Editorial

Serum Cholesterol
Doing the Right Thing

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A recent editorial in Circulation1 calls for a “change in direction” of health policy on blood cholesterol. It proposes to “pull back” and “put on hold” the underlying strategy of the present cholesterol control program. The thrust of the editorial is to give up populationwide efforts to achieve, by dietary means, a healthier lifestyle aimed at shifting downward the present too-high cholesterol level. It proposes to abandon efforts to identify in the general population large numbers of people with definite hypercholesterolemia. Instead of the current combined populationwide and high-risk strategy, the editorial urges that the cholesterol control effort be limited to “those with coronary disease or other reasons for being at a comparable very high risk of CHD [coronary heart disease] death.” This advice means giving up on primary prevention of CHD and letting stand, for most people, the unfavorable lifestyle patterns—particularly nutritional—that promote atherogenesis and underlie the CHD epidemic.

The present national health policy to turn back the coronary epidemic has developed since 1961 and is based on considered and reconsidered assessments of the scientific evidence. Its foundation is the extensive concordant data accrued with use of every research method—animal experimental, pathologic, clinical, and epidemiologic.2-16 The cornerstone of this policy has been improved lifestyles (better nutrition, smoking cessation, and more physical activity). While quantitative estimates of the impact of favorable changes in specific risk factors can be of only limited precision,17-23 it is reasonable to infer that implementing this policy—including its nutritional recommendations related to serum cholesterol—has contributed to the remarkable 50% reduction in coronary and cardiovascular disease death (CVD) that has occurred since the 1960s and to the years added to life expectancy for adults. This policy to combat the coronary epidemic is apparently a winner. Why then abandon or drastically revise it?

The editorial by Hulley et al1 gives three reasons to justify “put[t]ing on hold” this strategy for primary prevention of CHD: (1) an observed “association between low blood cholesterol and noncardiovascular deaths in men and women”; (2) “no association between high blood cholesterol and cardiovascular deaths in women”; and (3) in primary prevention trials of cholesterol intervention, observation of “...an increase in non-CHD death rates that is similar in magnitude to the decrease in CHD death rates.”1 Are these claims sound? Are they based on proper assessment of all the data available?

Low Cholesterol and Death Rates From Non-CVD Diseases

The decisive issue is whether low blood cholesterol causes higher non-CVD mortality rates. A valid answer to this question can be obtained only by studying cholesterol-mortality associations for specific diseases, given their varied etiologies. The cited editorial states it considered cause-specific mortality for a “...large and diverse set of causes,”11 but careful reading shows this is inaccurate. In fact, it relied on data from an overview24 that did not report on the relation of cholesterol to cause-specific mortality for a “large and diverse set of causes” but rather for only four specific causes of death—CHD, colon cancer, breast cancer, and lung cancer. These data showed that for CHD, the lower the cholesterol, the lower was the death rate; for colon and breast cancer, no significant differences in death rates were related to serum cholesterol level. For lung cancer, low cholesterol was significantly associated with excess lung cancer deaths among the large cohort screened for the Multiple Risk Factor Intervention Trial (MRFIT), dealt with separately in the overview (see below). All the remaining data on cholesterol and mortality were presented in the overview for broad categories such as “respiratory diseases,” “digestive diseases,” and “trauma,” but these broad categories are of limited or no use for assessing disease causation. For example, respiratory diseases involve 50 separate disease entities in the International Classification of Diseases, 9th Revision (ICD-9).25 The same is true for “digestive diseases” (50 entities) and even more so for traumatic causes of death.

For information on the relationships of low serum cholesterol to cause-specific mortality, the most extensive data are from the 12-year follow-up of more than 350,000 men screened for MRFIT.26 Findings are published on 22 specific diseases, including 19 non-CVD causes of death. As expected, for the MRFIT men, the lower the cholesterol, the lower was the mortality rate from CHD, the largest single cause of death. The CHD death rate for those with cholesterol of less than 160

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mg/dL was one third that of men with a level of 240 mg/dL or higher. For nonhemorrhagic stroke and diabetes as well, the lower the cholesterol, the lower was the death rate.

