Prevention and Regression of Coronary Atherosclerosis*

Is It Safe and Efficacious Therapy?

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Objective: Atherosclerotic coronary heart disease (CHD) continues to be the dominant disease in Western society. A large body of evidence directly linking serum cholesterol levels and CHD risk has stimulated population treatment strategies designed to reduce cholesterol and CHD risk. Data indicating a relation between low cholesterol and non-CHD risk have, however, suggested that cholesterol reduction may not always be desirable. The primary goal of this evaluative review of the available evidence was to answer the following question: Is prevention/regression therapy for CHD safe and effective?

Data sources: Three lines of evidence were reviewed: epidemiologic studies; primary and secondary prevention trials with clinical end points; and secondary prevention trials with quantitative coronary angiography as a surrogate end point for clinical CHD.

Study selection: Original studies and meta-analyses were reviewed. The principal selection criteria for the epidemiologic studies were large size and prolonged follow-up; for the trials, randomization and viable clinical (CHD events, CHD mortality, total mortality) or angiographic end points.

Data extraction: The data were initially extracted by a single reviewer using common qualitative guidelines. The data were then evaluated by all authors serving as a data interpretation team.

Data synthesis: Overall, the epidemiologic data revealed excess risk of fatal and nonfatal CHD events was directly related to total cholesterol and low-density lipoprotein (LDL) cholesterol levels, for both men and women and for both younger (<65 years) and older (≥65 years) patients, over a wide range of serum cholesterol levels. The predictive value was higher in younger men than older men and women, although part of this quantitative interaction may be due to fewer studies, with fewer end points, in the older and female populations. The CHD events and CHD mortality, but not total mortality, were consistently reduced in trials of cholesterol-lowering therapy. The regression trials, predominantly in CHD patients with high cholesterol values (mean 7.1 mmol/L), demonstrated improvement in angiographic atherosclerosis in every study. The evidence for elevated risk of non-CHD death at very low levels of cholesterol is uncertain and controversial. The most likely possibilities for this apparent relationship are unknown confounding variables and the play of chance.

Conclusions: Serum cholesterol levels are directly associated with CHD risk, and there is no threshold level below which there is no risk. Reduction of high serum cholesterol levels reduces CHD risk. Whether lipid-lowering and adjunctive antithrombotic therapies are effective and safe in the majority of CHD patients who have desirable or borderline cholesterol levels remains undetermined.

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ACE = angiotensin converting enzyme; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein

Atherosclerosis, the complex interaction of serum cholesterol with the cellular components of the arterial wall, leading to coronary heart disease (CHD) and other occlusive vascular diseases continues to be the leading cause of morbidity and mortality in adults in developed countries. A large body of evidence has gradually accumulated directly linking serum cholesterol levels and CHD risk.1-7

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Until recently, clinicians tended to undervalue the importance of cholesterol as a modifiable risk factor for CHD. A principal contribution to the qualitative change which has occurred in physicians' attitudes towards cholesterol and its potential for effective modification has been the realization that even modest, but prolonged, reductions in total and low-density lipoprotein (LDL) cholesterol in persons with marked elevation of cholesterol levels is associated with a clinically significant reduction in CHD risk.8-10 The publication of consensus panels of expert opinion11,12 has also helped mold contemporary patterns of practice.

Concurrently, and perhaps as importantly, therapeutic modalities have been developed that can lower serum cholesterol up to 50 percent.13 This
The effect size is greatly beyond what has been seen with previously available cholesterol-lowering therapy, which is more often in the range of 20 to 25 percent. This greater than usual effect of the new cholesterol-lowering drugs has helped to capture the attention, and shape the practice patterns, of many clinicians.

Conversely, an increased risk of non-CHD death at low levels of cholesterol has also been suggested. This has stimulated an ongoing controversy, which, unless resolved, may diminish physicians' inclination to prescribe appropriate cholesterol-lowering therapy for patients at increased risk for CHD. It may also contribute to the development of a negative public attitude toward CHD risk and its clinical reduction.

