

Original Article

Lipid and Blood Pressure Control for the Prevention of Cardiovascular Disease in Hypertensive Patients: A Subanalysis of the OMEGA Study

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Aim: The aim of this analysis was to investigate the relationships between dyslipidemia, achieved blood pressure (BP) values and the lipid levels, as well as the control of four cardiovascular risk factors (BP, low-density lipoprotein: LDL cholesterol, hemoglobin A1c: HbA1c and smoking) and the incidence of cardiovascular disease (CVD), in Japanese patients receiving antihypertensive therapy.

Methods: A total of 13,052 patients with no history of CVD were included in this subanalysis of the prospective observational OMEGA study in Japanese hypertensive patients treated with olmesartan. Multivariable Cox regression models were used to evaluate the relationship with the risk of CVD.

Results: The incidence of CVD during the 36-month study period was 5.59/1,000 patient-years among the patients with dyslipidemia ($n=6,297$) and 5.57/1,000 patient-years among the patients without dyslipidemia ($n=6,755$), with no significant differences between the two groups. Higher achieved BP values tended to be associated with an increased CVD risk in both the patients with and without dyslipidemia. In addition, the risk of CVD tended to be higher in the patients with an achieved LDL cholesterol level of ≥ 120 mg/dL than in those with an LDL level of < 120 mg/dL (trend $p=0.0005$) and in the patients with an achieved high-density lipoprotein cholesterol level of < 60 mg/dL than in those with an HDL level of ≥ 60 mg/dL (trend $p=0.0017$). Furthermore, the risk of CVD was higher among the patients with fewer controlled risk factors than among those with control of all four risk factors (trend $p<0.0001$).

Conclusions: In order to prevent CVD in olmesartan-treated hypertensive patients with no history of CVD, it is important to control both the lipid and BP levels and aim for comprehensive risk factor control.

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Key words: Cardiovascular event, Dyslipidemia, Hypertension, Comprehensive risk factor control, Olmesartan medoxomil

Introduction

Atherosclerotic cardiovascular disease (CVD) is a

leading underlying cause of death in Japan, whose population is aging rapidly. Therefore, effective strategies for preventing CVD are urgently needed.

One such strategy is to aggressively control both dyslipidemia and hypertension. Dyslipidemia is an important risk factor for CVD, and epidemiologic studies have shown that higher low-density lipoprotein (LDL) cholesterol¹⁾ and non-high-density lipoprotein (HDL) cholesterol levels²⁾ and lower HDL

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cholesterol levels³⁻⁵) are associated with an increased incidence of coronary heart disease (CHD). Another important risk factor for CVD is hypertension. Hypertension is closely related to cerebrovascular disorders^{6, 7}; individuals with higher blood pressure (BP) values are more likely to develop cerebrovascular diseases^{8, 9}. Furthermore, the coexistence of dyslipidemia and hypertension increases the risk of arteriosclerosis⁴.

Among hypercholesterolemic patients with hypertension, aggressive LDL cholesterol-lowering treatment may prevent the incidence or recurrence of ischemic heart disease and stroke¹⁰. In addition, diet therapy combined with pravastatin treatment is effective in the primary prevention of CVD, reducing the risk of cerebral infarction by 46%, in Japanese patients with mild-to-moderate dyslipidemia complicated by hypertension¹¹. However, few reports have addressed the relationship between the achieved BP value, lipid levels and incidence of CVD in Japanese patients in clinical practice.

The Japan Atherosclerosis Society *Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases* recommend the comprehensive control of dyslipidemia, hypertension and other risk factors, such as diabetes mellitus and smoking, in order to prevent atherosclerotic disease¹². However, few reports have addressed the relationship between comprehensive risk factor control and the incidence of CVD in Japanese patients in clinical practice.

The Olmesartan Mega Study to Determine the Relationship Between Cardiovascular Endpoints and Blood Pressure Goal Achievement (OMEGA study) is a large-scale prospective observational study designed primarily to evaluate the relationships between the achieved BP, metabolic syndrome, lifestyle factors (e.g. dietary habits), other risk factors and the incidence of CVD in Japanese hypertensive patients treated with olmesartan medoxomil. We previously reported the relationships between the achieved BP, dietary habits, metabolic syndrome and the incidence of CVD¹³. In addition, we reported that diabetes mellitus is an important risk factor for CVD, cerebrovascular events (stroke) and CHD and that dyslipidemia is an important risk factor for CHD¹⁴. In addition, previous reports have described the relationships between diabetes mellitus, achieved BP, hemoglobin A1c (HbA1c, National Glycohemoglobin Standardization Program) and the incidence of CVD¹⁵.

Aim

Our aim was to investigate the relationships

between the incidence of CVD and dyslipidemia, achieved BP and the lipid levels in patients with no history of CVD using data obtained from the OMEGA study. The relationship between the comprehensive control of four CVD risk factors (BP, LDL cholesterol, HbA1c and smoking) and the incidence of CVD was also analyzed.

Methods

The OMEGA study was conducted as a prospective, large-scale observational study from July 2005 to March 2010 by Sankyo Co., Ltd. (presently Daiichi Sankyo Co., Ltd.). The study protocol was approved by the Ethics Committee of Sankyo Co., Ltd., as well as the Ministry of Health, Labour and Welfare of Japan before commencement, and conformed with the pharmaceutical affairs laws of Japan. Furthermore, the study conformed to the Helsinki Declaration of 1975 as revised in 1983 and was carried out at registered medical institutions according to Good Post-marketing Study Practices in Japan. The survey data were collected via the Internet using a validated electronic data-capturing system (PostMaNet; Fujitsu FIP, Tokyo, Japan). The protocol for the OMEGA study is described briefly below. Further details of the protocol are available in a previous publication¹⁶.

Patients

Male and female outpatients 50-79 years of age with essential hypertension who had not been previously treated with olmesartan were enrolled in the OMEGA study. The exclusion criteria were a history of myocardial infarction, stroke, coronary artery bypass grafting or percutaneous coronary intervention within six months prior to enrollment, as well as scheduled coronary intervention, congenital or rheumatic heart disease, severe arrhythmia, severe hepatic or renal disease, cancer that was currently under treatment and pregnancy or the potential to become pregnant.

The patients were enrolled using the central registration system. Written informed consent was obtained from each patient, and a questionnaire survey regarding lifestyle and habits was conducted prior to the start of the study. This subanalysis was carried out in order to investigate the incidence of initial CVD in patients without a history of the disorder.

Observation Items and Period

The observation items included the following information: patient characteristics, lifestyle factors and habits; exposure to olmesartan and concomitant

drugs; concomitant therapies; BP; pulse rate; laboratory results; and incidence of CVD. The observation period was three years from the start of treatment with olmesartan. Observation was continued even if the olmesartan treatment was discontinued and terminated if a patient was lost to follow-up or withdrew their consent. The method of BP measurement was not specified, and the BP values were obtained according to the routine procedures used at each institution. Data for the BP, pulse rate and laboratory tests were collected before study initiation and every six months thereafter. If available, any applicable values measured in daily clinical practice during the study period were also collected.

