Original Article

Class of Antihypertensive Drugs, Blood Pressure Status, and Risk of Cardiovascular Disease in Hypertensive Patients: A Case-Control Study in Japan

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The purpose of this study was to compare the effect of different classes of antihypertensives on the risk of cardiovascular events in a case-control study of hypertensive patients. The subjects consisted of 171 hypertensive patients who had experienced a cardiovascular event and 537 randomly selected hypertensive controls who were matched to the cases by gender, age, and hospital/clinic. Both cases and controls had been under antihypertensive medication for at least 6 months before the onset of the cardiovascular event (cases) or before the enrollment (controls). A total of 134 physicians across the nation recruited cases and controls, and reported details of the prescription of antihypertensives and clinical and behavioral variables of their patients. Although there was no measurable difference in the risk of cardiovascular events according to the class of antihypertensives, statistically significant increases in the risk of cardiovascular events were observed for non-use of calcium antagonists among patients with angina pectoris and for non-use of the renin-angiotensin system inhibitor (angiotensin-converting enzyme inhibitor and angiotensin II receptor blockers combined) among patients with diabetes mellitus. Higher levels of blood pressure were associated with an increased risk of cardiovascular events. The findings suggest that appropriate control of blood pressure is more important in the treatment of hypertension than the choice of antihypertensives. (*Hypertens Res* 2005; 28: 811–817)

***Key Words*: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, cardiovascular disease, case-control study**

Introduction

Hypertension is associated with increased risk of cardiovascular diseases, and it has been well established that pharmacological treatment for hypertension substantially reduces the risk of stroke, coronary heart disease, and other cardiovascular diseases (*1–3*). Much interest has recently been drawn to the question of whether any one class of antihypertensive drugs is more effective than the others. A meta-analysis suggested that calcium antagonists were inferior to other types of antihypertensives in reducing the risk of major cardiovascular events (*4*). In another meta-analysis, however, there was no overall difference in major cardiovascular events among the three treatment regimens of angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, and diuretics and β-

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blockers combined (*5*). The Antihypertensive and Lipid-Lowering Treatment Trial indicated that diuretic was superior to calcium antagonists and ACE inhibitors in preventing one or more major cardiovascular events (*6*, *7*). Furthermore, losartan, an angiotensin II receptor blocker, was shown to have a greater effect of reducing cardiovascular events than atenolol in a randomized trial (*8*), while a recent trial showed no overall difference in cardiovascular events between a calcium antagonist and an angiotensin II receptor blocker (*9*).

In Japan, one study reported a more frequent occurrence of cerebrovascular events in patients allocated to receive a calcium antagonist as compared with those receiving an ACE inhibitor (*10*), but another trial found no difference in cardiac events between an ACE inhibitor and a calcium antagonist (*11*). We therefore carried out a case-control study of patients under antihypertensive medication to address the question of whether the effect of antihypertensive drugs on the risk of cardiovascular events (stroke, myocardial infarction, and sudden and unexpected death) differs by the class of antihypertensive drugs.

Methods

Both cases and controls were Japanese patients who had been receiving medication for hypertension for a period of at least 6 months before the onset of the cardiovascular event (cases) or before the enrollment (controls). The cardiovascular events under study were stroke (cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage), myocardial infarction, and sudden and unexpected death. Both cases and controls had no prior history of symptomatic stroke, myocardial infarction, or intervention procedures for the coronary, carotid, and cerebral arteries. Patients with severe life-limiting conditions such as renal dialysis and malignant neoplasm under treatment were not eligible. A total of 134 physicians across the nation participated in the study, and they were in charge of recruitment of patients and collection of information on clinical and behavioral variables. The study was designed and implemented in accordance with the Helsinki Declaration, and was approved by the Institutional Review Board of each participating institution. Written informed consent was given by each participating patient or a proxy family member if the patient was deceased at the time of recruitment.

Cases

Cases were hypertensive patients aged 50–79 years who first experienced the above-specified cardiovascular event during the period from October 2001 to March 2002. They had to have been under medication for hypertension over 6 months or longer prior to the onset of the cardiovascular event. The diagnosis of cerebral hemorrhage, cerebral infarction, and subarachnoid hemorrhage was based on acute neurological symptoms and imaging techniques such as computed tomography and magnetic resonance imaging. Myocardial infarction was defined based on clinical symptoms accompanied with diagnostic serum enzyme elevations or electrocardiographic findings. Sudden and unexpected death was defined as death occurring within 24 h after the onset of severe symptoms in the absence of known conditions other than coronary heart disease and stroke. The definition of sudden and unexpected death was a modified version of the criteria used in the Lipid Research Clinics Coronary Primary Prevention Trials (*12*).

