Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial

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Summary

Background **Evidence-based treatment for hypercholesterolaemia in Japan has been hindered by the lack of direct evidence in this population. Our aim was to assess whether evidence for treatment with statins derived from western populations can be extrapolated to the Japanese population.**

Methods **In this prospective, randomised, open-labelled, blinded study, patients with hypercholesterolaemia (total cholesterol 5·69–6·98 mmol/L) and no history of coronary heart disease or stroke were randomly assigned diet or diet plus 10–20 mg pravastatin daily. The primary endpoint was the first occurrence of coronary heart disease. Statistical analyses were done by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT00211705.**

Findings **3966 patients were randomly assigned to the diet group and 3866 to the diet plus pravastatin group. Mean follow-up was 5·3 years. At the end of study, 471 and 522 patients had withdrawn, died, or been lost to follow-up in the diet and diet plus pravastatin groups, respectively. Mean total cholesterol was reduced by 2·1% (from 6·27 mmol/L to 6·13 mmol/L) and 11·5% (from 6·27 mmol/L to 5·55 mmol/L) and mean LDL cholesterol by 3·2% (from 4·05 mmol/L to 3·90 mmol/L) and 18·0% (from 4·05 mmol/L to 3·31 mmol/L) in the diet and the diet plus pravastatin groups, respectively. Coronary heart disease was significantly lower in the diet plus pravastatin group than in the diet alone group (66 events *vs* 101 events; HR 0·67, 95% CI 0·49–0·91; p=0·01). There was no difference in the incidence of malignant neoplasms or other serious adverse events between the two groups.**

Interpretation **Treatment with a low dose of pravastatin reduces the risk of coronary heart disease in Japan by much the same amount as higher doses have shown in Europe and the USA.**

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See **Comment** page 1135

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Introduction

Several large-scale primary and secondary prevention trials[1–10] have reported that cholesterol-lowering therapy can reduce the rates of the first occurrence and recurrence of coronary heart disease by about 20–40%. However, little is known of the relation between decreasing cholesterol concentrations and risk reduction for coronary heart disease in Japan, since many of the trials were done in countries with higher incidences of coronary heart disease than those seen in Japan.[11,12] Whether the results of clinical studies done outside Asia can be extrapolated to Japanese patients with hypercholesterolaemia is not known because of the differences in lifestyle and the incidence of coronary heart disease and stroke between Japan and western countries (about a third lower and two times higher, respectively).

This prospective randomised controlled trial was designed to assess the primary preventive effect of a statin against coronary heart disease in daily clinical practice in Japan. The dose of pravastatin used in this study is consistent with the approved dose in Japan and lower than the doses used in previous large-scale clinical trials done in western populations. Thus, the results from this trial will provide valuable guidance about the future treatment of hypercholesterolaemia in Japan.

Methods

Patients

The details of this prospective randomised, open-labelled, blinded-endpoint[13] study have been reported previously.[14] Briefly, men and postmenopausal women aged 40–70 years with a bodyweight of 40 kg or more and hypercholesterolaemia (total cholesterol concentration 5·69–6·98 mmol/L) were eligible for study enrolment between February, 1994, and March, 1999. Major exclusion criteria were familial hypercholesterolaemia and a history of coronary heart disease or stroke. Other exclusion criteria have been previously described.[14] Written informed consent was obtained from outpatients who met all the inclusion criteria. Subsequently, serum lipid concentrations were measured from these patients at a central laboratory to confirm eligibility for randomisation.

The trial was done in compliance with the ethical principles of the Declaration of Helsinki and the Japanese Ministry of Health, Labor and Welfare regulations for postmarketing surveillance.

