Long-Term Effectiveness and Safety of Pravastatin in Patients With Coronary Heart Disease

Sixteen Years of Follow-Up of the LIPID Study

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Background—We aimed to assess the long-term effects of treatment with statin therapy on all-cause mortality, cause-specific mortality, and cancer incidence from extended follow-up of the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial.

Methods and Results—LIPID initially compared pravastatin and placebo over 6 years in 9014 patients with previous coronary heart disease. After the double-blind period, all patients were offered open-label statin therapy. Data were obtained over a further 10 years from 7721 patients, by direct contact for 2 years, by questionnaires thereafter, and from mortality and cancer registries. During extended follow-up, 85% assigned pravastatin and 84% assigned placebo took statin therapy. Patients assigned pravastatin maintained a significantly lower risk of death from coronary heart disease (relative risk [RR] 0.89; 95% confidence interval [CI], 0.81–0.97; *P*=0.009), from cardiovascular disease (RR, 0.88; 95% CI, 0.81–0.95; *P*=0.002), and from any cause (RR, 0.91; 95% CI, 0.85–0.97; absolute risk reduction, 2.6%; *P*=0.003). Cancer incidence was similar by original treatment group during the double-blind period (RR, 0.94; 95% CI, 0.82–1.08; *P*=0.41), later follow-up (RR, 1.02; 95% CI, 0.91–1.14; *P*=0.74), and overall (RR, 0.99; 95% CI, 0.91–1.08; *P*=0.83). There were no significant differences in cancer mortality, or in the incidence of organ-specific cancers. Cancer findings were confirmed in a meta-analysis with other large statin trials with extended follow-up.

Conclusions—In LIPID, the absolute survival benefit from 6 years of pravastatin treatment appeared to be maintained for the next 10 years, with a similar risk of death among survivors in both groups after the initial period. Treatment with statins does not influence cancer or death from noncardiovascular causes during long-term follow-up. **(*Circulation*. 2016;133:1851-1860. DOI: 10.1161/CIRCULATIONAHA.115.018580.)**

Key Words: cardiovascular diseases ■ cholesterol ■ coronary disease ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ lipids

Many trials have shown that inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (or statins) reduce the risk of death and major cardiovascular events after acute myocardial infarction and unstable angina pectoris.[1–4] One of these, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, showed that 6 years of pravastatin treatment resulted in better survival.[4]

Clinical Perspective on p 1860

The longer-term effects of statins on cause-specific mortality and net clinical benefit are still debated, particularly in terms of effects on cancer and other noncardiovascular disease (CVD) mortality. Older epidemiological and randomized studies of cholesterol lowering had raised safety concerns,

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including possible increased incidence of cancer, overall or for particular cancer sites.[5–8] Conversely, the possibility of beneficial effects of statins on other non-CVD deaths has also been raised.[9]

Large statin trials have demonstrated safety over an average of 5 years of treatment.[10] For outcomes such as cancer, there may be a long lag between a causal exposure and clinical evidence of disease. In this study, cancer incidence and mortality, and mortality from other causes, as well, were evaluated during 16 years follow-up in the LIPID trial. In addition, we undertook a meta-analysis of cancer events in LIPID together with those in other large statin trials during long-term follow-up.

Methods

Double-Blind Period

The design and results of the original study have been published.[4] Between 1990 and 1992, the trial randomly assigned 9014 patients from 67 centers in Australia and 20 centers in New Zealand with a previous diagnosis of acute myocardial infarction or unstable angina pectoris to pravastatin 40 mg per day or placebo. The primary study outcome was coronary heart disease (CHD) mortality.

Extended Follow-Up

Open-Label Treatment Period

After early closure of the placebo-controlled trial in 1997, after the prespecified difference in overall mortality had been reached, patients still alive were seen in clinics and offered open-label pravastatin, 40 mg daily, irrespective of their original assigned therapy, and followed up for a further 2 years (Figure 1).[11]

Longer-Term Follow-Up Period

After completion of the 2-year open-label period, funding for clinic visits ceased and decisions about ongoing lipid-lowering treatment were made by patients and their usual doctors. Surviving patients were then followed up from the National Health and Medical Research Council Clinical Trials Centre until the end of 2007 by 2 methods. First, all patients were sent an annual questionnaire for 4 years related to changes in their statin treatment, general nominated next-of-kin, and vital status. Nonresponders were followed up by telephone or through previously nominated next of kin or local doctor. A final questionnaire was sent at the end of the long-term follow-up period. Second, information on cause-specific mortality and cancer incidence

