CHOLESTEROL AND CARDIOVASCULAR DISEASE

Review of lipid-lowering clinical trials in relation to observational epidemiologic studies

HERMAN A. TYROLER, M.D.

ABSTRACT A review of the experimental clinical trials and observational cohort evidence relating serum cholesterol level and its reduction to risks of coronary heart disease (CHD) discloses strong similarities among the quantitative and qualitative relationships found in these studies. Not only are the risk functions similar, but the percent reduction observed is the same as that predicted from the population experience and is proportional to the degree of cholesterol lowering. Furthermore, the risk function is continuous from the highest to the lowest serum cholesterol levels studied. These findings confirm the lipid hypothesis and indicate that lowering serum cholesterol reduces CHD risk. The understanding and control of CHD requires a dual approach: (1) identification and treatment of high-risk individuals, and (2) modification of environmental and behavioral determinants to achieve more favorable distributions of serum cholesterol in populations.


A LARGE NUMBER of different types of observational epidemiologic studies, performed in many populations, have confirmed that high total serum cholesterol is a risk factor for coronary heart disease (CHD). These investigations have included (1) comparisons of CHD mortality levels across populations, (2) migrant studies, and (3) cohort studies of mortality and morbidity of individuals within populations. The consistency of these epidemiologic findings — as well as experimental induction and regression of atherosclerosis in animals, experiments of nature in human familial hypercholesterolemia, and molecular biologic studies of lipid transport and metabolism — have left little doubt regarding the etiologic role of serum total and low-density lipoprotein (LDL) cholesterol in the pathogenesis of atherosclerosis and CHD. Earlier clinical trials had produced only equivocal results regarding the efficacy of serum cholesterol reduction in reducing CHD risk.

This presentation will review evidence from clinical trials conducted before the Lipid Research Clinics (LRC) Coronary Primary Prevention Trial to compare the quantitative results with those of the LRC Trial and of recently completed large-scale epidemiologic observational studies. The implications of these findings with regard to the clinical and population management of CHD via control of serum cholesterol levels will also be explored.

Overview of lipid-lowering trials. In 1981, before the completion of the LRC trial, the results of 11 clinical studies on the effects of lowering lipids were analyzed in an aggregate overview. As described by Mann and Marr,1 in an attribution to Peto, to be included in this overview an investigation had to be a unifactor, randomized, lipid-lowering trial in which either a drug or diet was used as intervention. By definition, then, multifactor trials (such as those combining lipid lowering with blood pressure lowering or smoking cessation) were excluded, as were studies in which maneuvers such as physical activity or surgery were used to lower lipids. The characteristics of these studies and the subsequent LRC trial2 are presented in table 1.

Six of the studies in the overview were diet trials3–8 and five were drug trials.9–13 None of the diet studies selected patients based on hypercholesterolemia, and all were secondary prevention trials. Two of the five drug studies were primary prevention trials, with selection based on hypercholesterolemia. None of the earlier trials selected participants based on LDL cholesterol levels. The LRC trial was a randomized, double-blind, primary prevention study in which the selection criteria included elevation of both total serum cholesterol and LDL cholesterol in middle-aged men free of clinically manifest CHD. The actively treated group received the bile acid sequestrant resin cholestyramine, the control group received placebo, and both adhered to a minimal cholesterol-lowering diet. The cholesterol reduction

