Lipid-Lowering Therapy for the Primary Prevention of Coronary Heart Disease
Antonio M. Gotto, Jr, MD, DPHIL.
New York, New York

For more than 40 years, observational epidemiologic studies have consistently documented that individuals with elevated serum total cholesterol are at increased risk for a first coronary heart disease (CHD) event (1–4). In general, clinical data indicate that CHD risk is 2% to 3% lower for each 1% decrease in total cholesterol concentration (1). Early clinical trials (5–9) demonstrated that drug-induced reductions in serum cholesterol would prevent first CHD events, yet these successes were plagued by uncertainties about the effect of such therapy on noncardiovascular morbidity and mortality. Because of these uncertainties and the modest lipid-modifying efficacy of the bile-acid-sequestrant and fibric-acid-derivative interventions used, many cardiologists and, hence, most clinicians did not embrace cholesterol-lowering drug therapy for primary prevention of CHD except in patients with severe genetic lipid disorders or high short-term risk for disease. However, the question of whether cholesterol lowering is beneficial has now been very clearly addressed with the advent of the HMG-CoA reductase inhibitors (statins), which have made possible very substantial reductions in low-density lipoprotein (LDL) cholesterol concentrations in clinical usage. In 1995 the West of Scotland Coronary Prevention Study (WOSCOPS) reported significant reductions in rates of first coronary events over five years with pravastatin therapy in middle-aged men with high baseline cholesterol concentrations (10). Most important, therapy was associated with no adverse noncardiovascular effects compared with placebo. Recently, the results of the five-year Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) of lovastatin in a cohort of asymptomatic men and women extended the coronary benefit of statin therapy in primary prevention to healthier individuals with cholesterol concentrations comparable with the national average (11).

In current adult practice guidelines from the U.S. National Cholesterol Education Program (NCEP) (12), candidates for lipid-lowering drug therapy in primary prevention are those at high risk for a CHD event in the near term (Table 1). High risk may be conferred by LDL cholesterol elevation alone when the average value is 190 mg/dL or higher or by LDL cholesterol of 160 mg/dL or higher in the presence of at least two other major risk factors for CHD. Patients with less severe LDL cholesterol elevations but with other risk factors (e.g., type 2 diabetes mellitus or a family history of premature CHD) may also be candidates in the NCEP algorithm. It is of great interest whether the AFCAPS/TexCAPS results, which extend the benefit of lipid-lowering drug therapy to a large segment of the population at risk for CHD, might prompt reconsideration of the NCEP action limits.

EARLY PRIMARY-PREVENTION DRUG TRIALS

The first major randomized clinical trial to assess whether drug treatment of hyperlipidemia would reduce rates of first coronary events was the five-year World Health Organization trial of clofibrate, a double-blind study that enrolled 15,745 men aged 30 to 59 years (5). The 9% reduction in cholesterol from baseline by clofibrate was associated with a significant 25% decrease in the rate of nonfatal myocardial infarction compared with placebo and a 20% reduction in all coronary events. However, there was a 47% excess of mortality during treatment in the clofibrate group although the difference was not significant when corrected for age at death (6,7). Excess mortality was reduced to 5% in eight years of follow-up after treatment ended (7). No particular disease accounted for the overall excess, and no causal link with clofibrate has been found. The mortality findings have remained a subject of debate for 20 years and have led to clofibrate’s being used very little in the U.S.

The results of the landmark Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), which were published in 1984 (8), are considered the first major proof of the lipid-lowering hypothesis with active drug intervention. In this randomized, double-blind study, 3,806 asymptomatic men aged 35 to 59 years with total cholesterol of 265 mg/dL or greater (type II hyperlipidemia) received either dietary modification and cholestyramine or diet and placebo. Over seven years, resin therapy reduced mean total and LDL cholesterol values 8% and 13% more than placebo, and the rate of CHD death or nonfatal myocardial infarction was 19% lower (p < 0.05) in the resin-treated group.
The Helsinki Heart Study (HHS) followed in 1987 and showed a significant 34% reduction (p < 0.02) in CHD incidence (cardiac death plus myocardial infarction) after five years of diet plus gemfibrozil therapy compared with diet plus placebo (9). The trial enrolled 4,081 asymptomatic men aged 40 to 55 years with non-high-density lipoprotein (non-HDL) cholesterol of 200 mg/dl or greater. Non-HDL cholesterol includes LDL, intermediate-density lipoprotein (IDL) and very-low-density lipoprotein (VLDL) cholesterol values and is a measure of all lipoproteins that contain apolipoprotein B. Lipid changes in the gemfibrozil group versus placebo were: total cholesterol —11%, LDL cholesterol —10%, serum triglyceride —43% and HDL cholesterol +11%. Non-HDL cholesterol was reduced by 14%. As in the LRC-CPPT, there was a nonsignificant, greater number of deaths with drug therapy due to accidents and violence (10 vs. 4). There were also more deaths from intracranial hemorrhage (five vs. one), although, again, the difference was not statistically significant. As in the LRC-CPPT, these deaths could not be directly linked to drug therapy. Between the LRC-CPPT and HHS, 5 of the 8 suicides were trial dropouts, 2 were homicide victims and, among the 10 subjects who died of an accident, 2 were trial dropouts, 3 had high blood alcohol at autopsy and another 3 had a history of psychiatric symptoms or treatment (14).