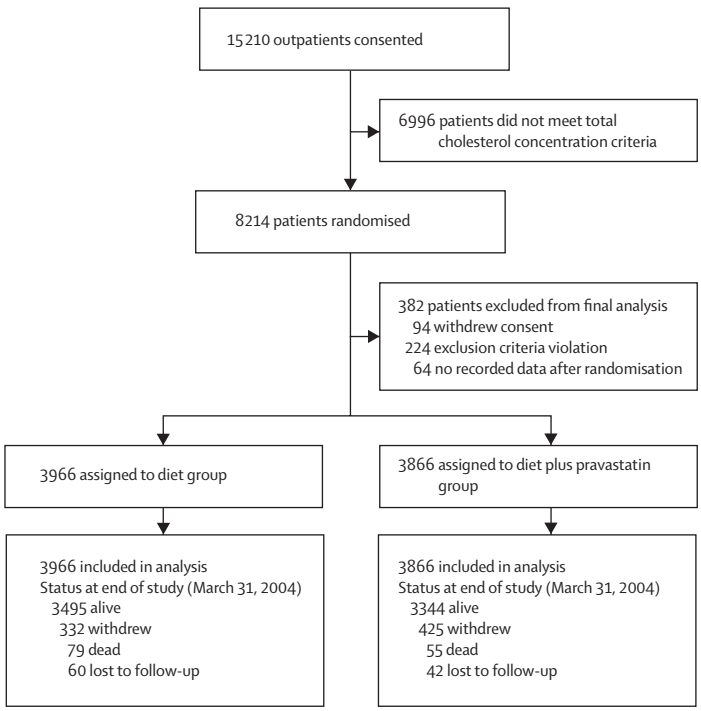

Figure 1: **Trial profile**

	Diet group (n=3966)	Diet plus pravastatin group (n=3866)
Demographics		
Age (years)	58·4 (7·2)	58·2 (7·3)
Women	2718 (69%)	2638 (68%)
Body-mass index (kg/m^2)	23·8 (3·0)	23·8 (3·1)
Systolic blood pressure (mm Hg)	132·4 (16·8)	132·0 (16·8)
Diastolic blood pressure (mm Hg)	78·8 (10·2)	78·4 (10·4)
Hypertension*	1664 (42%)	1613 (42%)
Diabetes*	828 (21%)	804 (21%)
Current/past smoker	791 (20%)	823 (21%)
Men	620 (50%)	660 (54%)
Women	171 (6%)	163 (6%)
Lipid concentrations		
Total cholesterol (mmol/L)	6.27 (0·31)	6·27 (0·31)
Triglyceride (mmol/L)†	1·44 (1·07–2·02)	1·44 (1·08–1·99)
HDL cholesterol (mmol/L)	1·49 (0·39)	1·49 (0·38)
LDL cholesterol (mmol/L)	4·05 (0·45)	4·05 (0·46)
Lipoprotein (a) (mmol/L)	0·88 (0·90)	0·88 (0·93)
Medications		
Antihypertensive drugs	1549 (39%)	1491 (39%)
Calcium-channel blockers	1048 (26%)	1017 (26%)
ACE inhibitors/ARB	512 (13%)	473 (12%)
β blockers	329 (8%)	318 (8%)
Diuretics	128 (3%)	111 (3%)
Aspirin	42 (1%)	36 (1%)

*Reported by physicians. †Data are median (IQR). All data are mean (SD) or number (%) unless otherwise indicated. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blockers.

Table 1: **Baseline characteristics**

Procedures

Eligible patients were randomly assigned either diet or diet plus pravastatin by computerised randomisation by the permuted-block method. Patients were stratified according to sex, age, and medical institution. The follow-up period was initially scheduled for 5 years; however, on the basis of recommendations from the data and safety monitoring committee, the study was continued for an additional 5 years to increase the number of events. Thus, patients who provided written consent at 5 years to continue the study were followed up until the end of March, 2004.

After randomisation, patients were followed up at months 1, 3, and 6 and thereafter every 6 months. At every visit, data on treatment compliance, concomitant use of other drugs, onset of events, occurrence of adverse events, and laboratory tests, including serum lipid, alanine aminotransferase, aspartate aminotransferase, and creatine kinase concentrations, were gathered by the investigators. Additionally, an electrocardiogram was obtained and assessed every year. At the end of the study, all events and adverse events were reconfirmed for all patients to ensure that case-report forms were accurate.

Patients in both groups were counselled to follow the National Cholesterol Education Program step I diet.[15] Treatment in the diet group was the step I diet throughout the study period. Physicians could prescribe mild hypolipidaemic drugs (eg, γ-oryzanol, riboflavin butyrate, pantethine) to patients in the diet group if they deemed that such treatment would be useful to prevent dropout. Treatment in the diet plus pravastatin group was started at 10 mg per day pravastatin. During follow-up, the dose of pravastatin could be adjusted by the treating physician, with uptitration to 20 mg per day if the total cholesterol concentration did not decrease to 5·69 mmol/L or less. This dose of pravastatin contrasts with the higher dose (20–40 mg) recommended in Europe and the USA. Patients in both groups who had total cholesterol concentrations above 6·98 mmol/L, even after alterations to the assigned treatment, could be switched to other aggressive treatments, including statin therapy. An independent data centre monitored the total cholesterol concentrations of all patients and alerted physicians if a patient's total cholesterol was high; treatment decisions for increasing the dose of pravastatin or changing the treatment were made by the patient's physician. Concomitant treatment for complications was not restricted in either group.

The primary composite endpoint was the first occurrence of coronary heart disease, which included fatal and non-fatal myocardial infarction, angina, cardiac and sudden death, and a coronary revascularisation procedure. Secondary endpoints included stroke, coronary heart disease plus cerebral infarction, all cardiovascular events, and total mortality. Data were gathered every 3–6 months and recorded on the case-report form by the patient's physician. All endpoints

were reviewed strictly by the endpoint committee, without knowledge of treatment allocations, and additional information obtained from the physician as needed. The endpoint criteria have been reported previously.[14]

Statistical analysis

The rationale for the sample size has been reported before.[14] Briefly, an incidence of fatal and non-fatal coronary heart disease of about 5·6 events per 1000 population per year and reductions in the rate of the composite coronary heart disease endpoint of 10% and 40% in the diet group and the diet plus pravastatin group, respectively, were assumed on the basis of health statistics data.[16] A sample size of 8000 individuals would have more than 80% power with α=0·10 (two-sided) and an assumed 20% dropout. Statistical analyses were done by intention to treat.[17]

