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* (%).

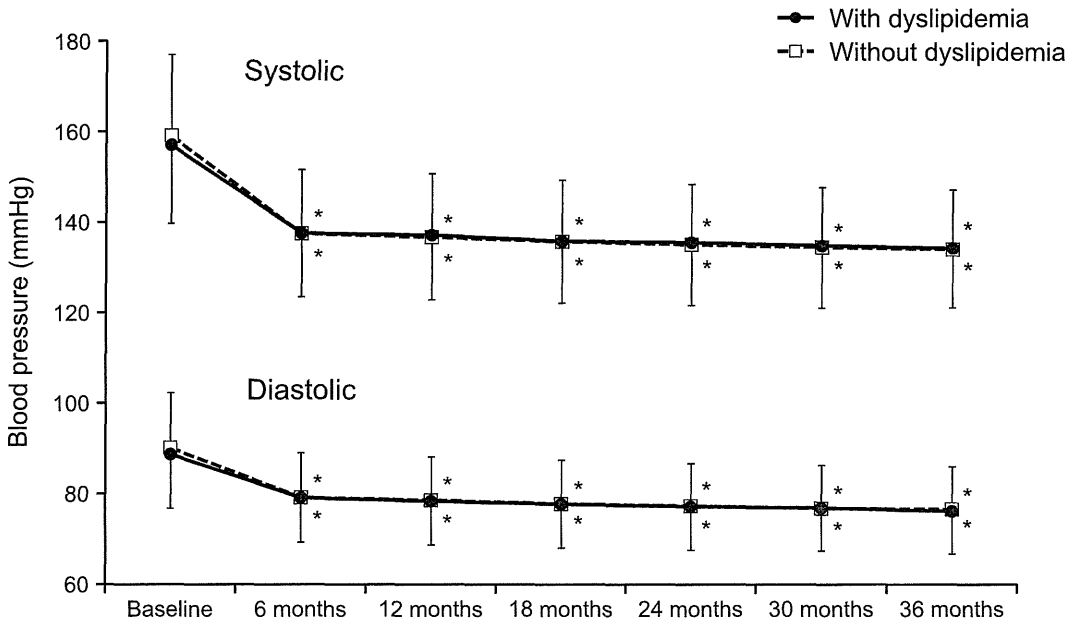

Fig. 2. Changes in blood pressure during the 36-month treatment period with olmesartan. $^*p<0.0001$ (versus just before the start of olmesartan treatment, Dunnett-Hsu test).

