Strategies for optimizing lipid treatment outcomes
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The relationship between increased levels of cholesterol and elevated risk for coronary heart disease (CHD) has been described in many epidemiologic and well-designed prospective trials. Since first being elucidated by the Coronary Primary Prevention Trial, reducing levels of blood cholesterol results in a corresponding reduction in CHD risk has been demonstrated by numerous trials. The evidence now indicates that cholesterol reduction by any number of means confers up to a 35% reduction in total mortality, coronary mortality, coronary artery procedures, stroke, and other CHD-related events.

This article reviews data that demonstrate cholesterol reduction decreases CHD risk, discusses current and emerging treatment modalities, and describes the methods healthcare practitioners can use to enhance lipid treatment outcomes. It also identifies educational tools that can be used to empower patients to improve their compliance and become actively involved in reducing their CHD risk.

(Key words: adherence, cholesterol, coronary heart disease, dyslipidemia, low-density lipoprotein cholesterol [LDL-C], compliance, outcomes, risk assessment)

Based on the decline of the death rate from coronary heart disease (CHD) during the past 10 to 15 years, public health efforts aimed at reducing cigarette smoking and implementing lipid-modification programs through dietary changes and use of statins appear to have had a positive effect on cardiovascular health. The data can be misleading, however, because despite the reduction in CHD-related mortality, hospitalization rates for myocardial infarction and other CHD events continue to rise.¹

On closer inspection, it appears that the decline in death from CHD is attributable to an improvement in peri-event procedures and care, such as coronary artery bypass grafts and angioplasty. At the same time, it appears that increased hospitalizations can be blamed on rapid increases in the prevalence of other CHD risk factors related to an aging population, the growing number of overweight Americans, and the increased prevalence of diabetes mellitus and hypertension. These observations partially explain the persistence of CHD as the leading cause of death among Americans. They also suggest that a renewed effort is required to reduce the cardiovascular risk burden among the US population.

Data from the Framingham Heart Study² demonstrate a direct correlation between cholesterol levels and 40-year survival in adults younger than 50 years. Lipid abnormalities are the chief culprit in the development of CHD and are therefore obvious targets for therapy.

Cholesterol and risk for coronary heart disease
Atherosclerosis results from the accumulation of low-density lipoprotein cholesterol (LDL-C) in the arterial wall. Over time, such LDL-C accumulation leads to the formation of atherosclerotic lesions. Large lesions are relatively stable, but they can cause obstructive symptoms such as angina pectoris. These lesions can be effectively treated with bypass grafts, angioplasty, or stents. Small, newer lesions are more prone to rupture and can result in the formation of a thrombus that can lead to myocardial infarction, unstable angina, sudden death, stroke, or occlusion of a peripheral artery.

The Framingham Heart Study³ was the first trial to propose that the risk of the development of CHD was linked to cholesterol, a concept that has been subsequently confirmed in numerous trials. The Framingham study was a prospective, epidemiologic trial that monitored blood lipid levels, blood pressure, smoking, and exercise habits in men and women for up to 28 years. A continuous, graded relationship between increasing cholesterol levels (total and LDL) and CHD risk was observed. Moreover, the results proposed that high-density lipoprotein cholesterol (HDL-C) levels were negatively associated with CHD risk. Data from the Framingham Study form the basis of the CHD risk assessment advocated by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III). An assessment tool for patients to calculate their 10-year risk of CHD is available on the Internet (Figure).

