Prevention of Coronary Heart Disease and the National Cholesterol Education Program

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The incubation period for the progression of atherosclerosis to clinical disease is long, which provides an opportunity for risk factor modification and prevention of coronary heart disease (CHD). The National Cholesterol Education Program (NCEP) utilized the Framingham risk score (FRS) to classify individuals by level of risk to receive drug therapy and/or dietary counseling to lower low-density lipoprotein cholesterol (LDL-C) and raise high-density lipoprotein cholesterol (HDL-C). The rationale for choosing specific cutpoints for treatment was based on 3 key variables: (1) the efficacy of drug therapy to reduce the CHD incidence, (2) the safety of drug therapy, and (3) the cost of therapy.

The Multi-Ethnic Study of Atherosclerosis (MESA) has reinforced previous observations that the guidelines are not being fully implemented. Many individuals are not treated or are undertreated. In MESA, only 54% were undergoing drug therapy, and only 40% of the dyslipidemic individuals had their blood cholesterol levels under control. This is overestimated, because individuals currently being treated with lipid-lowering drugs were dyslipidemic by NCEP criteria. Likely, many of these individuals were placed on therapy by doctors even if they did not meet the NCEP criteria. Not surprisingly, guidelines are being followed less for poorer individuals and minorities. A recent detailed report in Circulation discussed the reason for failure to follow guidelines and reduce lipid levels. Almost all of the successful studies of diet or drug intervention in atherosclerotic disease have used a combination of drugs targeting both LDL-C and HDL-C. The rationale for targeting HDL-C, as measured by apolipoprotein B or LDL particles, and total cholesterol is related to the extent of coronary atherosclerosis, as measured by coronary calcification. This evaluation has put in focus a substantial problem with the FRS and the NCEP guidelines. For example, 663 participants (19% of the total cohort) had coronary artery calcium (CAC) >400 Agatston units, which indicates a substantial risk of increased CHD based on major longitudinal studies of CAC. Only 350 (53%) had a drug therapy indication by the NCEP guidelines. We do not know how many of these 350 individuals were undergoing drug therapy as recommended for high-risk individuals. Even worse, there were 674 participants (34%) for whom drug therapy was recommended who had no CAC, almost all of whom probably had very low amounts of atherosclerosis and a very low risk of heart attack. There is possible substantial undertreatment and overtreatment. The mean age of the MESA sample was 62 years. Lloyd-Jones et al reported that at age 60, prediction of lifetime risk of CHD using the FRS was poor, especially for men, with a 48% lifetime risk of CHD in the highest tertile, 42% in the second tertile, and 37% in the third tertile. Prediction in women was somewhat better but only for those in the lowest risk category.

In the Cardiovascular Health Study, age ≥65 years, measures of subclinical disease, hypertension, and diabetes are the primary predictors of CHD. The LDL-C level is a relatively weak predictor of risk of CHD, and the FRS performs rather poorly in these older individuals. Two other recent reports have documented the differences between the FRS and CAC in population studies. Taylor et al reported that CAC and family history predicted CHD risk among young men (mean age 43 years; n=2000) better than the FRS over 3 years of follow-up. Among older individuals (mean age 71 years) in the Rotterdam Study, relative risk of CHD was strongly related to CAC scores. The FRS was not a strong predictor among different levels of CAC scores.

The NCEP guidelines were developed primarily to focus on high-risk individuals and short-term risk of CHD. The typical individual who succumbs to a sudden death or acute myocardial infarction does so with moderate levels of risk factors, so that statin treatment policies that focus only on those at the highest risk are anarchistic and fail to make use of the recent evidence. Another problem is the increase in obesity in the United States that, combined with the decline in LDL-C, has resulted in a new mix of risk factors of central obesity, high waist circumference, moderately elevated LDL-C, low HDL-C, high triglycerides, and insulin resistance. This has required a change in both risk identification and treatment strategies. There is a disconnect between lipoprotein levels, as measured by apolipoprotein B or LDL particles, and total LDL-C. The distribution of HDL particles, as well as apolipoprotein properties, probably plays a major role in determining the beneficial effects of raising HDL-C levels. Furthermore, a combination of drugs to modify both the low-density lipoprotein and high-density lipoprotein may be necessary to prevent atherosclerosis progression.
HDL-C and the moderately elevated LDL-C and the high number of apolipoprotein B and LDL particles is often required. The NCEP has tried to deal with this problem by classifying the metabolic syndrome as a risk equivalent, but unfortunately, this focuses on an artificially arbitrarily defined metabolic syndrome and not on the continuum of the key risk factors and underlying insulin resistance, as noted by Reaven.\(^\text{11}\)

