



JULIE C. HUANG, MD

Preventive Cardiology Section, Department of Cardiovascular Medicine, The Cleveland Clinic Foundation

BYRON J. HOOGWERF, MD

Preventive Cardiology Section, Department of Cardiovascular Medicine; Department of Endocrinology, Diabetes, and Metabolism, The Cleveland Clinic Foundation

Cholesterol guidelines update: More aggressive therapy for higher-risk patients

ABSTRACT

The 2004 update to the National Cholesterol Education Program guidelines goes farther than the 2001 version in suggesting an optional low-density lipoprotein cholesterol (LDL-C) goal of less than 70 mg/dL for patients at “very high risk.” It recommends starting both diet and drug therapy in all patients at high or very high risk whose LDL-C level is above the goal level, with the goal of reducing LDL-C by 30% to 40%. These more aggressive guidelines are based on results of five clinical studies published since 2001.

AS NEW EVIDENCE keeps coming in from clinical trials, guidelines for treating elevated cholesterol keep getting more aggressive. In 2004, an expert panel updated the 2001 guidelines of the National Cholesterol Education Program to reflect the results of recent clinical trials (FIGURE 1).¹ Among the key changes:

- The update creates a new category of “very high risk.” For patients in this category there is now an optional goal level of low-density lipoprotein cholesterol (LDL-C) of less than 70 mg/dL (see CASE 1).

- For patients at high or moderate risk, there is now an option for more aggressive therapy than in the past.
- When drug therapy is used in patients at high or moderate risk, the intensity of therapy should be enough to reduce LDL-C levels by 30% to 40%.
- For high-risk patients with elevated triglycerides or low levels of high-density lipoprotein cholesterol (HDL-C), more aggressive drug therapy with a fibrate or nicotinic acid in addition to a statin is recommended.

For practicing physicians, these guidelines are both an opportunity and a challenge. They are evidence-based, but they are quite complex and require physicians to stratify patients by calculating their long-term risk on the basis of a variety of risk factors. Further complicating matters, some of the most aggressive treatment recommendations are left as “options,” leaving the final decision to the physician to exercise his or her clinical judgment.

To clarify these issues, we will discuss the evolution of these guidelines and the clinical trials on which they were based, and outline several case examples to illustrate how the updated guidelines can be applied to patients.

WHAT THE 2001 GUIDELINES SAID

The 2004 update amended the recommendations by the 2001 National Cholesterol Education Program Expert Panel on the Detection, Evaluation, and Treatment of

The updated guidelines are both an opportunity and a challenge

*Dr. Hoogwerf has indicated that he has received grant or research support from the Amylin and Eli Lilly corporations, serves as a consultant for the Astra Zeneca, Bayer, Eli Lilly, McNeil, Merck, Pfizer, Takeda, and Wyeth corporations, and is on the speaker's bureaus of the Astra Zeneca, Aventis, Bristol Myers Squibb, Eli Lilly, King, Merck, Monarch, Novo Nordisk, Pfizer, Schering Plough, Takeda, and Wyeth corporations.

Case 1: A smoker with coronary heart disease

A 64-year-old man with a history of hypertension, current smoking, and a percutaneous coronary intervention to the left anterior descending artery 2 years ago presents for secondary prevention. He is taking a statin and has started therapeutic lifestyle changes, as his baseline low-density lipoprotein cholesterol (LDL-C) concentration had been 144 mg/dL.

RECENT LABORATORY VALUES

- Total cholesterol 172 mg/dL
- Triglycerides 185 mg/dL
- High-density lipoprotein cholesterol (HDL-C) 42 mg/dL
- LDL-C 93 mg/dL.

WHAT WOULD YOU RECOMMEND?

- No changes to the regimen (his LDL-C level is at the goal of < 100 mg/dL)
- Smoking cessation only
- Increase the statin dose to lower the LDL-C to less than 70 mg/dL
- Add a fibrate to the regimen

Discussion. His statin dose should be increased to lower his LDL-C to less than 70 mg/dL.

