Original Article

OMEGA Study: Design, Baseline Data, Metabolic Syndrome Prevalence in a Large-Scale Observational Study of Hypertensive Patients: The Olmesartan Mega Study to Determine the Relationship between Cardiovascular Endpoints and Blood Pressure Goal Achievement Study

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Elevated systolic blood pressure increases the risk of cardiovascular events, as shown by a number of meta-analyses of large-scale clinical trials. As concerns the prognostic impact of the metabolic syndrome on cardiovascular events, few large-scale studies are available in the Japanese hypertensive population. The prospective, large-scale, observational OMEGA (Olmesartan Mega Study to Determine the Relationship between Cardiovascular Endpoints and Blood Pressure Goal Achievement) study sought to examine the relationship between the incidence of cardiovascular disease (CVD) and achieved blood pressure, metabolic syndrome, lifestyle factors and other risk factors for CVD in patients with hypertension. Of the 15,313 enrolled patients from 2,219 institutions in Japan, we report here the baseline characteristics of the 14,841 eligible patients whose baseline data were collected as of October 31, 2007. Men and women 50 to 79 years old (mean age 65) with physician-diagnosed hypertension were enrolled, and all patients were treated with open-label olmesartan medoxomil (5 to 40 mg daily). The majority of patients (75%) had mild to moderate hypertension. The prevalences of dyslipidemia and diabetes mellitus were 48% and 24%, respectively. The metabolic syndrome was identified in 48% and 19% of the evaluable men and women, respectively, using the criteria of the Japanese Society of Internal Medicine. Men with the metabolic syndrome were at the greatest risk for CVD, and a greater proportion of men than of women had all five metabolic syndrome components. The complete follow-up data from the OMEGA study will provide much-needed information to guide treatment in patients with hypertension and the metabolic syndrome. (*Hypertens Res* 2008; 31: 2011–2017)

Key Words: essential hypertension, metabolic syndrome, olmesartan, prospective observational study

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Introduction

Increasing attention is being paid to the impact of the metabolic syndrome, which comprises a constellation of metabolic abnormalities including centrally distributed obesity, decreased high-density lipoprotein cholesterol (HDL-C), elevated triglycerides (TG), elevated blood pressure (BP), and hyperglycemia or diabetes. These metabolic abnormalities are interrelated, with the presence of abdominal visceral fat contributing to the development of the other abnormalities in the syndrome (1, 2). Various definitions of the metabolic syndrome have been published (Grundy *et al.* (3) and the International Diabetes Federation [The IDF Consensus Worldwide Definition of Metabolic Syndrome, 2005, available at: <http://www.idf.org/>]), and in 2005 new criteria for diagnosing it in Japanese patients were established by expert panels of the Japanese Society of Internal Medicine (1, 2).

A clear relationship between the metabolic syndrome and an increased risk for the development of incident cardiovascular disease (CVD), CVD mortality, and all-cause mortality has been demonstrated by prospective studies in general Western populations (4–12). Although there is little similar evidence in the Japanese population to date, two studies (13, 14) suggest that the metabolic syndrome is a robust risk factor for CVD in this population, with as high as a 2.2-fold increased risk.

Systolic blood pressure increases the risk of cardiovascular events in a linear fashion, as shown by a number of meta-analyses of large-scale clinical trials (15–18). In Western hypertensive populations, the prognostic impact of the metabolic syndrome on CVD events has been demonstrated by a few studies (19, 20); in contrast, few large-scale studies are available in the Japanese hypertensive population. In the Hisayama epidemiologic study, a significant excess risk of CVD events was found in persons with hypertension plus metabolic syndrome compared with those without metabolic syndrome (14). However, this finding is based on only 548 persons with hypertension. Therefore, a large-scale study is needed to confirm the risk of CVD in persons with hypertension and the metabolic syndrome.

