Special Report

Cholesterol Lowering as a Treatment for Established Coronary Heart Disease

John C. LaRosa, MD, Dean for Research, The George Washington University Medical Center, Professor of Medicine and Health Care Sciences, Director of the Lipid Research Clinic, and James I. Cleeman, MD, Coordinator, National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health

There is convincing evidence, based on animal and human experiments, population studies, and clinical trials, that cholesterol-lowering intervention is important in the treatment of patients with documented coronary heart disease (CHD). Nevertheless, inadequate attention has been paid to cholesterol lowering in patients with CHD, in part because of the emphasis previously placed on indexes of myocardial function as predictors of the course of coronary disease.1

On September 4–5, 1991, the American Heart Association and the National Heart, Lung, and Blood Institute cosponsored a meeting to discuss this issue. Experts in cardiology, lipidology, epidemiology, and health economics suggested approaches to cholesterol intervention in patients with established coronary disease. (The appendix is a list of the participants.) This report is not intended to preempt the recommendations to be developed by the new Adult Treatment Panel of the National Cholesterol Education Program (NCEP), which is being convened to update the existing cholesterol treatment guidelines for adults.

Current State of Affairs

There is considerable evidence indicating that reduction of low density lipoprotein cholesterol (LDL-C) levels is beneficial in preventing recurrent events in patients with established CHD. There is also evidence suggesting that increases in high density lipoprotein cholesterol (HDL-C) levels may likewise be beneficial in reducing the rate of recurrent events in these patients. Such evidence includes observations that LDL-C and HDL-C levels predict the risk of subsequent CHD death rates in both those with and those without established coronary heart disease (CHD).2 In addition, meta-analysis of trials of cholesterol lowering in patients with established disease have demonstrated significant declines in subsequent coronary events and in CHD and cardiovascular disease (CVD) death rates, as well as borderline significant declines in overall or all-cause mortality.3 Finally, regression studies using serial coronary angiograms have demonstrated the arrest of progression and even regression of coronary atherosclerotic lesions with cholesterol lowering induced by drugs,4–6 diet,7 or ileal bypass surgery.8 Both clinical trials and regression studies have shown that cholesterol lowering can be beneficial even in patients with advanced disease.

Current NCEP guidelines for detection, evaluation, and treatment of high blood cholesterol give special attention to patients with CHD9 in recognition of the fact that patients with CHD are at high risk of recurrent events and death; lower initiation and goal levels for cholesterol lowering in these patients are therefore set (Table 1). Thus, the initiation level for diet therapy in patients with CHD is an LDL level ≥130 mg/dl, as opposed to >160 mg/dl in patients without CHD (and with fewer than two other CHD risk factors); the initiation level for drug therapy is an LDL level ≥160 mg/dl, as opposed to >190 mg/dl in patients without CHD (and with fewer than two other risk factors); and the minimum goal for diet and/or drug therapy is to lower the LDL level to <130 mg/dl, as opposed to <160 mg/dl in patients without CHD (and with fewer than two risk factors).

However, recent evidence raises the question of whether even more intensive intervention should be considered in patients with CHD. Both animal10 and human11–8 studies suggest that LDL-C levels ≤100 mg/dl (lower than the current goal of ≤130 mg/dl) may be associated with the best results in terms of the regression or arrest of progression of coronary lesions. If such goals were adopted, evaluation of virtually all CHD patients would require an LDL determination. Current guidelines, however, do not explicitly require determination of lipoprotein profiles in patients with total cholesterol levels of <200 mg/dl but with established CHD.

There is evidence that physicians may be slow to institute cholesterol-lowering interventions in patients with established coronary disease. This appears to be true of general physicians as well as cardiologists. Although it is difficult to identify a precise figure, several studies have suggested that only one third of those with established coronary disease are undergoing treatment to lower cholesterol levels with either diet or drugs.11,12 The reasons for this are incompletely understood, but those suggested by conference participants include

1. The belief that survival after infarction is unaffected by cholesterol intervention
2. The feeling that coronary bypass surgery or angioplasty has cured the problem and that no further intervention is necessary
3. The physician's discomfort about providing nutritional counseling, which may be due to lack of specific nutritional training and information
4. The physician's lack of time to provide preventive counseling, including both nutritional and drug compliance advice
5. Patient resistance to lifestyle changes
6. Poor long-term compliance with drug regimens, due in part to a lack of understanding on the part of patients (and perhaps of physicians) that cholesterol-lowering therapy, like antihypertensive therapy, is a lifetime commitment
7. Concern that cholesterol lowering may have risks, including excess mortality from cancer, hemorrhagic stroke, and violent death (suicides, homicides, and accidents)
8. Concern about the expense of long-term cholesterol lowering and confusion about which physician or nonphysician health professional should provide preventive care to patients with established coronary disease

What Do We Know?