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TABLE 1
Lipid-lowering trials in overview1 and the LRC trial2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diet trials</th>
<th>Drug trials</th>
<th>LRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of trials</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Sample size, range</td>
<td>80–846</td>
<td>497–10,627</td>
<td>3806</td>
</tr>
<tr>
<td>Number of end points in control group, range</td>
<td>6–81</td>
<td>22–839</td>
<td>186</td>
</tr>
<tr>
<td>Reduction in cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute mg/dl, range</td>
<td>20–43</td>
<td>19–31</td>
<td>24</td>
</tr>
<tr>
<td>Relative %, range</td>
<td>8–16</td>
<td>8–12</td>
<td>8.5</td>
</tr>
<tr>
<td>Years duration, range</td>
<td>2–8</td>
<td>4–7</td>
<td>7.4</td>
</tr>
<tr>
<td>Years completed or reported, range</td>
<td>1963–1971</td>
<td>1971–1978</td>
<td>1983</td>
</tr>
<tr>
<td>Selection for hypercholesterolemia</td>
<td>0/6</td>
<td>2/5</td>
<td>Yes</td>
</tr>
<tr>
<td>Selection for elevated LDL cholesterol</td>
<td>0/6</td>
<td>0/5</td>
<td>Yes</td>
</tr>
<tr>
<td>Primary prevention of coronary heart disease</td>
<td>0/6</td>
<td>2/5</td>
<td>Yes</td>
</tr>
</tbody>
</table>

achieved in the pre-LRC studies was modest, ranging from 19 to 43 mg/dl; a 24 mg/dl reduction was achieved in the LRC trial. The amount of reduction in serum cholesterol achieved in the early studies was also modest when expressed in relative terms as a percentage of the entry level, ranging from 8% to 16%; in the LRC trial, an 8.5% greater reduction was achieved with cholestyramine than with placebo.

In his quantitative overview, Peto fit a regression equation relating the percent reduction in serum cholesterol to the relative risk of CHD (in the treated vs the control group) in each trial for the diet and drug studies separately. A significant relationship was reported for each of the two sets of trials, forcing the line of best fit through the origin; these results argued that there would be no change in relative risk if no reduction in cholesterol were achieved. The line of best fit for the diet trials indicated a 1.5% reduction in CHD risk for each 1% reduction in cholesterol; a 2% reduction in risk for each 1% reduction in serum cholesterol was estimated for the drug trials. In aggregate, then, these trials provided evidence of the efficacy of lipid lowering for reducing the risk of CHD and, further, indicated the presence of a dose (cholesterol-lowering)-response relationship.

The regression estimates approximately predicted the results of the LRC trial, given the reduction in cholesterol achieved in that study. The predicted reduction in CHD risk (with the 8.5% greater reduction in total serum cholesterol in the cholestyramine- than the placebo-treated group) in the LRC trial was 17%, based on the summarization equation derived from the aggregate regression analysis of the earlier drug trials; a 19% reduction in primary end points was observed. The point estimates for each trial and the regression lines of best fit for the diet and drug studies are presented in figure 1. The wide confidence interval around each trial’s estimate of efficacy (reported by Peto), reflecting the limited number of events in most of the trials, has been omitted from the figure. The statistical significance of each trial’s individual results (including the LRC trial) is not the issue here; rather, the aggregate evidence and the quantitative validity of the equation in predicting the outcome of the LRC trial is of importance in this test of the lipid hypothesis and the efficacy of serum cholesterol lowering.

The aggregate quantitative analysis of the drug trials yielded results similar to those for the diet trials. Although the estimate of change in coronary risk per unit change in serum cholesterol was larger in the drug studies, this may have been due to random variation, given the small number of trials analyzed at that time. Peto et al.13 presented an updated analysis, including a larger number of trials of serum cholesterol reduction. The aggregate test of the association between blood cholesterol and CHD reduction was highly statistically significant, and the quantitative relationship was similar to that published previously. Of particular note was the overall evidence of the efficacy of serum cholesterol lowering in both the diet and drug trials, despite the small amount and limited range of net total serum cholesterol reduction achieved in these studies.