In the consecutive series of 235 cases, 209 patients agreed to participate in the study, but 32 cases were found to be not eligible after the enrollment, and 5 cases had no matched control. Further, one case was excluded due to lack of compliance with the prescribed drug regimen. Thus 171 cases remained in the analysis. The types of cardiovascular events were as follows: cerebral infarction ($n=92$), cerebral hemorrhage ($n=18$), subarachnoid hemorrhage ($n=6$), myocardial infarction ($n=47$), and sudden and unexpected death ($n=8$).

Controls

The eligibility criteria of controls included no prior history of the cardiovascular events under study, an age of 50–79 years at the time of enrollment, and medication for hypertension for 6 months or longer before the enrollment. At the time of enrollment of each case, approximately 20 patients under medication for hypertension in a consecutive series were temporarily enrolled from the same institution as each case. Of these control candidates, at most 4 patients whose sex and age (within 5 years) were the same as those of the case were randomly selected. A total of 3,939 patients were temporarily enrolled in this manner, and 599 patients were randomly selected. Of these, 43 patients refused to participate in the study, 18 were found to be ineligible after collection of relevant information, and one had hardly taken the prescribed drug. After exclusion of these patients, 537 controls remained in the analysis. The numbers of controls matched to cases of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, myocardial infarction, and sudden and unexpected death were 283, 61, 23, 147, and 23, respectively.

Clinical and Behavioral Variables

The names of antihypertensive drugs and the duration of prescription before the onset of cardiovascular event (cases) or before the enrollment (controls) were reported by the participating physicians. In each case, a class of antihypertensive drugs was regarded as having been prescribed if the patient had taken it for at least 90 consecutive days at some point in the past 6 months. The study physicians also reported their judgment of the patient's compliance with the prescription (categorized as "taken 5+ days per week," "half-taken," and "hardly taken"), the frequency of clinic visits (open-ended question), and the monthly measurements of blood pressure in the period of 1–6 months prior to the event (cases) or

Table 1. Blood Pressure Status, Type of Prescribed Antihypertensives, and Other Characteristics among Cases of Cardiovascular Events and Controls

Characteristics	Cases (n=171)	Controls (n=537)
Male (%)	60.2	55.5
Age (years)[a]	68.5±7.0	68.7±6.4
Blood pressure (%)[b]		
Normal	36.3	49.3
Mild hypertension	52.0	43.9
Moderate to severe hypertension	11.7	6.7
Type of antihypertensives (%)		
Diuretics	6.4	5.4
β-Blockers	19.3	14.9
Calcium antagonists	71.3	71.1
ACE inhibitors	30.4	34.1
ARBs	23.4	22.2
Others	14.0	10.8
Good compliance (%)[c]	90.6	97.8
No. of visits (median (interquartile range))	7 (6–12)	7 (6–12)
Angina pectoris (%)	5.8	4.5
Diabetes mellitus (%)	28.7	16.6
Hypercholesterolemia (%)[d]	36.3	43.4
Nephritis/nephrosis (%)	3.5	2.4
Overweight (%)[e]	33.3	36.1
Regular physical activity (%)[f]	42.7	51.4
Current smoking (%)[f]	29.8	21.2
Current alcohol use (%)[f]	39.8	43.4

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker. [a]Data are mean±SD. [b]Based on the classification by the Japanese Society of Hypertension (*3*). [c]Taking 5 days or more per week. [d]Serum total cholesterol ≥220 mg/dl and/or statin use. [e]Body mass index ≥25 kg/m^2. Data were missing for 12 cases and 13 controls. [f]Data were missing for 5 controls, and they were categorized as non-participants in regular physical activity, nonsmokers, or nondrinkers

enrollment (controls). The average systolic and diastolic blood pressure were obtained from the monthly records. The median number of blood pressure measurements taken was 4 in both cases and controls, and 17 cases and 26 controls had only one recorded measurement of blood pressure. Based on the average systolic and diastolic blood pressure, blood pressure status was classified as normal (including optimal and high normal), mildly hypertensive, moderately hypertensive, and severely hypertensive according to the definition of the Japan Society of Hypertension (*3*), which is identical to the WHO/ISH statement definition (*1*). Moderate and severe hypertension were combined in the analysis because patients in these two categories were few.