Events

Cardiovascular disease was defined as a composite of the following events: stroke (cerebral infarction, cerebral hemorrhage or subarachnoid hemorrhage), CHD (myocardial infarction, cardiac intervention or hospitalization for angina) and sudden death. CVD was defined as a composite endpoint comprising the above three endpoints.

The diagnostic criteria for the various endpoints have been previously described in detail^{13, 16}.

Definition of Dyslipidemia

In this subanalysis, patients who met either of the following conditions were considered to have dyslipidemia and those who met neither condition were considered to be without dyslipidemia: patients who had been diagnosed by their physician as having dyslipidemia at the start of the study and those who were receiving treatment with any lipid-lowering drugs at the start of the study.

Statistical Analysis

The patient characteristics of the dyslipidemia and non-dyslipidemia groups were compared using the *t*-test for continuous variables and the chi-squared test for categorized variables. Data for BP, LDL cholesterol and HDL cholesterol were analyzed by comparing the values obtained at baseline and each visit using the Dunnett-Hsu test. The incidence of CVD during the study period was compared between the dyslipidemia and non-dyslipidemia groups using the log-rank test. The relationships between the achieved BP values and lipid levels and the risk of CVD were evaluated using the Cox proportional hazards model, including the achieved BP values or lipid levels as time-dependent covariates and sex, age, family history of coronary artery disease, HbA1c (time-dependent covariate), dyslipidemia (only in comparisons between

the dyslipidemia and non-dyslipidemia groups), body mass index and smoking as adjusted factors. BP was classified using cut-off values of 130/85 mmHg and 140/90 mmHg, in accordance with the JSH 2009 criteria¹⁷. In the analyses of the relationships between the lipid levels and the risk of CVD, the achieved BP value was also applied as a time-dependent adjusted factor. The lipid levels were classified using the following cut-off values: LDL cholesterol < 120 mg/dL, 140 mg/dL and 160 mg/dL, and HDL cholesterol < 40 mg/dL and 60 mg/dL, in accordance with the Japan Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases 2012¹².

The relationship between comprehensive risk factor control and the risk of CVD was evaluated using the Cox proportional hazards model, including each risk factor (LDL cholesterol, BP, HbA1c and smoking) or the number of controlled risk factors as covariates, adjusted for sex, age, family history of coronary artery disease and body mass index.

The degree of control of LDL cholesterol (adequately controlled: < 120 mg/dL), BP (adequately controlled: < 140/90 mmHg) and HbA1c (adequately controlled: < 6.9%) was assessed based on the mean measurements obtained during the study period. The degree of control of smoking (adequately controlled: non-smoking) was assessed based on the results of the patient questionnaire obtained at baseline, which classified patients as either 'non-smokers' (including subjects who answered 'never smoked' or 'quit smoking more than one year ago') or 'smokers' (including subjects who answered 'quit smoking within the past year' or 'currently smoking'). Since almost half of the study patients were elderly, the target BP for elderly patients defined by the JSH 2009 criteria¹⁷ (< 140/90 mmHg) was used as a target.

All statistical analyses were performed using the SAS version 9.2 software program (SAS Institute Inc., Cary, NC, USA), with a two-sided significance level of 0.05.

Results

Patients

A total of 15,313 patients were enrolled from 2,219 institutions across Japan, and baseline data for 15,255 patients were collected. Of these individuals, 534 were excluded: 51 patients who were later found to not have met the inclusion or exclusion criteria, six patients who received no dose of olmesartan, 244 patients for whom no on-treatment data were available (e.g. those who did not return to the institution after their first visit), 82 patients with no case report

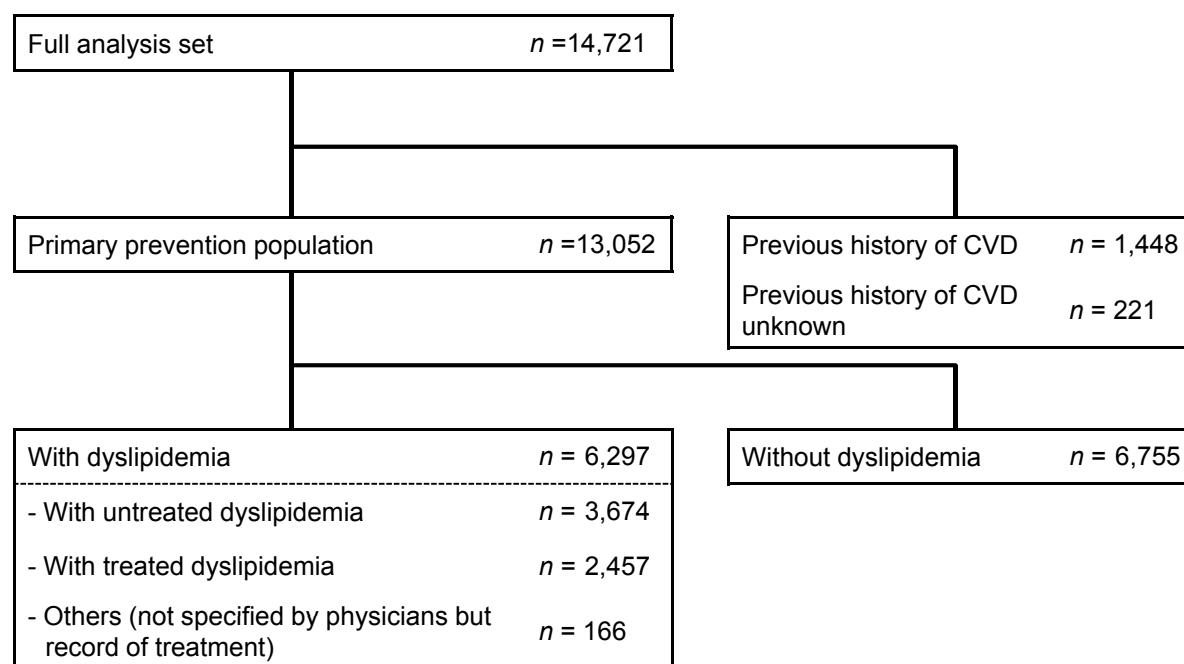


Fig. 1. Composition of the patients in the OMEGA study. CVD, cardiovascular disease.

form data at six months, 63 patients who withdrew their consent during the first six months of the study and 88 patients who were later found to have enrolled after the specified period of enrollment. Of the remaining 14,721 patients, 13,052 had no history of CVD, and their data were accordingly included in the sub-analysis (**Fig. 1**).