A meta-analysis of early primary-prevention trials showed that a 10% reduction in cholesterol led to 25%, 12% and 22% reductions in nonfatal, fatal and all myocardial infarctions (15). A subsequent meta-analysis added a nonsignificant 8% reduction in total mortality (16). Nevertheless, concerns about noncardiovascular mortality in the WHO trial, LRC-CPPT and HHS led to many analyses and commentaries about the safety of cholesterol lowering (17,18). Several suggested that drug treatment to lower cholesterol in primary prevention be reserved for only the highest-risk individuals or even that cholesterol screening be restricted (19,20). The Adult Treatment Panel of the NCEP, however, consistently held, as did many other experts (21,22), that the weight of evidence supporting CHD benefit by lipid-lowering therapy, including pharma-cotherapy, overshadowed any noncardiovascular risk. However, the NCEP algorithm endorses the most aggressive lipid modification in secondary prevention where the risk for recurrent disease is highest, and where primary prevention remained a much lower priority than secondary prevention (12). At the time the current NCEP adult guidelines were issued in 1993, there was a growing body of evidence demonstrating angiographic lesion benefit in patients with established atherosclerotic disease (23).

### STATIN PRIMARY-PREVENTION TRIALS

In WOSCOPS, which enrolled 6,595 men aged 45 to 64 years who had no history of myocardial infarction, pravastatin therapy with background diet doubled the LDL-cholesterol lowering seen in earlier primary-prevention trials. The All-cause mortality rate, which the trial was not designed to assess, was reduced by only 7%, reflecting an nonsignificant increase in noncardiovascular deaths. Of the causes of death, 11 were from accidents and violence in the drug group, compared with four in the placebo group. However, no convincing evidence has ever been presented that the excess deaths from accidents and violence were in any way related to the nonabsorbable resin (14). The lipid-lowering efficacy of cholestyramine in the LRC-CPPT was limited by the poor tolerability of the bile acid sequestrant. Sixty-eight of cholestyramine in the LRC-CPPT was limited by the nonabsorbable resin (14). The lipid-lowering efficacy of HMG-CoA reductase inhibitors in the AFCAPS/TexCAPS was limited by the lack of coronary atherosclerotic disease benefit (17,18). Several suggested that drug treatment to lower cholesterol in primary prevention be reserved for only the highest-risk individuals or even that cholesterol screening be restricted (19,20). The Adult Treatment Panel of the NCEP, however, consistently held, as did many other experts (21,22), that the weight of evidence supporting CHD benefit by lipid-lowering therapy, including pharmacotheraphy, overshadowed any noncardiovascular risk. However, the NCEP algorithm endorses the most aggressive lipid modification in secondary prevention where the risk for recurrent disease is highest, and where primary prevention remained a much lower priority than secondary prevention (12). At the time the current NCEP adult guidelines were issued in 1993, there was a growing body of evidence demonstrating angiographic lesion benefit in patients with established atherosclerotic disease (23).

### Table 1. Risk Status in Patients Without Known Atherosclerotic Disease

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Moderate Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C ≥190</td>
<td>LDL-C 190 to 220 in young adult men (&lt;35 years) and premenopausal women with no other risk*</td>
</tr>
<tr>
<td>LDL-C between 160 and 190 + ≥2 other CHD risk factors</td>
<td>LDL-C between 160 and 190 + &lt;2 other CHD risk factors</td>
</tr>
<tr>
<td>LDL-C between 130 and 160 + Risk of Severe Degree, e.g., type 2 diabetes mellitus or heavy cigarette smoking</td>
<td>LDL-C between 130 and 160 + ≥2 other CHD risk factors</td>
</tr>
</tbody>
</table>

