Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up

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Summary

Background The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study showed that pravastatin therapy over 6 years reduced mortality and cardiovascular events in patients with previous acute coronary syndromes and average cholesterol concentrations. We assessed the longer-term effects of initial treatment with pravastatin on further cardiovascular events and mortality over a total follow-up period of 8 years.

Methods In the main trial, 9014 patients with previous myocardial infarction or unstable angina and a baseline plasma cholesterol concentration of 4·0–7·0 mmol/L were randomly assigned pravastatin 40 mg daily or placebo and followed up for 6 years. Subsequently, all patients were offered open-label pravastatin for 2 more years. Major cardiovascular events and adverse events were compared according to initial treatment assignment.

Findings 7680 (97% of those still alive) had 2 years of extended follow-up. 3766 (86%) of those assigned placebo and 3914 (88%) assigned pravastatin agreed to take open-label pravastatin. During this period, patients originally assigned pravastatin had almost identical cholesterol concentrations to those assigned placebo, but a lower risk of death from all causes (219 [5·6%] *vs* 255 [6·8%], p=0·029), coronary heart disease (CHD) death (108 [2·8%] *vs* 137 [3·6%], p=0·026), and CHD death or non-fatal myocardial infarction (176 [4·5%] *vs* 196 [5·2%], p=0·08). Over the total 8-year period, all-cause mortality was 888 (19·7%) in the group originally assigned placebo and 717 (15·9%) in the group originally assigned pravastatin, CHD mortality was 510 (11·3%) versus 395 (8·8%), myocardial infarction was 570 (12·7%) versus 435 (9·6%; each p<0·0001), and stroke was 272 (6·0%) versus 224 (5·0%; p=0·015). Stronger evidence of separate treatment benefits than in the main trial was seen in important prespecified subgroups (women, patients aged ⩾70 years, and those with total cholesterol <5·5 mmol/L). Pravastatin had no significant adverse effects.

Interpretation The evidence of sustained treatment benefits and safety of long-term pravastatin treatment reinforces the importance of long-term cholesterol-lowering treatment for almost all patients with previous CHD events.

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Introduction

Trials have shown that inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase reduce the risk of death and major cardiovascular events after acute myocardial infarction[1–3] and unstable angina pectoris.[3] The three large-scale trials—the Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) study, and the Long-term Intervention with Pravastatin in Ischaemic Disease study (LIPID)—suggested a possible lag in the treatment effect of 1–2 years after treatment begins. The LIPID trial was terminated early, in 1997, owing to clear evidence of survival benefits with pravastatin treatment. At this time, there were few data on the long-term effectiveness or safety of HMG-CoA reductase inhibitors beyond 5–6 years of treatment. Therefore, after the termination of the LIPID study, all patients were offered pravastatin therapy, with the plan to assess outcomes and safety over at least a further 2 years. We also planned to assess the effects of pravastatin therapy in important subgroups of patients for which the initial study was not powerful enough to show independent significant effects. These subgroups included women, patients aged 70 years or older, and those with total plasma cholesterol concentrations of less than 5·5 mmol/L.

Methods

Double-blind period

The design and results of the original study have been published.[3,4] This randomised placebo-controlled trial was undertaken at 87 centres in Australia and New Zealand, and involved 9014 patients who had had an acute myocardial infarction or a hospital discharge diagnosis of unstable angina pectoris 3–36 months before study entry and whose total cholesterol concentration was 4·0–7·0 mmol/L. Patients were randomly assigned pravastatin 40 mg per day or placebo in addition to their usual treatment and dietary advice. The patient's own physician provided usual care during the study.

The primary study outcome was death from CHD. Secondary outcomes included death from any cause, death from cardiovascular causes, death from CHD or non-fatal myocardial infarction, myocardial infarction, any stroke, non-haemorrhagic stroke, and coronary revascularisation.

Open-label treatment period

After early closure of the placebo-controlled trial, all patients still alive were seen in clinic visits (wherever possible) and offered open-label pravastatin 40 mg daily, irrespective of their original assigned therapy (unless they were regarded as having specific contraindications, such as significant hepatic disease or previous discontinuation of the study drug because of an adverse

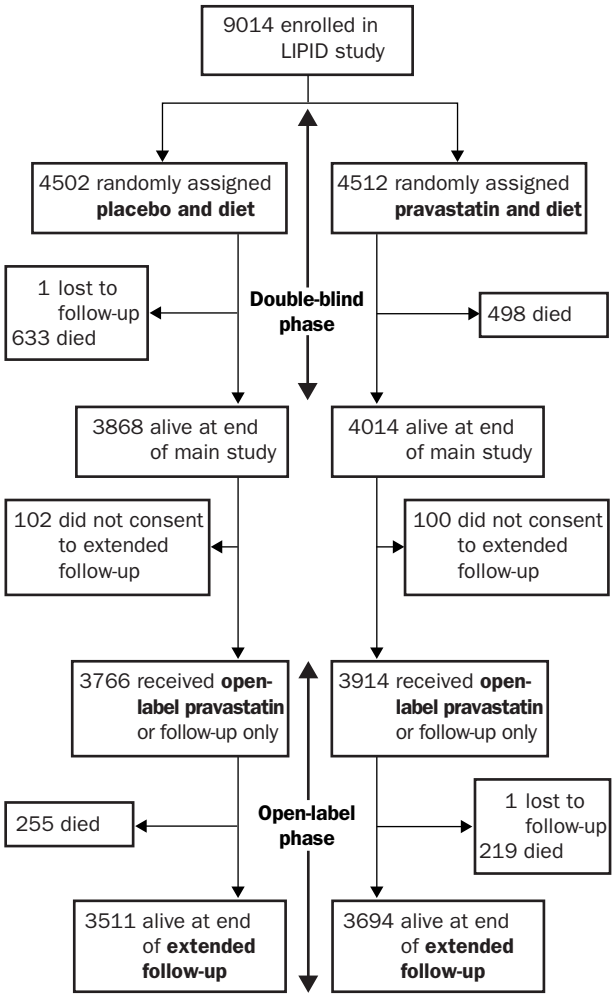

Figure 1: **LIPID study design and trial profile**

event). Patients were still unaware of their randomised treatment at the time they consented to long-term follow-up. Patients were also able to receive other treatments, including other cholesterol-lowering treatment, in consultation with their usual doctors.

