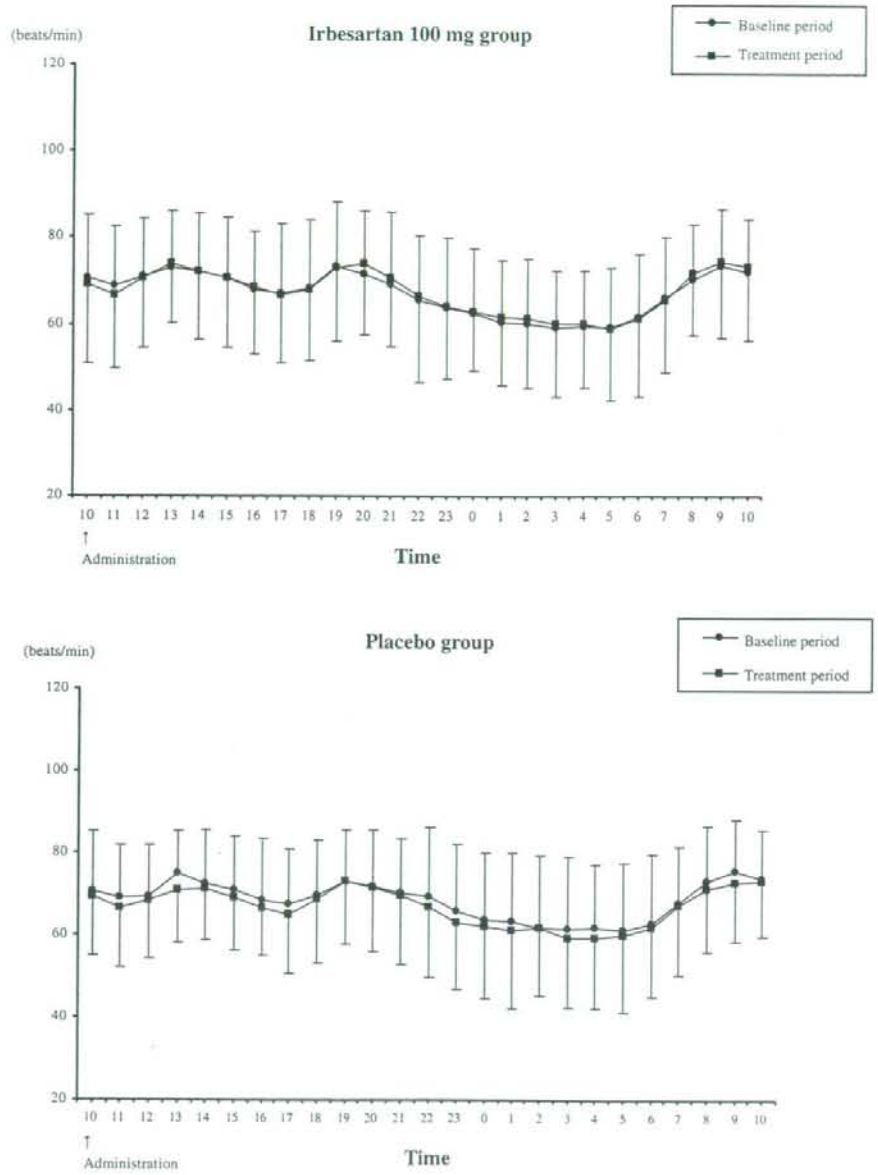

Fig. 4. *Twenty-four-hour pulse rate in the irbesartan and placebo groups. Mean ± SD.*

problems, *i.e.*, no adverse effects occurred); 2, slightly unsafe (mild adverse reaction occurred but no special treatment was needed and treatment was continued); 3, probably unsafe (dosage reduction or other measures were required); 4, unsafe (treatment with the investigational drug was, or should have been, discontinued); 5, no information available. In the event that treatment was discontinued for some reason, the investigator also evaluated the overall safety of use on the same scale. Patients for whom an evaluation could not be made for some reason were classified as "no information available."