Analysis sets were determined by the data review committee before the end of the study without knowledge of treatment allocation from prerandomisation patients' data to avoid the possibility of introducing bias. Time-to-event curves for the primary and secondary endpoints were estimated by the Kaplan-Meier method for the entire follow-up period in both groups. The log-rank test was used to compare the incidence of endpoints between the two groups. Hazard ratios and CI were estimated with the Cox's proportional hazards model. Subgroup analyses were done by much the same

	Year 1	Year 3	Year 5	Year 7	Year 9
Diet group					
Patients*	3814	3627	2604	455	237
Actual visits†	3705	3354	2291	447	222
No lipid-lowering drug	3070 (83%)	2398 (71%)	1518 (66%)	259 (58%)	115 (52%)
Pravastatin	311 (8%)	586 (17%)	520 (23%)	147 (33%)	86 (39%)
Other statin	20 (1%)	49 (1%)	43 (2%)	6 (1%)	5 (2%)
Other lipid-lowering drug	304 (8%)	321 (10%)	210 (9%)	35 (8%)	16 (7%)
Diet plus pravastatin group					
Patients*	3678	3473	2545	467	259
Actual visits†	3574	3251	2252	451	242
20 mg pravastatin	230 (6%)	461 (14%)	374 (17%)	114 (25%)	54 (22%)
15 mg pravastatin	4 (0·1%)	12 (0·4%)	10 (0·4%)	3 (0·7%)	3 (1%)
10 mg pravastatin	2896 (81%)	2322 (71%)	1522 (68%)	285 (63%)	152 (63%)
5 mg pravastatin	265 (7%)	207 (6%)	130 (6%)	15 (3%)	7 (3%)
Other statin	6 (0·2%)	7 (0·2%)	17 (0·8%)	3 (0·7%)	5 (2%)
Other lipid-lowering drug	14 (0·4%)	29 (1%)	22 (1%)	8 (2%)	5 (2%)
No lipid-lowering drug	159 (4%)	213 (7%)	177 (8%)	23 (5%)	16 (7%)

*Number at risk of total mortality. †Number of patients who visited the hospital. Any patients who fitted in several categories were assigned to upper category in the table.