The OMEGA (Olmesartan Mega Study to Determine the Relationship between Cardiovascular Endpoints and Blood Pressure Goal Achievement) study, a prospective, large-scale, observational study, was designed to examine the relationship between the incidence of CVD and achieved BP, metabolic syndrome, lifestyle factors (*e.g.*, intake of high-salt foods), and other risk factors for CVD. The OMEGA study was initiated as a post-marketing surveillance study by Dai-ichi Sankyo Co., Ltd. in compliance with the Ministry of Health, Labour and Welfare regulations.

Methods

Patient Recruitment

Eligible for inclusion in the study entry were men and women who were 50 to 79 years old, diagnosed with hypertension by their physician and receiving treatment in outpatient clinics, and who had not been treated with the angiotensin II receptor blocker olmesartan medoxomil before study registration. Exclusion criteria were 1) history of myocardial infarction, stroke, coronary artery bypass graft surgery or percutaneous coronary intervention within 6 months of study enrollment, 2) scheduled coronary intervention at study enrollment, 3) congenital or rheumatic heart disease, 4) severe arrhythmia, 5) severe liver or renal disease, 6) current cancer treatment, and 7) pregnancy or the ability to become pregnant. Each patient was informed of the purpose and methodology of the study, the right to withdraw from the study at any time, and the measures for privacy protection. After providing informed consent and being prescribed olmesartan, patients were enrolled using the central electronic data capturing system. The study was registered at <http://www.clinicaltrials.jp/> with the identification number JapicCTI-050002.

Lifestyle Questionnaire

A self-administered lifestyle questionnaire was completed by each patient at the baseline examination, to provide information on cigarette smoking, alcohol intake, physical activity, and frequency of intake of specific foods (high-salt foods, fruits, fish, and soybean products) known to have an effect on hypertension and cardiovascular disease. Smoking status was classified as current smoker, ex-smoker (quit smoking within the previous year), ex-smoker (quit smoking > 1 year ago), or never smoker. Alcohol status was classified as current drinker, occasional drinker, ex-drinker, or never drank alcohol. Physical activity was classified into taking exercise, defined as rapid walking for >30 min at least twice/week, or the equivalent, during the previous year, or not exercising. Food intake was assessed for sodium, potassium, and soybean/fish content for each patient.

Endpoints

The primary endpoint was the incidence of CVD, defined as the occurrence of stroke, subarachnoid hemorrhage, myocardial infarction, angina pectoris requiring hospitalization including coronary intervention, or sudden and unexpected death (21, 22). Stroke and subarachnoid hemorrhage were diagnosed as a loss of neurologic function caused by an ischemic or hemorrhagic event with residual symptoms at least 24 h after onset or leading to death plus documentation by computed tomography or magnetic resonance imaging. Myocardial infarction was diagnosed as ischemic symptoms

Table 1. Baseline Characteristics

Number of patients	14,841
Age (median, years)	64.9±8.2
Women, %	49.5
Systolic blood pressure, mmHg	157.3±17.7
Diastolic blood pressure, mmHg	88.8±12.1
Body mass index, kg/m ²	24.8±3.6
Current smokers, <i>n</i> (%)	2,721 (18.3)
Alcohol drinking, <i>n</i> (%)	6,917 (46.6)
Physical activity,* <i>n</i> (%)	4,847 (32.7)
Main complications	
Dyslipidemia, <i>n</i> (%)	7,122 (48.0)
Diabetes mellitus, <i>n</i> (%)	3,609 (24.3)
Main history	
Stroke	599 (4.0)
Percutaneous coronary intervention	303 (2.0)
Myocardial infarction	235 (1.6)
Main concomitant drugs	
Antihypertensive drug, <i>n</i> (%)	5,727 (38.6)
Lipid-lowering drug, <i>n</i> (%)	3,116 (21.0)
Hypoglycemic drug, <i>n</i> (%)	1,984 (13.4)
Aspirin or antiplatelets, <i>n</i> (%)	1,377 (9.3)

Data are shown as means±SD. *Physical activity: rapid walking for >30 min at least twice/week or equivalent during the previous year.

plus changes in biochemical markers of myocardial necrosis (typical rise and gradual fall of troponin T or troponin I (23) level or rapid rise and fall of creatine kinase MB isoenzyme [CK-MB] and/or electrocardiogram changes indicative of ischemia). Sudden and unexpected death was defined as death occurring within 24 h after the onset of severe symptoms or without severe symptoms at last physician visit and no known non-cardiovascular disease as cause of death.

