The present study also demonstrated that 12-week therapy with daily doses of evacetrapib up to 500 mg as monotherapy, or daily doses of evacetrapib 100 mg in combination with atorvastatin 10 mg, was well tolerated, with a low number of treatment-related adverse events in Japanese patients with high LDL-C or low HDL-C levels. Administration of evacetrapib as monotherapy or in combination with atorvastatin was not likely to be associated with any significant change in either SBP or DBP at any time point. The isolated finding of increased SBP with evacetrapib 500 mg appears to be an incidental occurrence, because neither a dose-dependent effect of evacetrapib monotherapy on SBP nor an increase in SBP with evacetrapib in combination with atorvastatin was observed. In addition, SBP also increased 2.6 ± 1.8 mm Hg in the atorvastatin monotherapy group, thus showing inherent variability in BP measurements.

It is worth noting that evacetrapib did not have any adverse effects on mineralocorticoid or electrolyte measures, thus agreeing with data reported in the phase 2 study of evacetrapib in the United States and Europe,[6] in the phase 2 study of anacetrapib,[17] and in the phase 3 study of dalcetrapib.[18] The lack of unfavorable changes in mineralocorticoid and electrolyte parameters for evacetrapib, anacetrapib, and dalcetrapib further support the hypothesis that the safety findings demonstrated with the previously terminated CETP inhibitor, torcetrapib, were most likely off-target effects and not related to the CETP mechanism.[1] Preclinical data also support the lack of negative effects of evacetrapib on the renin-angiotensin-aldosterone system.[4] No BP elevation was observed in rats, dogs, or cynomolgus monkeys dosed with evacetrapib at high-exposure multiples compared with torcetrapib. In addition, in a human adrenal cortical carcinoma cell line (H295R cells), torcetrapib dramatically induced aldosterone and cortisol biosynthesis, whereas evacetrapib did not have any effect.[4]

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Disclosures

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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) cholesterol[1)] and non-high-density lipoprotein (HDL) cholesterol levels[2)] and lower HDL

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cholesterol levels[3-5] 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 arteriosclerosis[4].

Among hypercholesterolemic patients with hypertension, aggressive LDL cholesterol-lowering treatment may prevent the incidence or recurrence of ischemic heart disease and stroke[10]. 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 hypertension[11]. 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 disease[12]. 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 CVD[13]. 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 CHD[14]. In addition, previous reports have described the relationships between diabetes mellitus, achieved BP, hemoglobin A1c (HbA1c, National Glycohemoglobin Standardization Program) and the incidence of CVD[15].

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 Postmarketing 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 publication[16].

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

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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 arthery 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 criteria[17]. 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 2012[12].

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 arthery 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 criteria[17] ($<140/90$ 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

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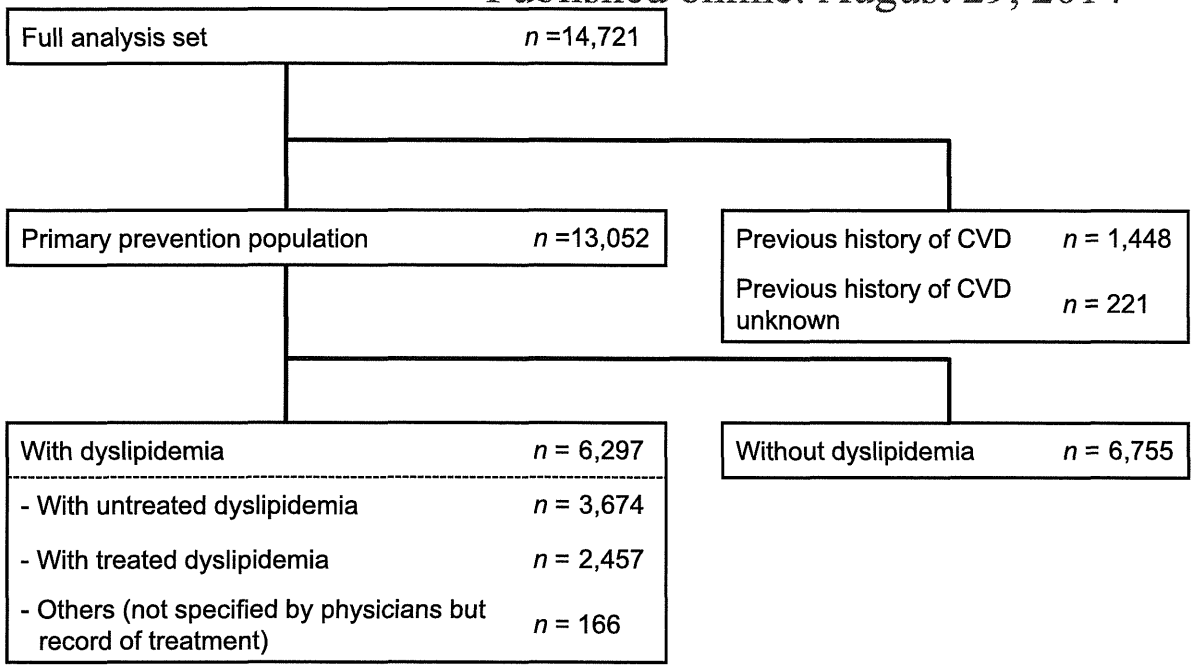

Fig. 1. Composition of the patients in the OMEGA study. CVD, cardiovascular disease.