Analysis

The primary objective was to compare the efficacy of 100 mg irbesartan compared with placebo group on reducing the mean 24-h BP from ABPM data. The statistical analysis was conducted using SAS version 6.12 (SAS Japan Inc., Tokyo, Japan). The differences between groups were evaluated by

Table 3. Reductions in 24-h, Daytime and Nighttime BP

Item and time period	Group	*n*	Baseline period mean	Treatment period mean	Reduction		Difference between treatment groups		
					Mean	95% confidence interval	*p**	Mean	95% confidence interval
Systolic BP									
24 h	Irbesartan	38	145.0	139.2	5.8	3.2–8.4	0.0001	7.5	3.8–11.1
	Placebo	38	142.9	144.6	−1.7	−4.3–1.0			
Daytime (11:00–21:00)	Irbesartan	38	150.1	143.8	6.3	3.2–9.5	0.0001	8.6	4.4–12.8
	Placebo	38	146.9	149.1	−2.3	−5.1–0.6			
Nighttime (0:00–5:00)	Irbesartan	38	134.8	129.5	5.3	2.3–8.3	0.0100	6.1	1.5–10.7
	Placebo	38	134.8	135.6	−0.8	−4.4–2.7			
Diastolic BP									
24 h	Irbesartan	38	95.0	91.7	3.4	1.6–5.1	0.0004	3.9	1.8–6.0
	Placebo	38	92.0	92.5	−0.5	−1.8–0.7			
Daytime (11:00–21:00)	Irbesartan	38	98.6	95.2	3.4	1.3–5.4	0.0018	3.9	1.5–6.4
	Placebo	38	95.0	95.6	−0.6	−2.0–0.8			
Nighttime (0:00–5:00)	Irbesartan	38	87.7	84.4	3.3	1.2–5.4	0.0218	3.4	0.5–6.2
	Placebo	38	86.0	86.1	−0.1	−2.1–2.0			

Unit: mmHg. BP, blood pressure. *t-test.

Table 4. *T/P* ratios as Determined by ABPM

Item	Group	*T* value (mmHg)	*P* value (mmHg)	*T/P* ratio	Placebo-corrected		
					T value (mmHg)	*P* value (mmHg)	*T/P* ratio
Systolic BP	Irbesartan 100 mg	6.6	7.8	0.84	6.9	9.0	0.77
	Placebo	−0.3	0.1				
Diastolic BP	Irbesartan 100 mg	4.3	5.4	0.78	3.7	5.8	0.64
	Placebo	0.5	0.5				

T, trough; *P*, peak; ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

the *t*-test. The secondary objectives were to assess some other measures of antihypertensive effects and the overall safety of use. The overall safety of use was assessed in an exploratory manner by tabulating the incidence, calculating descriptive statistics, and preparing tables and figures. All tests were two-sided and conducted at the 5% level of significance, unless otherwise specified.

Values are expressed as mean±SD and 95% confidence intervals were used. The Clopper-Pearson method was used to estimate the confidence interval of ratios.

Results

Baseline Characteristics

The patient characteristics, baseline values of BPs and pulse rate are shown in Tables 1 and 2. There were no significant differences between the irbesartan and placebo groups. The mean 24-h BP during the baseline period in the irbesartan group were 145.0±10.9 mmHg systolic and 95.0±8.8 mmHg diastolic and 142.9±10.6 mmHg systolic and 92.0±7.8 mmHg diastolic in the placebo group.

Changes in BP and Pulse Rate during ABPM

Systolic and diastolic BPs and pulse rate, as measured by ABPM, are shown in Figs. 3 and 4. At all measurement points, systolic and diastolic BPs during the treatment period in the irbesartan group were lower than those during the baseline period. In contrast, no marked differences in systolic and diastolic BPs were noted between the baseline and treatment periods for the placebo group. For pulse rate, no marked changes were observed between the baseline and treatment periods for either the irbesartan or the placebo group (Fig. 4).

In the irbesartan group, 24-h systolic and diastolic BPs were significantly reduced whereas the values in the placebo group were unchanged (Table 3). The differences between the groups in the mean reduction in BP were 7.5/3.9 mmHg in 24

h, 8.6/4.0 mmHg in daytime, and 6.1/3.4 mmHg in nighttime.

The reductions in trough systolic and diastolic BPs were 6.6 and 4.3 mmHg, respectively, in the irbesartan group and −0.3 and 0.5 mmHg, respectively, in the placebo group (Table 4). The differences in the reductions for both the trough systolic and diastolic BPs were statistically significant. Trough and peak values were calculated from the mean reduction in BP during 24 h. The *T/P* ratios for systolic and diastolic BPs in the irbesartan group were 0.84 and 0.78, respectively (Table 4). Placebo-corrected *T/P* ratios were also calculated by taking the mean reduction in trough and peak BPs and correcting it for the mean reduction in the placebo group. The placebo-corrected *T/P* ratios for systolic and diastolic BPs were 0.77 and 0.64, respectively.

