European Heart Journal (2002) **23,** 207–215
doi:10.1053/euhj.2001.2775, available online at http://www.idealibrary.com on IDEAL®

Effects of pravastatin on mortality in patients with and without coronary heart disease across a broad range of cholesterol levels

The Prospective Pravastatin Pooling project

J. Simes[1], C. D. Furberg[2], E. Braunwald[3], B. R. Davis[4], I. Ford[5], A. Tonkin[6], J. Shepherd[5], for the Prospective Pravastatin Pooling project investigators

[1]*University of Sydney, Sydney, Australia;* [2]*Wake Forest University, Winston-Salem, NC, U.S.A.;* [3]*Brigham and Women's Hospital, Boston, Mass., U.S.A.;* [4]*University of Texas School of Public Health, Houston, Texas;* [5]*University of Glasgow, Glasgow, Scotland;* [6]*National Heart Foundation, Melbourne, Australia*

Aims To assess the effects of pravastatin on all-cause mortality and cause-specific mortality and to compare the effects for patients with prior coronary heart disease with those for patients without, using pooled data from the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, the Cholesterol and Recurrent Events (CARE) study, and the West of Scotland Coronary Prevention Study (WOSCOPS).

Methods and Results 13 173 patients with coronary heart disease and 6595 men with elevated cholesterol and no prior coronary disease received pravastatin, 40 mg daily, or placebo for an average of 5 to 6 years. Data were analysed according to a pre-specified, published protocol. For all three trials combined, the mortality among patients assigned pravastatin was significantly lower, at 7·9%, than the 9·8% among those assigned placebo, a relative risk reduction of 20% (95% confidence interval (CI) 12–27%, $P<0·0001$). Active treatment was associated with a reduction in coronary mortality (24%, 95% CI 14–33%). Larger reductions in absolute risk were estimated in those with prior coronary heart disease than in those without.

Conclusion Treatment with pravastatin over 5 years reduces all-cause mortality and coronary mortality in patients with and those without a history of coronary heart disease. The size of the benefit was related principally to the baseline risk.
(Eur Heart J, 2002; 23: 207–215, doi:10.1053/euhj.2001. 2775)

Key Words: Lipids, mortality, meta-analysis, clinical trial, coronary disease, cholesterol.

See page 183, doi: 10.1053/euhj.2001.2959 for the Editorial comment on this article

Introduction

Epidemiological studies have provided strong evidence of a continuous association between cholesterol concentration and the risk of subsequent coronary heart disease events[1,2]. Early trials using treatments with modest effects on lipids had shown significant reductions in such events[2,3]. However, the effect of treatment on mortality had remained uncertain, particularly for patients with average or below-average cholesterol levels, and for patients with a history of coronary heart disease.

Large-scale trials have now evaluated the effects of HMG-CoA reductase inhibitors across a broad spectrum of patients with or without elevated cholesterol levels and with or without a history of coronary heart disease[4–8]. Three of these trials used common trial designs and the same treatment, pravastatin[5–7].

The Prospective Pravastatin Pooling project, initiated in 1992, was designed to provide more reliable estimates

Revision submitted 1 May 2001, accepted 2 May 2001, and published online 22 August 2001.

The Prospective Pravastatin Pooling Project is funded by an investigator-initiated grant from Bristol-Myers Squibb to Wake Forest University.

Correspondence: Professor John Simes, NHMRC Clinical Trials Centre, Mallett Street Campus, University of Sydney, NSW 2006, Australia.

0195-668X/02/030207+09 $35.00/0

Table 1 Prospective Pravastatin Pooling project: baseline characteristics

Factor		LIPID n=9014 %	CARE n=4159 %	WOSCOPS n=6595 %	Total n=19 768 %
Age (years)*		62 (55,67)	60 (52,66)	55 (51,60)	59 (52,64)
Age group					
<55		23	32	49	34
55–64		38	37	50	42
65–69		24	19	1	15
≥70 yrs		15	12	0	9
Female		17	14	0	11
History of CHD					
Stable angina		50	21	5†	29
Unstable angina (no MI)‡		36	0	0	17
Prior MI‡		64	100	0	50
Diabetes mellitus		9	14	1	7
Current smoker		10	16	35	20
Hypertension history		42	43	16	33
Lipids					
Total cholesterol					
mmol . l^{-1}	mg . dl^{-1}				
<5·5	<213	43	56	0	31
5·5–6·4	213–249	40	44	16	33
≥6·5	≥250	17	0	84	36
LDL cholesterol					
<3·5	<135	30	42	0	22
3·5–4·4	135–174	50	58	17	41
≥4·5	≥175	20	0	83	37
HDL cholesterol					
<1·0	<39	63	57	31	51
≥1·0	≥39	37	43	69	49
Triglycerides					
<1·5	<133	45	42	39	42
1·5–2·4	133–219	37	43	43	41
≥2·5	≥220	18	15	18	17