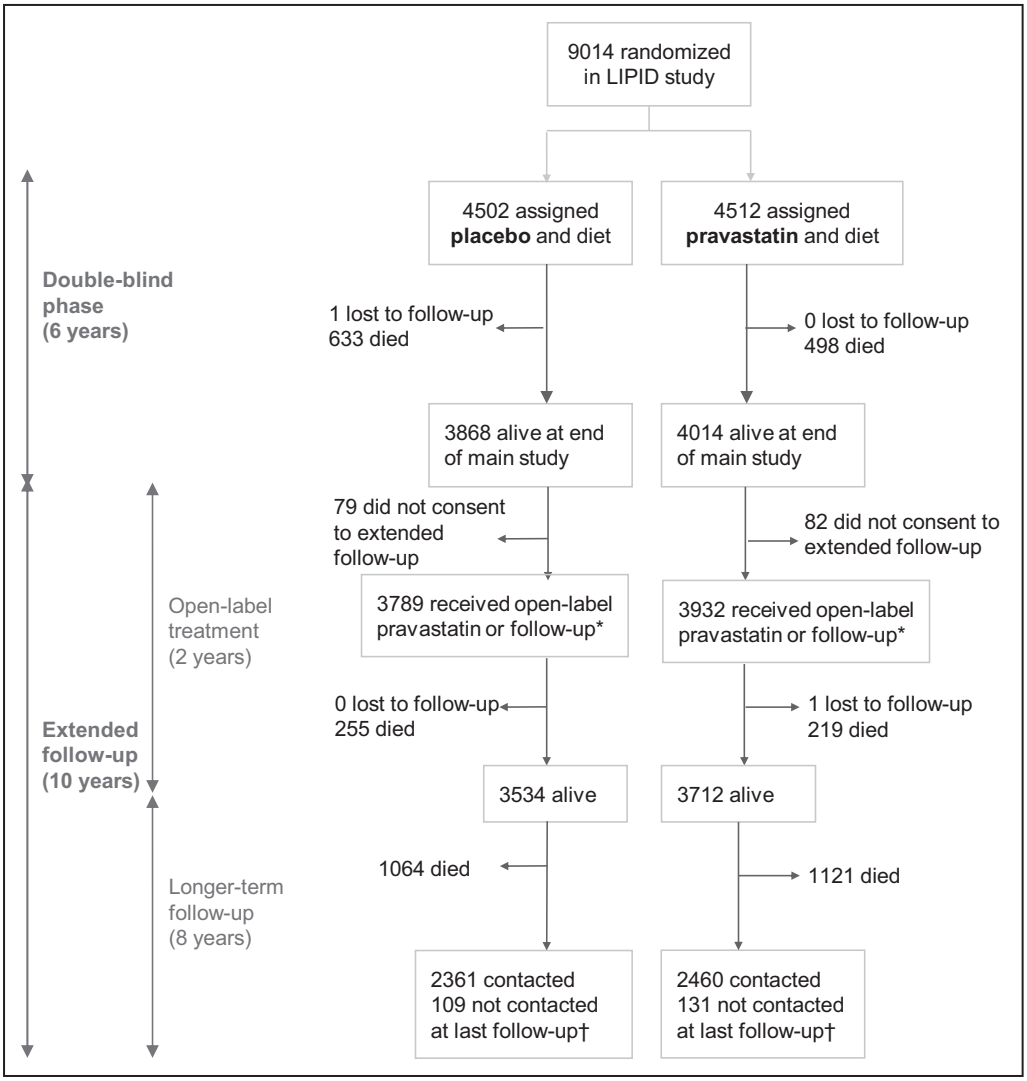

Figure 1. Patient enrolment and progress through follow-up. *Additional patients subsequently consented to follow-up and completed questionnaires in the open-label phase (23 [placebo] and 18 [pravastatin] more than previously reported).[11] †The 240 patients not contacted were tracked through registries, so vital status was complete on >99% of the whole cohort.

Table 1. Baseline Characteristics of All Patients in the Randomized Phase of the Study and Those Followed Up Only in the Subsequent Open-Label Phase

Characteristic	Whole Study*		Followed up in the Open-Label Phase	
	Placebo (n=4502)	Pravastatin (n=4512)	Placebo (n=3789)	Pravastatin (n=3932)
Age				
Median (interquartile interval)	62(55–68)	62(55–67)	62 (55–67)	62 (55–67)
Age group, y, n (%)				
<55	1021 (23)	1065 (24)	928 (24)	979 (25)
55–64	1708 (38)	1706 (38)	1484 (39)	1520 (39)
65–69	1087 (24)	1081 (24)	860 (23)	920 (23)
≥70	686 (15)	660 (15)	517 (14)	513 (13)
Sex, n (%)				
Men	3742 (83)	3756 (83)	3127 (83)	3269 (83)
Women	760 (17)	756 (17)	662 (17)	663 (17)
Qualifying event, n (%)				
Myocardial infarction	2875 (64)	2879 (64)	2413 (64)	2495 (63)
Unstable angina	1627 (36)	1633 (36)	1376 (36)	1437 (37)
CHD risk factors, n (%)				
Current smoker	444 (10)	425 (9)	351 (9)	353 (9)
Ex-smoker or never-smoker				
History of hypertension	1891 (42)	1867 (41)	1582 (42)	1621 (41)
Diabetes mellitus	386 (9)	396 (9)	284 (7)	311 (8)
Obesity (BMI ≥30)	788 (18)	823 (18)	659 (17)	697 (18)
Other vascular disease, n (%)				
Peripheral vascular disease	467 (10)	438 (10)	368 (10)	357 (9)
History of stroke	198 (4)	171 (4)	145 (4)	133 (3)
History of transient ischemic attack	176 (4)	156 (3)	137 (4)	130 (3)
Revascularization, n (%)				
Percutaneous coronary intervention only (PCI)	486 (11)	502 (11)	437 (12)	468 (12)
Coronary artery bypass only (CABG)	1219 (27)	1217 (27)	1020 (27)	1061 (27)
Both PCI and CABG	133 (3)	135 (3)	115 (3)	121 (3)
Medication use, n (%)				
Aspirin	3684 (82)	3718 (82)	3132 (83)	3282 (83)
ACE Inhibitor	713 (16)	720 (16)	531 (14)	570 (14)
β-Blocker	2151 (48)	2078 (46)	1831 (48)	1852 (47)
Calcium channel blocker	1574 (35)	1538 (34)	1291 (34)	1329 (34)
Nitrate	1331 (30)	1346 (30)	1067 (28)	1115 (28)
LIPID risk score†	6 (4–8)	6 (4–8)	6 (3–8)	6 (3–8)
Lipid concentrations, mmol/L, median (interquartile interval)				
Total cholesterol	5.7 (5.1–6.2)	5.7 (5.1–6.2)	5.7 (5.1–6.2)	5.7 (5.1–6.2)
LDL cholesterol	3.9 (3.4–4.4)	3.9 (3.4–4.4)	3.9 (3.4–4.4)	3.9 (3.4–4.4)
HDL cholesterol	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.1)
Triglycerides	1.6 (1.2–2.1)	1.6 (1.2–2.2)	1.6 (1.2–2.1)	1.6 (1.2–2.2)
Total cholesterol/HDL ratio	6.1 (5.1–7.1)	6.1 (5.1–7.2)	6.1 (5.1–7.1)	6.1 (5.1–7.1)