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,

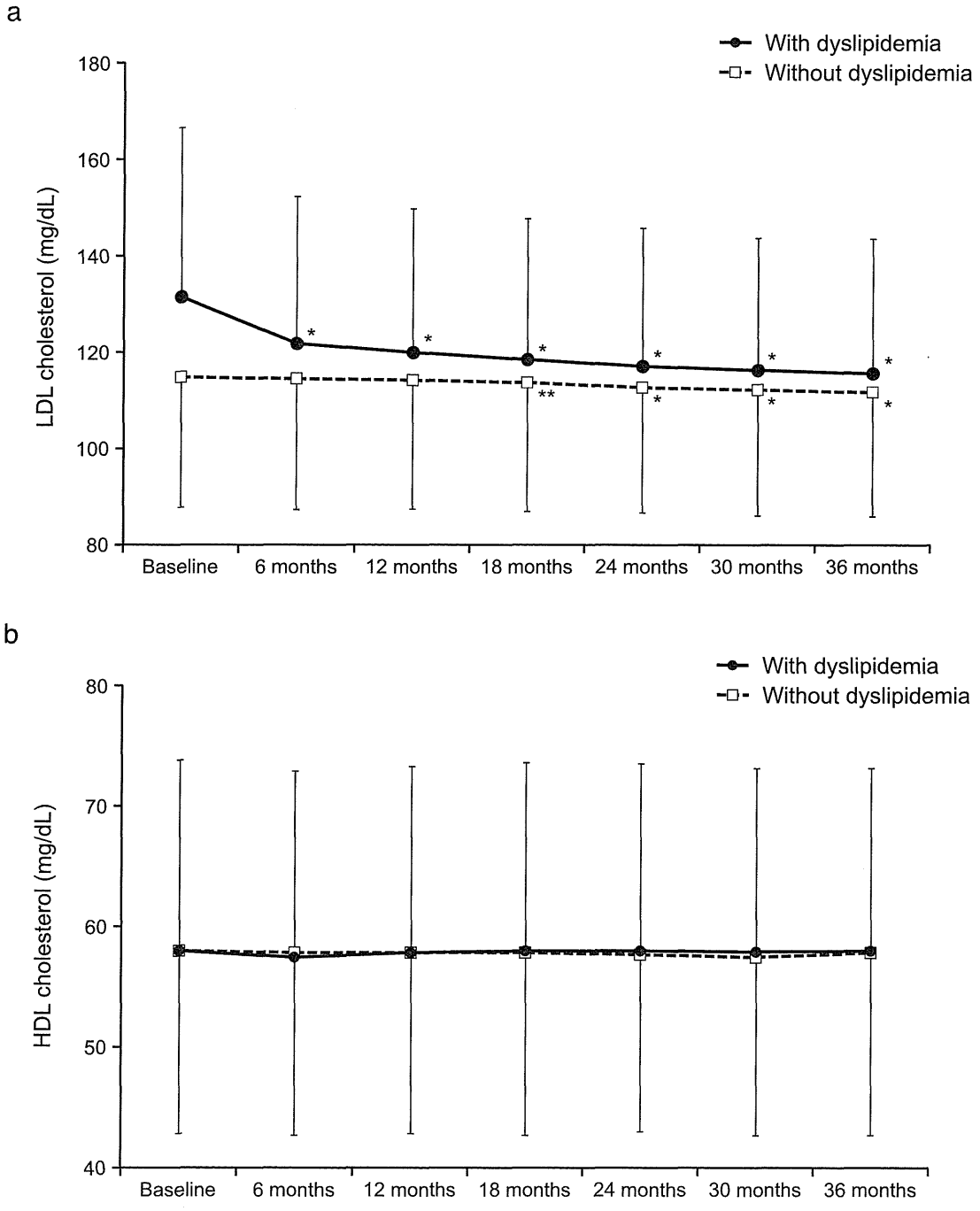

Fig. 3. Changes in the (a) low-density lipoprotein (LDL) cholesterol and (b) high-density lipoprotein (HDL) cholesterol levels during the 36-month treatment period with olmesartan. $^{*}p<0.0001$, $^{**}p<0.05$ (versus just before the start of olmesartan treatment, Dunnett-Hsu test).

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

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**).

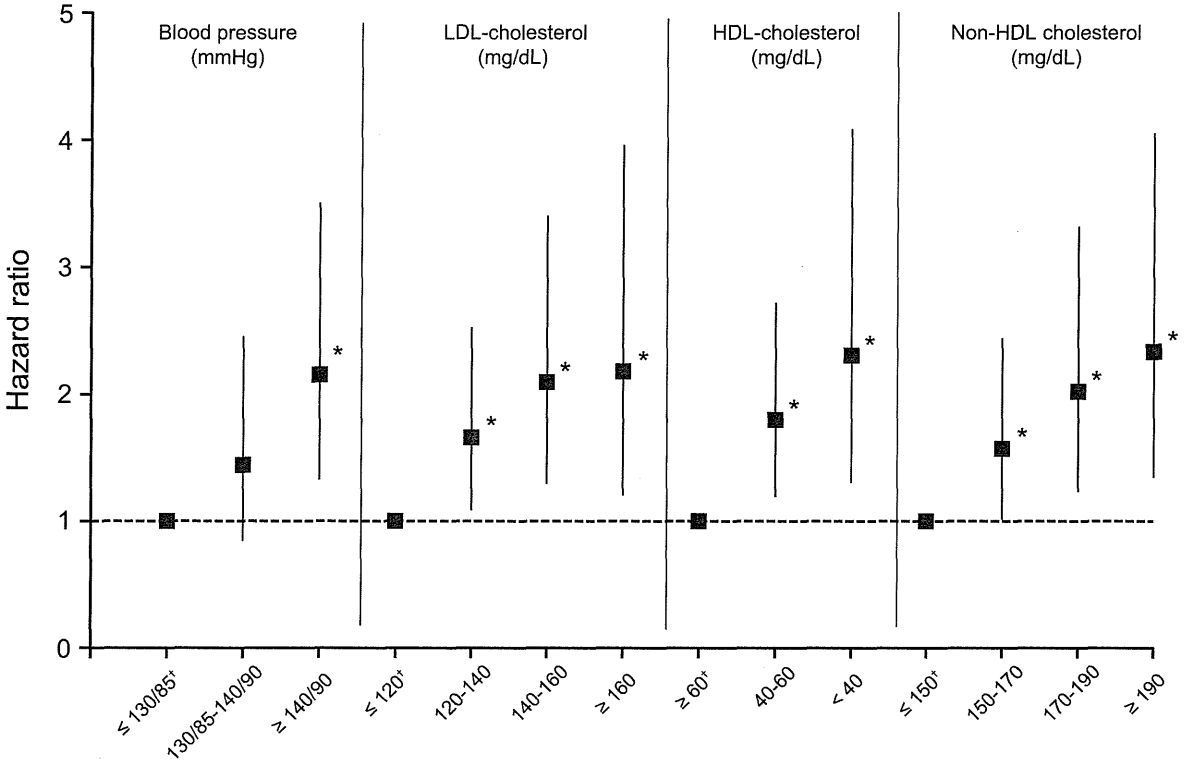

Fig. 4. Relationships between the mean achieved blood pressure, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and non-HDL cholesterol values and the risk of cardiovascular disease in the primary prevention population. *$p<0.05$, 95% confidence interval (Cox proportional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