As previously stated, there is considerable evidence that cholesterol-lowering interventions, particularly those that lower levels of LDL-C, will reduce the rate of both fatal and nonfatal events in those with established coronary disease. In addition, there is evidence that increasing HDL levels and lowering triglyceride levels may also be beneficial in these patients. The absolute risk of myocardial infarction is much higher in those with established disease. Control groups in secondary prevention trials have experienced rates of infarction of 6% annually, compared with 1% in primary prevention trials. LDL-C lowering, then, has the potential to prevent many more events in a population with established disease than in one without. The reduction in recurrent coronary event rates by cholesterol lowering compares favorably with other medical therapies, including aspirin and \( \beta \)-blocker, in reducing subsequent events.

Cholesterol lowering is also of value in those who have undergone bypass surgery as well as in those who have undergone angioplasty, although the magnitude of the benefit after these procedures is still under investigation. If the effects of these invasive interventions are compared with cholesterol lowering, it is apparent that bypass surgery and angioplasty provide immediate patency and enhanced coronary blood flow but have uncertain effects on recurrent event rates and subsequent morbidity and mortality. Conversely, lowering of LDL-C levels does little to improve immediate coronary flow but substantially reduces the risk of subsequent coronary events, including both recurrent infarction and coronary death.

At a recent workshop on the issue of low cholesterol levels and total mortality, it was found that statistical confounding was a likely factor in the association between low cholesterol levels and certain diseases, including cancer of the lung, in observational studies. No cause-and-effect relation has been established, and there is little evidence from clinical trials that cancer mortality is increased or, in fact, that the very low levels of cholesterol statistically associated with increased cancer risks are achievable in most patients with coronary heart disease.

In meta-analysis of primary prevention trials, excess mortality from violent or traumatic death, including suicides, homicides, and accidents, has been observed. No such relation has been confirmed in meta-analysis of secondary prevention, nor has any cause-and-effect relation been established. Indeed, these effects are apparently unrelated to cholesterol lowering itself, because many of the patients who suffered violent or traumatic deaths were not undergoing cholesterol-lowering therapy at the time.

Some population studies indicate a relation between very low cholesterol levels and an increased risk of hemorrhagic stroke. Again, direct evidence of a cause-and-effect relation is lacking.

The long-term safety of cholesterol lowering is the subject of continued investigation. The issue of low cholesterol levels and possible disease associations, however, is far less pressing in patients with established CHD. Over 80% of deaths in these patients are from CVD. The risk of death from CHD in such patients far outweighs any small theoretical risk from a low cholesterol level.

Based on several published studies of serial coronary angiography, there is general agreement that cholesterol lowering can slow, halt, or even reverse the progression of coronary atherosclerosis. Only one, the Program on the Surgical Control of the Hyperlipidemias (POSCH), is large enough to explore the relation between arrest of atherogenesis and event rates. Although little regression was observed in this study, arrest of progression was associated with a reduction in coronary events.

Lack of association of regression (as opposed to arrest of progression) with coronary events is not necessarily unexpected. While the most severe lesions demonstrate the most regression with cholesterol lowering, current evidence suggests it is not necessarily the most severe lesions that are ultimately responsible for coronary events.
Cost-effectiveness of cholesterol lowering in those without CHD is a matter of considerable debate when alteration of cholesterol levels, particularly with drugs, is considered in those free of clinical coronary disease. Analysis, however, indicates that cholesterol lowering is cost effective in patients with CHD. In those with hypercholesterolemia (cholesterol levels >250 mg/dl) and CHD who are less than 65 years old (men) or 55 years old (women), models suggest that cholesterol lowering actually saves money by eliminating the cost of subsequent events, including bypass surgery and angioplasty. Because 50% of myocardial infarctions in a community occur in persons with preexisting clinical coronary disease, substantial savings can be expected from treating these patients. Cost considerations, therefore, support cholesterol intervention in patients with established disease.

**Issues Requiring Further Deliberation and Study**

**Selection of Patients for Treatment**

Current NCEP guidelines recommend selection of patients for therapy based on the level of LDL-C (Table 1). Some conference participants suggested that the presence of CHD alone might be a better way to select patients for therapy, since patients have different susceptibilities to coronary disease. It can be argued that patients with CHD, whatever their cholesterol levels, have already demonstrated their susceptibility to CHD and should therefore be treated vigorously.

