PATHOPHYSIOLOGY AND NATURAL HISTORY
CORONARY ARTERY DISEASE

High-density lipoprotein cholesterol and coronary heart disease in hypercholesterolemic men: The Lipid Research Clinics Coronary Primary Prevention Trial

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ABSTRACT Plasma levels of high-density lipoprotein cholesterol (HDL-C) at entry and subsequent changes from these baseline levels were inversely predictive of coronary heart disease (CHD) end points in hypercholesterolemic men followed for 7 to 10 years in the Lipid Research Clinics Coronary Primary Prevention Trial, especially in the 1907 participants receiving cholestyramine. When the men in this cohort were compared, each 1 mg/dl increment in baseline HDL-C (mean 44.3 mg/dl) was associated with a 5.5% decrement in risk of “definite” CHD death or myocardial infarction (Z = -5.4), and each 1 mg/dl increase from baseline HDL-C levels (mean increase = 1.6 mg/dl) during the trial was associated with a 4.4% risk reduction (Z = -2.2). In the 1899 participants receiving placebo, the corresponding risk decrements were 3.4% and 1.1%. Although baseline HDL-C level (mean = 44.4 mg/dl) remained a significant risk predictor (Z = -3.8) in the placebo cohort, increases in HDL-C (mean increase 0.5 mg/dl) were not significantly predictive of CHD (Z = -0.6) unless “suspect” as well as “definite” end points were analyzed (Z = -2.0). When the associations between HDL-C (baseline plus change) and incidence of definite CHD end points within each treatment cohort were compared, their difference approached nominal significance (Z = 1.9). The results suggest a synergistic interaction, in which cholestyramine treatment reduced CHD risk most substantially in men maintaining the highest HDL-C levels.

Circulation 74, No. 6, 1217–1225, 1986

AN INVERSE ASSOCIATION of high density lipoprotein cholesterol (HDL-C) levels and rates of coronary heart disease (CHD) incidence and mortality has been observed in prospective epidemiologic studies conducted in several countries.1–9 In six of these studies,1–4,8,9 this inverse association was statistically significant and remained so after adjustment for other risk factors. Although the underlying mechanism for this inverse association is not fully understood, it is hypothesized that HDL promotes the removal of free cholesterol from peripheral tissues and its transport to the liver for eventual clearance.10

The present report addresses the degree to which HDL-C levels predicted fatal and nonfatal CHD outcomes in initially asymptomatic 35- to 59-year-old hypercholesterolemic men who participated in the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT).11–14 This multicenter, double-blind, randomized clinical trial tested the hypothesis that lowering plasma low-density lipoprotein cholesterol (LDL-C) levels would reduce the combined incidence of definite CHD death and nonfatal myocardial infarction. The incidence of CHD manifestations was significantly lower among the 1907 men assigned to receive diet plus cholestyramine resin than among the 1899 men assigned to receive the identical diet plus a placebo.15 Within each of these two treatment cohorts, CHD incidence was found to be lowest among men

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Supported by NHLBI contracts N01-HV12156, N01-HV22914, Y01-HV30010, N01-HV22913, N01-HV12158, N0-HV12161, N01-HV22915, N0-HV22917, N0-HV12243, N0-HV32961, and N0-HV62941.

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Received June 16, 1986; revision accepted Aug. 28, 1986.
who attained the greatest reductions in plasma LDL-C levels. We have now analyzed the relationship of HDL-C levels to the incidence of various manifestations of CHD in the two LRC-CPTT treatment cohorts to assess the importance of HDL-C as a risk factor in hypercholesterolemic men and to determine how changes in HDL-C levels during treatment of hypercholesterolemia altered CHD risk.

**Methods**

**Study participants.** Participants in the LRC-CPTT were 35- to 59-year-old male volunteers meeting the following entry criteria: (1) plasma cholesterol ≥265 mg/dl with LDL-C ≥190 mg/dl, (2) plasma triglyceride ≤300 mg/dl, (3) plasma LDL-C ≥175 mg/dl after introduction of study diet (see below), (4) no history of myocardial infarction, angina pectoris, or congestive heart failure, (5) absence of resting electrocardiographic findings indicative of ischemic CHD, and (6) no medical condition that would interfere with survival or alter lipid metabolism. Plasma HDL-C level was not a selection criterion.