All patients who started open-label pravastatin were seen in the clinic after 3 months for measurement of concentrations of serum alanine aminotransferase and plasma cholesterol and review for any adverse effects of therapy. All patients (whether receiving pravastatin or not) were approached to give informed consent for long-term follow-up. Patients not wishing to attend for annual visits were usually followed up by telephone and through their local doctors. At each clinic visit, patients' assessments were the same as those during the main trial and included a review for any major clinical outcomes and any adverse events. Long-term follow-up was approved by the ethics committee at each participating centre.

Supplies of open-label pravastatin were provided to patients for a mean of 2 years beyond the end of the double-blind phase of the trial. During this time, at the second annual visit, patients were advised that further cholesterol-lowering treatment would be arranged through their usual doctors and with further contact from study personnel by mail and telephone. Patients originally assigned pravastatin are referred to as the pravastatin group, and those originally assigned placebo as the placebo group (figure 1).

	Placebo (n=3766)	Pravastatin (n=3914)
Age (years)		
Median (IQR)	62 (55–67)	62 (55–67)
<55	923 (25%)	974 (25%)
55–64	1474 (39%)	1511 (39%)
65–69	857 (23%)	918 (23%)
⩾70	512 (14%)	511 (13%)
Sex		
Men	3108 (83%)	3253 (83%)
Women	658 (17%)	661 (17%)
Qualifying event		
Myocardial infarction	2402 (64%)	2487 (64%)
Unstable angina	1364 (36%)	1427 (36%)
Coronary risk factors		
Current smoker	351 (9%)	351 (9%)
Ex-smoker	2339 (62%)	2527 (65%)
History of hypertension	1569 (42%)	1615 (41%)
Diabetes mellitus	282 (7%)	307 (8%)
Obesity (body-mass index >30)	654 (17%)	693 (18%)
Other vascular disease		
Claudication	366 (10%)	357 (9%)
Stroke	144 (4%)	130 (3%)
Transient ischaemic attack	136 (4%)	130 (3%)
Coronary-artery revascularisation		
Angioplasty	548 (15%)	587 (15%)
Coronary-artery bypass	1130 (30%)	1178 (30%)
Medication use		
Aspirin	3117 (83%)	3266 (83%)
β-blocker	1820 (48%)	1844 (47%)
Calcium antagonist	1281 (34%)	1320 (34%)
ACE inhibitor	526 (14%)	565 (14%)
Nitrate	1062 (28%)	1108 (28%)
Diuretic	528 (14%)	505 (13%)
LIPID risk score,* median (IQR)	6 (4–8)	6 (4–8)
Lipid concentrations (mmol/L, median [IQR])		
Total cholesterol	5·66 (5·10–6·20)	5·66 (5·08–6·23)
LDL cholesterol	3·88 (3·40–4·40)	3·88 (3·38–4·39)
HDL cholesterol	0·92 (0·80–1·09)	0·92 (0·79–1·08)
Triglycerides	1·56 (1·18–2·12)	1·61 (1·17–2·21)
Total cholesterol/HDL ratio	6·05 (5·11–7·12)	6·09 (5·13–7·14)

Except for baseline triglyceride concentrations (p=0·023), there were no significant differences between groups. ACE=angiotensin-converting-enzyme. *Derived from risk model for CHD death or non-fatal myocardial infarction.[5]

Table 1: **Baseline characteristics of surviving patients followed up during extended phase**

Outcomes and subgroups

All deaths, myocardial infarctions, and strokes, during the double-blind and extended phases of the trial, were reviewed by the Outcomes Assessment Committee or the Stroke Adjudication Committee, whose members had no knowledge of the patients' original treatment assignment. Prespecified subgroups for analysis were sex, qualifying event, age (<55, 55–64, 65–69, or ⩾70 years), hypertension or not, diabetes mellitus or not, smoking status, total cholesterol concentration (<5·5, 5·5–6·5, or ⩾6·5 mmol/L), LDL cholesterol concentration (<3·5, 3·5–4·5, or ⩾4·5 mmol/L), HDL cholesterol concentration (<1·0 or ⩾1·0 mmol/L), and serum triglyceride concentration (<1·5, 1·5–2·5, or ⩾2·5 mmol/L) at baseline. The prespecified primary endpoint for subgroup analysis was the composite of CHD death and non-fatal myocardial infarction.

Statistical analyses

We assessed the delayed or sustained effect of pravastatin beyond the double-blind phase of the trial by comparing the patients (still alive at the start of extended follow-up) originally assigned pravastatin with those originally assigned placebo. These groups were compared for each cardiovascular outcome in a Cox's

regression analysis. Analyses were unadjusted and also adjusted for baseline risk factors identified in the LIPID risk-factor model[5] and for non-fatal cardiovascular events occurring during the earlier double-blind phase of LIPID.