However, for the 6% of men with cholesterol of less than 160 mg/dL, there was a significant excess of deaths persisting over time from nine specific causes: lung cancer in heavy smokers, chronic obstructive lung disease in smokers, hepatic cirrhosis, alcohol-dependence syndrome, liver cancer, suicide, lymphatic and hematopoietic cancers, and intracerebral hemorrhage in hypertensives.26 These associations pose a question about cause-and-effect—they do not give an answer. For these diseases, is low cholesterol a marker for other causative factors rather than a cause itself? It should be noted that the first four (and most common) of these nine specific causes of death are overwhelmingly due to smoking and/or heavy drinking, and for two remaining causes—liver cancer and suicide—heavy drinking is a known major risk factor for excess death.

For eight other specific non-CVD causes of death, there was either no evidence of an inverse relation to cholesterol level (eg, colon cancer) or only a weak nonsignificant association that tended to diminish over time (eg, esophageal and rectal cancer, injuries).27 For one cause (pancreatic cancer), there was a significant inverse association; this also diminished over time, suggesting that preexisting disease at the time of screening produced the low cholesterol and not vice versa. Other data sets also show a diminution over time in low cholesterol—cancer associations.29-31

A mortality pattern similar to that in MRFIT was reported by the Whitehall Civil Servants Study of more than 17,000 men followed for 18 years.32 There, too, specific diseases related to heavy smoking and alcohol made up much of the excess non-CVD mortality in the low-cholesterol group.

Data from both studies suggest that the low end of the cholesterol distribution in middle-aged adults includes—together with healthy people—a disproportionate number of people who are already ill or have occult disease or unhealthy lifestyles, traits tending to both lower cholesterol and increase risk for the cited diseases.

The tendency for serum cholesterol to fall with development of some chronic diseases is documented in the 6-year trial of the more than 12,000 men randomized into MRFIT. Both cholesterol and weight declined markedly in the 1 or 2 years before death from cancers in both the intervention and usual care groups.31 Cholesterol also declined more in the 116 men who developed hepatic cirrhosis—on average by 19.6 mg/dL during the years of the trial, compared with 9.5 mg/dL for the 11,919 men who were free of cirrhosis. At baseline in the Whitehall Study, cholesterol was lower in men with respiratory symptoms, with low FEV1, unexplained weight loss, and lower socioeconomic status.32 These factors largely accounted for the inverse relationship observed between cholesterol level and non-CVD mortality.

Several additional studies demonstrate that when dealing with a healthier population sample—healthier either by selection of participants or because of younger age—excess death rates in those with low cholesterol are either absent or much less evident. One such data set is from the Honolulu Heart Study, with a 23-year follow-up of 8006 men of Japanese ancestry.33 The investigators divided the group into a “confounded” stratum—heavy drinkers or heavy smokers or those with medical conditions such as gastrectomy, cirrhosis, colectomy, or intestinal diseases. In comparing this “confounded” group (n=1874) with the remaining “healthy” group (n=6132), the investigators found excess all-cause mortality with low cholesterol only in the “confounded” stratum. They concluded that “… the increased mortality among [those] with low cholesterol is explained by habits and medical conditions present at baseline.”33

In the WHO trial of the drug clofibrate,34 two control groups were established—one with high cholesterol (mean, 247±29 mg/dL) and one with low cholesterol (mean, 181±29 mg/dL). Entry criteria excluded men with prior CVD, malignancies, cirrhosis, or renal disease. Follow-up was for more than 10 years. In this relatively healthy cohort, for the more than 5000 men with low cholesterol, not only was CHD mortality 59% lower than for the 5000 in the high-cholesterol group and CVD mortality 54% lower, but also the cancer death rate was 12% lower and the rate for death from accidents and violence was 15% lower. Other medical deaths were equal in the two groups; all-cause mortality was more than one third lower in those with low cholesterol.