The hypothesis that cholesterol levels are associated with the risk of CHD was further confirmed in the Multiple Risk Factor Intervention Trial (MRFIT). MRFIT demonstrated a curvilinear relationship between rising cholesterol levels and CHD risk. Risk increased slightly as total cholesterol levels rose from 150 mg/dL to 200 mg/dL, at which point, risk increased twofold when
cholesterol levels reached 250 mg/dL, and fourfold at levels greater than 300 mg/dL.\textsuperscript{4}

**Outcomes trials**

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was the first large study that proved interventions that reduce cholesterol levels lead to a reduction in CHD-related morbidity and mortality. The LRC-CPPT randomly assigned men with primary hypercholesterolemia to receive cholestyramine or placebo daily for an average of 7.4 years. The cholestyramine-treated group had a 9% reduction in CHD-related mortality and nonfatal myocardial infarction. These benefits were most strongly linked to a decrease in total cholesterol and LDL-C levels.

The LRC-CPPT also provided one of the earliest demonstrations of the principle that every 1% reduction in LDL leads to a 2% reduction in CHD risk.\textsuperscript{5} Since publication of the LRC-CPPT results, numerous clinical trials have added evidence from a variety of patient populations using multiple modes of lipid-lowering therapy.

The Scandinavian Simvastatin Survival Study (4S) demonstrated a reduction in CHD-associated mortality and morbidity in patients with CHD who had high total cholesterol and LDL-C levels. The 4S was also the first to show a reduction in overall mortality with lipid-lowering therapy.\textsuperscript{6}

The West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated a reduction in CHD risk in patients with elevated cholesterol levels who had no CHD at enrollment.\textsuperscript{7}

Subsequently, the Cardiac and Recurrent Events (CARE) trial and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed that the risk of CHD could be reduced in patients who had normal or near-normal cholesterol levels.\textsuperscript{8} In addition, the CARE trial provided evidence of benefit in a secondary-prevention setting, whereas the AFCAPS/TexCAPS was conducted in a primary-prevention population.

The Heart Protection Study (HPS) demonstrated a significant reduction of the CHD risk in a large population of patients with CHD and CHD risk equivalents who had only moderately elevated LDL-C levels.\textsuperscript{9}

Although the bulk of recent evidence demonstrating the benefits of lipid-lowering therapy on CHD outcomes is derived from statin-oriented trials, other drugs have proved beneficial. The Helsinki Heart Study showed a reduction in CHD risk with gemfibrozil.\textsuperscript{10} More recently, the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) demonstrated a benefit with gemfibrozil in patients who did not have elevated levels of total cholesterol or LDL-C levels but who had low levels of HDL-C. Patients receiving gemfibrozil showed no significant change in levels of LDL-C, though their HDL-C levels were increased by 6%.\textsuperscript{11}

**Current treatment modalities**

The National Cholesterol Education Program Adult Treatment Panel III recommendations retain the NCEP’s historical endorsement of dietary modification and regular exercise—therapeutic lifestyle changes (TLC)—as essential elements of risk-reduction therapy. The ATP III set of guidelines suggests a trial of TLC before initiating drug therapy, though some high-risk patients will require pharmacologic intervention from the outset of treatment. Therapeutic lifestyle changes are intended to reduce CHD risk by helping to decrease LDL-C and triglyceride levels and raise the HDL-C level.

Diet modification is the cornerstone of therapy for mild to moderate dyslipidemia. The ATP III recommends a TLC diet that includes a reduction of saturated fats to less than 7% of total calories, a reduction of dietary cholesterol intake to less than 200 mg/d, the addition of plant sterols/stanols (commercially available in special margarines) to a level of 2 g/d, and the incorporation of viscous fiber into the diet at a level of 10 g/d to 25 g/d.\textsuperscript{12}

If followed faithfully, dietary therapy can result in a 12% to 18% reduction in total cholesterol; however, there is no clear evidence that demonstrates a diet low in saturated fat and cholesterol

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**Figure.** Schematic of risk assessment tool for patients to estimate their 10-year risk of development of hard coronary artery disease (myocardial infarction and coronary death). This tool uses information from the Framingham Heart Study to predict a person’s chance of having a heart attack in the next 10 years. It is designed for adults aged 20 and older who do not have heart disease or diabetes. It, with appropriate explanations of each parameter, is available to patients at: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof. Accessed December 27, 2002.
will improve CHD outcomes. Systematic reviews of observational studies found that increased consumption of fruits and vegetables is associated with a lower incidence of myocardial infarction and stroke; however, these data are limited.

