

GAO

Report to the Ranking Minority Member,
Committee on Science, House of
Representatives

May 1996

CHOLESTEROL TREATMENT

A Review of the Clinical Trials Evidence



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**Program Evaluation and
Methodology Division**

B-266080

May 14, 1996

The Honorable George E. Brown, Jr.
Ranking Minority Member
Committee on Science
House of Representatives

Dear Mr. Brown:

The death rate from coronary heart disease (CHD) declined dramatically during the past decade, but CHD is still the most prevalent cause of death in the United States. Public health efforts to prevent heart disease have emphasized reducing risk factors such as smoking, hypertension, and elevated blood cholesterol levels. The National Institutes of Health (NIH) established the National Cholesterol Education Program (NCEP) in 1985 to encourage Americans to modify their diet and lifestyle and to provide clinical guidelines to help health care professionals identify and treat persons whose risk of heart disease is high because their cholesterol levels are high. The NCEP guidelines suggest that 52 million American adults are candidates for dietary treatment and that 9 million to 18 million of these have cholesterol levels that are sufficiently high to warrant drug treatment.

High cholesterol is now widely recognized by the scientific community and the general public as an important risk factor for heart disease. Physicians and the public are generally aware of the need to lower cholesterol, and treating patients by lowering their cholesterol has met with some success. National survey data indicate that the proportion of adults whose cholesterol is high (greater than or equal to 240 mg/dl) declined from 26 percent to 20 percent between 1976 and 1991.¹ The NCEP guidelines have contributed to this decline, but key aspects of them have been debated since the mid-1980s. A number of critics have questioned whether the available scientific evidence clearly demonstrates that the benefits of treatment outweigh any possible health risks and whether the benefits are broad enough to support widespread screening and treatment of the population as the NCEP guidelines advocate.

Concerned about the translation of medical knowledge into national policy and about the high costs of cholesterol treatment, the former Subcommittee on Investigations and Oversight of the House Committee on Science, Space, and Technology asked us to review the clinical trials

¹C. T. Sempos et al., "Prevalence of High Blood Cholesterol Among U.S. Adults," Journal of the American Medical Association, 269 (1993), 3009-14.

evidence that was used to support the development of the NCEP guidelines. The guidelines were developed from a broad set of research that included not only clinical trials but also epidemiological, animal, pathologic, and genetic studies. We were asked to review the clinical trials because they are uniquely designed to assess the effectiveness of interventions to reduce the incidence of a disease.

The equivocal results of the many individual clinical trials that have been conducted over the past 30 years, however, have made it difficult to determine the efficacy of cholesterol-lowering treatments in preventing CHD. Several trials have shown clear reductions in heart disease rates for persons who were treated, but many trials showed no improvement either because the types of treatment were not particularly effective in lowering cholesterol or because the studies were not large enough to adequately measure the expected benefits.

Recently completed studies called meta-analyses, which quantitatively combine the results of many individual trials, provide new insights into the interpretation of the overall benefits and risks of cholesterol-lowering treatments. Therefore, we examined the benefits and risks of lowering cholesterol reported from meta-analyses of available clinical trials. We report these and the results of two recently completed clinical trials that used newer, more effective drug treatments that were not included in the published meta-analyses. These trials provide important new evidence regarding cholesterol treatment and the reduction of CHD. In addition, we assessed the extent to which the trials provide information on different population subgroups, and we determined whether the clinical trials that are currently planned are likely to fill any data gaps that exist.

Results in Brief

Meta-analyses that combine previous clinical trial findings consistently show that persons who receive cholesterol-lowering treatment, regardless of whether or not they have a history of heart disease, have significantly fewer nonfatal heart attacks than persons who do not receive treatment. The evidence on CHD fatalities (deaths attributable to CHD) also shows a modest treatment benefit, but the meta-analyses show that it is found mainly in the group of trials that assessed persons who already had CHD. A reduction in CHD fatality rates is also found for persons who had high cholesterol and no history of CHD; however, the differences between treatment and nontreatment groups are not statistically significant.

With respect to total fatalities—that is, deaths from CHD and all other causes—most meta-analyses show no significant difference and thus no improvement in overall survival rates in the trials that included either persons with known CHD or persons without it. This is partly because of an increase in non-CHD deaths across the trials. This finding, that cholesterol treatment has not lowered the number of deaths overall, has been worrisome to many researchers and is at the core of much of the controversy on cholesterol policy.

Various researchers have attributed the increase in non-CHD deaths to chance, to the biological means by which cholesterol is lowered, to the short duration of the trials, or to the side effects of some treatments. However, several recent meta-analyses have identified important factors that appear to help explain it. They show, for example, that the overall death rate fell in the trials that included persons whose risk for CHD was highest and in the trials in which cholesterol reductions were large. The overall death rate rose significantly among persons whose risk of CHD was lower, whose cholesterol was reduced less, or whose treatment used certain drugs.

The finding that reductions in coronary events are greater with greater amounts of cholesterol reduction is confirmed by two trials completed too recently to be in the meta-analyses we reviewed. Using a new class of cholesterol-lowering drugs—the statins, or HMG CoA reductase inhibitors—they lowered cholesterol 20 to 25 percent. Previous trials using other drugs lowered it 10 percent, on the average. One of the trials, conducted in Scandinavia on persons who already had had a heart attack, found that both CHD outcomes and total deaths fell significantly for those who received treatment. The second trial, conducted in Scotland on persons who had no previous history of heart disease, also found reductions in coronary events, although the reductions in coronary deaths and total deaths did not quite achieve statistical significance.

While the existing cholesterol trials provide important results about CHD outcomes, they are not representative of the population at large. The trials focused predominantly on middle-aged white men considered to be at high risk of CHD. They provide very little information on women, minority men and women, and elderly men and women. The few trials that opened enrollment to these subgroups generally did not have large enough numbers of them to conduct separate analyses. What is known about these groups has been obtained from other types of research that cannot be

used to make causal inferences about how lowering cholesterol affects coronary outcomes.

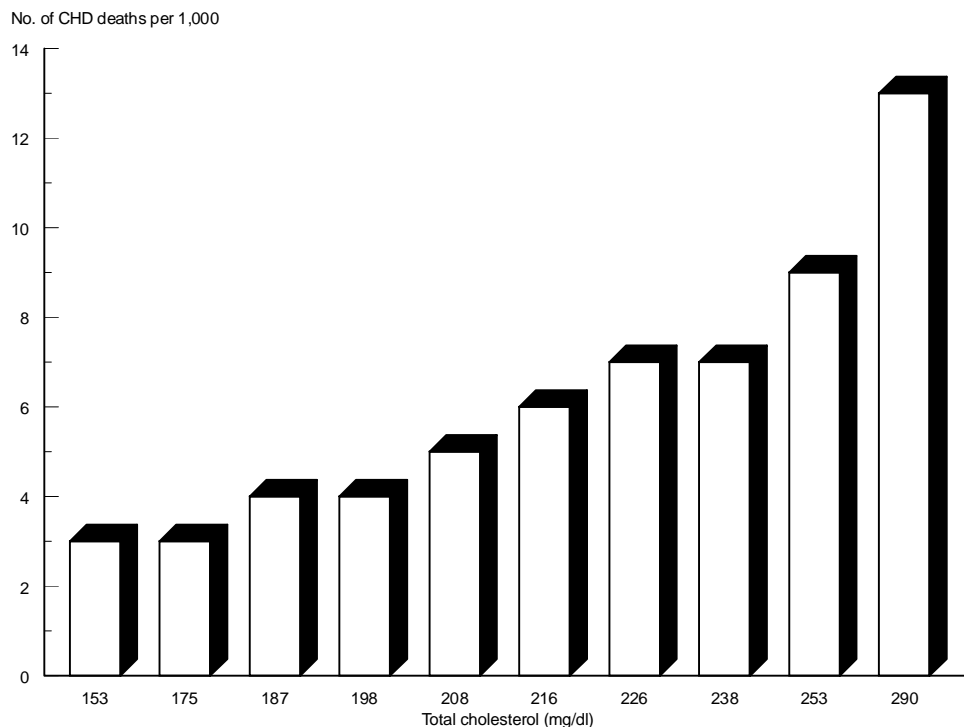
Several new clinical trials under way are intended to provide additional information about treatment outcomes regarding total fatalities, persons whose short-term risk of a coronary event is moderate, and the longer-term effects of the newer drugs being used. These trials will be large and open to participants from a broader portion of the population than previously studied. However, the numbers actually enrolled in many of these trials have not yet been determined, so that the extent to which the trials will provide information on groups other than middle-aged white men is not yet known.

Background

Nearly half a million persons die from heart disease each year. As many women as men die from CHD, although women die about 7 to 10 years later than men on the average. The American Heart Association estimates that heart disease costs \$55 billion or more each year. Taken together, these figures provide a strong rationale for prevention and treatment.

Many factors can contribute to the development of CHD. A heart attack—a temporary interruption of blood flow to the heart—stems partly from the chronic buildup of fatty plaque in the arteries. For example, as figure 1 shows, there is a continuous and upward-sloping association between higher cholesterol levels and the incidence of CHD. Some of the best-known risk factors, such as high blood cholesterol, cigarette smoking, diabetes, obesity, hypertension, and physical inactivity, can be treated or modified; others, such as age and family history of heart disease, cannot.

Figure 1: CHD Deaths by Cholesterol Level Among Men Screened for the MRFIT Trial^a



^aDeaths over 6 years among more than 355,000 men screened in the early 1970s.

The National Cholesterol Education Program

National Heart, Lung, and Blood Institute (NHLBI) education campaigns address several of the modifiable risk factors, including high blood cholesterol levels, smoking, obesity, and hypertension. As a result of an NIH consensus development conference in 1984, NHLBI established NCEP to inform the public of the risks associated with cholesterol and to provide guidelines for physicians on how to manage and reduce those risks. Accordingly, NCEP both promotes the reduction of cholesterol levels in the general population through lifestyle changes and encourages the identification of persons whose cholesterol is high as candidates for intensive treatment to lower it.

In the latter, high-risk approach, the NCEP guidelines recommend that all adults be tested for cholesterol at least once every 5 years. Test results are used to classify each person free of CHD into one of three groups: desirable,

borderline-high, or high total cholesterol levels.² Taking other risk factors into consideration, physicians then identify candidates for further testing (to determine low-density lipoprotein (LDL) cholesterol levels) and cholesterol-lowering treatment. The first line of intervention against high cholesterol levels is diets that emphasize lowering the consumption of fat (particularly saturated fat) and dietary cholesterol. Prescription drugs are advised if cholesterol goals are not met through diet. For most patients, treatment is maintained over the course of a lifetime in order to keep cholesterol levels down.

NCEP revised several elements of the guidelines for adults in 1993, principally by (1) including age with regard to gender in determining risk status and in making treatment decisions; (2) increasing the emphasis on screening and treating persons whose risk of CHD is high, such as elderly persons and those who already have evidence of CHD; and (3) recognizing the importance of high-density lipoprotein (HDL) cholesterol as an independent risk factor for CHD.³

The Controversy on Cholesterol Policy

Debate after the NCEP guidelines were issued focused on the efficacy of lowering cholesterol, on its possible risks, and on the advisability of screening for cholesterol and lowering it among the many population subgroups that had not been included in the trials the guidelines had been based on. Additional, more recent data have brought greater agreement that cholesterol treatment helps prevent deaths among persons who have a history of CHD. Controversy remains, however, on how useful cholesterol-screening is to the broader population of healthy people. The American College of Physicians, professionally representing 85,000 U.S. internists, recently published guidelines under which groups for whom cholesterol-screening has no proven benefit would not be screened.

While there is considerable agreement about the risks associated with high cholesterol, concerns have been raised about the extent to which cholesterol-lowering treatments reduce the rates of death from CHD and from all causes. Some researchers argue that the clinical trials have shown no difference in total fatalities between groups of people who received

²Desirable is below 200 mg/dl, borderline high is 200-239 mg/dl, and high is equal to or above 240 mg/dl. Approximately 50 percent of the U.S. adult population has total cholesterol levels of 200 mg/dl or higher.

³For example, the guidelines no longer recommend drug treatment for men younger than 35 and premenopausal women, both of whom tend to experience lower rates of CHD. HDL cholesterol, a component of total cholesterol, is believed to help remove excess cholesterol from the blood and prevent the buildup of plaque. A higher level of HDL cholesterol is associated with a lower risk of heart disease, while a lower level of HDL cholesterol can increase the risk of heart disease.

treatment and those who did not and that cholesterol-lowering treatments may increase the number of deaths from non-CHD causes. Advocates of the NCEP guidelines argue that the trials were not designed to be large enough or long enough to assess overall mortality; they say that the increases in rates of non-CHD deaths within the treatment groups are likely to have resulted from chance or specific treatments rather than from any adverse effects of lowering cholesterol.

Because the clinical trials focused almost exclusively on men who had either existing CHD or high cholesterol or both, they provide little information about anyone whose risk of heart disease is lower. Some researchers and health policy analysts therefore suggest that the U.S. guidelines should be more limited in scope, as they are in some other nations. Advocates of the current guidelines, however, believe that some trial data and other, nonclinical trial research, such as epidemiological and laboratory studies, allow the generalization that if cholesterol-lowering benefits the tested groups, it will benefit others.

Objectives, Scope, and Methodology

As we stated previously, the main objective of our study was to examine the NCEP guidelines' clinical-trials base of evidence regarding cholesterol-lowering treatment.⁴ We limited our scope to mainly randomized clinical trials that, by virtue of their design features, provide the best evidence for assessing the effectiveness of interventions to reduce the incidence of a disease. Other important research was also used in developing the NCEP guidelines. For example, many epidemiological studies have compared population groups across nations, monitored the health status of entire community populations, and assessed changes in the health outcomes of recent immigrants. These studies have increased knowledge about the link between diet, elevated cholesterol levels, and increased risk of CHD. Because we did not review other types of cholesterol-related research, we did not evaluate or report the overall adequacy or utility of the scientific support for the guidelines.

We reviewed the clinical outcomes of cholesterol-lowering trials through the published results of 15 meta-analyses.⁵ The meta-analyses, which

⁴In a clinical trial, participants are screened and randomly assigned to a group that receives treatment or to a group that does not, which allows an unbiased comparison of outcomes between the two groups.

⁵We selected meta-analyses that aggregated data from cholesterol-lowering trials across one or more of the following health outcomes: nonfatal heart attacks, CHD fatalities, CHD incidence (nonfatal and fatal events combined), non-CHD fatalities, and total fatalities. Not all the meta-analyses, however, reported on each of these outcomes.

statistically summarize the results of a number of individual trials, give an overall assessment of treatment outcomes. By combining the results of several trials, meta-analyses can increase statistical power and the precision of results. Within certain methodological limits, they also provide a means of comparing different subgroups of trials and of exploring issues in ways that individual trials, which may be constrained by their design or intent, cannot.

The many clinical trials that have evaluated cholesterol-lowering treatments represent diverse types of treatment, health characteristics, overall sample sizes, duration of trial and follow-up, and outcomes. The main treatments consisted of different diets and drugs (alone or in combination). Some studies focused on persons who had existing symptoms of CHD (secondary prevention trials); others concentrated on those who had no evidence of CHD (primary prevention trials); a few combined both. Although virtually all the trials were designed to assess CHD outcomes, not all measured and reported the same outcome variables.

The meta-analyses that combined the numerical results of these trials are also diverse. They used different rules for deciding what trials to include and exclude; in fact, all excluded one type of trial or another. Most of the meta-analysts, for example, excluded trials that used more than one intervention to treat persons who had multiple risk factors, and most also excluded the hormone trials because the type of hormone treatment they used is no longer recommended for men. As a result, the meta-analyses included as few as 6 to as many as 35 trials.

To determine the benefits and risks of cholesterol-lowering treatments, we present the results of the meta-analyses.⁶ We examined the similarities and differences among them, in terms of the individual trials they included and their analyses. We then compared reported odds ratios (a measure of the relative difference in outcomes between persons who were treated and those who were not treated in the trials) and determined the extent to which there was agreement or disagreement in the direction and statistical significance of the results.

To address the issue of the coverage and comprehensiveness of the clinical trials data, we identified the demographic and risk-related

⁶We did not conduct our own meta-analysis because each of the meta-analyses that we selected to review responded to the objectives of our study. The results of the different meta-analyses are not statistically independent because many of the larger clinical trials tend to be included in most of the meta-analyses. As a result, even though there is diversity among the meta-analyses, some convergence of findings is to be expected.

characteristics of participants in trials included by meta-analysts, the types of treatment they received, and the outcomes. In the same vein, to identify the important data gaps that others have found, we reviewed NHLBI documents, medical literature, and other sets of guidelines developed elsewhere. We also identified and reviewed the designs of ongoing and planned trials in order to determine which data gaps may be filled in the near future.⁷

Principal Findings

The Benefits and Risks of Lowering Cholesterol

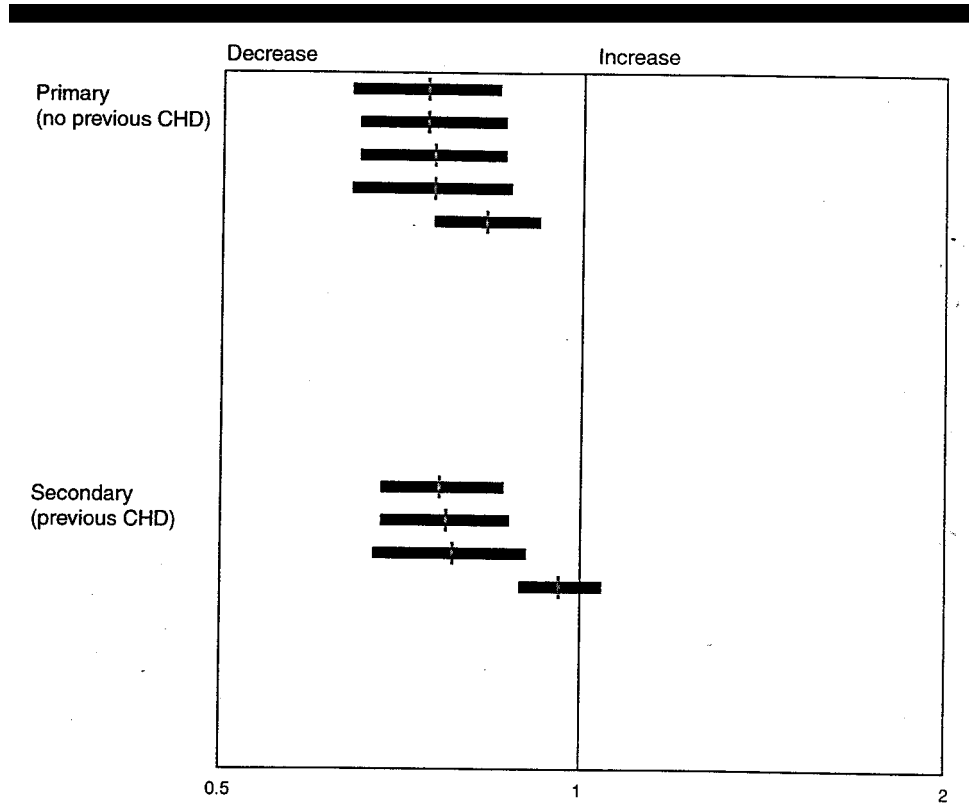
Nonfatal and Fatal CHD Outcomes

The meta-analyses we reviewed consistently reported a statistically significant reduction in the rates of nonfatal heart attacks for the trial participants who were treated for high cholesterol compared to those who did not receive treatment. As shown in figure 2, this finding holds true for both individuals without existing evidence of CHD—that is, in the primary prevention trials—and those with it—that is, in the secondary prevention trials.⁸

⁷Appendix I describes in detail our scope and methodology and their strengths and limitations. In appendixes II and III, we summarize our findings from the meta-analyses and discuss the data gaps in the clinical trials. Appendix IV describes U.S. cholesterol policy in the United States and abroad.

⁸Our findings on the benefits and risks of lowering cholesterol from the meta-analyses are tabulated and discussed further in appendix II.