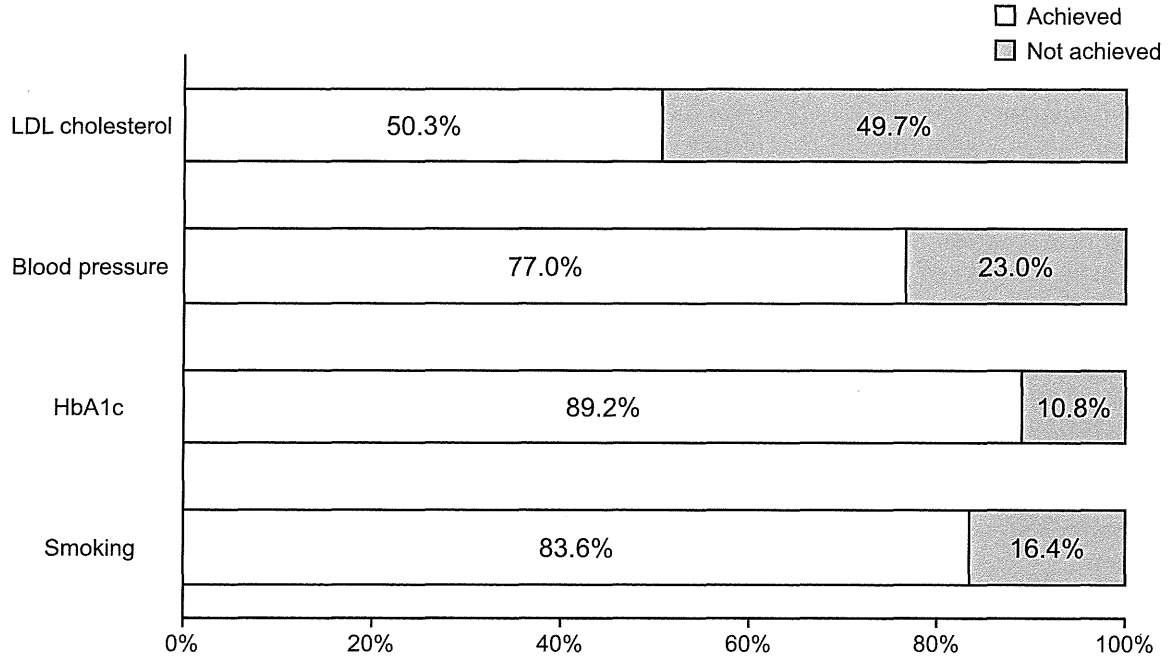

Fig. 5. Proportion of patients who achieved control of each risk factor in the group with three controlled risk factors. Criteria for controlled risk factors: LDL cholesterol, mean achieved value < 120 mg/dL; blood pressure, mean achieved value < 140/90 mmHg; hemoglobin A1c (National Glycohemoglobin 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

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.

Acknowledgments

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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.

Sources of Funding

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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Editorial page 2503

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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.

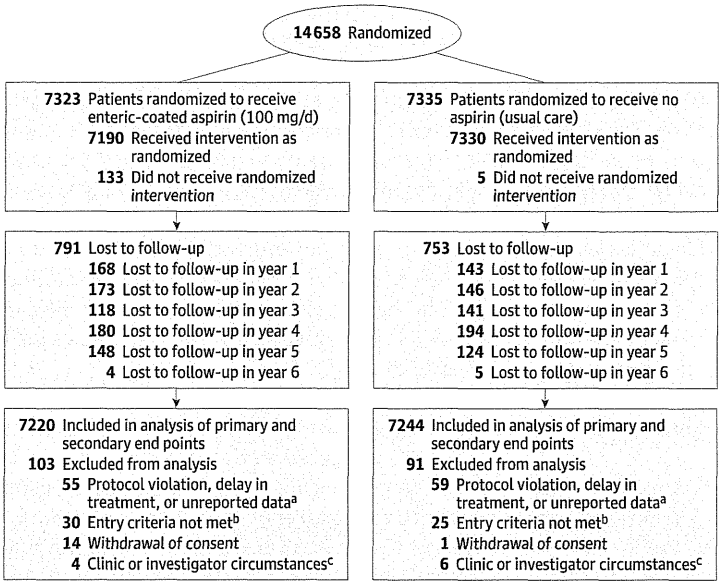
Study Design

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

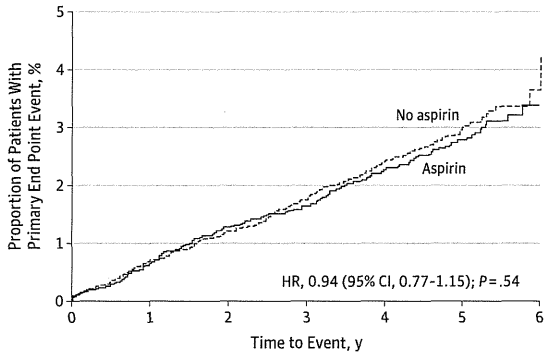
Composite Primary End Point

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

Table 2. Fatal and Nonfatal Events Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin or No Aspirin (Modified Intention-to-Treat Population)