The eligibility of each volunteer for the LRC-CPTT was assessed in five screening visits scheduled at monthly intervals. At the second screening visit (visit 2), a modest cholesterol-lowering diet, in which the ratio of polyunsaturated to saturated fat was targeted at 0.8 and the daily cholesterol intake at 400 mg, was introduced. All study participants were counseled to adhere to this diet for the duration of the trial. At the final screening visit (visit 5), 1907 men were randomly assigned to receive the bile acid sequestrant cholestyramine (24 g daily in six 4 g packets), and 1899 men were assigned to receive a placebo. Participants were seen at bimonthly intervals during the trial. All surviving participants were followed for at least 7 (but less than 10) years; none were lost to follow-up.

**Endpoints.** The primary end point of the LRC-CPTT was the combined incidence of definite CHD death and definite nonfatal myocardial infarction. Secondary end points included death from any cause, suspect nonfatal myocardial infarction, angina pectoris, and a positive submaximal exercise tolerance test. A blinded panel of cardiologists reviewed hospital and other medical and vital records to confirm the clinical or electrocardiographic diagnosis of definite or suspect myocardial infarction by explicit criteria established at the beginning of the study, and to assign an underlying cause for all deaths (definite or suspect CHD, or non-CHD). The diagnosis of angina pectoris was based on the participant’s response to the Rose questionnaire administered at each bimonthly visit. A submaximal treadmill exercise tolerance test was administered at the second screening visit (baseline) and annually during the trial. Exercise tests were coded centrally to ensure uniformity of standards. A positive test required the observation of 1 mm or 10 μV-sec ST segment depression or elevation during or immediately after exercise. Detailed definitions of these end points are published elsewhere.

We considered four progressively broad composite diagnostic groupings of incident CHD (fatal and nonfatal) end points. Their definitions and cumulative incidences during the LRC-CPTT are summarized in table 1.

**Lipid measurements.** Plasma samples were obtained from fasting participants at 2 month intervals throughout the study. Plasma lipid and lipoprotein levels were determined with identical methods at each of the 12 clinics. Plasma HDL-C was determined on whole plasma samples from which apo-B-containing lipoproteins had been precipitated by addition of Mn- heparin. Plasma LDL-C was estimated by the method of Friedewald et al. Plasma LDL-C was estimated by the method of Friedewald et al. A rigorous central standardization program was maintained throughout the study to ensure comparability among the centers and over time.

**TABLE 1**

<table>
<thead>
<tr>
<th>CHD grouping</th>
<th>Placebo</th>
<th>Cholestyramine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Definite CHD death</td>
<td>187/1899</td>
</tr>
<tr>
<td></td>
<td>Definite MI</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Definite or suspect CHD death</td>
<td>256/1899</td>
</tr>
<tr>
<td></td>
<td>Definite or suspect MI</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Definite or suspect CHD death</td>
<td>421/1897</td>
</tr>
<tr>
<td></td>
<td>Definite or suspect MI</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Definite or suspect CHD death</td>
<td>577/1740</td>
</tr>
<tr>
<td></td>
<td>Definite or suspect MI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angina pectoris (Rose questionnaire)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive submaximal ETT (annual)</td>
<td></td>
</tr>
</tbody>
</table>

MI = nonfatal myocardial infarction; ETT = exercise tolerance test.

Number of incident cases divided by number at risk. Note the exclusion of six (erroneously randomized) men with angina pectoris at baseline from the denominators for groups II and III and the exclusion of 319 men with a positive exercise test at baseline from the denominators for group III. Note also that one participant (with no CHD end points) who, because of a clerical error, was included in the placebo cohort in earlier publications is now correctly counted on the cholestyramine roster.

**Other measurements.** Blood pressure was measured with a random zero sphygmomanometer after the participant had been seated for 5 min. Habitual physical activity, alcohol consumption, and cigarette smoking were assessed annually by questionnaire. One-day dietary recalls were administered 1 month before and 1 month after the initial dietary instruction and at semiannual intervals during the trial. Participants were asked to return any study medication packets that had not been used during the 2 month interval between clinic visits. We then estimated intake of the study medication (in packets/day) by subtracting the number of packets returned from the number issued and dividing by days elapsed.