Figure 2: Nonfatal Heart Attacks Reported in Meta-Analyses of Cholesterol-Lowering Trials^a



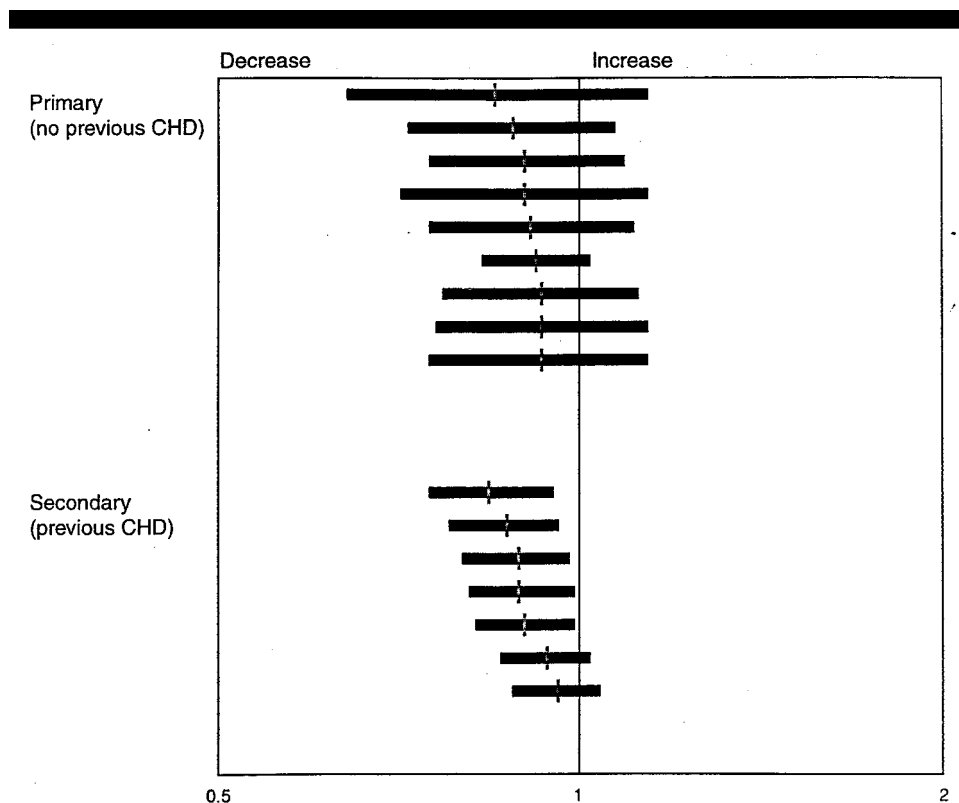
^aThe horizontal bars represent estimates (at the 95-percent confidence interval) of the difference in the odds of nonfatal heart attacks occurring in the treatment and nontreatment groups studied in meta-analyses. At 1, the center of the figure, treatment and nontreatment groups show no difference in the likelihood that participants in either group will have a nonfatal heart attack; bars to the left of 1 indicate that treatment leads to a decrease in the rate of nonfatal heart attack; bars to the right, that it leads to an increase. Bars that overlap 1 indicate that differences between treatment and nontreatment groups are not statistically significant. The line at the center of each bar represents the common odds ratio, or the point estimate of that difference (that is, it is the ratio of the odds of nonfatal heart attacks occurring in the treatment groups to the odds of nonfatal heart attacks occurring in the nontreatment groups). (Appendix II, table II.1, details the numerical estimates for each meta-analysis.)

The results that the meta-analyses reported for deaths from CHD present a somewhat different picture, shown in figure 3. All the meta-analyses reported a reduction in the rate of coronary death among the participants who were treated compared to those who were not but not as great a relative reduction as that in nonfatal outcomes. Also, a different pattern is apparent for the death rate of participants who were treated and had a history of CHD compared to participants who were treated and did not. For those who had a history, most of the meta-analyses found a significant

reduction favoring the treatment groups. For those who did not, the meta-analyses that examined CHD deaths point in the direction of a small reduction but none found it statistically significant.⁹

⁹Another useful measure comparing the effects of treatment is the number of persons who would have to be treated in order to prevent one adverse event. One meta-analysis calculated this number for death from CHD and found a large difference between those who had existing CHD and those who did not: to prevent one death from CHD, 38 persons with existing CHD would have to be treated while 675 persons with no evidence of CHD would have to be treated. This calculation does not reflect the larger number of nonfatal heart attacks relative to fatal attacks and the proportionately larger number of nonfatal attacks prevented by lowering cholesterol, nor does it reflect treatment with the statin drugs. See J. S. Silberberg and D. A. Henry, "The Benefits of Reducing Cholesterol Levels: The Need to Distinguish Primary from Secondary Prevention. I. A Meta-Analysis of Cholesterol Lowering Trials," Medical Journal of Australia, 155 (1991), 665-70.

Figure 3: CHD Fatalities Reported in Meta-Analyses of Cholesterol-Lowering Trials^a



^aThe horizontal bars represent estimates (at the 95-percent confidence interval) of the difference in the odds of CHD fatalities occurring in the treatment and nontreatment groups studied in meta-analyses. At 1, the center of the figure, treatment and nontreatment groups show no difference in the likelihood that participants in either group will have a fatal heart attack from CHD. Bars to the left of 1 indicate that treatment leads to a decrease in the rate of fatal heart attack; bars to the right, that it leads to an increase. Bars that overlap 1 indicate that differences between treatment and nontreatment groups are not statistically significant. The line at the center of each bar represents the common odds ratio, or the point estimate of that difference (that is, it is the ratio of the odds of CHD fatalities in the treatment groups to the odds of CHD fatalities in the nontreatment groups). (Appendix II, table II.2, details the numerical estimates for each meta-analysis.)

The lack of a statistically significant reduction in the rate of death among participants in the primary prevention trials may be because the trials generally lowered cholesterol levels by only a modest amount and the number of events attributable to CHD during the trials was so small that detecting statistical differences between the treatment and nontreatment groups was difficult.¹⁰ Several of the recent meta-analyses found that the

¹⁰Cholesterol reduction across the individual trials ranged from around 1 percent to more than 20 percent, with an average of about 10 percent.

degree to which cholesterol is lowered is related to reductions in CHD events among the trials. For example, one study reported that when cholesterol was lowered by 10 percent or more, deaths from CHD fell significantly, by 13 percent, and another reported that nonfatal heart attacks and CHD deaths fell by 18 percent.¹¹ Another meta-analysis found that lowering cholesterol by 12 percent or more corresponded to a 27-percent fall in the death rate from CHD.¹²

The extent to which the rate of death from CHD falls is also associated with the level of risk for CHD that participants have at the start of a trial. In one meta-analysis, participants in primary and secondary trials were categorized according to higher, medium, and lower levels of risk. The results showed a significant 26-percent fall in the rate of death from CHD for those in the higher-risk category but no significant benefit for those in the medium- and lower-risk categories. The higher-risk category was dominated by participants who had a history of CHD (secondary prevention trials), whereas the lower-risk category was dominated by participants who did not (primary prevention trials).¹³

Non-CHD and Total Fatalities

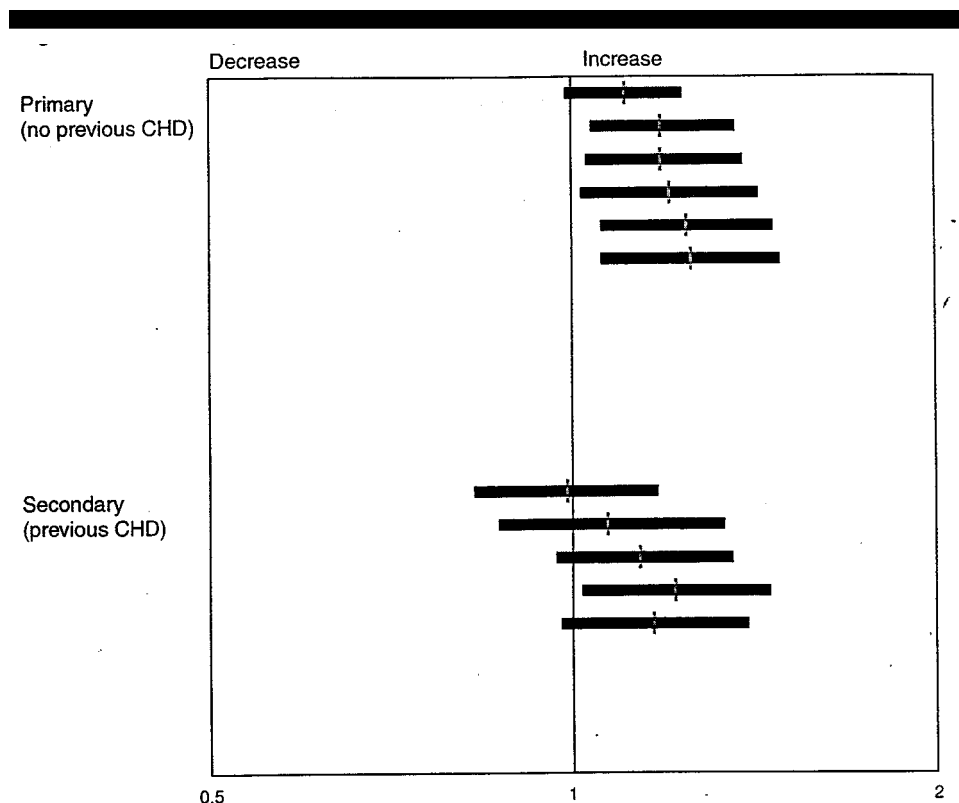
The extent to which overall survival rates improve from lowering cholesterol has been addressed mainly in the meta-analyses. The individual trials were mostly too short and had too few participants to assess whether death from all causes fell. As shown in figure 4, the meta-analyses that reported on deaths from non-CHD causes mainly show a statistically significant increase within the primary prevention trials for those who received treatment. The meta-analyses similarly point toward an increase within the secondary prevention trials, but only one found it to be statistically significant.

¹¹A. L. Gould et al., "Cholesterol Reduction Yields Clinical Benefit," *Circulation*, 91 (1995), 2274-82, and M. R. Law et al., "By How Much and How Quickly Does Reduction in Serum Cholesterol Concentration Lower Risk of Ischaemic Heart Disease?" *British Medical Journal*, 308 (1994), 367-73.

¹²D. J. Gordon, "Cholesterol Lowering and Total Mortality," in B. M. Rifkind (ed.), *Lowering Cholesterol in High-Risk Individuals and Populations* (New York: Marcel Dekker, 1995), pp. 33-48.

¹³G. D. Smith, F. Song, and T. A. Sheldon, "Cholesterol Lowering and Mortality: The Importance of Considering Initial Level of Risk," *British Medical Journal*, 306 (1993), 1367-73.

Figure 4: Non-CHD Fatalities Reported in Meta-Analyses of Cholesterol-Lowering Trials^a

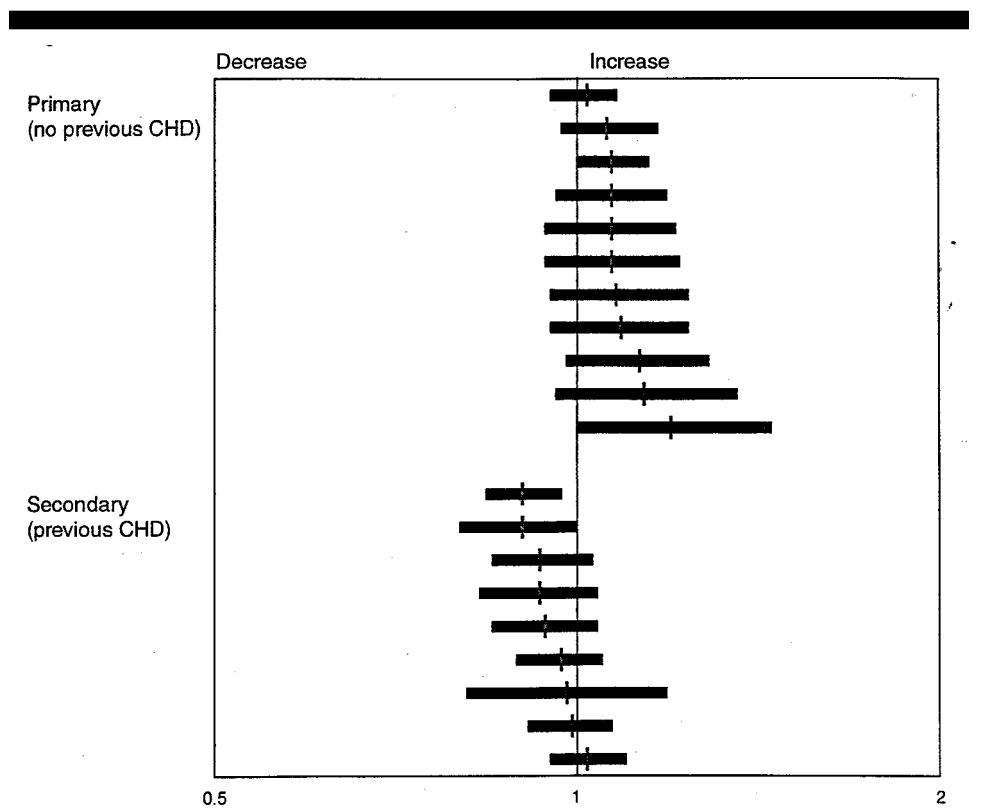


^aThe horizontal bars represent estimates (at the 95-percent confidence interval) of the difference in the odds of non-CHD fatalities occurring in the treatment and nontreatment groups studied in meta-analyses. At 1, the center of the figure, treatment and nontreatment groups show no difference in the likelihood of non-CHD fatalities among participants in either group. Bars to the left of 1 indicate that treatment leads to a decrease in the rate of non-CHD fatalities; bars to the right, that it leads to an increase. Bars that overlap 1 indicate that differences between treatment and nontreatment groups are not statistically significant. The line at the center of each bar represents common odds ratio, or the the point estimate of that difference (that is, it is the ratio of the odds of non-CHD fatalities in the treatment groups to the odds of non-CHD fatalities in the nontreatment groups). (Appendix II, table II.2, details the numerical estimates for each meta-analysis.)

When the trial data are aggregated through the meta-analyses, total fatality rates increase among treated participants who had no evidence of CHD (see figure 5). However, none of the meta-analyses found these rates to be statistically greater among participants who were treated than among those who were not. The meta-analyses found a small relative decrease in total fatalities for participants who were treated and had a history of CHD;

only one found it to be statistically significant (see figure 5).¹⁴ That total fatalities did not fall significantly after cholesterol-lowering treatment may be because fatality rates from non-CHD causes were high among these participants. These high rates were large enough to cancel out the modest reduction in CHD deaths after cholesterol-lowering treatment.

Figure 5: Total Fatalities Reported in Meta-Analyses of Cholesterol-Lowering Trials^a



^aThe horizontal bars represent estimates (at the 95-percent confidence interval) of the difference in the odds of total fatalities occurring in the treatment and nontreatment groups studied in meta-analyses. At 1, the center of the figure, treatment and nontreatment groups show no difference in the likelihood of total fatalities among participants in either group. Bars to the left of 1 indicate that treatment leads to a decrease in the rate of total fatalities; bars to the right, that it leads to an increase. Bars that overlap 1 indicate that differences between treatment and nontreatment groups are not statistically significant. The line at the center of each bar represents the common odd ratio, or the point estimate of that difference (that is, it is the ratio of the odds of total fatalities in the treatment groups to the odds of total fatalities in the nontreatment groups). (Appendix II, table II.2, details the numerical estimates for each meta-analysis.)

¹⁴The one meta-analysis that found a statistically significant reduction weighted the result for the degree of cholesterol-lowering.

Some analysts explain the increase in non-CHD fatalities as a matter of chance. Others speculate that lowering cholesterol itself produces these results. Still others point to the side effects of one or more of the drugs used for treatment. Although the meta-analyses have not resolved this issue—because non-CHD deaths were not as carefully reported in some of the individual trials as were deaths from CHD—they have shed some light and have identified areas that warrant further investigation.

When one meta-analyst differentiated between the trials whose participants had higher, medium, and lower risk for CHD, deaths from all causes fell significantly among those who were at higher risk for CHD and received cholesterol-lowering treatment, whereas deaths increased significantly for those who were at lower risk. Furthermore, a few other meta-analyses have shown that the more that cholesterol is lowered, the greater is overall survival.¹⁵ Finally, recent meta-analyses have found that the greater numbers of non-CHD deaths associated with cholesterol-lowering treatment are more likely to be seen in trials that used certain drug treatments, particularly hormones and fibrates.

Two Recent Cholesterol-Lowering Trials

The Scandinavian Simvastatin Survival Study (4S), a secondary prevention trial, and the West of Scotland Coronary Prevention Study (WOSCOPS), a primary prevention trial, treated men whose total cholesterol averaged more than 260 mg/dl with either a statin drug or a placebo.¹⁶ The results of both trials are consistent with the several meta-analyses that found that greater reductions in cholesterol yielded greater reductions in CHD events.

The 4S trial is the first to find that lowering cholesterol can significantly reduce the total fatality rate of cardiac patients who are at very high risk for heart attack. The WOSCOPS trial found that lowering cholesterol lowered CHD fatalities, although this fell short of statistical significance. There were no increases in non-CHD fatality, and total fatalities fell. The reduction in CHD deaths in 4S means that 29 patients diagnosed with CHD would have to be treated with simvastatin at the trial dosages for 5.4 years (the median length of the trial) to prevent one CHD death. Given the WOSCOPS trial data, 143 middle-aged men with no evidence of a previous heart attack would

¹⁵One meta-analysis found that when cholesterol was lowered by at least 10 percent, total mortality fell about 10 percent. Another reported that a 12-percent or greater reduction in cholesterol led to a 20-percent reduction in total mortality.

¹⁶Scandinavian Simvastatin Survival Study Group, "Randomized Trial of Cholesterol Lowering in 4,444 Patients with Coronary Heart Disease: The Scandinavian Simvastatin Study (4S)," *Lancet*, 344 (1994), 1383-89, and J. Shepard et al., "Prevention of Coronary Heart Disease with Pravastatin in Men with Hypercholesterolemia," *New England Journal of Medicine*, 333 (1995), 1301-7.

have to be treated for 5 years to prevent one death from cardiovascular causes.

Another concern in the controversy is that lowering cholesterol may simply substitute one cause of death for another. The meta-analyses summarizing most past trials found that lowering cholesterol had the clearest benefit among men who had been diagnosed with CHD, that the magnitude of coronary benefits is related directly to the degree to which cholesterol is lowered, and that higher rates of non-CHD fatality are likely to be associated with specific treatments. The 4S and WOSCOPS trials, which did not find a greater risk of death from non-CHD causes, support the meta-analytic findings that it is particular treatments to lower cholesterol, rather than the lowering itself, that increase non-CHD fatality rates. These data may be encouraging, but it should be noted that these were 5-year studies and that drug treatment would be expected to continue for longer periods.

The Population and Treatment Gaps in the Clinical Trials

The Population Studied

The clinical trials conducted over the past 30 years concentrated on white, middle-aged men who were considered to have a high risk of CHD. Useful trial data are lacking for women, minority men and women, elderly men and women, and people who have moderate cholesterol readings and are generally at lower risk. The trials that did enroll them did not do so in numbers large enough to allow for separate analyses of the trial results. To achieve sufficient statistical power at the least cost, researchers selected the participants they felt were most likely to experience a large number of CHD events within a trial's duration.

Because the numbers for women and elderly men and women are so small and the trials did not separate them out for analysis, the meta-analyses generally did not report them separately either. Fewer than half the trials considered in the meta-analyses were open to women, and women constitute only about 7 percent of the participants across all the trials. The average age of participants in the trials ranged from 45 to 66, with a median of about 52 across all the trials.

The trials examined in the meta-analyses provide very little information about people whose risk of heart disease as defined by the NCEP guidelines is moderate. Most trials included either persons who were known to have evidence of CHD or persons who had no evidence of CHD but had high cholesterol and other risk factors. Even primary prevention trials included high-risk groups. The median total cholesterol for all trials was close to 260 mg/dl.

Types of Treatment

Several of the trials tested various dietary treatments, but most of these used diets that differ from the ones that are now recommended and used to treat persons with high cholesterol. The diet trials were also conducted mainly in institutions, where the participants' diet could be strictly controlled. Therefore, several reviewers of the trials have questioned the extent to which their findings apply to people who do not live in institutions.

The older drug treatments, those predominantly used in the trials we examined, have some side effects, and a few have seriously negative effects. The long-term effects of the statins, now the most widely used cholesterol-lowering drugs, have not been extensively investigated. These drugs were developed and marketed in the 1980s, after most of the existing trials were designed or conducted.

Planned Clinical Trials

The gaps in what is known about the relationship between lowering cholesterol and CHD outcomes are generally recognized by most experts, including the authors of NCEP's reports. Many are being addressed by new trials that should help answer some of the questions about non-CHD deaths and total fatalities, CHD outcomes for persons whose short-term risk of heart disease is moderate, CHD outcomes for population groups other than middle-aged white men, and the long-term effects of the statin drugs.

We identified 13 large trials in different stages of design and implementation in the United States and Europe. They tend to be large and long and should have greater statistical power than previous trials to assess total fatalities.¹⁷ Most will use one of the statin drugs. Therefore, trial investigators expect larger improvements in CHD outcomes.

Many of the trials plan to provide information about different levels of CHD risk. At least 3 trials will study participants who have no history of CHD,

¹⁷All but one of these trials will have 2,500 participants or more. One trial will have a follow-up period of 3 years; the others will run for 5 years or more.

and 5 have broadened the range of cholesterol levels generally studied to include borderline-high cholesterol levels of 200 to 240 mg/dl. Three will evaluate whether drug treatment can raise HDL cholesterol levels and thus improve CHD outcomes. Previous trials have not generally focused on treating persons whose HDL cholesterol was low.

