NEW STANDARDS FOR LOWERING CHOLESTEROL IN DIABETIC, FEMALE, AND ELDERLY PATIENTS: A CLINICIAN’S POINT OF VIEW

Mark Greathouse, MD*

ABSTRACT

With the release of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines, future risk of cardiac event supplanted the cholesterol number as the driving force behind intervention. These new prevention guidelines, based on recent subanalyses from major lipid-lowering clinical trials, support the concept of more aggressive cholesterol-lowering therapy for 3 groups who are currently undertreated: female, elderly, and diabetic patients. Results from the Heart Protection Study support the concept that cardiac risk can be significantly reduced with aggressive lipid-lowering therapy in these 3 groups. While the target levels of low-density lipoprotein, high-density lipoprotein, and triglyceride now advised by the NCEP are attainable, clinicians should be aware that monotherapy with statins may be inadequate for achieving the full set of lipid goals. Many patients may require combination regimens involving statins, bile acid sequestrants, niacin, or fibrates. (Advanced Studies in Medicine 2002;2(18):641-646)

The clinical guidelines published in 2001 by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) do more than narrowly define the cholesterol target numbers for cardiovascular disease (CVD). They also shift the emphasis from lipid numbers alone to the overall risk of a future cardiac event in individual patients. The array of aggregate risk is now calculated using a new formula based on multiple risk factors (Table 1).

Of special importance, the new standards encourage practitioners to look beyond the “typical” high-risk patient with CVD, represented by the middle-aged white male, to other high-risk groups who may also benefit from aggressive therapy, including female patients, diabetic patients, and elderly patients. This article reviews the rationale behind the new risk-driven NCEP recommendations and comments on the practical challenges in meeting these evolving standards.

A TRANSITION IN THERAPY

The release of the new NCEP guidelines is already redirecting the efforts of clinicians in preventing CVD. Certainly, the measurement of low-density lipoprotein cholesterol (LDL-C) levels remains a central principal in these prevention efforts—with the guidelines calling for everyone to obtain a full lipid profile every 5 years, beginning at age 20. An LDL-C level of less than 100 mg/dL is now considered optimal, and the categorical high-density lipoprotein cholesterol (HDL-C) has been raised from 35 mg/dL or less to 40 mg/dL or less because the latter figure is a better measure of depressed HDL-C. The triglyceride cutoffs have also been lowered to emphasize the dangers of even moderate elevations.1

* Director, Program for the Prevention of Heart Disease, Allegheny General Hospital, Pittsburgh, Pennsylvania.
Address correspondence to: Mark Greathouse, MD, Director, Program for the Prevention of Heart Disease, West Penn Allegheny Health System, Allegheny General Hospital, Pittsburgh, PA 15212.
As with previous NCEP guidelines, specific lipid-lowering interventions are then recommended for various lipid profiles. But the narrow definition of acceptable LDL and non-LDL cholesterol levels is also prompting a transition in the therapies required to meet the new goals. In the decade following the release of the Scandinavian Simvastatin Survival Study (4S), clinicians relied heavily on the statin class of drugs for lipid lowering. But single-agent statin therapy—even high-dose statin therapy—may no longer be adequate to meet the new goals, and the NCEP now clearly endorses the use of statins as well as resins, nicotinic acid, and fibrates.

Why does single-agent statin therapy fall short of the goal? An obvious reason is the lay public’s perception of these drugs. While recent evidence suggests that the chances of reversible chemical hepatitis at the highest recommended doses of statins is less than 2.5%, most patients are convinced that doses higher than 10 mg to 20 mg are unavoidably dangerous. Another practical problem involves the pharmacology of statins. These agents are most effective at the lower starting doses; doubling the dose reduces the LDL-C by only an additional 6%. Thus, faced with these persistent hurdles of public perception and pharmacokinetics, the concept of using smaller doses of multiple drugs to achieve target goals is becoming more appealing. This new acceptance of using low-dose combination therapy and other strategies to target and treat special at-risk populations are discussed in the following sections.