The long-term effects of initial randomised treatment over 8 years of follow-up were compared in intention-to-treat survival analyses according to the original assigned therapy. Time-to-event analyses used the log-rank test stratified by qualifying event. Estimates of relative risk reduction and 95% CIs used Cox's proportional hazards model. Prespecified subgroup analyses examined the variation in treatment effect on the composite outcome of CHD death and non-fatal myocardial infarction, based on tests for interaction in Cox's model and with continuous variables for age and baseline lipid values. P values were not adjusted for multiple comparisons. Analyses were undertaken with SAS version 8.02 (SAS Institute Inc, Cary, NC, USA).

Role of the funding source

The study was initiated, designed, conducted, analysed, and reported by the investigators independently of the sponsor and coordinated by the NHMRC Clinical Trials Centre, University of Sydney, under the auspices of the National Heart Foundation of Australia.

Results

Between June, 1990, and December, 1992, 9014 patients were randomised into the LIPID study (figure 1). Patients were followed up during the double-blind phase of the trial for a mean of 6·0 years; one patient was lost to follow-up. Of the 7882 patients alive at the end of this phase, 7680 (97%) consented to long-term follow-up; 3914 had been initially assigned pravastatin (pravastatin group) and 3766 placebo (placebo group). The randomised groups were well balanced for baseline characteristics, and the two groups of surviving patients followed up during the extended phase were also well matched for these prerandomisation characteristics (table 1). Patients who did not consent to further follow-up were equally likely to have been previously assigned placebo (n=102) or pravastatin (n=100) and were of similar risk profile (mean LIPID score 6·06) to patients who consented to further follow-up (mean score 6·08).[5] A further 2·0 years of follow-up was completed for all but one of the 7680 patients.

Adherence to treatment and lipid changes

During the double-blind phase of LIPID, pravastatin was associated with a 1·0 mmol/L lower plasma total cholesterol concentration on average compared with placebo, a 1·0 mmol/L lower LDL cholesterol concentration, a 0·20 mmol/L lower plasma triglyceride concentration, and a 0·05 mmol/L higher HDL cholesterol concentration (figure 2). By closure of the double-blind phase at 6·0 years, 852 (19%) of patients assigned pravastatin had discontinued the study medication, and 1071 (24%) of those assigned placebo had commenced open-label cholesterol-lowering therapy.

At the start of the open-label phase, 3446 (88%) of pravastatin patients and 3225 (86%) of the placebo group commenced open-label pravastatin treatment. Additional patients received other cholesterol-lowering treatment, so that in total 90% of both the pravastatin and placebo groups were on some cholesterol-lowering therapy at the start of the open-label phase. As a result of this treatment, the mean cholesterol concentrations in the placebo group fell significantly to match those of the pravastatin group almost exactly during the extended follow-up phase (figure 2). For pravastatin patients, total cholesterol averaged over the 2-year open-label phase was 4·54 mmol/L and average LDL cholesterol was 2·66 mmol/L; for placebo patients, total cholesterol was 4·50 mmol/L and LDL cholesterol 2·63 mmol/L.

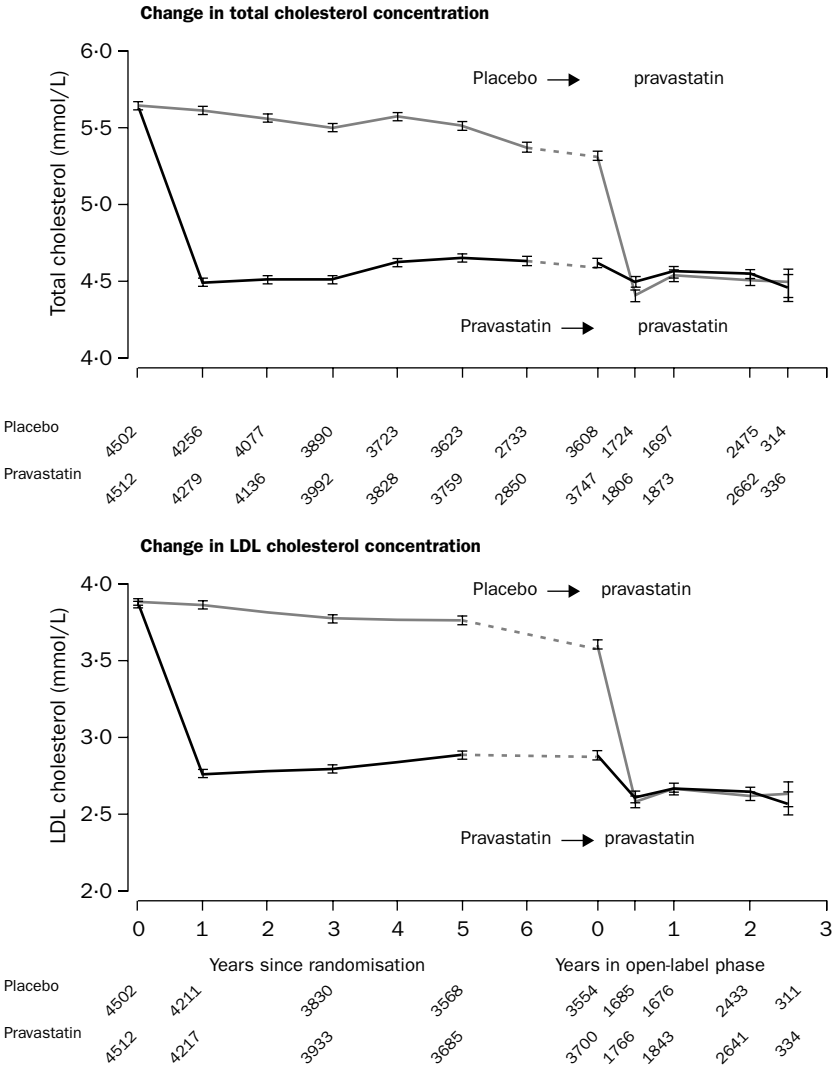

Figure 2: **Serum cholesterol changes for patients initially assigned placebo or pravastatin**
Points show means with 95% CIs at each timepoint after randomisation and after final visit of main trial. During open-label phase, lipid measurements were undertaken on more than 87% of patients annually. Numbers under graphs are numbers of patients whose data were analysed at these times.