The 2004 update to the 2001 guidelines¹ created a category of “very high risk” in which the goal LDL-C level is at least less than 100 mg/dL and optionally less than 70 mg/dL. This patient would be classified as being at very high risk on the basis of his history of coronary heart disease, along with the significant uncontrolled risk factor of continued cigarette smoking. Other factors that would shift a patient into the very high risk category include, in combination with an established history of coronary heart disease, multiple major risk factors such as diabetes mellitus, the metabolic syndrome, and acute coronary syndrome.

Although an LDL-C concentration lower than 100 mg/dL remains an acceptable goal, clinical trial evidence suggests that further benefit may be derived from lowering it further, a preferred strategy in this patient. Other benefit may be derived from treatment with niacin or a fibrate; however, the guidelines² place emphasis on treatment of LDL-C as the primary target. All smokers should be encouraged to quit.

High Blood Cholesterol in Adults (also called the Adult Treatment Panel III or ATP III),² which incorporated many of the findings of landmark clinical trials in lipid-lowering conducted in the 1990s.

Compared with earlier cholesterol guidelines,^{3,4} the 2001 guidelines placed greater emphasis on primary prevention, in addition to secondary prevention. The indications for treatment and the goals of therapy were based not only on the patient’s LDL-C level, but also on his or her overall cardiovascular risk. Thus, one patient with a fairly low LDL-C concentration but high cardiovascular risk might be a candidate for lipid-lowering drug therapy, whereas another patient with a higher LDL-C level but low risk might not require drug therapy.

Three categories of risk

The 2001 treatment algorithm divided patients into three risk categories on the basis of clinical characteristics and Framingham 10-

year risk score, a calculation that yields an estimate of the risk of having a cardiovascular event over the next 10 years.

High risk (10-year risk > 20%). Patients in this category have any of the following:

- Established coronary heart disease
- Peripheral vascular disease
- Abdominal aortic aneurysm
- Symptomatic carotid disease
- Diabetes mellitus
- A calculated 10-year risk of a coronary event greater than 20% (to calculate risk see www.nhlbi.nih.gov/guidelines/cholesterol).

Thus, those without overt coronary artery disease but with diabetes mellitus or otherwise at high risk were considered to have the equivalent of coronary artery disease risk.

Moderate risk is defined by having two or more of the following major risk factors:

- Age 45 years or older (men) or 55 years or older (women)

