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ORIGINAL ARTICLE

Relationship between achieved blood pressure, dietary habits and cardiovascular disease in hypertensive patients treated with olmesartan: the OMEGA study

This article has been corrected since Advance Online Publication, and a corrigendum is also printed in this issue.

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We investigated the relationship between cardiovascular disease (CVD) and the achieved blood pressure, dietary habits and the presence/absence of metabolic syndrome (MetS) in hypertensive patients treated with olmesartan medoxomil. A prospective cohort study with a 3-year follow-up was conducted in 14 721 olmesartan-naive outpatients (mean age: 64.9 years, 49.6% women) with essential hypertension. The association of CVD with achieved blood pressure, dietary habits and MetS was investigated by Cox proportional hazards analysis. There were 3059 patients (31.8%) with MetS (Japanese criteria) among 9625 evaluable patients. The mean baseline blood pressure was 157.4/88.8 mm Hg, which decreased to 134.0/76.1 mm Hg during treatment ($P<0.0001$). The annual incidence of CVD was 7.15 per 1000 persons during the study period. When the achieved blood pressure was stratified according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009), the risk of CVD increased significantly along with the severity of hypertension ($P<0.0001$), especially the risk of stroke. Investigation of dietary habits revealed a significant association between salt intake and the risk of stroke. Higher salt intake was associated with a significantly higher risk of stroke than lower salt intake (hazard ratio, 1.897; 95% confidence interval, 1.003–3.590). Blood pressure was well controlled in both patients with and without MetS, and there was no significant difference in the incidence of events between the two groups. In conclusion, the severity of hypertension (achieved blood pressure) is associated with the incidence of CVD, and the results of this study suggest that tight blood pressure control and salt restriction are important for preventing stroke.
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Keywords: cardiovascular disease; metabolic syndrome; olmesartan; salt intake; stroke

INTRODUCTION

Hypertension is known to be one of the main risk factors for cardiovascular disease (CVD).[1,2] A number of large-scale studies on the relationship between hypertension and CVD have indicated that strict blood pressure control is important for preventing CVD.[3,4]

Accumulation of risk factors is related to the morbidity and mortality of CVD, so metabolic syndrome (MetS) has been attracting more attention in this context over the past decade. Diagnostic criteria for this syndrome have been published overseas,[5,6] and also eight Japanese academic societies have jointly published diagnostic criteria for MetS in 2005.[7] Several reports regarding the relationship between MetS and CVD in hypertensive patients have been published overseas.[8–10] In Japan, the Hisayama study[11] and the Tanno and

Sobetsu study[12] have provided evidence that MetS is a significant risk factor for CVD in the general population. However, no large-scale studies have been conducted in Japan to assess the risk factors for CVD in hypertensive patients who also have MetS.

The INTERSALT study[13] and other studies have shown that excessive salt intake is related to high blood pressure, whereas the DASH-Sodium study[14] and other large-scale studies have suggested that reducing the intake of salt is effective for lowering the blood pressure. Increased potassium intake has also been recommended for reducing the blood pressure, but there is no supportive epidemiological evidence available. Furthermore, it has been reported that intake of soy protein and omega-3 unsaturated fatty acids can be effective for preventing coronary heart disease (CHD).[15–17]

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According to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009),[18] angiotensin II receptor blockers (ARBs) are positively indicated for treating hypertensive patients with various organ complications, and should be used as the first choice for patients with complications of the heart, kidneys or brain, and those with diabetes mellitus. The ARB olmesartan medoxomil (Daiichi Sankyo Co., Ltd, Tokyo, Japan) has a carboxyl group and a hydroxyl group that bind to the angiotensin 1 receptor, which is called a double-chain domain. Compared with other ARBs, olmesartan binds more strongly to the angiotensin 1 receptor and has a more potent antihypertensive effect.[19,20]

We conducted a large-scale prospective cohort study, the OMEGA study (olmesartan mega study to determine the relationship between cardiovascular endpoints and blood pressure goal achievement) during treatment with olmesartan medoxomil. We also investigated the relationship between blood pressure, MetS and the incidence of CVD. Furthermore, we performed a questionnaire survey to assess the intake of sodium, potassium, soybeans and fish, to investigate the relationship between dietary habits, such as salt intake and the incidence of CVD.

We have already reported the study design, baseline data[21] and relationship between dietary habits and the occurrence of MetS.[22]

METHODS
Study design
The OMEGA study was a prospective, large-scale observational study designed to examine the relation between the incidence of CVD in Japanese hypertensive patients and the achieved blood pressure, the presence of MetS, dietary habits, such as salt intake, and other CVD risk factors. The OMEGA study was initiated in September 2005 as a post-marketing surveillance by the Sankyo Co., Ltd (presently Daiichi Sankyo Co., Ltd), in compliance with the regulations of the Japanese Ministry of Health, Labor and Welfare.