Outcome	Period	Placebo group (n=4502; 3766)*	Pravastatin group (n=4512; 3914)*	Relative risk reduction (95% CI)	p†
CHD death	Double-blind phase	373 (8·3%)	287 (6·4%)	24% (12–35)	0·0004
	Open-label phase	137 (3·6%)	108 (2·8%)	25% (3–42)	0·026
	Total period	510 (11·3%)	395 (8·8%)	24% (14–34)	<0·0001
Death from any cause	Double-blind phase	633 (14·1%)	498 (11·0%)	22% (13–31)	<0·0001
	Open-label phase	255 (6·8%)	219 (5·6%)	18% (2–32)	0·029
	Total period	888 (19·7%)	717 (15·9%)	21% (13–29)	<0·0001
CVD death	Double-blind phase	433 (9·6%)	331 (7·3%)	25% (13–35)	0·0001
	Open-label phase	163 (4·3%)	130 (3·3%)	24% (4–40)	0·019
	Total period	596 (13·2%)	461 (10·2%)	25% (15–33)	<0·0001
CHD death or non-fatal myocardial infarction	Double-blind phase	715 (15·9%)	558 (12·4%)	24% (15–32)	<0·0001
	Open-label phase	196 (5·2%)	176 (4·5%)	16% (–2 to 32)	0·08
	Total period	911 (20·2%)	734 (16·3%)	22% (14–29)	<0·0001
Myocardial infarction	Double-blind phase	463 (10·3%)	337 (7·5%)	29% (18–38)	<0·0001
	Open-label phase	107 (2·8%)	98 (2·5%)	15% (–12 to 35)	0·26
	Total period	570 (12·7%)	435 (9·6%)	26% (16–35)	<0·0001
Total stroke	Double-blind phase	204 (4·5%)	169 (3·7%)	19% (0–34)	0·048
	Open-label phase	67 (1·8%)	54 (1·4%)	24% (–9 to 47)	0·14
	Total period	272 (6·0%)	224 (5·0%)	20% (4–33)	0·015
Non-haemorrhagic stroke	Double-blind phase	197 (4·4%)	155 (3·4%)	23% (5–37)	0·016
	Open-label phase	58 (1·5%)	45 (1·1%)	27% (–8 to 50)	0·12
	Total period	255 (5·7%)	200 (4·4%)	24% (8–37)	0·004
CABG or PTCA	Double-blind phase	710 (15·8%)	586 (13·0%)	20% (10–28)	0.0001
	Open-label phase	188 (5·0%)	174 (4·4%)	16% (–4 to 31)	0·10
	Total period	898 (19·9%)	760 (16·8%)	19% (11–26)	<0·0001

CHD=coronary heart disease; CVD=cardiovascular disease; CABG=coronary-artery bypass surgery; PTCA=percutaneous transluminal coronary angioplasty. *Number in double-blind phase analysis; number in open-label phase analysis. Denominator for total period is number at risk for double-blind phase. †Based on stratified log-rank test.

Table 2: **Cardiovascular events during main LIPID study, during extended follow-up, and over total period by original treatment group**