How to determine the goal LDL level and whether to start drug therapy

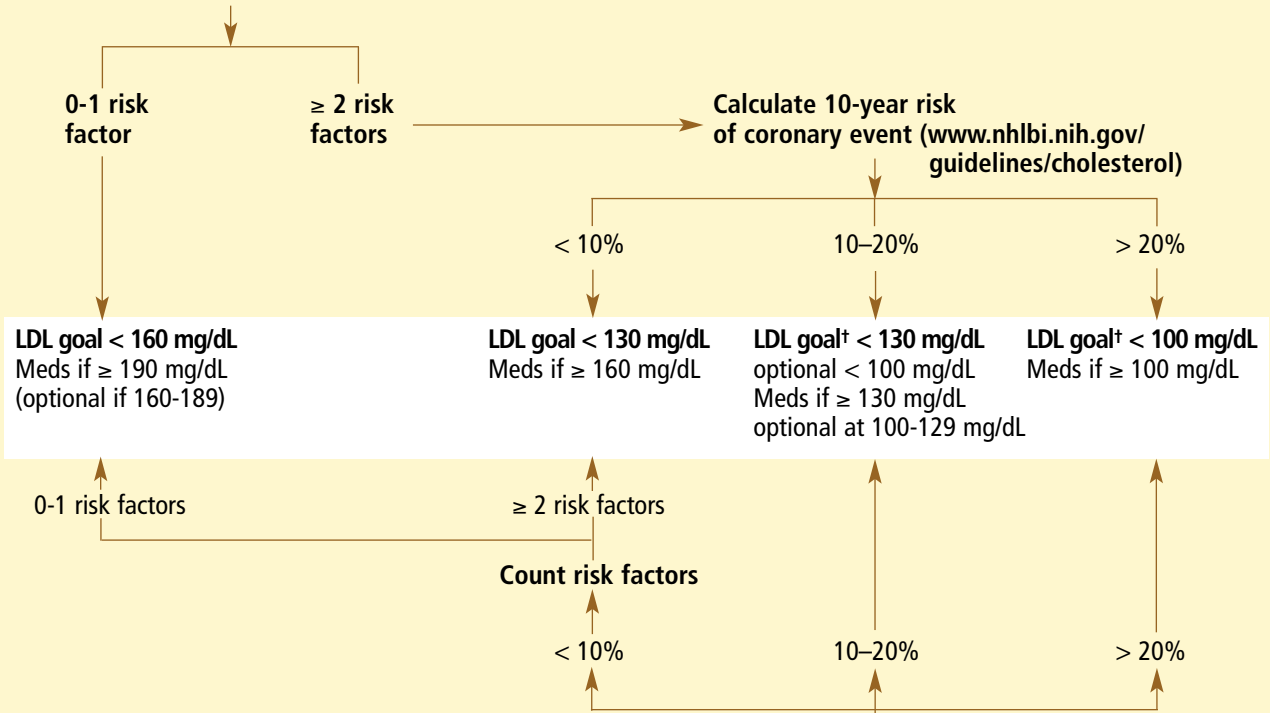
If any

- Coronary artery disease
- Peripheral vascular disease
- Abdominal aortic aneurysm
- Symptomatic carotid disease
- Diabetes mellitus

LDL goal < 100 mg/dL
 (<70 mg/dL optional in acute coronary syndrome or cardiovascular disease with other risk factors)
 Meds if ≥ 100 mg/dL

If none of the above, count risk factors*

- Hypertension (blood pressure $\geq 140/90$ mm Hg or taking meds)
- Cigarette smoking
- HDL < 40 mg/dL (subtract 1 risk factor if HDL is ≥ 60)
- Age ≥ 40 years (men) or ≥ 55 years (women)
- Family history of coronary artery disease (before age 55 in a male first-degree relative or before age 65 in a female first-degree relative)



*Alternatively, calculate 10-year risk of coronary event (www.nhlbi.nih.gov/guidelines/cholesterol) first

If LDL goal is reached, treat secondary targets

Triglycerides. If triglyceride level is ≥ 200 mg/dL, calculate non-HDL level (total cholesterol minus HDL); goal is 30 mg/dL higher than the LDL goal

Metabolic syndrome. If three or more of the following are present, treat with weight reduction, increased physical activity, antihypertensive treatment (if blood pressure is elevated), aspirin (if coronary disease is present), and therapy to reduce triglycerides and raise HDL levels

- Waist > 40 inches (men) or > 35 inches (women)
- Triglyceride level ≥ 150 mg/dL
- HDL level < 40 mg/dL (men) or < 50 mg/dL (women)
- Blood pressure $\geq 130/85$ mm Hg
- Glucose level ≥ 110 mg/dL

†For patients at high and moderate risk requiring drug therapy, clinicians should seek to lower LDL levels 30% to 40%

FIGURE 1

ADAPTED FROM SPRECHER DL, FROLKIS JP. USING THE NEW CHOLESTEROL GUIDELINES IN EVERYDAY PRACTICE. CLEVE CLIN J MED 2001; 68:617-622.

Case 2: A healthy 36-year-old woman

A healthy 36-year-old woman presents for primary prevention. Her family history is notable for myocardial infarction in her 62-year-old mother.

FASTING LIPID PROFILE

- Total cholesterol 234 mg/dL
- Triglycerides 130 mg/dL
- HDL-C 52 mg/dL
- LDL-C 156 mg/dL.

WHAT WOULD YOU RECOMMEND?

- Aggressive lipid-lowering therapy; goal LDL-C concentration lower than 70 mg/dL
- Lipid-lowering therapy; goal LDL-C lower than 130 mg/dL
- Therapeutic lifestyle changes
- No specific therapy at this time

Discussion. This patient needs no specific therapy at this time. She has the single cardiac risk factor of a family history of coronary heart disease in a

female first-degree relative younger than 65 years and so remains in the low-risk category (0–1 risk factor); her calculated Framingham risk score is less than 1%. In this category, the updated guidelines¹ did not change the LDL-C goal from the 2001 guidelines²: it is still less than 160mg/dL with initiation of therapeutic lifestyle changes at levels above 160 mg/dL. Lipid-lowering therapy should be instituted for an LDL-C 190 mg/dL or higher, and optionally for the range of 160 to 189 mg/dL.