**Statistical models.** The effect of cholestyramine and other
potentially influential factors on plasma HDL-C levels was assessed at 2, 4, and 6 years of follow-up. Since the majority of participants reported daily packet counts of either five or more (good adherence) or less than 1 (poor adherence) in any given 2 month interval, this analysis was simplified by omitting men with intermediate packet counts and treating adherence as a binary variable. An unadjusted comparison of good and poor adherers in each treatment cohort was obtained from a two-way (treatment assignment and adherence) analysis of variance of ΔHDL-C in the combined cohorts. The interaction term estimated the specific effect of cholestryramine intake (vs placebo) on HDL-C. An adjusted estimate of this effect was obtained by an analysis of covariance, incorporating terms for baseline HDL-C and the following known or suspected correlates of HDL-C: alcohol consumption, physical activity, cigarette smoking, Quetelet index, calories consumed per kilogram body weight, the ratio of carbohydrate to fat calories, and the ratio of polyunsaturated to saturated fat intake. (Baseline HDL-C was first adjusted for baseline levels of the other six variables to reduce potential colinearity.) Regression analyses treating packet count as a continuous variable gave similar results.

As in our previous report, the relationship of changing plasma HDL-C levels to CHD risk was quantified and adjusted for relevant baseline covariates by proportional hazards analysis. Models for baseline HDL-C level, change in HDL-C (in mg/dl) rather than as a proportion of baseline during the 2 years preceding the date on which each CHD endpoint occurred, and “current” HDL-C level (baseline plus change) were computed. When HDL-C was missing for any bimonthly visit, we substituted either the most recent previous measured value, if within 1 year, or the baseline level for longer absences. This procedure, which represents a minor modification of our earlier method, yielded essentially equivalent results. As described earlier, the baseline HDL-C level was assumed to represent a stable pretrial level for each participant in the calculation of early 2 year averages. The proportional hazards regression coefficients (β) were converted to percent change in risk corresponding to a 1 mg/dl increment in HDL-C as follows:

% ΔRisk = 100 • (expβ - 1)

When β < 1, this percent change in risk is approximately 100β.

Statistical significance. Although significance levels do not have the same rigorous meaning when CHD incidence rates are compared within (rather than between) the randomized treatment groups, the Z scores and corresponding p values for the intragroup analyses are still useful gauges of the strength of evidence relating levels of HDL-C and rates of CHD. Here, “significance” has been arbitrarily defined in terms of the twosided threshold for p ≤ .05, i.e., |Z| ≥ 1.96. When |Z| ≥ 2.58 (the two-sided threshold for p ≤ .01), the evidence for association may be considered to be quite strong.

Results

Baseline HDL-C levels and risk. The distribution of plasma HDL-C levels was virtually identical in the two LRC-CPPT treatment cohorts at baseline, as would be expected with randomization (figure 1). The mean HDL-C in the combined LRC-CPPT cohort, 44.4 mg/dl, was similar to the mean value of 44.8 mg/dl observed in the 1680 similarly aged white male participants in the LRC Prevalence Study who were sampled randomly from populations at the same centers and studied by identical laboratory methods. The standard deviation was somewhat smaller in the LRC-CPPT (8.9 vs 11.9 mg/dl), in which baseline HDL-C levels were averages of four determinations. The combination of selection criteria for total cholesterol, LDL-C, and triglyceride may also have restricted the distribution of HDL-C without necessarily altering its mean.

Plasma HDL-C was a strong predictor of CHD incidence in both LRC-CPPT treatment cohorts. The incidence and mortality rates from CHD were approximately twice as great among men with baseline HDL-C levels under 40 mg/dl as among men with baseline HDL-C levels of 50 mg/dl or higher (figure 2). Intermediate rates were observed among men with HDL-C levels between 40 and 49 mg/dl. The trends were similar, regardless of whether one considered all incident CHD death and myocardial infarction (group I), only definite incident cases (group 0), or only fatal CHD. CHD incidence was lower in the drug than in the placebo cohort for each of the three HDL-C strata.