*Median (25th, 75th percentile).
†Based on positive response to Rose questionnaire.
‡Prior MI 3 to 36 months before enrolment (LIPID) or 2 to 3 months before randomization (CARE). Unstable angina refers to hospitalization for unstable angina without MI during the qualifying period.
CHD=coronary heart disease, MI=myocardial infarction, LDL=low-density lipoprotein, HDL=high-density lipoprotein.

of pravastatin treatment on all-cause mortality, coronary heart disease mortality, and total coronary heart disease events in different populations by pooling the data from three large-scale trials: the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study,[7] the Cholesterol and Recurrent Events (CARE) study[6] and the West of Scotland Coronary Prevention Study (WOSCOPS)[5]. Collectively, these studies provided data on 19 768 patients, 106 131 person-years of follow-up and 1748 deaths. This paper describes the effects of treatment on all-cause and cause-specific mortality according to pre-specified objectives[9].

Design and methods

Study design

The overall project aim was to assess the effect of pravastatin on mortality, coronary heart disease morbidity and other specific events, overall and within important subgroups. This paper reports the effects on total mortality and cause-specific mortality and examines the consistency of these effects across the constituent trials. The objectives included determining the effect of pravastatin therapy on all-cause mortality in the secondary prevention trials (LIPID and CARE), and in the three trials combined (LIPID, CARE and WOSCOPS), as well the effect of pravastatin therapy on cause-specific mortality for all three trials.

The three studies were selected for inclusion because of their common design features and the closeness of their completion dates. Each study was a randomized, double-blind, placebo-controlled, clinical trial lasting approximately 5 years or more, using a dose of 40 mg pravastatin once daily. LIPID was a secondary prevention trial involving 9014 men and women with a history of myocardial infarction or hospitalization for unstable angina and total cholesterol at enrolment in the range

Table 2 Prospective Pravastatin Pooling project: compliance and lipid effects

Factor	LIPID n=9014	CARE n=4159	WOSCOPS n=6595	Total n=19 768
Compliance				
% on active treatment (placebo group)				
1 year	3	2	—*	2
5 years	18	8	—*	10
% discontinued pravastatin treatment				
1 year	6	4	16	9
5 years	16	6	30	18
Total cholesterol				
Baseline (mmol . l^{-1})†	5·66	5·43	6·96	6·00
% change at 1 year‡	− 20	− 21	− 18	− 20
% change at 5 years‡	− 16	− 18	− 16	− 16
LDL cholesterol				
Baseline (mmol . l^{-1})†	3·88	3·57	4·89	4·19
% change at 1 year‡	− 28	− 30	− 23	− 27
% change at 5 years‡	− 25	− 25	− 21	− 24
HDL cholesterol				
Baseline (mmol . l^{-1})†	0·93	0·98	1·11	1·01
% change at 1 year‡	6	5	5	5
% change at 5 years‡	5	4	5	5
Triglycerides				
Baseline (mmol . l^{-1})†	1·60	1·63	1·67	1·63
% change at 1 year‡	− 12	− 14	− 9	− 11
% change at 5 years‡	− 8	− 13	− 9	− 9

*Not recorded in WOSCOPS.
†To convert values for cholesterol to mg . dl^{-1} multiply by 38·7; to convert values for triglycerides to mg . dl^{-1} multiply by 88·6.
‡Percentage point difference relative to baseline for the pravastatin group vs the placebo group, using intention-to-treat analysis.

4·0–7·0 mmol . l^{-1} (155–271 mg . dl^{-1}). CARE was a secondary prevention trial involving 4159 men and women with a history of myocardial infarction and normal or only mildly elevated cholesterol levels (LDL cholesterol 3·0–4·5 mmol . l^{-1} (115–174 mg . dl^{-1})). WOSCOPS was predominantly a primary prevention trial of 6595 men who had hypercholesterolaemia (LDL cholesterol 4·5–6·0 mmol . l^{-1} (174–232 mg . dl^{-1})) but no documented myocardial infarction.

Outcomes

Cause-specific mortality

Three categories of fatal secondary cardiovascular outcomes were studied: fatal coronary heart disease (due to definite or possible myocardial infarction, sudden death, or other coronary heart disease); other fatal cardiovascular disease (stroke or other vascular disease); and any fatal cardiovascular disease (including coronary heart disease). Non-cardiovascular mortality was described separately as total and cause-specific non-cardiovascular diseases. Specific categories of non-cardiovascular fatal outcomes were: cancer mortality; trauma mortality (accidental death and suicide); and other non-cardiovascular mortality. Cause-specific mortality was examined for all patients, for those with prior myocardial infarction or unstable angina (LIPID and CARE), and for those without coronary heart disease (WOSCOPS). Definitions and classification of all outcomes were agreed upon prospectively by the Prospective Pravastatin Pooling Project Steering Committee and incorporated in the full protocol[9].