Dose-response relationships in the LRC trial. The analysis reviewed above drew inferences by comparing results

FIGURE 1. Relative risk of CHD in relation to serum cholesterol lowering in clinical trials of diet and drugs. (Adapted from Mann and Marr.1)
in subjects randomly assigned to treatment or to no treatment; analyses were based on the experimental design. In addition, internal analyses restricted to the experience of participants within the cholestyramine-treated group of the LRC trial (and therefore of a nonexperimental, observational nature), disclosed a dose-relationship between the amount of cholesterol reduction achieved and the reduction in relative risk. In figure 2, the points representing the relative risk of CHD within the cholestyramine group are arrayed in a stepwise fashion in relation to cholesterol reduction. The point representing the overall result of the LRC trial in its experimental mode (comparing cholestyramine to placebo) falls close to that predicted from the experience within the cholestyramine group.

In contrast to the overview of lipid-lowering trials, in which the level and range of total serum cholesterol reduction achieved was quite low, analysis of the experience of men within the actively treated cholestyramine group of the LRC trial permits comparison over a wide range of total cholesterol reduction achieved by individuals. A sizable proportion of individuals in this group had a reduction in serum cholesterol greater than or equal to 25% with a predicted reduction in CHD risk of 50% and an observed reduction in excess of this amount. These analyses cannot unequivocally be attributed to the treatment regimen per se, since the observations were not derived from an experimental (randomized) design. They may reflect the influence of factors other than, or in addition to, cholestyramine treatment. However, a different risk associated with different levels of drug-taking adherence behavior per se, independent of any associated pharmacologic action, is an unlikely explanation for the findings in the LRC trial. This is shown by the fact that individuals randomly assigned to placebo demonstrated no such association between amount of drug (placebo) taken and CHD risk.

The markedly reduced risk observed (and predicted) with serum cholesterol reductions of 25% or greater in the LRC study indicate the potential for major clinical impact, but this has not been as apparent in the overall efficacy noted in any of the trials reported to date (with a maximum average cholesterol reduction of 16% reported). When the diet and drug trials are considered separately, little relationship between either absolute or percent reduction in serum total cholesterol and baseline cholesterol level is evident (figure 3). It should be noted that regression to the mean would be expected to produce an association between the baseline level and change. This discussion of association is not intended to imply any causal relationship between these measures. It indicates, rather, that the overall cholesterol reduction achieved in these studies was minimal, despite the range of more than 156 mg/dl of serum cholesterol levels at baseline across trials (many with participants whose serum cholesterol levels were considered clinically normal at the time of investigations). The demonstration of reduction in CHD risk under these circumstances leads to optimism regarding the potential for enhanced efficacy with the greater serum cholesterol lowering that should be achievable with the agents now available.
In summary, then, the aggregate evidence from clinical trials suggests coherence of the end point results of CHD risk reduction, consistency among studies, a dose-response relationship, and predictive validity in both the experimental mode and observations of individuals within a treatment group. The LRC investigators tested for, but did not find, several potential biases identified in other clinical trials. These included the so-called healthy participant effect in which event rates in the placebo group were observed to be markedly lower among trial volunteers than event rate estimates derived from population surveys. The end point event rate predicted from the Framingham experience was almost exactly that observed in the LRC trial placebo group. An adherer placebo effect (that is, a dose-response relationship between adherence to the placebo regimen and reduction in end point events) detected in other studies was not observed in the LRC trial. The only dose-response relationship was that which was accompanied by a reduction in serum cholesterol. Efficacy was demonstrable within the preplanned 7 year duration of the randomized, blinded trial; additional time was not necessary for a treatment effect to become apparent.

Secondary end points in the LRC trial. The efficacy of cholesterol lowering in the LRC trial was estimated by assessment of the primary end points of definite CHD death or definite nonfatal myocardial infarction. The estimates of efficacy were generally similar when other cardiovascular end points were studied. The cholestyramine-treated group showed reductions of 20% in the incidence of angina (as ascertained by the Rose questionnaire), 25% reduction in the development of a positive exercise test result, and 21% in the incidence of coronary bypass surgery. More than 20% of all individuals in the placebo group experienced one or more of these cardiovascular events; therefore, the impact of an effective program of total cholesterol reduction on high-risk men (such as those in the LRC trial) is of considerable clinical importance and greatly exceeds the difference between the event rates in the placebo and cholestyramine groups when attention is focused solely on the primary end points of the trial — that is, 9.8% vs 8.1%. It is of further importance and interest that the quantitative estimate of efficacy of cholesterol reduction was similar among all the major cardiovascular end points analyzed in the trial.