Patient Characteristics

The patient characteristics at baseline are summarized in **Table 1A**. A total of 6,297 patients (48.2%) had dyslipidemia. The proportion of women was higher in the dyslipidemia group than in the non-dyslipidemia group. However, there were no differences in age between the two groups. In the dyslipidemia group, the duration of hypertension was significantly longer, although the systolic BP (SBP) and diastolic BP (DBP) values were both lower. Meanwhile, the LDL cholesterol and non-HDL cholesterol values were higher in the dyslipidemia group, whereas the HDL cholesterol values were similar between the groups. In addition, the patients with dyslipidemia were more likely to have diabetes mellitus and hepatic and/or renal impairment. **Table 1B** shows the patient characteristics at baseline according to the comprehensive risk factor control category. The mean age ranged from 61.0 to 65.9 years, the mean body mass index ranged from 24.56 to 24.96 kg/m² and the mean duration of hypertension ranged from 4.21 to 4.77

years.

Exposure to Olmesartan and Concomitant Drugs

The daily dose of olmesartan at baseline was 17.2 ± 5.6 mg in the dyslipidemia group versus 17.3 ± 5.4 mg in the non-dyslipidemia group. At 36 months, the daily doses were 17.3 ± 8.6 mg and 17.2 ± 8.3 mg, respectively. The proportion of patients who were still receiving treatment with olmesartan at 36 months was similar between the dyslipidemia group and non-dyslipidemia group (91.3% and 90.9%, respectively).

The proportion of patients who received any antihypertensive drugs other than olmesartan prior to the start of the survey was 53.3% in the dyslipidemia group and 43.6% in the non-dyslipidemia group. Meanwhile, the number of antihypertensive drugs, including olmesartan, used at baseline and at 36 months was similar between the groups (1.5 ± 0.7 and 1.6 ± 0.9 , respectively, in the dyslipidemia group, compared with 1.4 ± 0.7 and 1.6 ± 0.9 , respectively, in the non-dyslipidemia group). **Table 2** shows the rate of use of olmesartan and concomitant antihypertensive drugs at baseline, after six months and at study completion. The percentage of patients taking olmesartan was similar between those with and without dyslipidemia at all time points. The percentage of patients taking antihypertensive drugs other than olmesartan increased by approximately 10% after six months and approximately 15% at study completion, compared

Table 1A. Patient characteristics at baseline^{§1}

	Non-dyslipidemia group	Dyslipidemia group	<i>p</i> ^{§2}
<i>n</i>	6755	6297	
Male	3,716 (55.0)	2,726 (43.3)	<0.0001
Female	3,039 (45.0)	3,571 (56.7)	
Age (years)	64.7 ± 8.2	64.3 ± 8.1	0.0248
Body mass index (kg/m ²)	24.30 ± 3.58	25.26 ± 3.59	<0.0001
Duration of hypertension (years) ^{§3}	4.35 ± 4.21	4.97 ± 4.23	<0.0001
Blood pressure immediately before treatment (mmHg)			
Systolic	159.1 ± 17.9	157.1 ± 17.4	<0.0001
Diastolic	90.1 ± 12.2	88.7 ± 11.9	<0.0001
Pulse rate (beats/min) immediately before treatment	73.9 ± 10.6	74.0 ± 10.7	0.9154
Coexisting diseases			
Diabetes mellitus	1,186 (17.6)	1,856 (29.5)	<0.0001
Heart disease	121 (1.8)	112 (1.8)	0.9565
Cerebrovascular disease	12 (0.2)	14 (0.2)	0.5673
Hepatic disease	561 (8.3)	1,013 (16.1)	<0.0001
Renal disease	333 (4.9)	546 (8.7)	<0.0001
Malignant neoplasm	33 (0.5)	24 (0.4)	0.3525
Smoking status			
Current smoker	1,348 (20.0)	1,084 (17.2)	<0.0001
Stopped smoking ≤ 1 year ago	222 (3.3)	179 (2.8)	
Stopped smoking > 1 year ago	1,385 (20.5)	1,179 (18.7)	
Never smoked	3,450 (51.1)	3,632 (57.7)	
Unknown	350 (5.2)	223 (3.5)	
HDL cholesterol (mg/dL)	57.98 ± 15.17	57.99 ± 15.83	0.9883
LDL cholesterol (mg/dL)	114.80 ± 26.96	131.48 ± 35.13	<0.0001
Non-HDL cholesterol (mg/dL)	137.67 ± 29.10	163.99 ± 36.81	<0.0001
Triglycerides (mg/dL)	116.89 ± 60.12	171.00 ± 117.73	<0.0001
HbA1c (NGSP value) (%)	6.22 ± 1.26	6.56 ± 1.40	<0.0001
Receiving statin therapy at start of treatment	0 (0.0)	2221 (35.3)	<0.0001

HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program.

^{§1}Values expressed as *n* (%) or mean ± SD.

^{§2}Chi-squared test for categorical data and unpaired *t*-test for quantitative data.

^{§3}Duration ≥ 10 years was treated as a duration of hypertension of 10 years.

with that observed at baseline among the patients with and without dyslipidemia.

The proportion of dyslipidemic patients using any lipid-lowering drugs slightly increased from baseline (41.7%) to 36 months (53.7%). Most of the lipid-lowering drugs used during the study period were statins (35.3% at baseline and 46.0% at 36 months). In the non-dyslipidemia group, the proportion of patients who used any lipid-lowering drugs at 36 months was 7.9% (statins: 6.5%).

Changes in Blood Pressure and Lipid Levels

The changes in BP from baseline to 36 months in the dyslipidemia and non-dyslipidemia groups are shown in **Fig. 2**. The SBP/DBP values in the dyslipid-

emia group were significantly decreased at six months (137.6 ± 14.1/79.1 ± 9.8 mmHg) compared to that noted at baseline (157.1 ± 17.4/88.7 ± 11.9 mmHg), and the lower BP values were maintained at 36 months (134.2 ± 13.2/76.1 ± 9.4 mmHg) (*p* < 0.0001 at six and 36 months, compared with baseline). In addition, the SBP/DBP values in the non-dyslipidemia group also decreased significantly from baseline (159.1 ± 17.9/90.1 ± 12.2 mmHg) to six months (137.5 ± 14.1/79.2 ± 9.8 mmHg) and 36 months (134.0 ± 13.1/76.6 ± 9.3 mmHg) (*p* < 0.0001 at six and 36 months, compared with baseline).

The changes in the LDL and HDL cholesterol levels from baseline to 36 months in the dyslipidemia and non-dyslipidemia groups are shown in **Fig. 3**.