BMI indicates body mass index (kg/m^2); HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*This includes 663 patients in the placebo group and 498 in the pravastatin group who had died by the end of the double-blind phase and therefore were not available for long-term follow-up.

†Median (interquartile interval). Risk score variables: total cholesterol, HDL cholesterol, age, sex, smoking, previous myocardial infarction, timing of previous revascularization (before or after randomization), previous stroke, diabetes mellitus, and history of hypertension.

was obtained through data linkage with national death registries and state-based cancer registries in Australia and New Zealand. Linkage was by probabilistic matching of demographic details followed by clerical review and confirmation of possible matches.

A validation study comparing cause-specific mortality data obtained by clinic staff in the earlier randomized phase of the trial with Australian national death registry data showed reasonable concordance in major groupings (sensitivity, 93%; specificity, 90%).[12]

Statistical Analyses

Data were analyzed according to the patients' originally assigned therapy, referred to as the pravastatin group and the placebo group.

Estimates of relative risk and 95% confidence intervals used Cox models for the double-blind period and the period of extended follow-up, because of nonproportional hazards, in a time-partitioned analysis. Relative risk for the total period was a weighted average of the estimates of the 2 periods.[13] All *P* values for these models were from log-rank tests. These analyses were unadjusted for other baseline risk factors. A sensitivity analysis of treatment effects adjusted for main baseline factors was also undertaken. Analysis for the extended follow-up period was based on data from the survivors, who consented to additional follow-up, at the end of the double-blind period. Prespecified subgroup analyses examined the variation in treatment effect on the primary outcome of CHD death, based on tests for interaction in Cox models. *P* values were not adjusted for multiple comparisons. In addition, a competing-risk analysis was performed for cause-specific mortality and cancer incidence, producing very similar results. Analyses were undertaken with SAS version 9.1 (SAS Institute Inc, Cary, NC).

Meta-Analysis of Cancer in Long-Term Statin Trials

A meta-analysis of cancer incidence and cancer mortality was performed for large randomized trials with extended follow-up. Eligible studies were randomized trials of statin therapy in comparison with no statin or usual care with at least 1000 patients, treatment duration of at least 2 years, and with at least 5 years' follow-up after the randomized trial period. Studies were sourced from all trials registered in the Cholesterol Treatment Trialists' Collaboration up to 2005 by a literature search of published results and by contact with each trial group directly.[10]

Estimates of treatment effect of initial statin therapy versus placebo on cancer incidence and mortality were obtained as combined risk ratio estimates from each trial by the Mantel-Haenszel method using Cochrane Collaboration Review Manager software, version 5.2,[14] for the double-blind period, the period of extended follow-up, and the total period.

Ethics Approval

The LIPID trial was approved by the ethics committee at each participating center. All patients gave written informed consent for the trial and separately for further clinic or remote follow-up.

Results

A total of 9014 patients were randomly assigned, and 7882 survived the double-blind period (mean, 6.0 years). All but 161 (2.0%) patients consented to long-term follow-up and all but 241 (3.1% of the surviving patients) completed an average further 10 years of remote follow-up (Figure 1). Vital status was determined from direct contact or registry for >99% of this cohort. Patients' characteristics were very well balanced at baseline and remained so among those patients who were alive and followed up in the extended follow-up period (Table 1). Patients surviving the initial double-blind period, who were then followed up long term, were somewhat younger (median, 62 versus 65 years), with less history of smoking, diabetes mellitus, or other CVD, and with a better LIPID risk score (median, 6 versus 7),[15] than those patients followed only during the double-blind period (data not presented).

Long-Term Statin Adherence

At the end of the double-blind treatment period, 852 (19%) of patients assigned pravastatin had discontinued this therapy, whereas 1071 (24%) of those assigned placebo had commenced cholesterol-lowering therapy.[11] During extended follow-up, at the start of the 2-year open-label treatment period, 88% of patients in the pravastatin group and 86% in the placebo group commenced statin therapy. After the open-label period, data on the use of statins among survivors was obtained by questionnaire from 99% for the first 4 years (87% from written responses and the additional 12% via phone follow-up) and subsequently from 86% from the final questionnaire (when no additional phone follow-up was done). Among those completing questionnaires, 85% of the original pravastatin group and 84% the placebo group continued taking statin treatment (averaged over this period; Figure 2). However, the type of statin changed over time. Pravastatin was the most common statin prescribed initially, at 49%, decreasing to 25% in 2007, whereas use of simvastatin increased (from 27% to 32%), as did use of the newer statins: atorvastatin (from 19% to 31%) and others (from 3% to 11%; Figure I in the online-only Data Supplement). Although statin dose was not recorded on questionnaires, routine daily doses prescribed at the time were pravastatin 40 mg, simvastatin 20 mg, and atorvastatin 10 mg. There was reasonably good agreement between consecutive questionnaires on whether patients reported ongoing statin use (average κ statistic, 0.66) and type of statin used (average κ statistic, 0.85).