The physician's diagnoses of angina pectoris, diabetes mellitus, and nephritis or nephrosis were recorded, along with any use of nitrites, oral hypoglycemic drugs, insulin, and statins, and the results of serum total cholesterol measurement. Patients were defined as hypercholesterolemic if their serum total cholesterol was ≥220 mg/dl and/or if they were under statin treatment. The activity of daily living (ADL) was assessed by using 4 precoded answers: completely independent, independent but with supportive devices and aids, under partial care, and bedridden. There was no bedridden patient in either the cases or controls as defined in the eligibility criteria.

Height, body weight, physical activity, smoking habit, and alcohol use were based on the report by patients (or a proxy of the family when a patient had deceased). The answer to the question regarding physical activity was dichotomous: hardly done (<1 times per week) or regularly done (≥1 times per week). Ever-smoking was defined as the daily use of cigarettes for 1 year or longer, and a smoking habit was categorized as lifelong nonsmoking, former smoking, and current smoking. With alcohol use defined as drinking alcohol at least once per week over 1 year or longer, individuals were classified as lifelong nondrinkers, former drinkers, and current drinkers.

Statistical Analysis

Conditional logistic regression analysis was used to estimate the odds ratio (OR) and its 95% confidence interval (CI) with and without adjustment for the clinical and behavioral variables. The 95% CI was estimated by using the standard error of the conditional logistic regression coefficient. Dichotomous variables were used for compliance with antihypertensive medication, angina pectoris, diabetes mellitus, hypercholesterolemia, regular physical activity, and the ADL. Indicator variables were created to represent the three categories of blood pressure status, smoking, and alcohol use. The OR was considered to be statistically significant if the 95% CI did not include unity. Interactions between the type of antihypertensives and clinical risk factors were explored with a statistical significance level of 0.10 (two-sided). Statistical assessment of the interaction was done by the likelihood ratio test comparing the two models with and without an interaction term. All computations were made using the statistical software SAS release 8.2 (SAS Institute Inc., Cary, USA).

Results

The characteristics of cases and controls are summarized in Table 1. The age distribution in the cases and controls was almost identical, although the proportion of men was slightly greater in the case group. While there was no material difference in the class of antihypertensives between cases and controls, patients with mild and moderate/severe hypertension and those with poor compliance were more frequent in cases than in controls. Diabetes mellitus and smoking were more prevalent, and regular physical activity and alcohol use were slightly less prevalent in the cases.

As expected from the proportions for each class of antihy-

Table 2. Use of Specific Antihypertensive Drugs and the Risk of Cardiovascular Events

Type of antihypertensives	No.[a]	Crude OR[b] (95% CI)	*p*-value	Adjusted OR[c] (95% CI)	*p*-value
Diuretics	11/29	1.11 (0.52–2.34)	0.79	1.05 (0.46–2.41)	0.90
β-Blockers	33/80	1.42 (0.88–2.27)	0.15	1.44 (0.84–2.48)	0.19
Calcium antagonists	122/382	1.01 (0.68–1.50)	0.95	1.01 (0.65–1.56)	0.98
ACE inhibitors	52/183	0.82 (0.55–1.21)	0.31	0.80 (0.51–1.23)	0.31
ARBs	40/119	1.05 (0.69–1.61)	0.81	1.02 (0.63–1.66)	0.92
Others	24/58	1.35 (0.79–2.31)	0.27	1.19 (0.65–2.16)	0.57

OR, odds ratio; CI, confidence interval; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker. [a]Numbers of cases/controls. [b]Matched with sex, age, and institution. The referent group used antihypertensive drugs other than the specified class of drugs. [c]Adjusted for blood pressure status, compliance with antihypertensives, angina pectoris, diabetes mellitus, hypercholesterolemia, regular physical activity, smoking, alcohol use, and activity of daily living in addition to the matched variables (sex, age, and hospital). The referent group used antihypertensive drugs other than the specified class of drugs.