Table 1B. Patient characteristics at baseline according to the comprehensive risk factor control category^{§1}

	No. of controlled risk factors				
	4	3	2	1	0
<i>n</i>	1,974	4,181	4,070	2,207	583
Male	931 (47.2)	1,917 (45.9)	1 968 (48.4)	1 153 (52.2)	453 (77.7)
Female	1,043 (52.8)	2,264 (54.1)	2,102 (51.6)	1,054 (47.8)	130 (22.3)
Age (years)	65.9 ± 7.8	65.0 ± 8.1	64.4 ± 8.2	63.5 ± 8.1	61.0 ± 7.8
Body mass index (kg/m ²)	24.56 ± 3.43	24.66 ± 3.54	24.92 ± 3.72	24.96 ± 3.76	24.70 ± 3.56
Duration of hypertension ^{§2}	4.77 ± 4.25	4.74 ± 4.22	4.73 ± 4.22	4.41 ± 4.26	4.21 ± 4.15
Blood pressure immediately before treatment (mmHg)					
Systolic	153.8 ± 17.2	156.2 ± 17.0	159.0 ± 17.6	162.3 ± 17.7	164.9 ± 18.7
Diastolic	87.5 ± 11.6	88.4 ± 11.5	89.5 ± 12.1	91.6 ± 12.5	94.3 ± 12.9
Pulse rate (beats/min) immediately before treatment	72.6 ± 10.0	73.3 ± 10.1	74.7 ± 10.9	74.7 ± 11.3	76.3 ± 11.7
Coexisting diseases					
Dyslipidemia	891 (45.1)	2,024 (48.4)	1,941 (47.7)	1,026 (46.5)	238 (40.8)
Diabetes mellitus	366 (18.5)	911 (21.8)	1,018 (25.0)	592 (26.8)	149 (25.6)
Heart disease	40 (2.0)	78 (1.9)	74 (1.8)	37 (1.7)	4 (0.7)
Cerebrovascular disease	6 (0.3)	8 (0.2)	6 (0.1)	4 (0.2)	2 (0.3)
Hepatic disease	225 (11.4)	506 (12.1)	508 (12.5)	264 (12.0)	71 (12.2)
Renal disease	136 (6.9)	237 (5.7)	270 (6.6)	179 (8.1)	54 (9.3)
Malignant neoplasm	9 (0.5)	19 (0.5)	19 (0.5)	8 (0.4)	2 (0.3)
Smoking status					
Current smoker	0 (0.0)	455 (10.9)	890 (21.9)	653 (29.6)	434 (74.4)
Stopped smoking ≤ 1 year ago	0 (0.0)	91 (2.2)	152 (3.7)	104 (4.7)	54 (9.3)
Stopped smoking > 1 year ago	636 (32.2)	961 (23.0)	685 (16.8)	282 (12.8)	0 (0.0)
Never smoked	1,338 (67.8)	2,601 (62.2)	2,166 (53.2)	977 (44.3)	0 (0.0)
Unknown	0 (0.0)	73 (1.7)	177 (4.3)	191 (8.7)	95 (16.3)
Not reported	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HDL cholesterol (mg/dL)	60.18 ± 16.71	58.35 ± 15.36	57.39 ± 15.26	57.13 ± 15.17	53.88 ± 14.19
LDL cholesterol (mg/dL)	111.89 ± 30.30	121.85 ± 31.49	127.16 ± 32.99	132.28 ± 32.62	124.97 ± 32.58
Non-HDL cholesterol (mg/dL)	137.84 ± 33.72	149.44 ± 34.36	155.41 ± 35.88	161.28 ± 36.50	156.30 ± 35.68
Triglycerides (mg/dL)	133.42 ± 84.65	142.92 ± 94.03	147.31 ± 99.56	153.6 ± 115.17	158.58 ± 96.95
HbA1c (NGSP value) (%)	5.94 ± 0.91	6.21 ± 1.13	6.56 ± 1.37	7.01 ± 1.75	7.01 ± 1.86
Receiving statin therapy at start of treatment	440 (22.3)	799 (19.1)	653 (16.0)	285 (12.9)	39 (6.7)

HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program.

^{§1}Values expressed as *n* (%) or mean ± SD.^{§2}Duration ≥ 10 years was treated as a duration of hypertension of 10 years.

Consequently, the LDL cholesterol levels in the dyslipidemia group were significantly decreased at 36 months (115.6 ± 27.9 mg/dL) compared to that observed at baseline (131.5 ± 35.1 mg/dL, $p < 0.0001$). The LDL cholesterol levels in the non-dyslipidemia group also decreased significantly from baseline (114.8 ± 27.0 mg/dL) to 36 months (111.7 ± 25.8 mg/dL, $p < 0.0001$); however, the difference was smaller than that seen in the dyslipidemia group. In contrast, the high-density cholesterol levels did not change significantly during the study period in either the dyslipidemia group (58.0 ± 15.8 mg/dL at baseline and $58.0 \pm$

15.1 mg/dL at 36 months, $p = 0.9932$) or non-dyslipidemia group (58.0 ± 15.2 mg/dL at baseline and 57.8 ± 15.1 mg/dL at 36 months, $p = 0.8257$).

Incidence of Cardiovascular Disease

The incidence of CVD, stroke and CHD during the study period was 5.59, 2.40 and 3.29 per 1,000 patient-years, respectively, in the dyslipidemia group, and 5.57, 3.06 and 2.11 per 1,000 patient-years, respectively, in the non-dyslipidemia group. The rate of CHD differed significantly between the two groups ($p = 0.0323$), whereas the frequency of CVD and

Table 2. Use of antihypertensive drugs^{§1}

	Non-dyslipidemia group			Dyslipidemia group		
	Baseline	6 months	Study completion	Baseline	6 months	Study completion
<i>n</i>	6,755	6,310	6,755	6,297	5,920	6,297
Olmesartan	6,755 (100.0)	6,029 (95.5)	5,987 (88.6)	6,297 (100.0)	5,667 (95.7)	5,611 (89.1)
Concomitant antihypertensive drugs	2,260 (33.5)	2,796 (44.3)	3,390 (50.2)	2,525 (40.1)	2,916 (49.3)	3,410 (54.2)
Diuretics	229 (3.4)	390 (6.2)	613 (9.1)	255 (4.0)	423 (7.1)	610 (9.7)
α -blockers	138 (2.0)	195 (3.1)	214 (3.2)	140 (2.2)	181 (3.1)	205 (3.3)
β -blockers	317 (4.7)	370 (5.9)	457 (6.8)	376 (6.0)	413 (7.0)	498 (7.9)
Calcium channel blockers	1,931 (28.6)	2,389 (37.9)	2,829 (41.9)	2,192 (34.8)	2,505 (42.3)	2,942 (46.7)
Angiotensin-converting enzyme inhibitors	99 (1.5)	113 (1.8)	125 (1.9)	155 (2.5)	146 (2.5)	160 (2.5)
Angiotensin receptor blockers	30 (0.4)	63 (1.0)	242 (3.6)	47 (0.7)	49 (0.8)	190 (3.0)
Others	19 (0.3)	24 (0.4)	60 (0.9)	10 (0.2)	17 (0.3)	60 (1.0)

^{§1}Values expressed as *n* (%).