The basic function of the NCEP is to define individuals eligible for drug interventions. Total blood cholesterol levels in the United States have fallen, in part because of the decrease in saturated fat and cholesterol in the diet, which is now down to \(\approx 11\%\) (saturated fat) of total calories.\(^\text{10}\) Reduction of an individual’s LDL-C by diet alone is feasible but requires substantial dietary changes and expert guidance from trained nutritionists.\(^\text{15}\) There is no evidence that the recommendation of smaller changes in diet or limited counseling in physicians’ offices has any major effect in reducing LDL-C levels. There is also no evidence that these modest reductions of LDL-C reduce the risk of CHD for individuals who already have significant atherosclerosis. Unfortunately, it is possible that a 30% reduction in LDL-C may be needed to reduce the risk of CHD among those who already have fairly extensive atherosclerosis, as was noted in recent studies, such as the lipid component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).\(^\text{16}\)

It is very possible that the amount of lipid lowering required to prevent the development of atherosclerosis or early progression is substantially less than that required to prevent advanced atherosclerosis or clinical CHD. The role of diet may therefore be in the primary prevention of atherosclerosis and the early slowing of progression.

Primary prevention of atherosclerosis is feasible, as has been shown by follow-up of the Multiple Risk Factor Intervention Trial cohort and studies of the Chicago, Ill, occupational cohorts.\(^\text{17}\) The lowering of LDL-C to \(\approx 100\) mg/dL, control of systolic blood pressure to \(< 120\) mm Hg, and prevention of cigarette smoking and an increasing waist circumference will likely prevent the development and progression of atherosclerosis in most of the population. Our recent data from the Healthy Women Study suggested an LDL-C \(\leq 94\) mg/dL and HDL-C \(\geq 64\) mg/dL at a mean age of 47 years is associated with a 70% probability for a CAC score of zero 15 years later at age 62 years among nonsmoking women. Clearly, primary prevention of atherosclerosis, which is only given lip service in current NCEP guidelines, would have the greatest overall effect on CHD rates and the health of the population.

The MESA group\(^\text{1}\) suggested that a trial is needed to determine whether individuals with high CAC scores but who are not candidates for drug therapy based on the NCEP guidelines would benefit from aggressive risk factor modification with drug therapy. Such a trial is unnecessary and probably unethical given the evidence that subclinical measurements are highly correlated with atherosclerosis\(^\text{18}\) and predict clinical CHD events even within FRS classifications,\(^\text{7,8,18}\) and given that slowing of progression,\(^\text{2,4}\) at least with pharmacological therapies, is feasible and is associated with a reduction in the risk of CHD.\(^\text{19}\) The efficacy of LDL lowering to reduce risk of CHD in both primary and secondary prevention has been established with multiple studies.\(^\text{16}\) The small increased benefits of new secondary prevention studies are valuable but not really as important as primary prevention of atherosclerosis.

Trials are needed to determine the best approach to preventing the progression of atherosclerosis for both men and women. We have estimated that the incidence of new CAC for women aged \(\geq 50\) years is \(\approx 6\%\) per year, which results in \(\approx 80\%\) of women having CAC by the age of 80 years.\(^\text{20}\) We do not know the mix of diet, exercise, and lipoprotein modifications that will prevent and slow atherosclerosis for the majority of adults in the United States.\(^\text{21}\)

The major limitations of the use of subclinical measurements are cost and reproducibility when used in a broader clinical setting. Much of the screening can be automated. The cost of drug therapy will drop substantially. The safety of the drugs has been well-established. The major issue, therefore, will be the proper use of the drugs in reducing the risk of atherosclerosis and CHD in combination with diet, exercise, and modification of other risk factors. Is it logical now to put middle-aged, healthy individuals on lifelong lipid-lowering therapy without knowledge of the presence of subclinical atherosclerosis? The amount of subclinical disease and risk of CHD among older individuals, especially men, is so high that probably all should be considered at high risk until proven otherwise.

We should abandon the statistical gyrations of trying to position the FRS against subclinical atherosclerosis. The FRS is not in competition with the measurement of subclinical atherosclerosis but provides the basis for estimating the likelihood of presence or extent of subclinical atherosclerosis, especially for middle-aged individuals. Because of variations in host susceptibility, ie, genetic factors, variability of the risk factor measurements over time, and the incubation period, risk prediction of the extent of atherosclerosis is limited except at extremes. The combination of the FRS and measures of subclinical disease is probably better than the use of either alone.

MESA\(^\text{1}\) described the failure of implementation of primary prevention within the NCEP guidelines. The guidelines are out of date and do not focus on primary prevention. The need is not for another study to prove that we could not implement the current NCEP guidelines in practice but rather to replace these guidelines with much simpler approaches based on the ability to image atherosclerosis and vascular disease.

We have been remarkably successful in reducing CHD mortality in the United States; however, we clearly can do much better. We need a much better commitment to primary prevention of atherosclerosis, with objective proof of efficacy and effectiveness in the community. Doing good and having good results are, unfortunately, not the same thing.

Disclosures

None.

References

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