Information on lipid profiles was only collected during the first 2 years of open-label treatment (the extended follow-up period). During this period, average low-density lipoprotein cholesterol levels were almost identical for the 2

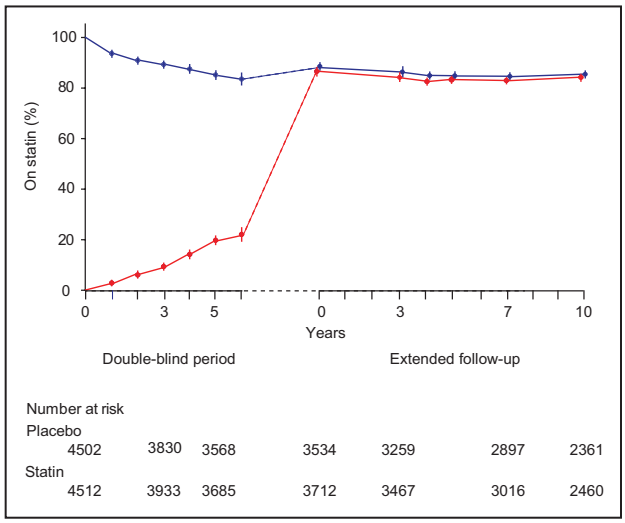

Figure 2. Proportions of patients on statin treatment during each period of the LIPID study over an average of 16 years.

groups: 2.66 mmol/L for placebo patients and 2.63 mmol/L for pravastatin patients.[11]

Sustained Treatment Effects on Cause-Specific Mortality

The effects of initial assignment to pravastatin on cause-specific mortality during the double-blind phase and during the extended follow-up period are shown in Table 2 and Figure 3. Over the 16-year follow-up period, the reductions in the risk of death from CHD, CVD, and any cause remained highly statistically significant.

During the extended follow-up period, when both groups were receiving similar statin therapy, there was no significant difference between the original treatment groups in the risk of death from any cause, overall (relative risk [RR], 0.97; 95% confidence interval [CI], 0.90–1.05; *P*=0.46) or from any specific cause, including CHD, CVD, and cancer (Table 2).

The relative effect of initial pravastatin treatment declined over time from a relative reduction of 23% in all deaths at the

Table 2. The Effect of Pravastatin on Cause-Specific Mortality in the LIPID Study, by Trial Period

Trial Period and Cause of Death	Events, n (%)		Relative Risk (95% CI)*	*P*
	Placebo	Pravastatin		
All-cause				
Double-blind	633 (14.1)	498 (11.0)	0.77 (0.69–0.87)	<0.001
Extended follow-up	1319 (34.8)	1341 (34.1)	0.97 (0.90–1.05)	0.46
All years	1952 (43.4)	1839 (40.8)	0.91 (0.85–0.97)	0.003
Cardiovascular				
Double-blind	433 (9.6)	331 (7.3)	0.75 (0.65–0.87)	<0.001
Extended follow-up	765 (20.2)	756 (19.2)	0.94 (0.85–1.04)	0.27
All years	1198 (26.6)	1087 (24.1)	0.88 (0.81–0.95)	0.002
CHD				
Double-blind	373 (8.3)	287 (6.4)	0.76 (0.65–0.88)	<0.001
Extended follow-up	606 (16.0)	612 (15.6)	0.97 (0.86–1.08)	0.54
All years	979 (21.7)	899 (19.9)	0.89 (0.81–0.97)	0.009
Vascular (non-CHD)				
Double-blind	60 (1.3)	44 (1.0)	0.72 (0.49–1.07)	0.10
Extended follow-up	159 (4.2)	144 (3.7)	0.87 (0.60–1.09)	0.21
All years	219 (4.9)	188 (4.2)	0.83 (0.68–1.00)	0.05
Noncardiovascular				
Double-blind	200 (4.4)	167 (3.7)	0.82 (0.67–1.01)	0.06
Extended follow-up	554 (14.6)	585 (14.9)	1.01 (0.90–1.13)	0.87
All years	754 (16.7)	752 (16.7)	0.96 (0.87–1.06)	0.42
Cancer				
Double-blind	141 (3.1)	128 (2.8)	0.89 (0.70–1.13)	0.35
Extended follow-up	321 (8.5)	357 (9.1)	1.06 (0.91–1.24)	0.43
All years	462 (10.3)	485 (10.7)	1.01 (0.89–1.15)	0.87
Respiratory or infection				
Double-blind	28 (0.6)	22 (0.5)	0.77 (0.44–1.35)	0.36
Extended follow-up	53 (1.4)	52 (1.3)	0.94 (0.64–1.37)	0.72
All years	81 (1.8)	74 (1.6)	0.88 (0.64–1.21)	0.43
Other†				
Double-blind	31 (0.7)	17 (0.4)	0.54 (0.30–0.97)	0.04
Extended follow-up	180 (4.8)	176 (4.5)	0.94 (0.76–1.15)	0.54
All years	211 (4.7)	193 (4.3)	0.88 (0.72–1.07)	0.19

CHD indicates coronary heart disease; and CI, confidence interval.