The recently published 14-year follow-up of the representative sample of the US population first examined in NHANES I in 1971 through 1975 notes disappearance of excess deaths in the low-cholesterol group after 10 years (suggesting preexisting disease when cholesterol was measured).35 It also reports that excess deaths were concentrated in older persons who were inactive and/or had a history of significant weight loss. The authors conclude that “… underlying health status rather than a mortality-enhancing effect of low cholesterol likely accounts for the excess risk of death among persons with low cholesterol.”36

Recent data on long-term follow-up of young people—generally those who were too young when first examined for major preclinical disease to have been the cause of low cholesterol—show a direct impact of cholesterol on both CVD and non-CVD mortality.37 There was no evidence of excess mortality with low cholesterol. Male medical students at The Johns Hopkins University (average age, 22 years) had repeated serum cholesterol measurements during their student years. After graduation, they were followed for as long as 42 years. Risks of subsequent cardiovascular disease, coronary disease, CVD mortality, non-CVD, and all-cause mortality were lowest in the lowest cholesterol quartile (118 to 172 mg/dL; mean, 158 mg/dL). Of the 1017 examined, 97 developed CHD at an average age of 53 years. Risk of heart attack was fivefold higher for the 25% of men who had the highest cholesterol levels (mean, 231 mg/dL) than for the 25% with lowest cholesterol (35% versus 7%).

Findings are similar for the more than 7800 young white men, ages 25 to 39, examined in the Chicago Heart Association Detection Project in Industry (CHA). With 15 years of follow-up, risk of coronary death was 14-fold higher in those with cholesterol of 240 mg/dL or greater than in the low-cholesterol (less than 160 mg/dL) group. Cancer death rates were more than
double, and all-cause mortality was more than fourfold higher with high versus low cholesterol.

In conclusion regarding the editorial’s first reason, all the above data sets reinforce the conclusion that there is, in fact, no convincing evidence that low cholesterol causes excess mortality. However, the data on specific diseases with a persistent relation of low cholesterol to excess risk warrant three policy recommendations for public health and medical care. First, since several of these specific diseases are overwhelmingly due to heavy smoking and alcohol abuse, efforts to prevent and control these addictions must be intensified at both the public health and clinical levels. Second, to reduce further the incidence of intracerebral hemorrhage, efforts to prevent and control high blood pressure need to be continued and enhanced. Third, since people with low cholesterol are a mix of healthy and not healthy individuals, those for whom low cholesterol is a marker of adverse causes—genetic, nutritional, addictive, and metabolic—need to be identified early so that clinical attention is given to diagnosis and treatment. Conversely, those whose low cholesterol is due to healthy lifestyles and/or favorable genetic makeup need to be reassured and encouraged to maintain their healthy lifestyles.

High Blood Cholesterol and Cardiovascular Deaths in Women

The editorial states that “in contrast with the evidence for men, there is a surprising absence of association between high blood cholesterol and cardiovascular [emphasis added] deaths in women.” This statement is not supported by the data on US women. Among cardiovascular deaths in women ages 25 to 74, more than half are from CHD, and there are abundant data showing that risk of CHD death markedly increases with higher cholesterol in both men and women. In Framingham, for example, with a cholesterol level higher by 40 mg/dL, the risk of coronary death for those aged 35 to 64 is increased 38% in men and 32% in women; in the Chicago Heart Association Study, these increased risks are 34% and 20% for middle-aged men and women, respectively; and for ages 60 to 74, CHD mortality risk with cholesterol 40 mg/dL higher is greater by 18% for men and 30% for women. With this large increased CHD mortality risk with higher cholesterol and with CHD deaths constituting a majority of CVD deaths, it is not plausible for there to be no association between cholesterol level and all cardiovascular mortality.

To support the statement that there is no increased cardiovascular risk for women with higher cholesterol, the cited editorial referred again to the overview report that included six US studies and five from abroad. Again, careful reading of the overview, with attention to details, shows this to be an inaccurate conclusion. In fact, the pooled data from the 11 studies show a CVD death rate 14% higher for women with serum cholesterol of 240 mg/dL or more compared with those with less than 160 mg/dL. Furthermore, in multiple regression analyses, nine of 11 population samples—the six from the United States—had a positive relationship between serum cholesterol and risk of CVD death for women.