Table 2: **Visit and medication compliances**

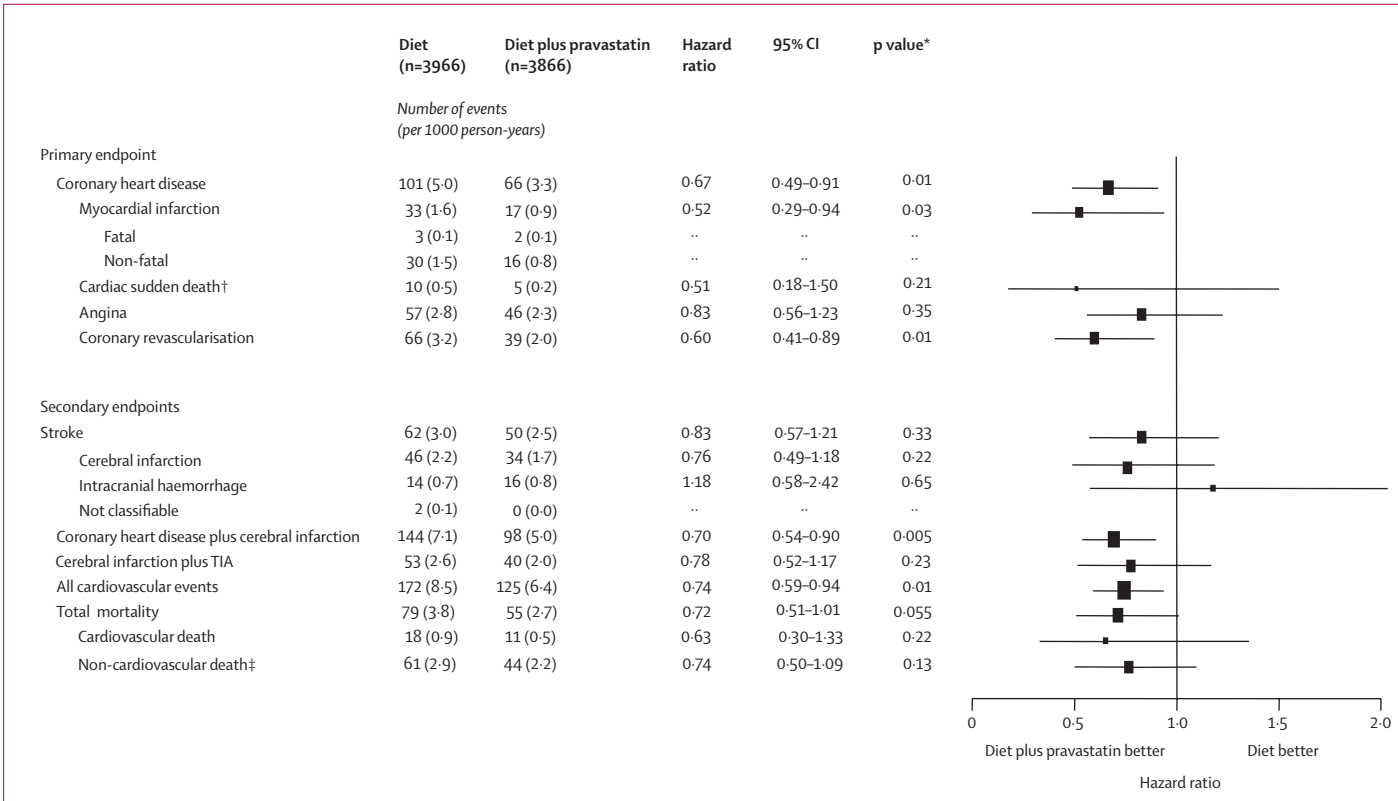

Figure 2: **Incidence of primary and secondary endpoints and Cox's proportional hazards for endpoints**

TIA=transient ischaemic attack. *p values based on log-rank test. †Cardiac/sudden death consists of death within 24 h for unknown reason. ‡Including unknown death (13 in diet group, four in diet plus pravastatin group). Bars represent the relative risk with 95% CI, and square size is proportional to the number of events for each endpoint.

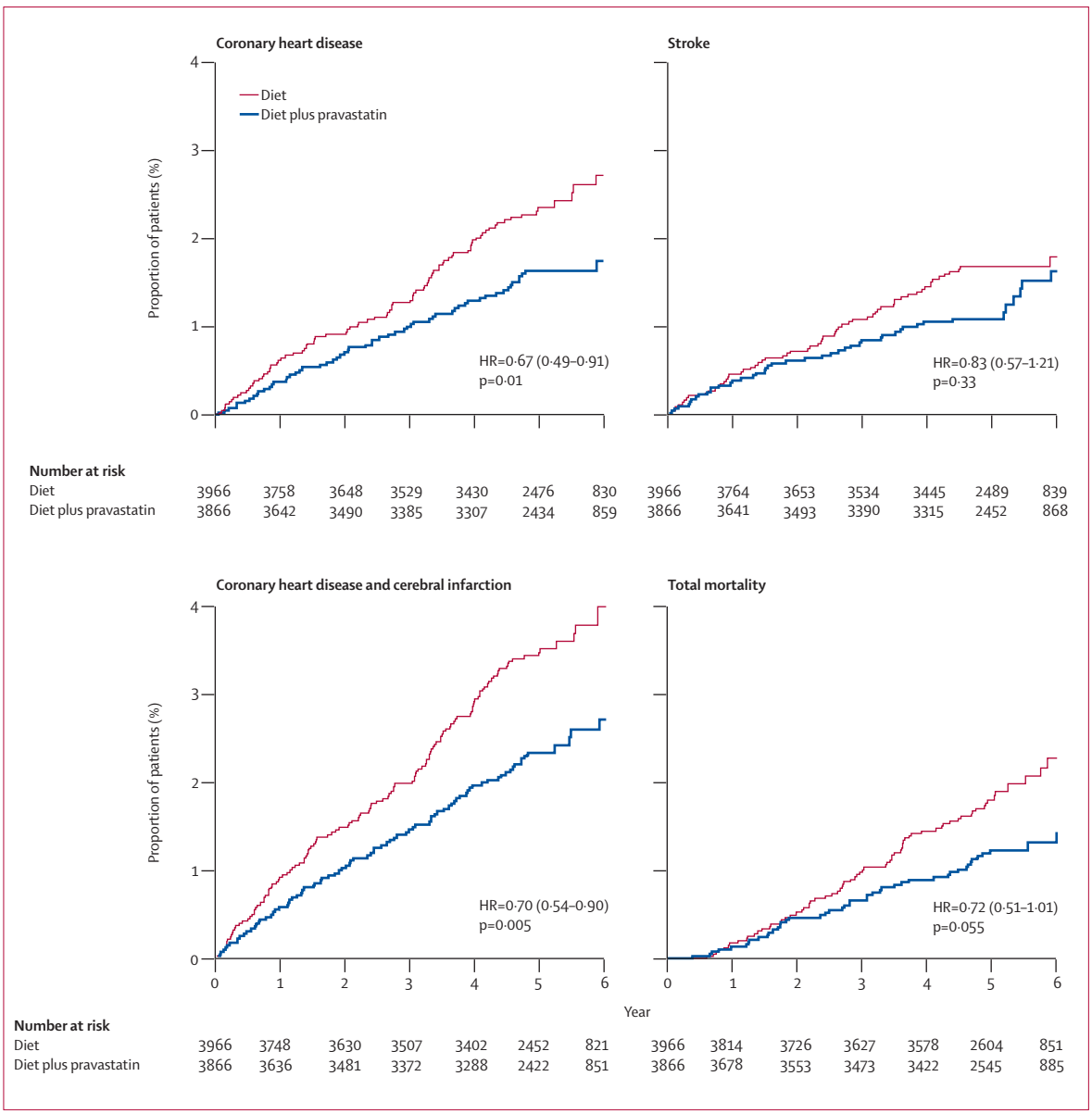

Figure 3: **Kaplan-Meier curves for the primary and secondary endpoints**

methods. The Cox's proportional hazards model was used to identify clinically relevant interactions between treatment and prognostic factors, including sex, age, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride concentrations, diabetes, hypertension, body-mass index, and whether the patient was a current or past smoker. Analyses were also done for the initially scheduled 5-year period to confirm consistency with all periods. All p values are two-sided. Statistical analyses were done with SAS version 8.2.