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 subanalysis (**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/m^2 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

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Table 1A. Patient characteristics at baseline[§1]

	Non-dyslipidemia group	Dyslipidemia group	p[§2]
n	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 dyslipidemia 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**.

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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
n	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 ± 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

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Table 2. Use of antihypertensive drugs[§1]

	Non-dyslipidemia group			Dyslipidemia group		
	Baseline	6 months	Study completion	Baseline	6 months	Study completion
n	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* (%).

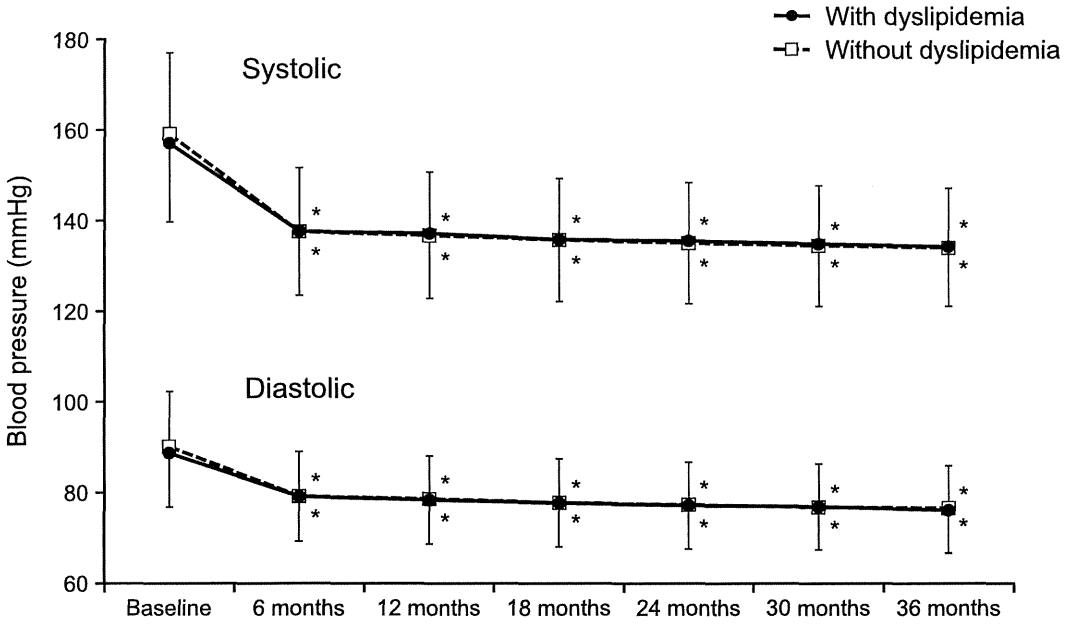

Fig. 2. Changes in blood pressure during the 36-month treatment period with olmesartan. *$p<0.0001$ (versus just before the start of olmesartan treatment, Dunnett-Hsu test).

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,

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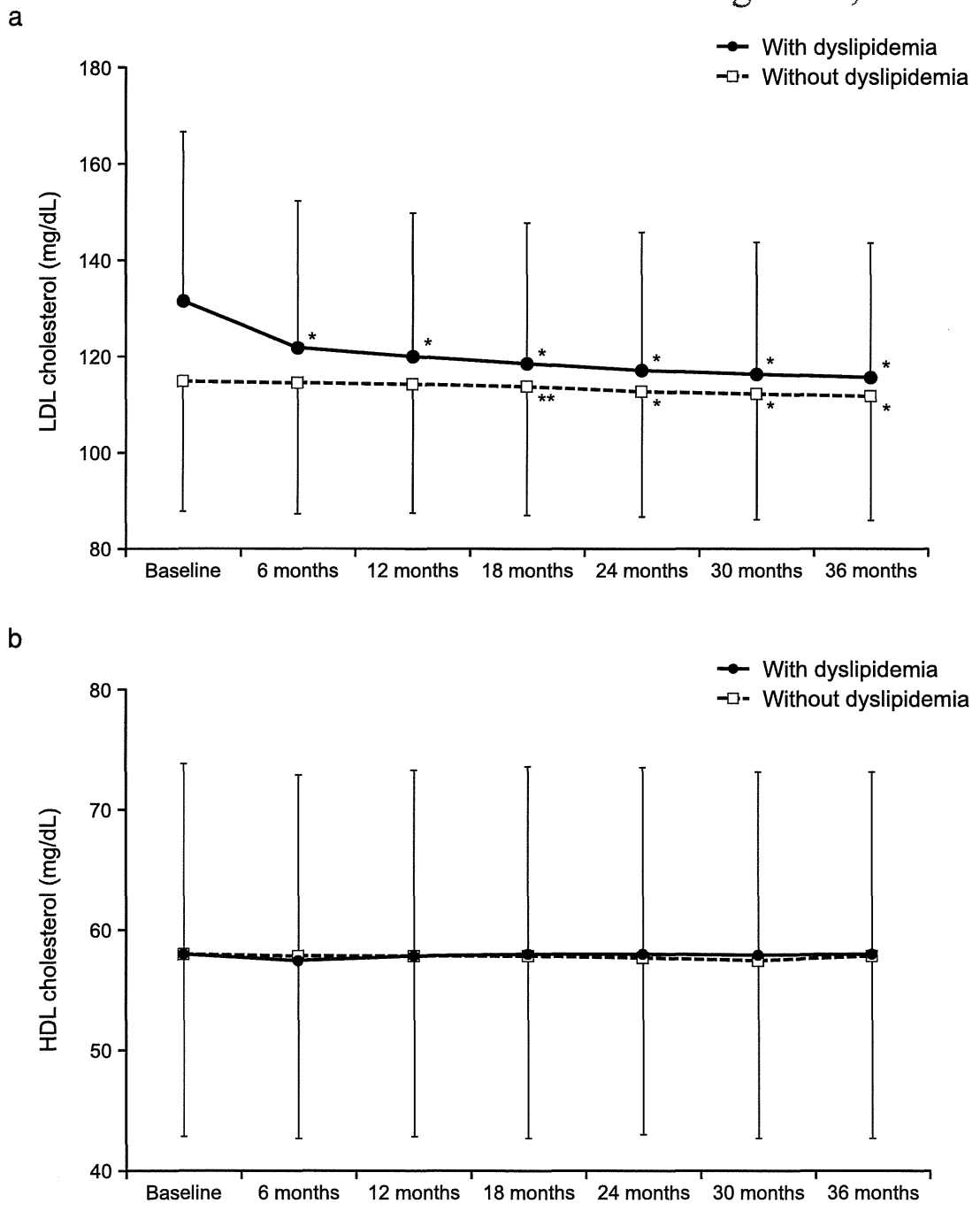