The overview did not present data on individual studies, but examination of data from multiple studies of US women documents that, as for men, the higher the serum cholesterol, the greater is the CVD mortality risk. In the Framingham study, cholesterol higher by 40 mg/dL increased risk of CVD death in women ages 35 to 64 by 32%. In the Chicago Heart Association Study, this increase in risk was 17% for women both ages 40 to 59 and 60 to 74 at baseline. In the Rancho Bernardo study, CVD death rate in women ages 40 to 79 was 30% greater with cholesterol 40 mg/dL higher. In the Lipid Research Clinics follow-up for women ages 40 to 69, a 40 mg/dL higher cholesterol predicted a CVD death rate higher by 26%. For women in the Systolic Hypertension in the Elderly trial, ages 60 and above at entry, the positive correlation of serum cholesterol with CVD death was also evident. CVD death rate was 13% higher with cholesterol higher by 40 mg/dL. All the above analyses were age adjusted, and most were also adjusted for other major risk factors, eg, smoking and blood pressure.

Thus, a review of key studies in women in the United States confirms two truths that are part of the foundation for the public health policy seeking to encourage lower levels of cholesterol in women as well as in the whole population—cardiovascular mortality in women is high in our country, and there is a positive relation between cholesterol level and CVD deaths in women as well as in men. These data provide no justification for the called-for change in that policy.

Non-CHD, CHD, and All-Cause Mortality in Trials to Lower Serum Cholesterol

The cited editorial points to meta-analyses of findings in primary prevention trials to lower cholesterol and concludes that they show an increase in non-CHD deaths similar in magnitude to the decrease in CHD death rates. This then becomes the third reason to discontinue identification or treatment of elevated cholesterol in the general population. But can one judge whether lowering cholesterol is beneficial or has a neutral or even harmful effect by combining data from selected trials, regardless of the means used to lower cholesterol? What if results truly differ by type of intervention? By type of participant? Or by length of follow-up? What if results from different trials cancel each other out, eg, with one type of drug showing an adverse effect while lifestyle intervention shows a favorable effect? Can one validly conclude from a meta-analysis of such trials whether lowering cholesterol was useful unless detailed attention is given to their diverse nature, particularly their means of intervention? A brief review of these trial features follows.

Reports from meta-analyses deal with as few as six and as many as 32 trials. Of the 32, a majority were secondary prevention trials, and the editorial agrees that cholesterol lowering is useful for people with clinical CHD. Reports are available from 13 primary prevention trials.

Among these 13 trials, there was a mixture of drug and lifestyle interventions, unifactor and multifactor. Six different drugs were used, including two fibrac acid derivatives, lovastatin, probucol, and two resins. There were two types of nutritional intervention: a diet involving a high intake of polyunsaturated and therefore of
total fat, and a diet like that recommended by the American Heart Association and the National Cholesterol Education Program.

Results reported from meta-analyses of these trials have depended on the trials selected, a process fraught with risk of introducing bias. Thus, one meta-analysis, cited in the editorial as demonstrating unfavorable effects on non-CHD and all-cause mortality, selected only six of the 13 primary prevention trials. The six trials selected used either a high-polysaturated diet or a drug as the single treatment to lower cholesterol.

Three multifactor trials—not included in that meta-analysis—are of particular importance for the present overall national policy for primary prevention of CHD, which includes nutritional efforts to achieve healthier levels of cholesterol, elimination of smoking, and control of high blood pressure. These trials, the MRFIT, Oslo, and WHO European Collaborative trials, are the only ones among all the clinical trials that lowered serum cholesterol with a diet like that being recommended by US policy—reduction in intake of total fat, saturated fat, and cholesterol and only a moderate increase in polyunsaturated fat. This diet was their only intervention to lower blood cholesterol. (The fourth such multifactor trial was minimally successful in its intervention.)