Epidemiologic observational studies. The relationship between CHD incidence and initial total serum cholesterol levels over 7.4 years for seven observational cohort studies, and the relationship of CHD mortality and initial total cholesterol levels for one 7 year study in middle-aged men, is presented in table 2 for comparison with the LRC trial placebo group.

An exponentially increasing risk of CHD with increasing baseline levels of total serum cholesterol has been reported within each study. There has been debate in the past as to whether or not the summarization of these observations by a single, monotonically increasing function best represents the relationship. Some observers have argued, for instance, that a threshold value exists below which there is no association of serum cholesterol with CHD, or that there may be a curvilinear relationship with an increase in some forms of cardiovascular disease (such as cerebrovascular disease) at the lowest levels of total serum cholesterol.

| TABLE 2 |
|-----------------|-----------------|-----------------|-----------------|
| **Multiple logistic coefficients for a single determination of total cholesterol as predictor of first myocardial infarction or CHD death (male subjects)** |
| Study (reference) | n | Mean years of follow-up | Age (years) | Mean total cholesterol | Regression coefficient |
| Framingham | 1089 | 11.5 | 40-54 | 226.5 | .0068 |
| Albany | 1675 | 9.9 | 40-43 | 229.1 | .0080 |
| Chicago — Gas | 934 | 9.7 | 40-54 | 237.5 | .0048 |
| Chicago — Western Electric | 1806 | 8.5 | 40-54 | 247.7 | .0057 |
| Tecumseh | 563 | 8.0 | 40-54 | 230.5 | .0197 |
| United States Railroad — seven countries | 2404 | 5.0 | 40-59 | 239.3 | .0090 |
| Europe — seven countries | 8728 | 5.0 | 40-59 | 211.4 | .0100 |
| MRFIT subjects | 325,384 | 5.0 | 35-57 | 215.0 | .0079 |
| LRC — placebo | 1900 | 7.4 | 35-39 | 293.7 | .0079 |

The coefficients of all studies were covariance adjusted for systolic blood pressure and cigarette smoking. Those for the "seven countries" populations were also adjusted for age and body mass index. The coefficient for the LRC trial was based on a proportional-hazards rather than a logistic model and was adjusted for age, high-density lipoprotein cholesterol, triglyceride, and exercise test outcome at baseline, as well as smoking and systolic blood pressure.
Stratified analyses of most earlier studies have been inconclusive, since partitioning the cohort by quantiles of cholesterol levels produced strata too small to yield stable estimates of risk. In contrast, the recently reported 5 year mortality follow-up of the more than 300,000 white male subjects in the Multiple Risk Factor Intervention Trial (MRFIT) disclosed a step function with no evidence of a threshold value on stratified quintile analysis.\(^{17}\) In addition to continuity of the relationship, of particular note is the quantitative similarity of the logistic regression coefficients among most of the earlier reported studies and the similarity of the recently reported logistic regression coefficient of the mortality follow-up of the MRFIT and Framingham subjects and the LRC trial placebo group. These findings not only indicate an increasing incidence of fatal and nonfatal CHD with increasing serum cholesterol levels in each of the studies, but show that the rate of increase is similar across these investigations. These slopes, each relating differences in CHD risk to differences in initial total cholesterol levels, were controlled for the other standard risk factors.

The epidemiologic observational data of the Framingham study were used to estimate the expected event rate in the placebo group of the LRC trial during its planning and design. The partial regression coefficient estimating the increase in CHD risk with increasing cholesterol level, controlling for the other major risk factors, was similar in the two studies (.0068 for Framingham and .0079 for the LRC trial), as was the average level of CHD.