Fig. 3. Changes in the (a) low-density lipoprotein (LDL) cholesterol and (b) high-density lipoprotein (HDL) cholesterol levels during the 36-month treatment period with olmesartan. *$p<0.0001$, **$p<0.05$ (versus just before the start of olmesartan treatment, Dunnett-Hsu test).

1.442; $p=0.1789$) as well as the ≥ 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

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Table 3. Incidence of cardiovascular disease among the patients with and without dyslipidemia[§1]

	Non-dyslipidemia group	Dyslipidemia group	p[§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	p	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**).

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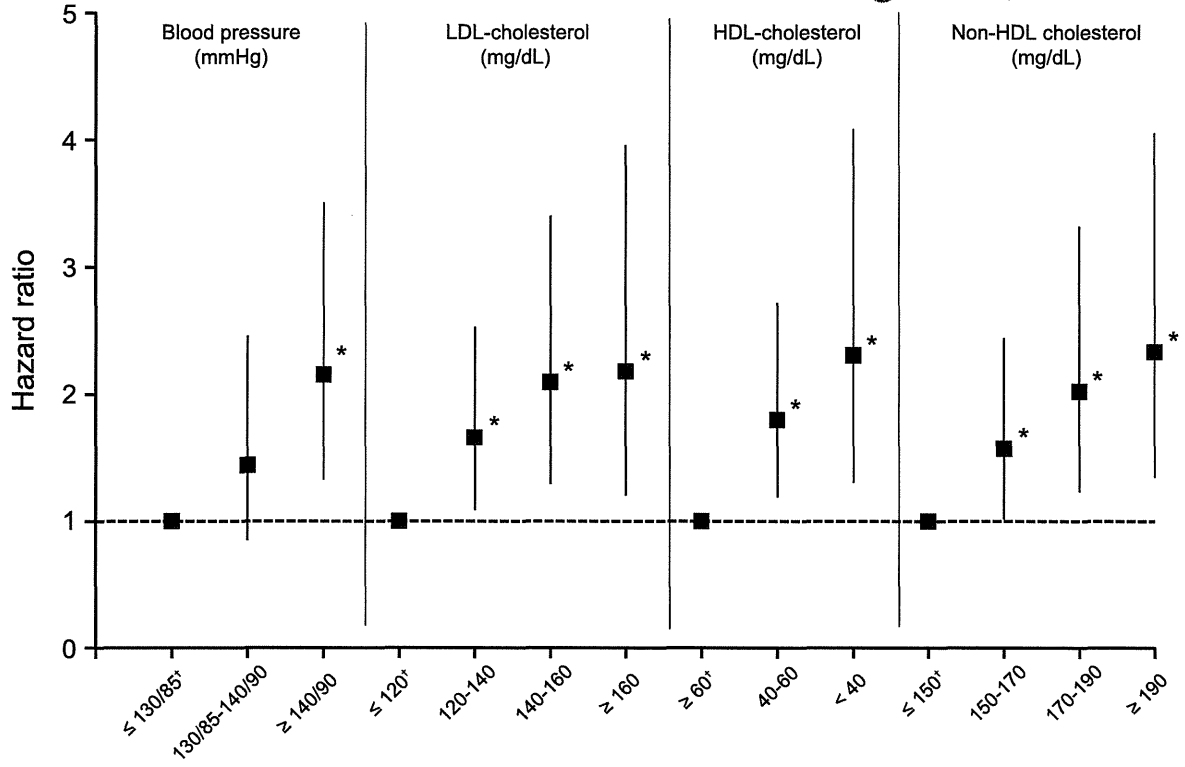

Fig. 4. Relationships between the mean achieved blood pressure, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and non-HDL cholesterol values and the risk of cardiovascular disease in the primary prevention population. *$p<0.05$, 95% confidence interval (Cox proportional 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-