Several of the new trials will enroll older participants. One is designed only for elderly participants. Two of the new trials will include a high percentage of women, but it may be difficult to attribute any observed outcome to cholesterol-lowering treatment because both will use several interventions to target different risk factors. Women will number fewer than 20 percent of the participants in the other new trials. Depending on how many women in all are actually enrolled, there may or may not be sufficient information to assess coronary outcomes with respect to cholesterol-lowering treatment. Only one trial will recruit a large percentage of African Americans.

Conclusions

We have four main conclusions from our evaluation of the meta-analyses and the clinical trials they studied:

1. The meta-analyses have consistently shown that cholesterol-lowering treatment benefits middle-aged white men who have high cholesterol levels and a history of heart disease. This appears to be so particularly when the treatment is effective in lowering cholesterol.
2. The meta-analyses also show that men with moderate-to-high cholesterol levels and no history of heart disease have lower rates of nonfatal heart attacks but no statistically significant reductions in rates of CHD death or total fatalities as a result of cholesterol-lowering treatment.
3. The trials generally have not evaluated the efficacy of cholesterol-lowering treatment for several important population groups, such as women, elderly men and women, and minority men and women. Thus, they provide little or no evidence of benefits or possible risks for these groups.
4. Two recent trials using a new drug class, the statins, show greater reductions in coronary events with their greater reductions in cholesterol and no increase in non-CHD fatalities. One trial studied men and women who had CHD and found a significant reduction in total fatalities; the other,

which studied only men who did not have CHD, showed encouraging but not statistically significant reductions in CHD fatalities.

Recommendation

While the clinical trials have answered many important questions about the benefits and risks of various cholesterol-lowering treatments, they also leave unanswered several questions about likely coronary outcomes for persons at different levels of CHD risk and for persons in population subgroups that they have not thoroughly studied. These questions will be answered to some extent by several trials that are under way, but it is likely to be several years before they are completed. We recommend that the director of NHLBI take steps to closely monitor these trials, evaluate their outcomes, and determine whether additional trials should be planned in order to fill in data presently lacking on women, elderly men and women, minority men and women, and persons whose cholesterol levels are relatively low or who otherwise are members of low-risk groups.

Agency Comments

Officials from NHLBI reviewed a draft of this report and provided the written comments that are reprinted in appendix VI. In general, the officials found our report to be technically accurate and agreed with our main findings. They believed, however, that we placed too much emphasis on the aggregated results of the previous trials and not enough on the two recently completed trials that NHLBI believes conclusively demonstrate the benefits of lowering cholesterol for patients who do and do not have CHD. We agree that these recent trials did produce relatively large CHD reductions compared to previous trial results, and we have tried to reflect this in our report. While the results of the new trials are compelling, it is important to recognize that they were designed to demonstrate the efficacy and safety of particular statin treatments in only selected high-risk populations for a period of 5 years.

NHLBI was also concerned that in our report we did not sufficiently take into account the other sources of nontrial evidence that it believes provides a basis for treating various population subgroups. We agree that our report is limited by our not having reviewed other nontrial sources of information about cholesterol treatment. While it is important to consider the full range of evidence, we were asked to review clinical trials because they provide the strongest evidence for establishing treatment benefits. In light of this request, our study findings can help the Congress and other readers understand the limits of the trial information that was available in

the past while cholesterol policy and treatment efforts were being developed in this country.

As we arranged with your office, unless you publicly announce the report's contents earlier, we plan no further distribution until 30 days after the date of this letter. At that time, we will send copies of this report to the National Institutes of Health and other health-related agencies. We will also make copies available to others on request. If you have any questions or would like additional information, please call me at (202) 512-3092. Major contributors to this report are listed in appendix VII.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Kwai-Cheung Chan', with a stylized flourish at the end.

Kwai-Cheung Chan
Director of Program Evaluation
in Physical Systems Areas

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Abbreviations

4S	Scandinavian Simvastatin Survival Study
ACP	American College of Physicians
ALLHAT	Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack
CHD	Coronary heart disease
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
WOSCOPS	West of Scotland Coronary Prevention Study

Objectives, Scope, and Methodology

The Objectives and Scope of Our Study

Our work is set within the context of NIH's NCEP guidelines. We describe the guidelines and compare them with cholesterol-screening treatment guidelines developed elsewhere, particularly in Australia, Canada, and Europe. (See appendix IV.) We did not evaluate the process by which the guidelines were developed or the adequacy or utility of either the NCEP guidelines or others. We focused on clinical trials evidence, one portion of the broad base of evidence that undergirds the NCEP guidelines. Accordingly, our three objectives were to

- review the benefits and risks associated with the cholesterol-lowering treatments in published randomized clinical trials,
- review the extent to which the information from these trials provides information on different population groups, and
- identify and review the ongoing and planned cholesterol-lowering clinical trials to determine whether identified data gaps are likely to be filled.

Our first objective encompasses 42 individual randomized cholesterol-lowering clinical trials and 15 meta-analyses of them.¹ The trials were conducted over the past 30 years and were mainly designed to test whether lowering cholesterol reduces the incidence of coronary heart disease. The meta-analyses were published from 1987 through April 1995.

The scope of our second objective includes the 42 completed cholesterol-lowering trials within the 15 meta-analyses whose designs we had examined for key demographic and risk-related characteristics among the participants. Our third objective considers the NCEP documents and medical literature we reviewed as well as the design characteristics of 13 planned or ongoing trials.

Our Methodology

Rationale

Our purpose was to assess the evidence regarding the efficacy of cholesterol-lowering interventions on measured health outcomes. We examined the benefits and risks associated with cholesterol-lowering through available clinical trials evidence. We selected randomized clinical

¹In the words of Glass, "meta-analysis" refers to "the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings" (G. V. Glass, "Primary, Secondary, and Meta-analysis," *Educational Researcher*, 5 (1976), 3, cited in H. Cooper and L. V. Hedges (eds.), *The Handbook of Research Synthesis* (New York: Russell Sage Foundation, 1994), p. 5). Meta-analysis is a relatively new analytic procedure, although its practice has been growing steadily over the past two decades.

trials because they are considered the “gold standard” in medical research. People who participate are assigned randomly to either a treatment group that receives the intervention or a nontreatment group that does not. This ensures that a comparison of the two groups’ outcomes will be unbiased because the two groups are more or less equivalent, differing only in the factor being tested—in our case, cholesterol-lowering interventions.

The NCEP guidelines were developed not only from the evidence from randomized clinical trials but also from a broad range of observational studies in epidemiology, animal physiology, pathology, and genetics. Many observational studies, for example, compared population groups across nations, monitored the health status of entire community populations, and assessed changes in the health outcomes of recent immigrants. These studies are important because they enlarged our knowledge of how diet, cholesterol, and the risk of CHD are linked. However, only randomized clinical trials are uniquely designed to attribute potential reductions in CHD specifically to cholesterol-lowering interventions.

However, the individual trials differed in the collection and reporting of outcome variables. Few of them were designed to respond to the debate about the ability of cholesterol-lowering to extend the life span; they often had too few participants or were too short in duration. Therefore, we summarized the results of cholesterol-lowering trials through the meta-analyses to examine the evidence for the effect that lowering cholesterol has on five health outcomes: CHD incidence (nonfatal and fatal heart attacks combined), nonfatal heart attacks, CHD fatalities, non-CHD fatalities, and total fatalities.²

Meta-analyses statistically combine the results of individual randomized cholesterol-lowering clinical trials to estimate the extent to which cholesterol-lowering treatments reduce the incidence of CHD events. Therefore, we elected to provide a descriptive synthesis of the meta-analyses whose purpose had been to assess the benefits and risks of cholesterol-lowering interventions.

Meta-analysis pools data from trials that have addressed essentially the same research question in a statistically rigorous manner, thereby (1) improving statistical power, (2) improving estimates of effect size, (3) resolving uncertainty where reports disagree, (4) answering theoretically relevant questions that were not initially posed or not

²We present these five outcomes separately since CHD incidence cannot be derived from summing nonfatal heart attacks and CHD fatalities. This is because any one trial participant may have more than one nonfatal heart attack.

possible to address within a single study, and (5) evaluating the conditions under which effects occur as well as exploring the mediating processes that may account for them. Meta-analysis can point toward fruitful directions for future primary research.

However, meta-analysis can be limited by the availability and quality of the studies whose results it aggregates. Some criticisms of meta-analysis are that it (1) does not detect publication bias and thus can lead to spurious conclusions, (2) obscures potentially relevant differences between combined trials, and (3) biases findings through its inclusion and exclusion criteria. Nevertheless, we examined the meta-analyses we did because we believed they offered the best available guide to what is generally known and not known about the effects of lowering cholesterol among U.S. adults. Since our intent was to shed light on the consistencies and inconsistencies in all the available and relevant trial data, we did not conduct our own meta-analysis.

We examined the clinical trials evidence and other policy groups' interpretation of that evidence. We also looked at the characteristics of the cholesterol-lowering clinical trials and their applicability to the NCEP guidelines. Specifically, we looked at the extent to which the available data applied to different population groups. Further, we examined ongoing and proposed new trials to determine if they would fill any of the data gaps that have been identified.

Our Database Development and Its Characteristics

Our Selection of Meta-Analyses

We searched MEDLINE, a comprehensive bibliographic database, and reviewed agency and other documents. We also surveyed 11 experts for their opinion on the relevance of the meta-analyses we had located and asked them for additional references that we had failed to uncover. In this way, we identified 42 meta-analyses and other studies that synthesized information from the available cholesterol-lowering trials. We judged 30 of these as inappropriate to our objectives for the following reasons: (1) individual trials were not quantitatively aggregated, (2) aggregated trials were not primarily cholesterol-lowering interventions, (3) analytic detail was insufficient (for example, we excluded a meta-analysis when we were unable to determine the number or identity of the studies it

included), (4) the number of individual trials was insufficient (for example, we excluded meta-analyses that included no more than two randomized trials of a year or more in duration), (5) the study was not published or not published in English, and (6) the clinical CHD outcomes we focused on had not been examined. To the 12 meta-analyses that passed this screen, we added 9 that were published or located after the NCEP guidelines were issued and otherwise passed our screen. This resulted in a core set of 21 meta-analyses.

Our Selection of Individual Clinical Trials

When we reviewed the results of this search, we located 85 references to 54 individual cholesterol-lowering studies. Most of the cholesterol-lowering clinical trials of the past 30 years were conducted in the United States and Europe with participants who were mainly middle-aged white men who were considered to be at high risk for CHD (see table III.1). We asked the 11 experts about our including these trials. They differed on whether we should include multifactor trials, hormone trials, and nonrandomized trials. One or more of them also voted to exclude some studies that had been included in a meta-analysis. We decided to consider all trials that had been referenced by a meta-analyst, thus restricting our review to the mainly randomized trials in the meta-analyses. (The meta-analyses and trials are listed in the bibliography.)

Our Analysis Decisions

Since more than one of the 21 meta-analyses were completed by the same lead author, we set the following criteria to reduce redundancy. (1) When more than one meta-analysis had been completed by the lead author, we selected the more recent one if it represented all previous trials and if it used similar configurations of trials to examine the same outcomes. (2) If the earlier meta-analysis reported on a specific outcome that was not addressed in the more recent meta-analysis, we retained the information from the earlier one. (3) If the more recent meta-analysis resulted in a substantial improvement in quality over a previous one, we replaced the earlier meta-analysis with the later one. (4) When an estimate was based on a very select set of studies that made comparisons with other meta-analyses improper, we dropped the estimate. When we had followed these criteria, the meta-analyses totaled 15, as listed in table I.1.³

³In table I.1, we retained only the Muldoon 1990 analyses that were not updated in Muldoon 1993. We did the same for Rossouw 1991 and 1995. The Law I 1994 meta-analysis (Law, Thompson, and Wald) relies on the same set of trials as the Law II 1994 meta-analysis (Law, Wald, and Thompson). The former includes data on women, and the two address different questions.

Appendix I
Objectives, Scope, and Methodology

**Table I.1: Basic Features of 15
 Meta-Analyses of
 Cholesterol-Lowering Trials^a**

Meta-analysis	Outcome	
	Clinical focus	Other
Yusuf 1987	CHD incidence and CHD and non-CHD fatality for diet and drug trials	Identified dose response relationship between lowering cholesterol and CHD incidence
Muldoon 1990 ^a	CHD, non-CHD, and total fatality (all trials); CHD and total fatality for diet versus drug trials	Summarized results for cancer and nonillness fatality (accident, violence, trauma, and suicide)
Rossouw 1991	Nonfatal, fatal, and all heart attacks; cardiovascular, noncardiovascular, and total fatality for drug trials	Summarized % reduction in heart attacks for primary and secondary prevention trials and by treatment type (diet and various drugs)
Silberberg 1991	CHD incidence, nonfatal heart attacks, and CHD and total fatality for drug trials	Compared CHD benefits of primary and secondary trials and estimated the number needed to prevent an event
Ravnskov 1992	Nonfatal heart attacks and CHD and total fatality	Compared CHD benefits by trial type and duration, gender, and diet and drug treatment type
CTF 1993 ^a	Nonfatal heart attacks and CHD, non-CHD, and total fatality	Summarized results for gallbladder events and death from cancer and violence
Cucherat 1993	CHD incidence, nonfatal heart attacks, and CHD and total fatality	Summarized results for death from cancer and death not related to illness; compared CHD benefits of primary and secondary prevention trials
Holme 1993	CHD incidence and total fatality in different trial types with different diet and drug treatments	Summarized dose-response relationship between lowering cholesterol and CHD incidence and total fatality
Muldoon 1993	CHD fatality in different trial types with different diet and drug treatments	Summarized results for nonillness-related suicide and death from trauma in different trial types with different diet and drug treatments
Smith 1993 ^h	CHD, non-CHD, and total fatality stratified by risk of CHD death	Summarized results for CHD, non-CHD, and total fatality stratified by risk of CHD death in drug and other interventions
Law I 1994 ⁱ	CHD fatality (all trials); non-CHD and total fatality in different trial types with different diet and drug treatments weighted by degree of cholesterol-lowering	Summarized results for death from accident, suicide, and cancer and other diseases

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Trial units ^b	Total number		Gender	Treatment	
	Participants ^c			Included	Expressly excluded ^d
19	36,050		Men, women	Diet, drug	Hormones, multifactor trials
6	24,847		Men	Diet, drug	Multifactor trials
4 diet, 8 drug	1,915 diet, 25,295 drug		Men, women	Diet, drug	Hormones, multifactor trials
9	26,609		Men, women	Drug	Hormones, multifactor trials
26	115,960		Men, women	Diet, drug, hormones, multifactor trials	^e
6	24,847		Men	Diet, drug	Multifactor trials
19	48,273		Men, women	Diet, drug, surgery ^f	Hormones, multifactor trials
22	125,673		Men, women	Diet, drug, multifactor trials, surgery ^f	^e
8	30,696		Men	Diet, drug, surgery ^f	^g
35	57,124		Men, women	Diet, drug, hormones, surgery ^f	ⁱ
28	52,350		Men, women	Diet, drug, surgery ^f	Hormones, multifactor trials

(continued)

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Objectives, Scope, and Methodology

Meta-analysis	Outcome	
	Clinical focus	Other
Law II 1994 ^j	CHD incidence weighted by degree of cholesterol-lowering by trial duration	Compared trial and treatment types for CHD incidence by trial duration differences
Gordon 1995	CHD incidence and CHD, non-CHD, and total fatality	Compared results by trial type, treatment type, and degree to which cholesterol was lowered
Gould 1995	CHD, non-CHD, and total fatality by trial type weighted by degree of cholesterol-lowering	Separated effects of lowering cholesterol from effects of treatment type
Rossouw 1995	CHD incidence, nonfatal heart attacks, and CHD, non-CHD, and total fatality	Summarized results for CHD incidence, lesion progression, and regression in angiographic trials

**Appendix I
Objectives, Scope, and Methodology**

Trial units ^b	Total number		Gender	Treatment	
	Participants ^c			Included	Expressly excluded ^d
28	46,254		Men ^k	Diet, drug, surgery ^f	Hormones
22	31,098		Men, women	Diet, drug, hormones, surgery ^f	Multifactor trials
35	71,313		Men, women	Diet, drug, hormones, multifactor trials, surgery ^f	ⁱ
5 primary, 14 secondary, 9 angiography	21,639 primary, 11,636 secondary, 1,435 angiography		Men, women	Diet, drug, surgery ^f	Hormones, multifactor trials

^aAll 15 meta-analyses summarized the published reports of varying numbers of the 42 clinical trials we reviewed. Muldoon (1990) and CTF included only primary prevention trials; all the other meta-analysts analyzed primary and secondary prevention trials. Complete facts of publication are given in the bibliography. Trial types are indicated in table I.2.

^bSome meta-analysts count the individual treatment arms of a single trial rather than analyzing the whole trial as a unit. Therefore, the number of trial units does not always match the totals in table I.2.

^cIncludes both treatment and nontreatment groups. Totals differ for different analyses.

^dExcludes other trial types also.

^eRavnskov (1992) and Holme (1993) specifically exclude angiographic trials—that is, trials in which measuring coronary arteries allows an assessment of the progression or regression rate of atherosclerosis. Angiographic trials used various cholesterol-lowering treatments and recorded clinical outcomes that could be included in a meta-analysis.

^fPartial ileal bypass surgery.

^gMuldoon (1993) excluded 7 randomized secondary prevention trials that failed to report nonillness-related fatalities (trauma and suicide) in addition to CHD fatalities.

^hIncluded unpublished data.

ⁱNot reported.

^jLaw I and Law II included the same set of 28 randomized trials, supplemented by unpublished data.

^kA small minority of women were included when gender-specific data were unavailable.

We did not develop formal criteria for evaluating the quality of the meta-analyses we selected.⁴ The investigators used accepted approaches for quantitatively combining results, and most of the meta-analyses appeared in peer-reviewed journals. Only one meta-analysis reported having assessed the variability in the methodological soundness of the clinical trials that it aggregated. However, each meta-analysis included mainly randomized trials. We gave all the meta-analyses equal weight.

Our Comparisons of the Meta-Analyses

The meta-analyses we examined included as few as 6 clinical trials up to as many as 35 trials, for quantitatively aggregated information on a range of about 1,500 to more than 125,000 participants. Their strategies differed by whether they analyzed data only on men; by whether they considered treatment duration, the effects of specific drug interventions, and the degree of cholesterol-lowering; and on how they analyzed trials that included more than one treatment.⁵ The studies also differed by how they classified mixed-risk interventions—trials that included participants both with and without manifest CHD. The more recent meta-analyses differed from the earlier ones in being able to include more-recent trials and additional follow-up data.

We compared the 15 meta-analyses for the descriptive characteristics displayed in table I.1. The meta-analysts' decision rules differed. For example, 9 included a trial that used a surgical intervention. Six included trials in which elevated cholesterol, treated with diet, was only one of several risk factors treated; these are multifactor trials. All but 4 meta-analyses excluded trials with only hormone interventions (because they represented cholesterol-lowering interventions that are no longer recommended as a treatment option for men). Nine of the 15 meta-analysts included trials that had an angiographic component.⁶ Some meta-analysts used trial data that had been reported in published articles; others

⁴One difficulty in doing this relates to publication practice. For example, the description of a meta-analyst's search strategy is one important criterion on which to base a quality assessment. However, only 5 meta-analysts discussed their literature search strategy. This failure could mean that no systematic search had been undertaken, or it could mean that the search strategy was not reported because of the journal's space limitations.

⁵This is a particular problem for the large Coronary Drug Project study, which receives considerable weight in a meta-analysis. The trial as designed had five treatments (clofibrate, niacin, estrogen 5.0 mg, estrogen 2.5 mg, and dextrothyroxine). The last three were discontinued early in the trial when adverse effects were observed. Therefore, an investigator who includes all five treatments may bias results in a negative direction. Some analysts pool the data from the clofibrate and niacin treatments, which can bias results in a positive direction.

⁶In angiography, measurement of the coronary arteries allows investigators to assess the effect of cholesterol-lowering on the rate of progression or regression of atherosclerosis.

obtained additional data directly from the authors of the individual trials. In all, the 15 meta-analyses included varying numbers of the 42 individual trials we reviewed.

Table I.2 shows that none of the meta-analyses examined all 42 of the individual trials. Seven contained less than half. Still, 9 meta-analysts included 18 of the same trials; this overlap means that the results of the meta-analyses are not statistically independent of one another.