**Diabetic Patients**

More aggressive or earlier therapy—perhaps including a transition to combination therapy—may be especially appropriate to meet new NCEP guidelines in newly designated high-risk groups such as patients with diabetes mellitus. The new guidelines, following the lead of the American Diabetes Association 1999 position paper, now officially recognize these patients as having a cardiac risk level that is equivalent to that of patients who have had a prior cardiovascular (CV) event.

In fact, the NCEP expert panel showed their concern about metabolic aberrations by emphasizing the metabolic syndrome (“syndrome X”) as a marker for CHD risk. This constellation of lipid and nonlipid risk factors, which is linked to insulin resistance, is managed with weight control, physical activity, and specific treatment of lipid and nonlipid disorders. Based on the levels of HDL-C and triglyceride (TG) values defining risk in this classification (Table 2), the designation of the metabolic syndrome as a secondary target of therapy seems warranted, espe-

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<tr>
<th>Table 1. How NCEP Zeroes in on Multiple Risk Factors</th>
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<td>- Raises persons with diabetes and coronary heart disease (CHD), most of whom have multiple risk factors, to the risk level of CHD risk equivalents</td>
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<td>- Uses Framingham projections of 10-year absolute CHD risk to identify certain patients with multiple (2+) risk factors for more intensive treatment</td>
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<td>- Identifies persons with multiple risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle change</td>
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<th>Table 2. Clinical Identification of the Metabolic Syndrome</th>
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<td><strong>Risk Factor</strong></td>
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<td>Abdominal obesity (waist circumference)</td>
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<tr>
<td>Men</td>
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<tr>
<td>Women</td>
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<tr>
<td>Triglycerides</td>
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<td>HDL-C</td>
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<td>Blood pressure</td>
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HDL-C = high-density lipoprotein cholesterol.
cially considering the current lack of outcomes data in treating these patients specifically.

Results of major trials have confirmed that patients diagnosed with diabetes receive tremendous benefits from lipid-lowering interventions. In the 4S trial, for example, statin therapy produced a 55% reduction in events as compared to that achieved by dietary intervention. However, despite solid evidence of benefit and a clear mandate for treatment, the diabetic patient often poses a challenge for statin monotherapy because of the lipid profile commonly seen in these individuals, including patients with acceptable hemoglobin A1c levels:

- Moderate LDL-C elevation,
- Moderately severe TG elevation,
- Depressed HDL-C levels

Statins may lower LDL-C almost to goal levels in a diabetic patient with such a distinctive profile, but the effects on HDL-C and TGs are typically mild. To reach the new NCEP goals, many diabetic patients will require combination therapy.

Statins can be combined successfully with bile acid sequestrants, nicotinic acid, or fibrates to achieve the multiple lipid goals in diabetic patients, but there are certain precautions. Most statin doses should be reduced to the standard initiating dose or lower (eg, atorvastatin 10 mg, simvastatin 10 mg) when combined with niacin or fibrates. With the possible exception of pravastatin, statins should be used cautiously in combination with gemfibrozil because of the increased risk of rhabdomyolysis. There is insufficient information about the interactions of fenofibrate and the statins, but, there may be fewer drug interactions with pravastatin because of this agent's lack of cytochrome P450 metabolism. Similarly, statin doses should be reduced initially when these agents are combined with nicotinic acid. Generally, niacin should not be used in diabetic patients with fasting blood sugars of over 115 mg/dL unless frequent monitoring of blood sugars is ensured.

Another consideration in lipid therapy for patients with diabetes is the likelihood of multiple medications and, therefore, drug-drug interactions in these patients. One classic study reported that 50% of patients taking 4 drugs and 90% of patients taking 8 drugs experience interactions. Use of bile acid sequestrants, the only nonsystemic lipid-lowering agents, can limit this risk of entangled therapeutic regimens in the diabetic population.

