Editorial

Health Policy on Blood Cholesterol

Time to Change Directions

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A U-shaped association between the level of blood cholesterol and subsequent mortality has been reported in many studies over the past two decades.[1-3] The right-hand limb of the U is the well known higher risk of death from coronary heart disease (CHD) at higher levels of blood cholesterol; this positive association, shown in clinical trials to be causal and reversible, is the cornerstone of U.S. policies directed at lowering high blood cholesterol.[4] The left-hand limb of the U is the higher risk of deaths from non-CHD causes at lower levels of blood cholesterol; the basis for this negative association remains poorly understood, and its implications for health policy have received inadequate attention.[5,6]

This issue of *Circulation* contains a report on the 1990 National Heart, Lung, and Blood Institute Conference on Low Blood Cholesterol: Mortality Associations that presents a statistical overview of available cohort studies. The unprecedented size of the study (68,406 deaths)

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provides a unique opportunity to examine cause-specific mortality at the low end of the cholesterol distribution in both sexes. In the women, moreover, there are unexpected findings pertaining to the right-hand, high cholesterol limb.

Low Blood Cholesterol and Noncardiovascular Deaths

Beginning with the left-hand limb, the study finds a significantly increased risk of noncardiovascular death in both men and women with total cholesterol levels below 160 mg/dl for a surprisingly large and diverse set of causes. In round numbers, such men had a 20% higher age-adjusted rate of cancer deaths than those with cholesterol levels between 160 and 199 as well as a 40% higher rate of noncardiovascular noncancer deaths; the latter included increased rates of injury deaths (by 35%), respiratory system deaths (by 15%), digestive system deaths (by 50%), and "other" causes of death (by 70%). The respiratory and digestive system death rates showed a graded response throughout the cholesterol distribution, which continued to decline with increasing cholesterol levels above 200 mg/dl. Among women, the patterns of the association between low blood cholesterol and increased rates of various causes of noncardiovascular deaths were similar to those in men, except that the excess in cancer mortality was smaller (about 5%).

What is the explanation for the association between low cholesterol and higher risk of death? Among the five possibilities,[6,7] *chance* is extremely unlikely at the probability values reported. *Bias,* or experimental error, is also an unlikely explanation with such hard end points and high-quality studies. Two statistical sources of bias that are undoubtedly present but do not explain the findings are competing mortality and regression dilution bias. Competing mortality—the fact that if low cholesterol is associated with a low rate of cardiovascular deaths, then more people with low cholesterol will be available to die from other causes—can only have a trivial effect when the large majority (in this case 90%) of the cohort is still alive. Regression dilution bias—the underestimate in the strength of an association caused by random error[8]—means that the true associations between low blood cholesterol and mortality in the population are actually even larger than the effect sizes noted in the pooled sample.

The third possibility, *effect-cause,* has been the favorite until now. Many experts have held, for example, that preclinical cancer already present in some individuals at the time of the blood cholesterol measurement may have lowered the cholesterol level.[2,3] Effect-cause, however, is not likely to explain many of the low-cholesterol associations, because the conference report analyses excluded deaths occurring during the first 5 years after the cholesterol measurement, and a recent report on the largest single cohort has shown the excess in many categories of noncardiovascular deaths—cancer of the lung and liver, pulmonary disease, cirrhosis, and suicide—to continue undiminished for 12 years after the cholesterol measurement.[9] Moreover, effect-cause makes little biological sense for the observed excess of acute causes of death such as stroke or trauma.

The two remaining explanations, as noted in the conference report, are *confounding* and *cause-effect.* Obviously, it is vitally important to know which of these is operating, but at present our ability to make this distinction is limited.