*In young men <35 yr and premenopausal women with LDL-C in the range 160 to 220 mg/dl and no other risk factors, drug therapy should be delayed in favor of lifestyle intervention. For most young adult men and premenopausal women, drug therapy should be considered when LDL-C is very high (>220 mg/dl) or multiple other risk factors are present. Note: All LDL-C values are mg/dl. Source: Data from Jones et al. (13). CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol.
trials. The 26% reduction was associated with a significant 31% reduction in definite coronary events (CHD death or nonfatal myocardial infarction) at five years compared with placebo. All-cause mortality rate was reduced by 22%—the reduction just missing statistical significance (p = 0.051). Noncardiovascular disease end points were not changed, including violent deaths and cancers, between active treatment and placebo. A divergence in CHD effect between the pravastatin and placebo groups began to emerge as soon as six months after the beginning of the trial although the difference was not significant at that date (10). Pravastatin therapy was well tolerated.

Coronary risk in WOSCOPS was related to lipid concentrations at baseline, namely, LDL cholesterol and triglyceride above median and HDL cholesterol below median (treatment also reduced triglyceride by 12% and increased HDL by 5%). Enrollment in WOSCOPS required LDL cholesterol of at least 155 mg/dL during two screening visits with at least one value ≥174 mg/dL and one value ≤232 mg/dL and fasting triglyceride no higher than 530 mg/dL. Mean baseline LDL cholesterol was 192 mg/dL, and, although WOSCOPS was begun before development of current NCEP guidelines, 77% of its patients fell within NCEP categories for consideration of lipid-lowering pharmacotherapy, given that all had received dietary therapy (24). The NCEP recommendation of using pharmacotherapy in high-risk patients without prior myocardial infarction was validated, and the efficacy and safety of the statin therapy catapulted this class of agent to the forefront of primary prevention.

Despite the positive results of WOSCOPS, several questions remained. All four primary-prevention drug treatment trials included only middle-aged men; none included men aged 65 or older or women. The focus of intervention was in individuals with substantial elevations in cholesterol, as demonstrated by the mean baseline LDL-cholesterol values of the LRC-CPPT (204 mg/dL), HHS (188 mg/dL) and WOSCOPS (192 mg/dL) and the median total cholesterol value of the WHO clofibrate group (247 mg/dL) (Fig. 1). For most patients, total cholesterol of 240 mg/dL corresponds roughly to LDL cholesterol of 160 mg/dL (12). Also, because conclusive findings on overall mortality were not reported, some still voiced concern about the safety of lowering cholesterol with medication.

The AFCAPS/TexCAPS results (11) shed important light on several of these issues. Indeed, a number of features of the trial distinguish the study from earlier primary-prevention trials. Of the trial’s 6,605 subjects, 997 were women and 1,416 were aged 65 to 73 years. Mean baseline total and LDL cholesterol values were only 221 and 150 mg/dL—comparable with values in the 51st and 60th percentiles of the third National Health and Nutrition Examination Survey (NHANES III: 1988–1994) reference population (Fig. 1) (25).

In WOSCOPS, a small percentage of patients had a history of angina pectoris according to the Rose questionnaire (5%) or intermittent claudication (3%), but the AFCAPS/TexCAPS participants had no history, signs or symptoms of definite myocardial infarction, angina, claudication, cerebrovascular accident or transient ischemic attacks. As noted, total and LDL cholesterol values were in the average range for the U.S. population (enrollment criteria 180 mg/dL to 264 mg/dL and 130 mg/dL to 190 mg/dL, respectively, with triglyceride ≤400 mg/dL). In addition, participants had reduced HDL cholesterol: a mean of 36 mg/dL in men and 40 mg/dL in women (16th and 25th NHANES III percentiles; enrollment criteria ≤45 and ≤47 mg/dL). Other enrollment criteria included age 45 to 73 in men and age 55 to 73 and postmenopausal status in women (among whom about 30% were taking hormone replacement therapy). Also, if necessary, lovastatin dosage was titrated from 20 mg/day to 40 mg/day to achieve a target LDL cholesterol goal of 110 mg/dL, reflecting more closely the usual clinical practice of treating patients with the minimum effective dosage of drug.