This review objectively evaluated all the available data linking cholesterol and CHD risk. Its primary goal was to answer the following question: Is prevention/regression therapy for CHD safe and effective? Subsidiary goals were to clarify important deficiencies in our present knowledge base, in order to provide insights for future research.

The Epidemiologic Evidence

Epidemiology has been defined by William Kannel as, "the study of the way morbid processes arise, evolve and terminate in general population samples rather than individual persons." Population studies of CHD have provided not only a picture of incidence and natural history, but also insights into pathogenesis and risk vulnerability.

Epidemiology studies have consistently established the importance of serum cholesterol level as a modifiable risk factor for CHD, together with diastolic and systolic hypertension and smoking. Moreover, the relationship of serum cholesterol level and risk of CHD death has been established as continuous over a wide range of baseline cholesterol levels. In fact, there appears to be no evidence of a threshold serum cholesterol level below which there is no CHD risk.

Interestingly, in a population with, on average, low total cholesterol, Chen et al have suggested that a 4 percent difference in cholesterol concentration was associated with a 21 percent difference in CHD mortality. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) had previously reported that a 10 percent decrease in serum cholesterol was associated with a 20 percent decrease in CHD risk. The LRC-CPPT data have led to the "1-2" rule—a 1 percent reduction of total cholesterol resulting in a 2 percent reduction in CHD risk. Overall, a 1:3 ratio may be closer to the average truth, if results from prolonged studies and the systemic underestimation effect of using only a single cholesterol measurement in many studies are taken into account. As pointed out by Jacobs et al, CHD risk reduction is related not only to the degree of cholesterol lowering, but also to the duration of the lowering, a concept which he termed the "strength of the intervention."

The totality of the evidence relating serum cholesterol and CHD risk can best be demonstrated by overview analyses in which the weight of pooled evidence from all available cohorts is assessed and even small differences, in the range of 10 to 20 percent, can be reliably detected. Manolio et al have performed such an overview on 25 populations from 22 studies, using the most recent follow-up data available to them (average, 15 years; range, 3 to 28 years). The results of this overview of the relationship of cholesterol and CHD mortality risk are summarized in Table 1.

Briefly, this study found that total serum cholesterol and LDL cholesterol levels predicted CHD mortality in younger (< 65 years) and older (≥ 65 years) men and women (Table 1). The power and consistency of the association was highest in younger men (relative risk of total cholesterol ≥ 6.2 mmol/L vs < 5.2 mmol/L, + 73 percent) and least in older women (relative risk, + 12 percent); it was intermediate in older men and younger women (Table 1).

Part of the decreased power of the relationship in women and older persons may have been secondary to the fewer studies, with smaller sample sizes and fewer CHD outcomes, among women and older people, relative to younger men (Table 1). It may also be due to a truly lower relative risk among women and older persons. However, as pointed out by Manolio et al, when a risk factor is common in a population, as elevated cholesterol is among the elderly, it does not have to be very powerful to produce a large absolute risk, that is a large number of excess cases in the population.

A strong inverse relationship between high-density lipoprotein (HDL) cholesterol and CHD risk has been described. The data from the Framingham and other major epidemiologic studies which examine the relationship between HDL cholesterol and CHD risk have consistently confirmed this inverse relationship, suggesting that approximately a 0.026 mM increment in HDL cholesterol can be associated with a 2 percent reduction in CHD risk in men and a 3 percent risk reduction in women.

The role of elevated triglycerides as an independent CHD risk factor appears less clear. Univariate analyses of case control studies have suggested that this may be an independent risk factor. Prospective studies, however, have failed to confirm this independent risk association when controlled for
HDLC cholesterol in multivariate analysis. Further research on the relationship between HDL risk and triglycerides and other lipid subfractions such as apolipoprotein B and Lp(a) is necessary to define their respective roles as risk factors as well as in the underlying atherogenic mechanisms.

The Evidence From Clinical Trials

More than 30 randomized trials testing the effect of cholesterol-lowering therapy on CHD morbidity and mortality have been carried out. These have included both primary and secondary prevention trials. The interventions have included diet and drugs to reduce cholesterol, as well as adjunctive therapy to reduce other risk factors, such as cessation of smoking and reduction of hypertension.