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Objectives, Scope, and Methodology

Table I.2: Fifteen Meta-Analyses and the Cholesterol-Lowering Trials They Studied^a

Trial by prevention type	Treatment	Yusuf 1987	Muldoon 1990	Rossouw 1991	Silberberg 1991
Primary					
LA VA (1969, 1971)	Diet	•	•	• ^b	
Oslo DA (1981) ^c	Diet, other				
MRFIT (1982) ^c	Diet, other				
WHO F (1983, 1986) ^d	Diet, other				
Gothenburg (1986) ^c	Diet, other				
Minnesota (1975, 1989) ^e	Diet	•	•		
Retinopathy (1969) ^f	Clofibrate				
Begg (1971)	Clofibrate				
Upjohn (1978)	Colestipol	•	•		• ^g
Finnish (1985) ^c	Diet, clofibrate, probucol, other				
Helsinki (1987, 1988)	Gemfibrozil		•	•	•
WHO (1978, 1980, 1984, 1992)	Clofibrate	•	•	•	•
LRC CPPT (1984a, 1984b, 1992)	Cholestyramine	•	•	•	•
Excel (1990, 1991, 1992)	Lovastatin				
Secondary					
Corn Oil (1965)	Diet	• ^j			
MRC Low Fat (1965)	Diet	•		•	
Oslo DH (1966, 1970)	Diet	•		•	
MRC Soya (1968, 1974)	Diet	• ^k		•	
Sydney (1978)	Diet	•			
DART (1989)	Diet				
India (1992)	Diet				
Estrogen (1961)	Estrogen				
Long-Term Estrogen (1962)	Estrogen				
Chicago (1963)	Estrogen				

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Ravnskov 1992	CTF 1993	Cucherat 1993	Holme 1993	Muldoon 1993	Smith 1993	Law I 1994	Law II 1994	Gordon 1995	Gould 1995	Rossouw 1995
•	•	•	• ^b	•	• ^b	•	•	•	•	
•			•						•	
•			•						•	
•			•							
			•						•	
•	•	•	•	•	•	•	•			
					•					
						•	•			
•	•	•	• ^g	•	• ^g	• ^g	• ^g		•	•
•			•						•	
•	•	•	•	•	•	•	•	•	•	•
•	•	•	•	• ^h	• ^h	• ^h	• ^h	• ^h	• ^h	• ^h
•	•	•	•	•	•	•	•	•	•	•
		• ^j			• ^j	• ^j	• ^j			
•		•	•		•	•	•		•	• ^j
•		•	•		•	•	•	•	•	•
•		•	•		•	•	•	•	•	•
•		•	•		•	•	•	•	•	•
					•	•	•		•	•
					•					
•					•			•	•	
• ^l					•					
•					•					

(continued)

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Objectives, Scope, and Methodology

Trial by prevention type	Treatment	Yusuf 1987	Muldoon 1990	Rossouw 1991	Silberberg 1991
Newcastle (1971)	Clofibrate	•		•	•
Scottish (1971, 1972)	Clofibrate	•		•	•
Acheson (1972)	Clofibrate	•			
St. Vincents (1973)	Colestipol				
Veterans Cardiology (1968, 1974)	D-thyroxine; D-thyroxine + estrogen; estrogen + nicotinic acid; nicotinic acid	• ^m			• ^m
Veterans W. Roxbury (1981)	Probucol				
NHLBI (1984)	Cholestyramine, diet ^o	•		p	
CDP (1970, 1972, 1973, 1975, 1986)	Clofibrate, D-thyroxine, estrogen 2.5 mg, estrogen 5.0 mg, niacin	• ^q		• ^q	• ^q
CLAS (1987)	Colestipol, niacin ^o			p	
Stockholm (1977, 1980, 1988)	Clofibrate, nicotinic acid	•		•	•
FATS (1990)	Lovastatin + colestipol; niacin + colestipol ^o			p	
Lifestyle (1990) ^c	Diet, other ^o				
POSCH (1990)	Partial ileal bypass surgery				
SCOR (1990) ^t	Colestipol, lovastatin, niacin ^o				
Restenosis (1991, 1992)	Lovastatin ^o				
STARS (1992)	Diet, diet + cholestyramine ^o				
Ancillary Helsinki (1993)	Gemfibrozil				
MARS (1993)	Lovastatin ^o				
Trials (total = 42)^v		17	6	11	9
% of total trials		40	14	26	21

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Ravnskov 1992	CTF 1993	Cucherat 1993	Holme 1993	Muldoon 1993	Smith 1993	Law I 1994	Law II 1994	Gordon 1995	Gould 1995	Rossouw 1995
•		•	•		•	•	•	•	•	•
•		•	•		•	•	•	•	•	•
			•		•				•	
					• ^m	• ^m	• ^m	• ^m	• ^m	• ^m
					• ⁿ	• ⁿ	• ⁿ			
		•			•	•	•	•	•	•
• ^q		• ^q	• ^q	• ^q	• ^q	• ^q	• ^q	• ^q	• ^q	• ^q
					•	•	•		•	•
•		•	•		•	•	•	•	•	•
					•	•	•		• ^r	•
					• ^s					
		•	•	•	•	•	•	•	•	•
					•					•
					•	•	•		•	
					•	•	•	• ^u	• ^u	•
					•	•	•	•	•	•
										•
22	6	18	22	8	35	28	28	18	29	23
52	14	43	52	19	83	67	67	43	69	55

^aComplete facts of publication for the 15 meta-analyses and the reports of the 42 individual trials in this table are given in the bibliography.

Appendix I
Objectives, Scope, and Methodology

^bThis trial had primary and secondary prevention components. All meta-analysts treated it as a primary prevention trial except Holme, who classified it as secondary. Roussouw (1991) did not classify diet trials by prevention type; Smith did not conduct analysis by trial type.

^cA multifactor trial, targeting multiple risk factors simultaneously with more than one intervention.

^dA multifactor trial that randomized 66 factories (comprising 49,781 men) rather than individuals.

^eThis trial had primary and secondary prevention components; primary predominated.

^fParticipants were being treated for diabetic retinopathy. About 40 percent were diagnosed as having peripheral or coronary vascular disease.

^gAll meta-analysts treated this as a primary prevention trial except Silberberg, who separated its primary and secondary components; Holme, who treated the trial as secondary; and Law I and Law II, who classified it as a "mixed" trial. Smith did not analyze it by trial type.

^hIncluded the results of the WHO 1992 intention-to-treat analysis.

ⁱThis trial had primary and secondary prevention components. Cucherat treated it as primary, Smith did not analyze it by trial type, and Law I and Law II classified it as a "mixed" trial.

^jYusuf and Rossouw (1995) included both corn oil and olive oil components.

^kTreated as a drug trial.

^lCombined three estrogen treatments: anvene, lynoral, and premarin.

^mSilberberg and Rossouw (1995) included the nicotinic acid trial arm only; Yusuf, Law I, and Law II included the nicotinic acid arm and the arm containing estrogen and nicotinic acid; Gordon and Gould included all trial arms except estrogen only; Smith included all five treatment arms.

ⁿThis trial had primary and secondary prevention components. Smith did not conduct the analysis by treatment type. Law I and Law II classified it as a "mixed" trial.

^oA trial in which measuring coronary arteries allows an assessment of the progression or regression rate of atherosclerosis. Angiographic trials used various cholesterol-lowering treatments and recorded clinical outcomes that could be included in a meta-analysis.

^pDiscussed the three angiographic trial results descriptively; they are not in the trials total.

^qEstrogen 2.5 mg and 5.0 mg and dextrothyroxine were discontinued because of toxic side effects. Yusuf, Roussouw (1991 and 1995), Silberberg, and Cucherat treated the clofibrate and niacin arms as two separate trials; Holme, Muldoon (1993), and Law I and Law II combined them as one. Gordon and Gould treated the clofibrate, D-thyroxine, and niacin arms separately. Ravnskov treated the five arms as separate trials; Smith combined them.

^rSeparated results for colestipol and lovastatin from results for colestipol and niacin.

^sSmith later corrected his original analysis to say that he should not have included this multifactor trial with the other, single-intervention trials; the one death recorded for it did not affect his results.

^tParticipants had heterozygous familial hypercholesterolemia. About half of the nontreatment group received a low dose of colestipol.

^uGordon treated diet and drug components separately. Gould analyzed cholestyramine and diet together but also analyzed diet separately.

^vTotals are only for the number of trials included in each meta-analysis, not the number of treatment arms totaled in table I.1.

Eleven of the 15 meta-analysts combined data across all trial types and interventions to investigate one or more of the health outcomes we focused on. This allowed them to see whether the effect of lowering cholesterol could be discerned for a common risk factor among trials whose designs varied greatly. However, clinical and statistical heterogeneity can make it difficult to interpret findings if aggregating some trials with others disproportionately affects the results. NCEP acknowledges that broad aggregation can yield such heterogeneity and that it is potentially misleading.

Eight of these 11 meta-analysts conducted separate analyses by trial type—primary and secondary prevention trials—which enabled them to create less heterogeneous trial groupings.⁷ The results of 4 meta-analyses were reported only at lower levels of aggregation, such as those that considered results mainly for primary prevention trials. Some meta-analysts also analyzed the aggregated trials to isolate the effect of dietary treatment from that of drugs. Technically, these subgroup analyses are also meta-analyses. Almost all the 15 meta-analysts thus conducted multiple meta-analyses, and we report some of the main results in the tables in appendix II.

How We Report Cholesterol-Lowering Effects

The meta-analyses we studied statistically combined individual trial results to improve the precision of the estimates of the extent to which their cholesterol-lowering treatments reduced CHD risk with regard to CHD incidence, nonfatal heart attacks, and CHD, non-CHD, and total fatalities. Most of the meta-analyses expressed their results in terms of a common odds ratio and confidence interval.

For an individual trial, the odds ratio is the ratio of two ratios. It is defined as the odds of events—such as death from coronary heart disease—to nonevents in the treatment group divided by the odds of events to nonevents in the nontreatment group. An odds ratio lower than 1 (such as 0.90) indicates that the rate of CHD events within the treatment group fell compared to the nontreatment group. An odds ratio higher than 1 (such as 1.12) indicates that the rate of CHD events within the treatment group rose

⁷The distinction between primary and secondary trial participants is regarded as somewhat artificial from clinical and methodological standpoints. From a clinical standpoint, participants in primary prevention trials may have had underlying coronary atherosclerosis as evidenced by those who developed clinical symptoms during the trial. From a methodological standpoint, investigators have used different criteria for classifying primary and secondary prevention trials so that such classifications do not directly reflect a stratification of the risk of death from CHD.

compared to the nontreatment group. For aggregated trials in a meta-analysis, a common odds ratio is similarly interpreted.

The imprecision that results from combining individual odds ratios is expressed by a confidence interval. In the meta-analyses that reported a common odds ratio, the confidence interval was set at 95 percent, meaning that if a meta-analysis were replicated 100 times and the confidence interval were calculated for each odds ratio, 95 of these 100 confidence intervals would contain the true odds ratio, even if it were not precisely known.

With one exception, we did not attempt to re-analyze the common odds ratios of meta-analyses that reported them.⁸ However, to present our findings consistently, we converted the results of meta-analyses that used a different measure to common odds ratios or obtained confidence intervals.⁹ We forwarded all our changes to the studies' authors for their review, and we point them out in our tables in appendix II.

Not all meta-analysts reported on all five health outcomes or on pertinent groupings of them, such as primary or secondary prevention trials or specific treatments. Therefore, the tables do not show 15 meta-analysis entries for each outcome. Our tables show the direction of effects and indicate the findings' statistical significance (that is, whether the findings showed that differences between the treatment and nontreatment groups were not likely to have occurred by chance alone).

In summarizing the meta-analyses' reports of treatment effects, we used the following general rule. If the 95-percent confidence interval for a common odds ratio included 1 (the point of equivalent odds), then there was no statistically significant difference (at the 0.05 level) between the treatment and nontreatment groups on the outcome of interest. In summarizing the statistical significance of their findings, we recognize that a statistically significant effect is not necessarily a clinically meaningful

⁸We recalculated the odds ratios in Muldoon's 1993 meta-analysis in order to include his published, updated data.

⁹We used the Mantel-Haenszel method and the STAT XACT program produced by Cytel Software of Cambridge, Massachusetts. This program uses the Breslow-Day method of testing for homogeneity of odds ratios. We also calculated the confidence intervals surrounding the odds ratios with the STAT XACT program, basing our calculations on the variance estimation method of Robins, Breslow, and Greenland. See N. Mantel and W. Haenszel, "Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease," *Journal of the National Cancer Institute*, 22 (1959), 719-48; N. E. Breslow and N. E. Day, *The Analysis of Case-control Studies* (Lyon, France: IARC Scientific Publications, 1980); and J. Robins, N. Breslow, and S. Greenland, "Estimators of the Mantel-Haenszel Variance Consistent in Both Sparse Data and Large-strata Limiting Models," *Biometrics*, 42 (1986), 311-23.

one. Where the meta-analysts' results were discrepant, we provide potential explanations for the discrepancies.

Not all the detail that the meta-analysts reported is summarized in the tables in appendix II. Several meta-analysts provided information on how their results were influenced by degree of cholesterol reduction, duration of trials, individual risk status, and interventions in which adverse effects outweighed the benefits of treatment. Since analyses that considered these factors are important in the interpretation of the effects of lowering cholesterol, we discuss them in the body of appendix II.

The Strengths and Limitations of Our Study

Summarizing and integrating studies through meta-analysis is, like primary research, a research process in its own right. Meta-analysis imposes methodological standards and statistical principles that require the analyst to adhere to explicit research and reporting rules. These in turn allow other researchers to replicate the study. Further, meta-analysis helps develop comprehensive knowledge beyond the limits of individual studies. It is for these reasons that we chose to review and summarize meta-analyses rather than perform a more traditional literature review.

Meta-analysis techniques capitalize on accumulating evidence by making estimates more precise and reliable; they also permit the testing of hypotheses that may not have been addressed in the individual trials. Moreover, these techniques enable meta-analysts to evaluate the circumstances of the effects, such as how different treatment modalities or the characteristics of different population groups are related to an effect. They also allow meta-analysts to explore what may underlie an effect, such as the particular degree to which cholesterol has been lowered.

Because meta-analysis can increase statistical power and the precision of estimates of effects, it facilitates the examination of noncoronary fatalities, even where recorded deaths from specific causes were few in number. Moreover, meta-analysis allows investigators to examine whether lowering cholesterol affects the life span. Most individual trials were not designed to test the effect on total deaths of lowering cholesterol: either they had too few participants, rendering them low in statistical power, or they were too short in duration to examine this outcome.

The meta-analysis results we present were intended to yield a coherent, general conclusion about the benefits and risks associated with

cholesterol-lowering treatments. However, the trials' considerable clinical heterogeneity in terms of participants and treatments can result in statistical heterogeneity such that the meaningfulness of any overall estimate can be called into question. This problem is not always detected in formal testing. Although only a few of the meta-analyses specifically addressed this issue, their various subgroup analyses did derive from its recognition as they attempted to provide more homogeneous groups of participants and treatments.

Therefore, it is important to note that the overall significance tests we present in our tables do not imply that a treatment effect existed in all primary or secondary trial circumstances. The common odds ratios that are a guide to overall treatment benefit do not accurately estimate the treatment benefit or risk achieved in any particular trial. The confidence interval that expresses the statistical precision achieved for a common odds ratio does not allow for any potential variation in the magnitude of true effect between trials (or between treatments or types of participants). The results of the meta-analyses we report should not be extrapolated beyond the circumstances from which they were derived.

Further, since the individual clinical trials did not report the effects of lowering cholesterol on the incidence of nonfatal diseases other than CHD, the meta-analysts could not evaluate these effects. Finally, the results of the different meta-analyses are not statistically independent when they include the same trials. Many of the larger single-intervention trials that the analysts included weigh heavily in the results. This means that some convergence of findings can be expected despite the diversity of the meta-analyses.

The meta-analyses considered only total serum cholesterol levels, because LDL and HDL were not always recorded in the individual trials. It is noteworthy that the NCEP guidelines call for treatment decisions that base distinctions on LDL and HDL levels. Therefore, the results may be less applicable to population groups in which the configuration of total cholesterol subfractions differs from those found in the trials. The guidelines also call for basing cholesterol-lowering treatment on distinctions of age and gender, but the major participants in the clinical trials were mainly middle-aged white men with elevated cholesterol levels.

Only a few of the clinical trials combined in the meta-analyses that we reviewed used recent, more efficacious treatments such as the statin drugs. Some of the interventions for men in large trials that weigh heavily

in the results have been discontinued or had cholesterol-lowering treatment regimens that have declined in use. Nonetheless, it is important to examine the results of the meta-analyses that aggregated these data because the cholesterol-lowering trial results are integral to the evidence on which the NCEP treatment guidelines were based.

The Meta-Analyses of Cholesterol-Lowering Trials and the Health Outcomes They Report

In this appendix, we summarize our major findings from the 15 meta-analyses for the five health outcomes we focused on: CHD incidence (fatal and nonfatal heart attacks combined), nonfatal heart attacks, CHD fatalities, non-CHD fatalities, and total fatalities. The results apply mainly to middle-aged white men who had elevated serum cholesterol levels, because they have had the greatest representation in the cholesterol-lowering clinical trials over the past 30 years. Meta-analysts continue to actively analyze these data. We discuss in appendix III the issue of extrapolating data to other population groups.

A Summary of Our Major Findings

The trials included in the meta-analyses we reviewed lowered serum cholesterol 10 percent on the average (the range in the individual trials was from less than 1 percent to more than 20 percent). Several meta-analysts identified the extent to which cholesterol was lowered as a mediating factor in the efficacy of cholesterol-lowering interventions. Deaths from causes other than CHD were not related to a reduction in cholesterol level. In fact, these fatalities were fewer when cholesterol reduction was greater. This suggests that excess non-CHD risk results not from lowering cholesterol itself but from particular types of cholesterol-lowering treatment.

With some differences in the magnitude of benefits, the meta-analysis results concur that participants with and without manifest heart disease benefit from cholesterol-lowering interventions. Statistically significant reductions in the rates of CHD incidence and nonfatal heart attacks favor treatment groups.

Statistically significant reductions in CHD fatality rates were found mainly for high-risk participants in treatment groups and for treated participants in secondary prevention trials. For lower-risk participants who had elevated cholesterol levels and for participants in primary prevention trials, evidence was absent that cholesterol-lowering interventions reduced CHD fatality rates more in treatment than in nontreatment groups.

Lower-risk participants who had elevated cholesterol levels and treatment groups in the primary prevention trials showed statistically significant increases in non-CHD fatalities. In secondary prevention trials, lowered rates of CHD death appear to offset the increased rates of non-CHD death. As a result, the overall death rates for treatment groups were mainly favorable but differences from nontreatment groups were not statistically significant.

For drug trials, the meta-analyses show statistically significant reductions in rates of CHD incidence and nonfatal heart attacks favoring treated participants. However, increases in rates of death from non-CHD causes among treatment groups compared to nontreatment groups were also statistically significant. There were no statistical differences between drug treatment and nontreatment groups in CHD fatalities or total fatalities. CHD death rates favored treatment groups, whereas overall fatality rates were close to 1 (the point of equivalent odds between treatment and nontreatment groups). Two recent meta-analyses identified two broad classes of cholesterol-lowering interventions—fibrates and hormone treatment in men—as accounting for statistically significant increases in non-CHD fatality rates. The beneficial effects of treatment outweighed the adverse effects of resins and niacin.

Generally, overall survival rates did not improve for cholesterol-lowering treatment groups compared to nontreatment groups. Survival rates were shown to improve when analyses specifically considered the participants who were at the highest risk or accounted for the extent of cholesterol reduction. Greater reductions in serum cholesterol were associated with a reduction in deaths from all causes.

The diet trials included in the meta-analyses used dietary interventions that are not currently recommended. The meta-analyses mainly show no distinctions between dietary treatment groups and nontreatment groups with regard to the five health outcomes.

Three Recent Research Trends

Three recent trends in cholesterol-lowering research are notable before we present the details of our findings in the text and tables in this appendix. The first trend is that angiographic trials have been included in meta-analyses of cholesterol-lowering trials more frequently since 1993 than before. Angiographic trials are secondary prevention trials because their participants are at very high risk or had existing symptoms of heart disease. Although the trials' principal end point is the arteriographic measurement of coronary arteries, their clinical outcomes in cholesterol-lowering trials are available for meta-analysis. Collectively, they have shown that intensive cholesterol-lowering slows the progression of atherosclerotic lesions; in some patients, it even causes the lesions to regress. Interventions as diverse as dietary therapy, drugs, and partial ileal bypass surgery yield similar results.

The second trend relates to ongoing trials of the statin drugs, a relatively new drug class that appears to lower LDL cholesterol levels 20 to 40 percent, although their long-term safety is still being evaluated. Two recently completed statin trials found clinical benefits favoring treatment groups and no differences in adverse effects between treatment and nontreatment groups. In 4S, the total cholesterol of cardiac patients fell 25 percent. Among other clinical benefits, the study demonstrated statistically significant reductions in the frequency of nonfatal heart attacks, fatal heart attacks, and total fatalities favoring participants treated with simvastatin within its 5-year span.¹ The study's authors cautioned against extrapolating their results to other secondary prevention trials using other statin agents, and they also advised caution in the extrapolation of their results to primary prevention trials.

WOSCOPS, a study of men who had never had a heart attack, lowered total cholesterol levels by 20 percent with the drug pravastatin. The results, which favored the treatment group, showed statistically significant reductions in fatal and nonfatal heart attacks combined, all cardiovascular deaths, and death from definite and suspected CHD (but not definite CHD deaths considered independently). The results almost reached statistical significance for reductions in the rates of death from all causes.