Details of the study design and the baseline clinical characteristics of the patients have been reported previously.[21] Eligible patients were men or women aged 50–79 years, with physician-diagnosed hypertension, who were attending outpatient departments of the participating institutions and had not been treated with olmesartan. Exclusion criteria were a history of myocardial infarction, stroke, coronary artery bypass grafting or percutaneous coronary intervention within 6 months before enrollment, as well as scheduled coronary intervention, congenital or rheumatic heart disease, severe arrhythmia, severe hepatic or renal disease, cancer that was under treatment, and pregnancy or the potential to become pregnant. Each patient was informed of the purpose and methods of the study, as well as their right to withdraw from the study at any time and the measures taken for confidentiality. After providing written informed consent and being prescribed olmesartan, the patients were enrolled in a central electronic data capturing system. The method of blood pressure measurement was not specified, so blood pressure was measured according to the routine procedure at each institution. Data were collected before study initiation and every 6 months after initiation. We collected information on adverse events (occurrence or exacerbation of symptoms/objective findings, and other events and abnormal changes in laboratory values) recorded at each institution. This study was registered at http://www.clinicaltrials.jp/ (identification number: JapicCTI-050002). The study protocol was approved by the Ethical Committee of Sankyo Co., Ltd, and it conformed with the pharmaceutical affairs laws of Japan and was approved by the Ministry of Health, Labor and Welfare of Japan before commencement. This study conformed with the Declaration of Helsinki and was carried out at medical institutions that were registered according to Good Post-Marketing Surveillance Practice in Japan.

Classification of blood pressure
Blood pressure was classified in accordance with JSH 2009, which defines normal blood pressure as a systolic blood pressure (SBP) <130 mm Hg and diastolic blood pressure (DBP) <85 mm Hg, high normal blood pressure as an SBP of 130–139 mm Hg or DBP of 85–89 mm Hg, stage I hypertension as an SBP of 140–159 mm Hg or DBP of 90–99 mm Hg, stage II hypertension as an SBP of 160–179 mm Hg or DBP of 100–109 mm Hg, and stage III hypertension as an SBP ⩾180 mm Hg or DBP ⩾110 mm Hg.

Diagnostic criteria for MetS
MetS was defined according to criteria established by the Japanese Society of Internal Medicine. As all of the study subjects had hypertension, one criterion for the syndrome was fulfilled at the time of enrollment. In addition, patients had to have central obesity with a waist circumference ⩾85 cm for men or ⩾90 cm for women, plus dyslipidemia (serum triglycerides ⩾150 mg dl^{-1}, or high-density lipoprotein cholesterol <40 mg dl^{-1}) and/or fasting hyperglycemia (plasma glucose ⩾110 mg dl^{-1}), or a diagnosis of diabetes.

Diet questionnaire
A simple questionnaire on diet was completed by the patients, which included questions on salt intake (salted fish, dried fish, fish sausage, Japanese pickles, ham/sausage, traditional Japanese and Chinese soups with a high salt content (noodle and miso soup), and use of salt and soy sauce) and on the intake of potassium (fruit) and soybeans/fish (bean curd, non-salted fermented soybeans and fish). High-salt foods were selected according to the 'Outline of the Results of the National Health and Nutrition Survey Japan, 1997.' Although both fruit and vegetables have a high content of potassium, we only assessed fruit consumption, because fruits tend to be eaten raw and retain potassium, whereas vegetables often lose potassium during cooking. The soybean foods selected were traditional Japanese dishes.

The frequency of sodium, potassium and soybean/fish intake was classified into the following 4 categories: no intake (1 point), eaten once or twice weekly (2 points), eaten 3–5 times/week (3 points) and eaten every day (4 points). For the traditional Japanese and Chinese soups, the frequency and volume of intake were investigated separately, and the intake score was calculated as the square root of the product of the frequency score and the volume score. The dietary sodium intake score was calculated as the total of the 8 intake scores and ranged from 8 to 32 points, whereas the dietary potassium intake score ranged from 1 to 4 points. The dietary soybean/fish intake score was the total of the 3 intake scores and ranged from 3 to 12 points. Lower sodium intake was defined as a score <15.8 points (below the 25th percentile), whereas lower intake of potassium or soybeans/fish was defined as <2 and <6 points (below the 25th percentile), respectively.

Endpoints
The endpoints were stroke (cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage), CHD (myocardial infarction and angina pectoris requiring cardiovascular intervention or hospitalization) and sudden death. CVD was defined as a composite of these three endpoints.

Stroke was diagnosed if either CT or MRI showed cerebral infarction or hemorrhage in patients who had neurological symptoms persisting for more than 24 h or in patients who died within 24 h of the onset of neurological symptoms.

Myocardial infarction was diagnosed if either the electrocardiogram or the levels of cardiac enzymes suggested infarction in patients who had symptoms consistent with acute myocardial infarction or if cardiovascular intervention was carried out to treat myocardial infarction. Stroke and myocardial infarction were not classified as fatal or non-fatal. Angina pectoris requiring cardiovascular intervention or hospitalization was diagnosed if cardiovascular intervention (including percutaneous coronary intervention or coronary bypass grafting) was performed for suspected myocardial infarction or angina pectoris, or if hospitalization was required for angina. Sudden death was defined as death within 24 h of the onset of symptoms that were most likely to have been associated with cerebrovascular disease/CVD, provided that there were no other possible causes.

Study population size
The target number of subjects was calculated from the assumptions shown below, to determine the risk of CVD in hypertensive patients with dyslipidemia: (1) 40% of patients with essential hypertension would have dyslipidemia,

(2) dyslipidemia would increase the risk of CVD by 1.3-fold, and (3) the 3-year cumulative incidence of CVD in patients without dyslipidemia would be 4%.[23,24] Statistical significance was set at a probability of 0.05 (two-sided) and a power 80%. As a result, the number of CVD events required was 435, and the number of subjects required was 9710. Considering the potential for dropouts, the target number of subjects was set as 12 000.