The issue of primary or secondary prevention has been the focus of innumerable discussions and publications, based on the suggested dichotomy that cholesterol lowering is beneficial in secondary but not in primary prevention. Obviously, participants in secondary prevention trials are at higher risk for CHD events, and the benefit in secondary trials could be higher than in primary prevention trials of low risk patients. The proportional reductions in CHD risk noted in these two groups of trials are, however, not statistically different.

Individually, many of the trials failed to achieve statistical significance in reductions of important clinical end points. Overall, the drug trials have also shown a greater trend toward reductions in CHD risk than the diet trials. In order to obtain a more conclusive view based on the collective evidence from the trials, overview analyses have been conducted. There have been several such overview analyses of the primary and secondary CHD clinical trials. The results of these overview analyses are summarized in Table 2.

The meta-analysis of 9 primary and 13 secondary trials by Yusuf et al revealed an overall 23 percent reduction in risk for CHD events and a 10 percent reduction in CHD mortality. The authors felt these effects were directly related to both the degree and the duration of cholesterol lowering. These authors also found that there was no heterogeneity in the lipid-lowering effect on CHD events with drug or dietary interventions, in primary prevention or secondary intervention settings, or on fatal or nonfatal

Table 2—Summary of the Clinical Effects of Lipid-Lowering Therapy as Defined by Overview Analyses of Primary and Secondary Prevention Trials*

<table>
<thead>
<tr>
<th>Author</th>
<th>Primary</th>
<th>Secondary</th>
<th>n</th>
<th>Percent Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yusuf et al 8</td>
<td>9</td>
<td>13</td>
<td>40</td>
<td>-23 (-28, -18)</td>
</tr>
<tr>
<td>Jacobs et al 14</td>
<td>. .</td>
<td>. .</td>
<td>42</td>
<td>-10 (-16, -2)</td>
</tr>
<tr>
<td>Muldoon et al 21</td>
<td>6</td>
<td>0</td>
<td>25</td>
<td>-9 (-14, -4)</td>
</tr>
<tr>
<td>Holme 22</td>
<td>7</td>
<td>12</td>
<td>&gt; 50</td>
<td>-9 (-14, -4)</td>
</tr>
<tr>
<td>Smith and Pekkanen 23</td>
<td>7</td>
<td>0</td>
<td>35</td>
<td>-29 (-45, -10)</td>
</tr>
</tbody>
</table>

*Abbreviations the same as Table 1. Percent risk reduction data are expressed as the mean and 95 percent confidence limits. The Yusuf and Jacobs data were directly reproduced from the original. The data of the other authors were estimated from data originally expressed as odds ratios. When event rates are low, relative risk and odds ratios are very similar.

†Reported as similar to previous meta-analysis and significant at p < 0.001.
‡Dietary interventions.
§Drug interventions.
CHD outcomes. In a subsequent updated meta-analysis, Jacobs et al\textsuperscript{14} reported similar significant risk reductions for CHD events and CHD mortality.

Muldoon et al\textsuperscript{21} published a meta-analysis of several trials, all of which were primary prevention trials. Muldoon and his coworkers\textsuperscript{21} found a treatment-related reduction in CHD mortality similar to that reported by Yusuf et al.\textsuperscript{8} Holme\textsuperscript{22} analyzed 19 trials, 7 primary and 12 secondary, and found a significant reduction in CHD events and no difference in total mortality among the intervention groups receiving the lipid-lowering therapies. Holme\textsuperscript{22} confirmed a greater than 2 percent reduction in CHD events for every 1 percent reduction in serum cholesterol levels. This analysis also indicated that therapy was more effective in subjects at higher risk, such as those with higher baseline cholesterol levels. In accord with the findings of Yusuf et al,\textsuperscript{8} Holme also suggested there was a dose-dependent therapeutic effect—with a greater reduction in CHD risk in those patients who demonstrated a greater reduction in serum cholesterol levels.\textsuperscript{23}

