Screening for Total Cholesterol
Do the National Cholesterol Education Program’s Recommendations Detect Individuals at High Risk of Coronary Heart Disease?

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Background. The National Cholesterol Education Program (NCEP) has provided guidelines for identification of persons at high risk of coronary heart disease (CHD) because of lipid abnormalities. These recommendations are based on total cholesterol as the initial screening tool and have become the stimulus for clinic- and community-based screening programs nationwide. However, the use of the guidelines may be problematic because individuals may have total cholesterol levels in the desirable range but low density lipoprotein (LDL) or high density lipoprotein (HDL) levels considered at high risk. This study evaluates the ability of the NCEP screening recommendations to identify correctly persons at high risk of CHD because of lipid abnormalities.

Methods and Results. Using the NCEP guidelines, we simulated a population-based screening program with data from visits 1 and 2 of the Lipid Research Clinics Program Prevalence Study. Individuals were considered to be at high risk of CHD if they had LDL levels greater than 160 mg/dl or HDL levels less than 35 mg/dl. Following the NCEP process, 21% of those with high LDL concentrations and 66% of those with low HDL concentrations would not be routinely referred for immediate treatment. Overall, 41% of those at high risk of CHD would not be promptly evaluated. The sensitivity of the guidelines for promptly identifying individuals with lipoprotein abnormalities is 59%.

Conclusions. This relatively low sensitivity of total cholesterol as a screening tool should be the impetus for rethinking the screening guidelines. Specifically, the cost–benefit ratio of routine screening for lipoproteins, particularly HDL cholesterol, needs to be carefully considered. (Circulation 1991;83:1287–1293)

The National Cholesterol Education Program (NCEP) convened by the US National Institutes of Health has provided guidelines for identification and treatment of individuals at high risk of coronary heart disease (CHD) because of increased cholesterol levels.¹ The NCEP has also defined “borderline high” and “desirable” levels of total and low density lipoprotein (LDL) cholesterol. The recommendations for identifying high risk individuals are based on screening measures of total cholesterol, although the recommendations for treatment are based on concentrations of LDL cholesterol. Low levels of high density lipoprotein (HDL) cholesterol (<35 mg/dl) are considered by the NCEP to be a major independent lipid risk factor for CHD.

Total cholesterol was recommended as the initial screening test for three reasons: High levels of LDL cholesterol are associated with an increased risk of CHD; there is a high correlation between total cholesterol and LDL cholesterol; and testing for total cholesterol is easier and less expensive than testing for LDL. The NCEP recommended that HDL cholesterol be measured in persons with high total cholesterol levels or in those with borderline high levels and a high CHD risk profile.

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The use of total cholesterol to identify individuals at high risk of CHD is problematic because individuals may have total cholesterol levels within the desirable range (e.g., <200 mg/dl) and also have LDL levels considered at high risk (e.g., ≥160 mg/dl). This same situation can occur in individuals with low HDL levels (i.e., total cholesterol levels within the desirable range but HDL levels considered at high risk [e.g., <35 mg/dl]). The potential exists that individuals at high risk for CHD because of lipopro-
tein levels will be misclassified as low risk with a total cholesterol screen.

The NCEP recommendation that total cholesterol be measured in all adults over 20 years of age has been the impetus for community-level screening programs across the United States. Therefore, the purpose of this analysis was to assess, in a general population sample, the ability of total cholesterol screening to identify individuals at high risk of CHD because of lipid abnormalities. To accomplish this goal, data from the Lipid Research Clinics (LRC) Program were used to simulate a population-based cholesterol screening program, following as closely as possible the recommendations of the NCEP.

Methods

Population

The data used are from the LRC Prevalence Study, which was conducted in 10 North American clinics between 1972 and 1976. Detailed descriptions of this population have been published²⁻³; however, a brief overview is provided here.

The Prevalence Study was designed to identify the prevalence and correlates of dyslipoproteinemias in North America. A total of 81,926 individuals from targeted populations were invited for a clinic visit (visit 1), where they answered a questionnaire and provided blood for total cholesterol determinations. There were 60,502 persons who participated in visit 1. A 15% random sample of visit 1 participants plus all persons with elevated total cholesterol and all those taking lipid-altering medications were invited for a second visit (visit 2).