The 4S and WOSCOPS trials were too recent to be included in the meta-analyses we reviewed. However, their results—which showed no statistical difference in deaths from noncardiovascular causes between the treatment and nontreatment groups—tend to support meta-analysis reports of earlier trials in which increases in non-CHD fatality rates were associated not with lowering cholesterol but with particular cholesterol-lowering treatments.

The third research trend is that investigators are more frequently trying to analyze specific interventions, independently of how well they lower cholesterol, in order to determine their specific effects on clinical outcomes. Treatments with hormones and fibrates have shown statistically significant increases in non-CHD fatalities and total fatalities. Hormone treatments at doses used in several individual trials examined by meta-analysts are not currently recommended for men. The fibric acid derivatives clofibrate and gemfibrozil are effective primarily in lowering triglycerides, but the use of clofibrate declined after the World Health

¹Other beneficial results included statistically significant reductions in major coronary events for women and for patients younger and older than 60. Fewer coronary bypass surgery and angioplasty procedures were conducted for patients taking simvastatin; the differences between treatment and nontreatment groups were statistically significant.

Organization trial results were published.² Gemfibrozil is currently recommended only for the treatment of primary prevention patients who have a combination of high triglycerides, elevated LDL, and low HDL.

Primary and Secondary Prevention Trial Results Compared

As we discussed in appendix I, the individual trials represent considerable clinical heterogeneity in treatments and patients. The meta-analyses show the overall average effect of lowering cholesterol across these trials and introduce both clinical and statistical heterogeneity that can make results difficult to interpret and less reliable. For greater homogeneity, investigators classify trials broadly by prevention type (primary or secondary) or by treatment type (diet or drugs) or both. We summarized the meta-analysts' findings for diet and drug treatment trials earlier in this appendix. As for prevention, the relative risk of death for participants who already show evidence of CHD (secondary prevention trials) is about five to seven times greater than that for participants who do not (primary prevention trials). We summarize these results below.

CHD Incidence and Nonfatal Heart Attacks

Table II.1 shows the results of the meta-analysts who examined CHD incidence and nonfatal CHD. It separates the results of the meta-analysts who combined the primary prevention trials from the results of those who combined the secondary prevention trials. The predominant finding is statistically significant reductions in the rates of CHD incidence and nonfatal heart attacks for participants in cholesterol-lowering treatment groups compared to nontreatment groups.³ Across primary prevention trials, the common odds ratios range from 0.85 to 0.77 for CHD incidence and from 0.83 to 0.74 for nonfatal CHD.⁴ Similar benefits are reported across secondary prevention trials. The odds ratios range from 0.86 to 0.76 for CHD incidence and from 0.96 to 0.76 for nonfatal CHD.⁵

²The Food and Drug Administration approves clofibrate for patients who have very high triglycerides and who are at risk for pancreatitis and for patients with familial dysbetalipoproteinemia.

³Nonfatal heart attacks predominate in the CHD incidence category, which represents the combination of fatal and nonfatal heart attacks.

⁴This range does not include the separate estimate for diet trials indicated for Holme (1993) in table II.1. In this meta-analysis, dietary treatment lowered cholesterol 3.2 percent, but the dietary trials were mainly multifactor trials, which taken as a group lowered total cholesterol only 0.7 percent.

⁵The difference between treatment and nontreatment groups in Ravnskov (1992) lacked statistical significance. Among meta-analysts examining nonfatal CHD, only Ravnskov included hormone trials, but the analysis has been strongly criticized.

Appendix II
The Meta-Analyses of Cholesterol-Lowering
Trials and the Health Outcomes They Report

Table II.1: Meta-Analysis Results for CHD Incidence and Nonfatal CHD^a

Meta-analysis	Primary prevention				Secondary prevention			
	CHD incidence		Nonfatal CHD		CHD incidence		Nonfatal CHD	
	Odds ratio	Interval	Odds ratio	Interval	Odds ratio	Interval	Odds ratio	Interval
Yusuf 1987 ^b	0.85	0.76-0.96			0.81	0.74-0.88		
Silberberg 1991	0.77	0.67-0.89	0.75	0.64-0.87	0.79	0.71-0.88	0.78	0.67-0.90
Ravnskov 1992			0.83	0.75-0.92			0.96	0.89-1.04
CTF 1993			0.74	0.64-0.85				
Cucherat 1993	0.82	0.74-0.92	0.74	0.65-0.86	0.76	0.70-0.83	0.76	0.68-0.86
Holme 1993	0.78 ^c	0.68-0.89 ^c			0.80 ^c	0.71-0.89 ^c		
Gordon 1995 ^d	0.77	0.67-0.87			0.86	0.79-0.93		
Rossouw 1995 ^e	0.80	0.71-0.89	0.75	0.65-0.86	0.83	0.76-0.90	0.77	0.68-0.87

^aComplete facts of publication are given in the bibliography. CHD incidence is fatal and nonfatal heart attacks combined. Intervals are 95-percent confidence intervals for the common odds ratios. The meta-analyses did not report data for the empty cells.

^bFor consistency, we recalculated the results from risk ratios and combined diet and drug trials for primary and secondary prevention trials. Using the Breslow-Day (B-D) method, we tested for homogeneity of the odds ratios. The B-D statistic was 8.40 (p = .08) for primary prevention trials and 36.55 (p = .05) for secondary prevention trials.

^cThese data are for drug trials. Separately reported results for diet trials were primary prevention CHD incidence 1.02, 0.94-1.10; secondary prevention CHD incidence 0.78, 0.63-0.96.

^dFor consistency, we recalculated the results from percentage change in risk for primary and secondary prevention trials. We recalculated results for primary and secondary trials combined in order to obtain confidence intervals. Using the Breslow-Day (B-D) method, we tested for homogeneity of the odds ratios. The B-D statistic was 1.30 (p = .73) for primary prevention trials and 33.6 (p = .05) for secondary prevention trials.

^eRoussouw's separate analysis for secondary prevention angiography trials showed a statistically significant reduction in CHD events for the treatment groups. The 0.55 odds ratio had a wide 95-percent confidence interval of 0.30-0.99.

CHD Fatalities

Table II.2 shows that in the primary prevention trials, CHD fatality rates fell with treatment, but because all the confidence intervals exceed 1, the possibility cannot be ruled out that the CHD death rate increases in treatment groups compared to nontreatment groups. Gould (1995) suggests that differences between treatment and nontreatment groups may not be apparent because of the greater variability of the estimate when primary prevention trials are aggregated, the small number of univariate primary prevention trials, and the narrow range of cholesterol reductions in these trials, all of which decrease the precision necessary to find statistical significance.

Appendix II
The Meta-Analyses of Cholesterol-Lowering
Trials and the Health Outcomes They Report

Table II.2: Meta-Analysis Results for CHD, Non-CHD, and Total Fatality^a

Meta-analysis	Primary prevention					
	CHD		Non-CHD		Total	
	Odds ratio	Interval	Odds ratio	Interval	Odds ratio	Interval
Yusuf 1987 ^b	0.93	0.76-1.14	1.19	1.04-1.37		
Muldoon 1990					1.07	0.94-1.21
Silberberg 1991	0.85	0.64-1.14			1.14	0.96-1.36
Ravnskov 1992	0.92	0.83-1.02			1.02	0.95-1.08
CTF 1993	0.90	0.71-1.14	1.19	1.03-1.39	1.07	0.94-1.22
Cucherat 1993	0.90	0.75-1.09			1.07	0.96-1.19
Holme 1993					1.20 ^c	1-1.45 ^c
Muldoon 1993 ^d	0.93	0.77-1.12				
Law I 1994 ^e			1.11	0.99-1.24	1.06	0.97-1.17
Gordon 1995 ^f	0.93	0.75-1.14	1.26	1.06-1.49	1.13	0.98-1.29
Gould 1995	0.88	0.72-1.07	1.21	1.02-1.43	1.09	0.95-1.24
Rossouw 1995	0.91	0.75-1.11	1.25	1.06-1.47	1.08	0.95-1.24

Appendix II
The Meta-Analyses of Cholesterol-Lowering
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Secondary prevention

CHD		Non-CHD		Total	
Odds ratio	Interval	Odds ratio	Interval	Odds ratio	Interval
0.89	0.80-0.98	1.14	0.97-1.36		
0.84	0.75-0.95			0.90	0.80-1
0.96	0.88-1.04			1.02	0.95-1.10
0.87	0.78-0.96			0.93	0.85-1.03
				0.93 ^c	0.83-1.04 ^c
		0.99	0.83-1.18	0.90	0.84-0.97
0.90 ^g	0.82-0.99 ^g	1.22	1.02-1.46	0.97	0.89-1.05
0.94	0.86-1.02	1.17	0.98-1.40	0.99	0.91-1.07
0.89	0.81-0.99	1.07	0.87-1.34	0.94	0.85-1.04

^aComplete facts of publication are given in the bibliography. Intervals are 95-percent confidence intervals for the common odds ratios. The meta-analyses did not report data for the empty cells.

^bFor consistency, we recalculated the results from risk ratios and combined diet and drug treatments for primary and secondary prevention trials. Using the Breslow-Day (B-D) method, we tested for homogeneity of the odds ratios. The B-D statistic for primary prevention trials was 4.34 (p = .30) for CHD fatality and 6.35 (p = .17) for non-CHD fatality; for secondary prevention trials, it was 19.42 (p = .11) for CHD fatality and 4.68 (p = .46) for non-CHD fatality.

^cThese data are for drug trials. Separately reported results for diet trials were primary prevention total fatality 1.07, 1-1.5; secondary prevention total fatality 0.98, 0.81-1.19.

^dThese data are the result of our recalculating Muldoon's data after we included the WHO 1992 intention-to-treat analysis furnished by Muldoon. Using the Breslow-Day (B-D) method, we tested for homogeneity of the odds ratios. The B-D statistic was 9.30 (p = .10). Muldoon's results excluding this analysis were 0.85, 0.69-1.05.

^eOdds ratios are relative odds per 0.6 mmol/l (10 percent) cholesterol reduction.

^fFor consistency, we recalculated the results from percentage change in risk for primary and secondary prevention trials and recalculated the odds ratios given for primary and secondary trials combined in order to obtain confidence intervals. Using the Breslow-Day (B-D) method, we tested for homogeneity of the odds ratios. The B-D statistic for primary prevention trials was 4.46 (p = .22) for CHD fatality, 2.04 (p = .56) for non-CHD fatality, and 4.50 (p = .21) for total fatality. For secondary prevention trials, it was 29.68 (p = .05) for total fatality; we used Gordon's calculations for CHD and non-CHD fatalities.

^gGordon reported these data as statistically significant with a 0.996 upper bound of the confidence interval. Tests for homogeneity of odds ratios were not reported.

Looking at the ranges of the odds ratios shows that cholesterol-lowering treatment has nearly the same effect size in primary prevention trials (0.93 to 0.85) as in secondary prevention trials (0.96 to 0.84). Reductions in CHD death rates in the secondary prevention trials favored the treatment groups; moreover, differences between treatment and nontreatment groups were statistically significant, except in Ravnskov (1992) and Gould (1995).⁶

Putting these results in context requires looking at patients' risk levels. For example, Smith and his colleagues demonstrated in 1993 that the magnitude of net benefit depends on the level of CHD risk. They found statistically significant reductions in CHD death rates only for treatment groups with the highest risk. The common odds ratios for participants treated for elevated cholesterol who were at lower risk showed that their rate of CHD death increased.⁷

Although odds ratios are similar for primary and secondary trials in terms of absolute risk, lowering cholesterol has the clearest benefit for participants in secondary prevention trials who are at greater risk and who have higher fatality rates. For example, an analysis directly comparing drug interventions in primary and secondary prevention trials estimates that one death from CHD could be prevented by treating 675 participants in primary prevention trials but only 38 participants in secondary prevention trials (Silberberg, 1991).⁸

In reporting an additional analysis that considered how much cholesterol was reduced, Gould (1995) found that for every 10 percentage points of cholesterol-lowering, CHD death rates fell 13 percent ($p < .002$).

⁶Ravnskov (1992), Gordon (1995), and Gould (1995) were the only meta-analysts examining CHD fatalities in secondary prevention trials who included hormone trials. Gordon and Gould included the dextrothyroxine arm of the large Coronary Drug Project. Ravnskov included all three hormone arms—estrogen 2.5 mg, estrogen 5.0 mg, and dextrothyroxine—but all three were discontinued early in this trial because of their toxic side effects.

⁷This analysis was stratified by the degree of risk of CHD death that is represented by the CHD fatalities in the nontreatment groups. The odds ratios (and confidence intervals) were 0.74 (0.60-0.91) for participants at high risk of CHD fatality (more than 50 deaths per 1,000 person years); 0.92 (0.77-1.09) for participants at medium risk (10-50 deaths per 1,000 person years); 1.15 (0.80-1.64) for participants at lower risk (fewer than 10 deaths per 1,000 person years). See G. D. Smith, F. Song, and T. A. Sheldon, "Cholesterol Lowering and Mortality: The Importance of Considering Initial Level of Risk," *British Medical Journal*, 306 (1993), 1367-73.

⁸Silberberg's meta-analysis did not include treatments with the recent statin drugs. These drugs' greater ability to lower cholesterol may affect CHD fatality and, in turn, change these numbers. For example, in 4S, which used simvastatin, the estimated number of those who had to be treated to prevent one CHD death was 29.

Non-CHD Fatalities

The investigators who examined deaths from noncoronary causes as an outcome in primary and secondary prevention trials also focused on the potentially adverse effects of specific treatments used in lowering cholesterol and the concern that lowering it may simply exchange one cause of death for another. Table II.2 shows that decreases in CHD fatality rates in primary prevention trials were not sufficient to offset non-CHD fatality rates. As a result, total fatality rates were unfavorable for treatment groups, but differences from nontreatment groups were not statistically significant. The rates of death from non-CHD causes were higher for participants who received cholesterol-lowering treatment; the higher rate was statistically significant in all but one meta-analysis. The common odds ratios range from 1.11 to 1.26.

Similarly, the non-CHD death rate was mostly higher for treatment groups than for nontreatment groups in secondary prevention trials. The common odds ratios range from 0.99 to 1.22. Except in Gordon (1995), the differences between treatment and nontreatment groups were not statistically significant. In the secondary prevention trials, unlike the primary, reductions in rates of CHD fatalities do appear to have offset the higher non-CHD fatalities but not to the extent of achieving a statistically significant reduction in overall deaths.

Smith and his colleagues in 1993 reported a favorable but not statistically significant reduction in non-CHD fatality rates for higher-risk treatment groups but unfavorable non-CHD fatality rates for medium-risk and lower-risk treatment groups. The odds ratios show that compared to nontreatment groups, non-CHD fatality rates increased. For the lower-risk participants, the increase was statistically significant.⁹ Drug treatment trials, but not nondrug trials, showed higher death rates from causes other than CHD.

One problem in interpreting these data is that in some trials, deaths from causes other than heart attack were not reported. The earlier meta-analyses either attributed the increases in non-CHD death in cholesterol-lowering intervention trials to chance or considered the increases reasonable given that CHD deaths decreased and that death from other causes could be expected. Because non-CHD deaths recorded in individual trials were few in number, the greater statistical power of meta-analysis could potentially find any real differences between treatment and nontreatment groups in noncoronary fatality outcomes.

⁹The odds ratios (and confidence intervals) were 0.95 (0.65-1.40) for participants at high risk, 1.07 (0.94-1.21) for participants at medium risk, and 1.33 (1.09-1.63) for participants at lower risk.

However, large individual trials with adverse effects that pertain to specific treatments can dominate the findings of a meta-analysis that combines such trials with smaller ones.

The results from several sizable individual trials have alerted the medical community to the risks associated with fibrates, dextrothyroxine, and high estrogen dosage in men. The biological means through which these drugs lower cholesterol plausibly account for the higher non-CHD death rates.¹⁰ Less readily explained are the higher, statistically significant rates of fatality not related to illness (as from accident, violence, and suicide) among participants in treatment groups compared to nontreatment participants in primary prevention trials. Muldoon (1993) addressed these findings.¹¹ The increases in non-CHD death rates have led recent investigators to examine whether lowering cholesterol is itself harmful or whether the treatment that lowers it is responsible for the adverse effects.

Total Fatalities

Table II.2 reveals greater increases in rates of death from any cause in treatment groups in primary prevention trials. The odds ratios range from 1.02 to 1.20. Differences between treatment and nontreatment groups were not statistically significant in any meta-analysis. The confidence intervals extend on either side of 1. Holme (1993), who aggregated diet and drug primary prevention trials separately, is an exception.

The odds ratios range from 0.90 to 1.02 for total fatalities in secondary prevention trials. They all fall in a favorable direction except in Ravnskov (1992), although only Law I (1994) shows statistically significant reductions in the rate of total deaths in cholesterol-lowering treatment groups.¹² In the remaining meta-analyses, the confidence intervals extend on either side of 1. Therefore, the possibility cannot be ruled out that overall death rates in secondary prevention trials increase in

¹⁰For example, non-CHD fatality was higher and statistically significant in the World Health Organization primary prevention trial that used clofibrate. These deaths were caused by stroke, cancers (mainly of the liver and gastrointestinal tract), gallbladder disease, and CHD that may have been related to drug toxicity. The Coronary Drug Prevention secondary prevention trial also weighs heavily in a meta-analysis; as noted above, the three hormone interventions were discontinued early because of their adverse effects.

¹¹He found statistically significant increases in fatality rates not related to illness in treatment groups for primary but not for secondary prevention trials and in drug but not diet interventions. The results of the analysis suggest an association between greater nonillness-related fatalities and cholesterol-lowering but are not regarded as definitive.

¹²Law, Thompson, and Wald weighted the odds ratio from each trial by a 0.6 mmol/l (about 10 percent) reduction in serum cholesterol concentration.

cholesterol-lowering treatment groups; the same is true for primary prevention trials.

Smith and his colleagues found a net benefit in terms of overall survival but only among trial participants whose initial CHD risk was highest.¹³ Lower-risk participants in treatment groups had higher, statistically significant death rates compared to those in nontreatment groups.¹⁴

The failure of cholesterol-lowering treatment to extend the life span has become an active topic of investigation and is debated among meta-analysts and others. Some investigators have shown that total fatality results may be mediated by the degree to which cholesterol is lowered. Holme, for example, found in 1992 that when cholesterol was not lowered at all, the risk of death rose about 10 percent. He also noted that cholesterol had to fall at least 8 to 9 percent to outweigh treatment's adverse side-effects on overall survival rates.¹⁵ In his 1993 meta-analysis, Holme noted that greater reductions in cholesterol were related to greater reductions in total fatalities. In contrast, Ravnskov (1992) found no relationship between the net mean cholesterol reduction in each trial and total mortality.¹⁶

However, Gould (1995) demonstrated that for every 10 percentage points that cholesterol fell, total fatality rates also fell 10 percent ($p < .03$). When Gordon (1995) regrouped the trials he had analyzed by whether cholesterol reductions were greater or less than the overall median of 12 percent, he found 11 trials that exceeded this median and that reduced total fatality by 20 percent ($p < .002$).¹⁷ These findings are consistent with those of the 4S secondary prevention trial, in which total cholesterol fell by 25 percent and total fatalities fell by 30 percent.

¹³This net benefit can be expected in nontreatment groups in which the rate of CHD death is greater than 3 percent a year. Conversely, total mortality can be expected to increase when CHD death in untreated participants is less than 3 percent.

¹⁴The odds ratios (and confidence intervals) were 0.74 (0.60-0.92) for participants at high risk, 0.96 (0.90-1.02) for participants at medium risk, and 1.22 (1.06-1.42) for participants at lower risk.

¹⁵I. Holme, "Meta-Analysis of Cholesterol Reduction Trials: Coronary Disease and Mortality," *Primary Cardiology*, 18:7 (1992), 63-70.

¹⁶Law I (1994) criticized Ravnskov's analysis because he did not specify his methods and, therefore, his analysis cannot be replicated.

¹⁷Gordon's regrouped analyses are not reflected in table II.3, which reports only common odds ratios and confidence intervals for CHD, non-CHD, and total fatalities.

A Final Note

The results from the meta-analyses point to important issues warranting further investigation into the potentially adverse effects of cholesterol-lowering interventions. Collaborative meta-analyses that have been planned will include results from recently completed and ongoing statin trials that may help resolve questions about the effects of lowering cholesterol. Because such analyses will be prospective, they will have the advantage of specifying in advance the relationships to be tested.

Data Gaps in Randomized Clinical Trials

A formal accounting of the data gaps in the clinical trials shows that much data are still needed from direct clinical trial evidence, or from complementary nontrial data, if patients, doctors, and policymakers are to be well-informed about the benefits and risks of lowering cholesterol. NCEP's evolution has been toward recommending less treatment for less-researched groups; however, NCEP's policy would continue intensive, physician-directed cholesterol-lowering for several of these groups.

In this appendix, we report the kinds of data we did not find when we examined the individual trials aggregated in the meta-analyses we studied. We also report on whether the published commentary of NHLBI, other cholesterol policy groups, and researchers proposing new cholesterol-lowering trials confirms the gaps we found.¹ We also discuss recent and proposed clinical trials that may fill the data gaps by 2000.