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Confounding would be present if the association between the predictor variable of interest (blood cholesterol) and the outcome (mortality) were a result of both factors being related to a third, confounding factor. Alcohol intake, for example, might both lower blood cholesterol level and be a cause (either directly or through lifestyle companions like cigarette smoking and depression) of cancer, pulmonary disease, cirrhosis, and suicide. The conference report examined this possibility by stratification—looking separately at nondrinkers, light drinkers, and moderate-to-heavy drinkers—and found that low blood cholesterol had similar associations with noncardiovascular mortality in all three strata. Similarly, the associations were present after adjusting for age, blood pressure, body mass indext, and cigarette smoking. It remains possible that improved measurements of these potential confounders would produce different results (e.g., through a better ability to separate out the heavy drinkers); that these potential confounders do explain some of the individual cause-specific associations within the overall noncardiovascular mortality outcome that was examined by stratification; or that other confounders, which were not studied, might have been operating (e.g., socioeconomic status). A recent report from the Whitehall Study[10] indicates that lower socioeconomic status and health state at baseline may partly explain the association between low blood cholesterol and respiratory deaths and suggests that better measures of these phenomena might have more completely explained the association. The Whitehall Study was too small to examine most of the cause-specific associations between low blood cholesterol and mortality noted in the conference report.

A second strategy for distinguishing between confounding and cause-effect is to consider other lines of evidence that contribute to causal inference. Randomized blinded trials are the best such evidence because the role of confounders, whether measured or not, is limited to chance maldistributions that are taken into account in the tests of statistical significance. The randomized trials of cholesterol interventions are summarized briefly in the conference report and examined in detail elsewhere.[11–17] Alarmingly, meta-analysis of primary prevention trials reveals higher rates of noncardiovascular deaths in men receiving active treatment to lower their blood cholesterol level; these increases are statistically significant for both injury and cancer mortality. Although this finding is not present in the secondary prevention trials,[13,18] statistically significant results in randomized trials strongly suggest causality.

Interventions that change blood cholesterol from high to moderate levels might well influence disease rates through biological mechanisms that differ from those responsible for the effects of native low blood cholesterol levels in people who have not received an intervention. Therefore, despite the superficial similarities (increased rates of dying from cancer and injuries) between the clinical trial findings and the epidemiological findings, the two sets of results may be unrelated. The clinical trial findings may represent adverse effects of drugs, especially the fibric acid derivatives clofibrate and gemfibrozil, more than effects of dietary intervention.[14] The epidemiological findings of higher death rates from various causes in those with cholesterol levels below 160 mg/dl are probably a mixed bag, due to confounding, partly to effect-cause, and partly to cause-effect through mechanisms to be clarified.[19–22]

High Blood Cholesterol and Cardiovascular Deaths in Women

Before considering policy implications, we will turn to a second major finding in the conference report. The right-hand limb of the cholesterol-total mortality curve is almost flat in women; Figure 1 and Table 3 of the report show that among women high blood cholesterol is not associated with all-cause mortality nor even with cardiovascular mortality.

This surprising observation is explained partly by the fact that cardiovascular deaths are comprised not only of deaths caused by CHD but also of those caused by other vascular diseases, including stroke. Looking just at CHD mortality (in Table 6 of the Jacobs et al conference report and in a meta-analysis by Manolio et al[23] from another recent National Institutes of Health conference) reveals the expected positive association; the risk ratio is almost as large for middle-aged women as it is for middle-aged men. Neither of these reports examines the relation between blood cholesterol and stroke, but other studies have established the existence of a significant negative association between the blood cholesterol level and risk of death from hemorrhagic stroke in men[24,25] and in women.[24] Hemorrhagic stroke, although much less common than CHD in both sexes, makes up a higher proportion of the total cardiovascular deaths in women because of their lower CHD rates.[26]

Therefore, in middle-aged men the negative association between blood cholesterol and hemorrhagic stroke death is numerically less important than the positive association with CHD death.[25] However, in middle-aged women it may be that this negative association (perhaps combined with negative associations for other components of cardiovascular death) has a substantial impact on the association between high blood cholesterol and overall cardiovascular death rates. This has implications for policy decisions on preventing cardiovascular disease in women.