	Aspirin (n = 7220)	No Aspirin (n = 7244)
Fatal events	56	56
Cerebral infarction	2	7
Intracranial hemorrhage	5	5
Subarachnoid hemorrhage	2	4
Myocardial infarction	7	9
Other fatal cardiovascular events	40	31
Nonfatal events	137	151
Cerebral infarction	83	94
Intracranial hemorrhage	23	10
Subarachnoid hemorrhage	8	4
Myocardial infarction	20	38
Undefined cerebrovascular events	3	5

Figure 2. Time to Primary End Point Composite Event[a] Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin vs No Aspirin (Modified Intention-to-Treat Population)



No. at risk

Aspirin	7220	7021	6771	6583	6322	3639	169
No aspirin	7244	7073	6861	6645	6359	3711	182

HR indicates hazard ratio. The *P* value was determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). The HRs were calculated using the Cox proportional hazards model.

[a] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), and nonfatal myocardial infarction.

death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction (**Table 2** and **Figure 2**). The estimated HR for aspirin vs no aspirin was 0.94 (95% CI, 0.77-1.15; *P* = .54). At 5 years after randomization, the cumulative primary event rate was similar in participants in the aspirin group (2.77% [95% CI, 2.40%-3.20%]) and those in the no aspirin group (2.96% [95% CI, 2.58%-3.40%]). Overall, few deaths from cardiovascular causes or nonfatal stroke or myocardial infarction were reported with aspirin (n = 193) or no aspirin (n = 207) (Table 2).

Assessment of the primary end point in subgroups of patients defined by the presence or absence of 8 different disease or demographic risk factors (hypertension, dyslipidemia, diabetes mellitus, male sex, aged at least 70 years, body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] of 25 or higher, smoking, or family history of premature cardiovascular disease) did not reveal significant differences between study groups; detailed results from these subgroup analyses are reported in **Figure 3**.

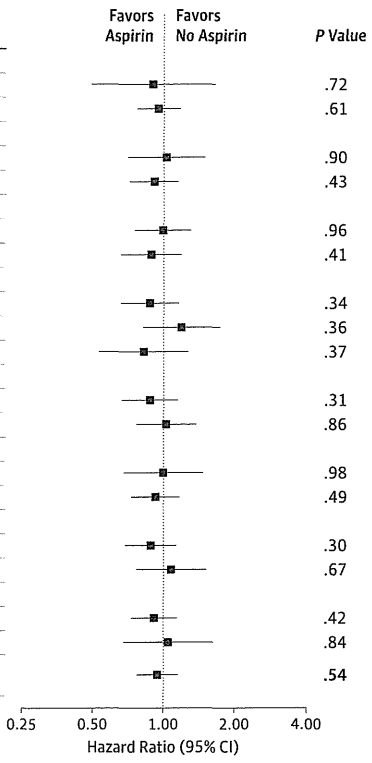
Regression analyses indicated that the risk of a primary end point event was higher in patients 70 years or older vs those younger than 70 years (parameter estimate, 0.92; HR, 2.51 [95% CI, 2.00-3.14]; *P* < .001), in patients with diabetes mellitus vs those without diabetes mellitus (parameter estimate, 0.52; HR, 1.68 [95% CI, 1.38-2.06]; *P* < .001), in patients who were smoking vs nonsmoking (parameter estimate, 0.53; HR, 1.70 [95% CI, 1.31-2.20]; *P* < .001), in men vs women (parameter estimate, 0.34; HR, 1.41 [95% CI, 1.14-1.74]; *P* = .002), and in patients with hypertension vs those without hypertension (parameter estimate, 0.42; HR, 1.52 [95% CI, 1.10-2.09]; *P* = .01). The risk of a primary end point event was not increased in patients with dyslipidemia vs those without dyslipidemia (parameter estimate, 0.13; HR, 1.13 [95% CI, 0.91-1.42]; *P* = .27) or in patients with a BMI of 25 or higher vs those with a BMI lower than 25 (parameter estimate, -0.13; HR, 0.88 [95% CI, 0.72-1.09]; *P* = .24). The risk of a primary end point event was also not significantly lower with aspirin vs no aspirin, irrespective of whether patients had a risk score lower than 4 (1.53% [95% CI, 1.14%-2.05%] for aspirin vs 1.47% [95% CI, 1.08%-1.98%] for no aspirin; HR, 1.09 [95% CI, 0.72-1.63]; *P* = .69) or a risk score of 4 or higher (3.79% [95% CI, 3.21%-4.46%] for aspirin vs 4.19% [95% CI, 3.59%-4.90%] for no aspirin; HR, 0.90 [95% CI, 0.72-1.13]; *P* = .35).