We further analyzed the relationship of baseline HDL-C levels to subsequent CHD incidence with the proportional hazards model (table 2). Inverse trends far exceeding conventional criteria for statistical significance (Z ≤ −3.6) were observed in both cohorts for all four CHD end point groupings. These trends were weakened somewhat by adjustment for baseline levels of other CHD risk factors but remained statistically significant (Z ≤ −2.7). The relationship of HDL-C and CHD was generally stronger in the cholestryramine than in the placebo cohort. However, the difference between regression coefficients in the two treatment cohorts was not statistically significant for any of the four CHD groupings (Z < 1.6).
FIGURE 2. CHD incidence and mortality as a function of baseline HDL-C level in the LRC-CPPT placebo (P) and cholestyramine (C) cohorts. In the top panel, the numbers of “definite” and “suspect” cases are given for each stratum. In the bottom panel, the numbers of deaths from CHD (definite plus suspect) and from all other causes combined are given for each stratum.

In each treatment cohort, the incorporation of the positive submaximal exercise test into the definition of CHD (group III) markedly weakened the relationship between HDL-C levels and CHD incidence (table 2). Further analyses (not shown) indicated that men with lower HDL-C levels were significantly less likely to complete the exercise test than were men with higher HDL-C levels. Because of this ascertainment bias, the association of HDL-C with group III end points is difficult to interpret and will not be considered further in this report.

An inverse trend relating HDL-C to total mortality was also evident in the cholestyramine but not in the placebo cohort (figure 2, bottom). In both cohorts, total mortality rates were lowest among men with HDL-C levels of 50 mg/dl or higher at baseline. However, in the placebo cohort there were only six non-CHD deaths in men with HDL-C levels under 40 mg/dl at baseline, and total mortality was lower in these men than in men with intermediate HDL-C levels. When proportional hazards models for all-cause mortality were computed (not shown), the inverse relationship of baseline HDL-C to all-cause and CHD mortality approached nominal statistical significance only in the cholestyramine cohort. However, because there were only 139 deaths, the difference between the regression coefficients for the two treatment cohorts was not statistically significant and may well have been due to chance.

Changes in HDL-C. Mean plasma HDL-C levels increased gradually over the first 4 years of treatment from 44.3 to 46.8 mg/dl in the cholestyramine cohort and from 44.4 to 45.6 mg/dl in the placebo cohort (figure 3). Mean HDL-C levels declined slightly thereafter in both cohorts but remained significantly above

TABLE 2
Baseline plasma HDL-C levels and CHD incidence

<table>
<thead>
<tr>
<th>HDL-C grouping</th>
<th>Treatment cohort</th>
<th>%ΔRisk for 1 mg/dl increment in HDL-C&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Placebo</td>
<td>-3.4 (-3.8)</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>-5.5 (-5.4)</td>
</tr>
<tr>
<td>I</td>
<td>Placebo</td>
<td>-3.7 (-4.8)</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>-5.5 (-6.5)</td>
</tr>
<tr>
<td>II</td>
<td>Placebo</td>
<td>-3.4 (-5.7)</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>-3.9 (-6.1)</td>
</tr>
<tr>
<td>III</td>
<td>Placebo</td>
<td>-1.8 (-3.6)</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>-2.2 (-4.2)</td>
</tr>
</tbody>
</table>

<sup>a</sup>See table 1 for definitions.
<sup>b</sup>Based on proportional hazards regression model. Z scores are indicated in parentheses.
<sup>c</sup>Covariates include age, cigarette smoking, systolic blood pressure, plasma low-density lipoprotein cholesterol, plasma triglyceride, and exercise test outcome at baseline.

![FIGURE 3](https://example.com/figure3.png)

FIGURE 3. Changes in mean plasma HDL-C levels during the LRC-CPPT in the cholestyramine and placebo cohorts. Each participant’s HDL-C level during a particular year of follow-up is an average of measurements taken at one to six bimonthly visits; missing values have not been imputed.
the mean baseline level. The mean HDL-C level in the cohort receiving cholestyramine exceeded that in the cohort receiving placebo by at least 1.1 mg/dl (Z > 3.3) in each year of treatment. However, although the mean difference between treatment cohorts was statistically significant, no significant association could be demonstrated between the amount of cholestyramine taken and changes in HDL-C levels. In the combined drug and placebo cohorts, alcohol consumption, Quetelet index, cigarette smoking, and habitual physical activity accounted for 16.7% of the variance in HDL-C at baseline and for 0.9%, 3.2%, and 2.5% of the variance in ΔHDL-C at the second, fourth, and sixth annual visits, respectively. The combination of treatment cohort, packet count, and their interaction accounted for no more than 1.3% of the variance in ΔHDL-C at these annual visits. Diet (i.e., caloric intake per kg body weight, ratio of carbohydrate to fat intake, and ratio of polyunsaturated to saturated fat intake) accounted for less than 0.5% of the variance in baseline HDL-C levels or in ΔHDL-C. Thus, when individual participants within each cohort were analyzed, HDL-C changes appeared to be multifactorial, and more of their variance was attributable to participant-initiated health behaviors than to the dietary counseling and medication they received.