Marked extrapolation of the LRC trial experience to extremely lower values, therefore, is not justified; however, the overall similarities of the risk functions for the hypercholesterolemic men and the population sample suggest that some extrapolation is meaningful. The rationale and justification for this extrapolation has been increased by the availability of the mortality follow-up experience of the MRFIT subjects.

The findings, both across the clinical trials and within the LRC trial, suggest similarities in the relationship of experimental reduction in total serum cholesterol to the reduction of CHD risk, as predicted from the observational, population-based epidemiologic studies, and further suggest efficacy of reduction at all levels of total serum cholesterol. This, of course, must be evaluated in the context of the absolute risk of CHD, which is lower at lower levels of serum cholesterol. The difficulty with the measurement of the efficacy of serum cholesterol reduction at less than markedly elevated levels of serum cholesterol is related to the extremely large sample sizes required in experiments of this type when clinical end points are assessed. Extrapolations, therefore, must be made from clinical trials including patients with higher levels of total serum cholesterol. Under these circumstances, safety considerations become particularly relevant; since the absolute risk decreases with decreasing levels of total serum cholesterol, any hazard induced by the intervention technique assumes increasing importance.

**All-cause mortality.** Although the incidence of definite and suspect CHD death was reduced by 24% and 30%, respectively, in the cholestryamine-treated group in the LRC trial, all-cause mortality was reduced by only 7% and was not significantly different from zero. Inspection of the causes of mortality by major categories (in addition to the cardiovascular deaths), such as the aggregate of malignancies, disclosed no differences that were noteworthy, with the exception of 11 deaths from accidents and violence in the cholestryamine-treated group compared with four in the placebo group. Since no cause or connection could be established between cholestryamine treatment and violent or accidental death, the LRC investigators concluded that this difference was a chance occurrence. Notice was made, however, of the fact that several other primary prevention trials reported higher noncardiovascular mortality rates in their active treatment groups. In contrast to the excess in violent deaths observed in the actively treated group of the LRC trial, in other studies the excess resulted from a variety of medical causes. In drug studies of this type, explanations must include the possibility of iatrogenesis directly related to the specific pharmacologic agents used in reducing serum lipids. Several prior studies disclosed evidence of possible toxic effects from drugs such as clofibrate,\(^{11}\) high-dose estrogen in men,\(^{18}\) and dextrothyroxine.\(^{19}\) Although there is no significant evidence of an excess mortality as a result of medical conditions within the cholestryamine-treated LRC group, this cohort will continue to be observed for long-term sequelae.

Observational epidemiologic studies have yielded inconsistent findings regarding the association between serum cholesterol levels and all-cause mortality, which is quite different from the consistent association seen between total serum cholesterol and CHD events. In some population studies (for example, the Oslo\(^{20}\) and Chicago Gas Co. and Chicago Western Electric Co. studies\(^{21}\)), the relationship has been positive — a stepwise increase in mortality from all causes with increasing cholesterol levels. In other populations, the relationship has been curvilinear, with increases in mortality at both the high and low extremes of cholesterol levels; this has been observed in the
Framingham,22 Evans County,23 and Honolulu24 studies. It should be noted, however, that increased mortality, when present, occurred at levels of cholesterol far below the mean population value. An inverse relationship of total cholesterol to mortality from all causes has been reported in the New Zealand Maori25 and Yugoslavia26 studies. Clarification of the epidemiologic findings and their relevance to clinical trials of cholesterol lowering among hypercholesterolemic men awaits further research.

