Relationship Between Plasma LDL Concentrations During Treatment With Pravastatin and Recurrent Coronary Events in the Cholesterol and Recurrent Events Trial

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Background—Although LDL lowering has been shown to reduce recurrent coronary events in patients with coronary heart disease, little direct information is available on the extent of LDL lowering required to achieve this outcome.

Methods and Results—The Cholesterol and Recurrent Events (CARE) trial compared pravastatin and placebo in patients who had experienced myocardial infarction (MI) who had average concentrations of total cholesterol (baseline mean, 209 mg/dL) and LDL cholesterol (LDL) 115 to 174 mg/dL (mean, 139 mg/dL). Pravastatin reduced coronary death or recurrent MI by 24%. In multivariate analysis, the LDL concentration achieved during follow-up was a significant, although nonlinear, predictor of the coronary event rate ($P = .007$), whereas the extent of LDL reduction was not significant, whether expressed as an absolute amount ($P = .97$) or a percentage ($P = .76$). The coronary event rate declined as LDL decreased during follow-up from 174 to $\approx 125$ mg/dL, but no further decline was seen in the LDL range from 125 to 71 mg/dL. In multivariate analysis, triglyceride but not HDL concentrations during follow-up were weakly but significantly associated with the coronary event rate.

Conclusions—The LDL concentrations achieved during treatment with pravastatin or placebo were associated with reduction in coronary events down to an LDL concentration of $\approx 125$ mg/dL. LDL concentrations <125 mg/dL during treatment were not associated with further benefit. Absolute or percentage reduction in LDL had little relationship to coronary events. (Circulation. 1998;97:1446-1452.)

Key Words: lipoproteins ■ cholesterol ■ coronary disease ■ drugs

The beneficial effects of cholesterol-lowering therapy for the primary and secondary prevention of CHD have been conclusively demonstrated in large-scale clinical trials.1–5 Meta-analysis of trials in hypercholesterolemic patients suggested that the reduction in cardiovascular events and in total mortality is directly proportional to the mean percentage reduction of elevated plasma cholesterol concentrations.1 However, there are limitations to such a conclusion. First, the predominantly high pretreatment LDL concentrations of patients in these trials are not representative of the LDL concentrations of the majority of contemporary CHD patients.6–8 Second, the mean LDL cholesterol concentration during therapy was also relatively high, 125 to 175 mg/dL.2,3,9,10 corresponding to the average pretreatment range for North American and European populations with CHD.6–8 There is no information on the relationship between LDL during treatment and coronary events with LDL concentrations <125 mg/dL that can now be regularly achieved in the majority of patients with CHD using inhibitors of HMG-CoA reductase. For these reasons, the relationship between LDL concentrations and their reduction during treatment and the incidence of recurrent coronary events requires further definition.

The CARE trial5 provides the opportunity to study the effect of lowering LDL to levels not previously achieved in large-scale clinical trials on coronary events. The combination of a pretreatment range of LDL concentrations of 115 to 175 mg/dL, encompassing approximately the 20th to 80th percentiles of the North American population of patients with CHD, and an average reduction of LDL of 32% in the pravastatin group produced LDL concentrations during the trial ranging from 71 to 136 mg/dL. Pravastatin treatment significantly reduced the incidence of the primary end point of the trial, fatal CHD or nonfatal MI, by 24%, and of coronary revascularization procedures by 27%. In this report, the relations between several measures of the effect of pravastatin on the risk of coronary events were investigated: the LDL concentration achieved during therapy, the absolute reduction of LDL, and the percentage lowering of LDL. In addition to lowering LDL, pravastatin raises HDL and lowers triglycerides. A secondary goal was to investigate the rela-
tionship of HDL and triglyceride concentrations during follow-up to the reduction in coronary events with pravastatin.

Methods
The design of the CARE trial has been published. In summary, 4159 patients, 576 women and 3583 men, were assigned at random to either pravastatin 40 mg/d or placebo and remained on therapy for a median duration of 5 years (range, 4 to 6 years). The major eligibility criteria were MI between 3 and 20 months before randomization, age 21 to 75 years, total cholesterol <240 mg/dL, LDL cholesterol 115 to 174 mg/dL, triglycerides <350 mg/dL, and left ventricular ejection fraction >25%. Lipid levels were measured on two occasions during screening to determine eligibility and after 6 weeks, 3 months, 6 months, and every 6 months afterward for the duration of the trial. The primary end point was coronary death or nonfatal MI confirmed by a clinical events committee. The trial was conducted at 80 clinical centers in Canada and in the United States. The sites and investigators are listed elsewhere. The study was approved by the Institutional Review Boards of the centers, all patients gave informed consent, and the procedures were in accordance with institutional guidelines.