The traditional bile acid sequestrants such as cholestyramine and colestipol have been used safely with statins, niacin, or fibrates. Unfortunately, these older resins are poorly tolerated due to adverse gastrointestinal effects. In addition, these 2 drugs are traditionally avoided in patients with significantly elevated TGs because of the drugs' tendency to induce notable rises in TG as the liver produces a greater amount of very low-density lipoprotein.

The new bile acid sequestrants represented by colesvelam have dramatically improved gastrointestinal tolerance, while also providing a more neutral effect on TGs. This latter effect suggests that the new-engineered polymers, in addition to increasing fecal sterol excretion, somehow also deplete the bowel lumen bile pool and interfere with cholesterol absorption. A recent study of colesvelam (650 mg, 6 tablets per day) with 10 mg simvastatin lowered LDL-C by an amount that was essentially equivalent to that expected with patients taking 80 mg statin monotherapy.

**FEMALE PATIENTS**

Historically, the diagnosis and treatment of heart disease in women has been pursued less aggressively than in men. The problem is rooted in societal misperceptions as well as in diagnostic difficulties and an initial lack of inclusion of women in large treatment studies. The problems are slowly being resolved but much work remains, including expanded efforts to include at-risk women, both premenopausal and postmenopausal, in lipid-lowering initiatives.

Delay in diagnosis is an ongoing reason for poor outcomes in women with cardiovascular disease—a result of women's persistently low-level awareness of CVD risk after menopause. In the United States, CVD is responsible for the deaths of 513 000 women annually; while approximately 40 000 women die from breast cancer and 4400 die from cervical cancer each year. And yet most women are more aware of their risk of having reproductive cancers than having CVD. Women are more aware of the importance of—and make more physician queries about—Papanicolaou tests, breast self-examinations, and mammography than the importance of cholesterol levels or other cardiac risk factors.

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presumption of low cardiac risk contributes directly to delays in women seeking attention for chest-related symptoms.

Once a physician examines them, these women are more likely to receive an accurate cardiac diagnosis. Traditional electrocardiograms and nuclear stress tests are considered less sensitive and specific in women, thus contributing to the general perception that workups using noninvasive tests are less accurate in female patients than in male patients. However, new tests for inflammatory markers of active or vulnerable plaque appear to be accurate risk predictors for CVD in both men and women. For example, a clinically available, new blood assay for highly sensitive C-reactive protein (hs-CRP) combined with total cholesterol/HDL-C has been shown to accurately gauge cardiac risk in female patients. Two other plasma tests, plasma interleukin-6 and serum amyloid a, equally predict risk for CVD in male and female patients, but the tests are currently only available as research tools.

Results from several major trials show that lipid-lowering therapy equally benefits men and women in high-risk categories.

- In the Pravastatin Pooling Project (PPP), which analyzed just under 20,000 patients for 110,000 patient-years with the common endpoints of CV death and nonfatal myocardial infarction, women experienced a statistically significant 27% reduction in events as compared to a 23% reduction for men.
- In the 4S trial, involving treatment of patients with high total and LDL-C levels, the cardiac event rate was reduced by 29% in women as compared to 26% in men.
- In the Heart Protection Study, findings of a 33% reduction in event rate following statin therapy in high-risk (but not necessarily high LDL-C) patients applied equally to all treatment groups including women.

In sharp contrast to the previous version of the NCEP guidelines (ie, ATP II published in 1993), the new guidelines no longer endorse estrogen therapy for lowering lipids in postmenopausal women. This important change resulted from findings of key studies such as the Heart and Estrogen/Progestin Replacement Study (HERS), Women's Health Initiative (WHI), and reports from the Women's Health Initiative. Results from these large, well-controlled clinical studies show that the procoagulant effects of conjugated estrogens outweigh any potential vascular health benefits. Based on these findings, the NCEP guidelines recommend that estrogens should not be used as primary or secondary cardiovascular agents. In conjunction with this advisory, the American Heart Association now recommends that hormone replacement therapy (HRT) should not be prescribed for a woman at high risk of heart disease. If a woman on HRT has a cardiac event, then the HRT should be discontinued.