Patients who do not respond to the recommended dietary changes or who have difficulty complying with the recommendations should be referred to a dietician or a nutritionist for medical nutrition therapy.

The American Heart Association now recognizes persistent physical inactivity as an independent risk factor, raising the risk of CHD twofold. Physical activity raises HDL-C levels and decreases the concentration of very-low-density lipoprotein cholesterol and triglycerides. Exercise that results in weight loss contributes to LDL-C reduction. Weight reduction can reduce LDL-C levels and ameliorate the risk factors associated with the metabolic syndrome by improving insulin sensitivity and serum glucose uptake and thus reducing the risk of diabetes.

Cigarette smoking remains a CHD risk factor, and smoking cessation can contribute to an increased HDL-C level.

Failure of TLC to modify the LDL-C level or to achieve LDL-C goals or the presence of high CHD risk warrants the use of pharmacologic therapy. Despite the initiation of drug therapy, TLC should be maintained and continually reinforced by the physician. Treatment goals and lipid thresholds for initiating drug therapy are dependent on the patient’s risk category calculated using the Framingham risk assessment tool advocated by ATP III (Figure).

Risk category 1 includes patients with a 10-year risk greater than 20% (eg, definite CHD or CHD risk equivalents). For these patients, the LDL-C threshold for initiating therapy is greater than or equal to 130 mg/dL (after a 3-month trial of TLC) and the treatment goal is less than 100 mg/dL. For patients whose LDL-C cholesterol level is 100 mg/dL to 129 mg/dL, drug therapy is optional and physicians are encouraged to use clinical judgment to determine if drug therapy is appropriate.

Risk category 2 encompasses patients without definite CHD or CHD risk equivalents but who have at least two major risk factors that confer a 10-year CHD risk of 20%. For patients with a 10-year CHD risk of less than 10%, the LDL-C threshold is greater than or equal to 160 mg/dL and the target level is less than 130 mg/dL. In patients who have a 10-year risk of 10% to 20%, the treatment threshold is greater than or equal to 130 mg/dL and the target level is less than 130 mg/dL. In both instances, lipid-modifying drug treatment may not be necessary after a 3-month trial of TLC.

Risk category 3 includes patients without CHD and with zero to one major risk factor. Drug treatment should be considered for these patients if their LDL-C level is greater than or equal to 190 mg/dL after 3 months of TLC. For patients in this category, the LDL-C goal is less than 160 mg/dL.

Therapeutic goals in patients with the metabolic syndrome must consider up to three lipoprotein abnormalities, including increased LDL-C, increased triglyceride concentration, and low HDL-C level. These patients should be provided with a 3-month trial of TLC. If TLC does not favorably alter the lipid profile, an agent that reduces LDL-C, and possibly triglycerides, should be added to the lifestyle therapy. For high-risk patients who have elevated triglyceride concentrations (>200 mg/dL), drug therapy can be added if weight reduction and increased physical activity fail to have a triglyceride-lowering effect.

Pharmacologic therapy for lowering the LDL-C level should be monitored at 6-month intervals to determine if progress is being made toward goal, to evaluate patient tolerability and adherence to therapy, and to provide the patient with education. If the LDL-C goal is not achieved, therapy should be intensified with an increase in the drug dose or the addition of a second LDL-C-lowering drug with a different mechanism of action.

Even if the LDL-C goal is attained, physicians and patients are encouraged to identify and treat other CHD risk factors such as hypertension or diabetes. Once the LDL-C levels are within a desirable range, patients should be monitored every 6 to 12 months for any event that may have an impact on their compliance to therapy.