The first manifestation of CHD, however, may be catastrophic, including sudden death. Therefore, identification of a larger group of susceptible people relies on the development of noninvasive techniques (for example, carotid echocardiography, exercise stress testing, or myocardial imaging techniques) for identifying those with subclinical coronary disease. In fact, this approach has been approximated in the current NCEP guidelines by specifying lower cutpoints for selection for treatment and lower targets for treatment in those with clinically apparent CHD, or those with other coronary risk factors (who, by virtue of those risk factors, are more susceptible to disease). Unfortunately, there is currently no widespread agreement about which noninvasive procedures might be expected to efficiently identify those with subclinical disease. Moreover, if selection involves relatively expensive procedures such as exercise testing, the issue of cost-effectiveness is again an important consideration.

In selecting patients for therapy, it must also be pointed out that half of all patients with CHD have only modest cholesterol elevations (<240 mg/dl). Some may have LDL-C levels in the 100–130 mg/dl range. Relatively little evidence directly addresses the value of cholesterol interventions in persons with CAD yet with these relatively low LDL-C levels. In the Cholesterol Lowering Atherosclerosis Study (CLAS), those with low cholesterol levels had the same degree of regression as those with higher cholesterol levels; again, the implication is that there may be a susceptible population at particular risk. Several field studies are being conducted that will be helpful in further delineating the benefit of lowering LDL-C levels to <130 mg/dl. At present, it is necessary to rely on a few regression studies for evidence of that benefit. Clearly, further research in this area is necessary, both to better identify persons who are susceptible and to determine the value of cholesterol intervention in those without (by current definitions) significant hypercholesterolemia.

Future recommendations to lower LDL-C targets below current levels in those with established disease must take into account the necessity of completing that research. Recommendations should not, if possible, discourage participation in such clinical trials.

**Which Circulating Lipid Fractions Should Be Targets for Intervention?**

**Low Density Lipoprotein Cholesterol**

LDL-C lowering is the primary target of intervention. There is justification, based on both animal and human regression studies, for a target level of LDL-C ≤100 mg/dl in those with established disease, and, in fact, for selecting anyone with an LDL-C level above that (and with established CHD) for either diet therapy or a combination of diet and drug therapy. As noted, enthusiasm must be tempered with the understanding that the benefit of cholesterol lowering to that degree is not yet established.

The conventional sequence of diet therapy before drug therapy is appropriate for patients with coronary disease. Those with established coronary disease, however, may be motivated to try more stringent fat-restricted diets. A lower target LDL-C level, moreover, may require more frequent use of drug combinations. In this respect, combinations of bile acid sequestrants with any of the systemic lipid-lowering drugs are safe and quite effective. Combinations of two systemic drugs, while also efficacious, may increase the likelihood of toxicity. They should be used with both caution and careful monitoring, particularly for evidence of drug-induced myopathy or hepatic dysfunction.

**High Density Lipoprotein Cholesterol**

HDL-C and triglycerides are more problematic targets of therapy. In studies of the regression of coronary disease, regression was associated with both lowering of LDL-C levels and increases in HDL-C levels. There is strong evidence, moreover, from population studies that the HDL-C level is an important predictor of risk in patients with CHD. There is little to suggest, however, that in patients with isolated low HDL-C levels (without elevated triglyceride levels), HDL-C levels can be significantly increased with either diet or drug therapy. A reasonable approach is to attempt to increase HDL-C levels whenever possible, particularly when triglyceride levels are elevated, but to continue to regard lowering of LDL-C levels as the main objective of therapy.

**Triglycerides.** Considerable evidence links elevated triglyceride levels to CHD, particularly when associated with decreases in HDL-C levels, increases in LDL-C levels, or the presence of a particular form of small, dense LDL, which is thought to be particularly atherogenic. Only one clinical trial, the Stockholm Prospective Study, demonstrated that lowering of triglyceride levels was associated with a decline in coronary events. That study did not independently examine the effect of changes in LDL-C or HDL-C levels. However, efforts to lower triglyceride levels, particularly with weight loss, diet, and exercise, are important in correcting associated lipoprotein abnormalities, including low HDL-C levels and increased small, dense LDL.
In its 1988 Adult Treatment Panel Report,3 the NCEP endorsed the conclusions of the 1983 National Institutes of Health Consensus Conference,26 which recommended that drug therapy be considered in persons whose triglyceride levels were ≥250 mg/dl after diet therapy and who also have established CHD, low HDL-C levels, or high LDL-C levels. A recent review of this topic by an international panel recommended essentially the same approach but suggested lowering the triglyceride threshold to 200 mg/dl.13 The subject of elevated triglyceride and low HDL levels was considered by a consensus conference of the National Institutes of Health in February 1992 and is being considered by the new Adult Treatment Panel.