Analysis plan

All analyses were on an intention-to-treat basis, with primary analyses stratified by trial but unadjusted for other covariates. Analyses adjusted for patient covariates used the Cox proportional-hazards regression model. Mortality plots used Kaplan–Meier estimates. Relative risks were estimated from the hazard ratio, and heterogeneity of treatment effects across study populations was examined using tests for study–treatment interaction in the proportional-hazards model. In addition, a model based on a weighted combination of the effects seen on each specific cause of death was developed, enabling estimation of an 'expected' net

Table 3 Prospective Pravastatin Pooling project: causes of death

Cause of death	LIPID		CARE		WOSCOPS		Total	
	Pravastatin n=4512 n (%)	Placebo n=4502 n (%)	Pravastatin n=2081 n (%)	Placebo n=2078 n (%)	Pravastatin n=3302 n (%)	Placebo n=3293 n (%)	Pravastatin n=9895 n (%)	Placebo n=9873 n (%)
Fatal CHD	287 (6·4)	373 (8·3)	96 (4·6)	119 (5·7)	42 (1·3)	63 (1·9)	425 (4·3)	555 (5·6)
Definite MI	34	74	14	26	14	24	62	124
Possible MI	19	15	10	12	3*	9*	32	36
Sudden death	182	211	47	48	24	28	253	287
Cardiac failure	36	46	9	15	0	0	45	61
Other CHD	16	27	16	18	1	2	33	47
Other fatal CVD	44 (1·0)	60 (1·3)	16 (0·8)	11 (0·5)	8 (0·2)	10 (0·3)	68 (0·7)	81 (0·8)
Stroke	22	27	10	5	6	4	38	36
Other CVD	22	33	6	6	2	6	30	45
Total CVD	331 (7·3)	433 (9·6)	112 (5·4)	130 (6·3)	50 (1·5)	73 (2·2)	493 (5·0)	636 (6·4)
Total non-CVD	167 (3·7)	200 (4·4)	68 (3·3)	66 (3·2)	56 (1·7)	62 (1·9)	291 (2·9)	328 (3·3)
Cancer	128	141	49	45	44	49	221	235
Trauma or suicide	6	11	8	4	5	6	19	21
Other	33	48	11	17	7	7	51	72
Total deaths	498 (11·0)	633 (14·1)	180 (8·6)	196 (9·4)	106 (3·2)	135 (4·1)	784 (7·9)	964 (9·8)

*Not included in the original publication[5].
CHD=coronary heart disease; MI=myocardial infarction; CVD=cardiovascular disease.

mortality reduction for any given risk population. Based on the proportions of different types of deaths in each trial, this enabled more robust reductions in total mortality to be estimated.

Project organization

The project steering committee was established in 1992, with representatives from all three trials, an epidemiologist and a chairman. A study protocol was finalized in July 1995, before any results of treatment from any of the three trials were known[9]. An individual patient data set was created for each trial, which enabled time-to-event outcomes and individual patient covariates to be examined. The sponsor supported the collaboration and the pooling of the trial data, but all analyses and assessment of the results were conducted independently of the sponsor.

Results

Study populations

The mean age at baseline was 59 years; 24% were aged 65 years or older (Table 1). Women on average were 4·5 years older than men, primarily owing to the inclusion criteria for the trials contributing the data.

More than 2000 participants were women, all from the secondary prevention trials. Half of the participants had a prior myocardial infarction, and two-thirds had a history of coronary heart disease. Participants in WOSCOPS, almost all without documented coronary heart disease, had significantly higher lipid levels and were more often current smokers, but WOSCOPS had the lowest prevalence of diabetes and hypertension. LIPID and CARE were both restricted to patients with coronary heart disease and were similar in profile. Baseline factors were well balanced according to randomized treatment.