Secondary Outcomes

When TIA, angina pectoris, and arteriosclerotic disease requiring surgery or intervention were added to the composite primary end point, the difference between the aspirin group (event rate, 4.00% [95% CI, 3.55%-4.50%]) and no aspirin group (event rate, 4.59% [95% CI, 4.11%-5.13%]) remained nonsignificant (HR, 0.89 [95% CI, 0.75-1.04]; *P* = .14) (**Figure 4**). There were also no significant differences between the 2 study groups for time to any cause of death (event rate, 4.29% [95% CI, 3.83%-4.82%] for aspirin vs 4.11% [95% CI, 3.66%-4.62%] for no aspirin; HR, 0.99 [95% CI, 0.85-1.17]; *P* = .93), death from cardiovascular disease (event rate, 0.86% [95% CI, 0.66%-1.12%] for aspirin vs 0.78% [95% CI, 0.60%-1.02%] for no aspirin; HR, 1.03 [95% CI, 0.71-1.48]; *P* = .89), death from causes other than cardiovascular disease (event rate, 3.46% [95% CI, 3.04%-3.94%] for aspirin vs 3.36% [95% CI, 2.94%-3.83%] for no aspirin; HR, 0.99 [95% CI, 0.82-1.18]; *P* = .87), nonfatal cerebrovascular disease (ischemic or hemorrhagic) (event rate, 1.65% [95% CI, 1.37%-1.99%] for aspirin vs 1.64% [95% CI, 1.36%-1.98%] for no aspirin; HR, 1.04 [95% CI, 0.80-1.34]; *P* = .78), angina pectoris (event rate, 0.66% [95% CI, 0.49%-0.89%] for aspirin vs 0.81% [95% CI, 0.61%-1.07%] for no aspirin; HR, 0.86 [95% CI, 0.58-1.28]; *P* = .46), and arteriosclerotic diseases requiring surgery or intervention (event rate, 1.08%

Figure 3. Hazard Ratios for Aspirin vs No Aspirin and Event Rates for the Primary Composite Outcome Measure[a] Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors (Modified Intention-to-Treat Population)

	Aspirin			No Aspirin				
Disease Risk Factor	No. of Events	No. of Patients	Event Rate per 5 Years, % (95% CI)	No. of Events	No. of Patients	Event Rate per 5 Years, % (95% CI)	Hazard Ratio (95% CI)	P Value
Hypertension								
No	20	1087	1.74 (1.08-2.80)	23	1099	2.12 (1.40-3.20)	0.90 (0.49-1.63)	.72
Yes	173	6133	2.95 (2.54-3.44)	184	6145	3.11 (2.68-3.60)	0.95 (0.77-1.17)	.61
Dyslipidemia								
No	56	2022	2.89 (2.21-3.78)	56	2044	2.93 (2.26-3.81)	1.02 (0.71-1.48)	.90
Yes	137	5198	2.73 (2.30-3.23)	151	5200	2.97 (2.52-3.50)	0.91 (0.72-1.15)	.43
Diabetes mellitus								
No	107	4775	2.30 (1.89-2.79)	109	4786	2.36 (1.95-2.86)	0.99 (0.76-1.30)	.96
Yes	86	2445	3.70 (2.99-4.58)	98	2458	4.14 (3.38-5.06)	0.89 (0.66-1.18)	.41
Family history[b]								
No	94	4058	2.44 (1.98-3.00)	109	4086	2.72 (2.24-3.30)	0.87 (0.66-1.15)	.34
Yes	61	1981	3.13 (2.42-4.03)	52	1982	2.83 (2.16-3.72)	1.19 (0.82-1.72)	.36
Unknown	38	1181	3.33 (2.41-4.59)	46	1176	4.01 (2.98-5.37)	0.82 (0.54-1.26)	.37
Sex								
Men	99	3055	3.42 (2.80-4.18)	114	3068	3.85 (3.19-4.65)	0.87 (0.67-1.14)	.31
Women	94	4165	2.30 (1.87-2.83)	93	4176	2.32 (1.88-2.85)	1.03 (0.77-1.37)	.86
Age, y								
<70	52	3234	1.67 (1.27-2.21)	53	3259	1.73 (1.31-2.28)	1.00 (0.68-1.46)	.98
≥70	141	3986	3.67 (3.10-4.34)	154	3985	3.98 (3.39-4.67)	0.92 (0.73-1.16)	.49
BMI								
<25	122	4576	2.75 (2.29-3.29)	141	4640	3.21 (2.71-3.79)	0.88 (0.69-1.12)	.30
≥25	71	2644	2.82 (2.22-3.57)	66	2604	2.53 (1.97-3.25)	1.08 (0.77-1.50)	.67
Smoker								
No	150	6261	2.48 (2.10-2.92)	167	6310	2.71 (2.32-3.17)	0.91 (0.73-1.14)	.42
Yes	43	959	4.76 (3.51-6.43)	40	934	4.69 (3.43-6.40)	1.05 (0.68-1.61)	.84
Overall	**193**	**7220**	**2.77 (2.40-3.20)**	**207**	**7244**	**2.96 (2.58-3.40)**	**0.94 (0.77-1.15)**	**.54**



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared). Data shown for the overall population and for subgroups defined by disease risk factor and by patient characteristics. The *P* values were determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). Hazard ratios were calculated using the Cox proportional hazards model.