Useful randomized clinical trials data are generally lacking for women, minority men and women, elderly men and women, young men, the majority of Americans with the most common total cholesterol readings (those between 200 and 231 mg/dl), and groups whose risk of heart disease is moderate. Clinical trial data on the most common modern interventions—low-fat diets and widely prescribed cholesterol-lowering drugs—are minimal. The effect of lowering cholesterol on non-CHD and total fatality rates has been poorly explored.

Completed Clinical Trials

The clinical trials that have evaluated cholesterol-lowering treatments represent diverse treatments, risk categories, overall sample sizes, and trial durations.² Most looked at lowering cholesterol through a single intervention, the main ones being diet and drugs, but several studied other interventions. Most studies focused on people who had existing symptoms of CHD (secondary prevention trials) while others concentrated on those who had no evidence of CHD (primary prevention trials) and a few combined both. Many trials were very small, half being constituted of fewer than 500 subjects, while the largest included more than 10,000. Although virtually all trials intended to assess CHD outcomes, not all trials reported the same outcome variables. Table III.1 summarizes the individual clinical trials we examined.

¹Virtually all the clinical trials we studied were examined for the NCEP guidelines.

²The trials were conducted mainly in the United States and Europe and were funded by government agencies or the private sector. NIH has funded a relatively small number of the trials but some of these have been among the largest, such as MRFIT and LRC.

**Appendix III
Data Gaps in Randomized Clinical Trials**

Table III.1: Basic Features of 42 Cholesterol-Lowering Trials^a

Trial by prevention type^b	Treatment	Duration (years)	No. of participants
Primary			
LA VA (1969, 1971) ^d	Diet	≤8	846
Oslo DA (1981) ^e	Diet, other	6-7.5	1,232
MRFIT (1982) ^e	Diet, other	6-8	12,866
WHO F (1983, 1986) ^e	Diet, other	5-6	49,784 ^f
Gothenburg (1986) ^e	Diet, other	10	20,015
Minnesota (1975, 1989) ^d	Diet	1	9,057
Retinopathy (1969) ^g	Clofibrate	1	63
Begg (1971) ^h	Clofibrate	5	155
Upjohn (1978) ^d	Colestipol	2	2,278
Finnish (1985) ^e	Diet, clofibrate, probucol, other	5	1,222
Helsinki (1987, 1988)	Gemfibrozil	5	4,081
WHO (1978, 1980, 1984, 1992)	Clofibrate	5	10,627
LRC CPPT (1984a, 1984b, 1992)	Cholestyramine	7	3,806
Excel (1990, 1991, 1992) ^d	Lovastatin	0.9	8,245
Secondary			
Corn Oil (1965)	Diet	2	80
MRC Low Fat (1965)	Diet	3	264
Oslo DH (1966, 1970)	Diet	5	412
MRC Soya (1968, 1974)	Diet	2-7	393
Sydney (1978)	Diet	2-7	458
DART (1989)	Diet	2	2,033
India (1992)	Diet	1	406
Estrogen (1961)	Estrogen	5	100
Long-Term Estrogen (1962)	Estrogen	5	432
Chicago (1963)	Estrogen	5	275
Newcastle (1971)	Clofibrate	3.5	497
Scottish (1971, 1972)	Clofibrate	3	717
Acheson (1972)	Clofibrate	7	95
St. Vincents (1973)	Colestipol	1-3	52
Veterans Cardiology (1968, 1974)	D-thyroxine; D-thyroxine + estrogen; estrogen; estrogen + nicotinic acid; nicotinic acid	5	570
Veterans W. Roxbury (1981) ^d	Probucol	1	118

**Appendix III
Data Gaps in Randomized Clinical Trials**

Participants' characteristics				
Gender	Age		Ethnic group	Cholesterol^c
	Absolute	Average		
Men		66	White 90%; nonwhite 10%	233
Men	40-49	45	3	25
Men	35-57	46	2	53
Men	40-59	48	2	16
Men	47-55			250
Men 49%; women 51%	30-70			207
Men and women	40-59			250+
Men 48%; women 52%		Men 51; women 57	Men: white 86%, nonwhite 14%; women: 76%, nonwhite 24%	Men 308; women 321
Men	40-55	48		275
Men	40-55			270
Men	30-59			248
Men	35-59	48	White	288
Men 59%; women 41%	18-70	Men 54; women 58	White 92%; nonwhite 8%	266
		55		259
Men	Up to 65			263
Men	30-64	56		296
Men	Up to 60			270
Men	30-59			282
Men	30-69	57		250
Men 90%; women 10%		51		227
Men	35-64			236
Men	50-70		White 74%; Jewish 11%; black 10%; Mexican 5%	
Men	Up to 50			248
Men 80%; women 20%		Men 52; women 54		Men 246; women 265
Men 83%; women 17%	40-69	Men 52; women 54		Men 269; women 290
Men 68%; women 32%				288
Men 29%; women 71%	36-80	Men 55; women 58		310
Men	28-75	51	White 92%; nonwhite 8%	241
Men		50	White 98%; black 2%	305

(continued)

Appendix III
Data Gaps in Randomized Clinical Trials

Trial by prevention type^b	Treatment	Duration (years)	No. of participants
NHLBI (1984)	Cholestyramine ⁱ	5	143
CDP (1970, 1972, 1973, 1975, 1986)	Clofibrate, D-thyroxine, estrogen 2.5 mg, estrogen 5 mg, niacin	6	8,341
CLAS (1987)	Colestipol, niacin ⁱ	2	188
Stockholm (1977, 1980, 1988)	Clofibrate, nicotinic acid	5	555
FATS (1990)	Lovastatin + colestipol; niacin + colestipol ⁱ	2.5	146
Lifestyle (1990) ^e	Diet, other ⁱ	1	48
POSCH (1990)	Partial ileal bypass surgery	9.7	838
SCOR (1990) ^k	Colestipol, lovastatin, niacin ⁱ	2	97
Restenosis (1991, 1992)	Lovastatin ⁱ	2	157
STARS (1992)	Diet, diet + cholestyramine ⁱ	3	90
Ancillary Helsinki (1993)	Gemfibrozil	5	628
MARS (1993)	Lovastatin ⁱ	2	270

**Appendix III
Data Gaps in Randomized Clinical Trials**

Participants' characteristics				
Gender	Age		Ethnic group	Cholesterol ^c
	Absolute	Average		
Men 81%; women 19%	21-55			325
Men	30-64		White 93%; nonwhite 7% ⁱ	251
Men	40-59			244
Men 80%; women 20%		Men 59; women 63		248
Men	Up to 62			271
Men and women	35-75		2	36
Men 90%; women 10%	30-64	51	2	51
Men 43%; women 57%	19-72		3	72
Men and women	6	0	20	9
Men	Up to 66		2	79
Men	4	9	27	1
Men 91%; women 9%	35-67	58	2	30

^aData were not available for empty cells.

^bComplete facts of publication for the reports of the individual trials are given in the bibliography.

^cMean baseline cholesterol in mg/dl.

^dThis trial had primary and secondary prevention components; primary predominated.

^eA multifactor trial—that is, a trial that targets multiple risk factors simultaneously with more than one intervention.

^fThis trial randomized 66 factories comprising 49,784 men.

^gParticipants were being treated for diabetic retinopathy. About 40 percent were diagnosed as having peripheral or coronary vascular disease.

^hLittle information from this report is available in English.

ⁱA trial in which angiography measured changes in cardiovascular lesions effected by lowering lipid levels. While angiography was the main measured result, clinical outcomes were also recorded.

^jThese percentages are from the clofibrate, nicotinic acid, and nontreatment arms.

^kParticipants had heterozygous familial hypercholesterolemia.

Treatments

Many of the trials that used diet to lower cholesterol were published before 1985, but most of them were designed in the 1960s and 1970s and do not reflect current judgments about the need to reduce saturated fat and overall fat. They represent participants in institutions whose experience may not typify that of individuals who are outside institutions and concerned about their cholesterol. Similarly, the completed drug trials we examined hardly included tests of today's most commonly prescribed preventive drugs—the statin drugs and estrogen replacement therapy for women. Few trials have studied these interventions, although some trials of statin drugs have recently been completed.

Population Groups

Women

More than half of the trials we examined either did not include women as participants or did not report that they did. The remainder included in total more than 8,500 women. Women usually constituted less than 25 percent of the participants in a trial; in some, their numbers were too small to be analyzed.³ Where women numbered more than 25 percent of a trial's participants, the trial either had very few participants or was too brief to yield clinical differences in coronary outcomes. In some cases, the major publication reporting trial results did not fully include the women's data.

The three trials that included at least 500 women reveal why so little concrete evidence on the efficacy of lowering women's cholesterol resulted from them. The Minnesota primary prevention dietary trial in mental hospitals has limited value because the diets are no longer recommended, the study design suffered from the shifting of the institutional population, and it is questionable whether an institutional diet is applicable to the general population. The data on women in the Upjohn primary prevention trial were not included in the original analysis. The EXCEL trial was too brief (0.9 year) to show a clinical benefit.⁴

³Because women's rates of coronary events are much lower than men's until after the age of 70, a small group of women in a trial is not likely to be analyzed separately.

⁴When Walsh and Grady pooled the primary prevention data on women who had no history of heart disease, they found no significant difference in CHD fatality in the group whose cholesterol was lowered. When they pooled the secondary prevention data on women who had a history of heart disease, they did find a significant benefit in terms of CHD fatality. See J. M. E. Walsh and D. Grady, "Treatment of Hyperlipidemia in Women," *Journal of the American Medical Association*, 274:14 (1995), 1152-58.

The Old and the Young

Most clinical trials have focused on middle-aged men, although participants' ages are not consistently reported. Many of the trials set upper age limits; when average ages are given, they ranged from 45 to 66. The young and the old are therefore underrepresented in the clinical trials data.

Minority Men and Women

Almost no clinical trials data exist on groups other than white men. No clinical trials focus on the largest U.S. minority groups—blacks and Hispanics. Therefore, we have little understanding of the efficacy of lowering cholesterol for the genetic diversity represented in the United States.

Risk Profiles

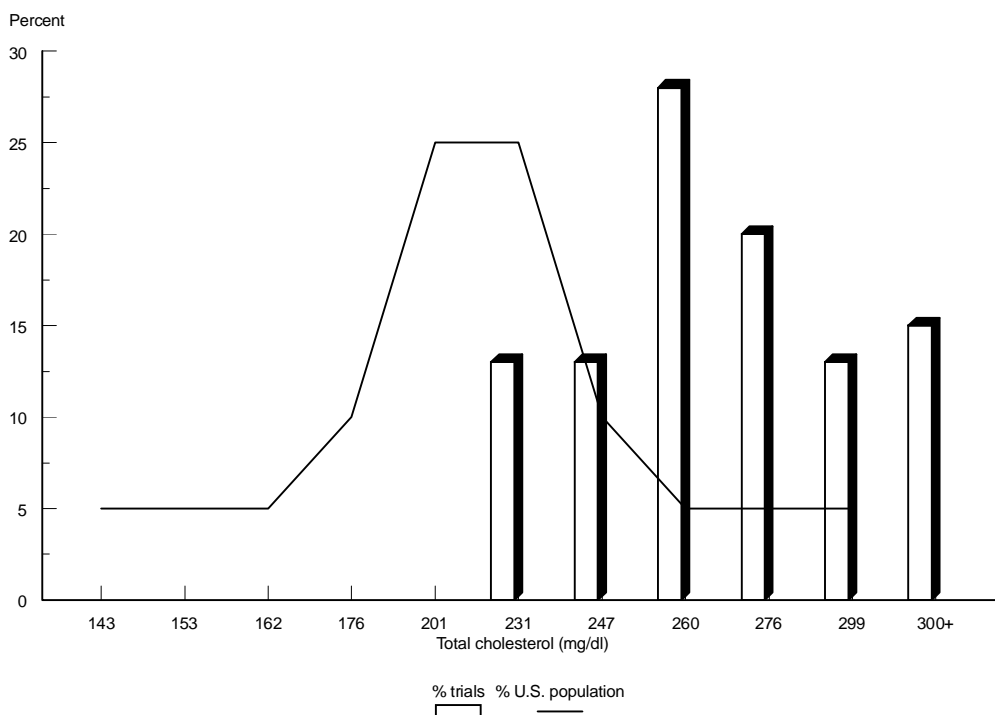
Most clinical trials focused on middle-aged white men who had already had a heart attack or were otherwise at very high risk in order to make the trials practicable: these were the people who would experience the largest number of CHD events in the trials' 2-to-5-year periods. When the researchers did recruit non-CHD patients, even these were middle-aged white men who had multiple risk factors. Very few trials other than those in institutions included participants whose risk was low or moderate. Thus, even the primary prevention trials typically included very-high-risk groups.

The participants of all but 14 of the 42 trials either had had a heart attack or had been diagnosed with CHD. It is not known how the results from the high-risk primary prevention trials or from the secondary prevention trials apply to non-CHD participants whose cholesterol levels are only moderate and who have few risk factors.

The trial participants commonly had high cholesterol levels, as shown in table III.1. According to the NCEP guidelines, total cholesterol between 200 mg/dl and 239 mg/dl is borderline high and beyond the desirable, but there are few clinical trials data on persons within this range. When we compared average baseline cholesterol levels in the trials to the most recent U.S. cholesterol distribution, we found that most of the trials chose participants with total cholesterol levels of 240 mg/dl or higher, while most U.S. adults had total cholesterol levels below that.⁵ (See figure III.1.)

⁵In the most recent U.S. national sample, 75 percent of adult cholesterol had fallen to below 231 mg/dl, average adult cholesterol to 204 mg/dl.

Figure III.1: Cholesterol Levels in the Clinical Trials Compared to U.S. Adult Total Cholesterol Distribution



Thus, there is a gap in what we know about the most common cholesterol levels. The NCEP guidelines' recommendations for lowering common cholesterol levels have largely been generalized from trials whose participants had higher cholesterol levels and from observational and other studies. In contrast to the clinical trials, the observational studies did not lower cholesterol; instead, they compared disease rates at different cholesterol levels and found better CHD outcomes at lower total cholesterol levels.

Trials Proposed and Under Way

Table III.2 summarizes the data gaps that NHLBI, other policy groups, and the designs for proposed trials have identified. It demonstrates the considerable agreement among these sources and supports our conclusions. It also indicates that newer studies are attempting to fill some of the gaps by the end of the century.⁶

⁶New studies include trials too recent to be included in the meta-analyses of the 42 trials we describe. Some new studies are planned; others are under way; several have been completed.

**Appendix III
Data Gaps in Randomized Clinical Trials**

Table III.2: Data Gaps in Cholesterol-Lowering Trials and 13 New Studies Attempting to Fill Them^a

Data gap	Source identifying gap ^a			No. of new studies ^b
	NHLBI	Other policies	New trials	
Treatment				
Diet	•	•	•	1
Statin drugs	•	•	•	11
Estrogen ^c	•	•	•	1
Other	•	•	•	4
Population				
Women	•	•	•	11
Younger than 40, older than 60	•	•	•	9
Non-Caucasian	•	d	d	3
Risk group				
Low-risk non-CHD	•	•	•	3
Borderline-high cholesterol	•	•	•	5
Low HDL cholesterol	•	•	•	3
Genetic variation	•	•	d	1
Outcome				
Non-CHD events	•	•	•	5
Fatal CHD		•	•	6
Total fatality	•	•	•	4
Quality of life	•	•	•	5
Statistical power ^d	•	•	•	12

^aSources include published and unpublished information available from the U.S. General Accounting Office, Program Evaluation and Methodology Division. “Other policies” include non-NHLBI national policies and other sources such as interviews and selected published meta-analyses.

^bIncludes only trials with 1,000 or more participants.

^cWe did not review the several estrogen replacement studies as cholesterol-lowering trials. We did, however, include the Women’s Health Initiative because it combines estrogen therapy with low-fat diet.

^dThe source did not identify a gap.

Treatments

Most of the new trials will use the widely prescribed and highly effective cholesterol-lowering statin drugs. Estrogen replacement therapy is under study in preventing cardiac disease in postmenopausal women, but it is not a cholesterol-lowering treatment.

Population Groups

Women will be included in 11 of 13 new trials, but because their numbers will generally be restricted to 20 percent or less, these trials may or may not allow analysis of the women's data.⁷ The Women's Health Initiative will incorporate 48,000 older women in a randomized trial of a fat-restricted diet and 25,000 women in an estrogen-replacement trial, but it reportedly has design flaws. Critics of this trial have reservations about its similarities to MRFIT, another large multiple-intervention trial, in which the results were difficult to attribute to specific interventions. Several commentators have also expressed concern that ensuring that a low-fat diet is actually maintained for 10 years seems infeasible.

As for ethnic minorities, only ALLHAT will include a large number of African Americans. Indeed, it appears to be bearing the burden of past studies' limitations regarding women, black men and women, and elderly persons. Since it studies more than one intervention, trying to lower both cholesterol and blood pressure, it may be difficult to attribute differences in results, if any, to particular sources.

Risk Profiles

Three new trials will focus on persons who have never had a heart attack; 5 others will include mainly persons with borderline-high cholesterol levels (200 to 239 mg/dl). These trials will go a long way toward filling critical gaps in what is known about these moderate-risk groups.

Outcomes

Four of the new trials are planned to detect changes in total fatalities. Not even the largest of the previous trials found significant reductions in total fatalities. Although the planned trials will mostly study more than 3,000 participants, their designs may still not yield data that will fill the gaps. Investigators are counting on substantial lowering of cholesterol from the new drugs to reduce total fatalities, within the limits of the participant populations and trial durations.

Statistical Power

Most of the new studies will increase statistical power over that of the 42 existing studies that we reviewed by recruiting large numbers of participants, primarily participants whose risk for coronary events is very high, or by running their trials longer. There is a prospective plan to combine the analyses of several of the trials in a meta-analysis that may yield more information than individual trials. All this suggests that some of

⁷Two exceptions are the Women's Health Initiative, with only women participants, and the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) study, with fewer than 50 percent women.

the constraints on the statistical power of past trials may be overcome, providing answers to several outstanding questions about how to reduce the rates of CHD and non-CHD fatality and how to lengthen the survival of persons who have certain attributes. However, pressure to recruit high-risk participants continues; thus, answers to several remaining questions will be found at the expense of finding out whether lowering cholesterol benefits lower-risk groups.

Cholesterol Policy in the United States and Abroad

Cholesterol policies to prevent coronary heart disease by lowering cholesterol in the United States and other nations typically follow two complementary and simultaneous strategies: (1) a population-based strategy that educates the general public about dietary change and (2) a high-risk strategy that identifies persons whose high cholesterol levels warrant physician-directed measures to reduce CHD risk. The policies differ considerably, though, in the breadth of cholesterol-screening they recommend and in their definition of “high risk.” NCEP recommends testing all adult blood cholesterol levels and suggests various intensities of cholesterol-lowering treatment depending on individual risk. The guidelines indicate that 29 percent of U.S. adults need a physician’s assistance to lower their cholesterol. Several other U.S. and foreign policies recommend screening and intensive cholesterol-lowering for fewer adults.

Coronary heart disease, a major cause of death and disability in most developed nations, is believed to be partly the result of high-fat diets, little exercise, obesity, and smoking and, thus, appears to be preventable. Formulating policy, however, is complicated by the interpretation of the underlying data. A large number of clinical trials have tested cholesterol-lowering treatments. Although clinical trials are the most rigorous type of evidence for establishing the efficacy of a medical treatment, they do not include the range of patients, treatments, and outcomes in medical practice, limiting the ability to predict risks and benefits for many groups.

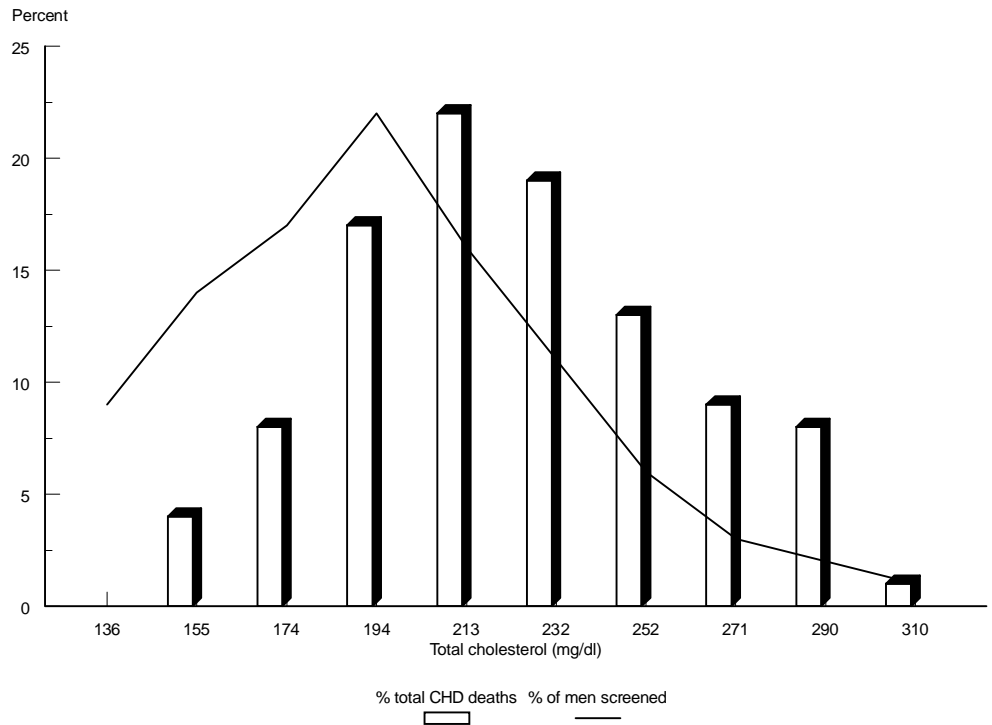
Further, while small average reductions in a population’s cholesterol may result in dramatic reductions in CHD fatality rates, this may provide only a negligible chance of improvement for any particular person. This has been termed the paradox of public health prevention.¹ While CHD rates rise with rising cholesterol levels, the ability to predict outcomes for individuals is poor. Many who have died from heart disease did not have elevated cholesterol levels.