Treatment and follow-up

The mean study duration was 4·9 years for WOSCOPS, 5·0 years for CARE and 6·0 years for LIPID. Among patients allocated pravastatin, 18% had discontinued therapy at 5 years. Among those allocated placebo, 13% had commenced active lipid-lowering therapy at 5 years. Higher rates of discontinuation occurred in the WOSCOPS study of patients without known coronary heart disease, whereas higher rates of commencing active therapy occurred in LIPID, where a patient's standard care (including adding lipid therapy) was left to the patient's usual doctor (Table 2). Percentage changes in lipid levels relative to baseline between treatment groups are also provided. Among those assigned pravastatin, there was a 0·97 mmol . l^{-1} greater average decrease in cholesterol over 5 years (compared with placebo), 0·94 mmol . l^{-1} decrease in LDL cholesterol, 0·05 mmol . l^{-1} increase in HDL cholesterol and 0·18 mmol . l^{-1} decrease in triglycerides. By comparison, among patients who received their allocated treatment for 5 years, the average differences with treatment were 1·07, 1·03, $-0·06$ and 0·20 mmol . l^{-1}, respectively.

Table 4 Effects of treatment on total mortality and CHD mortality within major subgroups

Group	*n*	Pravastatin %	Placebo %	Hazard ratio	95% CI	*P**
Total mortality						
Age						
<65 years	14 925	5·5	6·6	0·83	0·73–0·95	0·006
≥65 years	4843	15·4	19·5	0·78	0·68–0·89	<0·001
Sex						
Men	17 676	7·8	9·8	0·78	0·71–0·87	<0·001
Women	2092	9·1	9·6	0·96	0·73–1·27	0·77
History						
Prior MI	9913	10·5	12·5	0·83	0·75–0·94	0·002
Unstable angina	3260	9·7	13·0	0·74	0·60–0·91	0·004
No prior CHD	6595	3·2	4·1	0·78	0·60–1·00	0·051
CHD mortality						
Age						
<65 years	14 925	3·0	3·7	0·79	0·67–0·95	0·01
≥65 years	4843	8·4	11·4	0·72	0·60–0·87	<0·001
Sex						
Men	17 676	4·2	5·6	0·75	0·66–0·86	<0·001
Women	2092	4·8	6·1	0·80	0·55–1·15	0·23
History						
Prior MI	9913	6·1	7·8	0·78	0·67–0·90	0·001
Unstable angina	3260	5·0	6·6	0·74	0·55–0·98	0·04
No prior CHD	6595	1·3	1·9	0·66	0·45–0·98	0·04

*There was no significant heterogeneity of treatment effect ($P>0·10$) within these subgroups.

Table 5 Estimated absolute risk reduction and numbers needed to treat over 5 years

Patient group	Relative risk reduction (%)*	Absolute risk (placebo group)†	Absolute risk reduction (%)	Numbers needed to treat (NNT) over 5 years (95% CI)
Prior myocardial infarction	20	10·0	2·0	50 (30–135)
Prior unstable angina	19	9·7	1·8	54 (35–200)
Non-CHD	18	3·8	0·7	146 (90–520)

*Relative risk reduction estimated as a weighted average of the all combined relative risk reductions in CHD mortality, other vascular mortality and other mortality, as indicated in Fig. 1. Weights for each patient group are based on the proportion of each cause of death in the respective placebo group.
†Actuarial risk of death at 5 years in the placebo group.

Total mortality

Effects of treatment on total mortality are shown in Figs 1 and 2. For the three trials combined, there was a significant reduction in total mortality of 20% (95% CI 12–27%). The relative reduction in total mortality in the secondary prevention trials (LIPID and CARE) combined, at 19%, was similar to that seen in WOSCOPS, at 22%. Mortality curves begin to diverge at some point after 6 months, with possibly larger effects seen later. However, tests for non-proportionality of hazards were not significant, consistent with a similar relative reduction in risk for each year on study. The actuarial risk of death at 5 years was reduced from 9·9% to 8·7% for LIPID and CARE combined, compared with 4·1% to 3·2% in WOSCOPS (Fig. 2).

Cause-specific mortality

Causes of death for patients are detailed in Table 3. Death from coronary heart disease accounted for 56% of deaths (58% in those with prior coronary heart disease and 44% in those without). The principal cause of coronary heart disease death in each of the three trials was sudden cardiac death. Deaths from stroke accounted for 4% of all deaths. The principal cause of non-cardiovascular death was cancer (26% of all deaths).