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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	*p*
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	*p*	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-

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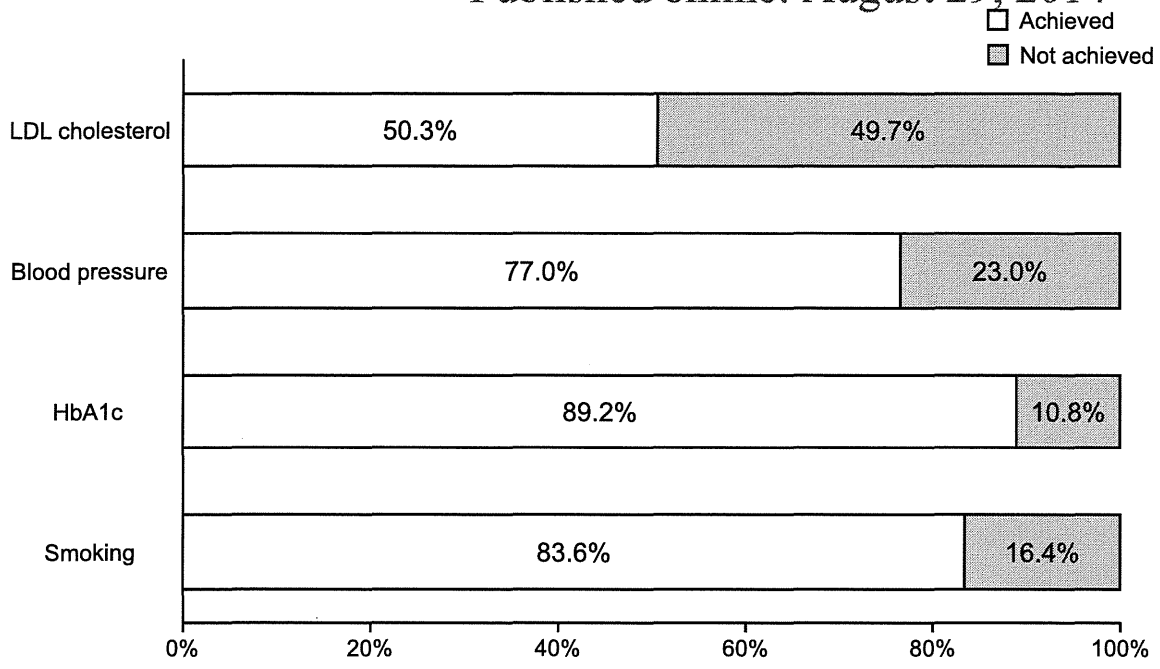

Fig. 5. Proportion of patients who achieved control of each risk factor in the group with three controlled risk factors. Criteria for controlled risk factors: LDL cholesterol, mean achieved value <120 mg/dL; blood pressure, mean achieved value <140/90 mmHg; hemoglobin A1c (National Glycohemoglobin Standardization 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 olmesartan[19] 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 effects[20] and/or prevention of the progression of coronary atherosclerosis[21], 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 ≤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

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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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Original Investigation

Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Japanese Patients 60 Years or Older With Atherosclerotic Risk Factors
A Randomized Clinical Trial

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Supplemental content at jama.com

IMPORTANCE Prevention of atherosclerotic cardiovascular diseases is an important public health priority in Japan due to an aging population.

OBJECTIVE To determine whether daily, low-dose aspirin reduces the incidence of cardiovascular events in older Japanese patients with multiple atherosclerotic risk factors.

DESIGN, SETTING, AND PARTICIPANTS The Japanese Primary Prevention Project (JPPP) was a multicenter, open-label, randomized, parallel-group trial. Patients (N = 14 464) were aged 60 to 85 years, presenting with hypertension, dyslipidemia, or diabetes mellitus recruited by primary care physicians at 1007 clinics in Japan between March 2005 and June 2007, and were followed up for up to 6.5 years, with last follow-up in May 2012. A multidisciplinary expert panel (blinded to treatment assignments) adjudicated study outcomes.

INTERVENTIONS Patients were randomized 1:1 to enteric-coated aspirin 100 mg/d or no aspirin in addition to ongoing medications.

MAIN OUTCOMES AND MEASURES Composite primary outcome was death from cardiovascular causes (myocardial infarction, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal myocardial infarction. Secondary outcomes included individual end points.

RESULTS The study was terminated early by the data monitoring committee after a median follow-up of 5.02 years (interquartile range, 4.55–5.33) based on likely futility. In both the aspirin and no aspirin groups, 56 fatal events occurred. Patients with an occurrence of nonfatal stroke totaled 114 in the aspirin group and 108 in the no aspirin group; of nonfatal myocardial infarction, 20 in the aspirin group and 38 in the no aspirin group; of undefined cerebrovascular events, 3 in the aspirin group and 5 in the no aspirin group. The 5-year cumulative primary outcome event rate was not significantly different between the groups (2.77% [95% CI, 2.40%-3.20%] for aspirin vs 2.96% [95% CI, 2.58%-3.40%] for no aspirin; hazard ratio [HR], 0.94 [95% CI, 0.77-1.15]; $P = .54$). Aspirin significantly reduced incidence of nonfatal myocardial infarction (0.30 [95% CI, 0.19-0.47] for aspirin vs 0.58 [95% CI, 0.42-0.81] for no aspirin; HR, 0.53 [95% CI, 0.31-0.91]; $P = .02$) and transient ischemic attack (0.26 [95% CI, 0.16-0.42] for aspirin vs 0.49 [95% CI, 0.35-0.69] for no aspirin; HR, 0.57 [95% CI, 0.32-0.99]; $P = .04$), and significantly increased the risk of extracranial hemorrhage requiring transfusion or hospitalization (0.86 [95% CI, 0.67-1.11] for aspirin vs 0.51 [95% CI, 0.37-0.72] for no aspirin; HR, 1.85 [95% CI, 1.22-2.81]; $P = .004$).