[a] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), and nonfatal myocardial infarction.

[b] History of premature cardiovascular disease.

[95% CI, 0.86%-1.36%] for aspirin vs 1.24% [95% CI, 0.99%-1.55%] for no aspirin; HR, 0.89 [95% CI, 0.65-1.21]; *P* = .46) (Figure 4). However, compared with no aspirin, aspirin significantly reduced the risk of nonfatal myocardial infarction (event rate, 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 TIA (event rate, 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). Conversely, the risk of extracranial hemorrhage requiring transfusion or hospitalization was higher with aspirin than with no aspirin (event rate, 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).

Exploratory Analysis

A post hoc exploratory analysis was conducted at the time of study discontinuation (1 year after the second interim analysis) when 400 primary end point events had occurred. It showed that the predictive probability of reaching a significant difference in favor of aspirin over no aspirin was 28% if the study had continued until it was adequately powered (ie, 624 events had occurred).

Safety and Tolerability

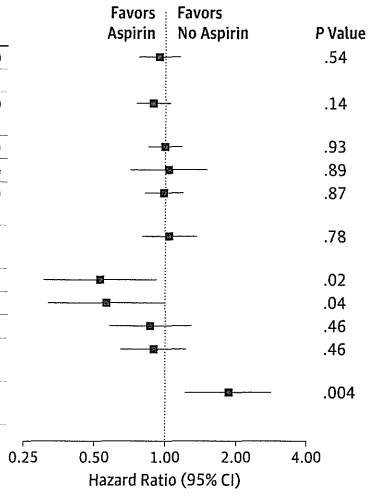
Analysis of gastrointestinal adverse events of interest indicated that these events were reported in a higher proportion of patients receiving daily low-dose aspirin than in those not receiving aspirin (**Table 3**).

Discussion

This study was designed to assess whether primary prevention with once-daily, low-dose aspirin would reduce the combined risk of death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction in Japanese patients (aged ≥60 years) with hypertension, dyslipidemia, or diabetes mellitus. The study was terminated early based on a futility assessment, but an exploratory analysis sug-

Figure 4. Hazard Ratios for Aspirin vs No Aspirin and Event Rates for Secondary End Points Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors (Modified Intention-to-Treat Population)

End Point	Aspirin (n = 7220) No. of Events	Aspirin (n = 7220) Event Rate Over 5 Years, % (95% CI)	No Aspirin (n = 7244) No. of Events	No Aspirin (n = 7244) Event Rate Over 5 Years, % (95% CI)	Hazard Ratio (95% CI)	P Value
Primary end point[a]	193	2.77 (2.40-3.20)	207	2.96 (2.58-3.40)	0.94 (0.77-1.15)	.54
Secondary end point						
Any atherosclerotic or cardiovascular event[b]	280	4.00 (3.55-4.50)	319	4.59 (4.11-5.13)	0.89 (0.75-1.04)	.14
Any cause of death	297	4.29 (3.83-4.82)	303	4.11 (3.66-4.62)	0.99 (0.85-1.17)	.93
Death from cardiovascular disease	58	0.86 (0.66-1.12)	57	0.78 (0.60-1.02)	1.03 (0.71-1.48)	.89
Death from causes other than cardiovascular disease	239	3.46 (3.04-3.94)	246	3.36 (2.94-3.83)	0.99 (0.82-1.18)	.87
Nonfatal cerebrovascular disease (ischemic or hemorrhagic)	117	1.65 (1.37-1.99)	114	1.64 (1.36-1.98)	1.04 (0.80-1.34)	.78
Nonfatal myocardial infarction	20	0.30 (0.19-0.47)	38	0.58 (0.42-0.81)	0.53 (0.31-0.91)	.02
Transient ischemic attack	19	0.26 (0.16-0.42)	34	0.49 (0.35-0.69)	0.57 (0.32-0.99)	.04
Angina pectoris	46	0.66 (0.49-0.89)	54	0.81 (0.61-1.07)	0.86 (0.58-1.28)	.46
Arteriosclerotic diseases requiring surgery or intervention	75	1.08 (0.86-1.36)	85	1.24 (0.99-1.55)	0.89 (0.65-1.21)	.46
Serious extracranial hemorrhage requiring transfusion or hospitalization	62	0.86 (0.67-1.11)	34	0.51 (0.37-0.72)	1.85 (1.22-2.81)	.004



Data shown for the overall population. The *P* values were determined using the log-rank test stratified for underlying disease (hypertension, dyslipidemia, or diabetes). Hazard ratios were calculated using the Cox proportional hazards model.

[a] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), and nonfatal myocardial infarction.

[b] Death from cardiovascular causes, nonfatal stroke (ischemic or hemorrhagic), nonfatal myocardial infarction, transient ischemic attack, angina pectoris, and arteriosclerotic disease requiring surgery or intervention.