Pravastatin significantly reduced coronary heart disease mortality by 24% (95% CI 14–33%, $P<0·0001$) with risk reductions in coronary heart disease mortality seen among patients with prior coronary heart disease (23%) and those without (34%) (Fig. 1). Coronary heart

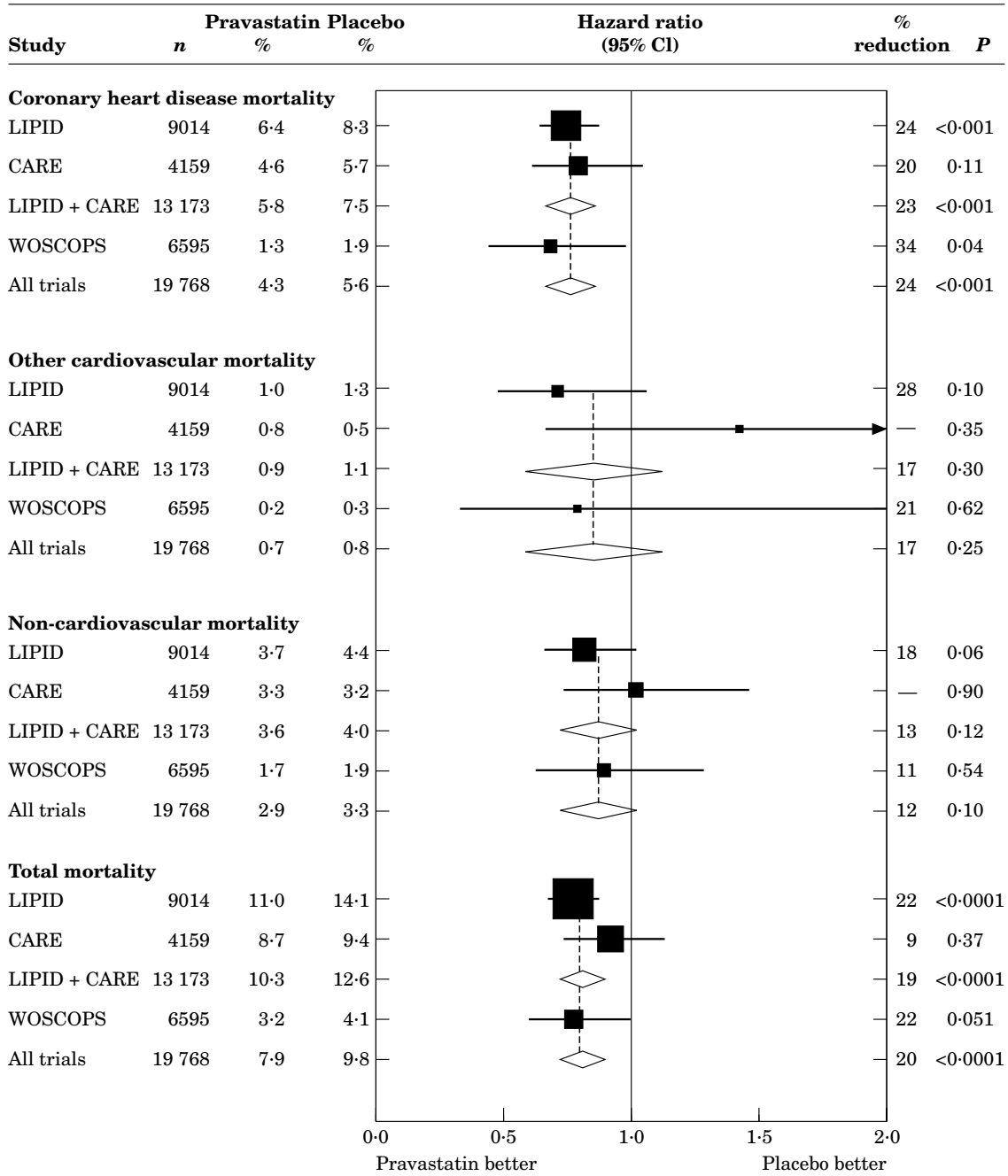
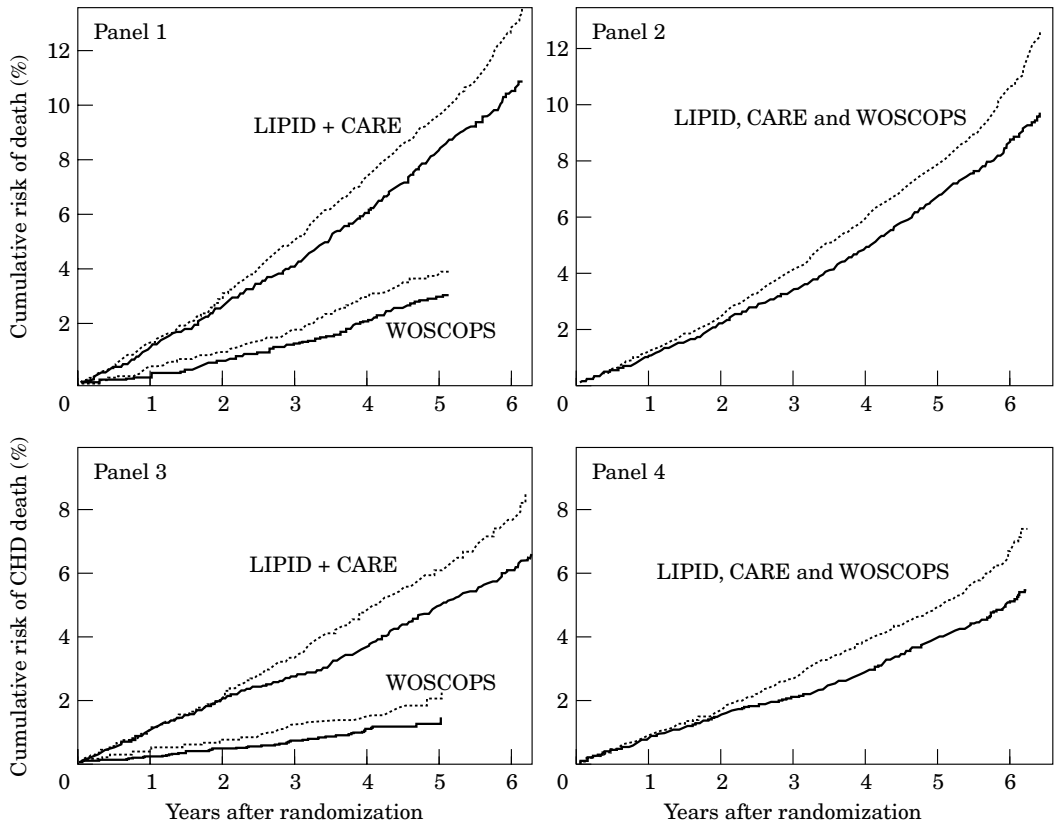