The NCEP panel also recommended a similarly aggressive lipid-lowering approach in both men and women. The assessment and treatment of women with, or at risk for, coronary heart disease should be greatly assisted by the sex-specific Framingham Prediction Scores that are central to the new NCEP guidelines.

**Elderly Patients**

Elderly patients also have been an understudied and undertreated group in trials of primary and secondary cardiology prevention. But in major trials where an older patient subgroup has been analyzed, the benefits of lipid-lowering therapy are clearly identified:

- In the PPP, event rates were reduced by 22% in patients younger than 64 years and by 26% in patients older than 65 years.
- In the 4S, the data suggest a 34% reduction in events and a 40% reduction in revascularization procedures in patients 65 years and older.
- In the Heart Protection Study, which includes over 5805 patients older than 70 years at entry, the data suggest reductions of at least one third in major vascular events.

**Stroke**

One particularly impressive, and unexpected, result in many recent trials has been the consistent ability of lipid-lowering therapy to reduce stroke risk in elderly patients. Observational studies had suggested no predictive value of serum cholesterol levels in relation to strokes. Despite this, lipid lowering reduced the incidence of transient ischemic attacks and cerebrovascular accidents by 28% in the 4S trial and 22% in the PPP study. In a recent retrospective analysis, lipid-
lowering therapy has also been associated with reductions in nonvascular dementia in elderly patients, a positive change not seen in groups receiving other common cardiac risk-factor modifiers such as angiotensin-converting enzyme inhibitors or beta-blockers in hypertension. Based on the high rates of (and considerable fear of) strokes and dementia in the elderly population, these findings should encourage clinicians to adopt a more aggressive approach to lipid reduction in their elderly patients.

In all patient types, and particularly in older patients, the actual physiologic benefit conferred by lipid-lowering agents may relate to their anti-inflammatory effects. The levels of fibrinogen, interleukin-6, and tumor necrosis factor all increase as people age, especially in patients with prior myocardial infarction, cerebrovascular accidents, or claudication. The inflammation marker hs-CRP is a strong, although nonspecific, predictor of cerebrovascular accidents, or claudication. The inflammation marker hs-CRP is a strong, although nonspecific, predictor of cerebrovascular accidents in elderly patients. Lipid-lowering agents predictably reduce levels of these inflammatory markers along with rates of cerebral and cardiac events in elderly patients as well as other age groups. Therefore, lipid-lowering therapy should not be withheld arbitrarily from patients due to age; indeed, cholesterol reduction in patients 65 years and older should be encouraged.

Conclusions

Cardiovascular disease prevention now involves more than a single-minded quest for a magic target cholesterol level in all patients with high LDL-C. As the new NCEP guidelines have thoughtfully advised, clinicians must think less about numbers and more about patients. The improved prevention approach first considers a patient's overall level of cardiac risk—of which lipids, not just LDL-C but also HDL-C and TGs, are a part—and then pursues appropriate therapy for that patient.

The new focus on patient risks includes an increased willingness to manage risks in previously undertreated populations such as elderly patients, diabetic patients, and female patients. The initial reports issued by the Heart Protection Study support the concept of such aggressive lipid-lowering treatment of cardiac risk in these key populations. And as recommended by the NCEP, in the highest risk situations (eg, patients hospitalized for major coronary events) drug therapy should be initiated immediately to ensure cholesterol-lowering therapy.

In a large percentage of patients, the levels of LDL-C, HDL-C, and TGs recommended by the NCEP will be attainable only with a multidrug regimen. Fortunately, the medications for such combination therapy are now readily available to clinicians.

References