Three interim analyses were done in September, 2000, September, 2001, and September, 2002, in accordance with the predefined statistical analysis plan. Multiplicity of testing in the interim analyses of the primary and secondary endpoints was adjusted by the O'Brien-Fleming method.[18] An adjusted significance cut-off of 0·0495 was used for the primary and secondary endpoints at the final analysis.

The trial is registered at ClinicalTrials.gov, number NCT00211705.

Role of funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

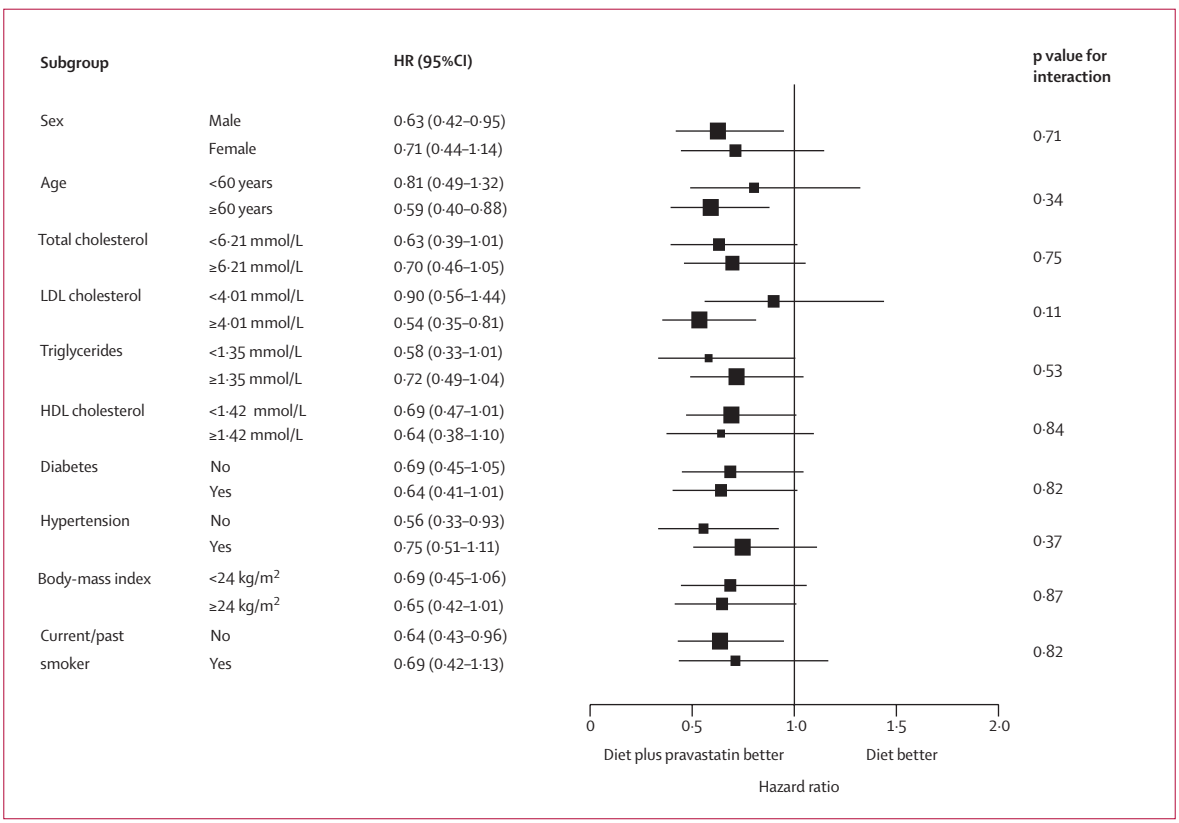

Figure 4: **Cox proportional hazards for coronary heart disease in pre-defined subgroups**
Bars represent the relative risk with a 95% CI, and square size is proportional to the number of events for every endpoint. p values for interaction test for heterogeneity of treatment across subgroups. History of diabetes and hypertension on the basis of physician diagnosis. Smoking habit included current and past smoking.

Results

Figure 1 shows the trial profile. Of 7832 patients who were analysed, 2223 consented and 1013 refused to extend follow-up. The remaining 4596 patients completed the study at 5 years. The baseline characteristics of the analysed patients are presented in table 1.