Particularly because two of these three trials were of large size, inclusion—or exclusion—of their findings in a meta-analysis strongly influences its results. Each of these trials was designed with a sample size estimated to give high statistical power to detect a significant influence of multifactorial intervention on CHD but not on all-cause mortality. Nevertheless, each had favorable results not only for CHD (incidence, mortality) but also, with long-term follow-up, for death from all causes. The WHO trial involved more than 60,000 working men from 40 pairs of factories that were randomly assigned to intervention and control. Intervention was associated with reductions of 10.2% in total CHD events (P = 0.07) and 5.3% in all deaths (P = 0.40). Regression analyses assessed the relation of net changes in risk factor scores for men in intervention versus control factories (40 pairs). Greater net decrease in risk factor score during the trial for intervention men was significantly related to greater reduction in fatal CHD, all CHD, and all deaths (P < 0.05, two-tailed test). In MRFIT, with 10.5 years of follow-up of the 12,866 men, mortality rates were lower for the special intervention than for the usual care group by 10.6% for all CHD (P = 0.12, one-tailed test), 24.3% for acute myocardial infarction (P = 0.02), and 7.7% for all causes (P = 0.10). The Oslo trial involved 1232 hypercholesterolemic men, almost 80% were smokers, and all were nonhypertensive. Nutritional recommendations led to a sustained net decrease in serum cholesterol of the intervention men, on average 10%, more than that achieved in the WHO and MRFIT intervention groups. Influence on smoking was modest, with a quit rate of 24% in the intervention group and 17% in the controls. At the end of the planned 5 years of intervention, incidence of major CHD events was 47% lower in the intervention than in the control group (P = 0.028, two-tailed test); CHD mortality was 56% lower (P = 0.06); and all-cause mortality was 31% lower (P = 0.246). At 15-year follow-up, CHD mortality was 48% lower in the intervention than the control group (P = 0.006, two-tailed), and all-cause mortality was 26% lower (P = 0.056, two-tailed test). None of these three trials showed excess non-CVD mortality in the intervention groups.

The control group in each of these studies had a larger number of nonfatal coronary events than the intervention group during the trial. Data from MRFIT show that those who had such a nonfatal attack had considerably higher death rates in subsequent years. This increased the differences over time between the randomized groups in death rates from both CHD and all causes. This finding emphasizes the importance of achieving healthier levels of serum cholesterol for prevention of first heart attacks, ie, primary prevention, and not restricting efforts— as the cited editorial suggests—to secondary prevention only.

A word of caution is appropriate here. The above comments should not be interpreted to mean that all questions are resolved on the issue of the most appropriate means to reduce the risk associated with high cholesterol. One meta-analysis of 22 published trials (again, not all trials) reports an overall 9% higher non-CHD death rate in intervention versus control groups, made up of a significant 27% higher rate in 13 trials where drugs were used to lower cholesterol (again, combining varied classes of drugs) and a nonsignificant 3% higher rate in eight dietary intervention trials plus one mixed diet-drug trial. A similar distinction between drug and diet trial results was made in a meta-analysis of eight primary prevention trials. It is an old truism that there is no such thing as a risk-free drug, and this means that if and when drug treatment is used to lower cholesterol, careful monitoring is needed in both trials and practice. It means also that trial evidence of safety as well as overall benefit of individual drugs is clearly important. The experience with clofibrate is a sobering example: in the WHO clofibrate trial, the intervention group had a non-CHD death rate 70% higher than the control group, with about half this excess in cancer deaths.

But this caution about drugs, or about certain drugs, cannot and should not be used to divert us from the main thrust of prevention—ie, a populationwide effort to reduce the exposures, mainly nutritional, that are responsible for the high cholesterol found in a majority of US adults and that underlie the still high coronary incidence and mortality rates in our country. The national consensus and effort to improve cholesterol levels in the United States have never proposed drug treatment as a central means to accomplish this. Rather, the thrust has been a widely based undertaking to help all Americans—young, middle-aged, and older—to lessen unfavorable exposures common in the US diet, including high total fat, high saturated fat, high cholesterol, and high calories. The recommendation has also been to reserve use of cholesterol-lowering drugs for those at highest risk when dietary intervention is not sufficiently effective in lowering this risk. Appropriate concern to limit the numbers on long-term drug treatment requires intensified efforts on populationwide and individual bases for improved lifestyles to shift population cholesterol levels down and thereby reduce numbers of people possibly needing drugs—not retreat in
the cholesterol control program, as the cited editorial proposes.