CONCLUSIONS AND RELEVANCE Once-daily, low-dose aspirin did not significantly reduce the risk of the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction among Japanese patients 60 years or older with atherosclerotic risk factors.

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The World Health Organization estimates that annual global mortality due to cardiovascular diseases (including myocardial infarction and stroke) will approach 25 million by 2030.[1] A recent study of secular trends in cardiovascular disease in Japan indicated that, from 1960 to 2000, the prevalence of smoking decreased and blood pressure control among hypertensive individuals improved significantly. Conversely, a steep increase in the prevalence of glucose intolerance, hypercholesterolemia, and obesity was observed,[2] probably due to the adoption of Western diets and lifestyles. Over this period, a decreasing trend in stroke incidence has slowed, and the incidence of myocardial infarction has not changed.[2] By 2030, it is estimated that 32% of the Japanese population will be 65 years or older.[3] This aging population, combined with the increasing prevalence of well-documented risk factors, means that the prevention of atherosclerotic disease remains an important public health challenge in Japan.

In 2009, the Antithrombotic Trialists' Collaboration (ATTC) reviewed the benefit-risk profile of low-dose aspirin for the primary prevention of vascular disease in a meta-analysis of 6 primary prevention trials. Use of low-dose aspirin was associated with a 12% proportional reduction in serious vascular events compared with no aspirin (annual event rate, 0.51% for aspirin and 0.57% for no aspirin; $P = .001$), mainly due to a reduction in nonfatal myocardial infarction of approximately 20%.[4] Aspirin increased major gastrointestinal and extracranial bleeding compared with control (annual increase, 0.10% for aspirin and 0.07% for control; $P < .001$).[4]

In Japan, the use of aspirin for primary prevention of ischemic heart disease has not been widespread.[5,6] The Japanese Primary Prevention Project (JPPP) was designed to determine whether once-daily, low-dose, enteric-coated aspirin reduces the total number of atherosclerotic events (ischemic heart disease and stroke) compared with no aspirin in Japanese patients 60 years or older with hypertension, dyslipidemia, or diabetes mellitus.

Methods

Patient Selection

Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Studies and was approved by the institutional review board of each participating center. Details of the study design and methods have been published previously.[7]

This multicenter, randomized, open-label, parallel-group clinical trial was conducted at 1007 clinics in the 47 prefectures of Japan that routinely offer outpatient care for hypertension, hyperlipidemia, or diabetes. Patients were recruited consecutively at each clinic by primary care physicians between March 2005 and June 2007. The last included patient completed follow-up in May 2012.

Patients were screened when they attended their local clinic on a routine visit if they were aged 60 to 85 years and had not been diagnosed with atherosclerotic disease. Patients were eligible if, at screening, they met Japanese guideline criteria for hypertension (systolic blood pressure [SBP] ≥140 mm Hg or diastolic blood pressure [DBP] ≥90 mm Hg),[8] dyslipidemia (total cholesterol ≥220 mg/dL or low-density lipoprotein [LDL] cholesterol ≥140 mg/dL or high-density lipoprotein [HDL] cholesterol <40 mg/dL or triglycerides ≥150 mg/dL; to convert total, LDL, and HDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113),[9] or diabetes mellitus (fasting morning blood glucose ≥126 mg/dL or any blood glucose ≥200 mg/dL or 2-hour blood glucose ≥200 mg/dL in the 75-g glucose tolerance test, or glycated hemoglobin ≥6.5%; to convert glucose to millimoles per liter, multiply by 0.0555).[10]

Key exclusion criteria were a history of coronary artery disease or cerebrovascular disease (including transient ischemic attack [TIA]), atherosclerotic disease requiring surgery or intervention, or atrial fibrillation (confirmed or suspected). Patients with peptic ulcer or conditions associated with bleeding (eg, von Willebrand disease) and those with serious blood abnormalities (eg, clotting factor deficiencies) were also excluded. In addition, patients with aspirin-sensitive asthma or those with a history of hypersensitivity to aspirin or salicylic acid could not participate, nor could patients who were receiving antiplatelet agents, anticoagulants, or long-term treatment with nonsteroidal anti-inflammatory drugs. The use of antiplatelet (eg, ticlopidine, cilostazol, dipyridamole, trapidil) and anticoagulant agents (eg, warfarin) was prohibited after enrollment.