Table 3. Risk of Cardiovascular Events for Use of Calcium Antagonists and Renin-Angiotensin System (RAS) Inhibitors Compared with Use of Other Antihypertensive Drugs

Type of antihypertensives	No.[a]	Crude OR[b] (95% CI)	*p*-value	Adjusted OR[c] (95% CI)	*p*-value
Calcium antagonists only	70/222	0.86 (0.41–1.81)	0.69	0.84 (0.37–1.90)	0.68
RAS inhibitors only[d]	38/123	0.82 (0.37–1.82)	0.63	0.78 (0.33–1.85)	0.58
Both calcium antagonists and RAS inhibitors	52/160	0.89 (0.42–1.89)	0.76	0.82 (0.36–1.90)	0.65
Others[e]	11/32	1.00 (referent)	—	1.00 (referent)	—

OR, odds ratio; CI, confidence interval. [a]Numbers of cases/controls. [b]Matched with sex, age, and institution. The referent group used antihypertensive drugs other than the specified class of drugs. [c]Adjusted for blood pressure status, compliance with antihypertensives, angina pectoris, diabetes mellitus, hypercholesterolemia, regular physical activity, smoking, alcohol use, and activity of daily living in addition to the matched variables (sex, age, and hospital). [d]RAS inhibitors included angitotensin-converting enzyme inhibitors and angiotensin II receptor blockers. [e]Drugs other than calcium antagonists and RAS inhibitors.

pertensives shown in Table 1, the crude ORs for the use of an individual class of antihypertensive drugs were not very different from unity, and the results did not change after adjustment for blood pressure status, compliance, and other cardiovascular risk factors (Table 2). On the other hand, the grade of blood pressure status was positively associated with the risk of cardiovascular events. The crude ORs (95% CIs) for normal blood pressure, mild hypertension, and moderate/severe hypertension were 1.00 (referent), 1.70 (1.14–2.53), and 2.51 (1.29–4.87), respectively. After adjustment for the covariates except compliance, the ORs (95% CIs) for normal blood pressure, mild hypertension, and moderate/severe hypertension were 1.00 (referent), 1.69 (1.10–2.60), and 2.20 (1.08–4.45), respectively.

Further analysis was done by breaking down the antihypertensive drugs into three groups: calcium antagonists; renin-angiotensin system (RAS) inhibitors, which included both ACE inhibitors and angiotensin II receptor blockers; and other drugs, including diuretics and β-blockers. The number of patients who were prescribed the combination of a calcium antagonist plus a RAS inhibitor was 52 cases and 160 controls. Very few patients received calcium antagonists and/or RAS inhibitors in combination with antihypertensives other than these drugs (data not shown). Neither calcium antagonists nor RAS inhibitors were specifically associated with the risk of cardiovascular events (Table 3).

We explored the interactions of each group of antihypertensive drugs (calcium antagonists, RAS inhibitors, and the traditional drugs) with the clinical risk factors for cardiovascular events. Possible interactions were noted between calcium antagonists and angina pectoris (interaction $p=0.037$) and between diabetes mellitus and RAS inhibitors (interaction $p=0.098$). A statistically significant 5-fold increase in the risk of cardiovascular events was observed for non-use of calcium antagonists in the presence of angina pectoris (Table 4), and non-use of RAS inhibitors was associated with a statistically significant 3-fold increase in the risk among patients with diabetes mellitus (Table 5).

Discussion

The present study did not show any material difference in the risk of cardiovascular events among hypertensive patients under medication with different types of antihypertensive

Table 4. Risk of Cardiovascular Events in Relation to the Combination of Angina Pectoris and Calcium Antagonists[a]

Angina pectoris	Calcium antagonists	No.[b]	Adjusted OR (95% CI)[c]	*p*-value
(−)	(−)	44/151	1.00 (referent)	—
(−)	(+)	117/362	1.11 (0.70–1.75)	0.65
(+)	(−)	5/4	5.08 (1.08–23.9)	0.04
(+)	(+)	5/20	0.71 (0.21–2.45)	0.59

OR, odds ratio; CI, confidence interval. [a]Interaction $p=0.037$. [b]Numbers of cases/controls. [c]Adjusted for blood pressure status, compliance with antihypertensives, diabetes mellitus, hypercholesterolemia, regular physical activity, smoking, alcohol use, and activity of daily living in addition to the matched variables (sex, age, and hospital).