Blood was collected into evacuated tubes containing edetic acid after at least an 8-hour fast. Plasma was separated at the clinics by centrifugation, packaged with coolant, and sent by overnight courier after at least an 8-hour fast. Plasma was separated at the clinics by centrifugation. The mean LDL cholesterol concentrations by calculation and the regression equation had a slope of 0.974, an intercept of 0.6 mg/dL, and a correlation coefficient of .963 (n = 6778). The core laboratory was standardized by the Lipid Standardization Program of the Centers for Disease Control, and it was a member of the Cholesterol Reference Method Laboratory Network of the Centers for Disease Control, which verifies performance of clinical laboratories and manufacturers in the measurement of total and HDL cholesterol.

Statistical Methods
Cox proportional hazards analyses with time-dependent covariates were used. In these Cox analyses, the follow-up lipid measurement (LDL cholesterol, HDL cholesterol, or triglycerides) was the time-dependent covariate. The lipid concentrations were updated for each patient as the analysis progressed through patients’ follow-up periods. The primary end point (fatal CHD or nonfatal MI) and an expanded end point (fatal CHD, nonfatal MI, CABG, or PTCA) were used as the outcome variables. The primary analysis of lipid levels during treatment combined patients in the pravastatin and placebo groups together into a single group called the “total cohort.” Additional analyses examined the pravastatin and placebo groups separately. Unless otherwise stated, multivariate models adjusted for the baseline variables of age, sex, smoking history, diabetes, hypertension, and left ventricular ejection fraction. The initial Cox proportional hazards models evaluated the assumption of a linear relationship between follow-up lipid concentrations and coronary event rates. However, to explore the possibility of nonlinearity, the lipid concentrations were divided into deciles, with indicator variables to identify these deciles in a time-dependent manner, with the decile of highest lipid concentration or least reduction in lipid concentration being the referent.

The influence of follow-up LDL cholesterol, HDL cholesterol, and triglycerides on coronary events was investigated in time-dependent Cox analyses separately and then together. Lipid concentrations during treatment, the percentage reduction from baseline, and the absolute reduction in concentration from baseline were studied. To determine which of these three variables most highly predicted the coronary event rate, the follow-up lipid concentration and either the percentage or absolute change in lipid concentration were included simultaneously as time-dependent covariates in the Cox analyses. The corresponding baseline lipid concentrations were included in analyses as appropriate. In other analyses, treatment group was added as a covariate to investigate to what extent the lipid concentrations during treatment explained the reduction in coronary events. Relative risks were computed for the treatment group before and after adjustment for LDL, HDL, and triglycerides during treatment. For this purpose, other covariates, baseline lipids, and the risk factors were not added.

Two definitions of follow-up lipid concentrations (LDL, HDL, triglycerides) were used. The average follow-up lipid concentration refers to a weighted average of postrandomization follow-up concentrations. Because more measurements were obtained in the first year than in later years of follow-up, the average was computed so that each year had the same weight. The most recent lipid concentration refers to the most recent lipid measurement before a patient had a coronary event or the final lipid measurement in the trial for patients who did not experience an event during follow-up.

Results
The principal baseline characteristics of the enrolled patients were summarized as follows: mean age, 59 years; women, 14%; diabetes, 14%; current smoking, 21%; history of hypertension, 43%; and mean left ventricular ejection fraction, 53%. Aspirin was taken by 83% of the patients, and a revascularization procedure had been performed before enrollment in 54%. Mean baseline lipid levels (mg/dL) were total cholesterol, 209; LDL cholesterol, 139; HDL cholesterol, 39; and triglycerides, 155. At the end of the trial, the percentages of patients taking assigned study medication were 94% and 86% in the pravastatin and placebo groups, respectively.

Pravastatin lowered LDL cholesterol by an average of 32% in the first year, and this reduction was maintained for the duration of the study (Fig 1). The difference in LDL concen-
The relationship between average LDL during treatment and the expanded coronary end point in the pravastatin group, considered separately, was also significant overall ($P = .02$) but nonlinear (Fig 4). In the pravastatin group, the highest event rate was in the highest decile, median LDL was 136 mg/dL, and the event rates were similar across all the other 9 deciles, which had medians of 117 to 71 mg/dL. The results were similar for the primary end point and when the most recent LDL concentration was used. Adherence, defined as taking study medication for at least 3 of the 5 years of follow-up, was 92% in the highest decile of LDL during treatment, 94% to 95% in the 8th and 9th deciles, and 98% to 99% in the remaining deciles. The average decrease in LDL concentration that resulted in the median LDL concentration during follow-up of 125 mg/dL was 25 mg/dL, or 17% of the pretreatment concentration. Lower LDL concentrations that were produced by larger decreases in LDL by up to 53 mg/dL, or by 43%, from baseline were not associated with reductions in the coronary event rate below that associated with an LDL concentration of 125 mg/dL.