The large 1982 MRFIT trial demonstrates the paradox. Men whose total cholesterol measured 291 mg/dl or higher constituted only 2 percent of the total study group and 2 percent of total CHD deaths (figure IV.1), but they represent the highest rate of CHD death (figure 1). Meanwhile, men whose total cholesterol was between 213 and 271 mg/dl experienced 63 percent of the CHD deaths, by far the majority. Thus, any who would make national cholesterol policy must determine whether to focus on (1) physician-

¹Geoffrey Rose, *The Strategy of Preventive Medicine* (New York: Oxford University Press, 1992).

directed cholesterol-lowering efforts at the highest end of the cholesterol range, where men have the greatest individual likelihood of having a heart attack, or (2) preventive activity in the middle range, where most heart attacks occur but individual risk is much lower. The latter choice would apply the high-risk procedures to many people with very low individual risk because the ability to predict individual outcomes is poor.

Figure IV.1: Cholesterol and CHD Death Distributions in the MRFIT Trial^a



^aMore than 355,000 men screened for the MRFIT trial were followed for 6 years. Cholesterol levels were lower than 155 mg/dl in about 9 percent of the CHD deaths.

Source: Adapted from Geoffrey Rose, *The Strategy of Preventive Medicine* (New York: Oxford University Press, 1992), p. 23.

The various cholesterol policymaking groups here and abroad have handled differently the data limitations and the paradox of prevention. For example, several North American policy groups concluded that applying an aggressive cholesterol-lowering policy to women, young men, and elderly persons does not seem warranted because of the absence of trial

data and the lack of support from nontrial studies. Similarly, several foreign policies have set drug cholesterol-lowering targets closer to those included in the trials and, therefore, considerably higher than NCEP's targets. Overall, the policies cover a wide spectrum, from screening and treating narrowly to NCEP's more comprehensive policy.

The National Cholesterol Education Program

The 1984 NIH consensus development conference concluded from the accumulated evidence of clinical, epidemiologic, metabolic, and animal research that CHD risk is related to serum cholesterol levels. A recently completed NHLBI-funded study of coronary heart disease among high-risk men who had never had a heart attack had found a significant reduction in combined CHD in the group whose cholesterol was lowered by means of drugs. The conference therefore proposed that Americans whose total blood cholesterol was above the 75th percentile of the population distribution be given advice and treatment to lower it. The conference also recommended the development of NCEP. Table IV.1 summarizes the past 12 years of NCEP policy.

**Appendix IV
Cholesterol Policy in the United States and
Abroad**

Table IV.1: National Cholesterol Education Program Milestones Since 1984

Year	Action	Background
1984	NIH consensus conference held	CHD associated with high total cholesterol Population distributions of cholesterol recommended for treatment: 75th percentile for diet, 90th for drugs Diet and exercise recommended as cholesterol-lowering treatments
1987	First adult treatment guidelines issued	Highest desirable cholesterol level set at 50th percentile Adult cholesterol measurement set at 5-year intervals Treatments established: diet first, followed by drugs
1988	Laboratory standards issued	
1990	Population strategy issued	
1991	Children's strategy issued	
1993	Adult guidelines revised	High risk redefined for treatment <ul style="list-style-type: none"> • Drug treatment reserved for groups with high CHD rates • HDL declared beneficial • Drug treatment delay recommended for men younger than 45 and women younger than 55

The guidelines of 1987 focused on identifying and treating high-risk adults but also recommended regular universal screening, defined various cholesterol levels as alerts and goals, and established a method of classifying a person's CHD risk. Recommendations were made in 1990-91 for cholesterol-screening for both the general population and children and adolescents. The adult treatment guidelines were revised in 1993, although they continue recommendations for universal adult screening and cholesterol levels. The current adult guidelines refine the risk assessment leading to treatment and differentiate cholesterol goals for different groups.

NCEP's Definition of CHD Risk

The NCEP guidelines recommend physician-directed interventions for high-risk adults and diet and exercise changes for the entire population. NCEP's definition of desirable, borderline, and high total blood cholesterol levels is uniform for men and women of all adult ages:

- desirable = 200 mg/dl or less
- borderline high = 200-239 mg/dl
- high = 240 mg/dl or higher.²

Risk factors that NCEP believes are associated with CHD and that can be modified are high blood cholesterol, obesity, physical inactivity, hypertension, diabetes, and cigarette smoking. Unmodifiable factors that also influence the probability of CHD and are, thus, included in the assessment of patient risk and decisions to treat include increasing age, being male, and having a family history of CHD.

The total cholesterol of about half of all adult Americans is higher than 200 mg/dl; the policy requires medical consideration of their total coronary risk profile, including risk factors. For this group, NCEP recommends intensive treatment to lower cholesterol for persons who have coronary heart disease or for those with no evidence of CHD but with two or more risk factors such as smoking or having a family history of coronary heart disease. Individuals from groups with moderate to low rates of CHD can also be recommended for vigorous cholesterol-lowering by NCEP's high-risk policy if they have two risk factors. For example, a man whose LDL cholesterol was 190 mg/dl or more would be a candidate for aggressive cholesterol-lowering if he were older than 45.

Classifying a Patient's CHD Risk

Under current U.S. policy, all adults are to have their cholesterol tested every 5 years in order to classify them by their need for cholesterol-lowering. Initial screening that reveals their total blood cholesterol and HDL levels informs the preliminary risk classification.³ Subsequent risk classification may include more cholesterol tests along with consideration of other equally weighted risk factors.

Figure IV.2, adapted from the latest NCEP guidelines, shows the schematic that they recommend that physicians follow in classifying a patient for treatment and advice. Starting with the original cholesterol screening (at the left of the figure), the physician can arrive at one of six recommendations for advice and treatment intensity. For example, adults

²According to the NCEP Adult Treatment Panel, these numbers were based partly on the arbitrary 50- and 75-percent levels for the population distribution of cholesterol and partly on the observation of the increasing rates of CHD incidence among persons with more than 200 mg/dl total cholesterol in the MRFIT study. See NIH, *Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* (Bethesda, Md.: 1989), p. 67.

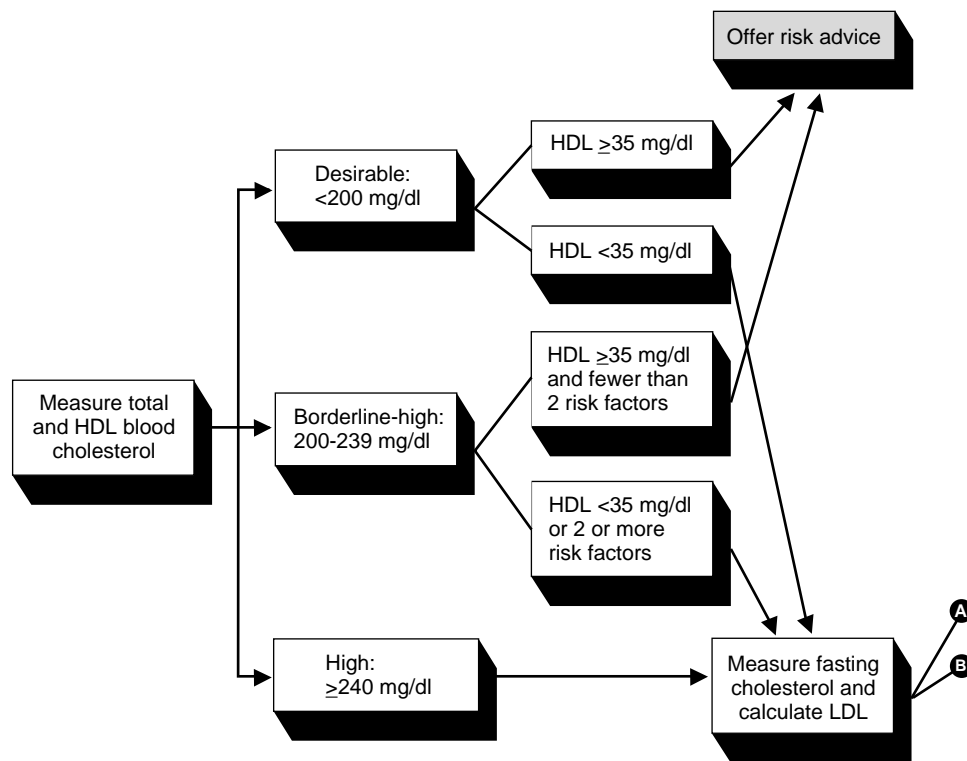
³As we noted earlier, LDL, usually the largest component of total serum cholesterol, leads to greater risk of CHD the higher it is. It is therefore the main target of cholesterol reduction. HDL is a much smaller component of total cholesterol and is beneficial: low amounts are considered to increase the risk of heart disease.

whose total cholesterol measure is “desirable,” or below 200 mg/dl, but whose HDL measures 35 mg/dl or more should be given general advice about CHD risk. (Approximately 51 percent of U.S. adults fall into this category.) Adults whose total cholesterol is between 200 mg/dl and 239 mg/dl and who have HDL lower than 35 mg/dl or two or more risk factors (the remaining 49 percent) should be given a second test, from which LDL cholesterol is calculated, and their risk should be reevaluated.⁴

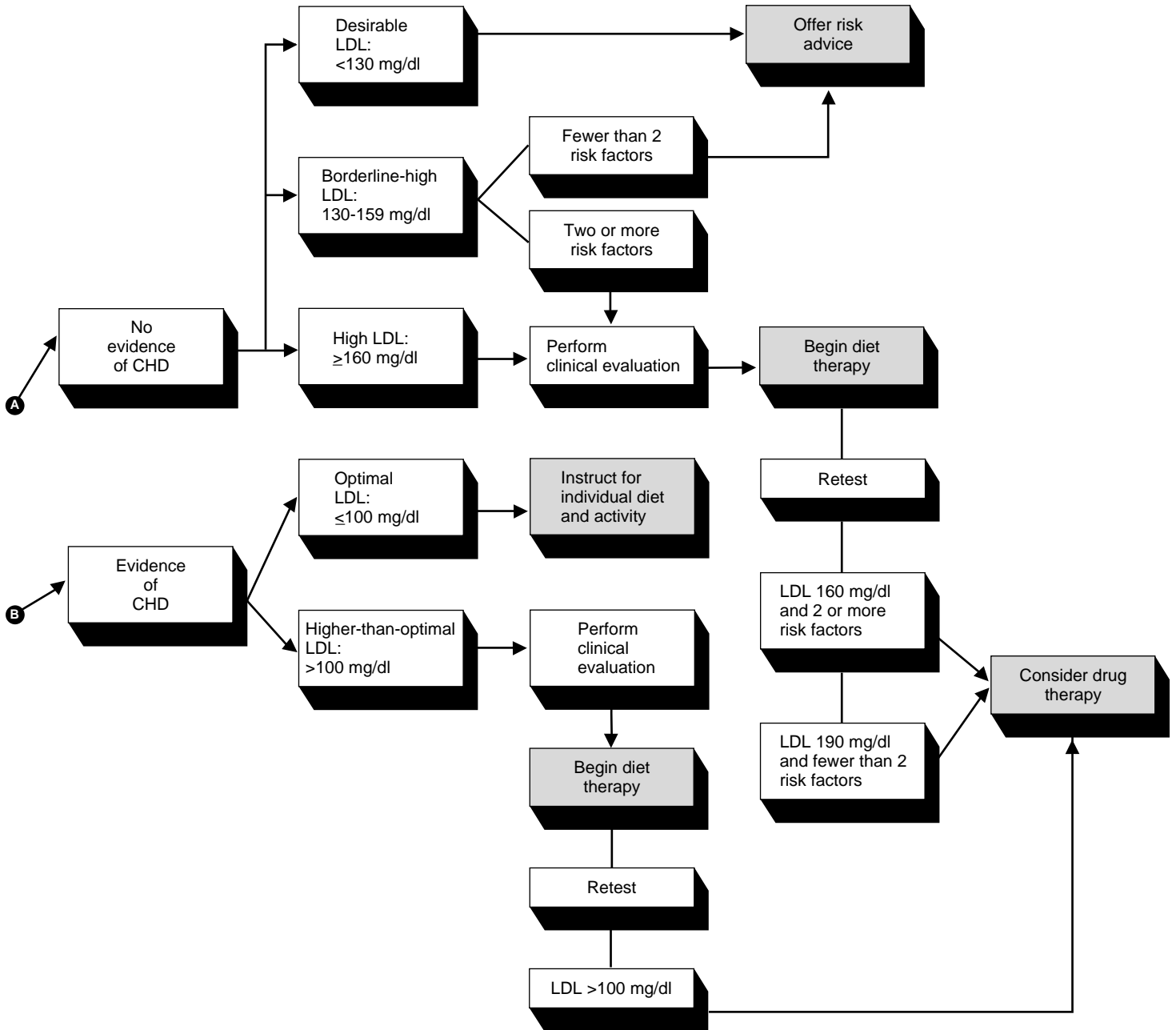
⁴In *Cholesterol Measurement: Test Accuracy and Factors That Influence Cholesterol Levels*, GAO/PEMD-95-8 (Washington, D.C.: 1994), we explored the considerable imprecision in typical cholesterol testing, concluding that decisions to classify patients should be based on the average of multiple measurements, as recommended by NCEP’s guidelines.

Appendix IV
Cholesterol Policy in the United States and
Abroad

Figure IV.2: Recommended Advice and
Treatment for U.S. Adults by
Cholesterol Level^a



**Appendix IV
Cholesterol Policy in the United States and
Abroad**



^aShaded areas are NCEP's alternative recommendations for advice and treatment intensity.

Source: Adapted from National Cholesterol Education Program, Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2nd report (Bethesda, Md.: 1993).

After determining whether or not the patient has evidence of CHD, the physician places the patient in an LDL category that then leads to one of the remaining recommendations, depending on the number of other risk factors. For example, according to figure IV.2, after performing a clinical evaluation, a physician should recommend a reduced-fat diet for a patient who has no evidence of CHD, LDL of at least 130 mg/dl, and two or more other risk factors. If dietary therapy does not successfully lower LDL to target levels, the physician may then consider cholesterol-lowering drugs, which are usually taken indefinitely.

Beyond this schematic, the guidelines advise physicians generally for certain subgroups. They urge more-vigorous efforts to lower the cholesterol of CHD patients and elderly persons, in both of whom CHD fatality rates are high. For groups with fewer CHD fatalities, such as premenopausal women (who are protected by higher HDL levels than men) and men younger than 45, the guidelines urge that drugs be delayed in favor of dietary intervention. They leave considerable discretion to the physician regarding how to treat several groups who register unsatisfactory cholesterol readings and have no other risk factor, such as men older than 45 and postmenopausal women with borderline-high cholesterol. These decisions hinge on the accuracy of the risk classification laid out in figure IV.2.⁵

Dietary and Drug Treatments

Reducing dietary fat is central to advice recommended for the general population; physician-directed diet therapy and subsequent drug therapy are reserved for high-risk persons. Dietary therapy follows one of two diets that limit total fat to 30 percent of calories. The Step I diet limits saturated fat to 8 to 10 percent of total calories, cholesterol consumption to 300 mg a day. If the Step I diet fails to lower cholesterol to appropriate levels, the Step II diet further restricts saturated fat to 7 percent of calories and cholesterol to less than 200 mg a day.⁶

⁵A recent assessment of NCEP's guidelines by Grover and colleagues found that they predicted fatal heart attacks at a rate 24-percent better than random chance. Their model, based on several large databases, predicted CHD fatality better than NCEP. That the NCEP guidelines quantify cholesterol only, weighting all other risk factors equally, may explain the lesser ability of the guidelines to predict risk. See S. A. Grover et al., "Identifying Adults at Increased Risk of Coronary Disease," *Journal of the American Medical Association*, 274 (1995), 10.

⁶The 30-percent fat limit demanded by these two diets is close to the diet consumed, on the average, in the United States. Nutrition experts have suggested that a lower limit might yield more dramatic results.

**Appendix IV
Cholesterol Policy in the United States and
Abroad**

Although NCEP’s guidelines estimate that the Step I diet can reduce serum cholesterol from 3 to 14 percent, Ramsay, Yeo, and Jackson have concluded that cholesterol-reduction in populations who live outside institutions averages only up to about 4 percent.⁷ These authors call for a more realistic assessment of dietary response to guide treatment practice. Thus, NCEP-recommended screening plus risk assessment can lead many patients through diet therapy to drug therapy.

Table IV.2 lists cholesterol-lowering drugs available in the United States and their major effects. Gastrointestinal distress and skin flushing are generally side effects of the older drugs, although a few have more serious negative effects. The newer statins generally produce few side effects, but their long-term effects are not known. Occasionally, they cause mild liver toxicity and muscle pathology.

Table IV.2: U.S. Cholesterol-Lowering Drugs and Their Effect

Class	Drug	Raises HDL	Lowers LDL	Lowers triglycerides
Bile acid-binding resin	Cholestyramine		•	
	Colestipol		•	
Estrogen	Multiple preparations	•	•	
Fibrate	Clofibrate	•		•
	Gemfibrozil	•		•
HMG-CoA reductase inhibitor	Fluvastatin		•	
	Lovastatin		•	
	Pravastatin		•	
	Simvastatin		•	
Nicotinic acid	Water-soluble vitamin	•	•	•
Probucol	Probucol	^a	•	

^aLowers HDL. Lower amounts of HDL increase the risk of heart disease.

Source: A. Chait, “The High Risk Strategy for Adults,” in B. M. Rifkind (ed.), Lowering Cholesterol in High Risk Individuals and Populations (New York: Marcel Dekker, 1995), pp. 1-32.

⁷L. E. Ramsay, W. W. Yeo, and P. R. Jackson, “Dietary Reduction of Serum Cholesterol Concentration: Time to Think Again,” British Medical Journal, 303 (1991), 953.

Other Cholesterol Policies Compared to NCEP

After reviewing NCEP, we compared it to six recent cholesterol policy statements from the United States and other nations with similarly high CHD rates. The four other nations share not only CHD problems of similar magnitude but also the published clinical trials, yet their policies differ in the breadth of screening they recommend and in the definition of the high-risk group they would treat intensively.⁸ Several groups recommending the less-active policies are in the United States. Differences in their willingness to generalize to untested groups from the results of a limited trial database are a possible source of policy variation.

In addition to reviewing the U.S. and foreign policies, we reviewed statements from two medical societies in the United States. Although the U.S. and foreign policies and statements differ considerably in their aims and contents, they can be compared in terms of the comprehensiveness of the groups to be screened for cholesterol and the use of cholesterol levels and other risk factors to trigger intensive treatment. One policy is similar to NCEP's recommendation of universal screening and lower cholesterol levels for intensive treatment. Others are directed toward a less ambitious program of screening fewer adults or propose different risk classifications. (See table IV.3.)

⁸In a recent comparative study of CHD rates, the United States shared the higher rates found in Australia, Britain, and Canada rather than the much lower rates in France and Japan. See Office of Technology Assessment, *International Health Statistics: What the Numbers Mean for the United States* (Washington, D.C.: 1993), p. 118.

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Table IV.3: Cholesterol-Lowering Policies in the United States, Australia, Canada, and Europe^a

Policy	Group screened ^b			Protocol ^c		
	Young	Middle age	Old	Total cholesterol ^d	Plus others	Treatment
Universal						
European Specialty Association 1992	Yes	Yes	Yes	250	No other	Diet
				250	Risk greater than 2%	Diet, drugs
				300	No other	Diet, drugs
NCEP 1993	Yes	Yes	Yes	Up to 200	CHD patient and LDL 100+	Diet, drugs
				200-239	Non-CHD patient and LDL 180+	Diet, drugs
				240+	No other	Drugs
Selective						
Canadian Health Examination 1993	No	Yes ^e	No	Up to 265	Male	None
				265+	Male	Diet, drugs
American College of Physicians 1995	No	Yes	No	f	f	f
U.S. Preventive Services Task Force 1995	No	Yes	No	f	f	f
Unspecified						
Australian 1992				250	Cardiovascular disease	Drugs ^g
				290	No cardiovascular disease	Drugs ^g
British 1993				200	CHD patient	Drugs
				250		Drugs

^aComplete facts of publication are in the bibliography. Data were not available for empty cells.