Table 5. Risk of Cardiovascular Events in Relation to the Combination of Diabetes Mellitus and Renin-Angiotensin System (RAS) Inhibitors[a]

Diabetes mellitus	RAS inhibitors	No.[b]	Adjusted OR (95% CI)[c]	*p*-value
(−)	(−)	55/218	1.00 (referent)	—
(−)	(+)	67/230	1.14 (0.72–1.82)	0.57
(+)	(−)	26/36	3.01 (1.48–6.10)	0.002
(+)	(+)	23/53	1.57 (0.78–3.14)	0.20

OR, odds ratio; CI, confidence interval. [a]Interaction $p=0.098$. [b]Numbers of cases/controls. [c]Adjusted for blood pressure status, compliance with antihypertensives, angina pectoris, hypercholesterolemia, regular physical activity, smoking, alcohol use, and activity of daily living in addition to the matched variables (sex, age, and hospital).

drugs. On the other hand, there was a positive relationship between blood pressure status and the risk of cardiovascular events. The findings reiterate the importance of achieving and maintaining an appropriate level of blood pressure in the management of hypertension, *i.e.*, below 130 mmHg in systolic blood pressure and below 85 mmHg in diastolic blood pressure (*3*).

We observed that the risk of cardiovascular events increased when the RAS inhibitor was not used among the patients with diabetes mellitus and when calcium antagonists were not used in patients with angina pectoris. Because these findings were the results of an exploratory analysis seeking for possible interactions, caution should be exercised in their interpretation. Nonetheless, these findings are consistent with previous observations as regards RAS blockers and calcium antagonists.

Both ACE inhibitors and angiotensin II receptor blockers were shown to improve insulin resistance in humans as well as in animals (*13*, *14*). These RAS inhibitors also reduced the incidence of new onset diabetes mellitus (*7*, *15*). In a randomized placebo-controlled trial of hypertensive patients with diabetes mellitus (*16*), the investigators noted that a reduction in the risk of cardiovascular events associated with ACE-inhibitor treatment was greater than that attributable to the decrease in blood pressure. Furthermore, randomized trials comparing the effects of ACE inhibitors and calcium antagonists among people with hypertension and diabetes mellitus reported that the ACE inhibitors were more effective at reducing cardiovascular events (*17*, *18*), although such a differential effect as regards diabetes mellitus was not always observed (*19*). Hypertension is the most common component of metabolic syndrome (*20*), and the choice of antihypertensive drugs may be an important matter in the treatment of hypertension among patients with diabetes mellitus (*21*).

As regards calcium antagonists, randomized trials based on coronary angiography showed that calcium antagonists suppressed the occurrence of new atherosclerotic lesions and progression of minimal coronary lesions in patients with coronary artery disease, although the drugs did not affect the progression or regression of advanced atherosclerotic lesions (*22*, *23*). Amlodipine (calcium antagonist) was shown to have the effect of slowing the progression of carotid artery atherosclerosis, but not of coronary atherosclerosis (*24*), and the occurrence of myocardial infarction among patients with hypertension treated with amlodipine was less than that in those treated with an angiotensin II antagonist (*9*).

Our present findings on the type of antihypertensive drugs used in clinical practice were also of interest. In the control group, over 70% of hypertensive patients received calcium antagonists, and the ACE inhibitor was the second most common agent (34%), followed by angiotensin II receptor blockers (22%), β-blockers (15%), and diuretics (6%). These figures probably represented the use of antihypertensive drugs in Japan (*25*), since physicians across the nation participated in the study. In a survey conducted during the period from September 2000 to March 2001 in Tottori, Japan (*26*), the overall prescription rates of calcium antagonists, ACE inhibitors, angiotensin II receptor blockers, β-blockers, and diuretics were 73%, 31%, 19%, 16%, and 10%, respectively.

Selection and information bias are methodological con-

cerns in case-control studies. In the present study, the cases were patients with defined cardiovascular events in a consecutive series, and the controls were a random sample out of a consecutive series of hypertensive patients under medication. These procedures in the recruitment of cases and controls minimized selection bias and ensured comparability between cases and controls. Prescription of antihypertensive drugs, blood pressure, and cardiovascular risk factors were ascertained retrospectively, but on the basis of recorded data. In this regard, the present findings are unlikely to have been ascribable to information bias, although comorbid conditions such as hypercholesterolemia and angina pectoris may not have been ascertained accurately. Classification of the antihypertensive drugs prescribed for each patient was based on the continuous prescription for at least 90 days in the past 6 months. Prescription in the immediate past might be more relevant to the risk of cardiovascular events.

