Applicability of Cholesterol-Lowering Primary Prevention Trials to a General Population

The Framingham Heart Study

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Background: Four large trials have shown cholesterol-reduction therapy to be effective for primary prevention of coronary heart disease (CHD).

Methods: To determine the generalizability of these trials to a community-based sample, we compared the total cholesterol and high-density lipoprotein cholesterol (HDL-C) distributions of patients in the 4 trials with those of Framingham Heart Study subjects. Lipid profiles that have not been studied were identified. Twelve-year rates of incident CHD were compared between subjects who met eligibility criteria and those who did not.

Results: The Framingham sample included 2498 men and 2870 women aged 30 to 74 years. Among Framingham men, 23.4% to 42.0% met eligibility criteria for each of the 4 trials based on their lipid levels; 60.2% met eligibility criteria for at least 1 trial. For the 1 trial that included women, 20.2% of Framingham women met eligibility criteria. In general, subjects with desirable total cholesterol levels and lower HDL-C levels and subjects with average total cholesterol levels and average to higher HDL-C levels have not been included in these trials. Among subjects who developed incident CHD during follow-up, 25.1% of men and 66.2% of women would not have been eligible for any trial. Most ineligible subjects who developed CHD had isolated hypertriglyceridemia (>2.25 mmol/L [>200 mg/dL]).

Conclusions: In our sample, 40% of men and 80% of women had lipid profiles that have not been studied in large trials to date. We observed a large number of CHD events in “ineligible” subjects in whom hypertriglyceridemia was common. Further studies are needed to define the role of lipid-lowering therapy vs other strategies for primary prevention in the general population.

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Dyslipidemia is a well-established risk factor for coronary heart disease (CHD). However, the risk associated with increasing total cholesterol and decreasing high-density lipoprotein cholesterol (HDL-C) levels is continuous and graded; there are no clear threshold values to discriminate subjects who will develop CHD from those who will not. For example, when examining univariate distributions of lipid parameters, there is considerable overlap between the total cholesterol distribution of men with and without prevalent CHD. Similarly, there is considerable overlap in the distribution of HDL-C for men with and without CHD. A simple method of graphically depicting the overlap of total cholesterol and HDL-C distributions to compare those with and without CHD is to plot bivariate ellipsoids representing the means ± 2 SDs of the 2 parameters simultaneously (Figure 1).

To date, there have been 4 large randomized placebo-controlled trials of cholesterol reduction aimed at primary prevention of CHD: the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), the Helsinki Heart Study (HHS), the West of Scotland Coronary Prevention Study (WOSCOPS), and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). These trials have demonstrated significant 19% to 37% reductions in the risk of first coronary events and/or mortality with cholesterol-lowering therapy compared with placebo. Such results provide encouraging evidence that more widespread use of lipid-lowering therapy for primary prevention could substantially reduce the extensive mortality and disability associated with CHD. However, the inclusion criteria for these trials have generally specified only perceived high-risk lipid profiles, and only AFCAPS/TexCAPS included women.

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PARTICIPANTS AND METHODS

STUDY SAMPLE

The Framingham Heart Study was established in 1948 when 5209 residents of Framingham, Mass, aged 28 to 62 years, were enrolled to evaluate potential risk factors for CHD. Members of this cohort have received follow-up evaluations every 2 years with medical history reviews and physical examinations as well as selected laboratory tests. In 1971, 5124 additional subjects (offspring of original cohort subjects and their spouses) were enrolled in the Framingham Offspring Study. These participants have received follow-up evaluations approximately every 4 years. All examinations and procedures have been approved by the institutional review board of Boston University School of Medicine, Boston, Mass.

The current study sample included original cohort participants in examination cycle 12 (1971-1974), and offspring cohort participants in examination cycle 1 (1971-1975). To determine the applicability of the 4 cholesterol-lowering primary prevention trials to a primary prevention population, we restricted our analyses to members of the original and offspring cohorts who were between ages 30 and 74 years and had fasting lipids measured at the index examination. Further, we excluded subjects with prevalent CHD (defined as history of definite angina pectoris, coronary insufficiency, or myocardial infarction).

FASTING LIPID MEASUREMENTS

Blood was drawn at the index examination after an overnight fast, and ethylenediaminetetraacetic acid plasma was used for all cholesterol and triglyceride measurements. Cholesterol levels were determined according to the Abell-Kendall technique, and HDL-C levels were measured after precipitation of very low-density lipoproteins or higher, the concentration of LDL-C was estimated directly after ultracentrifugation of plasma and measurement of cholesterol in the bottom fraction when plasma density was less than 1.006. For the purposes of this study, hypertriglyceridemia was defined as a triglyceride level higher than 2.25 mmol/L (200 mg/dL), and low HDL-C was defined as an HDL-C level lower than 0.90 mmol/L (35 mg/dL).