Figure 1 **Effects of pravastatin, compared with placebo, on mortality, based on the Cox proportional-hazards model. LIPID=Long-Term Intervention with Pravastatin in Ischaemic Disease study; CARE=Cholesterol and Recurrent Events study, WOSCOPS=West of Scotland Coronary Prevention Study.**

disease mortality curves diverged at about 2 years in patients with prior coronary heart disease (Fig. 2, panel 3), but a test for non-proportionality of hazards was not statistically significant. The actuarial risk of death from coronary heart disease at 5 years was reduced from 6·0% to 4·9% for LIPID and CARE combined, compared with 1·8% to 1·2% in WOSCOPS. There was a non-significant decrease in other cardiovascular deaths of 17% (95% CI −14–40%, $P=0·25$). When all cardiovascular deaths are combined (coronary heart disease and other cardiovascular deaths), treatment significantly reduced cardiovascular mortality by 24% (95% CI 14–32%). There were separate statistically significant reductions in cardiovascular mortality in patients with prior coronary heart disease ($P<0·0001$) and those without ($P=0·04$). There was no significant increase in the number of deaths from cancer, trauma or suicide, or other nonvascular causes. Overall, there was a non-significant 12% decrease in deaths from non-cardiovascular causes (95% CI −3–25%, $P=0·10$).



Numbers at risk

LIPID + CARE								All trials combined						
Placebo	6580	6482	6538	6227	6064	4755	1864	9873	9755	9612	9455	8947	6181	2022
Pravastatin	6593	6501	6397	6298	6166	4836	1961	9895	9793	9672	9551	9089	6302	2124
WOSCOPS														
Placebo	3293	3273	3254	3228	2883	1426								
Pravastatin	3302	3292	3275	3253	2923	1466								

Figure 2 **Mortality plots for the trials in the Prospective Pravastatin Pooling project. - - - -=placebo; ——=pravastatin. Panel 1: all-cause mortality for LIPID and CARE combined (patients with prior coronary heart disease) and for WOSCOPS (patients without prior coronary heart disease). Panel 2: all-cause mortality for the three trials combined. Panel 3: coronary heart disease mortality for LIPID and CARE combined and for WOSCOPS. Panel 4: coronary heart disease mortality for the three trials combined.**

Effects of treatment on mortality within major subgroups

Effects of treatment on total and coronary heart disease mortality within subgroups of age, sex and qualifying event are detailed in Table 4. No significant difference in the relative effects of treatment were found across any of these subgroups. There was a separately significant reduction in total mortality among patients 65 years or older ($P<0{\cdot}001$), among men ($P<0{\cdot}001$) and among patients with prior myocardial infarction ($P=0{\cdot}002$) and with unstable angina ($P=0{\cdot}004$).

Size of treatment effect

Treatment effect on total mortality was estimated for patients with prior myocardial infarction, with prior unstable angina but no myocardial infarction, and patients with no prior coronary heart disease, based on the assumption of a common relative risk reduction for each cause-specific mortality (Table 5). In this model the relative risk reduction for total mortality was similar for each patient group, but the absolute risk of death over 5 years was considerably higher among patients with a history of prior myocardial infarction or unstable angina than for patients without a history. Consequently, the numbers needed to treat to prevent a death were significantly lower among patients with prior coronary heart disease than those without.