7730 (98·7%) study patients completed follow-up after 5 years or more, and no difference was seen in the number of patients followed in both groups. The follow-up period was 41 195 person-years (mean follow-up period 5·3 years). In the diet group, the proportion of patients who received a statin (mostly pravastatin) was 9%, 25%, and 41% at 1, 5, and 9 years, respectively. In the diet plus pravastatin group, 95%, 90%, and 89% of patients were receiving pravastatin as assigned at 1, 5, and 9 years, respectively (table 2). The mean dose of pravastatin was 8·3 mg. Concomitant use of medications, including antithrombotic, antihypertensive, and diabetes-control drugs, was much the same in both groups (data not shown).

Figure 2 shows the incidence of coronary heart disease in both groups during the average 5·3-year follow-up; Kaplan-Meier curves for the primary and secondary endpoints are presented in figure 3. The incidence of coronary heart disease was significantly lower in the diet plus pravastatin group than in the diet group (hazard ratio 0·67, 95% CI 0·49–0·91; p=0·01). The number needed to treat (NNT) to prevent one coronary heart disease event was 119 during the average 5·3 years follow-up. The frequency of myocardial infarction was also significantly lower in the diet plus pravastatin group than in the diet group (0·52, 0·29–0·94; p=0·03; NNT 255). Treatment with pravastatin was associated with a lower incidence of stroke than diet alone, although this difference was not significant (HR 0·83, 0·57–1·21; p=0·33).

To investigate the overall therapeutic effect of pravastatin on ischaemic cardiac and cerebral diseases, the incidence of coronary heart disease plus cerebral infarction was assessed (figure 2). The incidence of coronary heart disease and cerebral infarction was significantly lower with pravastatin than with diet alone (0·70, 0·54–0·90; p=0·005; NNT 91). The rates of all cardiovascular events were significantly lower in the diet plus pravastatin group than in the diet group (0·74, 0·59–0·94; p=0·01; NNT 91).

Although treatment with pravastatin was associated with lower total mortality than with diet alone, this result was not significant (0·72, 0·51–1·01; p=0·055; figure 2).

	5 years (35 962 person-years)				End of study (41 195 person-years)			
	Diet group	Diet plus pravastatin group	HR (95% CI)	p value	Diet group	Diet plus pravastatin group	HR (95% CI)	p value
Coronary heart disease	85 (4·8)	57 (3·3)	0·70 (0·50–0·97)	0·03	101 (5·0)	66 (3·3)	0·67 (0·49–0·91)	0·01
Number at risk*	2476	2434			223	249		
Coronary heart disease plus cerebral infarction	127 (7·1)	81 (4·7)	0·66 (0·50–0·87)	0·003	144 (7·1)	98 (5·0)	0·70 (0·54–0·90)	0·005
Number at risk*	2452	2422			223	243		
Stroke	61 (3·4)	38 (2·2)	0·65 (0·43–0·97)	0·03	62 (3·0)	50 (2·5)	0·83 (0·57–1·21)	0·33
Number at risk*	2489	2452			233	248		
Total mortality	66 (3·6)	43 (2·4)	0·68 (0·46–1·00)	0·048	79 (3·8)	55 (2·7)	0·72 (0·51–1·01)	0·055
Number at risk*	2604	2545			237	249		

*At 9 years for end of study. Data are number (cases per 1000 patient-years)

Table 3: **Major endpoints at 5 years and end of study**

Subgroup analysis of the risk reduction of coronary heart disease with pravastatin did not show significant interactions in any subgroup (figure 4).

We also investigated the major endpoints at 5 years to assess the effect of extending the trial in those patients who consented to continue. The incidences of coronary heart disease and coronary heart disease plus cerebral infarction were reduced by much the same amount at study end as they were at 5 years (table 3). However, at 5 years, but not at the end of the study, significant reductions were noted for stroke (p=0·03) and total mortality (p=0·048; table 3), although these data are from much smaller numbers of patients.

Table 4 shows changes in lipid concentrations over the course of the study. Significant reductions in mean total cholesterol and LDL-cholesterol concentrations were noted in the diet plus pravastatin group compared with the diet group (total cholesterol: –11% in the diet plus pravastatin group *vs* –2% in the diet group, p<0·0001; LDL cholesterol: –18% *vs* –3%, p<0·0001; table 4). The mean change in HDL-cholesterol concentrations was 5% and 2% and the median change in the triglyceride concentration was –7% and –2% in the diet plus pravastatin and diet groups, respectively (p<0·0001 for HDL cholesterol and p=0·0015 for triglyceride; table 4).

The incidence of cancers in both groups is shown in table 5. There was no significant difference between the two groups in the incidence or primary site of malignancy, or for the site of malignant neoplasms.

In the diet group, aspartate aminotransferase and alanine aminotransferase concentrations exceeded 100 IU/L in 55 (1·4%) and 104 (2·8%) of 3729 patients, respectively, in the diet group and 50 (1·3%) and 107 (2·8%) of 3869 patients, respectively, in the diet plus pravastatin group. Abnormal creatine kinase concentrations (>500 IU/L) were seen in 98 (2·6%) of 3738 patients in the diet group and 111 (3·1%) of 3629 patients in the diet plus pravastatin group during the entire follow-up period. No clinical difference between the two groups was reported for non-cardiovascular deaths (figure 2) or for serious adverse events (data not shown). No rhabdomyolysis occurred in either group (data not shown).