We are coming to realize that the results of cardiovascular research in men, which represents the great majority of the effort thus far, may not apply to women. Although the proportion eventually dying of CHD is similar in the two sexes, the disease occurs 7–10 years later in women than in men. Low high density lipoprotein cholesterol may be a stronger risk factor and high low density lipoprotein (LDL) cholesterol a weaker risk factor in women than in men.[27] The attenuation of the strength of the cholesterol-CHD association in the elderly may be more pronounced in women than in men.[23] Blood cholesterol appears to be a risk factor for CHD recurrence or death among women who already have CHD, as it is in men.[28] However, almost all of the cholesterol-lowering intervention trials have been carried out in men. In women, we are limited to studies of intermediate outcomes, angiographic studies that have shown regression in atherosclerotic lesions after lowering LDL cholesterol levels among women with familial hypercholesterolemia.[29]

Conclusions

In summary, the field of cardiovascular disease epidemiology has recently been enriched by two new

bodies of evidence that have non-CHD deaths as outcomes of interest: one in the arena of observational cohort studies and the other in the arena of randomized clinical trials. Both bodies of evidence are based on meta-analyses that combine eligible studies to produce enough power for examining cause-specific mortality patterns. The findings call into question policies built over the past several decades on evidence that focussed only on CHD as the outcome. We are led to three conclusions: two related to the cohort study findings and one to the clinical trial findings.

First Cohort Study Finding

There is an association between low blood cholesterol and noncardiovascular deaths in men and women. There is no longer any doubt that the 6% of middle-aged adults with cholesterol values below 160 mg/dl are at increased risk of dying from a variety of causes, which includes lung cancer, other noncolon cancers, respiratory disease, digestive disease, trauma, hemorrhagic stroke, and other residual causes. While we await evidence on the causal basis for each of these associations (which probably differs for the different outcomes), it may be time to review national policies aimed at shifting the entire population distribution of blood cholesterol to the left.[5] A cholesterol-lowering diet may not be prudent[30] for those adults whose cholesterol levels place them on the left-hand limb of the total mortality U.

Second Cohort Study Finding

There is no association between high blood cholesterol and cardiovascular deaths in women. In contrast with the evidence for men, there is a surprising absence of association between high blood cholesterol and cardiovascular deaths in women. It appears that this is partly caused by a negative association between blood cholesterol and hemorrhagic stroke deaths, which counterbalances the positive association between blood cholesterol and CHD deaths (which are less numerous in women than in men among the middle-aged). While the causal basis for these phenomena. The sex difference calls into question the general practice of extrapolating to women the findings from epidemiological studies and clinical trials in men. With the exception of those who already have coronary disease or other reasons for being at a comparable very high risk of CHD death, it no longer seems wise to screen for and treat high blood cholesterol in women.

Randomized Trial Finding

Primary prevention trials of cholesterol intervention reveal an increase in non-CHD death rates that is similar in magnitude to the decrease in CHD death rates. It is only in secondary prevention trials of patients at high risk because they already have coronary disease that beneficial effects of cholesterol intervention on mortality have been observed. For primary prevention in patients who do not yet have manifestations of coronary disease (or other reasons for being at a comparable very high risk of CHD death), it now seems unwise to treat high blood cholesterol with drugs.

This last conclusion fits with the Canadian policy of not screening or treating high blood cholesterol in young adults, which is based on the very poor cost-effectiveness of doing so in this low-risk segment of our population.[31,32] It also fits with a growing set of recommendations by other experts.[14,16,33–35]

These three conclusions indicate the need for a change in direction for cholesterol policy. Efforts to identify and treat people with high blood cholesterol have been gaining momentum for several decades and have now reached the point that some experts recommend screening and treatment for blood cholesterol in children. The new evidence on non-CHD causes of death makes it clear that this pediatric policy is unwise[11,36] and indicates that we should draw back from universal screening and treatment of blood cholesterol for primary prevention in adults as well.

This change in direction—limiting cholesterol screening and intervention to the minority in our population for which the benefits clearly predominate over the harms (those with coronary disease or other reasons for being at a comparable very high risk of CHD death)—will not be easy. However, a willingness to be patient while we sort out the causal basis for the increases in non-CHD deaths rests on firm ethical grounds. The overriding ethical obligation is to do no harm. Particularly when considering the long-term use of drugs for people who are in good health, the burden of proof falls on the proponents of the intervention.[14,37,38] We need now to pull back our national policies directed at identifying and treating high blood cholesterol in the primary prevention setting and put on hold well-meant desires to intervene while we await convincing evidence that the net effects will be beneficial.

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