The absolute benefits of treatment may be underestimated in this intention-to-treat analysis by about 18% owing to some patients discontinuing active treatment and to some patients allocated placebo starting active treatment.

Discussion

The combined results of LIPID, CARE and WOSCOPS provide consistent and convincing evidence of reductions in coronary and total mortality with pravastatin in a broad spectrum of patients. There are separately significant reductions in total mortality in patients with prior myocardial infarction or prior unstable angina across a broad range of cholesterol levels, as well as some evidence of reduction in patients without a history of coronary heart disease but with elevated cholesterol levels.

The reduced risk for total mortality is due principally to the reduction in deaths from coronary heart disease but may also be related to some reduction in other cardiovascular deaths, such as deaths from stroke. The estimated effect of treatment on non-cardiovascular deaths was not significant, but the observed number of such deaths was somewhat lower in patients allocated pravastatin. This finding may be due to chance but does provide some reassurance of treatment safety regarding non-cardiovascular deaths over the study period. There is also the possibility that pravastatin causes a modest true reduction in non-cardiovascular deaths, for example, by preventing underlying cardiovascular disease otherwise contributing to deaths from other causes.

While a similar relative reduction in coronary heart disease mortality was observed across the three trials and major subgroups, the power to demonstrate moderate differences in mortality reduction was low. It is more reliable to examine treatment effects across patient subgroups, using the more frequent end-point of fatal coronary heart disease plus non-fatal myocardial infarction. Using this end-point across pre-defined subgroups we showed, for the most part, consistent relative effects of treatment according to age, sex, coronary risk factors and lipid levels[10]. In addition, the data presented here support mortality reductions from treatment separately in both primary and secondary prevention settings, in both young and old, and in patients with prior myocardial infarction or unstable angina.

This prospective combined analysis has examined the effect of one specific cholesterol-lowering drug, pravastatin. Other HMG-CoA reductase inhibitors (or statins) have also been shown to significantly reduce coronary events to a similar degree in a range of patient populations. The Scandinavian Simvastatin Survival Study (4S)[4] convincingly showed significant reductions in total mortality with simvastatin in patients with prior coronary heart disease and an elevated baseline cholesterol level ($5{\cdot}5$–$8{\cdot}0\ \mathrm{mmol}\,.\,1^{-1}$). The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[8] trial showed a significant reduction in coronary events with lovastatin in a primary prevention setting. The results from these trials, together with the pravastatin trials, are consistent with evidence of benefit across a broad spectrum of patients and broad range of initial cholesterol levels. The extent to which benefits of treatment are related to specific drugs, class effects or the change in lipid levels achieved is still unclear. Meta-analyses of trials using a range of cholesterol-lowering treatments have shown evidence of benefit in a variety of settings, with larger effects associated with treatments (such as the statins) that produce larger changes in lipids[11].

Pravastatin was associated predominantly with a reduction in LDL cholesterol, but to a lesser extent also improved lipid profiles through an increase in HDL cholesterol and a reduction in triglycerides. The results of Veterans Affairs High-Density Lipoprotein Cholesterol Intervention provide some indirect evidence that changing the other lipid levels may also be important[12]. Here, treatment with gemfibrozil, in patients with prior myocardial infarction, increased HDL cholesterol and reduced triglycerides, without changing LDL cholesterol, and resulted in a significant reduction in coronary events.

While the benefits of pravastatin treatment may be consistent just with changes in lipids, effects of therapy through a variety of mechanisms are also plausible[13]. Some, but not all, of these may be mediated through lipid changes. Mechanisms in addition to long-term reduction in atherosclerosis include plaque stabilization, improvement in endothelium and vascular reactivity, reduced lipid oxidation and reduced thrombotic tendency.

The prospective design of this combined analysis provides several important advantages over a retrospective meta-analysis. Prospective meta-analysis provides a powerful, scientifically rigorous approach to combining trial evidence[14,15] and the Cochrane Collaboration has now established a registry for future prospective meta-analyses. A further prospective overview of all major cholesterol trials is also planned by the Cholesterol Treatment Trialists' (CTT) Collaboration[14]. This prospective overview will include data from all recent and ongoing randomized, large-scale trials of cholesterol treatment and provide a broader overview of cholesterol treatment.