**Posttreatment HDL-C levels and CHD incidence.** Changes in HDL-C level were inversely related to subsequent incidence of group 0, I, and II CHD end points (table 3). As for baseline HDL-C, these relationships were consistently stronger in the cholestyramine than in the placebo cohort. In the placebo cohort, the association of ΔHDL-C and CHD was not significant for group 0 end points and barely attained nominal signifi-

**TABLE 3**

<table>
<thead>
<tr>
<th>CHD grouping</th>
<th>Treatment cohort</th>
<th>%ΔRisk for 1 mg/dl increment in HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>0</td>
<td>Placebo</td>
<td>-3.6 (-3.8)</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>-6.0 (-5.7)</td>
</tr>
<tr>
<td>I</td>
<td>Placebo</td>
<td>-4.1 (-5.1)</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>-6.0 (-6.8)</td>
</tr>
<tr>
<td>II</td>
<td>Placebo</td>
<td>-3.7 (-6.0)</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>-4.3 (-6.5)</td>
</tr>
</tbody>
</table>

*See table 1 for definitions.

*Based on proportional hazards regression model including baseline HDL-C and change in HDL-C and no other independent variables. Z scores are indicated in parentheses.

The difference (mg/dl) between a participant’s average HDL-C level during the 2 years preceding a particular point of follow-up and his baseline HDL-C level (see Methods).

**TABLE 4**

<table>
<thead>
<tr>
<th>CHD grouping</th>
<th>Treatment cohort</th>
<th>%ΔRisk for 1 mg/dl increment in HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Placebo</td>
<td>-3.2 (-3.6)</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>-5.8 (-5.7)</td>
</tr>
<tr>
<td></td>
<td>Differencec</td>
<td>2.7 (1.9)</td>
</tr>
<tr>
<td>I</td>
<td>Placebo</td>
<td>-4.0 (-5.1)</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>-5.7 (-6.8)</td>
</tr>
<tr>
<td></td>
<td>Differencec</td>
<td>1.9 (1.6)</td>
</tr>
<tr>
<td>II</td>
<td>Placebo</td>
<td>-3.6 (-5.9)</td>
</tr>
<tr>
<td></td>
<td>Cholestyramine</td>
<td>-4.3 (-6.8)</td>
</tr>
<tr>
<td></td>
<td>Differencec</td>
<td>0.8 (0.9)</td>
</tr>
</tbody>
</table>

*See table 1 for definitions.

*Based on proportional hazards regression model of HDL-C averaged over 2 years preceding a particular point of follow-up (see Methods). No covariates are included. Z scores are indicated in parentheses.

*Calculated as 100*[exp(βp - βh) - 1], where βp and βh are the regression coefficients for the placebo and cholestyramine cohorts, respectively. The Z score for the difference is calculated as (βp - βh)SE(βp - βh), where the standard error SE(βp - βh) = \sqrt{SE(βp)^2 + SE(βh)^2}.

The proportional hazards models relating HDL-C levels to CHD incidence in the two treatment groups are plotted in figure 4. The curves for the cholestyramine cohort are steeper than those for the placebo cohort, a consequence of the larger regression coefficients in the former group. Although the overall inci-
LDL-C during treatment with cholestyramine were weakly inversely correlated ($r = -0.1$), we attempted to assess the interplay of LDL-C and HDL-C as predictors of group 0 CHD end points. The relationship of LDL-C to group 0 CHD incidence is plotted in figure 5. In contrast to the corresponding plots for HDL-C (figure 4), the curves for the two cohorts are virtually identical. The risk curve for the placebo cohort, which agrees closely (in slope) with data from prospective observational studies, predicts that if its mean LDL-C level were shifted from 201.6 to 178.1 mg/dl (the mean posttreatment level in the LRC-CPPT cholestyramine cohort), the cumulative incidence of group 0 events ought to be reduced from 9.8% to 8.3%. This prediction agrees quite closely with the 8.1% cumulative incidence of group 0 events actually observed in the cholestyramine cohort. Thus close to 90% of the observed reduction in CHD incidence in the cholestyramine cohort relative to the placebo cohort (9.8 – 8.3) ⁄ (9.8 – 8.1) is accounted for by the – 23.5 mg/dl mean difference in LDL-C between the two cohorts.