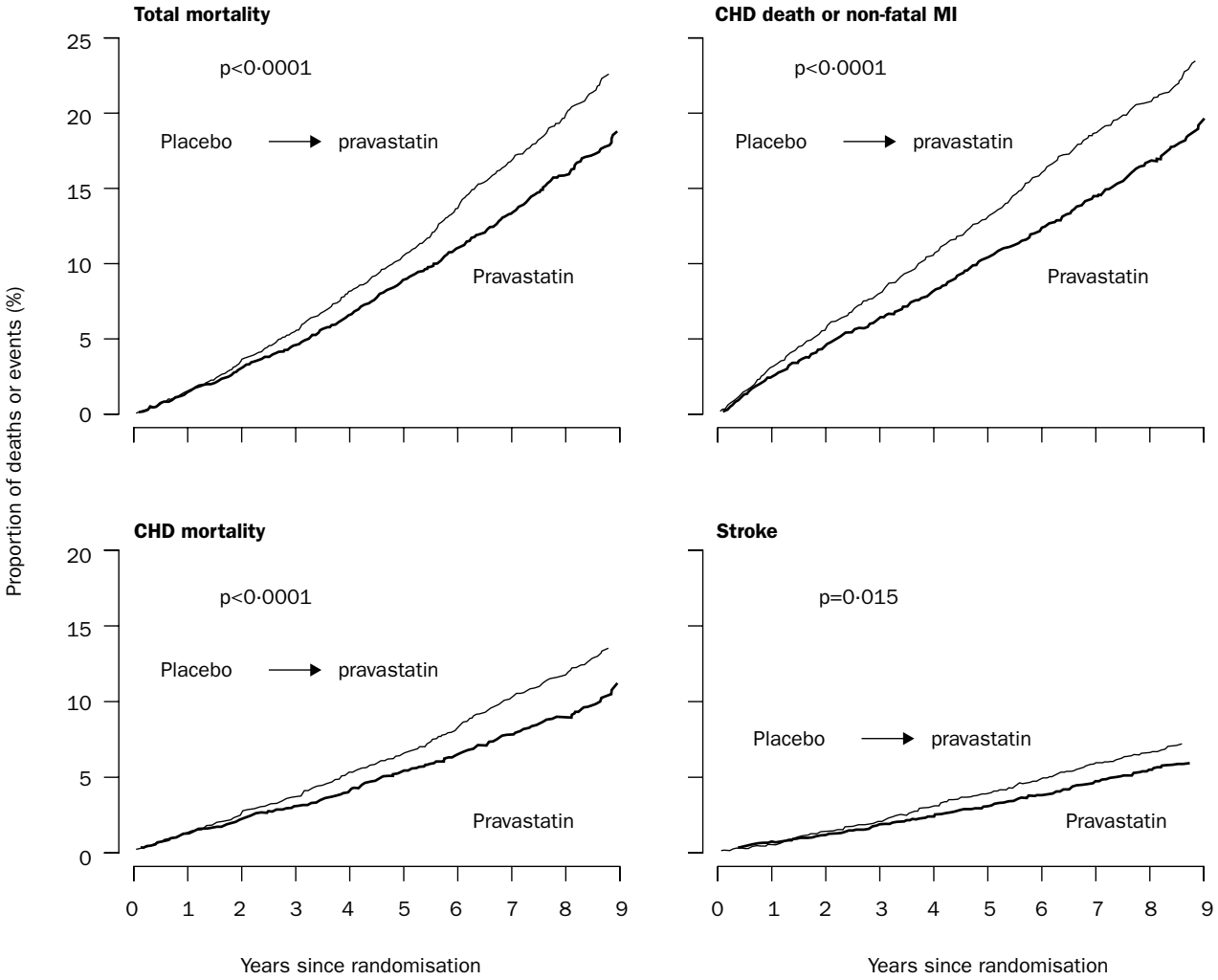

Figure 3: **Cumulative risk of major cardiovascular outcomes in group initially assigned pravastatin and group initially assigned placebo over total follow-up period**

Outcome	Adjustment in analysis*	Placebo group (n=3766)	Pravastatin group (n=3914)	Relative risk reduction (95% CI)†	p
CHD death	No adjustment	137 (3·6%)	108 (2·8%)	25% (3–42)	0·026
	Baseline factors	..	..	25% (3–41)	0·029
	Baseline factors+CVD events	..	..	24% (2–41)	0·033
Death from any cause	No adjustment	255 (6·8%)	219 (5·6%)	18% (2–32)	0·029
	Baseline factors	..	..	18% (1–31)	0·036
	Baseline factors+CVD events	..	..	17% (1–31)	0·038
CHD death or non-fatal MI	No adjustment	196 (5·2%)	176 (4·5%)	16% (–2 to 32)	0·08
	Baseline factors	..	..	16 (–2 to 32)	0·08
	Baseline factors+CVD events	..	..	17 (–2 to 32)	0·08

CHD=coronary heart disease; CVD=cardiovascular disease. MI=myocardial infarction. *Baseline risk factors (age, sex, smoking, diabetes, hypertension, qualifying event, multiple MI, coronary revascularisation, total cholesterol, HDL cholesterol); and non-fatal CVD events (MI, unstable angina, revascularisation, stroke). †Pravastatin *vs* placebo based on hazard ratio in Cox's regression.

Table 3: **Outcomes during extended follow-up by original treatment group (multivariate analyses adjusted for other baseline factors and CVD events during main LIPID study)**

Similarly, there were no significant differences in HDL cholesterol or triglycerides between the groups during the extended follow-up phase.

Effects on cardiovascular outcomes

The effects of initial assignment to pravastatin during the double-blind phase of the main trial and during the open-label extended follow-up phase are shown in table 2. Additional significant reductions in cardiovascular events in the pravastatin group compared with the placebo group were seen during the extended follow-up phase for death from any cause, cardiovascular death, and CHD death. The relative risk reductions during the extended phase were similar to those during the preceding double-blind phase of the trial, particularly for mortality outcomes, coronary revascularisation, and stroke. Consequently, the absolute benefits of treatment and the strength of the evidence for effectiveness were greater over the total 8-year follow-up period (double-blind phase plus extended follow-up) than over the 6-year double-blind phase alone (figure 3).

Delayed or sustained treatment effects

There was a significant reduction in total and CHD mortality during the extended open-label treatment phase of LIPID when both groups were receiving almost the same therapy and had matching lipid profiles. These reductions remained significant in multivariate analyses of risk reduction, after adjustment for baseline risk factors and non-fatal cardiovascular events during the double-blind phase of the trial, and were of similar magnitude to those estimated in the unadjusted analyses (table 3).

Treatment effects within subgroups

Table 4 shows subgroup analyses for the combined endpoint of CHD death and non-fatal myocardial infarction for all prespecified subgroups. There was no evidence of significant heterogeneity of treatment effect for any of these subgroups, and the relative risk reduction in each subgroup was consistent with the 22% reduction for the whole cohort over the total 8-year period of follow-up. Owing to the sustained treatment effect and the larger number of events, there was now greater evidence of treatment benefit among women, among patients aged 70 years and over, and among patients with total cholesterol concentrations of less than 5·5 mmol/L—groups identified as of particular interest before the extended phase of the trial.

Comparisons for these groups, and for patients with LDL cholesterol concentrations of less than 3·5 mmol/L are shown in table 5. In general, when compared with the results from the main study, the effects over the total study period showed a similar relative reduction, a larger difference in absolute risk, and a smaller p value for each subgroup and outcome. Although the evidence of benefit within each separate subgroup was somewhat stronger, individual tests with $p<0·05$ still only provide weak evidence of significance owing to the multiple tests undertaken.