STATISTICAL ANALYSIS

We compared the lipid levels of the Framingham Heart Study sample with the published entry lipid ranges of participants in each of the 4 trials to determine the number and proportion of Framingham subjects who met eligibility criteria for each study. Bivariate ellipsoids were constructed separately for men and women using the means ± 2 SDs to represent the total cholesterol and HDL-C distributions of the study sample. The entry lipid ranges of the trials were overlaid on the bivariate ellipsoids of the Framingham sample (Figure 2) to graphically display the relative proportions of eligible Framingham subjects.

Subjects were observed for 12 years for incident CHD events (defined as coronary insufficiency, myocardial infarction, or coronary death) using previously published criteria. Surveillance for CHD consisted of regular examinations at the Framingham Heart Study clinic, Framingham, Mass, and review of medical records from outside physician office visits and hospitalizations. We calculated the rates of incident CHD over 12 years for all Framingham Heart Study subjects, subjects who met eligibility criteria for each of the trials, and subjects who did not meet eligibility criteria for any of the trials. To characterize the lipid profiles that merit further study, we also examined the trial eligibility and lipid levels of subjects who had incident CHD events during follow-up.

RESULTS

The Framingham sample included 2498 men and 2870 women (aged 30-74 years) from Framingham who were free of prevalent CHD and had fasting lipid levels drawn at the index examination. The baseline characteristics of the Framingham sample and the participants in each of the 4 trials are given in Table 1. Three of the trials studied participants with mean pretreatment total cholesterol levels substantially higher than those observed in the Framingham sample. The AFCAPS/TexCAPS participants had similar total cholesterol levels but lower HDL-C levels compared with the Framingham sample. The prevalences of nonlipid CHD risk factors varied markedly across the 4 trial populations.

ELIGIBILITY FOR TRIALS

The bivariate ellipsoids for the total cholesterol and HDL-C distributions in the Framingham sample are shown in Figure 2 and Figure 3 for men and women, respectively. The overlaid rectangles represent the entry lipid levels for each of the 4 trials. Framingham subjects whose lipid levels met eligibility criteria for a given study would fall within the area covered by the rectangle for that study. As defined by their entry criteria, the trials have tended to include subjects with high total cholesterol levels and...
generally those with low HDL-C levels. As shown in Figure 2, men with desirable total cholesterol levels and lower HDL-C levels (lower left quadrant of the bivariate ellipsoid), and men with average total cholesterol levels and average to higher HDL-C levels (upper left quadrant of the bivariate ellipsoid) have not been included in these trials.

Table 2 gives the number and percentage of Framingham men and women who fell into the area covered by each of the studies. In men, the percentages ranged from a low of 23.4% who had lipid levels eligible for LRC-CPT, to a high of 42.0% who had levels eligible for AFCAPS/TexCAPS. In the aggregate, 60.2% of the men fell into an area covered by at least 1 of the studies, leaving 39.8% who would not have been eligible for any of the studies. Using AFCAPS/TexCAPS criteria, only 20.2% of Framingham women had lipid levels that met eligibility criteria for this trial, whereas 79.8% had lipid levels that did not.

OUTCOMES

During 12 years of follow-up, 275 men (11.0%) and 136 women (4.7%) developed CHD. The rates of incident CHD were 17.1%, 14.9%, 15.9%, and 12.9% in men eligible for LRC-CPT, HHS, WOSCOPS, and AFCAPS/TexCAPS, respectively. Among the men eligible for at least 1 of the trials, the rate of 12-year incident CHD was 13.7%; in women eligible for AFCAPS/TexCAPS it was 7.9%. The rates of 12-year incident CHD among men or women ineligible for all trials were half the rates observed in subjects eligible for at least 1 trial (Figure 4).
Of the 275 men with incident CHD, 69 (25.1%) would not have been eligible for any of the trials. Of these 69, most (n=62) had hypertriglyceridemia, representing 22.5% of all men with incident CHD. Among the 62 men with hypertriglyceridemia, 43 had isolated hypertriglyceridemia, and 19 had hypertriglyceridemia with associated low levels of HDL-C, representing 15.6% and 6.9%, respectively, of all men with incident CHD. Only 33.8% of the 136 women with incident CHD met eligibility criteria for AFCAPS/TexCAPS, whereas most (n=90 [66.2%]) did not. Of these 90 women, 83 (61.0% of women with incident CHD) had hypertriglyceridemia, and only 6 (4.4%) had associated low levels of HDL-C.