Which Other Lipoprotein Fractions Identify Those Susceptible to Heart Disease?

Measurement of circulating apolipoprotein levels may provide better predictors of coronary risk than more traditional measurements of LDL-C, HDL-C, and triglyceride levels. In particular, apolipoprotein B levels may predict risk even in the presence of normal cholesterol levels,27 although this greatly depends on how a normal cholesterol level is defined. Nevertheless, the lack of a sufficient epidemiological and clinical data base, plus the large coefficient of variation in the measurement of circulating apolipoprotein levels,28 limits their usefulness as parameters for either the selection of subjects for therapy or as targets for therapeutic intervention, and their routine use cannot currently be recommended.

In similar fashion, levels of lipoprotein a [Lp(a)], a strong predictor of coronary risk29 and a potentially powerful detector of persons who are susceptible, cannot currently be recommended for use in selecting patients for therapy. Such a recommendation awaits a better understanding of how to measure Lp(a), how to lower its levels, and what effect manipulation of its circulating levels has on coronary risk.

In summary, the lipoproteins currently targeted for intervention should remain the same. Lowering of LDL-C levels is most important, but in patients with CHD declines in triglyceride levels and increases in HDL-C levels may be sought whenever feasible.

What Should Be the Approach to Patients With Coronary Heart Disease and Multiple Risk Factors?

Other nonlipid risk factors must be considered whenever management of a patient with CHD is undertaken. Interaction of risk factors is multiplicative, not additive. In particular, diabetes mellitus, through mechanisms that may include insulin resistance and hyperinsulinemia, altered composition of lipoproteins, and glyco- sylation of circulating lipoproteins, promotes atherogenesis.30 Attention to cholesterol lowering is of particular importance in diabetes.

Blood pressure—lowering medications like thiazide diuretics and β-blockers without peripheral sympathomimetic activity may raise LDL-C levels and lower HDL-C levels, respectively.31 Increased exercise, on the other hand, may lower LDL-C levels, raise HDL-C levels, and improve compliance with other interventions, including smoking cessation, weight loss, and dietary regimens.32

Suggestions for Next Steps

Conference participants suggested the following:

1. Future iterations of national guidelines should emphasize specifically the importance of cholesterol intervention in the treatment of established coronary disease. Issues to be considered in future guidelines include:
   a. All patients with CHD should have a complete lipoprotein profile performed. Prior screening for total cholesterol level is not required.
   b. LDL-C should be the primary target of therapy. Patients with LDL-C levels ≥100 mg/dl should be considered candidates for both diet and, if necessary, drug therapy to lower such levels to <100 mg/dl. In addition, drug therapy may be considered in patients with LDL-C levels <35 mg/dl or triglyceride levels ≥250 mg/dl to raise HDL-C to >35 mg/dl and to lower triglyceride levels to <250 mg/dl.
   c. Special attention should be given to simultaneous intervention on other CHD risk factors. Diabetes mellitus, in particular, is associated with markedly increased risk of recurrent events, even when LDL-C levels are normal. Blood pressure—lowering medications that adversely affect lipoprotein levels should be avoided if other agents are as effective. However, a proven intervention, such as use of β-blockers after myocardial infarction, should not be avoided on the basis of the possibility that it might adversely affect lipoprotein levels. If necessary, lipoprotein abnormalities engendered by such interventions can be treated by other means.
   d. Once CHD is clinically manifest, gender and age should not substantially affect the intensity of intervention, except in those whose myocardial damage has resulted in very significant clinical manifestations (for example, severe congestive heart failure).
   e. Although the long-term safety of cholesterol reduction should continue to be (and is) the subject of careful investigation, such concerns remain theoretical and should not interfere with appropriate attention to cholesterol lowering, particularly in those with established disease.