Statistical analysis

Quantitative data are expressed as the mean ± s.d. In evaluating the relationship between achieved blood pressure and the incidence of cardiovascular events, the Cox proportional hazards model was used with a linear contrast to test for trend of the severity of hypertension as a time-dependent covariate, adjusted by sex, age, family history of coronary artery disease, diabetes, dyslipidemia, history of CVD, body mass index and smoking. The Cox proportional hazards model was also used to investigate the relationship between dietary habits or MetS and the incidence of cardiovascular events, adjusted by baseline factors. Subgroup analyses were conducted with subjects with/without CVD history. Adverse events were coded using MedDRA/J with the preferred term for each event and the system organ class. Events for which a causal relationship with olmesartan could not be excluded were classified as adverse drug reactions, and the incidence was tabulated. Statistical analyses were conducted using SAS Release 8.2 (SAS Institute, Cary, NC, USA). All P-values are two-sided and those under 5% were considered statistically significant.

RESULTS

Study profile and baseline characteristics

The study was performed between July 2005 and March 2010. A total of 15 313 patients were enrolled at 2219 medical institutions in Japan, and baseline data were collected from 15 255 patients. Subsequently, another 534 patients were excluded because of the following reasons: 51 patients were not eligible in accordance with the protocol inclusion/exclusion criteria, 6 patients failed to take olmesartan, 244 patients had no data after the administration of olmesartan, 82 patients had no 6-month data, 63 patients withdrew consent when the 6-month follow-up was carried out and 88 patients were found to have been enrolled outside the specified enrollment period. Accordingly, a total of 14 721 patients were evaluated for safety and efficacy.

The characteristics of the subjects are shown in Table 1. Their mean age was 64.9 ± 8.2 years and 49.6% of the patients were women. The blood pressure (SBP/DBP) at the start of olmesartan treatment was 157.4 ± 17.7/88.8 ± 12.1 mm Hg and the pulse rate was 74.0 ± 10.7 beats per min. A total of 6137 patients (41.7%) had stage I hypertension, whereas 532 patients (3.6%) had normal blood pressure and 1040 patients (7.1%) had high normal blood pressure at the initiation of olmesartan treatment. There were 7089 patients (48.2%) with dyslipidemia, 3598 patients (24.4%) with diabetes, 1780 patients (12.1%) with liver disease and 1062 patients (7.2%) with kidney disease. A total of 1448 patients (9.8%) had a history of CVD, including 749 patients (5.1%) with a history of stroke and 798 patients (5.4%) with a history of CHD. A total of 3544 patients (24.1%) had MetS according to the Japanese criteria. The mean follow-up period was 2.7 years.

Antihypertensive treatment

Antihypertensive treatment is shown in Table 2. The daily dose of olmesartan was 17.3 ± 5.5 mg at the start of the study and 17.2 ± 8.6 mg after 36 months of administration. The mean administration period was 922.7 ± 391.7 days. At the end of the study, 1725 patients (11.7%) were not taking olmesartan.

When administration of olmesartan was started, 5784 patients (39.3%) were already taking antihypertensive drugs, including

Table 1 Baseline characteristics of the study population

Parameter	n (%) or mean ± s.d.
No. of patients	14 721
Age (years)	64.9 ± 8.2
Women	7 303 (49.6)
BMI (kg m^{-2})	24.75 ± 3.61
SBP (mm Hg)	157.4 ± 17.7
DBP (mm Hg)	88.8 ± 12.1
Pulse rate (beats per min)	74.0 ± 10.7
Severity of hypertension (JSH 2009)	
Normal blood pressure	532 (3.6)
High normal blood pressure	1 040 (7.1)
Stage of hypertension	
Stage I	6 137 (41.7)
Stage II	4 743 (32.2)
Stage III	1 843 (12.5)
Complications	
Dyslipidemia	7 089 (48.2)
Diabetes mellitus	3 598 (24.4)
Hepatic disease	1 780 (12.1)
Renal disease	1 062 (7.2)
Malignancy	63 (0.4)
History	
CVD	1 448 (9.8)
Stroke	749 (5.1)
Cerebral infarction	600 (4.1)
Cerebral hemorrhage	120 (0.8)
Subarachnoid hemorrhage	58 (0.4)
CHD	798 (5.4)
Myocardial infarction	230 (1.6)
Cardiovascular intervention	301 (2.0)
Angina pectoris	704 (4.8)
HDL-C (mg dl^{-1})	57.65 ± 15.52
LDL-C (mg d^{-1})	122.77 ± 32.57
Triglycerides (mg d^{-1})	144.48 ± 97.35
Fasting blood glucose (mg d^{-1})	112.45 ± 38.04
Metabolic syndrome (Japanese criteria)	
Absent	7 235 (49.1)
Present	3 544 (24.1)
Unknown	3 942 (26.8)
Smoker	2 694 (18.3)
Alcohol drinker	3 848 (26.1)
Antihypertensive medication	7 090 (48.2)
Low-salt diet	5 765 (39.2)
Dietary therapy other than low-salt diet	1 924 (13.1)
Exercise therapy	3 772 (25.6)

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

calcium antagonists in 4985 patients (33.9%). At the end of the study, 7920 patients (53.8%) were taking other antihypertensive drugs, including calcium antagonists in 6734 patients (45.7%). At the start of the study, lipid-lowering drugs were being used by 3211 patients (21.8%) and antidiabetic drugs were being taken by 2042 patients (13.9%). At the end of the study, lipid-lowering drugs were

being used by 4393 patients (29.8%) and antidiabetic drugs were being taken by 2395 patients (16.3%).