Since diabetes may have confounded the relationship between hypertriglyceridemia and incident CHD, we examined whether the prevalence of diabetes was higher among subjects who developed CHD and were ineligible for the trials compared with those who met eligibility criteria. Among men who developed CHD, the prevalence of diabetes was 15.9% for those who were ineligible compared with 10.2% for those who were eligible (P=.20). Among women who developed CHD, the prevalence of diabetes was 20.0% for those who were ineligible compared with 10.8% for those who were eligible (P=.23).

In our community-based population of adults without CHD aged 30 to 74 years, 40% of men and 80% of women had lipid profiles that did not meet eligibility criteria for inclusion in the large primary prevention trials published to date. Men who have not been included in trials include those with desirable total cholesterol and low HDL-C levels, and those with average total cholesterol and average to higher HDL-C levels. Randomized trial data remain sparse for women across a wide range of lipid profiles (other than those in AFCAPS/TexCAPS).

**IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH**

Rates of incident CHD during follow-up were half as great among subjects who did not meet eligibility criteria for the trials compared with those who were eligible. This finding validates the inclusion criteria of the trials in that higher-risk individuals were selected for cholesterol-lowering intervention. Nonetheless, a substantial proportion of first CHD events (25% in men and 66% in women) occurred among subjects with lipid profiles that have not been studied. Most ineligible subjects with incident CHD had hypertriglyceridemia with or without low HDL-C levels. Therefore, further primary prevention trials targeting hypertriglyceridemia and low HDL-C levels seem warranted. In addition, further epidemiologic studies examining the population-attributable risk associated with hypertriglyceridemia would be useful.

With the current paucity of clinical trial data for primary prevention in women, clinicians may be using the published primary prevention trial results for men to inform treatment decisions for their female patients. However, because of the different endocrinologic and cardiovascular milieu present in women, extrapolation of results from male trial participants may be misleading. This may be true particularly for premenopausal...
women, who generally have a very low risk of incident CHD and may be much less likely to benefit from primary prevention than higher-risk subgroups. Women may currently be receiving drug therapy with little chance of benefit but some risk of adverse toxic effects. Further trials of the efficacy and safety of lipid-lowering therapy for primary prevention of CHD in women are therefore warranted.

IMPLICATIONS FOR PUBLIC HEALTH

The findings of this study have implications in terms of the cost-effectiveness of primary prevention with lipid-lowering agents. Currently, medical therapy of dyslipidemia has been firmly established as cost-effective for secondary prevention of CHD. Data from the Scandinavian Simvastatin Survival Study (4S) indicate that 13 patients with CHD would need to be treated for 5 years to prevent 1 recurrent major coronary event. In considering the cost-effectiveness of an intervention, the concept of “cost per year of life gained” is typically used. Interventions that cost less than $20000 per year of life gained are generally considered to be very cost-effective, and those that cost less than $40000 have been recommended by some authors, whereas those that cost more than $75000 are generally considered not cost-effective. From 4S, the direct costs per year of life gained using simvastatin for secondary prevention ranged from $3800 for 70-year-old men with a total cholesterol level of 8.0 mmol/L (309 mg/dL) to $27400 for 35-year-old women with a total cholesterol level of 5.5 mmol/L (213 mg/dL). When indirect costs were included, the costs per year of life gained ranged from a net savings in 35-year-old patients to a cost of $13300 for 70-year-old women with a cholesterol level of 5.5 mmol/L (213 mg/dL). Such data have led to the widespread acceptance of medical therapy for secondary prevention of CHD in patients with hypercholesterolemia.

In contrast, the role of medical therapy of dyslipidemia for the primary prevention of CHD remains controversial because of the potential costs involved in treating large segments of the population. From the 4 primary prevention trials, a range of approximately 40 to 75 patients would need to be treated for 5 years to prevent a single coronary event. As previously noted, these studies have selected patients with relatively high-risk lipid profiles that reflect a fairly small proportion of the general population. The study sample in AFCAPS/TexCAPS was most representative of the general population in that it was a healthy group of men and women with average total cholesterol and LDL-C values but below average HDL-C levels. In AFCAPS/TexCAPS, it was estimated that 53 patients would need to be treated with lovastatin for 5 years to prevent a single acute coronary event (including unstable angina and myocardial infarction).