Treatment and Study Procedure

No restriction was placed on prior antihypertensive drug treatment, with the exception of prior use of olmesartan, or on the use of combination antihypertensive drug treatment during the study. A central electronic data capturing system was used for patient data collection. Patients were seen at least every 6 months for 3 years after initiation of olmesartan treatment, for a total of six examinations for each patient. At each visit, BP, pulse rate, laboratory tests, drugs being taken concomitantly, and the occurrence of CVD events were recorded. All adverse events were also recorded by the patient's physician.

Diagnostic Criteria for Metabolic Syndrome

The metabolic syndrome was defined according to the criteria established by the Japanese Society of Internal Medicine (1,

Table 2. Distribution of WHO Hypertension Grade at Baseline

Optimal to high-normal	1,644 (11.1%)
Grade 1	6,343 (42.7%)
Grade 2	4,739 (31.9%)
Grade 3	1,862 (12.5%)
Not evaluable	253 (1.7%)

2). One criterion was fulfilled at study entry, since all study patients had hypertension. Furthermore, patients meeting the additional essential criteria of the presence of central obesity with a waist circumference ≥85 cm for men and ≥90 cm for women plus dyslipidemia (serum TG≥150 mg/dL, HDL-C <40 mg/dL) and/or fasting hyperglycemia (serum glucose ≥110 mg/dL) or diagnosis of diabetes were defined as having the metabolic syndrome.

Sample Size Determination

A sample of 12,000 patients, including drop-outs, was required to detect an increase in the incidence of cardiovascular events with an 80% power using a 0.05 level two-sided logrank test. A total of 435 events was required in 9,710 patients. Basic assumptions were a 1.3-fold increased risk with essential hypertension plus dyslipidemia and a cumulative incidence of 4% over 3 years in patients without dyslipidemia (24–27).

Statistical Analysis Plan

The Cox proportional hazards model and other statistical analyses will be used to investigate the relation between the incidence of cardiovascular events and baseline factors, including metabolic syndrome, diabetes, use of antihypertensive drug, and salt intake. In evaluating the association between on-treatment BP and the incidence of cardiovascular events, on-treatment BP will be used as a time-dependent covariate. Ancillary analyses with external data will be considered to obtain more valuable information, such as an estimation of the effect size of olmesartan in the hypertensive patients in OMEGA study compared with hypertensive patients not taking olmesartan.

Study Organization

The study organization and the members of the Medical Expert Advisory Committee of the OMEGA study are detailed in the Appendix.

Results

A total of 15,313 patients from 2,219 institutions across Japan were enrolled between July 2005 and March 2007. Five

Fig. 1. Contribution of each component to the diagnosis of metabolic syndrome. TG, triglycerides; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol.

Fig. 2. Contribution of each component to the diagnosis of metabolic syndrome by age group. TG, triglycerides; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol.

patients who were registered twice and 52 patients whose physicians were no longer available because of illness or departure from the hospital were excluded from the study analyses. We report here the data for 14,841 of the 15,256 patients eligible for analysis, whose baseline data were complete as of October 31, 2007.