Blood pressure and pulse rate

The changes in the blood pressure and pulse rate are shown in Figure 1. The blood pressure (SBP/DBP) was $157.4 \pm 17.7/88.8 \pm 12.1$ mm Hg before the start of administration (baseline), and it decreased to $137.5 \pm 14.3/78.9 \pm 9.9$ mm Hg after 6 months of administration and to $134.0 \pm 13.2/76.1 \pm 9.4$ mm Hg after 36 months. Thus, the antihypertensive effect of olmesartan persisted for 36 months. The mean change in blood pressure (SBP/DBP) from baseline was $-19.5/-9.7$ mm Hg after 6 months of administration and $-22.7/-12.3$ mm Hg after 36 months. Both SBP and DBP were significantly reduced throughout the administration period ($P < 0.0001$). The pulse rate was 74.0 ± 10.7 beats per min before the start of administration, 72.5 ± 10.0 beats per min at 6 months after the start of administration, and 72.0 ± 10.0 beats per min after

36 months. Therefore, the reduction of the pulse rate by olmesartan persisted for 36 months ($P < 0.0001$).

When changes in the blood pressure and pulse rate were compared in patients with MetS with patients without MetS, the baseline blood pressure (SBP/DBP) was $157.4 \pm 17.2/89.2 \pm 12.1$ and $158.7 \pm 17.6/89.5 \pm 11.9$ mm Hg in patients with and without MetS, respectively. After 6 months of olmesartan treatment, the blood pressure (SBP/DBP) was $139.2 \pm 14.3/80.0 \pm 10.0$ and $136.7 \pm 13.6/78.7 \pm 9.5$ mm Hg in patients with and without MetS, respectively, whereas the respective values after 12, 18, 24, 30 and 36 months were $138.4 \pm 14.6/79.2 \pm 9.6$, $137.4 \pm 14.1/78.5 \pm 9.6$, $137.2 \pm 14.3/78.0 \pm 9.6$, $136.2 \pm 14.0/77.4 \pm 9.7$, $135.4 \pm 13.0/76.8 \pm 9.4$ mmHg in patients with MetS, respectively and $136.2 \pm 13.6/78.1 \pm 9.3$, $135.1 \pm 13.3/77.3 \pm 9.4$, $134.3 \pm 13.2/76.9 \pm 9.3$, $133.8 \pm 13.1/76.5 \pm 9.2$, $133.4 \pm 13.0/76.1 \pm 9.3$ mm Hg in patients without MetS, respectively. Accordingly, a significant antihypertensive effect of olmesartan persisted for all measurement timing in both patient populations ($P < 0.0001$). The baseline pulse rate was 74.5 ± 11.0 and 73.6 ± 10.3 beats per min in patients with and without MetS, respectively. After 6 months, the pulse rate was 73.4 ± 10.3 and 71.9 ± 9.4 beats per min in patients with and without MetS, respectively, whereas the respective values after 12, 18, 24, 30 and 36 months were 73.0 ± 10.5, 72.9 ± 10.5, 72.9 ± 10.5, 72.7 ± 10.4, 72.8 ± 10.3 beats per min in patients with MetS, respectively and 71.8 ± 9.6, 71.9 ± 9.5, 71.7 ± 9.8, 71.6 ± 9.6, 71.5 ± 9.6 beats per min in patients without MetS, respectively. Therefore, the reduction of the pulse rate by olmesartan persisted for all measurement timing ($P < 0.0001$). Both SBP and DBP were approximately 2 mm Hg lower in the patients without MetS than in those with MetS, and the pulse rate was also lower in patients without MetS.

CVD events and incidence of CVD

The number of CVD events and the incidence of CVD (per 1000 persons annually) are shown in Table 3. All of the CVD events that are recorded in the Table fitted the diagnostic criteria mentioned earlier. The estimated incidence of CVD, stroke and CHD was 7.15, 3.42 and 3.55, respectively (per 1000 persons annually).

Table 2 Antihypertensive treatment ($n = 14\,721$)

	Pretreatment	Start of the study	End of the study
Olmesartan (%)	0 (0.0)	14 721 (100.0)	12 996 (88.3)
Concomitant antihypertensive drugs (%)	7 558 (51.8)	5 784 (39.3)	7 920 (53.8)
Calcium antagonist (%)	5 544 (37.7)	4 985 (33.9)	6 734 (45.7)
ARB (%)	2 579 (17.5)	94 (0.6)	521 (3.5)
ACE inhibitor (%)	1 057 (7.2)	330 (2.2)	358 (2.4)
β-blocker (%)	1 018 (6.9)	922 (6.3)	1 195 (8.1)
Diuretic (%)	612 (4.2)	600 (4.1)	1 432 (9.7)
α-blocker (%)	410 (2.8)	350 (2.4)	507 (3.4)
Number of antihypertensive drugs[a] (mean ± s.d.)	0.8 ± 0.9	1.5 ± 0.7	1.6 ± 0.9