Visit 2 occurred about 96 days (median) after visit 1 and included information from questionnaires and determinations of lipoproteins and total cholesterol. Nearly 85% (n=13,852) of those invited (n=16,335) to visit 2 participated.

The population for this analysis included all individuals at the visit 2 examination who were between 20 and 79 years of age and were randomly selected from the visit 1 population.

Laboratory Methods

Drawing of serum samples and determinations of total, LDL, and HDL cholesterol were done by standardized LRC methodology.⁴ Briefly, this procedure included a venipuncture, performed with the participant seated; use of a tourniquet, which was released before blood sampling (to avoid artifactual increases in lipid levels); immediate cooling of samples on wet ice; and standardized processing within 3 hours of venipuncture at each clinic.

Total cholesterol levels were determined by use of the Technicon AutoAnalyzer I or II (the ferric chloride–sulfuric acid method [I] or the Liebermann-Burchard procedure [II]). The lipoproteins were separated by ultracentrifugation at saline density (1.006 g/ml). HDL cholesterol was determined after precipitation with heparin and manganese chloride of the apo B lipoproteins. LDL cholesterol concentrations were calculated as d>1.006 g/ml−HDL cholesterol.

Data Source

Data for this analysis were derived from public use data tapes of the visits 1 and 2 Prevalence Study provided by the LRC Program.

Analytic Framework

The NCEP has outlined a strategy for the detection of individuals at high risk of CHD, recommending that all persons over 20 years of age have their total cholesterol measured. This strategy is presented graphically in Figure 1. If the first total cholesterol measurement is under 200 mg/dl, then those individuals are given general dietary advice and advised to have a repeat screening in 5 years.

If the initial measurement is greater than or equal to 200 mg/dl, then a repeat measurement of total cholesterol is done within 1–8 weeks. If the average of the two screening values is less than 200 mg/dl, then these persons are given general dietary advice and reminded to have a repeat measurement in 5 years. Thus, persons with an initial total cholesterol measurement less than 200 mg/dl and those with an average of two measurements less than 200 mg/dl are not further evaluated for 5 years (Figure 1, block A).

If the average of the two cholesterol values is between 200 mg/dl and 239 mg/dl, the decision for referral for lipoprotein analysis is based on the presence of CHD and associated risk factors (Figure 1, block B); that is, if an individual has a borderline high cholesterol level but is free of CHD and has less than two CHD risk factors (Figure 1, block B1), he or she is not further evaluated but is provided with dietary information and reevaluated annually. If the average of the two cholesterol measures is greater than or equal to 240 mg/dl, then the participant is referred for a fasting lipoprotein analysis (Figure 1, block C). The NCEP acknowledges that some experts recommend a lipoprotein analysis for individuals under 40 years of age who have borderline high total cholesterol levels or for individuals with borderline high levels and one CHD risk factor. However, a lipoprotein determination was not recommended by the NCEP as a general approach for these individuals, although the option for individualized clinical judgment was left to the private physician.

The goal of this specific analysis was to ascertain the proportion of persons who have either low HDL levels and/or high LDL levels but who, according to the guidelines, would not be identified and referred for immediate lipoprotein analysis (i.e., those in blocks A and B1).

Analytic Approach

The recommendations of the NCEP for identifying high risk individuals were followed. Visit 2 lipoprotein determinations and the cut points recommended by the NCEP were used to classify participants as at high risk of CHD due to lipoprotein abnormalities.
Thus, LDL levels greater than or equal to 160 mg/dl or HDL levels less than 35 mg/dl defined high risk.

Other risk factors for CHD are defined by the NCEP to be male sex, family history of premature CHD (definite myocardial infarction or sudden death before age 55 in a parent or sibling), cigarette smoking (more than 10 cigarettes a day), hypertension, low HDL cholesterol concentration, diabetes mellitus, history of definite cerebrovascular or peripheral vascular disease, and severe obesity (≥30% overweight). Definite CHD is defined by the panel as definite prior myocardial infarction or definite myocardial ischemia, such as angina pectoris. In this specific analysis, the definitions of male sex and cigarette smoking followed exactly the NCEP definitions. However, because of the wording in the visit 2 questionnaire and the nonspecificity of the NCEP in delineating several risk factors, definitions of risk factors used in this analysis vary somewhat from those listed above.