The scientific rationale for combining these three trials was based on the common design features, identical therapies and standardized outcomes. Combining trials evaluating treatment for patients with a history of coronary heart disease (LIPID and CARE) and without (WOSCOPS) was considered appropriate in that similar relative reductions in cause-specific mortality were expected. It was recognized that the effect of treatment on total mortality might vary because of the different proportions of coronary heart disease deaths in each trial. However, the model (using a common relative risk reduction for each cause-specific mortality) estimated similar relative effects on total mortality due to a similar proportion of coronary heart disease deaths among patients with and without coronary heart disease. This may reflect that the WOSCOPS population represented a group at higher risk than the general population. WOSCOPS patients were all male, had significantly elevated baseline cholesterol levels and were often smokers. However, they were still at lower risk of death

from any cause than patients with a history of coronary heart disease. Consequently, there is still a much larger absolute benefit in terms of deaths prevented in treating patients with a history of coronary heart disease (even with average cholesterol levels) than in treating those without coronary heart disease (even with elevated cholesterol levels).

Although pravastatin had less absolute benefit for patients without prior coronary heart disease in preventing death, therapy had significant value in preventing a range of fatal and non-fatal cardiovascular events (including myocardial infarction, unstable angina and coronary revascularization). In WOSCOPS, treatment of 1000 patients over 5 years helped prevent more than 30 major cardiovascular events. Within WOSCOPS, greater absolute benefits of treatment were estimated among those at highest risk of a major coronary event with treatment considered cost-effective if applied to that 40% of WOSCOPS subjects at highest coronary heart disease risk[16].

Individually, each of the three trials reported a high safety profile for pravastatin and collectively there was no increase in fatal adverse events over at least 5 years of follow-up. Since any long-term adverse effects of therapy, such as new cancers, require even longer follow-up, there are plans to continue following patients in WOSCOPS and LIPID[5,7] It is important that similar long-term safety profiles are obtained for other lipid-lowering therapies before these treatments become routine, particularly for lower-risk populations.

In conclusion, there is now good evidence of survival benefit without evidence of harm from 5 years of pravastatin therapy for patients both with and without established coronary heart disease. Therapy with such good evidence of benefit and safety should be considered for a broad cross-section of patients at sufficient risk of death from coronary heart disease.

We are indebted to all participating investigators in the three trials and the Pravastatin Pooling Project group. We acknowledge the support of Margot Mellies, Mark McGovern and Stephen Mosley from Bristol-Myers Squibb and thank Tim Craven for statistical analyses and advice.

References

[1] Stamler J, Wentworth D, Neaton JD Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356 222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 1986; 256: 2823–8.

[2] Law MR, Wald NJ, Thompson SG By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? BMJ 1994; 308: 367–72.

[3] Peto R, Yusuf S, Collins R Cholesterol lowering trial results in their epidemiological context. Circulation 1985; 72(Suppl III): III-51.

[4] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–9.

[5] Shepherd J, Cobbe SM, Ford I *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333: 1301–7.

[6] Sacks FM, Pfeffer MA, Moye LA *et al*. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996; 335: 1001–9.

[7] The LIPID Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339: 1349–57.

[8] Downs JR, Clearfield M, Weis S *et al*. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. JAMA 1998; 279: 1615–21.

[9] The PPP Project Investigators. Design, rationale and baseline characteristics of the prospective pravastatin pooling (PPP) project: a combined analysis of three large-scale randomized trials: Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID), Cholesterol and Recurrent Events (CARE), and West of Scotland Coronary Prevention Study (WOSCOPS). Am J Cardiol 1995; 76: 899–905.

[10] Sacks FM, Tonkin AM, Shepherd J *et al*. The effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors. The Prospective Pravastatin Pooling Project. Circulation 2000; 102: 1893–900.

[11] Bucher HC, Griffith LE, Guyatt G Systematic review on the risk and benefit of different cholesterol-lowering interventions. Arterioscler Thromb Vasc Biol 1999; 19: 187–95.

[12] Rubins HB, Robins SJ, Collins D *et al*. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999; 341: 410–8.

[13] Rosenson RS, Tangney CC Antiatherothrombotic properties of statins. Implications for cardiovascular event reduction. JAMA 1998; 279: 1643–50.

[14] Simes RJ for the PPP and CTT Investigators. Prospective meta-analysis of cholesterol-lowering studies: the Prospective Pravastatin Pooling (PPP) project and the Cholesterol Treatment Trialists (CTT) Collaboration. Am J Cardiol 1995; 76S: 122C–6C.

[15] Pogue J, Yusuf S Overcoming the limitations of current meta-analysis of randomised controlled trials. Lancet 1998; 351: 47–52.

[16] Caro J, Klittich W, McGuire A *et al*. The West of Scotland Coronary Prevention Study: economic benefit analysis of primary prevention with pravastatin. BMJ 1997; 315: 1577–82.