The current guidelines do not endorse a generalized, across-the-board lowering of LDL-C to less than 70 mg/dL, except as an option in patients at very high risk.

On the other hand, in everyday practice, it seems reasonable to encourage most patients with risk factors for coronary heart disease to pursue therapeutic lifestyle changes, regardless of cholesterol levels. In addition, use of nontraditional risk markers such high-sensitivity C-reactive protein,^{17,18} homocysteine,¹⁹ and microalbuminuria²⁰ may decrease the threshold at which to initiate therapy.

- Cigarette smoking
- Hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, or currently taking antihypertensive medications)
- A high-density lipoprotein cholesterol (HDL-C) level lower than 40 mg/dL in men or 50 mg/dL in women (an HDL-C level of 60 mg/dL or higher, on the other hand, is a “negative” risk factor and subtracts one risk factor from the total count.)
- Family history of premature coronary heart disease, ie, in a male first-degree relative younger than 55 years or in a female first-degree relative younger than 65 years. The moderate-risk category is further divided into **moderately high risk** (10-year risk 10%–20%) or **moderate risk** (10-year risk < 10%).

Low risk: zero or one risk factor (see **CASE 2**).

Drug therapy for LDL-C 100–129?

For patients at high risk, the 2001 guidelines defined the LDL-C goal as lower than 100 mg/dL (instead of the earlier goal of 130 mg/dL). To achieve this goal they called for diet therapy if the LDL-C level was 100 mg/dL or higher and drug therapy if it was 130 mg/dL or higher.

However, they did not mandate drug therapy in the LDL-C range of 100 to 129 mg/dL; rather, they listed the following as optional: intensified dietary therapy, LDL-lowering drugs, or drug therapy for elevated triglycerides or low HDL-C. At that time, there were not enough data to recommend more intensive drug therapy for this range of LDL-C (see **CASE 3**).

RECENT CLINICAL TRIALS IN HIGH-RISK PATIENTS

The rationale for the 2004 update comes from several randomized clinical trials that were published after the 2001 guidelines.



Heart Protection Study: Simvastatin beneficial regardless of baseline LDL-C

The Heart Protection Study⁵ evaluated the effects of simvastatin 40 mg daily vs placebo in 20,536 patients 40 to 80 years old at high risk for coronary heart disease, as defined by existing coronary disease, other occlusive arterial disease, or diabetes (analogous to the 2001 designation of “coronary heart disease risk equivalent”).

At 5 years, the all-cause mortality rate was 13% lower in the simvastatin group than in the placebo group ($P = .0003$). Similarly, the incidence of major vascular events was 24% lower, coronary death 18% lower, the combined end point of nonfatal myocardial infarction or coronary death 27% lower, fatal or nonfatal stroke 25% lower, and cardiovascular revascularization 24% lower.

All subgroups benefitted from treatment: patients with or without diagnosed coronary heart disease, men or women, patients younger or older than 70 years at entry, and patients with or without diabetes mellitus. Among diabetic patients, rates of first major coronary events, stroke, and revascularizations were about 25% lower with treatment, and about 33% lower in patients with diabetes but without diagnosed coronary disease.

One of the key findings of the trial was that simvastatin treatment lowered risk regardless of the baseline level of LDL-C, including in the subgroup with LDL-C concentrations lower than 116 mg/dL.

PROVE IT-TIMI 22: Intensive therapy for acute coronary syndromes

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial compared intensive therapy (atorvastatin 80 mg daily) vs standard therapy (pravastatin 40 mg daily) in 4,162 patients hospitalized for acute coronary syndromes.⁶ The hypothesis of the trial was that standard therapy would not be inferior to intensive therapy.

At 2 years the mean LDL-C level was 62 mg/dL in the intensive therapy group vs 95 mg/dL in the standard therapy group. More important, the incidence of the composite cardiovascular end point was 16% lower in the intensive therapy group than in the stan-

dard therapy group ($P < .005$). The rates of total mortality and of the combined end point of death or myocardial infarction were also lower with intensive therapy, although the differences were not statistically significant.