To assess the contribution of reduced LDL-C levels in the cholestyramine cohort to the drug’s apparent enhancement of the inverse relationship between

![Figure 4](https://circ.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.112.184830)

**FIGURE 4.** Relationship of HDL-C levels to incidence of group 0, I, and II CHD end points in the LRC-CPPT cholestyramine (C) and placebo (P) cohorts. The proportional hazards regression models for current HDL-C (table 4) were used to compute expected cumulative incidences corresponding to each level of HDL-C. The cumulative incidence of CHD end points in each treatment cohort (table 1) was assumed to represent the expected incidence corresponding to its mean HDL-C level (45.9 mg/dl for C and 44.8 mg/dl for P); these points are indicated by closed circles. The plots span the 5th to 95th percentiles of HDL-C during treatment.

Incidence of CHD end points in the cholestyramine cohort was nearly 20% lower than in the placebo cohort, this treatment-associated reduction in incidence appeared to be greatest among men with the highest HDL-C levels during treatment. The plots for group 0 and Group I end points show a crossover near 40 mg/dl.

Note also in figure 4 that the 1.1 mg/dl mean drug-placebo difference in HDL-C during treatment was far too small to have accounted for the observed drug-placebo differences in overall CHD incidence. For example, based on the model for group I end points in the placebo cohort (the end point for which the curve is steepest), a treatment that did nothing but increase the mean HDL-C level from 44.8 to 45.9 mg/dl ought to have reduced the incidence from 13.5% to 12.9%. The actual incidence of group I end points was 11.6% in the cholestyramine cohort, more than three times the expected reduction.

**FIGURE 5.** Relationship of LDL-C levels to incidence of group 0 CHD end points in the LRC-CPPT placebo and cholestyramine cohorts. Unadjusted proportional hazards regression models for current LDL-C ($\beta = .0085$ for C and .0074 for P) were used to compute expected cumulative incidences corresponding to each level of LDL-C. The cumulative incidences of CHD end points in each treatment cohort were assumed to represent the expected incidence corresponding to its mean LDL-C level (178.1 mg/dl for C and 201.6 mg/dl for P); these points are indicated by closed circles. The plots span the 2.5 to 97.5 percentiles of LDL-C during treatment.

**LDL-C, HDL-C, and CHD.** Given that cholestyramine is primarily an LDL-lowering rather than an HDL-raising drug, and given that changes in HDL-C and
HDL-C and CHD incidence, we estimated the incidence ratio (cholestyramine/placebo) for group 0 end points in subgroups of participants with HDL-C levels (mg/dl) (1) below 40, (2) 40 to 49, and (3) at least 50 (table 5). In the low HDL-C subgroup, treatment with cholestyramine conferred no apparent benefit (an incidence ratio of 1.00) despite a substantial (17.4 mg/dl) mean LDL-C reduction relative to placebo levels. The incidence of group 0 end points in cholestyramine-treated men with HDL-C levels under 40 mg/dl was 13% greater (adjusted incidence ratio of 1.13) than their mean LDL-C level would predict. Among cholestyramine-treated men with HDL-C levels of at least 50 mg/dl, the incidence of group 0 end points was 25% lower (adjusted incidence ratio of 0.75) than their mean LDL-C level would predict. The ratio of incidence ratios in the low and high HDL-C cohorts was 1.61 before and 1.51 after adjustment for LDL-C. (A ratio of 1.00 would imply equal treatment benefits in these two subgroups.) Thus, only about 16% of the apparent synergy between cholestyramine treatment and HDL-C as inverse predictors of CHD incidence could be explained by the smaller LDL-C reductions observed in the low HDL-C subgroup. Note again from the bottom line of table 5 that the overall reduction in CHD risk conferred by cholestyramine treatment is attributable almost entirely to its reduction of LDL-C levels (adjusted incidence ratio of 0.97).