In the past decade, the introduction and widespread use of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (the “statin” compounds) have clearly provided a major therapeutic advance in the treatment of hypercholesterolemia. Indeed, WOSCOPS and AFCAPS/TexCAPS observed greater relative reductions in coronary events with statins than did LRC-CPPT or HHS with cholestyramine and gemfibrozil, respectively, despite the fact that the latter 2 trials had higher baseline total cholesterol levels. However, statins are also significantly more costly than the older medications. The cost-effectiveness of cholesterol-lowering therapy for primary prevention has therefore been questioned.

Estimates of the cost-effectiveness of medical therapy for primary prevention vary widely, depending on the risk profile of the population studied. In one study by Goldman et al, therapy with statins was not cost-effective for any subgroup of women, and only men with multiple risk factors (eg, combined obesity, smoking, and hypertension) had costs per year less than $40000. In another analysis using Framingham risk equations, Hamilton and colleagues adjusted for the additional benefit of HDL level elevation seen with lovastatin therapy. They calculated costs of $28000 to $44000 per year of life gained for low-risk men aged 40 to 60 years and low-risk women aged 50 to 70 years. For higher-risk men, the costs ranged from $13000 to $33000.

Thus, the challenge for clinicians and policy makers is to identify higher-risk patients for whom medical therapy will be more cost-effective. Selection of high-risk patients using multivariate risk score or global risk assessment strategies is likely to improve the clinical effectiveness and cost-effectiveness of antihyperlipidemia drugs.

As CHD incidence was approximately half as great among those who did not meet eligibility criteria compared with those who were eligible, the cost-effectiveness of treating dyslipidemia in the large subgroup of ineligible patients may be poor. Similarly, the number of subjects who need to be treated to prevent 1 CHD event in this subgroup likely exceeds the value of 53 observed in AFCAPS/TexCAPS. Nonetheless, the high proportion of incident CHD events that occurred in the ineligible subgroup should be of concern to policy makers and clinicians alike. Therefore, other strategies including public health and individual measures aimed at aggressive dietary management and control of other coronary risk factors should also be considered in the treatment of patients with these unstudied lipid abnormalities. Such an approach may be preferable given that hypertriglyceridemia and low HDL-C levels are often markers of other metabolic risk factors for CHD, including hyperinsulinemia, central obesity, and hypertension.

It should be noted that none of the groups of Framingham subjects who met eligibility criteria for any of the trials had 10-year rates of CHD that exceeded the level of 20%, which has recently been recommended as a threshold for screening and treatment of coronary risk factors by the joint task force from the European societies of cardiology, atherosclerosis, and hypertension. Therefore, further study is needed of risk-stratification techniques designed to identify higher-risk patients among the ineligible subgroup. Such techniques might involve the routine incorporation of triglyceride and HDL-C data into risk assessment and might indicate further strategies to provide optimal risk reduction.
POTENTIAL LIMITATIONS

This study has several potential limitations. First, the original and offspring cohorts of the Framingham Heart Study are composed almost exclusively of white individuals. However, data from the NHANES (National Health and Nutrition Examination Study) surveys from the 1970s through the 1990s indicate that in the United States, mean cholesterol values vary by less than 5 points across different ethnic groups for men and women,\textsuperscript{26,191} and the proportions of individuals with hypercholesterolemia are remarkably similar across ethnicities.\textsuperscript{25} Therefore, our findings would likely apply to other ethnicities as well. Second, the Framingham sample represents the experience of a single municipality. There are known regional variations in both lipid values and rates of incident CHD within the United States. However, the risk profile of the Framingham subjects used in this report is quite similar to concurrent national profiles with regard to prevalence of smoking, diabetes, and hypertension, as well as hypercholesterolemia.\textsuperscript{24} It should be noted that the mean HDL-C level for women in our Framingham sample was 1.40 mmol/L (54 mg/dL), slightly higher than the mean HDL-C level for women in the NHANES II sample.\textsuperscript{26} Finally, to allow examination of follow-up events, we used data from Framingham subjects seen in the 1970s and observed into the 1980s, so incident rates of CHD from the Framingham sample may not be representative of a current sample. These data are likely to be more accurate than NHANES follow-up data, however, because national data must rely on death certificates, which can be unreliable when used to diagnose CHD.\textsuperscript{27}

CONCLUSIONS

In conclusion, a substantial proportion of CHD events occurs in individuals with lipid profiles that have not been included in primary prevention trials to date. Further research seems warranted in men with hypertriglyceridemia and in women with all lipid profiles. Given that the perceived high-risk lipid profiles have been studied, the role of lipid-lowering therapy vs other strategies to reduce risk in the unstudied groups is unclear.

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