Family history of premature CHD was defined here as any occurrence of CHD in parents or siblings before age 60. Hypertension was defined as the use of any hypertensive agents or systolic blood pressure over 140 mm Hg or diastolic blood pressure over 95 mm Hg. Although the NCEP guidelines state that HDL levels below 35 mg/dl are a major independent risk factor for CHD, it is inappropriate to consider low HDL as a risk factor in the screening process because low levels cannot be used to define risk if they have not been measured yet. Diabetes mellitus was defined as present if the participant reported it. Severe obesity was defined as a body mass index greater than 30 kg/m².

Definite cerebrovascular disease was defined as a history of stroke. Definite peripheral vascular disease was defined as a history of surgery for circulation problems of the extremities. Definite CHD was considered present if a participant had bypass surgery or a myocardial infarction or was using any of the following medications: blood thinners, digitalis, drugs for arrhythmias, or drugs for angina.

Visit 1 total cholesterol values were considered as the initial screening cholesterol test, and visit 2 cholesterol determinations were treated as a second screening test. Persons who were identified at visit 2 as having a high risk of CHD because of lipoprotein concentrations were then followed back through this simulated screening program, and those misclassified using the guidelines were identified.

**Results**

The number of participants and the number and percentage with elevated LDL and low HDL cholesterol are presented in Table 1. Of the 5,857 individuals eligible for this simulated screening program,
TABLE 1. Total Number of Participants and Number With Elevated Low Density Lipoprotein and Low High Density Lipoprotein Cholesterol by Age and Sex

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>LDL</td>
</tr>
<tr>
<td>20-39</td>
<td>1,229</td>
<td>158 (13%)</td>
</tr>
<tr>
<td>40-59</td>
<td>1,362</td>
<td>376 (28%)</td>
</tr>
<tr>
<td>60-79</td>
<td>348</td>
<td>118 (34%)</td>
</tr>
<tr>
<td>Total</td>
<td>2,939</td>
<td>652 (22%)</td>
</tr>
</tbody>
</table>

*Men and women 5,857* 1,163 718

(20%) (12%)

*There are missing values for either total, low density lipoprotein (LDL), and/or high density lipoprotein (HDL) cholesterol on 30 persons. Percentages for increased LDL and decreased HDL are based on total observations available.

One hundred fifty-five individuals had elevations in LDL cholesterol concurrent with low HDL cholesterol levels. Thus, 1,726 persons had elevated LDL and/or low HDL cholesterol levels.

- 5,827 had complete information on cholesterol and lipoproteins. Of these, 20% (n=1,163) had LDL levels greater than or equal to 160 mg/dl, and 12% (n=718) had HDL levels less than 35 mg/dl. Two percent (n=115) of the total population had elevated LDL and low HDL levels. Men were more likely than women to have lipoprotein abnormalities (i.e., elevated LDL and low HDL levels). Eighty-eight percent of participants were under 60 years of age.

- The number of persons with elevated LDL and low HDL levels who were missed with the total cholesterol screens is presented in Figure 2. Of the 1,163 persons who had LDL levels greater than or equal to 160 mg/dl, 81 had initial or average total

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**Figure 2.** Flowchart showing numbers of persons with high low density lipoprotein (LDL) and low high density lipoprotein (HDL) levels in the simulated total cholesterol screening program. CHD, coronary heart disease.
cholesterol levels less than 200 mg/dl, and 167 had borderline high cholesterol levels but not CHD or two or more CHD risk factors. Thus, 21% (248 of 1,163) of those with seriously elevated LDL levels were missed with the total cholesterol screening process, yielding a sensitivity of 79%.

Similarly, of the 718 participants who had HDL levels less than 35 mg/dl, 426 had initial or average total cholesterol levels less than 200 mg/dl and were not further evaluated (Figure 2, block A). An additional 49 persons with low HDL had borderline high total cholesterol levels but did not have CHD or other of its associated risk factors (Figure 2, block B1). Thus, a total of 475 individuals (66% of all persons with low HDL levels) were missed by following the NCEP guidelines (sensitivity, 34%).