The randomized controlled trial is a preferred method for evaluating the efficacy of therapeutic treatments, but observational studies complement the evidence from randomized clinical trials. The efficacy shown in a limited group of patients may not be directly applicable in routine practice. The effectiveness of the treatments under actual clinical conditions can be addressed in observational studies (*27*, *28*). Although prospective studies are generally regarded as superior to case-control studies, results from case-control studies are as valid as those from prospective studies if prescription is determined on the basis of recorded data. As illustrated in a study showing that poor control of blood pressure was clearly associated with an increased risk of stroke in routine practice (*29*), case-control studies are a valuable method of evaluating the effectiveness of a therapeutic regimen in a society in which randomized controlled trials are difficult to implement.

Appendix

The following physicians participated in the study: [Hokkaido district] Hirotsugu Imamura, Itaru Maeda, Shin-ichiro Satoh, Fumio Ishizaka; [Tohoku district] Yoshihisa Akino, Masatoshi Onoda, Takashi Kimura, Yoshiko Shibata, Toru Chiba, Koji Tsukuda, Ryo Ito, Masato Hayashi, Etsuko Fushimi, Hirohisa Sudo, Yukio Kubota, Yoshiharu Haga; [Kanto district] Kiyohiro Akada, Nobuyoshi Hatano, Atsuro Kato, Hiroyuki Kuroki, Manabu Narimiya, Soichiro Ishimoto, Yasuaki Ishimaru, Akiyoshi Ohtsuka, Ichiro Michishita, Mitsuo Amano, Terukuni Ideura, Masao Ishii, Masataka Shoda, Masayuki Nakao, Masahiko Kanna, Toshihiko Saito, Yukihiko Miura, Susumu Takano, Seinosuke Ryu, Mitsuhiro Miyazaki, Shoji Ohba, Yoshiaki Sohara, Osamu Sakayori, Akira Yamazaki, Takashi Funada, Haruo Iwakura, Takeshi Takei, Yuji Shimizu; [Chubu district] Makihiko Saeki, Tetsuji Kosaki, Mutsuo Kusunose, Atsushi Nomura, Tomoko Katoh, Tatsuji Furuta, Taisei Kawamura, Takeshi Kondo, Shinya Hiramitsu, Masayoshi Sarai, Masato Watarai, Motohiko Nishida, Yoshihiro Hattori, Makoto Hayakawa, Kei Iida, Kohzo Kawai, Sumio Mizuno, Jun-ichi Hirai, Kouji Maeno; [Kinki district] Kazumi Matsuda, Hirofumi Kusaka, Hidefumi Ito, Hisashi Ito, Masumi Sano, Toshihiko Sano, Yo Nagahama, Naoto Minamitani, Mitsushige Ohta, Hisahiro Yu, Shigefumi Nakamura, Atsushi Moriguchi, Takaya Hasegawa, Hideo Matsui, Terutaka Tsuda, Toru Miyajima, Nobuhiko Miki, Kunio Hashimoto, Yoshiaki Fukuoka, Kazuhiro Uragami, Tetsuro Ichida, Keiko Kano, Yoko Taniguchi, Tatsuhito Nakae, Akitsugu Nishiyama, Hirofumi Takashima, Yasuo Takayama, Takayuki Nakatsuka, Masahiro Amenomori, Yuusaku Minami; [Chugoku district] Kumiko Tabuchi, Kenji Doi, Shouko Oota, Michiyoshi Sato, Toshiyuki Dohi, Hiroshi Ochi, Shinichiro Suyama, Yasuaki Mino; [Shikoku district] Masaaki Hattori, Masahiro Iwamoto, Kazumi Tsuzaki, Nobuo Matsuoka, Katsuyuki Fukuta, Toshihiro Goto, Sadanori Takeda, Shin Kimoto, Kiyonobu Tanaka, Motofumi Maguchi, Hiroshi Fukuda; [Kyushu district] Shoji Arihiro, Yuichirou Nakamura, Hideo Ikeda, Sohichi Uekihara, Yutaka Horio, Kazuki Takeshima, Koji Shiga, Shuji Inoue, Seiji Nishi, Yoshiaki Hayashi, Akito Sato, Nobuhisa Fukumoto, Yoshinao Uezu, Kensuke Matsushima.