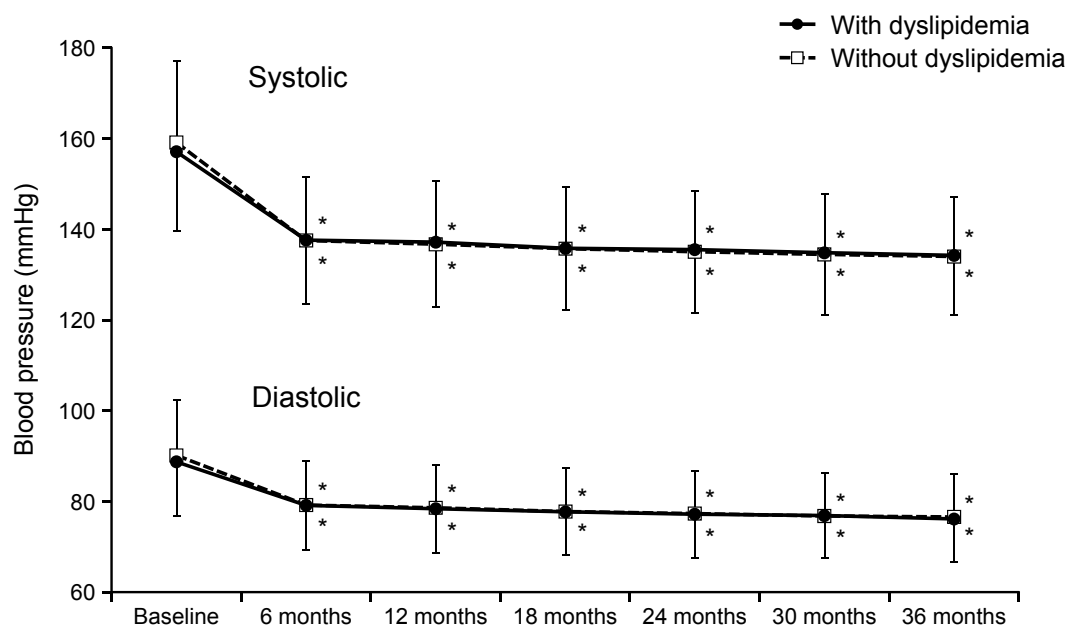


Fig. 2. Changes in blood pressure during the 36-month treatment period with olmesartan. * $p < 0.0001$ (versus just before the start of olmesartan treatment, Dunnett-Hsu test).

stroke did not ($p = 0.9733$ and $p = 0.2436$, respectively) (Table 3).

Relationships between Blood Pressure, the Lipid Levels and the Risk of Cardiovascular Disease

The relationship between the achieved BP values and the risk of CVD was evaluated in the dyslipidemia and non-dyslipidemia groups (Table 4). Consequently, no interactions for the relationship between the achieved BP value and the incidence of CVD were

found between the dyslipidemia and non-dyslipidemia groups ($p = 0.4367$).

The relationships between the achieved BP values and/or lipid levels and the risk of CVD were evaluated in the primary prevention population comprising both the dyslipidemia and non-dyslipidemia groups (Fig. 4). Compared with that observed in the $<130/85$ mmHg (based on the on-treatment BP values) group, the risk of CVD was higher in the $>130/85$ and $<140/90$ mmHg groups (hazard ratio, HR,

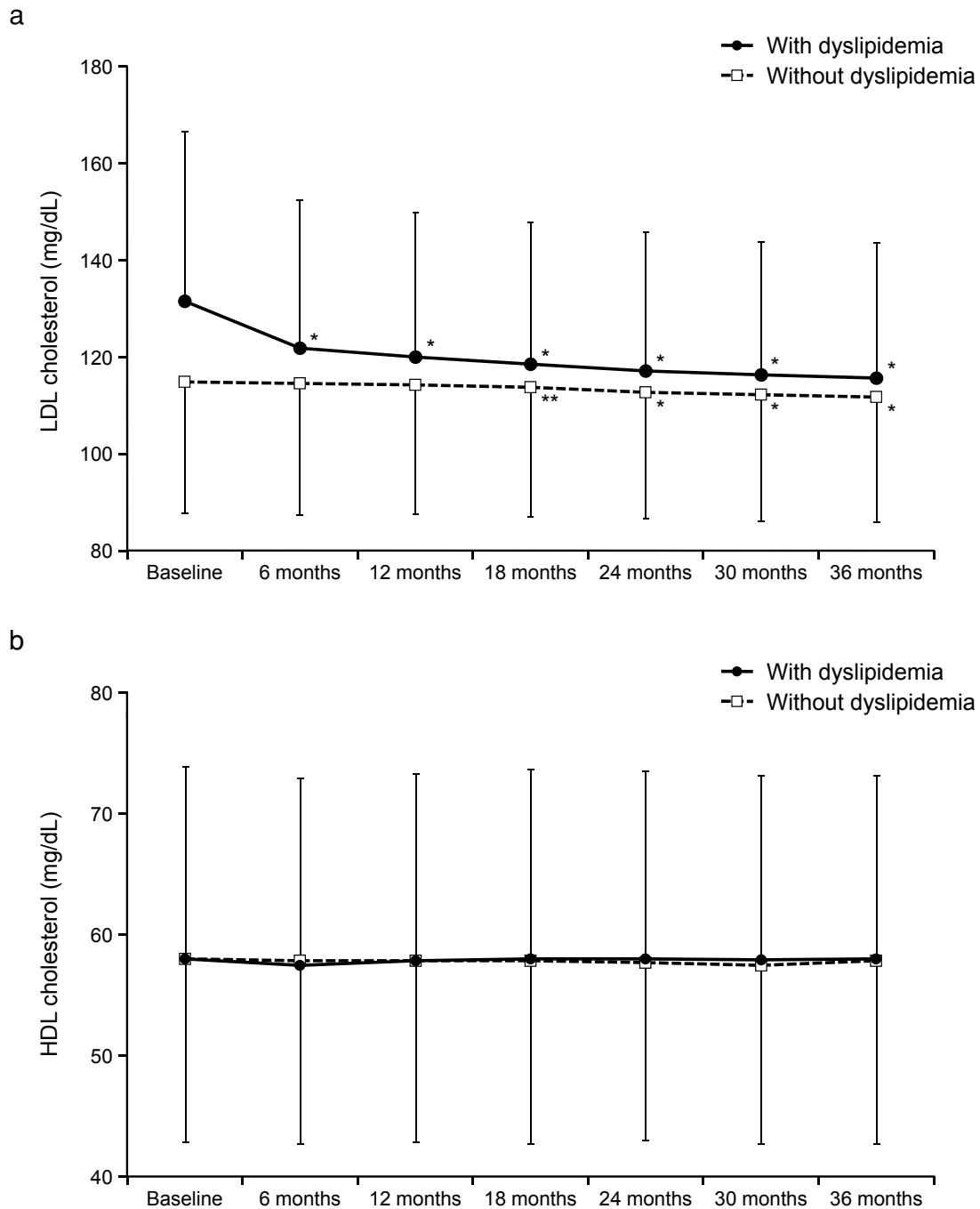


Fig. 3. Changes in the (a) low-density lipoprotein (LDL) cholesterol and (b) high-density lipoprotein (HDL) cholesterol levels during the 36-month treatment period with olmesartan. * $p < 0.0001$, ** $p < 0.05$ (versus just before the start of olmesartan treatment, Dunnett-Hsu test).

1.442; $p = 0.1789$) as well as the $\geq 140/90$ mmHg group (HR, 2.154; $p = 0.0020$). Therefore, the risk of CVD tended to increase in association with an increase in BP.