We considered the possibility that this analysis could not have detected reductions in coronary rates below an LDL concentration of 125 mg/dL. First, we calculated that the relative risk of an expanded coronary event in patients in the pravastatin group whose average follow-up LDL was ≤100 mg/dL was 0.97 compared with those with LDL 101 to 125 mg/dL, thereby demonstrating that the risks were nearly identical in both ranges of follow-up LDL. We then used CIs around this relative risk to calculate that the probability was 10% for a 15% reduction in end points in the LDL range ≤100 mg/dL compared with the range 101 to 125 mg/dL. This suggests that a clinically important reduction in events was unlikely to have been missed.

The LDL concentration during follow-up, the absolute change in LDL concentration, and the percentage change were examined in multivariate analyses to determine which had the strongest relationship to the coronary event rate. When LDL concentration was considered with either the absolute change or the percentage change, only the concentra-
tration significantly predicted the expanded coronary end point ($P = .007$ to .008 for LDL concentration, $P = .97$ for absolute change, $P = .76$ for percentage change) (Table 2). The findings were similar for the primary end point (Table 2) and when most recent LDL was used.

The HDL level during follow-up was not significantly associated with the coronary event rate after adjustment for baseline nonlipid risk factors (Table 1). The change in HDL also did not correlate significantly with the event rate. In contrast, the triglyceride level during follow-up was a significant predictor of coronary events, although less strongly than LDL (Table 1). The relative risk of a coronary event decreased from 1.0 in the highest triglyceride quintile (median, 260 mg/dL) to 0.90 in the middle quintile (median, 142 mg/dL) to 0.87 in the lowest quintile (median, 84 mg/dL). When the three lipids were considered together in the Cox model, LDL and triglycerides were the independent predictors. Adding the three baseline lipid concentrations to the models produced little change in these results.

We investigated whether there was an effect of pravastatin treatment on coronary incidence after the LDL, HDL, and triglyceride levels achieved during treatment had been taken into consideration. We did this by adding “treatment group” as an independent variable to the multiple regression model used previously (Table 1). This analysis requires that both treatment groups be represented in a substantial part of the LDL distribution of the total cohort. The percentage of patients in each LDL decile who were in the pravastatin group is shown in Fig 2 (right vertical axis). Pravastatin-treated patients composed 45% of the middle 4 deciles, 100 to 134 mg/dL. Thus, there was substantial representation from both treatment groups in the middle 40% of the follow-up LDL distribution in the total cohort. In this analysis, the unadjusted relative risk of an expanded coronary end point in the pravastatin compared with the placebo group was 0.76 (95% CI, 0.67 to 0.86). If LDL lowering was entirely responsible for the effect of pravastatin, the adjusted relative risk for treatment would be 1.0 when the LDL concentration was included with the treatment variable. The results showed that the relative risk of an expanded coronary end point in the pravastatin group was 0.92 (0.77 to 1.10) after adjustment for LDL levels during treatment, 0.95 (0.79 to 1.14) after adjustment for LDL and triglycerides, and 0.96 (0.80 to 1.15) after adjustment for LDL, triglycerides, and HDL. This left 33% of the total effect ($[1 - 0.92]/[1 - 0.76]$) unaccounted for by the LDL concentration and only 17% ($[1 - 0.96]/[1 - 0.76]$) unaccounted for by the concentrations of LDL, HDL, and triglycerides.
The CARE trial demonstrated that the HMG-CoA reductase inhibitor pravastatin significantly prevented recurrent coronary events in patients with average cholesterol levels who had experienced an MI.\textsuperscript{5} We now report that the rate of coronary events was associated strongly with the plasma LDL cholesterol concentrations during treatment in the total cohort consisting of the patients treated with pravastatin or placebo. This is not an unexpected finding, considering that the HMG-CoAs were developed primarily to reduce LDL concentrations and that a close relationship between plasma total or LDL cholesterol and coronary events is well established.\textsuperscript{14 –20} A central finding of this study is that the relationship between LDL during treatment and coronary events is not a linear one but rather appears not to decline further below a concentration of \(\approx 125 \text{ mg/dL}\). Pravastatin also has beneficial effects on plasma HDL cholesterol and triglycerides, and the reduction in triglyceride with pravastatin also appears to contribute to the reduction in coronary events.