Subgroup at baseline	Number of events		Risk reduction (95% CI)
	Placebo group (n=4502)	Pravastatin group (n=4512)	
Sex			
Women	134 (18%)	112 (15%)	16% (–8 to 35)
Men	777 (21%)	622 (17%)	23% (15–31)
Qualifying event			
Myocardial infarction	636 (22%)	516 (18%)	22% (12–30)
Unstable angina	275 (17%)	218 (13%)	24% (9–36)
Age (years)			
<55	164 (16%)	129 (12%)	27% (8–42)
55–64	309 (18%)	253 (15%)	20% (6–33)
65–69	247 (23%)	201 (19%)	22% (6–35)
⩾70	191 (28%)	151 (23%)	20% (1–35)
Hypertension*			
Yes	399 (21%)	349 (19%)	14% (1–25)
No	511 (20%)	385 (15%)	28% (18–37)
Diabetes			
Yes	111 (29%)	99 (25%)	19% (–7 to 38)
No	800 (19%)	635 (15%)	23% (15–31)
Smoking			
Current	119 (27%)	86 (20%)	28% (4–45)
Ex-smoker	592 (21%)	473 (16%)	26% (17–35)
Non-smoker	200 (16%)	175 (15%)	8% (–13 to 25)
Total cholesterol (mmol/L)			
<5·5	350 (18%)	288 (15%)	19% (6–31)
5·5–6·5	433 (22%)	343 (17%)	24% (13–34)
⩾6·5	128 (21%)	103 (17%)	24% (1–41)
LDL cholesterol (mmol/L)			
<3·5	237 (18%)	214 (16%)	13% (–4 to 28)
3·5–4·5	474 (20%)	371 (16%)	24% (13–34)
⩾4·5	200 (23%)	149 (18%)	29% (12–42)
HDL cholesterol (mmol/L)			
<1·0	620 (22%)	504 (17%)	23% (14–32)
⩾1·0	291 (17%)	230 (14%)	21% (6–33)
Triglycerides (mmol/L)			
<1·5	410 (20%)	310 (16%)	24% (12–35)
1·5–2·5	348 (19%)	274 (16%)	21% (8–33)
⩾2·5	153 (23%)	150 (18%)	21% (2–37)

*Defined as clinical history of hypertension.

Table 4: **Treatment effects within subgroups for the prespecified outcome, coronary heart disease (CHD) death or non-fatal myocardial infarction, over total study period by original treatment group within prespecified subgroups**

Subgroup and outcome	Main study				Total study period			
	Placebo (n=4502)	Pravastatin (n=4512)	Relative risk reduction (95% CI)	p*	Placebo (n=4502)	Pravastatin (n=4512)	Relative risk reduction (95% CI)	p*
Women								
CHD event†	104 (14%)	90 (12%)	14% (–15 to 35)	0·31	134 (18%)	112 (15%)	16% (–8 to 35)	0·17
CHD death	50 (7%)	39 (5%)	20% (–21 to 48)	0·29	75 (10%)	51 (7%)	31% (2–52)	0·04
Any death	78 (10%)	74 (10%)	3% (–33 to 29)	0·85	117 (15%)	102 (13%)	12% (–15 to 32)	0·35
Age ⩾70 years								
CHD event†	146 (21%)	120 (18%)	15% (–9 to 33)	0·20	191 (28%)	151 (23%)	20% (1–35)	0·04
CHD death	96 (14%)	80 (12%)	14% (–16 to 36)	0·32	133 (19%)	106 (16%)	19% (–5 to 37)	0·11
Any death	156 (23%)	133 (20%)	12% (–11 to 30)	0·28	224 (33%)	201 (30%)	9% (–10 to 25)	0·33
Total cholesterol <5·5 mmol/L								
CHD event†	271 (14%)	224 (12%)	18% (2–32)	0·03	350 (18%)	288 (15%)	19% (6–31)	0·007
CHD death	153 (8%)	1268 (7%)	18% (–3 to 35)	0·09	204 (11%)	168 (9%)	19% (1–34)	0·05
Any death	268 (14%)	230 (12%)	15% (–2 to 29)	0·07	364 (19%)	319 (17%)	14% (0–26)	0·05
LDL cholesterol <3·5 mmol/L								
CHD event†	185 (14%)	164 (12%)	14% (–6 to 30)	0·16	237 (18%)	214 (16%)	13% (–4 to 28)	0·13
CHD death	108 (8%)	92 (7%)	18% (–9 to 38)	0·17	141 (11%)	123 (9%)	16% (–7 to 34)	0·15
Any death	192 (15%)	161 (12%)	19% (0–34)	0·05	257 (20%)	224 (17%)	16% (0–30)	0·05

CHD=coronary heart disease. *p for each test unadjusted for other subgroup comparisons. †CHD death or non-fatal myocardial infarction.

Table 5: **Comparison of treatment effects in selected subgroups in main LIPID study and in total study period**

Size of treatment benefit

The additional absolute benefit of treatment over a mean of 8·0 years of follow-up compared with the double-blind phase of 6·0 years is shown in table 6. Since both groups received the same treatment during the extended follow-up phase, these benefits can only be attributed to the first 6 years of pravastatin treatment. For every 1000 patients originally assigned pravastatin, 38 deaths, 30 myocardial infarctions, and 11 strokes were prevented over 8 years, or 58 fewer patients had a myocardial infarction or stroke and/or died (table 6). This finding equated to needing to treat 17 patients to prevent one patient having any of these events, and represents a 24% increase in the size of the absolute benefit in preventing major cardiovascular events and a 27% larger mortality benefit than that seen during the main LIPID study.

Tolerability and safety

3 months after starting open-label therapy, 30 (0·80%) of the placebo group and 12 (0·31%) of the pravastatin group (p=0·004) permanently discontinued therapy because of suspected adverse drug reactions. Patients still did not know their original treatment assignment until after this visit.