Smith and Pekkanen\textsuperscript{23} reviewed the same six primary prevention trials as Muldoon et al,\textsuperscript{21} plus the Expanded Clinical Evaluation of Lovastatin (EXCEL) study.\textsuperscript{13} They reported similar results, although relative to the findings of Muldoon et al,\textsuperscript{21} their analysis showed a greater degree of risk reduction in CHD mortality for both dietary and drug interventions.\textsuperscript{23}

In summary, the weight of evidence from the available clinical trials data is consistent with the hypothesis that lipid-lowering therapy reduces the risk for CHD events and CHD mortality. The data do not, however, demonstrate a reduction in total mortality risk, although the confidence intervals allow for a reduction in total mortality of up to 18 percent (Table 2).

The most likely reason for these trials not showing a reduction in total mortality is they were not statistically powered to do so when deaths unrelated to CHD were included. That is, the differences in CHD mortality were not large enough to produce statistically significant differences in total mortality in the study populations with many other competing pathways of mortality risk.

If the goal of a trial was to achieve a significant difference in overall mortality, the available data suggest that the chances of success would be optimized by the following: selecting a very large population sample at high risk for CHD but at low risk for non-CHD events; use of as effective a lipid-lowering regimen as possible and for as prolonged a period as possible; and, by addition of other interventions designed to attack pathophysiological pathways in the atherosclerosis process complementary to the cholesterol pathway.

Even with such a best case study scenario, for example, a large (25 percent) decrease in total cholesterol in a high CHD mortality risk (2 percent/year) low non-CHD mortality risk (1.3 percent/year) cohort followed for 5 years, the estimated sample size to give a reasonable (85 percent power) certainty of detecting a difference in overall mortality at a conventional level of significance (2p < 0.05) has been estimated at 8,000 subjects.\textsuperscript{24} In contrast, a study of an intervention that was expected to produce only a 10 percent decrease in cholesterol in a low CHD risk cohort would require a sample size of 720,000 subjects.\textsuperscript{24} That is, in this worst case scenario, the risk of death from competing non-CHD causes would be substantial, and reduction in overall mortality produced by effective anti-CHD intervention would be very difficult to detect.\textsuperscript{24}

**The Evidence From Regression Trials**

There have been at least 14 secondary prevention trials at lipid-lowering and adjunctive therapies in which some quantitative angiographic measure of atherosclerosis was used as a surrogate end point for clinical CHD.\textsuperscript{25-38} Coronary angiographic changes have been widely accepted as logical surrogate endpoints for subsequent CHD clinical events. There is also the perceived advantage that changes in coronary angiographic end points are more common and are detectable earlier than clinical end points. Therefore, clinical trials using this surrogate end point need fewer patients with shorter durations of follow-up. The earlier angiographic trials were qualitative due to lack of reliable quantitative measures of angiographic changes in the coronary arterial lumen. The development of sensitive highly reliable computerized systems of quantitative analysis of coronary angiogram has led to a series of clinical trials referred to as “regression trials” because of the stated objective that active intervention with cholesterol lowering and other therapies can result in improvements in coronary atherosclerosis.

There have been no formal overview analyses of these “regression” trials, but the results of the 14 individual published reports are summarized in Table 3.

Characteristic of the regression trials was their, on average, small sample size (mean, n = 162) and short duration (mean, 28 months) (Table 3). Moreover, the average total cholesterol level was 7.1 mmol/L, indicating a relatively high-risk overall population (Table 3). There was a wide variation of interventions, although lipid-lowering diet and/or drugs were the mainstay, and there was nonuniformity of angiographic measurement techniques (Table 3). There was also a dichotomy of clinical CHD out-

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comes, with approximately half of the trials reporting improvement and the other half, no improvement (Table 3). Angiographically, however, there was overwhelming consistency in the coronary angiographic results from the regression trials—they all demonstrated improvement (Table 3). This is remarkable and somewhat unexpected. It would be reasonable to expect that one or more of the trials' results would have been negative by chance alone.