Process to improve lipid therapy outcomes

The ATP III guidelines offer the opportunity to take significant steps in reducing the risk for CHD among Americans. The challenge, however, is in the implementation of the guidelines. Successful implementation leads to increased adherence and ultimately, better clinical and economic outcomes. In general, physicians recognize the importance of lipid control and they are familiar with the basics of the guidelines. Yet, fewer than 40% of dyslipidemic patients are being treated and many who receive treatment are not reaching target levels. Less than half of primary-prevention patients have an LDL-C level of less than 130 mg/dL, and fewer than 20% of patients with CHD who receive treatment have an LDL-C level of less than 100 mg/dL. Persistence with therapy is another challenge, as 70% of patients do not maintain therapy beyond 1 year.

Noncompliance is not always the result of patient misunderstanding or intrinsigence. Healthcare professionals share the responsibility of assisting patients to reach goal. Some of the reasons physicians are not adherent to the guidelines include:

- lack of awareness,
- disagreement with published guidelines
- perceptions of uncertain outcomes,
- time barriers in a busy clinical practice,
- no reminders or prompts, and
- ineffective educational materials.

Strategies to improve physician adherence include educational seminars to review the guidelines and their implementation with physicians and using reminders to prompt physicians to make lipid screening and management a priority. Another strategy is to designate a patient advocate in the office who is responsible for identifying and tracking high-risk patients.

Patients who need lipid-lowering therapy are likely to require long-term treatment, perhaps for a lifetime; however, many patients do not adhere to their prescribed lipid-modification reg-
imen, even when an effective, well-tolerated agent is prescribed. Improving adherence to therapy requires educating patients, encouraging physicians, and establishing new ways to deliver lip-modifying care. Clearly, numerous reasons account for patients’ discontinuing therapy. Consequently, no single strategy will improve adherence in all patients.

Perhaps the best strategy is to use a systematic approach of providing education about the disease and encouraging patients to take increased responsibility for their own care. Educational efforts include teaching patients about cardiovascular risk equivalents, demonstrating the potential benefits of therapy, documenting evidence of preclinical disease, using graphs that document progress, and persistently using reminders for follow-up and return visits. Tools that can support this effort include the Internet, videos, informational brochures, and telemedicine. Additionally, physicians should:

- Encourage the patient’s family or friends or both to become involved in the treatment plan.
- Schedule more frequent visits.
- Strive to keep the treatment regimen as simple as possible.
- Provide clear instructions.
- Discuss adherence for at least a few minutes at each visit.

Patients who do not reach goals, who miss appointments, or who require complex therapeutic regimens to reach treatment goals should receive special attention.

Adherence is also improved by devising new avenues of screening for CHD risk, therapy, and patient education. Targeting inpatients during hospitalization for an acute coronary event or interventional procedure is an effective way to identify the patients at highest risk for CHD and initiate appropriate therapy before discharge.

Multidisciplinary lipid-management clinics that address many aspects of CHD have proved to be effective in increasing adherence and improving both clinical and economic outcomes, particularly when treating patients at highest risk. The use of a patient advocate (eg, a nurse, pharmacist, or other allied healthcare professional to identify, monitor, and educate patients) has also proven to be effective. Another approach is to collaborate with community pharmacists to identify, educate, and treat high-risk patients. Recently, the American Heart Association began placing kiosks in many pharmacies to provide CHD risk screening and education.

Comment

The ongoing challenge in healthcare is to encourage physicians and patients to use strategies that lead to improved clinical and economic outcomes. Adherence to the ATP III guidelines by both physicians and patients is critical to reproducing the magnitude of benefit in CHD risk reduction demonstrated in clinical trials of lipid lowering. A significant effort must be made to maximize compliance to attain the highest possible level of reduction of CHD risk. Thus, the ATP III recommends the use of state-of-the-art multidisciplinary methods targeting the patients, clinicians, and healthcare delivery system to achieve full-population effectiveness for reduction of CHD risk factors and for disease prevention.

References