*Estimated by hazard ratio (95% confidence interval) for statin vs placebo or control within the 2 periods and as a weighted average of these 2 for all years.

†Not vascular, cancer, respiratory, or infection.

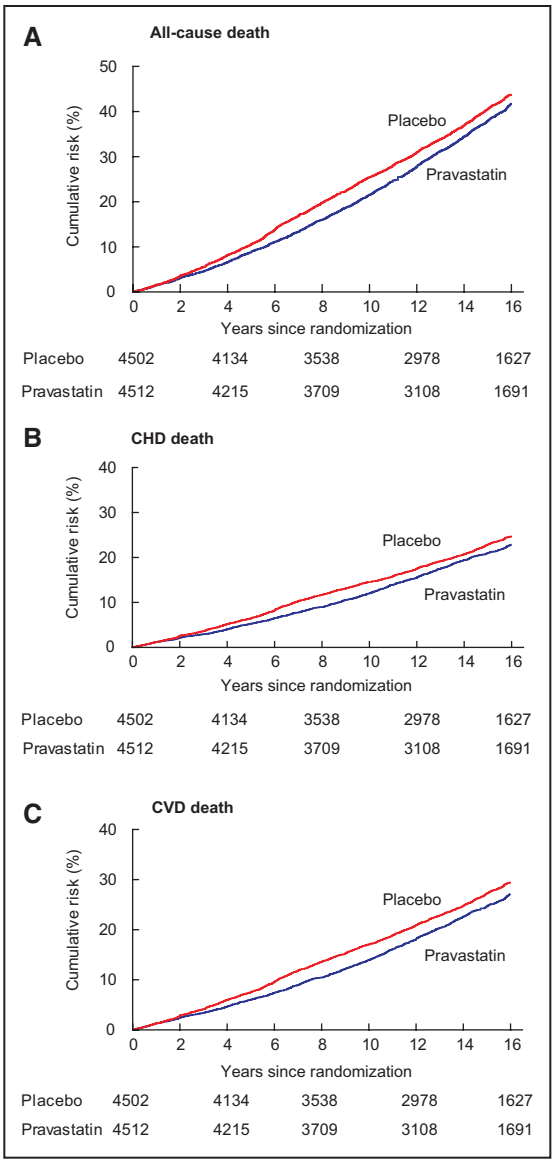

Figure 3. Cumulative risk of cause-specific death over 16 years of follow-up among patients randomly assigned to initial pravastatin or placebo for an average of 6 years followed by optional statin therapy, with numbers of patients alive and followed up. Deaths from any cause (**A**), from CHD (**B**), and from CVD (**C**). CHD indicates coronary heart disease; and CVD, cardiovascular disease.

end of the double-blind period to 9% at the end of 16 years, but the absolute effects of the initial 6 years of statin therapy remained similar: for every 1000 patients assigned pravastatin, in comparison with placebo, over 16 years there were 26 fewer deaths (versus 31 over 6 years); 25 fewer CVD deaths (versus 23 over 6 years), and 18 fewer CHD deaths (versus 19 over 6 years) (Table 2).

There was no significant difference in the risk of death from non-CVD causes over the 16-year period (Figure 4). There were no differences in the specific category of deaths from respiratory disease or infection (Table 2). The risk of death from other causes (non-CVD, cancer, respiratory, or infection) appeared reduced by pravastatin treatment during the double-blind phase (RR, 0.54; 95% CI, 0.30–0.97; P=0.04), but was

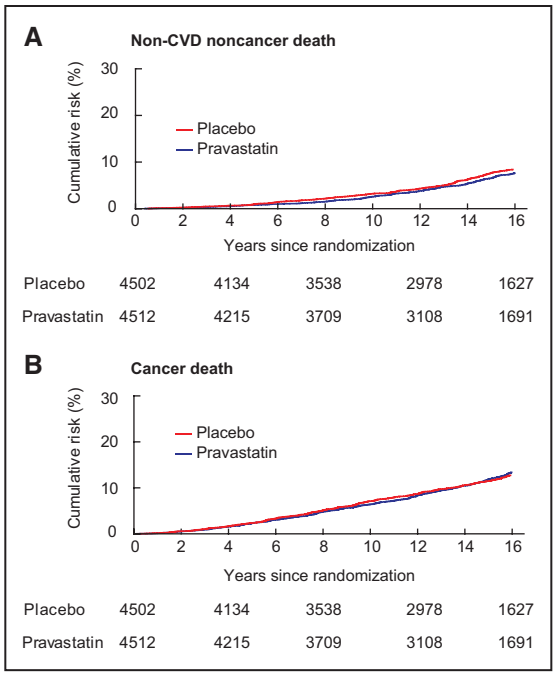

Figure 4. Cumulative risk of death from non-CVD and noncancer causes (**A**) and from cancer (**B**) over 16 years of follow-up among patients randomly assigned to initial pravastatin or placebo for an average of 6 years followed by optional statin therapy, with numbers of patients alive and followed up. CVD indicates cardiovascular disease.

not significantly different during the extended follow-up period or overall (RR, 0.88; 95% CI, 0.72–1.07; P=0.19). An analysis of treatment effects on cause-specific mortality adjusted for other baseline factors did not materially alter these findings.