Nearly 30% of this entire sample, or 1,766 persons (1,048 with elevated LDL, 563 with low HDL, and 155 with both), are at high risk of CHD because of lipid abnormalities. With the NCEP screening guidelines, 723 individuals (248 with elevated LDL, 427 with low HDL, and 48 with both), or 41% of those at high risk for CHD, were not referred for prompt lipoprotein evaluation. Overall, the sensitivity of the NCEP guidelines for identifying those with lipoprotein abnormalities was 59%.

Of those 1,689 individuals who went for immediate lipoprotein analysis (blocks B2 and C), 9% (n=159) had LDL cholesterol levels less than 130 mg/dl. The vast majority (72%) of these “false positives” were persons with borderline high cholesterol levels.

Individuals with low HDL levels (<35 mg/dl) and very low LDL levels (<100 mg/dl) may not be at risk of CHD. In this simulation, there were 99 such individuals. If these 99 persons (12% of those with low HDL) are excluded from the analysis, then 47% of those with low HDL levels were missed (sensitivity, 53%), and 35% of those at high risk from any lipoprotein abnormalities were not immediately identified.

Discussion

The purpose of this analysis was to assess how well a total cholesterol screen identifies persons at high risk of CHD because of lipid abnormalities. Based on this simulation, our conclusion is that the processes defined by NCEP miss a significant proportion of persons who are at high risk of CHD from lipoprotein abnormalities. Furthermore, the use of very strict cut points for determining high CHD risk, which was done here for both LDL and HDL cholesterol, results in misclassification estimates that are conservative. For example, if the intention is to identify individuals with borderline as well as high LDL levels (≥130 mg/dl), then 47% of persons with LDL greater than or equal to 130 mg/dl are missed following the guidelines (sensitivity, 53%). In the Framingham Study, men with HDL concentrations less than 53 mg/dl and women with HDL concentrations less than 67 mg/dl were at high risk of developing CHD. Similarly, 76% of persons with HDL values under 55 mg/dl are missed.

There are several limitations to this analysis. We attempted to follow the NCEP screening recommendations as strictly as possible but were unable in some situations to adhere rigidly to them. Because of the LRC Program protocol, nearly everyone at visits 1 and 2 had been fasting between 12 and 16 hours, and the median time from visit 1 to visit 2 was nearly 14 weeks. This protocol is in contrast to that of the NCEP, which stated that fasting was not necessarily required of participants and that a second screening test for those with total cholesterol greater than or equal to 200 mg/dl at the first screen should occur 1–8 weeks after the first. It is not clear to what degree and in what direction these deviations from the NCEP protocol would affect the estimates presented here. However, total cholesterol is not strongly influenced by time since last meal, and variability in cholesterol measurements should only increase over time. Therefore, it seems reasonable that these two deviations would not markedly influence the misclassification estimates.

These data were gathered during the LRC Program between 1972 and 1976. Thus, if the prevalence of elevated LDL and/or low HDL cholesterol in the US population has changed substantially in the last 15 years, these results would be either overestimations or underestimations of the misclassification that would occur in screening programs today. However, no data are available on the change in prevalence of elevated LDL and/or low HDL cholesterol levels during this period. Therefore, the LRC Program data represent the current best estimate of the prevalence of dyslipoproteinemia in the US population.

Some of the definitions of risk factors used in this analysis are slightly different from those proposed by the NCEP. Again, it is unclear how these differences in the definitions of risk factors would affect the misclassification estimates. Because several of the NCEP definitions of CHD risk factors are nonspecific, definitions of community-based screening programs will also be variable.

There are also several strengths of this analysis. The lipid determinations are of high quality and are done in a standardized manner according to a strict protocol in which LRC laboratories are used. The visit 2 random sample represents a nationwide sample of individuals from a variety of backgrounds who may be likely to undergo cholesterol screening. Furthermore, ascertainment of nonlipid CHD risk factors was done in a standardized manner.