The evaluation of the relationships between the

achieved lipid levels (LDL cholesterol, HDL cholesterol and non-HDL cholesterol) and the risk of CVD showed that higher LDL cholesterol and non-HDL cholesterol levels and lower HDL cholesterol levels tended to be associated with a higher CVD risk, even

Table 3. Incidence of cardiovascular disease among the patients with and without dyslipidemia^{§1}

	Non-dyslipidemia group	Dyslipidemia group	<i>p</i> ^{§2}
Cardiovascular disease	100/6,755 (5.57)	95/6,297 (5.59)	0.9733
Stroke	55/6,755 (3.06)	41/6,297 (2.40)	0.2436
Cerebral infarction	48/6,755 (2.67)	31/6,297 (1.82)	0.0945
Cerebral hemorrhage	7/6,755 (0.39)	6/6,297 (0.35)	0.8604
Subarachnoid hemorrhage	0/6,755 (0.00)	5/6,297 (0.29)	0.0224
Coronary heart disease	38/6,755 (2.11)	56/6,297 (3.29)	0.0323
Myocardial infarction	10/6,755 (0.55)	19/6,297 (1.11)	0.0690
Myocardial infarction, angina pectoris requiring cardiovascular intervention	23/6,755 (1.28)	27/6,297 (1.58)	0.4385
Hospitalization because of angina pectoris requiring no intervention	5/6,755 (0.28)	13/6,297 (0.76)	0.0443
Sudden death	7/6,755 (0.39)	3/6,297 (0.18)	0.2408

^{§1}Values expressed as events/patients at the last evaluation (events/1,000 patient-years).

^{§2}Log-rank test.

Table 4. Incidence of cardiovascular disease according to the achieved blood pressure (BP) values in the patients with and without dyslipidemia[§]

Achieved BP (mmHg)	Events/patients at last evaluation (%)	Hazard ratio	95% confidence interval	<i>p</i>	Interaction (dyslipidemia group × achieved BP group)
Non-dyslipidemia group					
< 130/85	18/1,995 (0.9)				0.4367
> 130/85 to ≤ 140/90	22/2,189 (1.0)	1.762	0.760-4.086	0.1866	
≥ 140/90	59/2,559 (2.3)	3.025	1.412-6.480	0.0044	
Dyslipidemia group					
< 130/85	15/1,826 (0.8)	1.668	0.688-4.042	0.2576	
> 130/85 to ≤ 140/90	33/2,077 (1.6)	2.068	0.910-4.698	0.0828	
≥ 140/90	47/2,386 (2.0)	2.714	1.252-5.884	0.0114	
Unable to calculate	1/20 (5.0)				

[§]Covariates: dyslipidemia, BP during the observation period (time-dependent covariate), sex, age, family history of coronary artery disease, HbA1c (time-dependent covariate), body mass index and smoking habits.

after adjusting for the achieved BP value (trend *p* = 0.0005, 0.0017 and 0.0002, respectively).

Comprehensive Risk Factor Control

The relationships between adequate or inadequate control of each CVD risk factor (LDL cholesterol, BP, HbA1c and smoking) and the risk of CVD were evaluated in the primary prevention population (**Table 5**). Consequently, the CVD risk was significantly higher among the patients with inadequately LDL cholesterol, BP and/or HbA1c values. On the other hand, no significant differences in the risk of CVD were found between non-smokers (risk factor adequately controlled) and smokers (risk factor inadequately controlled).

The relationship between the number of adequately controlled risk factors and the risk of CVD

was also evaluated. The HR for CVD, compared with the group with four controlled risk factors, was 4.395 (95% confidence interval, CI, 1.739-11.110) in the group with three controlled risk factors, 7.684 (95% CI, 3.089-19.116) in the group with two controlled risk factors, 15.938 (95% CI, 6.358-39.953) in the group with one controlled risk factor and 42.739 (95% CI, 16.385-111.484) in the group with no controlled risk factors. A smaller number of adequately controlled risk factors was associated with a higher CVD risk (trend *p* < 0.0001, **Table 6**). In the group with three controlled risk factors, only 50.3% of the patients achieved control of LDL cholesterol; this proportion was lower than that for all other risk factors (77.0-89.2%) (**Fig. 5**).

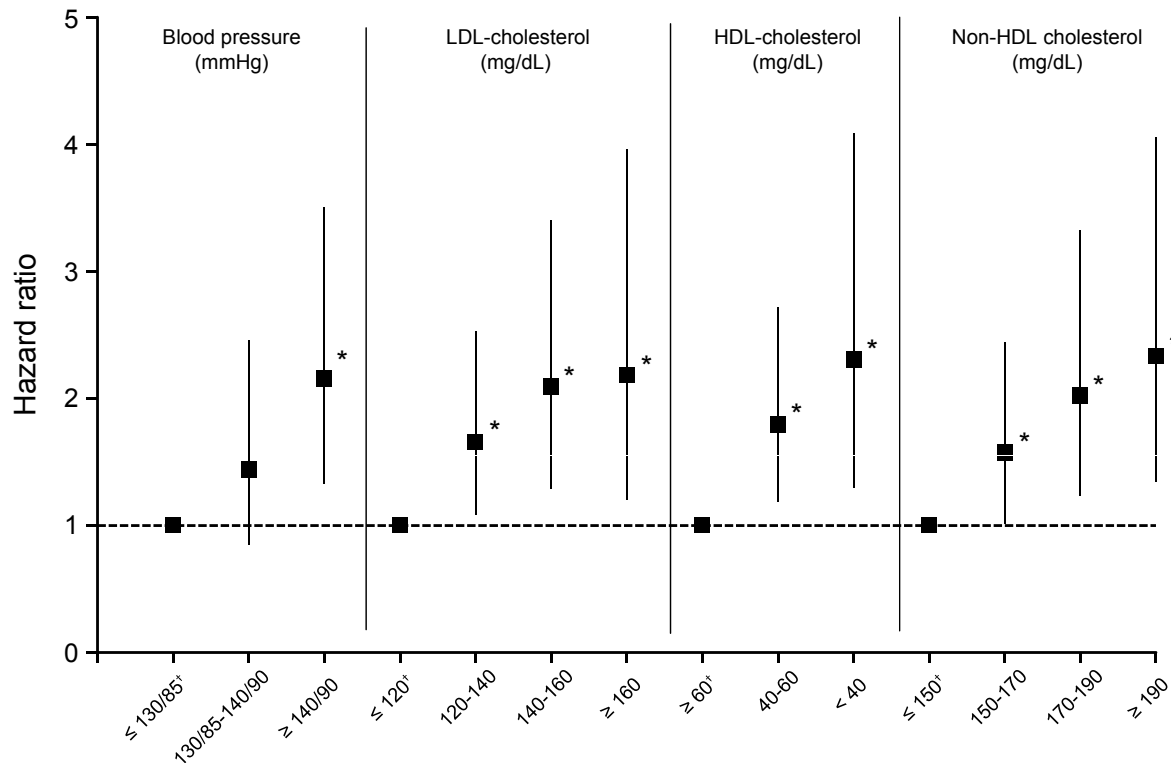


Fig. 4. Relationships between the mean achieved blood pressure, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and non-HDL cholesterol values and the risk of cardiovascular disease in the primary prevention population. * $p < 0.05$, 95% confidence interval (Cox proportional hazards model with adjusted factors of the achieved blood pressure (time-dependent covariate), sex, age, family history of coronary heart disease, HbA1c (time-dependent covariate), body mass index and smoking). †Attained adequate control.