One speculative explanation for these consistent findings is that quantitative coronary angiography is a very sensitive end point for measuring the atherosclerotic process, particularly in higher-risk CHD patients. Another possible explanation is that the distribution of results is, in fact, following the play of chance, but by chance alone, no negative results have yet been recorded. A third possibility is that negative results have been seen, but not reported; or they were missed in the literature search for this review.

Also in the realm of speculation is whether the results of regression interventions would be qualitatively similar, if quantitatively smaller, in CHD patients with lower baseline cholesterol levels. This is a very important unanswered question, since more than half the attributable risk of serum cholesterol to CHD in the population at large is in persons with total cholesterol in the desirable or borderline ranges, that is less than 6.2 mmol/L.\textsuperscript{39}

\*Abbreviations: NHLBI = NHLBI type II coronary intervention study; Leiden = Leiden Intervention Trial; CLAS-I and CLAS II = First and Second Cholesterol-Lowering Atherosclerosis Studies; MILAN = Milan study of nifedipine, propranolol and isosorbide dinitrate; INTACT = International Nifedipine Trial on Antithrombotic Therapy; LHT = Lifestyle Heart Trial; POSCH = Program on the Surgical Control of the Hyperlipidemic; FATS = Familial Atherosclerosis Treatment Study; SCOR = Specialized Center of Research study on familial hypercholesterolemia with combined drug regimen; MHI = Montreal Heart Institute nicardipine study; IFPK = Institut für Pr\" aventive Kardiologie fenofibrate study; STARS = St Thomas' Atherosclerosis Regression Study; MUH = Medizinische Universitatsklinik Heidelberg exercise and diet study; n = the number of patients who completed each protocol; TC = total serum cholesterol; QCA = quantitative coronary angiography.

\|\hline
Trial & n & Duration, mo & Baseline Cholesterol, mmol/L & Lipid (diet/drug) & Other & Angio & Results & Improved Clinical & Improved Angio \\
\hline
NHLBI\textsuperscript{25} & 116 & 60 & TC 8.4 & +/- & 0 & + & 0 & - & + \\
 & & & LDL 6.5 & & & & & & \\
Leiden\textsuperscript{24} & 39 & 24 & TC 6.9 & +/0 & 0 & + & + & - & + \\
 & & & LDL & & & & & & \\
CLAS-I\textsuperscript{17} & 162 & 24 & TC 6.3 & +/- & 0 & + & 0 & 0 & + \\
 & & & LDL 4.4 & & & & & & \\
CLAS-II\textsuperscript{25} & 103 & 48 & TC 6.3 & +/- & 0 & + & 0 & 0 & + \\
 & & & LDL 4.4 & & & & & & \\
MILAN\textsuperscript{24} & 113 & 24 & TC 6.2 & 0/0 & + & 0 & + & - & + \\
 & & & LDL 4.5 & & & & & & \\
INTACT\textsuperscript{20} & 348 & 36 & TC 6.7 & 0/0 & + & 0 & + & 0 & + \\
 & & & LDL 4.7 & & & & & & \\
LHT\textsuperscript{21} & 41 & 12 & TC 6.1 & +/0 & + & 0 & + & + & + \\
 & & & LDL 4.1 & & & & & & \\
POSC\textsuperscript{22} & 634 & 60 & TC 6.5 & +/0 & + & 0 & + & + & + \\
 & & & LDL 4.6 & & & & & & \\
FATS\textsuperscript{23} & 120 & 30 & TC 7.0 & +/- & 0 & 0 & + & + & + \\
 & & & LDL 4.8 & & & & & & \\
SCOR\textsuperscript{24} & 72 & 26 & TC 9.7 & +/- & 0 & 0 & + & 0 & + \\
 & & & LDL 7.2 & & & & & & \\
MHI\textsuperscript{23} & 335 & 24 & TC 6.9 & 0/0 & + & 0 & + & 0 & 0\textsuperscript{1} \\
 & & & LDL & & & & & & \\
IFPK\textsuperscript{24} & 21 & 21 & TC 8.0 & +/- & 0 & 0 & + & - & + \\
 & & & LDL 6.1 & & & & & & \\
STARS\textsuperscript{37} & 74 & 39 & TC 7.2 & +/- & 0 & 0 & + & + & + \\
 & & & LDL 5.0 & & & & & & \\
MUH\textsuperscript{28} & 92 & 12 & TC 6.1 & +/0 & + & + & + & + & + \\
 & & & LDL 4.2 & & & & & & \\
\hline