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
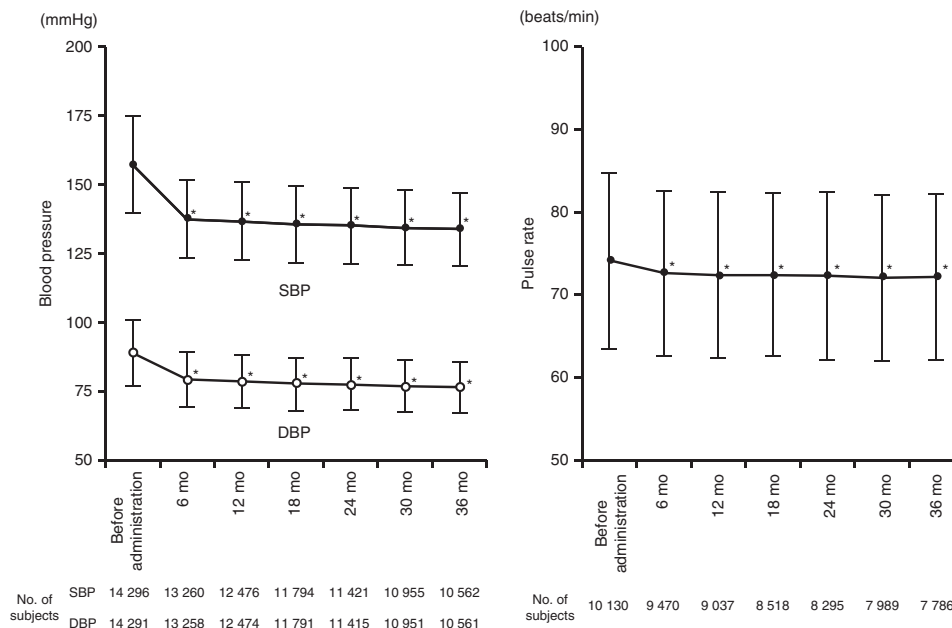[a]Olmesartan is included except for pretreatment.

Figure 1 Changes of blood pressure and pulse rate during administration of olmesartan. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure. *$P < 0.01$, Dunnett-Hsu test.

No. of subjects	Before administration	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo
SBP	14 296	13 260	12 476	11 794	11 421	10 955	10 562
DBP	14 291	13 258	12 474	11 791	11 415	10 951	10 561

No. of subjects	Before administration	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo
	10 130	9 470	9 037	8 518	8 295	7 989	7 786

Table 3 Number of patients and incidence of CVD and events in 14 721 patients

	Number of events	Incidence (95% CI)
CVD	281	7.15 (6.36, 8.04)
Stroke	135	3.42 (2.89, 4.05)
Cerebral infarction	110	2.78 (2.31, 3.36)
Cerebral hemorrhage	20	0.50 (0.33, 0.78)
Subarachnoid hemorrhage	6	0.15 (0.07, 0.34)
CHD	140	3.55 (3.01, 4.19)
Myocardial infarction	38	0.96 (0.70, 1.32)
Cardiovascular intervention for angina pectoris	82	2.08 (1.67, 2.58)
Hospitalization due to angina pectoris other than cardiovascular intervention	25	0.63 (0.43, 0.93)
Sudden death	14	0.35 (0.21, 0.60)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease.

The estimated incidence of cerebral infarction and angina pectoris requiring cardiovascular intervention was 2.78 and 2.08, respectively (per 1000 persons annually).

Relation between blood pressure and CVD in all subjects

The findings with regard to CVD, stroke and CHD in all subjects are shown in Figure 2a.

There was a significant relationship between the blood pressure and the occurrence of CVD or stroke. The risk of CVD and the risk of stroke both increased along with the severity of hypertension ($P < 0.0001$ for trend analysis), but the risk of stroke showed a greater increase than that of CVD. The hazards ratio (HR) for CVD and stroke in patients with stage III hypertension was 5.185 (95% confidence interval (CI), 3.013–8.921) and 8.952 (95% CI, 4.273–18.755), respectively.

Unlike CVD and stroke, the risk of CHD did not increase along with the severity of hypertension ($P = 0.0787$ for trend analysis), although it was significantly higher in patients with stage III hypertension (HR, 2.514; 95% CI, 1.043–6.063).

Analysis of patients without a history of CVD

The risk of CVD, stroke and CHD in the patients without a history of CVD is shown in Figure 2b.

In this subgroup, the relationship between blood pressure and the occurrence of CVD was more obvious compared with that in all subjects. There was a significant relationship between the blood pressure and the occurrence of CVD or stroke, as was noted in all subjects.

The risk of CVD and stroke also increased along with the severity of hypertension ($P < 0.0001$ for trend analysis), and the HRs were highest for patients with stage III hypertension, being 6.088 (95% CI, 3.200–11.583) for CVD and 12.140 (95% CI, 4.895–30.108) for stroke.

As was found in all subjects, the risk of CHD did not increase along with the severity of hypertension ($P = 0.1055$ for trend analysis), but it was significantly higher for patients with stage III hypertension (HR, 3.089; 95% CI, 1.146–8.326).