Discussion

The results demonstrate that plasma HDL-C level was a strong inverse predictor of the incidence of clinical manifestations of CHD (CHD death, myocardial infarction, and angina pectoris) in the hypercholesterolemic men who participated in the LRC-CPPT, more so in the cohort receiving cholestyramine than in the cohort receiving placebo. Changes in HDL-C levels were also inversely predictive of CHD incidence, although to a lesser degree than were baseline levels, and again more so in the cohort receiving cholestyramine than in the cohort receiving placebo.

The experience of the LRC-CPPT placebo cohort, which received only a minimal cholesterol-lowering diet that had little impact on HDL-C levels, approximated a natural history study in hypercholesterolemic 35- to 59-year-old men. If one sets aside the exercise test results (which were biased by the tendency of men with lower HDL-C levels not to complete the test), the combined incidence rate of fatal and nonfatal CHD end points fell by 3.4% to 3.7% for each 1 mg/dl increment in the baseline plasma level of HDL-C (table 2). After adjustment for baseline covariates, the corresponding risk decrements were 2.5% to 2.8%. For comparison, among men aged 30 or older in the follow-up phase of the LRC Prevalence Study, a 1 mg/dl increment in baseline HDL-C was associated with a 3.2% decrement in age-adjusted CHD mortality rates (3.5% after additional adjustment for smoking, systolic blood pressure, Quetelet index, plasma LDL-C, and triglyceride). In the Framingham Study, a 1 mg/dl increment in HDL-C was associated with a 3.9% decrement in CHD incidence (men, aged 50 or older; adjusted for age, smoking, systolic blood pressure, and serum LDL-C). Thus the relationship of HDL-C to CHD in the LRC-CPPT placebo cohort appears quantitatively similar to those reported in these population-based observational studies, in which a full range of plasma total and LDL cholesterol values was represented.

Although the LRC-CPPT was not designed to assess the hypothesis that increasing HDL-C reduces CHD risk, men in the placebo cohort whose plasma levels of HDL-C rose during treatment suffered fewer CHD end

### TABLE 5

Effect of cholestyramine on group 0 CHD incidence in three HDL-C strata

<table>
<thead>
<tr>
<th>Plasma HDL-C† (mg/dl)</th>
<th>LDL-C (C-P)† (mg/dl)</th>
<th>CHD incidenceb</th>
<th>Incidence ratio (C/P)c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>&lt;40</td>
<td>−17.4</td>
<td>71/559</td>
<td>76/597</td>
</tr>
<tr>
<td>40 to 50</td>
<td>−25.3</td>
<td>62/813</td>
<td>80/833</td>
</tr>
<tr>
<td>≥50</td>
<td>−26.7</td>
<td>22/535</td>
<td>31/469</td>
</tr>
<tr>
<td>All participants</td>
<td>−23.5</td>
<td>155/1907</td>
<td>187/1899</td>
</tr>
</tbody>
</table>

C = cholestyramine cohort; P = placebo cohort.

†Averaged over the 2 years immediately preceding an LRC-CPPT visit selected at random for each participant.

bEstimated as the number of men with average plasma HDL-C level in the indicated range during the 2 years preceding their group 0 end point, divided by the number of men in the entire cohort with average plasma HDL-C level in the indicated range during the 2 years preceding an LRC-CPPT visit selected at random.

cThe observed incidence in the cholestyramine cohort was divided by (unadjusted) the observed incidence in the placebo cohort or (adjusted) the incidence predicted by the proportional hazards model relating LDL-C to incidence of group 0 CHD events in the placebo cohort (figure 5).
points than did those whose HDL-C levels remained steady or declined (table 3). However, given that the magnitude of the Z score for the association of ΔHDL-C and CHD did not exceed 2.0 for any of the three diagnostic groupings, these data provide only suggestive evidence that HDL-C increases were independently beneficial in this cohort.