Discussion

Using data from the OMEGA study, we investigated changes in BP and the lipid levels in patients with and without dyslipidemia, as well as the incidence of CVD in patients with and without dyslipidemia, the relationships between the achieved BP values and lipid levels and the risk of CVD and the relationship between comprehensive risk factor control and the risk of CVD.

The comparisons of the patient characteristics between the dyslipidemia group and the non-dyslipidemia group showed that the dyslipidemic patients were more likely to have had diabetes mellitus and hepatic and/or renal impairment. These findings suggest that hypertensive patients with dyslipidemia exhibit greater accumulation of CVD risk factors. In the dyslipidemia group, the duration of hypertension was longer and the patients were more likely to have used at least one antihypertensive drug prior to the start of the study. In addition, the comparisons of the

patient baseline characteristics according to the comprehensive risk factor control category showed no major differences in age, body mass index, duration of hypertension or coexisting diseases, factors that were not included in the assessment of comprehensive risk factor control.

In both the dyslipidemia group and the non-dyslipidemia group, the BP values were decreased significantly at six months compared with that observed at baseline, and the significantly lower BP values were maintained at 36 months. This finding highlights the long-term antihypertensive effect of olmesartan-based treatment, regardless of whether dyslipidemia is present.

The low-density lipoprotein cholesterol levels in the dyslipidemia group were also significantly decreased at 36 months, which may have partly resulted from the slight increase in the proportion of patients using lipid-lowering drugs. This finding shows that the patients with dyslipidemia had appropriate lipid control. Furthermore, the LDL cholesterol levels were sig-

Table 5. Relationships between the controlled risk factors and the risk of cardiovascular disease (multivariate analysis)

Value or target for risk factor	Events/patients evaluated (%)	Hazard ratio [§]	95% confidence interval	<i>p</i>
LDL cholesterol		1.745	1.169-2.605	0.0064
Achieved (< 120 mg/dL)	67/6,013 (1.1)			
Not achieved (≥ 120 mg/dL)	70/4,999 (1.4)			
Unknown	58/2,040 (2.8)			
Blood pressure		2.013	1.352-2.996	0.0006
Achieved (< 140/90 mm/Hg)	81/8,118 (1.0)			
Not achieved (≥ 140/90 mmHg)	83/4,544 (1.8)			
Unknown	31/390 (7.9)			
HbA1c (NGSP value)		3.302	2.206-4.942	< 0.0001
Achieved (< 6.9%)	60/7,009 (0.9)			
Not achieved (≥ 6.9%)	51/1,644 (3.1)			
Unknown	84/4,399 (1.9)			
Smoking		1.249	0.781-1.997	0.3534
Achieved (non-smoking)	118/9,646 (1.2)			
Not achieved (still smoking)	70/2,833 (2.5)			
Unknown	7/573 (1.2)			

HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program.

[§]Adjusted for sex, age, family history of coronary artery disease and body mass index.

Table 6. Relationships between the number of controlled risk factors and the risk of cardiovascular disease (multivariate analysis)

No. of controlled risk factors ^{§1}	Events/patients evaluated (%)	Hazard ratio ^{§2}	95% confidence interval	<i>p</i>	Test for trend
4	5/1,974 (0.3)				< 0.0001
3	42/4,181 (1.0)	4.395	1.739-11.110	0.0018	
2	63/4,070 (1.5)	7.684	3.089-19.116	< 0.0001	
1	54/2,207 (2.4)	15.938	6.358-39.953	< 0.0001	
0	29/583 (5.0)	42.739	16.385-111.484	< 0.0001	
Unknown	2/37 (5.4)				

^{§1}Low-density lipoprotein cholesterol < 120 mg/dL, blood pressure < 140/90 mm/Hg, hemoglobin A1c (National Glycohemoglobin Standardization Program value) < 6.9% and non-smoking.

^{§2}Compared with the group with four controlled risk factors. Adjusted for sex, age, family history of coronary artery disease and body mass index.

nificantly decreased in the non-dyslipidemia group, although the decrease was smaller than that noted in the dyslipidemia group. In contrast, the HDL cholesterol levels did not change significantly in either the dyslipidemia group or the non-dyslipidemia group.

The incidence of CVD in the OMEGA study was 281/14,721 patients (7.15/1,000 patient-years)¹³, which is lower than that assumed prior to the start of the study (435/9,710 patients, 15/1,000 patient-years)¹⁶. The incidence of CVD in this subanalysis was 95/6,297 patients (5.59/1,000 patient-years) in the dyslipidemia group and 100/6,755 patients (5.57/1,000 patient-years) in the non-dyslipidemia group. The incidence of stroke was significantly higher in the

non-dyslipidemia group, whereas that of CHD was significantly higher in the dyslipidemia group.

Even among the patients with dyslipidemia, who are expected to be at increased risk of cardiovascular events, the incidence of CVD was lower than expected. The low incidence of CVD may be attributed to the widespread use of angiotensin II receptor blockers as first-line therapy, the implementation of revised guidelines recommending strict BP control and improvements in the medical environment as well as the treatment of complications of hypertension, such as dyslipidemia.

Moreover, among the patients with dyslipidemia, 35.3% were treated with statins and demonstrated sig-