Treatment Effects in Subgroups

The effect of initial pravastatin on long-term CHD mortality in prespecified subgroups is shown in Figure II in the online-only Data Supplement. For each of the subgroups (by age, sex, history of qualifying event, hypertension, diabetes mellitus, smoking, and lipid categories), there was no evidence of heterogeneity of the treatment effect on CHD mortality in the double-blind phase or the overall 16-year period.

Treatment Effects on Cancer

The risk of death from cancer did not differ significantly between the 2 groups during the double-blind phase, the follow-up period, or overall (Table 2, Figure 4).

There were no significant differences between the original treatment groups in cancer incidence during the double-blind phase (RR, 0.94; 95% CI, 0.82–1.08; P=0.41), later follow-up (RR, 1.02; 95% CI, 0.91–1.14; P=0.74), or overall (RR, 0.99; 95% CI, 0.91–1.08; P=0.83) and no significant differences in the incidence of organ-specific cancers over these periods (Figure 5, Table I in the online-only Data Supplement). During the extended follow-up period, there was an apparent slight reduction in the incidence of melanoma with initial pravastatin (RR, 0.71; 95% CI, 0.51–0.98; P=0.04) and an apparent slight increase in bladder or kidney cancer (RR, 1.38, 95% CI, 0.97–1.97, P=0.07), but this was not significant over the total period (Table I in the online-only Data Supplement, Figure 5).

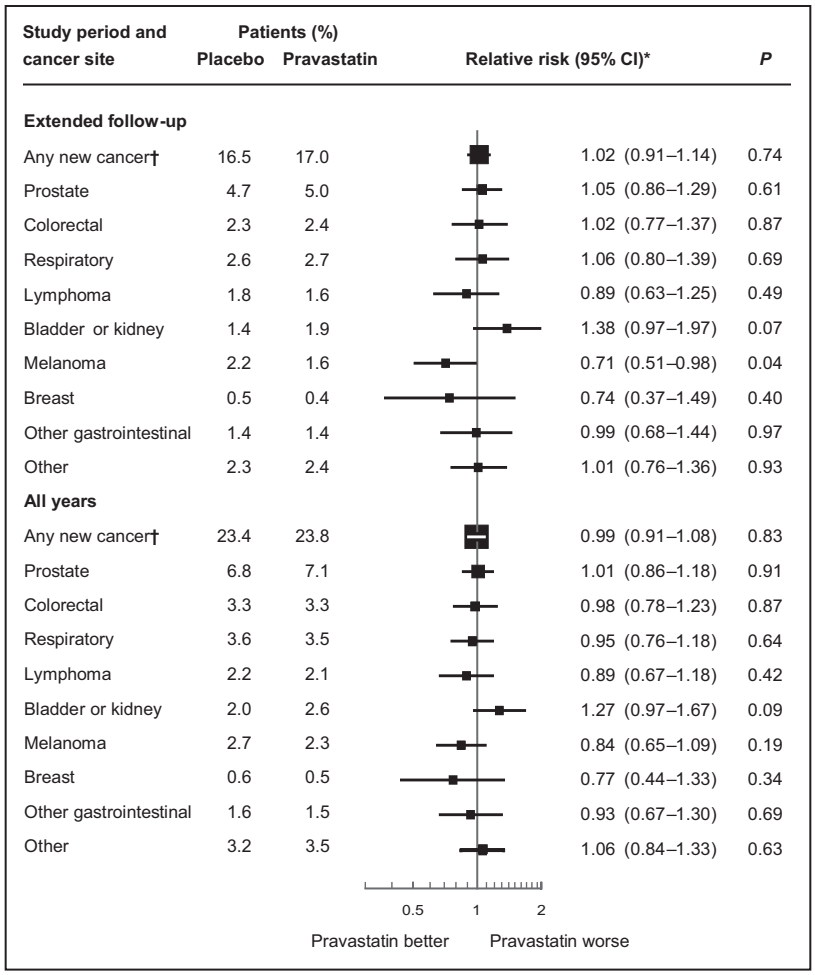

Figure 5. Cancer incidence, overall and by organ-specific site, over 16 years of follow-up among patients randomly assigned to initial pravastatin or placebo for an average of 6 years. Patients with at least 1 new cancer during the extended follow-up period and over all years. *Relative risk estimated by hazard ratio for statin vs placebo or control. CI indicates confidence interval.

A meta-analysis of the effects of statins on cancer in large-scale statin trials is shown in Figure 6 for the LIPID study, Heart Protection Study,[16] Scandinavian Simvastatin Survival Study (4S),[17] West of Scotland Coronary Prevention Study (WOSCOPS),[18] Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA),[9] and Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study.[19] These trials compared statin and placebo taken for a period of 3 to 6 years, followed by at least 5 years of optional statin therapy for both groups. During the extended follow-up periods of these trials, statin therapy was used to a similar extent in both randomized groups and by most patients (65%–85%), with the exception of WOSCOPS, in which posttrial statin use began at 35% to 40%. The original randomized groups showed no significant difference in cancer mortality or cancer incidence during the double-blind period, extended follow-up, or overall years (Figure 6 and Table II in the online-only Data Supplement).