The long-term safety of pravastatin over the total period, including the extended open-label phase, is shown in table 7. There were no significant increases in serious adverse events in the patients initially assigned pravastatin, either during the main trial or with the inclusion of events during extended follow-up. 1035 patients from the two groups developed new cancers over 8 years, and no increased risk in association with pravastatin was seen. Initial pravastatin was associated with an estimated risk reduction for cancer of 9% (95% CI 19 to –3) with no significant increase in the incidence of any specific cancer type.

Outcome	Main study period		Total study period	
	Events prevented per 1000 treated*	Number needed to treat†	Events prevented per 1000 treated*	Number needed to treat†
CHD death	19	52	26	39
Death from any cause	30	33	38	26
CHD event	35	28	40	25
MI	28	36	30	33
Stroke	8	127	11	93
Death, MI, or stroke	47	21	58	17

CHD=coronary heart disease; MI=myocardial infarction. *Number of patients with at least one event prevented for every 1000 patients originally assigned pravastatin treatment. †Number of patients needed to be assigned pravastatin to prevent at least one event in one patient.

Table 6: **Absolute benefits of pravastatin during main LIPID study and total study period**

Discussion

The main LIPID study showed that pravastatin reduced total mortality and all prespecified cardiovascular outcomes in patients with previous acute coronary syndromes and average baseline cholesterol concentrations. These effects were seen across a broad range of subgroups and lipid concentrations and were in addition to contemporary medical treatments as used at the time.[3] With extended follow-up, the LIPID study has now shown that the benefits of the first 6 years of cholesterol-lowering treatment with pravastatin continue to accumulate for at least a further 2 years. The absolute risk reduction

Event	Placebo (n=4502)	Pravastatin (n=4512)	Relative risk* (95% CI)
Cancer			
Prostate or testis cancer	145 (3·2%)	148 (3·3%)	1·00 (0·80–1·26)
Colorectal cancer	71 (1·6%)	75 (1·7%)	0·89 (0·63–1·24)
Respiratory cancer	85 (1·9%)	64 (1·4%)	0·76 (0·55–1·05)
Other carcinoma	89 (2·0%)	92 (2·0%)	0·99 (0·74–1·32)
Lymphoma or leukaemia	52 (1·2%)	37 (0·8%)	0·70 (0·46–1·07)
Bladder or kidney cancer	50 (1·1%)	60 (1·3%)	1·04 (0·71–1·52)
Melanoma or sarcoma	38 (0·8%)	39 (0·9%)	1·08 (0·69–1·70)
Any cancer†	526 (11·7%)	499 (11·1%)	0·91 (0·81–1·03)
Other serious adverse event‡			
Dermatological	235 (5·2%)	228 (5·1%)	0·94 (0·78–1·12)
Gastrointestinal	1098 (24·4%)	1046 (23·2%)	0·95 (0·87–1·03)
Hepatic or biliary	227 (5·0%)	234 (5·2%)	1·04 (0·87–1·25)
Myositis or myalgia§	71 (1·6%)	60 (1·3%)	0·83 (0·59–1·17)
Respiratory¶	756 (16·8%)	809 (17·9%)	1·08 (0·98–1·20)
Trauma‖	282 (6·3%)	272 (6·0%)	0·97 (0·82–1·15)

*Estimate from hazard ratio in Cox's regression model. †Any new cancer, excluding non-melanomatous skin cancer. ‡Life-threatening, fatal, resulted in hospital admission or permanently disabling. §No fatal episodes (one case of rhabdomyolysis in placebo group). ¶Infections, asthma, bronchitis, &c. ‖Suicides, accidents, violence.

Table 7: **Serious adverse events, including cancer, during total follow-up period and relative risk of adverse events with long-term pravastatin treatment (number of patients having at least one adverse event)**

has increased, suggesting that the cost-effectiveness of pravastatin in secondary prevention is also better than previously estimated.[6] Owing to the prolonged effects of treatment and the greater number of events with extended follow-up, separate evidence of treatment effectiveness in important subgroups and for each cardiovascular outcome is also somewhat stronger.

Patients in the LIPID,[3] CARE,[2] and 4S[1] trials were followed up for 6·0, 5·0, and 5·4 years, respectively, during the double-blind phases of these trials. Each study suggested a possible lag of 1–2 years before a treatment effect was seen, especially in terms of fatal outcomes. However, none of these trials provided clear evidence that the relative effects of treatment changed over time, and the possible lag to onset of benefit seen in these trials might have been a chance finding.[7] Nevertheless, if the onset of full treatment effects is delayed, the double-blind phase of each of these trials will underestimate the full long-term benefit of cholesterol-lowering treatment. This was the prespecified hypothesis for the extended phase of LIPID and the major rationale for continuing follow-up with face-to-face visits. That further significant reductions in cardiovascular mortality were seen during the open-label phase of therapy supports this hypothesis, since the patients were receiving essentially the same lipid treatment and had matching lipid profiles, and the additional treatment effects remained significant after adjustment for any differences in patients' risk profiles. Further, these effects are unlikely to be related to bias, because 97% of the main LIPID study survivors agreed to long-term follow-up (with all but one successfully followed up), and patients consented when they were not, as yet, aware of their original treatment assignment.