Relation between MetS and CVD

The incidence of cardiovascular events in patients with or without MetS is shown in Table 4. The incidence of CVD, stroke and CHD was higher in the patients with MetS than in the patients without MetS, but the differences were not significant in all subjects. However, the incidence of stroke was significantly higher in female patients with MetS than in female patients without MetS (HR, 2.590; 95% CI, 1.190–5.638).

Relation between dietary habits and CVD

The relation between dietary habits and events is summarized in Figure 3. The risk of CVD in relation to salt intake was investigated by classifying the subjects into two groups based on their scores for salt intake (<15.8 (lowest quartile) and $\geqslant 15.8$). The risk of stroke was significantly higher in the higher intake group than in the lower intake group (HR, 1.897; 95% CI, 1.003–3.590), but the risk of CVD and CHD did not significantly differ between the two groups. We also observed a lower stroke risk in the higher potassium intake and higher soybean/fish intake groups compared with the respective lower intake groups, but no significant differences were noted for stroke or for other endpoints.

Safety

The incidence of adverse drug reactions in all subjects was 4.41% (649/14 721). The common adverse drug reactions included dizziness (0.56%, 82 episodes), hyperkalemia (0.46%, 67 episodes), decreased blood pressure (0.22%, 32 episodes), hypotension (0.21%, 31 episodes) and hepatic impairment (0.20%, 29 episodes). The incidence of adverse drug reactions within 6 months after starting administration of olmesartan was 2.27% (334/14 721). Most adverse reactions occurred within 6 months of starting treatment, and the incidence of adverse reactions declined as the duration of olmesartan administration was prolonged.

DISCUSSION

In the present study, the annual incidence of CVD per 1000 persons was 7.15, and the HRs for CVD, stroke and CHD increased along with the severity of hypertension (classified in accordance with JSH 2009). This trend was most obvious with regard to the risk of stroke. In addition, the risk of stroke differed significantly between female patients with and without MetS. There was also a relationship between dietary habits and the risk of stroke, as the HR for stroke was significantly lower in subjects with a lower salt intake than in those with a higher salt intake.

On the basis of the results of previous studies,[23–25] we planned to investigate 9710 patients with an estimated 435 CVD events, but actually investigated 14 721 patients with 281 CVD events, so the number of events was lower than expected. There was no control group in this study, so we tried to compare our outcomes with the results of a similar cohort study. A study of the ARB telmisartan was conducted at approximately the same time with a similar objective, design, target patient population, number of subjects, definition of CVD and achieved blood pressure (J-TARGET study).[26] In that study, the annual incidence of CVD, stroke, CHD and sudden death per 1000 patients was 11.0, 5.0, 5.5 and 0.7, respectively, whereas in this study, the annual incidence was 7.15, 3.42, 3.55 and 0.35, respectively. Although direct comparison between the two studies is somewhat problematic, the incidence of events was lower in hypertensive patients receiving olmesartan therapy. The following three factors might have contributed to the lower incidence of events in this study in comparison with previous studies and a recent similar cohort study. First, recent hypertension treatment guidelines[18,27] released after earlier studies[23–24] have promoted stricter blood pressure
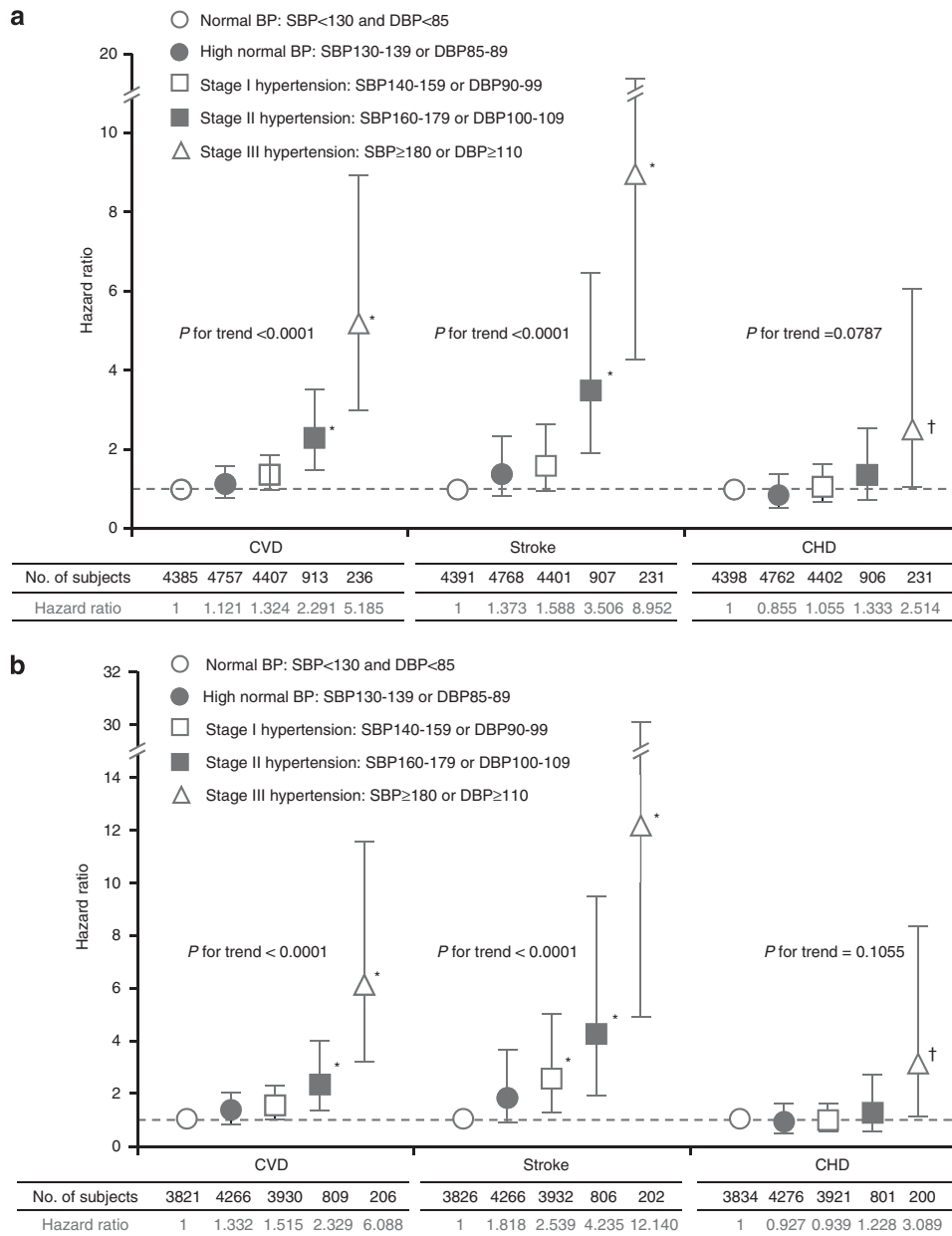
Figure 2 Relationship between the achieved blood pressure and occurrence of events during follow-up in all subjects (**a**) and in the patients without a history of CVD (**b**). Vertical lines denote 95% CIs. Cox proportional hazards model: Adjusted by sex, age, family history of coronary artery disease, diabetes, dyslipidemia, history of CVD, BMI and smoking. Number of subjects of each categories were shown as the counted number, based on the blood pressure of at final visit point or at last visit point before the event occurs. [†]P<0.05, [*]P<0.01 vs. normal BP. BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