LRC population surveys. The range, median, seventy-fifth, and ninety-fifth percentile values are illustrated as a cross-sectional relationship of lipid levels to age for the LRC population samples in North America in figure 4. Mean values of total and LDL cholesterol increased in parallel from adolescence to adulthood, with a continuing rise into the stratum of age eligibility for the LRC trial. This marked rise was also apparent in the seventy-fifth and ninety-fifth percentile values (the latter constituting eligibility for inclusion in the LRC trial). The magnitude of increase with age was considerable. For example, ninety-fifth percentile values for LDL cholesterol in white male subjects increased approximately 55 mg/dl (close to 40%), from approximately 145 mg/dl in the third decade to approximately 200 mg/dl in the fifth decade. The continuous nature of the risk function relating serum cholesterol to CHD and the high prevalence of moderate hypercholesterolemia — 25% of the population by definition — results in a large fraction of all excess CHD cases associated with hypercholesterolemia emerging from the moderate hypercholesterolemic pool. The same principle would apply if lower cut points were chosen. This quantitative reasoning, by the population attributable risk concept, estimates the proportion of all cases emerging from different levels of the distribution of serum cholesterol. A shift in the full distribution of serum cholesterol toward lower values is advocated for population control of CHD. Given current average levels of approximately 210 mg/dl in LRC population surveys of men, for example, lowering of LDL to mean values of 190 mg/dl is regarded as feasible, and levels below 160 mg/dl have been judged ideal from the perspective of controlling CHD in populations.27

Despite the high prevalence of moderate hypercholesterolemia in contemporary U.S. populations, sizable numbers of adults have cholesterol levels of 160 mg/dl or lower. In the LRC population surveys, the prevalence of total serum cholesterol levels of 160 mg/dl or lower was in excess of 30% at age 20 to 29 years, but decreased markedly with age — to 15% at ages 30 to 39 and to less than 10% at ages 40 and older28 (figure 5). This inversely mirrors the rise in mean values with age and highlights the need for prevention of a rise in serum cholesterol in adulthood, in addition to the need for medical care programs for the treatment of high-risk individuals with hypercholesterolemia after it has occurred, if CHD is to be controlled in populations as a whole in developed nations. Follow-up to date within the LRC population studies suggests that individuals

![Graph](https://example.com/graph.png)

**FIGURE 4.** Plasma total, LDL, and high-density lipoprotein (HDL) cholesterol values by age for white male participants in the LRC trial.
with markedly lower cholesterol values are at, as is to be expected, markedly lower risk of CHD mortality; in addition, there is no evidence of deleterious sequelae, as reflected in all-cause mortality.

Conclusions. This review of the experimental clinical trials and observational cohort evidence relating level and reduction of serum cholesterol to CHD risk has disclosed strong similarities in the relationships, both quantitative and qualitative, observed among studies. The risk functions are similar, the percent reduction observed in clinical trials is that predicted from the population experience and is proportionate to the amount of cholesterol lowering achieved, and the risk function is continuous from highest to lowest serum cholesterol levels studied. The similarities of risk functions across the wide range of serum cholesterol levels are particularly noteworthy given the marked differences in times and places of the studies (with CHD mortality markedly differing by place and time), and with differences in the personal characteristics of individuals studied. This suggests that, despite a wide variety of factors influencing the level of CHD in the population, the relationship of coronary disease risk to serum cholesterol is similar at "all" levels. These findings, added to the large body of extant evidence from other sources, not only confirm the lipid hypothesis but indicate that lowering serum cholesterol lowers CHD risk. The other major risk factors, in addition to cholesterol, appear to have similar effects in the general population and in high-risk individuals, although there is the potential for an interactive effect in high-risk individuals.

The specific treatment regimen for high-risk persons requires a tailored program with assessment of risks and benefits on an individual basis. The population approach requires consideration of cholesterol as a graded characteristic distributed in populations with increasing CHD risk at increasing levels. Identifying appropriate target populations and modalities for the safe, effective prevention or treatment of elevated plasma LDL cholesterol in individuals and populations as a whole requires a review of existing evidence in addition to the observational cohort and clinical trial results reviewed here, as well as further research.29

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