Prevention and Regression of Coronary Atherosclerosis (Montague et al)
THE NEGATIVE EVIDENCE

Concerns that serum cholesterol levels could reach "too low" levels and could result in increased stroke, cancer, and noncardiac mortality and morbidity have been raised in the last decade. Most recently, the subject has been addressed by a National Heart, Lung, and Blood Institute Conference. Presentations were given from 19 international cohort studies and the manuscript of a 20th was available for reference. The resulting manuscript, based on an overview analysis of the 19 presentations, reported a J or U shape for the relationship between total mortality and cholesterol levels in men and a flat shape in women. The left side of the J-shaped risk curve was caused by an inverse relationship between low cholesterol levels and some, but not all, cancers, respiratory disease, digestive disease, trauma, and residual deaths.

Definitive interpretations of the relationships between non-CHD deaths and low cholesterol levels were not felt to be possible. Most of the conference participants appeared to favor confounding variables as the explanation. At the conference, Yusuf et al presented the results of an overview of 32 clinical trials, an update of a previous meta-analysis of 22 trials. The data of Jacobs et al revealed an excess of non-CHD deaths in the treated compared to the control groups which was of borderline statistical significance and spread over numerous causes and not related to the strength of the intervention. They interpreted these findings as biologically implausible and unlikely to be the result of a cause and effect relationship. Rather, they felt they were likely secondary to the play of chance.

The study of 9,021 Chinese men and women by Chen et al was also discussed at the conference. Chen and coworkers showed a continuum of CHD risk even at cholesterol levels that were, on average, much lower than usual Western standards. Chen et al found no significant relationship between cholesterol and stroke or all cancer deaths. They did find relationships between low cholesterol and liver cancer and other liver diseases. They ascribed these relationships to a third confounding factor—the high prevalence of chronic hepatitis B infection in the Chinese population.

In an accompanying editorial for the conference manuscript, Hulley et al recommended a change in population-based policy for the primary prevention of CHD. They felt it was unwise to treat high serum cholesterol levels in persons without manifestations of CHD, in the absence of "other reasons for being at a comparable very high risk of CHD." Whether this recommendation is reasonable has to be viewed in the background that the majority of the CHD risk attributable to cholesterol in the general population is among persons with desirable or borderline serum cholesterol measurements.

For example, in a selected sample of 2,535 general hospital patients having serum cholesterol measurements within 48 h of admission in 1987 and 1988, Ginsburg et al reported that a total cholesterol level less than 5.2 mmol/L had a negative predictive value of only 36 percent for the clinical absence of CHD; that is, 64 percent of their sample population had CHD with desirable cholesterol levels. This was not much lower than the 74 percent incidence of CHD among patients with serum cholesterol 5.2 mmol/L or higher in the same sample. In a subset of 1,084 patients with total cholesterol levels less than 5.2 mmol/L, the same investigators found that HDL cholesterol levels less than 0.9 mmol/L predicted the presence of CHD with 69 percent certainty, indicating that this lipid subtraction truly identifies patients at increased risk, despite desirable total cholesterol levels. The value of HDL cholesterol levels of 0.9 mmol/L or higher in predicting the absence of CHD was, however, only 43 percent. That is, 57 percent of the sample with both desirable total and HDL cholesterol levels had CHD.

In a similar analysis of 740 consecutive CHD patients undergoing coronary angiography between 1977 and 1978, Miller et al studied the subsequent incidence of CHD events over the course of the next 13 years. In the patient subgroup with total cholesterol levels less than 5.2 mmol/L at baseline, the investigators found that reduced HDL cholesterol levels (<0.9 mmol/L) were associated with a predictive risk for a second CHD event of 75 percent. However, the presence of HDL 0.9 mmol/L or higher predicted the absence of subsequent CHD event with only a 55 percent certainty.