control, and progress in antihypertensive medications has led to the widespread use of ARBs as first-line therapy for the majority of patients receiving aggressive treatment. Second, progress in the general medical environment and in the treatment of other diseases, such as dyslipidemia, may have contributed to a better outcome.[28] Third, the more potent antihypertensive effect and longer duration of action of olmesartan,[29–31] as well as its pleiotropic effects,[32,33] could have had a favorable influence.

Staessen et al.[34] performed a meta-analysis and concluded that antihypertensive therapy was necessary for the prevention of CVD, and that the antihypertensive effect of drug therapy influenced the risk of CVD.[35] In addition, the results of the HOT study suggest that

the blood pressure should be maintained below 140/90 mm Hg for prevention of CVD.[3] In our study, the trends of CVD and stoke were more apparent when the achieved SBP and DBP were combined rather than being assessed separately. We classified blood pressure levels in accordance with JSH 2009, and we did not identify a J-curve in any group, unlike reports from overseas.[36] In fact, our findings suggest that it is important to at least achieve a normal blood pressure (SBP <130 mm Hg and DBP <85 mm Hg) and that the combined target blood pressure for SBP/DBP recommended by JSH 2009 is reasonable. In the present study, patients with a history of CVD comprised 10% of all subjects. In patients without a history of CVD, the increase in the risk of CVD along with the severity of hypertension

was more obvious. This was probably because the power of our study was insufficient owing to the small number of CVD events among patients with a history of CVD, as well as because a history of CVD is a risk factor for future CVD, and because of the influence of other risk factors, including dyslipidemia. In the present study, the risk of CHD did not show a significant increase along with the severity of hypertension, suggesting that CHD is less strongly influenced by hypertension compared with stroke. However, the risk of CHD was still increased in patients with severe hypertension (stage III according

Table 4 The incidence of CVD event according to the presence or absence of MetS (Japanese criteria)

	Incidence (per 1000 person-years)			
	MetS (−)	MetS (+)	HR (95% CI)	P-value
Total				
CVD	5.05	8.13	1.317 (0.944, 1.837)	0.1047
Stroke	2.57	3.92	1.240 (0.772, 1.990)	0.3732
CHD	2.46	3.92	1.248 (0.776, 2.006)	0.3608
Men				
CVD	7.80	8.96	1.162 (0.787, 1.716)	0.4503
Stroke	4.26	3.83	0.885 (0.505, 1.549)	0.6678
CHD	3.80	4.90	1.347 (0.784, 2.315)	0.2806
Women				
CVD	3.46	6.17	1.742 (0.958, 3.168)	0.0687
Stroke	1.59	4.11	2.590 (1.190, 5.638)	0.0165
CHD	1.68	1.64	0.916 (0.311, 2.698)	0.8739

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MetS, metabolic syndrome.

to JSH 2009). We plan to report the results of a detailed assessment of risk factors in the future.

In JSH 2009, either ARBs or angiotensin-converting enzyme inhibitors are recommended as first-line therapy for hypertension in patients with MetS, because these drugs can improve insulin resistance.[7] It has been reported that olmesartan improves insulin resistance by increasing cyclic adenosine monophosphate and decreasing tumor necrosis factor-α.[37] In the present study, the final blood pressure was 135.4/76.8 and 133.4/76.1 mm Hg for patients with and without MetS, respectively, so olmesartan showed a good antihypertensive effect regardless of whether patients had MetS.