The CARE trial was able to investigate the relationship between LDL concentration and coronary events in patients with a much lower range than previous trials did. The average LDL concentrations during follow-up in the active treatment groups in previous trials ranged from 125 to 175 mg/dL,\textsuperscript{2,3,9,10} whereas in the CARE trial, the LDL concentrations during treatment across deciles ranged from 71 to 136 mg/dL because of the substantial effects of the study drug, pravastatin, and the relatively low pretreatment concentrations (115 to 174 mg/dL). In CARE, the nonlinear relationship that was found between LDL during treatment and coronary events, with a cutpoint of 125 mg/dL, is consistent with the previously reported finding in CARE that a baseline LDL of \(>125 \text{ mg/dL}\) identified the portion of the population that subsequently experienced a reduction in coronary events.\textsuperscript{3} Approximately 80% of the patients in the pravastatin group had pretreatment LDL levels \(\geq 125 \text{ mg/dL}\). These findings from analysis of LDL concentrations before and during treatment suggest that LDL concentrations \(<125 \text{ mg/dL}\), present in most post-MI patients, have a clinically important influence on subsequent coronary events and that pravastatin is effective in reducing both the LDL concentration and the coronary event rate in this group.

The results in CARE on follow-up LDL concentrations and coronary events are supported by a recently reported meta-analysis,\textsuperscript{21} that included all published lipid trials. Coronary event rates among the trials were closely correlated with the average achieved total cholesterol level, as we found within the CARE trial for LDL cholesterol. The meta-analysis also found that the relationship between achieved total cholesterol concentration and coronary events was curvilinear, with no further decrease in events expected below \(\approx 150 \text{ mg/dL}\) (corresponding to an LDL concentration of \(\approx 110 \text{ mg/dL}\)), a result that is very similar to that found within the CARE trial.

### Figure 3
LDL cholesterol concentration during follow-up and coronary events. Placebo group, \(n=2078\) patients. Expanded end point: coronary death, nonfatal MI, CABG, or PTCA (430 patients with end point, 67 in 10th decile). Relative risk determined by Cox proportional hazards analysis with time-dependent covariates (see text). Data points show medians with 95% CIs for coronary events for deciles of follow-up LDL concentration.

### Figure 4
LDL cholesterol concentration during follow-up and coronary events. Pravastatin group, \(n=2081\) patients. Expanded end point: coronary death, nonfatal MI, CABG, or PTCA (430 patients with end point, 52 in 10th decile). Relative risk determined by Cox proportional hazards analysis with time-dependent covariates (see text). Data points show medians with 95% CIs for coronary events for deciles of follow-up LDL concentration. Adherence, defined as taking study medication for at least 3 of the 5 years of follow-up, was 92% in highest decile of follow-up, 94% to 95% in 8th and 9th deciles, and 98% to 99% in remaining deciles.
This suggests that the findings in CARE are compatible with the totality of available evidence from clinical end-point trials.

In a multivariate analysis that included LDL concentration during follow-up, the change in LDL from baseline, expressed either as a percentage or absolute change in concentration, was not found to be significantly related to coronary events. If atherosclerosis and the occurrence of coronary events are influenced by the absolute concentration of LDL, as suggested by epidemiological observations, then it is not surprising that the change in LDL is an imperfect indicator of atherogenic influence of LDL.

Evidence from various types of studies has been cited to support a continuous relationship between plasma cholesterol and coronary events that has no threshold. Most arteriographic trials have demonstrated slowing of progression of coronary disease with diet or drug therapy. However, quantitative reviews and meta-analyses of all arteriographic studies have not found a relationship between lower LDL concentrations achieved during therapy and improvement in coronary lesions. Epidemiological studies relating cholesterol to coronary events have demonstrated a continuous relationship from average to elevated concentrations. However, the relationship has not been clearly demonstrated within the lower range of total or LDL cholesterol concentrations that are readily achievable by treatment of patients with average cholesterol levels, who make up the majority of patients with coronary artery disease (such as those in CARE), with HMG-CoA reductase inhibitors. In the largest single prospective epidemiological study with 361 662 US men, the absolute change in cholesterol was 5 mg/dL. In a meta-analysis of 11 trials, the absolute concentration during follow-up and percentage change in concentration from baseline during follow-up were included together simultaneously as independent variables. In model 2, the absolute concentration during follow-up and the percentage change in concentration from baseline during follow-up were included together simultaneously. See Table 1 for definitions of end points.