In our institution, the incidence of total cholesterol levels less than 6.2 mmol/L in patients with acute myocardial infarction is approximately 60 percent (unpublished data).

Thus, the accumulated data at this time suggest that, in an adult general hospital population, either a total cholesterol level greater than 5.2 mmol/L, or HDL cholesterol less than 0.9 mmol/L even with a desirable level of total cholesterol, predicts a risk of approximately 70 percent for underlying CHD. Perhaps more importantly, the presence of either desirable total or HDL cholesterol levels is associated with less than a 50 percent chance of not having CHD.

The overall implication is that persons with desirable or borderline cholesterol levels must not be considered to be without risk for present or future CHD.
**Future Directions**

As indicated above, most patients with CHD have total cholesterol levels which are either slightly higher than, or within, the desirable range established for the adult population. Since cholesterol has central importance in the pathogenesis of atherosclerosis, this suggests that, in the majority of patients, these “normal” cholesterol levels may, in fact, be too high. Whether cholesterol-lowering therapy will produce CHD regression in patients with desirable or borderline cholesterol levels has not been clearly established in clinical trials specifically enrolling this group of patients.

Very few physicians would contend that cholesterol is the only causative factor in atherosclerosis. As indicated, more than half of the CHD patients have desirable or borderline cholesterol levels and, even in patients with severe hypercholesterolemia, the rate at which CHD progresses to the point of clinical expression varies from subject to subject. Therefore, in patients with “normal” cholesterol levels, it is reasonable to speculate that other mechanisms are important in the pathogenesis of atherosclerosis.

Studies investigating the effects of adjuvant (in addition to cholesterol lowering) therapy on the pathogenesis of atherosclerosis are being planned or ongoing. At present, in addition to lipid lowering therapy, two groups of drugs are particularly promising. Angiotensin converting enzyme (ACE) inhibitors have been observed to reduce cardiac ischemic events in clinical trials on patients with left ventricular dysfunction with and without manifest CHD after several months of use. Animal and laboratory studies also suggest that ACE inhibition has an antiatherogenic effect, causing inhibition of cell proliferation and decreased tendency for thrombosis in the arterial wall.

Antioxidants, such as vitamin E, probucol, vitamin C, and beta carotene can also be hypothesized to reduce the formation of oxidized LDL cholesterol. Epidemiologic data support the hypothesis that this form of therapy can reduce atherosclerosis-related events. If proven in randomized trials, ACE inhibition and antioxidants could greatly, and relatively inexpensively, reduce the morbidity and mortality associated with atherosclerotic CHD.

Two specific clinical trials illustrate the current research. The first is the Simvastatin/Enalapril Coronary Atherosclerosis Regression Trial (SCAT), conducted by the authors, and testing in a factorial design whether, in patients with established CHD and total cholesterol levels less than 6.2 mmol/L, treatment with cholesterol-lowering medication and/or ACE inhibition will promote regression or reduce progression of coronary atherosclerosis.

The other is a multicenter clinical trial of the ACE inhibitor ramipril and the antioxidant vitamin E in patients at high risk for CHD events, the Heart Outcomes Prevention and Evaluation (HOPE) Trial. Both trials are funded by the Medical Research Council of Canada and the pharmaceutical industry.

**Conclusions**

The weight of evidence directly linking cholesterol and CHD is, overall, consistent and compelling. Serum cholesterol levels are directly associated with CHD risk in all tested populations, and there is no threshold level below which there is no risk. Reduction of high serum cholesterol levels reduces CHD risk. It remains, however, undetermined whether lipid-lowering and adjunctive anti-atherosclerotic therapies are effective and safe in the majority of CHD patients who have desirable or borderline cholesterol levels. Further studies are needed.

In the interim, aggressive secondary prevention with all proven effective interventions, including cholesterol-lowering therapy, is indicated for CHD patients with cholesterol levels higher than 6.2 mmol/L. In persons without clinically apparent CHD, that is, for primary CHD prevention, treatment decisions concerning cholesterol reduction must be individualized, based on clinical assessment of risk status.

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