Table 3. Incidence of Prespecified Gastrointestinal Adverse Events Among Older Japanese Patients With Multiple Atherosclerotic Risk Factors Receiving Aspirin or No Aspirin (Randomized Population)

	No. (%) [95% CI]		
	Aspirin (n = 7323)	No Aspirin (n = 7335)	*P* Value
Stomach/abdominal discomfort	335 (4.57) [4.11-5.08]	175 (2.39) [2.05-2.76]	<.001
Heartburn	202 (2.76) [2.40-3.16]	137 (1.87) [1.57-2.20]	<.001
Gastroduodenal ulcer	191 (2.61) [2.26-3.00]	91 (1.24) [1.00-1.52]	<.001
Stomach/abdominal pain	168 (2.29) [1.96-2.66]	81 (1.10) [0.88-1.37]	<.001
Reflux esophagitis	160 (2.18) [1.86-2.55]	125 (1.70) [1.42-2.03]	.04
Gastrointestinal hemorrhage	103 (1.41) [1.15-1.70]	31 (0.42) [0.29-0.60]	<.001
Erosive gastritis	89 (1.22) [0.98-1.49]	40 (0.55) [0.39-0.74]	<.001
Nausea	79 (1.08) [0.85-1.34]	50 (0.68) [0.51-0.90]	.01
Stomach/abdominal pressure	31 (0.42) [0.29-0.60]	21 (0.29) [0.18-0.44]	.17

gested a 28% probability of finding a significant difference in favor of aspirin had the study been continued through the planned number of events. Therefore, there remains a possibility that the statistically nonsignificant reduction in the risk of death from cardiovascular causes, nonfatal stroke, and nonfatal myocardial infarction was due to the study being inadequately powered, rather than an absence of beneficial effect of aspirin. However, even if the result had become statistically significant through prolongation of the study, the clinical importance of aspirin in the primary prevention of cardiovascular events would have been less than originally assumed. Therefore, it appears that aspirin is unlikely to show a clinically important benefit in the overall population included in this study. We plan to conduct further analyses to establish whether aspirin had beneficial effects in particular subgroups of patients or if there were beneficial effects with respect to cancer prevention.

Study limitations need to be considered. Assessments of between-group differences in any end point in this study were confounded by a decreasing level of adherence with daily low-dose aspirin in the aspirin group (dropping to 76% in year 5) and increasing uptake of daily aspirin in the no aspirin group (reaching 10% in year 5). In addition, the number of patients lost to follow-up could be considered a limitation of large trials conducted in a real-world setting. However, use of Kaplan-Meier time-to-event analyses limits the effect of missing data, and the proportion of patients lost to

follow-up in this study (10.5%) was consistent with that reported for an earlier Japanese study (7.6%) with a similar design, but a shorter follow-up period.[24] This earlier study, the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study[24] among patients with type 2 diabetes, also had lower than planned power (because of low event rates). It is possible that the low incidence of fatal and nonfatal cardiovascular events is due to the characteristics of Japanese patients. Compared with other relevant studies (eg, JPAD, the Prevention of Progression of Arterial Disease and Diabetes [POPADAD] study,[25] and the Aspirin for Asymptomatic Atherosclerosis Trial [AAAT][26]), baseline characteristics in the JPPP study are broadly similar, except for an apparent lower prevalence of current smoking in JPPP (13.1% in JPPP vs 21%-32% in the other studies) and a lower mean BMI compared with POPADAD (24.2 in JPPP vs 28.7-29.2 in POPADAD), although this is likely to reflect a Japanese population compared with a Western population, because BMI was similar in JPPP and JPAD.[25,26]

The PROBE study design could be considered a limitation, because it does not have all the advantages of a double-blind, randomized, placebo-controlled trial. However, adjudication of end points was performed centrally by an expert committee blinded to treatment assignments. The PROBE design does not control for lack of ascertainment.

Because the study participants were unblinded, it is possible that patients receiving aspirin were more likely to report adverse events believed to be related to aspirin treatment than those not receiving treatment. In addition, it is possible that enrollment in the study led to patients having more physician contact, resulting in better control of risk factors than the general population; if so, this might account for the low observed event rates.

It is likely that some deaths occurred among participants lost to follow-up. However, the potential effect of this under-ascertainment on the study outcomes is likely to be small. Similarly, although exclusion of nonadherent persons after randomization could have biased the findings away from the null (in either direction), the magnitude of any such bias would be expected to be small.

Hemorrhagic stroke is more common in Japanese populations than in Western populations.[27] In this study, no increase was observed in fatal hemorrhagic strokes (intracerebral and subarachnoid) for aspirin vs no aspirin. However, more patients treated with aspirin had nonfatal intracerebral hemorrhage (23 patients) or subarachnoid hemorrhage (8 patients) than those not receiving aspirin (10 patients for nonfatal intracerebral hemorrhage and 4 patients for subarachnoid hemorrhage).