Over two thirds of those individuals with elevated LDL levels who are missed in this process have borderline high cholesterol levels but not CHD or two risk factors for CHD. In fact, 27% of those with borderline high cholesterol who go on for a lipoprotein screen (Figure 1, block B2) have elevated LDL levels compared with 20% of those who are not recommended for immediate follow-up (Figure 1, block B1). These data suggest that all individuals with borderline high cholesterol should be referred for a lipoprotein analysis. The NCEP guidelines state
that physicians have the option of requesting a lipoprotein profile regardless of the participant's total cholesterol level. However, this option is not well known, and it remains uncertain just how many physicians or other medical personnel who are offering the screening elect to follow it.

These data suggest that, overall, 40% of individuals at high risk of CHD because of lipoprotein abnormalities will not be identified immediately by the NCEP screening process. The screening process identifies a higher proportion of individuals with elevated LDL levels (79%) than with low HDL levels (34%). This differential sensitivity of the screening test is not surprising because the guidelines were based on LDL cholesterol as the lipoprotein fraction that confers risk. Two thirds of those misclassified with the total cholesterol screening were individuals with low levels of HDL. This finding raises the question of whether screening for low HDL levels is appropriate.

There is considerable debate among the scientific community regarding population screening for HDL cholesterol. Some believe that screening for HDL is not warranted because laboratory measurements of HDL are not standardized. Others argue that there is no evidence that increasing HDL cholesterol is useful; therefore, screening is inappropriate. The NCEP did not recommend screening for HDL, although they noted that increasing HDL levels, particularly by hygienic methods, is justified.

In our opinion, the apparent lack of a standardized laboratory measurement for HDL is an insufficient reason not to recommend screening for HDL. It is not generally known, but the Centers for Disease Control has had a standard procedure for assay HDL for a number of years. However, the materials are not generally available (Paul Backorik, personal communication). In addition, medical laboratories routinely assay HDL, and medical decisions are based on these nonstandardized values.

Even if nonstandardized HDL measurements vary from "truth" by as much as 25%, the choice of very low levels of HDL as a marker of CHD risk means that those identified as high risk in this sample are probably at high risk. That is, by use of a nonstandardized test with a 25% margin of error, someone with an HDL level of 35 mg/dl (the top of the "at risk" range) has a "true" HDL level that lies between 26 mg/dl and 44 mg/dl (i.e., at absolute levels that, according to data from Framingham, places them at high risk of CHD).

The second concern, that screening for HDL is not recommended because there is no clinical trial evidence that increasing HDL levels is beneficial, is probably shortsighted. It has been reported that future versions of these NCEP guidelines may focus more on HDL levels if a clinical trial, especially a pharmacological intervention in persons with low HDL but nonelevated LDL levels, has a positive outcome. However, the result of any such trial is at least a decade away. In addition, although there is no direct clinical trial of the effectiveness of increasing HDL levels to prevent CHD, there are data from several clinical trials and observational epidemiological studies suggesting that elevated HDL levels as a result of a pharmacological intervention (estrogen, alcohol, or gemfibrozil) are associated with lower rates of CHD. The protection against CHD afforded estrogen users and moderate consumers of alcohol has been attributed to their increased HDL levels.

Although measurements for HDL are nonstandardized and direct evidence from clinical trials is not available, we believe that population screening for HDL levels should be carefully considered at this time. Numerous studies have confirmed and the NCEP has concurred that a low HDL level is a major independent lipid risk factor for CHD. The independence of HDL as a risk factor has been clearly documented in an Israeli study, which showed that individuals with desirable total cholesterol levels (<200 mg/dl) and low HDL have a fourfold increased risk of CHD compared with those having desirable total cholesterol levels and high HDL concentrations. Furthermore, changes in HDL levels can be accomplished by hygienic as well as pharmacological intervention. Weight loss, exercise, and smoking cessation have all been shown to increase HDL levels.

In conclusion, one of the necessary requirements for any screening program is that the program identify a high proportion of at risk individuals (i.e., that the screening test have a high sensitivity). In this simulated screening program, which used cut points and definitions of the NCEP, 40% of persons at high risk of developing CHD because of lipoprotein characteristics were not identified as being at risk. This relatively low sensitivity of total cholesterol as a screening tool should be the impetus for reviewing guidelines that involve screening for lipid abnormalities. A cost–benefit analysis of routine screening for lipoproteins may be an appropriate next step.

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References


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