The results of greater benefit with extended follow-up are also consistent with long-term follow-up of earlier studies[8,9] and with epidemiological data that suggest that the long-term benefits of cholesterol lowering could be underestimated in randomised trials of about 5 years' duration.[10] The 4S trial, in particular, has provided similar evidence of a sustained effect of simvastatin in a population of patients with previous myocardial infarction and raised cholesterol concentrations.[9] After the main double-blind phase of this trial, most patients elected to take simvastatin treatment; a slightly higher proportion of those originally assigned simvastatin than of those assigned placebo took up the treatment (76% *vs* 72%). The simvastatin group had a lower rate of death than the placebo group (3·6% *vs* 4·9%) during this extended follow-up, and the relative reduction was similar to that during the double-blind phase. Although a small amount of this effect might have been related to the slightly higher rate of open-label simvastatin treatment in the group originally assigned simvastatin, most of the effect is consistent with a continued effect of earlier treatment, as seen in the LIPID study.

Evidence of the continued effect, in the LIPID study, was stronger for fatal events than non-fatal events. Some of this benefit might have been mediated through a reduction in earlier non-fatal cardiovascular events, since such events can strongly predict subsequent mortality. However, a regression analysis adjusted for these events during the main trial still showed significant reductions in mortality, suggesting that other mechanisms could be in operation.

By contrast with the evidence of late treatment benefits shown here, there is also evidence that HMG-CoA reductase inhibitors reduce the risk of cardiovascular events early, within 6 months of the start of treatment.[11–13] Such early effects, either through lipid changes or more directly, might be mediated through plaque stabilisation, improved endothelial function and vascular reactivity, and reduced thrombotic tendency.[11,14] We recently examined the role of lipid changes on CHD event reduction during the main LIPID trial and found that the all or most of the treatment effect was consistent with the amount of change in lipid concentrations.[15] However, the wide CIs on the proportion of the treatment effect explained by measured changes in lipids meant that additional non-lipid mechanisms were not excluded. Although different treatment mechanisms might operate for late and early effects, our trial can provide no direct evidence on this issue.

Treatment effects might thus be significantly greater when assessed over the longer term than from trials of medium-term (5 years') duration. This improvement will translate into larger absolute benefits of therapy, fewer numbers needed to treat to prevent major cardiovascular events, and better cost-effectiveness of treatment than previously realised. In the main LIPID trial, for every 1000 patients treated, death, myocardial infarction, or stroke was prevented in 47. With extended follow-up, these events were prevented in 58. However, this extra benefit was not associated with a further cost difference between the groups, since both groups were receiving the same treatment during the open-label phase. The estimated cost-effectiveness improved from about Australian $8000[6] to $6300 per life-year saved (US$4180 to $3290), making it a highly worthwhile intervention for almost all patients with CHD.

A further implication of this extended follow-up has been the clearer treatment benefits in important subgroups and for less common cardiovascular outcomes. However, the effects in subgroups are still weak relative to the whole cohort. These results are consistent with earlier results from large-scale trials[1,2,16] and the results of the Heart Protection Study (HPS).[17] Preliminary results from HPS, comparing simvastatin with placebo in over 20 500 patients with previous vascular disease or diabetes, have now provided strong evidence for a significant reduction in CHD events among women, patients older than 75 years, and those with LDL cholesterol concentrations of less than 2·6 mmol/L. HPS has therefore shown no threshold effect of treatment at lower baseline concentrations of cholesterol. The LIPID trial data with extended follow-up are also consistent with a policy of treatment for patients with previous CHD not determined by baseline lipid concentrations.

In LIPID, further events and continued lower rates of stroke among those originally assigned pravastatin, over an additional 2 years of extended follow-up, have strengthened the evidence that pravastatin reduces stroke.[18] The result is consistent with the results from other trials of HMG-CoA reductase inhibitors[1,2] and reinforced by the preliminary results from HPS.[17] Although epidemiological data do not provide a consistently positive relation between usual cholesterol concentration and stroke, prevention trials have now shown that HMG-CoA reductase inhibitors reduce the rate of ischaemic stroke.

Although LIPID and other trials have provided reassurance of the safety of pravastatin and simvastatin therapy over 5–6 years, cancers associated with long-term use of HMG-CoA reductase inhibitors might not appear over this period, so even longer follow-up would be needed to exclude this possibility. Epidemiological

studies[19] and a meta-analysis of highly selected randomised trials[20] had suggested a possible link between cholesterol lowering and cancer, but this possibility was not confirmed by systematic reviews of randomised trials.[21] Data over 7·4 years from 4S showed no excess of cancer deaths, but the result was based on small numbers of events (68 *vs* 52).[9] In our study, with more than 1000 cancers occurring over 9·4 years, the observed incidence of cancer in the patients originally assigned pravastatin is reassuringly lower than the rate among those originally assigned placebo. To obtain further evidence of long-term safety, we plan to continue to follow up all patients by way of a questionnaire, telephone calls, and health registries for at least a further 3 years.

The extended follow-up from LIPID, and the results of other large-scale trials, confirm the importance of treating almost all patients with previous CHD with HMG-CoA reductase inhibitors. Several registers of cardiovascular care show that the rates of the use of lipid-lowering therapy are still disappointingly low[22–25] and the discontinuation rates of such treatment too high.[26,27] Strategies that can increase the use of cholesterol-lowering treatment among patients with CHD continue to be as important to the reduction of the global burden of cardiovascular disease as the discovery of new treatments. Assuming there were at least 2 million deaths from cardiovascular disease worldwide each year,[28] which were potentially preventable by the greater use of lipid-lowering therapy, the treatment of an extra 25% of these patients could save more than 100 000 lives each year.

In conclusion, the extended follow-up of the LIPID trial has provided evidence of additional benefit and ongoing safety of cholesterol-lowering therapy continuing beyond the period of treatment difference in the trial. These results reinforce the importance of long-term cholesterol-lowering treatment for almost all patients with previous CHD events, and support taking a longer-term view in determining the net benefits of treatment.

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Conflict of interest statement

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