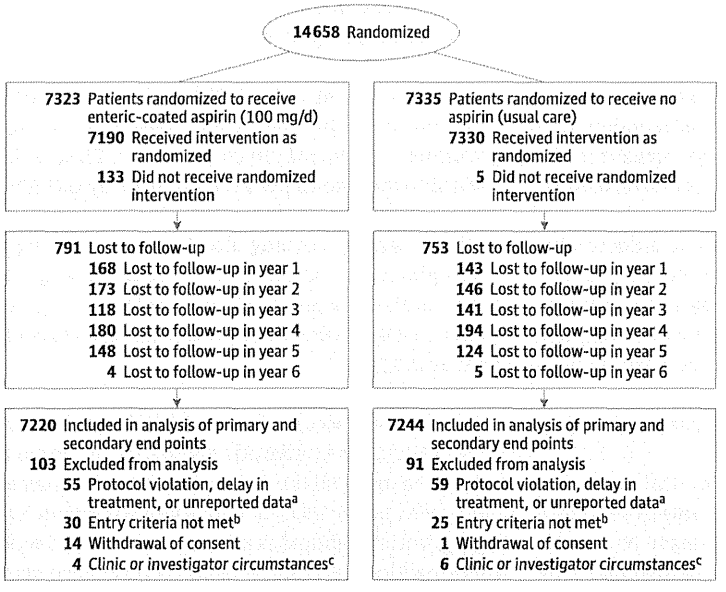
Study Design

Treatment to control hypertension, dyslipidemia, or diabetes (ie, the underlying risk factors for vascular events) was administered to all eligible patients at the screening visit and, in principle, throughout the study, in accordance with Japanese therapeutic guidelines.[9-11]

Approximately 1 month after the screening visit, patients returned for a baseline evaluation and were randomized 1:1 to receive either a 100-mg tablet of enteric-coated aspirin once daily or no aspirin, in addition to any ongoing medication (**Figure 1**). Randomization was stratified by the 3 underlying disease risk factors for atherosclerotic events (hypertension, dyslipidemia, or diabetes). Seven strata were used to account for all the different combinations of the 3 underlying disease risk factors because patients could have single or multiple risk factors (eg, diabetes mellitus, but no hypertension or dyslipidemia; diabetes and hypertension, but no dyslipidemia). The minimization method was applied to balance for sex and age within each stratum (eMethods in the Supplement). Pseudorandom numbers were generated using the Mersenne Twister method with a seed of 4989.[12] The study statistician generated the random allocation sequence using a central computerized system and study physicians were informed of treatment assignments via the study website or by fax.

At baseline and at each annual study assessment, the following variables were evaluated in the clinic when patients met

Figure 1. Flow of Patients Through the Japanese Primary Prevention Project (JPPP)



Data on patients assessed for eligibility are not available.

[a] Protocol violations (aspirin, n=19; no aspirin, n=22); delay in start of treatment (aspirin, n=10; no aspirin, n=15); unreported data by investigators in the clinics (aspirin, n=26; no aspirin, n=22).

[b] Reasons for not meeting inclusion criteria were serious blood abnormalities (aspirin, n = 2), history of prohibited drugs (aspirin, n = 12; no aspirin, n = 18), cerebrovascular disease (aspirin, n = 6; no aspirin, n = 7), atrial fibrillation (aspirin, n = 3), hypersensitivity to aspirin (aspirin, n = 3), peptic ulcer (aspirin, n = 2), atherosclerotic disease (aspirin, n = 1), or long-term use of nonsteroidal anti-inflammatory drugs (aspirin, n = 1).

[c] Clinic or investigator circumstances were closure of clinic and investigator death.

with the study physician: disease outcomes, adverse events, adherence with treatment (self-reported by patients), blood pressure, serum lipids, blood glucose, smoking status, and body weight.

To minimize loss of patients to follow-up, every effort was made to contact patients, including telephone calls, postcards, and visits from a traveling clinical research coordinator. Follow-up of patients ceased in the event of death or withdrawal of consent. If a patient was lost to follow-up because of death but the reason was unclear, the cause of death was established by obtaining the death certificate with permission from the Japanese government; this process was completed in April 2014.

The study was designed and overseen by a steering committee and decisions to amend or discontinue the study were made with advice from an independent data monitoring committee (DMC). Study end points were assessed centrally and biannually by an expert, multidisciplinary event adjudication committee that was blinded to treatment assignments in accordance with the Prospective Randomized Open Blinded Endpoint (PROBE) trial design.[13] A placebo-controlled study design was not used because the Japan Pharmaceutical Affairs Law limits the use of placebo in large, physician-led studies of approved products such as aspirin. Members of study committees and details of study clinic locations and investigators are provided in the eMethods in the Supplement.

Study End Points

The primary outcome was a composite of death from cardiovascular causes (myocardial infarction, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal myocardial infarction. The first secondary end point was also a composite that included the same events as the primary end point, plus TIA, angina pectoris, and arteriosclerotic disease requiring surgery or intervention. Other secondary end points were death from cardiovascular disease, death from noncardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), nonfatal myocardial infarction, TIA, angina pectoris, arteriosclerotic disease requiring surgery or intervention, and serious extracranial hemorrhage requiring transfusion or hospitalization.

Physicians at each study clinic diagnosed myocardial infarction according to the European Society of Cardiology and American College of Cardiology guidelines.[14] Imaging evidence of cerebral infarction or intracerebral hemorrhage accompanied by an acute regional neurological deficit maintained for 24 hours was required for a diagnosis of ischemic stroke.