Compared with baseline values, lovastatin (mean dosage, 30 mg/day) with diet background reduced LDL cholesterol by 25% (to 115 mg/dL), increased HDL cholesterol by 6% and decreased triglyceride by 15%. At five years, coronary event rates significantly reduced by active treatment included first acute major coronary event (unstable angina, myocardial infarction, and sudden cardiac death, −37%), fatal or nonfatal myocardial infarction (−40%), unstable angina (−32%) and revascularization (−33%). In each of these end point categories, a difference between the drug and placebo groups was seen in the first year and continued throughout the remainder of the trial. There were fewer primary end point events in lovastatin-treated women versus placebo (7 vs. 13), although this difference was not significant. The effect of treatment on first acute coronary event

Figure 1. Baseline lipid values from major primary-prevention trials in comparison with 50th percentile values from the National Health and Nutrition Examination Survey (NHANES III). AFCAPS/TexCAPS = Air Force/Texas Coronary Prevention Study; HDL-C = high-density lipoprotein cholesterol; HHS = Helsinki Heart Study; LDL-C = low-density lipoprotein cholesterol; LRC-CPPT = Lipid Research Clinics Coronary Primary Prevention Trial; Total-C = total cholesterol; WOSCOPS = West of Scotland Coronary Prevention Study. ◊ = AFCAPS/TexCAPS; ○ = HHS; △ = LRC-CPPT; ★ = NHANES III, 50th percentile; □ = WOSCOPS.
was consistent for patients above and below the median age by sex (57 years in men and 62 years in women) as well as for other predefined subgroups, such as smokers and those with hypertension. The AFCAPS/TexCAPS suggested that the benefit in women and older participants was comparable with that observed in the overall cohort. Clinical benefit was across all tertiles of baseline LDL cholesterol and HDL cholesterol without evidence of a threshold effect. Lovastatin therapy was well-tolerated, and there was no difference in noncardiovascular or total mortality rate between the drug and placebo groups.

Thus, AFCAPS/TexCAPS is the first primary-prevention trial of lipid modification to demonstrate coronary risk reduction in generally healthy men and women without clinical evidence of atherosclerotic disease and with only average cholesterol but below-average HDL cholesterol concentrations. In contrast to WOSCOPS, only 17% of the AFCAPS/TexCAPS participants would have met current NCEP criteria for drug therapy (11).

**COST-EFFECTIVENESS OF LIPID-LOWERING TREATMENT IN PRIMARY PREVENTION**

The AFCAPS/TexCAPS investigators calculate that using lovastatin to treat 1,000 men and women meeting the study criteria for 5 years would prevent approximately 12 myocardial infarctions, 7 presentations of unstable angina and 17 coronary revascularization procedures (11). However, the large pool of potential patients (approximately six million Americans meet the study’s age and lipid criteria but would not qualify for drug treatment according to current NCEP guidelines) raises important questions about the cost of implementing such treatment. Previous analyses of statin trials have reported that such therapy is cost-effective in secondary prevention (26–29). Analysis of WOSCOPS data has suggested that the cost-effectiveness of primary prevention improves as the number of CHD risk factors per subject increases and, hence, as their near-term risk for experiencing a CHD event increases (30).

A recent coronary prediction model based on Framingham data relies on the concept of risk factor clustering to predict the patient population most likely to benefit from primary-preventive treatments (31). An accompanying American Heart Association statement (32) emphasizes the value of this approach and supports the NCEP Adult Treatment Panel guidelines, which also adjust the decision to treat and the intensity of treatment according to the number and severity of risk factors. Such an analysis may be of value with the AFCAPS/TexCAPS population to ascertain which patient characteristics and risk factor clusters are most cost-effective for statin therapy in primary prevention.

**CLINICAL IMPLICATIONS OF THE STATIN TRIALS**

For patients, primary-care physicians and cardiologists, the results of WOSCOPS and AFCAPS/TexCAPS provide strong evidence for the benefits of primary prevention through lipid-regulating treatment, as well as reassurance concerning the safety of statin therapy. In particular, the AFCAPS/TexCAPS data extend the benefits to a large segment of the population at risk for a first CHD event. Both studies confirm the NCEP guidelines for high-risk patients without clinically evident atherosclerotic disease and underscore the necessity of measuring HDL cholesterol in clinical assessment. Future economic evaluation of the AFCAPS/TexCAPS trial will provide valuable information concerning the cost-effectiveness of treatment in selected patient groups. According to estimates based on phase 2 NHANES III data (1991–1994), only 1.4 million, or 6.6%, of 21.1 million U.S. adults who are currently eligible for cholesterol-lowering drug therapy by NCEP guidelines are receiving such therapy, including 14% of those eligible in secondary prevention and 4% of those eligible in primary prevention (33). Sixty-five percent of diet- or drug-eligible adults are receiving no therapy of any kind. These statistics are discouraging, especially in light of the substantial evidence demonstrating the benefit and general safety of such treatment, and demand continued vigilance in physician efforts to reverse the toll of atherosclerotic disease.

**REFERENCES**