^bYoung = men 20-34, women 20-44; middle age = men 35-65, women 45-65; old = men and women 65 and older.

^cThese are protocols that we selected for illustration from the many available in NCEP.

^dMean baseline cholesterol in mg/dl.

^eMen 30-59.

^fNot reported. Several policies reported only screening or only treatment advice.

^gThe Australian policy declines to specify "a threshold above which drug therapy should be given and below which it should not because the long-term net clinical benefit (total mortality and morbidity) has not been established for these patients." The policy considers HDL cholesterol of 58 mg/dl and higher to be protective.

For instance, while the European Specialty Association and NCEP policies recommend universal adult screening, two others in the United States and one in Canada recommend screening selectively.⁹ The Canadian Health Examination, the American College of Physicians, and the U.S. Preventive Services Task Force recommend screening only segments of the adult population for whom clinical trials have clearly shown that lowering cholesterol is beneficial—that is, mainly high-risk middle-aged white men.

The policies in table IV.3 also differ in their use of high cholesterol and other risk factors to determine whether to apply diet and drug treatments. As we noted in figure IV.2, NCEP's separation of desirable cholesterol (or up to 200 mg/dl) from borderline-high cholesterol (200-239 mg/dl) places many persons who are at moderate risk on a route to physician-directed treatment. However, NCEP also refines the cholesterol levels requiring dietary treatment or drugs, as do several other policies: they assign more-intensive action to groups whose CHD rate is high and less-intensive action to groups whose CHD rate is low.¹⁰ This focuses the most intensive preventive interventions on the patients who are most likely to benefit.

Another point of comparison between the policies is their willingness to generalize from the data on the populations studied in the randomized clinical trials. Most of the policies, including NCEP's, are based not only on the clinical trials but also on observational research that did not test an intervention or use controlled designs. This research included autopsy reports, cross-country comparisons, community studies, migration studies, and the like. Although the clinical trials evidence is mainly restricted to high-risk middle-aged white men, NCEP has generalized the data to try to

⁹On the European Specialty Association, see the task force of the European Society of Cardiology, European Atherosclerosis Society, and European Society of Hypertension, in *Atherosclerosis*, 110 (1994), 121-61. The Australian and British policies do not specify breadth of screening. Several policies refer only to general-population screening and do not comment on treatment or prevention. NCEP's alert levels for total cholesterol are the best known, but NCEP encourages physicians to incorporate LDL and HDL levels into their treatment decisions. LDL is the largest part of total cholesterol, calculated from total cholesterol, and, within a range, predictable from it.

¹⁰NCEP recommends different intensities of action for different risk groups, although these have not been widely publicized. For example, "if after an adequate trial of diet therapy, LDL cholesterol remains 190 mg/dl in the absence of risk factors, 160 in their presence, or 130 in subjects with established atherosclerotic disease, drug therapy is recommended." (See A. Chait, "The High-Risk Strategy for Adults," in Basil M. Rifkind (ed.), *Lowering Cholesterol in High-Risk Individuals and Populations* (New York: Marcel Dekker, 1995), p. 4.) The level for initiating cholesterol-lowering interventions in women otherwise free of coronary heart disease and with fewer than two other risk factors is 270 mg/dl (Rifkind, pp. 4-31).

cover some of the gaps.¹¹ Two of the four policies that recommend selective rather than universal screening are based primarily on the clinical trials evidence.

Several policies are less willing to generalize. For example, the European Specialty Association guidelines express the concern that “no randomized controlled trials have specifically addressed hyperlipidemia in women. It is not known whether the results of existing drug trials can be extrapolated to women.”¹² The Canadian Health Examination and the U.S. Preventive Services Task Force require at least one well-conducted clinical trial per population group before recommending screening or intensive cholesterol-lowering for that group.

To sum up, policies differ widely within North America. At one end, NCEP applies its physician-directed high-risk options most broadly: several untested groups, including elderly men and women, middle-aged men and women whose cholesterol levels are moderate, and others whose CHD risk is moderate, may be advised to pursue intensive physician-directed cholesterol-lowering therapy. At the other end, the Canadian Health Examination screens only middle-aged white men and treats no one, other than CHD patients, whose total cholesterol is lower than 265 mg/dl. The U.S. Preventive Services Task Force screens only middle-aged persons. Beyond North America, some policies are similar to NCEP’s in scope while others, such as the Australian, treat CHD patients whose total cholesterol is 250 mg/dl or higher but not others unless their cholesterol exceeds 290 mg/dl.

¹¹ “[E]vidence from RCT [randomized control trials] is strongest in middle-aged men with high initial cholesterol levels. However, the complete set of evidence, including the epidemiologic observations and animal experiments, strongly supports the generalization that reducing total and LDL cholesterol levels is also likely to reduce CHD in younger and older men, in women and in individuals with more moderate elevations of cholesterol.” (NIH, Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Bethesda, Md.: 1989), p. 16.) Similarly, the updated NCEP policy document states that “Lack of clinical trial data proving that cholesterol-lowering therapy reduces age-adjusted mortality in individuals with moderately high blood cholesterol and without other CHD factors, however, does not preclude efforts to reduce cholesterol levels in this group.” (National Cholesterol Education Program, Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2nd report (Bethesda, Md.: 1993), p. I-7.)

¹²K. Pyorala et al., “Prevention of Coronary Heart Disease in Clinical Practice: Recommendations of the Task Force of the European Society of Cardiology,” *Atherosclerosis*, 110 (1993), 151.

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Comments From the U.S. Department of Health and Human Services

Note: GAO comments supplementing those in the report text appear at the end of this appendix.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

December 13, 1995

Mr. Kwai-Cheung Chan
Director of Program Evaluation in
Physical Systems Areas
U.S. General Accounting Office
441 G Street, N.W., Room 4083
Washington, DC 20548

Dear Mr. Chan:

Enclosed are the Institute's comments on your draft report, "Cholesterol Treatment: A Review of the Clinical Trials Evidence."

The Institute appreciates the opportunity to comment on this draft report before its publication.

Sincerely yours,

A handwritten signature in black ink, appearing to read "C. Lenfant".

Claude Lenfant, M.D.
Director

Enclosure

Comments of the National Heart, Lung, and Blood Institute on the
General Accounting Office (GAO) Draft Report
Cholesterol Treatment: A Review of the Clinical Trials Evidence

The report raises two major issues: (1) the failure of meta-analyses of previous clinical trial data to show a decline in total mortality in primary prevention trials of cholesterol reduction; and (2) the applicability of trial results to populations other than white, middle-aged men. The Institute addresses both these issues in our comments.

TOTAL MORTALITY:

The report places too much reliance on meta-analysis of previous studies as its means of evaluating trial data despite the acknowledged limitations of this approach, especially the inclusion of outmoded drugs. Previous meta-analyses have clearly shown reductions in fatal and/or nonfatal heart attacks and have demonstrated a near-significant reduction in total mortality in secondary prevention trials (Rossouw et al. 1995). However, the meta-analyses did not find all-cause mortality to be significantly reduced in primary prevention trials, in part as a result of insignificant and variable increases in the non-coronary death rate. Some have attributed these increases to an adverse effect of cholesterol-lowering per se, but recent trials, which are described below, achieved large cholesterol reductions and did not show similar effects. **If cholesterol-lowering itself were harmful, one would expect that larger cholesterol reductions would be even more likely to produce increases in the non-coronary death rate. The absence of such an increase in the trials with the largest cholesterol reductions means that other explanations for the small increase in non-coronary mortality in earlier trials must be sought.** Other possibilities which have been suggested are the effects of specific drugs, or chance, given limitations in study power.

This uncertainty regarding non-coronary mortality has been the main residual concern surrounding cholesterol-lowering. This concern has been recently dispelled by two important studies, the Scandinavian Simvastatin Survival Study (4S) and the West of Scotland Coronary Prevention Study (WOSCOPS). While the GAO report acknowledges these studies it places insufficient emphasis on their importance in providing conclusive information on efficacy and safety.

To state the "bottom line" at the very outset, the results of the new statin trials together with those of the meta-analyses of previous studies indicate that cholesterol-lowering, when of sufficient magnitude, will result in substantial decreases in fatal and/or nonfatal heart attacks, together with consequent diminished use of coronary bypass surgery, other revascularization procedures, and costs associated with the treatment of nonfatal myocardial infarction. These benefits confirm the expectations raised by epidemiological and other studies of the relationship of cholesterol to coronary heart disease (CHD) and provide a sound basis for the central concepts underlying the National Cholesterol Education Program.

The 4S was a secondary prevention, randomized, placebo-controlled trial. It followed 4444 men or women aged 35-70 years at entry with an average cholesterol level of 262 mg/dL for a median duration of 5.4 years. Half of the patients were treated with 20-40 mg of simvastatin daily, resulting in mean changes of total, low density (LDL) and high density (HDL)-cholesterol levels of -25%, -35%, and +8% respectively, over the length of the study. The 4S findings consisted of a 30% reduction in deaths from all causes, a 42% reduction in definite coronary deaths, a 35% reduction in cardiovascular deaths, and a 34% decrease in all coronary events. The death rate from noncardiovascular causes was unaltered. The reductions in events were seen throughout the cholesterol range at entry, in both sexes, in younger and older participants, and in those with diabetes.

See comment 1.

See comment 2.

See comment 3.

See comment 4.

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WOSCOPS was a well-designed trial of primary prevention in 6595 men, 45-65 years at the start, with an average cholesterol at entry of 272 mg/dL, most of whom were free of CHD. Pravastatin treatment (40 mg each evening) lowered plasma cholesterol by 20% and LDL-C by 26%. Reductions of 22% in all-cause mortality, 28% in definite fatal coronary events, 32% in deaths from all cardiovascular causes, and 31% in all coronary events were observed. There were no increases in non-coronary deaths. The risk reductions were seen in all subgroups examined.

The various results from each of these studies are statistically, often highly, significant. The reduced total mortality in WOSCOPS was a hairsbreadth short of significance using a conventional test ($P=0.051$), but was significant using Cox Proportional Analysis ($P<0.039$). Coronary deaths were reduced in WOSCOPS but not significantly (possibly because of the much smaller number of events) but definite and suspect coronary deaths were reduced by 33% ($P<0.042$) as were all cardiovascular deaths ($P<0.033$).

These studies were well designed and implemented, and were characterized by much more cholesterol-lowering than has hitherto been achieved over the long term. They strongly confirm the benefits of cholesterol-lowering. They used drugs from a now widely prescribed and apparently safe class whose mode of action is understood. The consistent and substantial reductions in cholesterol levels which they obtained allowed the extent of the resulting benefits to be much more clearly demonstrated than hitherto, and provided better evidence that cholesterol-lowering is not harmful.

The findings are complemented by those from a series of recently reported, smaller trials that achieved commensurate cholesterol-lowering. Pooled analyses were performed of the results of 14 angiographic trials which employed various lipid-lowering modalities including statin drugs and which obtained an average LDL-cholesterol reduction of 26% (Rossouw, 1995). Cardiovascular events were significantly reduced by 47%. The reductions were significant and consistent across nearly all classes of intervention, including the statins. In another report, meta-analysis of 7 statin secondary prevention studies involving a total of 3,464 patients found a 44% reduction in all-cause mortality (McMurray and Slattery, 1994).

All in all, the newer statin studies and the meta-analyses of previous studies confirm the benefits of cholesterol-lowering in patients with and without coronary disease, and together with the results of epidemiological and other studies, provide a firm basis for the core recommendations of the National Cholesterol Education Program.

APPLICABILITY OF TRIAL RESULTS TO OTHER POPULATIONS:

The question of the extent to which findings from these trials are applicable to specific populations has been appropriately and periodically raised. Generally, in the situations evaluated, the benefits of cholesterol-reduction continued to apply. Treatment is effective from a relative standpoint, at high or moderate levels, in low or high risk patients, with different treatment modalities, in different age groups, in primary or secondary prevention, in men and women, and in diabetics. This strongly suggests that cholesterol lowering is beneficial in virtually all situations.

It is also important to note that while the trials constitute the most important line of evidence for establishing benefit, many other sources of evidence are highly relevant. For example, in considering generalizability to women it is important to note that the underlying atherosclerotic lesion is similar in men and women, thus strengthening the case that we are dealing with the same disease in both sexes. Female and male heterozygotes for familial hypercholesterolemia prematurely develop atherosclerotic lesions and clinical disease, as do those with familial dyslipoproteinemia and other inherited dyslipidemias; thus raised levels of LDL and other lipoproteins are atherogenic in both sexes. Prospective epidemiological studies have identified total and HDL-cholesterol as risk factors in both men and women. Women's cholesterol levels are raised by dietary

See comment 5.

See comment 6.

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saturated fat and cholesterol, and are lowered by the same drugs. Population mortality trends from CHD and cholesterol levels run parallel over time in men and women. The available trial data suggest that the natural history of coronary lesions (Havel) and the coronary event rate (4S) are favorably influenced by cholesterol-reducing treatment. Thus there are strong indications that cholesterol-lowering is beneficial in women.

Again, as far as treating lower levels of cholesterol are concerned, the implications of the continuous nature of the rising risk, starting at very low lipid levels, seen in observational studies is not accorded the importance it merits, nor is the consistency in the reduction of risk seen in each of the four quartiles of entry cholesterol in 4S subjects.

With respect to minorities, there is little reason to believe that the biology of atherosclerotic CHD is fundamentally different in these groups. The burden of CHD is greater in African Americans than in the general population, and evidence exists that cholesterol is an important coronary risk factor in minority populations. Accordingly, despite the fact that clinical trial data in minorities are limited, the overall body of evidence provides no basis for excluding minorities from the benefits of cholesterol-lowering.

CONCLUSIONS:

Based on the existing evidence from clinical trials as summarized above, the conclusions and recommendation of the report could better be restated as follows:

1. Meta-analyses of previous trials showed that cholesterol-lowering treatment benefits men with moderate to high cholesterol levels with or without a history of heart disease. Treatment reduces the frequency of fatal and/or non-fatal myocardial infarction, and its main component, non-fatal myocardial infarction. The smaller numbers of fatal infarctions also show a reduction which, however, does not reach formal statistical significance.
2. New trials using statin drugs have conclusively shown pronounced reductions in fatal and nonfatal coronary events, without adverse effects, the net outcome being reductions of total mortality. These results are unequivocal for men and strongly suggestive for women.
3. Results of the trials and the other extensive body of findings provide a sound scientific basis for the National Cholesterol Education Program and its central guidelines.
4. There is much indirect evidence that suggests the potential benefits of cholesterol-lowering for several important population groups, such as the elderly, women, and minorities. Direct trial data, however, are limited. Studies underway will address some of these issues.

RECOMMENDATION:

The NHLBI agrees that the Director of NHLBI should take steps to closely monitor and evaluate the outcomes of the planned trials and also to determine whether additional trials are warranted to deal with important groups such as women, the elderly, those with lower levels of cholesterol, and diabetics. However, such a determination should be made in the light of all the available information, and should take into account the costs and feasibility of studies.

The following are GAO's comments on the HHS December 13, 1995, letter.

GAO Comments

1. Since the 1980s, applying meta-analysis to health and medical research has been viewed as a research process in its own right. Meta-analysis offers a statistically rigorous way of pooling the results of clinical trials, and it has the advantage of increasing the statistical power of individual trials by combining them. In the absence of a constant bias pervading a whole set of trials, the bias of any one analyst within the set is minimized.

NIH has paid considerable attention to the use of meta-analysis in health and medical research, as evidenced by its 1986 Workshop on Methodological Issues in Overviews of Randomized Clinical Trials.¹ In June 1994, NHLBI sponsored a workshop specifically on meta-analyses of cholesterol-lowering trials. NCEP included meta-analyses in the evidentiary sources it cited in support of the Adult Treatment Panel II guidelines. The federal legislation that established the Agency for Health Care Policy Research required that guidelines on clinical practice be based on systematic reviews of research evidence.

Our task for this report was to provide an overview of the clinical trials evidence that had been used, among other evidence, to support the NCEP guidelines. Given that, and in view of the conflicting results among individual trials, we believe that our decision to systematically display and discuss the results of the meta-analyses that synthesized results across trials on the five health outcomes we were interested in was an appropriate and efficient way to summarize this large body of data.

Although the meta-analysts we studied differed in what they included and excluded, most of them excluded outmoded treatments such as hormone treatment in men. We have stated in the report that clinical trials using the more recently prescribed statin drugs are not well represented in the meta-analyses we reviewed. They do not include, for example, the results of 4S or WOSCOPS. However, they do include, to a greater or lesser degree, all the cholesterol-lowering randomized clinical trials that were available when the Adult Treatment Panel II guidelines were published.

2. Table II.2 displays the odds ratios for CHD, non-CHD, and total fatalities. Across the meta-analyses that examined primary prevention trials, we found no statistically significant differences in CHD fatality rates between

¹T. Colton, L. S. Freedman, and A. L. Johnson (eds.), "Proceedings of the Workshop on Methodologic Issues in Overviews of Randomized Clinical Trials, May 1986," *Statistics in Medicine*, 6:3 (1987), 217-410.

treatment and nontreatment groups. Further, a statistically significant increase in the non-CHD fatality rate for treated participants was in fact obtained in 5 of the 6 meta-analyses that examined this outcome. The failure to achieve statistically significant reductions in fatality rates from all causes in primary prevention trials should be viewed in the light of Gould's 1995 meta-analysis, which shows an adverse effect for treatment with fibrates. This drug class predominates in primary prevention trials using drug interventions.

3. Terge Pedersen and other 4S investigators have cautioned that the study's results should not be extrapolated to studies using other statin drugs, given differences in the cholesterol-lowering efficacy of various drugs. However, we note that both the 4S and WOSCOPS trials—which showed no statistical differences between treatment and nontreatment groups in deaths from noncardiovascular causes—support meta-analysis findings that increased non-CHD fatality rates in treatment groups were associated not with lowering cholesterol but with particular cholesterol-lowering treatments. We agree that safety and efficacy have been demonstrated for simvastatin and pravastatin for the types of primary and secondary patients who participated in these trials. It is also important to recognize that patients may be expected to continue with drug treatment (especially for primary prevention) for a period considerably longer than the 5-year duration of these trials, even while information is not yet complete about the long-term safety of the statin drugs.

4. A consideration of the cost-effectiveness of cholesterol-lowering treatment must also account for costs associated with prevention. For example, the 3.5-percent absolute CHD mortality risk reduction in 4S means that to prevent the death of one patient diagnosed with CHD, an estimated 29 patients would have to be treated with simvastatin at trial dosages. The WOSCOPS authors estimate that 1,000 middle-aged men with hypercholesterolemia and no prior evidence of myocardial infarction would have to be treated for 5 years to prevent 7 deaths from cardiovascular causes. They note that such findings compare favorably with treatment for mild hypertension in middle-aged persons. Nevertheless, any cost-benefit ratio will be less in a primary prevention setting than in a secondary prevention setting, because patients are treated whose risk levels are lower.

5. Clinical trials do constitute the most important type of evidence for the benefit of a medical intervention, because less-rigorously designed

cross-country comparisons and other descriptive studies may be confounded by many factors. However, the largest portions of the U.S. population have not been well-represented in cholesterol-lowering trials, including among others women, women and men minorities, young men, elderly persons, and persons with cholesterol levels lower than 250 mg/dl. Past cholesterol-lowering trials have usually been conducted with middle-aged, high-risk, white men and are thus limited in how well they can comment on the benefits of lowering cholesterol for others. When others have been included in trials, the data sets they provide are usually too small to analyze, leaving in question the applicability of cholesterol-lowering from one group to another.

The contrast that has been best studied is that between people who have already had a heart attack and those who have not. Generally, this can be understood as a contrast between very high-risk persons and those whose risk is lower, although even the primary trials tend to focus on individuals with multiple risks for CHD. The meta-analyses we reviewed consistently found a pattern of greater CHD benefit in secondary than in primary trials.

6. NHLBI cites selected research other than clinical trials in order to support the broad application of the benefits found in the trial results with high-risk men to other groups. Yet different treatments are recommended for men and for women in the guidelines. In 1993, NHLBI revised the NCEP guidelines to “delay” the application of cholesterol-lowering drugs to beyond age 55 for women. Similarly, NHLBI invited doctors to consider estrogen replacement rather than cholesterol-lowering drugs beyond menopause. Many of the women who display signs of high risk for CHD are older; indeed, elderly persons as a group are disproportionately women. A recent review found no direct evidence of benefit in lowering cholesterol among elderly persons and mixed evidence that higher cholesterol levels are associated with CHD.²

²Walter H. Ettinger and William R. Hazzard, “Dyslipoproteinemia in Older People,” in Basil M. Rifkind (ed.), Lowering Cholesterol in High-Risk Individuals and Populations (New York: Marcel Dekker, 1995).

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