The Hisayama study showed that the risk of CVD is significantly higher in hypertensive patients with MetS than in those without MetS,[12] but we found no significant difference with regard to the risk of CVD in the present study. This discrepancy was considered to have occurred because our study population consisted entirely of hypertensive patients, so that hypertension might be more closely associated with CVD than with other factors among MetS components, although the blood pressure of our MetS patients was reduced to almost the same level as that of the patients without MetS, and the difference of blood pressure between our subjects with and without MetS was very small. We also investigated the influence of gender in relation to MetS and found that the incidence of stroke was significantly higher in female patients with MetS than in female patients without MetS. We interpret the reason why the presence or absence of MetS influenced on the difference of stroke outcomes as that, in general, women associated with the fewer environmental risks, such as smoking (current smoking rate; men, 30.9%, women, 6.7%).

A meta-analysis of the results of 19 cohort studies suggested that the incidence of CVD, especially stroke, is higher in people with a high salt intake.[38] In the United States, the Third National Health and Nutrition Examination Survey revealed a higher mortality rate in
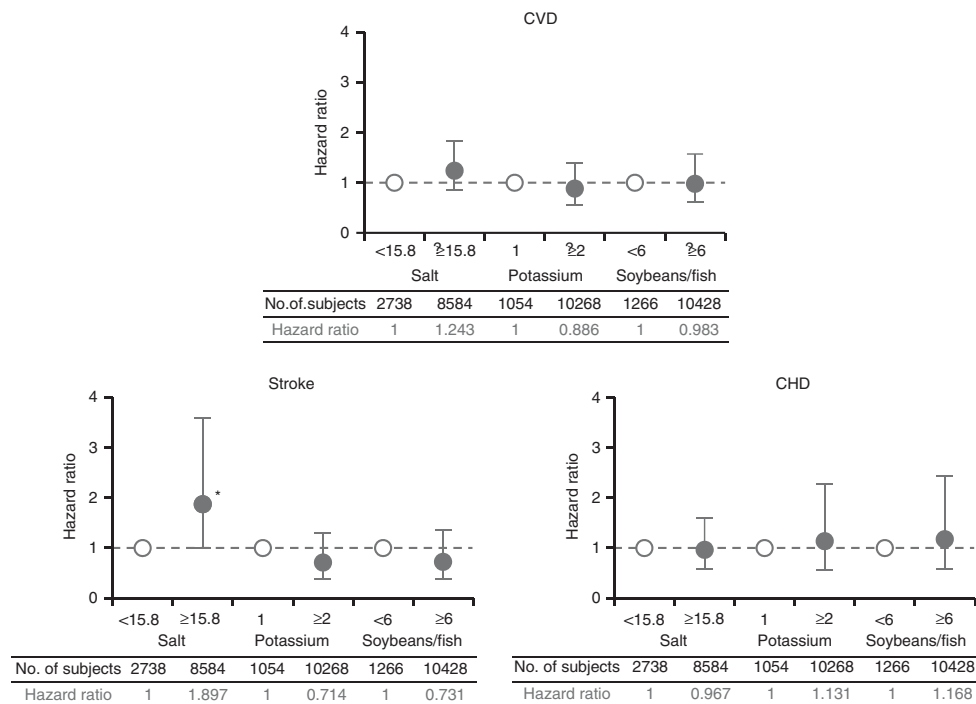

Figure 3 Relationship between dietary habits (food scores) and events. Vertical lines denote 95% CIs. Cox proportional hazards model: adjusted by sex, age, baseline blood pressure, family history of coronary artery disease, diabetes mellitus, dyslipidemia and smoking. *P<0.05. CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease.

people with a high sodium intake.[39] We classified the patients by their salt intake scores at lowest quartile (<15.8 and $\geqslant 15.8$) and found that the risk of stroke was significantly higher in the higher salt intake group than in the lower salt intake group. The salt intake score was significantly related to the risk of stroke, probably because hypertension due to excessive salt intake is one of the main risk factors for stroke. According to the equation of Arakawa et al.,[40] a salt intake score of 15.8 is equivalent to 9 g of salt daily for men and 6 g for women.

In the present study, potassium intake had no significant influence on blood pressure, possibly because potassium does not affect blood pressure as much as sodium. It is also possible that there were not enough items related to potassium intake in the questionnaire that we used. However, a combination of foods with a weak antihypertensive effect might show a stronger antihypertensive effect, so high intake of vegetables, fruits and fish, along with limited intake of cholesterol and saturated fatty acids may be important for the management of hypertension.

This study had several limitations. As there was no control group, we could not evaluate the effectiveness of olmesartan medoxomil itself. Also, subjects were only asked about MetS and their dietary habits at the start of the study rather than throughout the study period.

In conclusion, the severity of hypertension (achieved blood pressure) is associated with the incidence of CVD, and the results of this study suggest that tight blood pressure control and salt restriction are important for preventing stroke.

CONFLICT OF INTEREST

MS, KH and FK are employees of Daiichi Sankyo Co., Ltd.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)

APPENDIX

OMEGA Study Medical Expert Advisory Committee

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