Conclusion

How can we judge if we are "doing the right thing" in supporting current national policy aimed at lowering blood cholesterol in the general population for both primary and secondary prevention of CHD? The cited editorial suggests we put a hold on such efforts, at least for primary prevention, "while we await convincing evidence that the net effects will be beneficial." But where does this leave us? A do-nothing policy is also a policy; it, too, needs to be supported by convincing evidence. It is our judgment, as detailed above, that the evidence relied on in the cited editorial is not convincing. On the other hand, overwhelming evidence accumulated over decades has clearly demonstrated that there is a causal relation among atherogenic diet, high serum cholesterol, and coronary heart disease. If we put on hold the present national efforts to break this chain of causation, then this in effect is telling the American people that the healthiest way of living and of eating is the status quo—or really, the status quo of 30 years ago, before the American Heart Association dietary recommendations and before the public began to listen to and make changes based on these recommendations to reduce coronary risk. If the advice of the editorial is accepted, then efforts to adopt a healthier diet and achieve healthier levels of cholesterol would be restricted to those already having heart disease and to other adults with equally high risk. But once heart disease is present, risk of premature death increases severalfold. And for many people, secondary prevention is not an option since a high proportion of CHD deaths occur with first attacks, often as sudden death. Moreover, most CHD deaths occur in the large number with "moderate" risk. With our modern atherogenic diet, the first stages of atherosclerosis start in youth. Studies of young men who died of accidental or violent causes demonstrate not only the high frequency of atherosclerotic lesions even in adolescent and young adult years but also a significant relation between extent and severity of lesions and serum LDL plus VLDL as well as cigarette smoking.65 Findings in this autopsy study and the high coronary mortality rates reported above in the cohorts of young adults37 show that young people are not, as the cited editorial claims, a "low-risk segment of the population." On the contrary, these findings highlight the need for primary prevention, beginning early in life, of the major risk factors, including increased cholesterol.9,12-16,64

Is there evidence to judge if the present national policies are helping achieve this goal? The best answer is our national experience since populationwide prevention programs were undertaken. The American public, with increasing awareness that CHD is an epidemic that is preventable, has made important (although not yet sufficient) changes in dietary practice, with decreases in foods high in saturated fat and cholesterol—high-fat meat, butter, lard, eggs, and whole milk—and with increases in consumption of poultry, fish, low-fat and skimmed milk, vegetables, and fruit.64-67 Mean serum cholesterol data from population surveys indicate a fall for middle-aged men from about 233 mg/dL in the late 1950s to 211 mg/dL in the period 1976 through 1980, with a similar trend in women and with continuation of these trends in the 1980s.64,66-68 Parallel with the trends in diet and serum cholesterol have been the remarkable declines in mortality—eg, for the years 1967 through 1987, the CHD death rate was down 46%; the rate for all major CVD causes was down 42%; the rate for all non-CVD causes was down 11%; and the rate for all causes was down 26%, 38,69,70 While those parallel trends are consistent with cause-and-effect, they are not proof positive, but there are data available that do permit a test of the etiologic relationship. It is known that favorable changes in eating patterns as well as in smoking cessation and increased physical activity of leisure have more often been made among the more educated and more affluent.64-68,70-72 If there is a causal relation between national lifestyle trends and mortality trends, then the decline in mortality should be greater in the more educated and affluent than in other strata. There are now five studies reporting that this is so.73-77

Even though favorable trends are encouraging, we still suffer in the United States from unacceptably high coronary disease rates, with some lifestyle trends among young people (dietary, smoking) being cause for great concern. There are even indications in the past year of a falling away from the new healthier behaviors among adults.78

The present national policy to lower cholesterol in the general population, mainly through appropriate nutritional means, has the added merit that the recommended healthier eating patterns can be beneficial in preventing or controlling other chronic diseases as well as coronary disease.10,12,15 There is no sound evidence that justifies a withdrawal from this policy. On the contrary, we need to expand and intensify efforts to achieve its goals.

References


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