Discussion

With a total of 16 years of follow-up, the LIPID study provides clear evidence that an initial 6 years of pravastatin treatment results in sustained overall survival benefit primarily related to a sustained reduction in deaths from CVD. During the 10 years of extended follow-up, almost the same proportion of each group received statin therapy (≈85%), with likely similar lipid profiles achieved, so that all treatment benefit can be attributed to differences in pravastatin therapy in the first 6 years. Because no further benefit or harm on cause-specific mortality was seen over these additional 10 years, the relative effects of initial therapy on the total period were lessened, but the absolute benefits were largely similar to those seen after the initial 6 years.

Adherence to statin treatment in LIPID remained high and steady at ≈85% for the 10 years of open-label treatment and was similar to or higher than in the other large secondary prevention statin studies. This level is much higher than has been reported in clinical practice. For example, in Australia, only 57% at 6 months and 30% at 5 years remained on treatment,[20] whereas in the United States adherence has been reported as 60% at 3 months and 26% at 5 years.[21] The reason for the excellent long-term adherence in the LIPID study may be related to several factors, including the screening of patients with a placebo run-in phase, and hence the selection of a patient group more likely to adhere to long-term therapy, and ongoing encouragement of compliance during the trial and feedback of trial results, as well, showing the benefits of therapy at the end of the double-blind phase. In any event, they demonstrate the long-term tolerance of statin therapy among the large majority of patients.

The mechanisms by which the benefits of early statin treatment are durable well beyond the randomized treatment

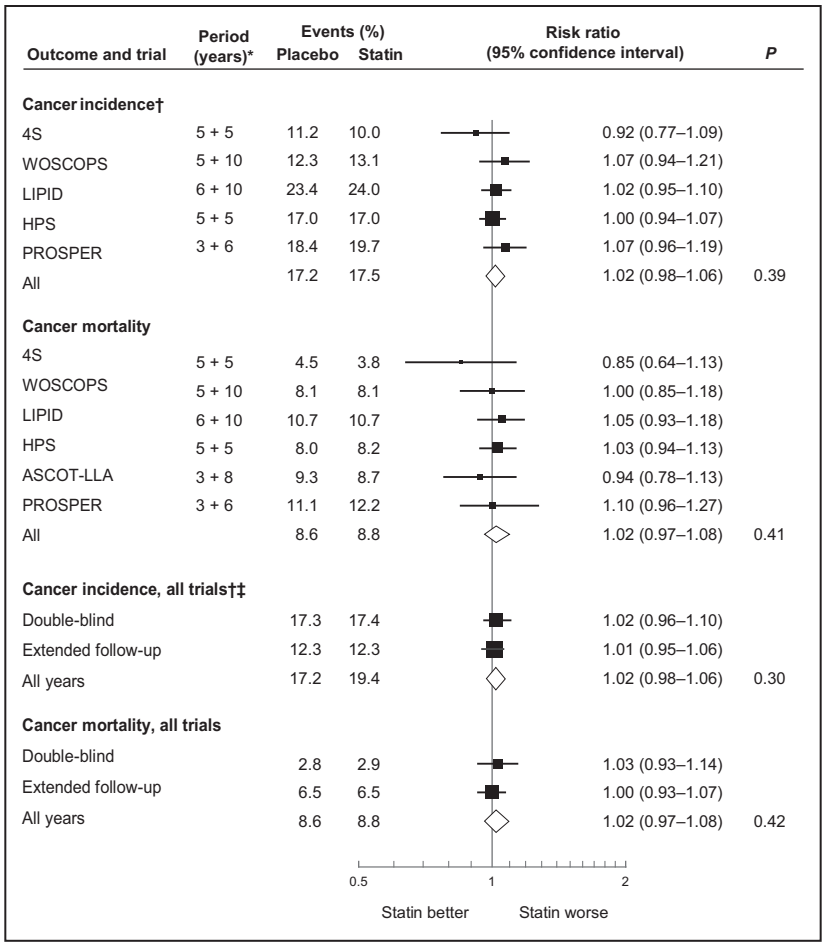

Figure 6. Risk ratios for cancer incidence and cancer mortality among patients randomly assigned to initial statin therapy or placebo in large-scale trials with extended follow-up: for the double-blind period, for extended follow-up, and for all years. *Total follow-up, shown as double-blind period plus extended follow-up. (For example, 5+10 means 5 years for double-blind period plus an additional 10 years of extended follow-up). †ASCOT-LLA not included in cancer incidence data. ‡4S not included in grouped cancer incidence data for period subcategories.

period remain incompletely understood. In some studies, ongoing treatment benefit or so-called legacy effects, with hazard ratios <1 beyond the randomized period have been seen in trials such as the ASCOT-LLA[9] and the recently reported extended follow-up from WOSCOPS.[22] In these trials, a within-trial slowing of the atherosclerotic process may leave treated participants with a long-term advantage, or favorable biological alterations, such as epigenetic changes, may persist beyond the trial period. If, after a coronary event, further events depend on development of a critical mass of new atheromatous disease, and statin therapy delays this for a number of years, then even where the statin therapy becomes equivalent, a long-term advantage would ensue among those who had been initially treated. For other trials, including 4S, HPS, and LIPID (over the longer term), early survival benefits have been largely maintained but without ongoing reductions in hazard ratios separately for the posttrial period. This suggests that the additional long-term survivors of such initial statin therapy may have at least as favorable a risk profile as other lower-risk patients surviving without such statin therapy. Regardless of the underlying mechanism, these data show long-term benefits of statins for at least a further decade after initial statin therapy.