Baseline Characteristics of the OMEGA Study Population

Table 1 details the baseline characteristics of the 14,841 patients (49.5% women) in this analysis. The mean age of the patients was 64.9 years; 7,717 patients (52.0%) were ≥ 65

Table 3. Prevalence of Metabolic Syndrome (Japanese Definition)

	Population	n	Men (%)	Women (%)	Mean age (years)	
					Men	Women
Niwa <i>et al.</i> (28)	general	2,176	9.0	1.7	56.4	55.9
Yoneda <i>et al.</i> (29)	general	416	13.9	2.7	53.3	58.2
Kobayashi <i>et al.</i> (30)	general	21,870	18.4	5.8	68.1	66.1
Shimajiri <i>et al.</i> (31)	diabetic	637	45.9	28.0	63.1	65.5
Ohta <i>et al.</i> (32)	hypertensive	290	39	18	63	65
OMEGA	hypertensive	11,308	48.1	18.5	63.8	65.9

years old. The mean body mass index (BMI) was 24.8 kg/m², and 5,616 (37.8%) of patients had a BMI $\geq$ 25 kg/m².

The prevalences of dyslipidemia and diabetes mellitus were 48.0% and 24.3%, respectively. The histories of stroke, percutaneous coronary intervention, and myocardial infarction were 4.0%, 2.0%, and 1.6% respectively. The distribution of hypertension grades, based on the 1999 World Health Organization/International Society of Hypertension criteria, is shown in Table 2. The majority of patients (75%) had mild to moderate hypertension. Grade 1 hypertension was identified in 42.7% of patients, Grade 2 in 31.9%, and Grade 3 in 12.5%.

The most frequently used initial daily dose of olmesartan was 20 mg (10,134 patients, 68.3%), followed by 10 mg (4,262 patients, 28.7%). Concomitant drug therapy was used in 9,174 patients (61.8%), antihypertensive drugs in 5,727 patients (38.6%), lipid-lowering drugs in 3,116 patients (21.0%), hypoglycemic drugs in 1,984 patients (13.4%), and aspirin or antiplatelets in 1,377 patients (9.3%). Antihypertensive drugs used were calcium channel blockers in 4,905 patients (33.1%), β -blockers in 914 patients (6.2%), and diuretics in 577 patients (3.9%). Statins were used in 2,650 patients (17.9%).

Prevalence of the Metabolic Syndrome

Of the 14,841 patients in this analysis, waist circumference data were missing for 3,043 patients and biochemical measures were missing for 490 patients—data that are required by the Japanese Society of Internal Medicine definition for the metabolic syndrome—leaving 11,308 (5,532 men and 5,776 women) for evaluation. All had hypertension as a criterion for study inclusion. The metabolic syndrome was identified in 48.1% of the men and 18.5% of the women who could be evaluated for its presence.

The contribution of high fasting plasma glucose (FPG), high TG, and low HDL-C to the diagnosis of the metabolic syndrome in the 2,663 men and 1,067 women with this diagnosis is shown in Fig. 1. The most frequent contributor in men and women was a high FPG, followed by a high TG, and low HDL-C, which contributed little to the diagnosis of the metabolic syndrome. More men than women had all three of these

components (6.0% vs. 2.9%, respectively).

Figure 2 shows the contribution of each component of the metabolic syndrome to its diagnosis by sex and age. High FPG was a greater contributor to the metabolic syndrome in men in their 70s than those in their 50s, whereas high TG was a greater contributor in their 50s than in their 70s. In women, there was no difference with respect to age for the contribution of high FPG, high TG, or low HDL-C to the development of metabolic syndrome.

Discussion

In the OMEGA population, the prevalences of metabolic syndrome were 48% and 19% of the evaluable men and women, respectively, according to the criteria of the Japanese Society of Internal Medicine. The prevalence of the metabolic syndrome in other studies using the same criteria is shown in Table 3. Although a direct comparison to our data is limited because it is not adjusted for the difference in age distribution across the populations, the prevalence of the metabolic syndrome in men and women seems to be higher in the OMEGA study than in the general population (28–30) and similar to that in a diabetic population (31) and a hypertensive one (32). The Hisayama Study (14) showed that the risk of incident CVD increased with the number of components of the metabolic syndrome present. In our study in patients with the syndrome, the greatest risk for CVD seemed to be in men, among whom there was a higher proportion with all five metabolic syndrome components than among women.