The main assessment of safety was the secondary end point of serious extracranial hemorrhage requiring transfusion or hospitalization. However, data on the occurrence of the following prespecified gastrointestinal adverse events associated with aspirin were also collected for safety and tolerability analyses: gastrointestinal hemorrhage; gastroduodenal ulcer; reflux esophagitis; erosive gastritis; stomach or abdominal discomfort, pain, or pressure; heartburn; and nausea. The overall incidence of adverse events was not a primary or secondary end point of the study. Adverse events were classified according to the Medical Dictionary for Regulatory Activities (MedDRA; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), Japanese version 16.0J. Each clinic provided case report forms via the study website or faxed the forms to a central data center for input into the study database.

Statistical Analyses

Based on Japanese epidemiological and interventional studies,[15-23] annual mortality due to cardiovascular causes, nonfatal strokes, and myocardial infarction was expected to be approximately 1.5% to 2% in individuals not receiving aspirin. Accordingly, a sample size of 10 000 patients was determined to be sufficient to provide 80% power to detect a relative risk reduction of 20% in the aspirin group compared with the no aspirin group over a mean follow-up period of 4 years at a 2-sided significance level of $\alpha = .05$. However, a preplanned review at the first annual general examination in July 2006 showed that the incidence of primary outcome events (14 events among 6745 enrolled patients) was much lower than originally estimated.

Therefore, based on the reduced observed event rate, which determined both the sample size and the timing of the final study analyses, the sample size and study duration were reestimated. Assuming that the maximum frequency of events in both groups was 0.79%, it was estimated that enrollment in the study would need to be increased to 14 960 patients for 624 primary end point events to occur over an extended follow-up of up to 6.5 years. The final analyses were to be performed when 624 events had occurred if this was sooner than the maximum follow-up period of 6.5 years. Using these revised assumptions, a reduction in the annual frequency of events from 0.87% with no aspirin to 0.70% with aspirin would be required to detect a 20% difference between the aspirin and no aspirin groups at the $\alpha = .05$ significance level with 80% power.

The primary objective was to test the hypothesis that treatment with once-daily, low-dose aspirin significantly prolongs the time to occurrence of the composite primary end point event compared with no aspirin treatment. Accordingly, the null hypothesis was that the time until such an event does not differ significantly between the 2 study groups. Time until onset of events was estimated using the Kaplan-Meier method in each study group. Between-group differences in the primary end point were assessed using the stratified log-rank test in all patients meeting the inclusion criteria, with stratification for underlying disease (hypertension, dyslipidemia, or diabetes) and a 2-sided significance level of $\alpha = .05$. Hazard ratios (HRs) were calculated using the Cox proportional hazards model and 95% CIs were determined; there was no evidence of violation of proportionality. Adjustment for factors used in the allocation of patients to the study groups and biased background variables were incorporated as needed.

The same statistical methods were used to evaluate between-group differences for each of the secondary end points. Prospectively defined subgroup analyses of the composite primary outcome measure were conducted in subgroups of patients defined by disease and patient demographic risk factors. Interactions between each of the subgroups and aspirin treatment were assessed by the likelihood ratio test in the Cox model. The risk of a primary end point event was also compared between subgroups (eg, in patients with hypertension vs without hypertension) and an estimate of the relative risk of occurrence of a primary end point event (a "parameter estimate") was calculated for each subgroup using Cox regression fitted to the primary end point. A total risk score for an individual patient was then calculated as the sum of the risk factors. Based on the subgroup parameter estimates, men were allocated a rounded risk score value of +1; 70 years or older, +3; smoker, +1.5; hypertension, +1; and diabetes mellitus, +1.5. The primary end point event rate and HR for aspirin compared with no aspirin were then determined in patients with risk score of less than the median value (ie, patients considered at low risk of primary end point events) or more than the median value (ie, high-risk patients).

All primary, secondary, and subgroup analyses were assessed using a modified intention-to-treat population. A modified population was used because a post hoc central assessment had to be performed after randomization to ensure that all randomized patients were eligible for, and actively participating in, the study. As a result of this assessment, the modified intention-to-treat population excluded the following patients: those who were randomized in error (did not meet the study entry criteria or had withdrawn consent), patients who could not be followed up owing to investigator or clinic circumstances (death of investigators or clinical closures), and patients with certain major systematic protocol violations or deviations. Protocol violations included lack of adherence to allocation by the site investigator and patients who had no follow up after randomization and for whom survival status could not be established; protocol deviation was delay in treatment initiation. Patients who were lost to follow-up were treated as censored cases at the last date at which survival had been verified if no primary or secondary end point event had occurred; missing data were not imputed.

The incidence of gastrointestinal adverse events was estimated in the randomized population using the precise CIs determined from the binomial distribution, and between-group differences were tested using the Fisher exact method. All statistical analyses were performed using SAS (SAS Institute), version 9.4.

Interim Analysis and Guidelines for Study Discontinuation

The independent DMC, which included medical experts and a statistician, regularly monitored the results of the trial in a blinded manner. Interim analyses were conducted at yearly intervals between 6 months after the end of patient enrollment and the final study analysis. Following review of each interim analysis, the DMC assessed whether the study should proceed or whether the study protocol should be amended. The study was to be discontinued if a significant difference in favor of aspirin compared with no aspirin was demonstrated for the primary end point at any of the interim analyses time points or if the DMC judged that there was very low likelihood of observing a significant difference if the study was continued.[7] The DMC could also recommend study discontinuation owing to the occurrence of unexpected or serious adverse reactions or an incidence of adverse reactions that was higher than expected, although there were no formal conditions for such decisions. The

other prespecified criteria for discontinuing the study or amending the protocol were publication of similar study results and ethical issues generated by changes in the social environment.