The results also provide reassurance on the long-term safety of statins in relation to non-CVD causes of death, cancer incidence, and cancer mortality. Early observational studies and randomized controlled trials of cholesterol lowering had raised the possibility of an increase in cancer risk with cholesterol-lowering therapies.[5,6] Some recent case-control studies have conversely suggested lower risks of breast, colorectal, and prostate cancer with statin use,[7,8] and some recent large cohort studies and reviews have found a higher incidence of prostate cancer[23] and a tendency for protection against colorectal cancer.[24] However, most have found no differences in cancers overall or specific cancers.[25–28] Importantly, the combined analysis of 175 000 participants in 27 randomized trials of statin therapy[10,29] did not find any significant increase or reduction in cancer incidence or cancer mortality over 5 years, overall, or for any site-specific cancer. Although these studies provide reassurance of no adverse effect from cancers in the short term, follow-up over at least a further 5 to 10 years is needed to assess any possible effect causing cancer. The LIPID study found no evidence of statin-related cancer risk either over the full 16-year period or during the extended follow-up period when any delayed effect might emerge.

Although studies such as WOSCOPS have provided important evidence on long-term outcomes, LIPID adds substantial new information to the long-term safety and effectiveness of statin treatment. In contrast to WOSCOPS, LIPID involved patients with previous CHD and with average cholesterol levels, included ≈1500 women and 7500 men, and accumulated data on >3700 deaths and 2000 cancers during 16 years of follow-up.

In previous studies, possible adverse effects of cholesterol-lowering treatment in relation to cancer have been reported in individual trials but not subsequently confirmed when all relevant randomized evidence has been assessed. For example, a higher risk of breast cancer in the Cholesterol and Recurrent Events (CARE) trial (12 cases versus 1; P=0.002)[2] was not seen when all other 26 studies in the Cholesterol Treatment Trialists' Collaboration meta-analysis were reviewed. A possible increase in prostate cancer in the WOSCOPS study during the randomized phase and at the end of 10 years of subsequent follow-up (P=0.03)[18] was not seen in the other studies.[29] In PROSPER, cancer incidence was slightly higher at the 4-year follow-up analysis,[30] but not at 10 years.[19] Cancer incidence was slightly higher in patients randomly assigned to pravastatin in the elderly subgroup of LIPID during the double-blind trial period,[31] but not with further follow-up. Finally, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study reported a higher risk of cancer with ezetimibe, which was not confirmed in 2 other large-scale randomized trials of this treatment.[32]

The combined results of all large-scale randomized trials of statins with long-term follow-up provide the best evidence on safety with respect to possible cancer. In addition to LIPID, 5 trials have published results with 5 to 10 years of follow-up beyond the double-blind period.[1,9,16–19] Together, these studies report on >8000 cancers in >46 000 patients, with no consistent evidence of increased cancer mortality risk or increased cancer incidence, providing additional reassurance of safety.

In most randomized studies, statins have had no appreciable effect on non-CVD mortality.[10] In the double-blind phase of LIPID, non-CVD mortality was slightly lower with pravastatin treatment, although not related to any specific cause, and this was not seen during the extended follow-up period or overall. These slight differences are consistent with chance effects. In the ASCOT-LLA study,[9] the rates of death from respiratory causes or infections appeared lower in the treatment group, especially in the follow-up period. Although rates of deaths from these causes were also slightly lower in the LIPID study, these were not statistically significant and have not been reported in other trials. Although non-CVD mortality was not clearly lower, the LIPID study does provide additional evidence of no harm in this regard over 16 years.

Although these data provide reassurance of long-term safety and effectiveness, there are some limitations. We were not able to obtain data directly from patients in the clinic over the full 16 years, in particular, morbidity data beyond 8 years. But mortality and cancer incidence data were obtained through registries, and previous analyses were undertaken to validate the approach.[12] Furthermore, although we did not undertake external validation of our questionnaires, data across consecutive questionnaires were internally consistent. The current analysis does not address any short-term benefits or harms of pravastatin where the additional 10 years of follow-up will dilute any differences seen early. This is best addressed from the double-blind period of therapy from LIPID and other large-scale trials.[10,13,29] An additional limitation is that the meta-analysis of large-scale statin trials here used aggregated data with varying periods of initial treatment and follow-up. Although this should not affect qualitative conclusions, analysis of individual patient data from all these trials on cause-specific mortality and cancer incidence would be of particular value.

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CLINICAL PERSPECTIVE

An ever-increasing number of patients are being prescribed statin therapy, so it has become more important to ensure that this drug class is very safe. After 16 years of follow-up, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study provides clear evidence that an initial 6 years of pravastatin treatment results in sustained overall survival benefit for patients with a history of coronary heart disease and average cholesterol levels. The survival benefit was primarily related to deaths from cardiovascular disease. The results will also reassure clinicians on the long-term safety of statins in relation to noncardiovascular causes of death, cancer incidence, and cancer mortality. The LIPID study found no evidence that pravastatin treatment affected cancer incidence during the 10-year extended follow-up period when any delayed effect might emerge. This finding was emphasized by the accompanying meta-analysis of long-term data from other statin trials. The high levels of adherence to pravastatin therapy also indicate that treatment is likely to be well tolerated by typical patients. These results strengthen the evidence supporting long-term continued use of statin therapy in patients who are at risk of further cardiovascular events.