The strengths of the OMEGA study include its large number of hypertensive patients and its waist circumference data. At present, studies providing evidence regarding the prognostic value of the metabolic syndrome for CVD events are available for the Western hypertensive population (19, 20); in contrast, few large-scale studies are available in the Japanese hypertensive population.

Schillaci *et al.* (19) showed that 34% of 1,742 patients with hypertension had the metabolic syndrome, based on the modified definition of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (3). The risk of developing cardiovascular events was still higher in patients with the metabolic syndrome than in those without,

after adjustment for age, gender, total cholesterol, creatinine, smoking, left ventricular hypertrophy and 24-h systolic BP (hazard ratio [HR] 1.73, 95% confidence interval [CI] 1.25–2.38). Pierdomenico *et al.* (20) showed that 27.2% of 802 patients with hypertension had the metabolic syndrome, based on the NCEP ATP III definition. After adjustment for several covariates, Cox regression analysis showed that cardiovascular risk was significantly higher in the patients with the metabolic syndrome than in those without (relative risk 2.64, 95% CI 1.52–4.58). It is not clear whether these results in Western patients apply to Japanese patients with hypertension, because of lifestyle differences such as diet. The OMEGA study used waist circumference as a measure of central adiposity, rather than BMI as used in Western studies. The OMEGA study has waist circumference data on 11,798 patients; thus, it is possible to more accurately diagnose the metabolic syndrome than it is in Western studies. Further, waist circumference is an essential component of the Japanese (1, 2) and International Diabetes Federation (IDF: <http://www.idf.org/>) definitions of the metabolic syndrome. However, the criteria to define central obesity are different. According to the Japanese definition, the cutoff points for waist circumference are 85 cm for men and 90 cm for women, whereas in the IDF definitions it is 90 cm for men and 80 cm for women. Thus, it will be possible to compare their prognostic ability for incident CVD at the end of the OMEGA study.

The Hisayama Study (14) showed that hypertension and diabetes are strong risk factors for CVD. In the analysis, the age- and sex-adjusted HR for CVD was significantly higher in hypertensive patients without metabolic syndrome (HR 1.81, 95% CI 1.35–2.43) than in patients without hypertension or metabolic syndrome. Further, a significant excess risk of CVD was found in hypertensive patients with metabolic syndrome compared with those without (HR 2.59, 95% CI 1.93–3.48). Similarly, the age- and sex-adjusted HR for CVD was significantly higher in diabetic subjects with metabolic syndrome (HR 2.75, 95% CI 1.93–3.93) than in those without diabetes or metabolic syndrome. About one-fourth of the OMEGA population was at high risk for CVD, with all having hypertension and 24% having diabetes mellitus.

In this study population, the histories of stroke, percutaneous coronary intervention, and myocardial infarction were 4.0%, 2.0%, and 1.6%, respectively. Thus, the impact of these risk factors on CVD events was limited.

About 75% of the study population had mild to moderate hypertension, which generally requires less aggressive drug treatment. However, if the metabolic syndrome confers an additional increased risk in the subset of patients with this diagnosis, it could be useful to improve risk stratification and guide therapeutic approaches.

The complete follow-up data from the OMEGA study will clarify the relationship between the incidence of cardiovascular disease and the metabolic syndrome, achieved blood pressure levels, lifestyle factors, and clinical risk factors in

Japanese patients with hypertension. This will provide much-needed information to guide treatment in these patients, in whom little evidence is available to date.

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Appendix

OMEGA Study Medical Expert Advisory Committee

Medical Advisors: Tamio Teramoto, Toshiro Fujita, Ryuzo Kawamori, Shigeru Miyazaki.

Statistical Advisor: Satoshi Teramukai.

Administrative Office: Post-Marketing Study Department, Dai-ichi-Sankyo Co., Ltd. (Tokyo, Japan).

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