In model 1, the absolute concentration during follow-up and absolute change in concentration from baseline during follow-up were included together simultaneously as independent variables. In model 2, the absolute concentration during follow-up and percentage change in concentration from baseline during follow-up were included together simultaneously. See Table 1 for definitions of end points.

Shanghai, China, in contrast, the relationship with coronary events appears to be stronger in the lowest half of the total cholesterol range, <160 mg/dL, and is attenuated in the upper half. The paradoxical shape of the curve in the Shanghai population is not consistent with other epidemiological studies of US and European populations or of a rural Japanese cohort and could be a chance finding due to the small number of coronary events, 13 in the lower half of the cholesterol range, or due to confounding by unmeasured risk factors such as obesity, diabetes, and physical inactivity, or by other less well-understood mechanisms.

Limitations of the analysis described here should be considered. In particular, this type of analysis is not based on randomized groups, and the possibility always remains of confounding by unidentified variables. However, the multivariate analysis did not find evidence for important confounding by the known nonlipid variables that affect outcomes in patients with coronary artery disease, such as age, sex, smoking, hypertension, diabetes, and left ventricular ejection fraction. The identification of a nonlinear relationship between follow-up LDL concentrations and coronary events with a cutpoint of 125 mg/dL is derived from an exploratory analysis and should be examined prospectively in future trials. Although there were 2450 patients whose average follow-up LDL was <125 mg/dL and 518 of them experienced an expanded coronary end point, a small reduction in coronary events within this range might not have been detected because of a type II error. However, we determined that the probability was high, 90%, that even a modest reduction in coronary events of 15% would have been detected. Finally, the relationship between LDL concentration and coronary events was investigated within the structure of a 5-year clinical trial in a population that had had many decades to develop clinical manifestations of atherosclerosis. The influence of LDL may be different in younger individuals and over a lifetime of exposure.

There are several strengths of this investigation in the population in the CARE trial. Adherence to the therapy was excellent for the entire duration of the trial, so that variation in compliance is unlikely to have affected the results. Multiple lipid measurements were obtained to characterize concentra-

| TABLE 2. Multivariate Analysis of LDL Concentration and Absolute Decrease and Percentage Decrease in LDL Concentration During Pravastatin Therapy: Relationship to Coronary Events |
|---------------------------------|-----|-----|-----|
|                                | Primary End-Point | Expanded End-Point |
|                                | Change in RR, %   | Change in RR, %   |
| Model 1                         | P               | P               |
| Absolute concentration, 25 mg/dL | 24 .006       | 16 .008       |
| Absolute change, 25 mg/dL       | .49 0.0         | .97 0.7        |
| Model 2                         | 29 .003       | 18 .007       |
| Absolute concentration, 25 mg/dL | 12 .27        | 2 .76         |
| Percentage change, 20%          |                |                |

In model 1, the absolute concentration during follow-up and absolute change in concentration from baseline during follow-up were included together simultaneously as independent variables. In model 2, the absolute concentration during follow-up and percentage change in concentration from baseline during follow-up were included together simultaneously. See Table 1 for definitions of end points.
tations during treatment, and coronary events were exhaustively searched for and validated. For these reasons, misclassification of LDL concentrations and end points would be minimal. In view of the strict double-blind conditions of the trial, it is difficult to imagine selective overreporting of coronary events in patients whose LDL concentrations were in the lower range of the population, which could have caused a nonlinear relationship of coronary events with LDL concentrations. The principal findings are robust, because several different approaches to defining the LDL concentration during treatment and both primary and expanded end points gave similar results. The findings are applicable to common clinical practice in which treatment is ordinarily begun in middle age or later.

In conclusion, the CARE trial established that the majority of patients with CHD, those with average cholesterol concentrations, should receive lipid treatment to reduce the risk of recurrent events. The findings in this report suggest that the effect of pravastatin to lower LDL cholesterol to 125 mg/dL was responsible for most of the reduction in coronary events. Realistically, coronary risk is unlikely to change abruptly at any specific cutpoint, and the LDL concentration of 125 mg/dL may represent an approximate rather than an exact boundary for clinical effectiveness. A conservative clinical application of these findings is to suggest a range for optimal LDL concentrations during lipid therapy, eg, 100 to 125 mg/dL. This is consistent with results of a recent meta-analysis that used the overall results of published lipid trials. Ultimately, combining evidence from major lipid trials, as is planned in a prospective pooling project should give the most precise estimate for treatment goals for prevention of coronary heart disease.

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References
24. 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 Ischemic Disease (LIPID), Cholesterol and Recurrent Events (CARE), and West of Scotland Coronary Prevention Study (WOSCOPS). Am J Cardiol. 1995;76:899–905.
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