More recent meta-analyses than the ATTC,[4] not using patient-level data, also included studies completed since 2009 (JPAD, POPADAD, and AAAT)[28-30] and suggested beneficial effects for aspirin in the primary prevention of cardiovascular events. In the meta-analysis performed by Raju and colleagues,[29] primary prevention with aspirin, compared with nonuse of aspirin, was associated with a reduction in all-cause mortality (relative risk [RR], 0.94 [95% CI, 0.88-1.00]), myocardial infarction (composite of fatal and nonfatal; RR, 0.83 [95% CI, 0.69-1.00]), ischemic stroke (RR, 0.86 [95% CI, 0.75-0.98]), and the composite of myocardial infarction, stroke, and cardiovascular death (RR, 0.88 [95% CI, 0.83-0.94]). Bartolucci and colleagues[28] reported in their meta-analysis that aspirin significantly decreased the risk of total cardiovascular events (odds ratio [OR], 0.87 [95% CI, 0.80-0.93]; $P = .001$) and nonfatal myocardial infarction (OR, 0.81 [95% CI, 0.67-0.99]; $P = .042$), compared with no aspirin. In the third meta-analysis, conducted by Seshasai and colleagues,[30] the association of aspirin (compared with no aspirin) with a significant reduction in the risk of cardiovascular events (OR, 0.90 [95% CI, 0.85-0.96]) was primarily accounted for by a large reduction in the risk of nonfatal myocardial infarction (OR, 0.80 [95% CI, 0.67-0.96]). No effect on fatal myocardial infarction was observed, but a modest nonsignificant reduction was apparent for all-cause mortality.

Despite inconsistent evidence for the benefit of aspirin in primary prevention of cardiovascular events, the benefits in secondary prevention are well documented, including in Japanese patients.[31-33] There is also a growing body of evidence to suggest benefits for aspirin in the prevention of colorectal and other cancers,[34,35] and the prevention of cancer recurrence, including in the Japanese population.[36] Reduction in the incidence of colorectal cancer may influence the overall benefit-risk profile of aspirin. Further analyses of the JPPP study data are planned, including analysis of deaths associated with cancers, to allow more precise identification of the patients for whom aspirin treatment may be most beneficial. In addition, other primary prevention studies using aspirin, such as ARRIVE,[37] ASCEND,[38] ASPREE,[39] and ACCEPT-D,[40] are in progress; however, these are being conducted in predominantly Western populations.

Conclusions

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.

ARTICLE INFORMATION

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Women

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan—2012 Version

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1. Age-Related Changes in Serum Lipids in Women

Age-related changes in the serum lipid levels significantly differ between men and women. The total cholesterol (TC) and LDL-cholesterol (LDL-C) levels are higher in men than in women until the fourth decade of life; however, these levels are higher in women than in men after the fifth decade of life due to menopause. The HDL-C levels in men decrease during puberty, while in women, these levels remain higher than those observed in men at any age. The triglyceride (TG) levels are lower in women than in men, particularly at younger ages[1].

2. Frequency of Cardiovascular Disease (CVD) in Japanese Women

Epidemiological studies conducted in Okinawa and Shiga have shown that the age-adjusted incidence of myocardial infarction in women 35 to 65 years of age is approximately 20% of that observed in men[2, 3]. In women, the incidence of coronary artery disease (CAD) increases after menopause; however, the risk is still lower than that observed in men. An epidemiological study conducted in 76 workplaces in Japan (the 3M study) found that the incidence of myocardial infarction in women in their 50s is approximately 20% of that observed in men[4]. The Vital Statistics collected by the Ministry of Health, Labour and Welfare also show that mortality from myocardial infarction in women is approximately 22% to 25% among women in their 50s, 25% to 33% among women in their 60s and 41% to 48% among women in their 70s compared with the rates observed in men[5]. Death from CAD in women is delayed by approximately 10 years compared with that observed in men at almost all ages[5, 6]. However, Japanese women live much longer than Japanese men, and the rate of mortality from myocardial infarction is increasing in older women[5]. Therefore, preventing CAD in Japanese women will become important in the near future.

The age-adjusted incidence of cerebral infarction in women is also lower than that observed in men. Epidemiological studies conducted in Okinawa and Shiga have shown that the incidence of cerebral infarction in women is approximately 50% of that observed in men[2, 7], while the Hisayama study reported that the incidence of this condition in women is approximately 75% of that observed in men[8]. Therefore, the difference in the incidence of cerebrovascular disease between men and women is smaller than that of myocardial infarction. According to the Vital Statistics compiled by the Ministry of Health, Labour and Welfare, the age-adjusted mortality due to cerebral infarction in women in 2008 was 64% of that observed in men[5]. Given that the incidence of cerebral infarction is higher than that of myocardial infarction in the general Japanese population and that the difference in the incidence of cerebral infarction between men and women is smaller than that of myocardial infarction, the prevention and management of cerebral infarction is also important in women.

3. Lifestyle Factors and CVD in Women

A 14-year follow-up of approximately 84,000 U.S. women (30 to 55 years of age at entry) found that the risk of CAD (nonfatal myocardial infarction + death from CAD) was significantly decreased to 0.4 in the women with three healthy lifestyle factors, including appropriate exercise, a negative history of smoking and proper dietary habits, compared with

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