Table 1. Baseline Characteristics for Japanese Patients Receiving Aspirin or No Aspirin (Modified Intention-to-Treat Population)

	Aspirin (n = 7220)	No Aspirin (n = 7244)
Patient demographics		
Age, mean (SD), y	70.6 (6.2)	70.5 (6.2)
Age, No. (%)		
<70 y	3234 (44.8)	3259 (45.0)
≥70 y	3986 (55.2)	3985 (55.0)
Men, No. (%)	3055 (42.3)	3068 (42.4)
Waist circumference, mean (SD), cm	85.2 (9.9)	84.7 (10.0)
Weight, mean (SD), kg	58.7 (10.4)	58.6 (10.3)
BMI ≥25, No. (%)	2644 (36.6)	2604 (35.9)
Risk factors for vascular events, No. (%)		
HT	6133 (84.9)	6145 (84.8)
DL	5198 (72.0)	5200 (71.8)
DM	2445 (33.9)	2458 (33.9)
HT and DL	4276 (59.2)	4264 (58.9)
DL and DM	1794 (24.8)	1798 (24.8)
HT and DM	1932 (26.8)	1939 (26.8)
HT, DL, and DM	1446 (20.0)	1442 (19.9)
BMI, mean (SD)	24.2 (3.5)	24.2 (3.4)
Blood pressure, mm Hg		
Systolic	137.1 (15.8)	137.2 (15.6)
Diastolic	77.7 (10.4)	77.6 (10.2)
Currently smoking, No. (%)	959 (13.3)	934 (12.9)
Family history of premature CV disease, No. (%)		
No	4058 (56.2)	4086 (56.4)
Yes	1981 (27.4)	1982 (27.4)
Unknown	1181 (16.4)	1176 (16.2)
Laboratory values, mean (SD)		
Cholesterol, mean (SD), mg/dL		
Total	202.9 (32.9)	203.6 (32.5)
Low-density lipoprotein[a]	119.2 (30.5)	119.8 (30.3)
High-density lipoprotein	57.8 (15.8)	58.2 (15.7)
Triglycerides, mean (SD), mg/dL	132.8 (76.0)	131.0 (75.9)
Fasting blood glucose, mean (SD), mg/dL	107.8 (31.2)	107.7 (32.0)
HbA_{1c}, mean (SD), %[b]	6.1 (1.0)	6.0 (1.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CV, cardiovascular; DL, dyslipidemia; DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin; HT, hypertension.

SI conversion factors: To convert total, LDL, and HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; glucose to mmol/L, multiply by 0.0555.

[a] Calculated based on the Friedewald formula and direct measurements.

[b] National Glycohemoglobin Standardization Program method.

Results

Patients

A total of 14 658 patients were randomized between March 2005 and June 2007, and all were included in the safety analyses. For analyses of the primary and secondary end points, 194 patients (1.3%) were excluded from the randomized population owing to protocol violations or deviations (untraceable patients, nonadherence, or delayed start of treatment), not meeting the inclusion criteria, withdrawal of consent, or clinic or investigator circumstances (Figure 1); the remaining 14 464 patients comprised the modified intention-to-treat population.

Baseline characteristics have been reported in detail previously and were balanced between the 2 study groups for patient demographics and disease risk factors.[7] The values reported in **Table 1** differ slightly from those reported previously because the modified intention-to-treat population had not been fixed at the time that the baseline characteristics were originally reported.

Based on the rate of primary end point events at the interim analyses in May 2008 and May 2011, the committee decided that the study was unlikely to show a difference in event rate if follow-up was continued for the maximum of 6.5 years. At the time of the second interim analysis in May 2011, only 290 of the 624 estimated primary end point events (46.5%) had occurred and the estimated HR for aspirin vs no aspirin was 0.95 (99.80% CI, 0.66-1.37). Therefore, the study was terminated prematurely owing to futility; it was judged that statistical power to detect a between-group difference in the primary end point would not be reached and continuing could put participants at unnecessary risk of drug-related adverse events. At the recommendation of the DMC, the final analysis was conducted at the next annual study assessment when patients had been followed up for a median 5.02 years (interquartile range, 4.55-5.33 years); the median follow-up period was similar in the aspirin and no aspirin groups (5.01 years for aspirin and 5.02 years for no aspirin).

Most patients were adherent with aspirin therapy. A total of 88.9% of patients reported that they were adherent in year 1; this value decreased to 76.0% in year 5 (eTable 1 in the Supplement). In the no aspirin group, the proportion of patients who started to take daily low-dose aspirin increased each year from 1.5% in year 1 to 9.8% in year 5. Most patients did not receive medicines (antiplatelet or anticoagulant agents) that had been, in principle, prohibited after enrollment; however, the proportion of patients receiving these prohibited medications increased over time in both the aspirin group (1.3% in year 1, 10.5% in year 5) and the no aspirin group (1.4% in year 1, 10.4% in year 5) (eTable 1 in the Supplement).

Effectiveness

Composite Primary End Point

There was no statistically significant difference between the 2 groups in time to the primary end point—a composite of