References

1. World Health Organization, International Society of Hypertension Writing Group: 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003; **21**: 1983–1992.
2. Chobanian AV, Bakris GL, Black HR, the National High Blood Pressure Education Program Coordinating Committee: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
3. Japanese Society of Hypertension Guidelines Subcommittee for the Management of Hypertension: Guidelines for the management of hypertension for general practitioners. *Hypertens Res* 2001; **24**: 613–634.
4. Pahor M, Pasty BM, Alderman MH, *et al*: Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* 2000; **356**: 1949–1954.
5. Blood Pressure Lowering Treatment Trialists' Collaboration: Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; **362**: 1527–1535.
6. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major cardiovascular events in hypertensive patients randomized to doxazosin *vs* chlorthalidone. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000; **283**: 1967–1975.
7. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotension-converting enzyme inhibitor or calcium channel blocker *vs* diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**: 2981–2997.
8. Dahlöf B, Devere RB, Kjeldsen SE, *et al*, for the Life Study group: Cardiovascular mortality in the Losartan Interven-

tion For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 995–1003.
9. Julius S, Kjeldsen SE, Weber M, *et al*, for VALUE trial group: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; **363**: 2022–2031.
10. The GLANT Study Group: A 12-month comparison of ACE inhibitor and Ca antagonist therapy in mild to moderate essential hypertension—the GLANT Study. *Hypertens Res* 1995; **18**: 235–244.
11. Yui Y, Sumiyoshi T, Kodama K, *et al*: Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) randomized trial. *Hypertens Res* 2004; **27**: 181–191.
12. The Lipid Research Clinics Program. The coronary primary prevention trail: design and implementation. *J Chronic Dis* 1979; **32**: 609–631.
13. Inukai O, Shimamoto K, Matsuda K, *et al*: Effects of angiotensin converting enzyme inhibitor on insulin sensitivity in fructose-fed hypertensive rats and essential hypertensives. *Am J Hypertens* 1995; **8**: 353–357.
14. Okada K, Hirano T, Ran J, Adachi M: Olmesartan medoxomil, an angiotensin II receptor blocker ameliorates insulin resistance and decreases triglyceride production in fructose-fed rats. *Hypertens Res* 2004; **27**: 293–299.
15. The Heart Outcomes Prevention Evaluation Study Investigators: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342**: 145–153.
16. Heart Outcomes Prevention Evaluation (HOPE) Study Iinvestigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; **355**: 253–259.
17. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW: The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-depended diabetes and hypertension. *N Eng J Med* 1998; **338**: 645–652.
18. Tatti P, Guarisco R, Pahor M, *et al*: Outcome results of the fosinopril *versus* amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998; **21**: 597–603.
19. Yui Y, Sumiyoshi T, Kodama K, *et al*: Nifedipine retard was as effective as angiotensin converting enzyme inhibitors in preventing cardiac events in high-risk hypertensive patients with diabetes and coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) subgroup analysis. *Hypertens Res* 2004; **27**: 449–456.
20. Ishizaka N, Ishizaka Y, Toda E, Hashimoto H, Nagai R, Yamakado M: Hypertension is the most common component of metabolic syndrome and the greatest contributor to carotid arteriosclerosis in apparently healthy Japanese individuals. *Hypertens Res* 2005; **28**: 27–34.
21. Hirose H, Saito I: Trends in blood pressure control in hypertensive patients with diabetes mellitus in Japan. *Hypertens Res* 2003; **26**: 717–722.
22. Lightlen PR, Hugenholtz PG, Rafflenbeul W, on behalf of the INTACT group investigators: Retardation of angiographic progression of coronary artery disease by nifedipine. Results of the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT). *Lancet* 1990; **335**: 1109–1113.
23. Waters D, Lespérance J, Francetich M, *et al*: A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis. *Circulation* 1990; **82**: 1940–1953.
24. Pitt B, Byington RP, Furberg CD, *et al*, for the PREVENT Investigators: Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation* 2000; **102**: 1503–1510.
25. Saito I, Kawabe H, Tsujioka M, Hirose H, Shibata H: Trends in pharmacologic management of hypertension in Japan one year after the publication of the JSH 2000 guidelines. *Hypertens Res* 2002; **25**: 175–178.
26. Yamamoto Y, Sonoyama K, Matsubara K, *et al*: The status of hypertension management in Japan in 2000. *Hypertens Res* 2002; **25**: 717–725.
27. Concato J, Sham N, Horwitz RI: Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000; **342**: 1887–1892.
28. Pocock SJ, Elbourne D: Randomized trials or observational tribulations? *N Engl J Med* 2000; **342**: 1907–1909.
29. Du X, Cruickshank K, McNamee R, *et al*: Case-control study of stroke and the quality of hypertension control in north west England. *BMJ* 1997; **314**: 272–276.