Changes in Casual BP and Pulse Rate

Changes in outpatient readings for sitting BP and pulse rate are shown in Fig. 5. In the irbesartan group, both systolic and diastolic BPs were significantly decreased at the second week (by 9.1 and 6.0 mmHg, respectively) of the treatment period, and remained significantly low up to the sixth week. In the placebo group, small but significant reductions in BPs were observed from the fourth week of the treatment. No marked changes in pulse rate were observed in either group.

Casual BP values during the baseline period and at the end of the treatment period as well as the reduction in BP are shown in Table 5. Systolic and diastolic BPs were significantly reduced in the irbesartan group and the difference between the groups was 9.0 mmHg systolic and 5.0 mmHg diastolic.

Adverse Events

Of the 79 patients (irbesartan group: $n=39$, placebo group: $n=40$), 20 (51.3%) patients in the irbesartan group experienced a total of 30 adverse events. The main adverse events included common cold syndrome (6 events), headache (2), diarrhea (2), rhinitis (2), and contusion (2). Of these, 2 (5.1%) patients reported adverse drug reactions: thirst (1) and gastric discomfort (1). In the placebo group, 20 (50.0%) patients experienced a total of 33 adverse events. The main adverse events included common cold syndrome (4 events), palpitation (3), insomnia (3), and headache (3). Of these, 5 (12.5%) patients reported adverse drug reactions: cerebral hemorrhage (1), cough (1), headache (1), palpitation (1), and anastomotic ulcer (1).

In the irbesartan group, eight abnormal changes in clinical laboratory findings were reported in six (15.4%) patients including increased creatine kinase (4 events). Of these, 2 (5.1%) displayed 3 adverse drug reactions: increased creatine kinase (1), microscopic hematuria (1), and increased urine WBC (1). In the placebo group, 11 (27.5%) patients experienced a total of 14 abnormal changes in clinical laboratory findings including increased serum uric acid (3 events) and increased serum bilirubin (2). Of these, 4 (10.0%) patients displayed adverse drug reactions: increased serum uric acid (2), increased serum cholesterol (1), and increased serum bilirubin (1).

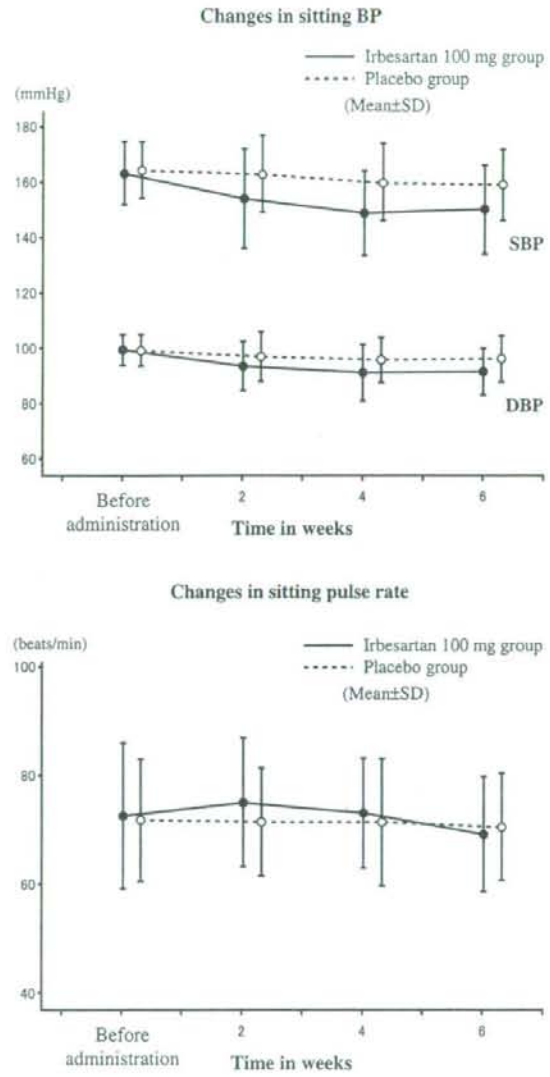

Fig. 5. *Changes in sitting blood pressure and pulse rate measured during outpatient visits. Mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

Overall Safety

The results of the overall safety evaluation are shown in Table 6. The safety rates (defined as the percentage of patients in whom the investigational drug was regarded as "safe") in the irbesartan and placebo groups were 92.3% (36/39) and 80.0%