2. Medical educational programs should be developed to highlight the unanimity of opinion among epidemiologists, lipoproteinologists, cardiologists, and health economists that cholesterol lowering is a medically effective and cost-effective therapy for patients with established disease. In this regard, cardiologists should be encouraged to recognize that
   a. A cause-and-effect relation between circulating cholesterol and CHD has been established.
   b. The benefit of cholesterol lowering in established CHD is very large—much larger even than the benefit in primary prevention.
   c. Invasive interventions, including angioplasty and coronary bypass surgery, are and will remain important in the acute management of CHD. Long-term reduction of recurrent events, however, is more dependent on medical interventions, including aspirin, β-blockers, and cholesterol lowering. Of these, only cholesterol lowering has been shown to arrest the progression and induce regression of atherosclerosis. Because of this, medical treatments, such as aspirin and β-blocker therapies, should not be viewed as alternatives but as additions to lipid-lowering interventions.
d. The endorsement of the attending cardiologist of any regimen, including cholesterol intervention, greatly increases the chances of patient compliance. Reluctance to provide such an endorsement should not be a result of the absence of proper resources in the cardiologist’s office or lack of interest in providing counseling about lifestyle changes and drug therapy. Instead, patterns of referral to a general physician who is able and willing to provide such counseling should be developed.

e. General physicians, on the other hand, should recognize that lifestyle intervention and drug therapy for cholesterol lowering are likely to be in their purview when acute management of the patient’s coronary disease is complete. This requires the development of resources to ensure proper lifestyle counseling, including patient education about the importance of such changes for the prevention of future events, and sustained compliance with necessary drug regimens. It is important to recognize that prevention of subsequent events is not guaranteed by the invasive interventions initiated by the first event. An artery that has undergone angioplasty or a bypass graft exposed to the same risk factors as the original vessel will likely eventually succumb to atherosclerosis.

The achievement of the steps suggested above will require the endorsement and cooperation of several organizations, including the NCEP, the American Heart Association, and other major professional organizations, such as the American College of Cardiology, the American College of Physicians, and the American Academy of Family Physicians. The NCEP provides an important forum for the development of this cooperative effort. Efforts within and among individual organizations to further these goals should also be pursued.

Appendix

Participants in the Conference on Cholesterol Lowering as a Treatment for Established Coronary Heart Disease

W. Virgil Brown, MD
Director
Division of Arteriosclerosis and Lipid Metabolism
Department of Medicine
Emory University
Post Office Drawer AG
Atlanta, GA 30322

James I. Cleeman, MD
Coordinator
National Cholesterol Education Program
National Heart, Lung, and Blood Institute
National Institutes of Health
Room 4A05
Building 31
Bethesda, MD 20892

Michael H. Criqui, MD, MPH
Professor of Community and Family Medicine
Division of Epidemiology, M-007
University of California at San Diego
La Jolla, CA 92093-0607

Curt D. Furberg, MD, PhD
Professor and Chairman
Department of Public Health Sciences
Bowman Gray School of Medicine
300 South Hawthorne Road
Winston-Salem, NC 27103

DeWitt S. Goodman, MD†
Tilden-Weger-Bieler Professor
Director, Institute of Human Nutrition
College of Physicians and Surgeons
Columbia University
630 West 168th Street
New York, NY 10032

Antonio M. Gotto Jr., MD, DPhil
Chairman, Department of Medicine
Baylor College of Medicine
Chief, Internal Medicine Service
The Methodist Hospital
6550 Fannin, Smith Tower
Mail Station 1423
Houston, TX 77030

K. Lance Gould, MD
Professor of Medicine
University of Texas Medical School
MSB-4.258
6431 Fannin Street
Houston, TX 77030

Scott M. Grundy, MD, PhD
Director, Center for Human Nutrition
University of Texas
Health Sciences Center, Room G-4100
5323 Harry Hines Boulevard
Dallas, TX 75235

William R. Harlan, MD
Director
Division of Epidemiology & Clinical Applications
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, MD 20892

Joel Hay, PhD
Senior Research Fellow
Hoover Institution
Stanford University
Stanford, CA 94305-6010

Donald B. Hunninghake, MD
Director, Heart Disease Prevention Clinic
Professor of Medicine and Pharmacology
401 East River Road Parkway
151 Variety Club Heart and Research Center
Box 192 UMHC
Minneapolis, MN 55455

Lewis H. Kuller, MD, DrPH
Professor and Chairperson
Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh
130 Desoto Street
Pittsburgh, PA 15261

Costas T. Lambrew, MD
Director, Division of Cardiology
Professor of Medicine
22 Bramhall Street
Portland, ME 04102

John C. LaRosa, MD
Dean for Research
The George Washington University Medical Center
Professor of Medicine and Health Care Sciences
Director of the Lipid Research Clinic
2300 Eye Street, NW
Suite 713
Washington, DC 20037

†Died November 4, 1991.
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J C LaRosa and J I Cleeman

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