The inverse relationship of both baseline levels of and subsequent increases in HDL-C to risk of CHD death and myocardial infarction (groups 0 and 1) appeared to be enhanced by treatment with cholestyramine. The association of baseline HDL-C levels and each of these CHD end points was steeper in the cholestyramine cohort (a 5.5% reduction in risk for a 1 mg/dl increment in HDL-C) than has been observed in the LRC-CPPT placebo cohort or in observational studies. The association of changes in HDL-C levels with incidence of CHD manifestations, although not as strong as that observed for baseline HDL-C, exceeded the conventional standard for significance (Z = −2.2 for group 0, −2.7 for group I, and −3.4 for group II).

Although the LRC-CPPT results provide only suggestive evidence that the enhancement of the inverse association of HDL-C and CHD incidence in the cholestyramine vs the placebo cohort was more than a chance finding, alternative interpretations should be considered. One such interpretation is that cholestyramine-mediated increases in HDL-C are more strongly protective than those mediated by other mechanisms. This explanation can probably be rejected, since pretreatment HDL-C levels as well as changes in HDL-C were more strongly related to CHD risk in the cholestyramine than in the placebo cohort. Moreover, although randomization ensured that exposure to cholestyramine was responsible for the entire 1.1 mg/dl HDL-C difference between the drug and placebo cohorts, exposure to cholestyramine explained less than 2% of the variation in HDL-C levels among individuals within these two cohorts. Thus only a small proportion of the changes in HDL-C in the cholestyramine cohort can be accurately described as “cholestyramine-mediated.”

The enhancement of the inverse association of HDL-C and CHD in men receiving cholestyramine is more consistently explained by a synergistic interaction of HDL-C levels and cholestyramine treatment, in which higher HDL-C levels before and during treatment predisposed to a greater beneficial effect of cholestyramine-mediated LDL-C reduction on CHD risk. The mechanism for this hypothesized synergy and its generalizability to other modalities of cholesterol lowering are unknown. However, in view of the report by Orlov et al. of variants of the apo A-I gene associated with low HDL-C levels and premature CHD, one may speculate that this genetic polymorphism might also be associated with differing responses to cholestyramine.

The contribution of HDL-C changes to the overall reduction of CHD incidence in the cholestyramine (vs the placebo) cohort is a product of the magnitude of the HDL-C difference between the two cohorts and the strength of the association of HDL-C and CHD risk. Despite the strength of this association in the LRC-CPPT, the potential impact of the 1.1 mg/dl mean drug-placebo difference in HDL-C on CHD incidence was far overshadowed by that of the −23.5 mg/dl mean drug-placebo difference in LDL-C (figures 4 and 5). The NHLBI Type II Intervention Trial, a double-blind, placebo-controlled secondary intervention trial of cholestyramine treatment in patients with hypercholesterolemia, employing angiographic measures of CHD, obtained similar results. Increases in HDL-C were strongly associated with reduced risk of angiographic progression within the combined cohort, more so in fact than were decreases in LDL-C. However, when the drug and placebo groups in that study are compared, the mean LDL-C difference was more than 20 times as great as the mean HDL-C difference (−41 vs 2 mg/dl). In the absence of evidence that the regression coefficient relating HDL-C to incidence of angiographic end points in that study was at least 20 times larger than the corresponding coefficient for LDL-C, a supposition not supported by the LRC-CPPT experience or by observational studies of clinical end points, the observed end point differences between drug and placebo groups (like those in the LRC-CPPT) are probably attributable more to differences in LDL-C than HDL-C levels.

In conclusion, HDL-C was an important inverse risk factor for most manifestations of CHD in the LRC-CPPT, especially in the cohort that received cholestyramine. Although reductions in LDL-C were primarily responsible for the lower incidence of CHD end points in the cholestyramine cohort (compared with the placebo cohort), plasma HDL-C levels at baseline and during treatment with cholestyramine appeared to influence the degree to which CHD incidence was reduced relative to men with similar HDL-C levels in the placebo cohort. Changes in HDL-C during treatment may also have directly influenced the risk of CHD. However, to assess properly whether raising HDL-C levels reduces CHD risk would require an intervention acting predominantly on HDL-C rather than LDL-C levels.
Computations for this manuscript were performed by Larry Wallman, Sherry Gates, Jeff Abolafia, and Hope Bryan. The LRC investigators also thank Dr. Robert Levy and Janet Bungay for their thoughtful criticism of this manuscript.

Appendix


References

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Circulation. 1986;74:1217-1225
doi: 10.1161/01.CIR.74.6.1217

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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