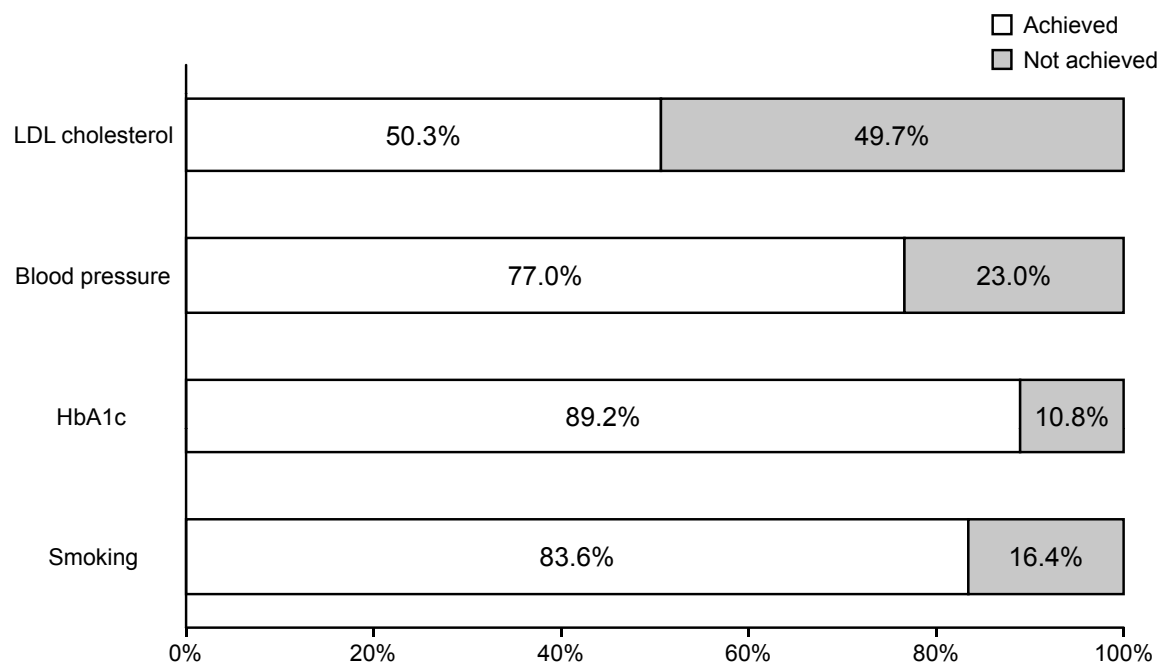


Fig. 5. Proportion of patients who achieved control of each risk factor in the group with three controlled risk factors. Criteria for controlled risk factors: LDL cholesterol, mean achieved value <120 mg/dL; blood pressure, mean achieved value $<140/90$ mmHg; hemoglobin A1c (National Glycohemoglobin Standardization Program value), mean achieved value $<6.9\%$; non-smoking (at baseline).

nificant improvements in the LDL cholesterol levels without changes to the HDL cholesterol levels, indicating appropriate management of the lipid profiles. We consider that this observation may have led to a reduction in the risk of CVD among the patients with dyslipidemia, who are considered to be at high risk of CVD.

It has also been reported that an increase in BP is associated with a significantly greater CVD risk in patients with dyslipidemia^{11, 18}. In the present study, a sustained antihypertensive effect of olmesartan was found in the patients with dyslipidemia, suggesting that the antihypertensive effects of the RAS inhibitor olmesartan¹⁹ may have helped to prevent CVD in this group of patients. Furthermore, it is possible that effects of the RAS inhibitor other than its antihypertensive effects, such as anti-inflammatory effects²⁰ and/or prevention of the progression of coronary atherosclerosis²¹, may have contributed to the preventive effects against CHD observed in the hypertensive patients with dyslipidemia; however, further studies are needed to verify this speculation.

The analysis of the relationship between the achieved BP values and the risk of CVD in the primary prevention population showed that an increased BP (i.e. a higher achieved BP value) is associated with

an increased CVD risk, which suggests that the BP value should be decreased to at least $\leq 140/90$ mmHg. Furthermore, the evaluation of the relationship between the lipid levels and the risk of CVD in the primary prevention population showed that the deterioration of lipid endpoints is associated with an increased CVD risk. Moreover, we conducted a subanalysis of the dyslipidemia group only. Similar to the results of the analysis of the primary prevention population, an increased lipid level was found to be associated with an increased CVD risk. However, the increase in HR was greater than that observed in the primary prevention population [LDL cholesterol: HR vs <120 mg/dL; 1.919 (≥ 120 mg/dL to <140 mg/dL), 2.630 (≥ 140 mg/dL to <160 mg/dL), 2.861 (≥ 160 mg/dL), trend $p=0.0033$; non-HDL cholesterol: HR vs <150 mg/dL; 2.053 (≥ 150 mg/dL to <170 mg/dL), 2.430 (≥ 170 mg/dL to <190 mg/dL), 3.427 (≥ 190 mg/dL), trend $p=0.0006$]. This finding emphasizes the importance of controlling the lipid levels, as well as BP, in hypertensive patients.

The association between comprehensive risk factor control and the risk of CVD was also evaluated. The assessed CVD risk factors included BP, HbA1c and LDL cholesterol, which by themselves are important risk factors for CVD, as well as smoking. Our

evaluation showed that having fewer controlled risk factors markedly increases the risk of CVD, underlining the importance of achieving comprehensive control of CVD risk factors. The HR for CVD was higher among the patients in whom three of four factors were adequately controlled, while the remaining factor was inadequately controlled, than for the patients who attained adequate control of all four risk factors. When the achievement of control was evaluated according to each risk factor, only half of the patients achieved control of LDL cholesterol. The OMEGA study was an observational study. Therefore, the results of this subanalysis suggest that many hypertensive patients have poorly controlled dyslipidemia in clinical practice and that achieving lipid control, in addition to BP and HbA1c control, is necessary for obtaining comprehensive risk factor control in hypertensive patients.

The present subanalysis, in which data from a single-arm observational study of hypertensive patients receiving olmesartan were retrospectively stratified and analyzed, is associated with various limitations. In the OMEGA study, the patients were treated by their primary physician based on their individual characteristics and condition, with no prespecified targets for BP or the lipid levels. Therefore, the relationships between the achieved BP values and/or lipid levels and the risk of CVD may have been confounded by unmeasured factors other than those chosen as factors for adjustment. With respect to smoking, the results of the baseline questionnaire were used for the analyses, as changes in smoking habits during the study period were not investigated.

Despite these limitations, the results of the present subanalysis are useful for application in clinical practice because angiotensin receptor blockers, such as olmesartan, are prescribed extensively to treat hypertension. Furthermore, we used data obtained from a large-scale study showing the therapeutic effects of olmesartan in hypertensive patients with various characteristics in real-world clinical practice.

Conclusion

In conclusion, this subanalysis of the OMEGA study showed that olmesartan-based treatment achieves a good antihypertensive effect in hypertensive patients with or without dyslipidemia and that adequately controlling lipids, in addition to BP, is important for the primary prevention of CVD in hypertensive patients with or without dyslipidemia.

The results of this subanalysis also emphasize the importance of comprehensively controlling BP, lipids,

HbA1c and smoking in order to prevent CVD. Lipid abnormalities, in particular, constitute a residual risk factor in many hypertensive patients. Therefore, controlling lipids, as well as BP and HbA1c, is necessary in order to achieve comprehensive control of the risk of CVD.

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Role of the Authors and Sponsor

Drs. Teramoto, Kawamori and Miyazaki helped develop the study protocol, assess the statistical analysis methods and interpret the analytical results as medical advisers.

The statistical analysis plan was developed by Daiichi Sankyo, and the statistical analyses were conducted under the direction and supervision of the statistical adviser (Dr. Teramukai).

All authors were involved in the preparation, review and granting of final approval of the manuscript.

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This study was carried out as a postmarketing specified drug-use survey by Daiichi Sankyo Co., Ltd.

Conflicts of Interest

T.T. has received honoraria and research funding from Daiichi Sankyo Co., Ltd. S.T. has received honoraria from Daiichi Sankyo Co., Ltd. Y.S., Y.O. and M.S. are employees of Daiichi Sankyo Co., Ltd. The other authors have no conflicts of interest.

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