	Diet group	Diet plus pravastatin group	p*
Total cholesterol			
Baseline	6·27	6·27	
1 year	6·19 (–1%)	5·52 (–12%)	<0·0001
5 years	6·09 (–3%)	5·52 (–12%)	<0·0001
9 years	5·94 (–5%)	5·41 (–14%)	<0·0001
Mean of follow-up period	6·13 (–2%)	5·55 (–11%)	<0·0001
LDL cholesterol			
Baseline	4·05	4·05	
1 year	3·97 (–2%)	3·30 (–19%)	<0·0001
5 years	3·84 (–5%)	3·28 (–19%)	<0·0001
9 years	3·67 (–9%)	3·17 (–22%)	<0·0001
Mean of follow-up period	3·90 (–3%)	3·31 (–18%)	<0·0001
Triglyceride†			
Baseline	1·44	1·44	
1 year	1·33 (–8%)	1·24 (–14%)	<0·0001
5 years	1·30 (–10%)	1·25 (–13%)	0·0038
9 years	1·37 (–5%)	1·21 (–16%)	0·0092
Median of follow-up period	1·41 (–2%)	1·34 (–7%)	0·0015
HDL cholesterol			
Baseline	1·49	1·49	
1 year	1·51 (1%)	1·56 (5%)	<0·0001
5 years	1·57 (5%)	1·59 (7%)	<0·0001
9 years	1·53 (3%)	1·61 (8%)	0·0516
Mean of follow-up period	1·52 (2%)	1·56 (5%)	<0·0001

Data are mean concentration in mmol/L (percentage change from baseline), unless otherwise indicated. *Diet plus pravastatin *vs* diet. †Data are median concentration in mmol/L (percentage change from baseline).

Table 4: **Lipid concentrations over the course of the study**

Discussion

This study shows that low doses of pravastatin can reduce the risk of coronary heart disease in Japanese patients, despite only small to moderate reductions in total cholesterol and LDL-cholesterol concentrations.

Thus, in low-risk populations—eg, hypercholesterolaemic Japanese patients with high HDL cholesterol—less aggressive cholesterol-lowering therapy might be sufficient to produce a substantial and beneficial risk reduction for the primary prevention of coronary heart disease.

This trial, done exclusively in Asian patients, goes some way to address the lack of data for evidence-based decision making by physicians for such patients. Whether findings in non-Asian patients, with different lifestyles, body size, and genetics, could be extrapolated to Asian populations was unclear. Our results show that Asian people obtain a benefit from statin treatment of much the same size to that seen in non-Asian populations.

There are important differences between the population of patients presented here and those in previous prevention studies. At baseline, our patients had a higher mean HDL-cholesterol concentration than their counterparts in the West of Scotland Coronary Prevention study (WOSCOPS)[1] study and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS;[2] 1·49 mmol/L *vs* 1·14 mmol/L and 0·98 mmol/L, respectively). The HDL-cholesterol concentration was high in both men and women (1·37 mmol/L and 1·54 mmol/L, respectively), and mean body-mass index was within the normal range (body-mass index 26 in WOSCOPS, 27 in AFCAPS/TexCAPS). We enrolled a higher percentage of women (68·4%) than in WOSCOPS (0%) or AFCAPS/TexCAPS (15%). The clinical baseline characteristics of our patients are consistent with observational studies of statins done in Japan.[19,20]

Furthermore, the incidence of non-fatal or fatal myocardial infarction and cardiac or sudden death in the diet group during the mean 5·3-year follow-up was about a seventh of that reported in WOSCOPS[1] and a third of that noted in AFCAPS/TexCAPS[2] during a comparable length of follow-up. This difference is much the same as trends reported in previous country-by-country surveys of the onset of coronary heart disease: data from the American Heart Association show that Japan has the lowest rate of coronary heart disease mortality for men and women aged 35–74 years (53 and 17 per 100 000 person-years, respectively), whereas in Scotland (247 and 98 per 100 000 person-years, respectively) and the USA (187 and 77 per 100 000 person-years, respectively), is much higher.[12] Thus, the lower risk of coronary heart disease in this study population than in previous prevention trials is an important characteristic of this study. The low incidence of such disease could be a result of the larger number of women, the higher HDL-cholesterol concentrations, or the lower mean body-mass index in this study than in previous studies, as well as the traditional Japanese low fat, fish-rich diet.

	Diet group	Diet plus pravastatin group	HR (95% CI)	p value
All cancers	126 (10; 6·2)	119 (11; 6·0)	0·97 (0·76–1·25)	0·81
Gastrointestinal	65 (6; 3·2)	58 (1; 2·9)	0·91 (0·64–1·30)	0·62
Respiratory	13 (1; 0·6)	10 (1; 0·5)	0·80 (0·35–1·82)	0·59
Breast	15 (2; 0·7)	10 (2; 0·5)	0·69 (0·31–1·53)	0·35
Female genitourinary	10 (1; 0·7)	14 (5; 1·0)	1·45 (0·64–3·27)	0·37
Other	30 (2; 1·5)	30 (2; 1·5)	1·03 (0·62–1·71)	0·91

Data in diet group and diet plus pravastatin group columns expressed as number (number in first 6 months; cases per 1000 patient years). In Female genitourinary row, the incidence ratio was calculated on the basis of the number of women (2637 patients in the diet group, 2559 patients in the diet plus pravastatin group).

Table 5: **Incidence of cancers**

Our results show that all populations will benefit from the preventive effects of statin therapy, whatever the risk of coronary heart disease, even with high HDL-cholesterol concentrations at baseline. Furthermore, statins might provide benefit irrespective of various demographic factors, including age, baseline lipid concentrations, and complications including hypertension and diabetes on primary prevention (figure 4).[1,2,8] However, risk reduction in the subgroup of individuals with LDL-cholesterol concentrations of less than 4·01 mmol/L was low in the present study, so further analysis is necessary to investigate the effect of statins on individuals with low LDL-cholesterol concentrations.

In the present study, the risk of coronary heart disease was 33% lower in the pravastatin group than in the diet-only group; the absolute risk reduction was 0·8% (95% CI 0·2–1·5). The NNT to prevent one coronary heart disease event was 119. Although this number is higher than in previous statin trials,[1,2,10] it provides valuable information about the best therapeutic strategy for a low-risk population. Furthermore, the observed risk reduction was larger than expected in relation to the degree of reduction of total cholesterol or LDL cholesterol in previous trials. The Lipid Research Clinics Coronary Primary Prevention Trial[21,22] showed that a 1% decrease in total cholesterol represented about a 2% reduction in the risk of coronary heart disease. In this study, despite smaller reductions in total cholesterol and LDL cholesterol in the diet plus pravastatin group than in previous statin trials (which recorded reductions of 15–24% in total cholesterol and 23–35% in LDL cholesterol), the risk of coronary heart disease was substantially reduced. The reasons for this unexpected risk reduction, despite a dose of pravastatin that is half the dose administered to western patients, are unclear and require further examination. Possible reasons include chance, the synergistic effect of diet therapy, or pleiotropic effects of pravastatin. Furthermore, Japanese people could be especially sensitive to pravastatin therapy because of their diet, or a beneficial reduction in the risk of coronary heart disease might be achieved with a small reduction in lipids. Recent data from secondary prevention trials suggest that aggressive treatment with a high dose of

statin might substantially reduce the risk of coronary heart disease further.[23–25] Yet, for primary prevention, our results, and those of an analysis[26] that compared the risk reductions associated with different degrees of total cholesterol and LDL-cholesterol reduction in previous primary prevention trials, provide important information. Further work is needed to define the necessary reduction in total cholesterol and LDL cholesterol to achieve beneficial risk reductions in low-risk populations.

The risk of all atherosclerotic cardiovascular diseases was reduced by about 30%. At the end of the trial, the reduction in stroke was less than expected, and not significant; likewise, the decrease in total mortality was not significant. However, significant differences were seen for the reductions in these two endpoints at 5 years (table 3). The difference in reduction at 5 years and at the end of the trial for these endpoints is by contrast with the reductions in coronary heart disease alone and coronary heart disease plus cerebral infarction. For total mortality, the difference was subtle, and the result seemed to be much the same for the two time frames. However, for stroke, the possibility of a chance outcome cannot be ruled out. There were no apparent differences in characteristics of patients at baseline, and before or after obtaining patient consent for the extended study period, between the diet group and the diet plus pravastatin group. The high uptake rate after 5 years for statin use in those assigned diet only could have resulted in more conservative outcomes in this intention-to-treat analysis.

In view of discussions in many countries about the potential benefit of low-dose, over-the-counter statins to address the steadily rising incidence of coronary heart disease, the evidence presented here on the long-term safety of statin therapy and the significant benefit of a low-dose regimen on coronary heart disease is useful. Indeed, the recent approval by the US Food and Drug Administration of a generic version of pravastatin permits people at low risk of coronary heart disease to obtain the benefits of such treatment at a reasonable out-of-pocket cost; in the USA and European countries, insurance schemes do not permit free on-patent statins for these patients.

Members of The Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA)

Details of the members of the MEGA Study group are in the webappendix.

See Online for webappendix

Contributors

All authors contributed to the study design, conduct, and interpretation. The randomisation, data collection, and analysis were done by an independent data centre established by the contract research organisation. The report was written by the MEGA study publication committee, comprised of H Nakamura, N Nakaya, K Mizuno, and Y Ohashi. Y Ohashi was the study statistician.

Conflict of interest statement

All authors have received travel grants or speaking honoraria from Sankyo Co Ltd for this study. K Arakawa has stock in Sankyo. H Nakamura, K Arakawa, H Itakura, N Nakaya, S Nishimoto, M Muranaka, A Yamamoto, K Mizuno, and Y Ohashi have received lecture fees from Sankyo or from Merk-Banyu and Pfizer Japan Ltd.

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