PROSPER:

Elderly patients benefit from a statin

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) compared pravastatin 40 mg daily vs placebo in 5,804 elderly patients (age > 70 years) at high risk for cardiovascular disease.⁷

At 3.2 years, the incidence of the composite end point (coronary death, nonfatal myocardial infarction, or fatal or nonfatal stroke) was 15% lower in the pravastatin group ($P = .014$). The results of PROSPER reinforced the results of earlier studies that elderly patients at high risk benefit from treatment.

ALLHAT-LLT:

High crossover rate, little risk reduction

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid-Lowering Trial (ALLHAT-LLT) compared pravastatin vs usual care in 10,355 older, moderately hypercholesterolemic, hypertensive patients with at least one additional coronary risk factor.⁸ African Americans, women, and the elderly were well represented. The study was not blinded.

At 4.8 years, the rates of all-cause mortality or coronary event rates were slightly lower in the pravastatin treatment group, but the differences were not statistically significant. However, in the usual care group, about 30% of patients crossed over to the pravastatin group. Consequently, the mean total cholesterol level was only 9.6% lower in the pravastatin group than in the usual care group.

Although the effects of pravastatin vs usual care were small, the cholesterol-lowering arm of ALLHAT is important because it confirmed the importance of the guidelines for African Americans and affirmed their applicability to women and the elderly.

ASCOT-LLA:

Therapy better than placebo

The Anglo-Scandinavian Cardiac Outcomes

The rationale for the update comes from several recent trials

Case 3: A man with diabetes

A 56-year-old man with a 2-year history of type 2 diabetes mellitus presents for primary prevention. He does not have hypertension and is treated with metformin alone.

LABORATORY VALUES

- Total cholesterol 184 mg/dL
- Triglycerides 120 mg/dL
- HDL-C 48 mg/dL
- LDL-C 112 mg/dL
- Hemoglobin A_{1c} 5.9%
- Urine albumin/creatinine ratio 1.5 mg/mmol.

WHAT WOULD YOU RECOMMEND?

- Therapeutic lifestyle changes
- Lipid-lowering therapy with a goal LDL-C concentration lower than 100 mg/dL
- Lipid-lowering therapy with a goal LDL-C less than 70 mg/dL
- No specific therapy at this time

Discussion. The patient should start both therapeutic lifestyle changes and lipid-lowering therapy with a goal LDL-C level of less than 100 mg/dL.

He has diabetes mellitus (a condition classified as a coronary heart disease risk equivalent) without diagnosed or manifest coronary heart disease. Therefore, he should be treated and his goal LDL-C concentration should be less than 100 mg/dL. Since his LDL-C level is 112 mg/dL, there is an option to begin statin lipid-lowering therapy as opposed to therapeutic lifestyle changes alone; the results of the Heart Protection Study suggested a benefit of statins in the diabetic population.⁵

However, there are insufficient data yet to recommend an LDL-C goal of less than 70 mg/dL in all patients with diabetes. This patient could be said to have “lower-risk diabetes,” since his diabetes is well controlled and he does not have hypertension or microalbuminuria. When one is initiating lipid-lowering therapy, however, the updated guidelines recommend an intensity of therapy to effect at least a 30% to 40% reduction in LDL-C: this patient’s LDL-C level may well approach or even fall below 70 mg/dL. It should be emphasized nonetheless that the absolute goal of less than 70 mg/dL is not applicable to all patients, nor even to all diabetic patients.

Trial (ASCOT)⁹ evaluated two antihypertensive regimens in patients with high blood pressure and at least three additional cardiovascular risk factors. More than 60% of the enrollees were 60 to 79 years old.

In the lipid-lowering arm of the study (ASCOT-LLA), 10,305 patients—more than half of the enrollees of ASCOT—were additionally randomized to receive atorvastatin 10 mg daily or placebo. The average LDL-C concentration was 132 mg/dL at baseline and was reduced by an average of 42 mg/dL (29%) in the atorvastatin group.

The study was stopped early (median follow-up 3.3 years) because of markedly positive findings in the atorvastatin group: a 29% lower rate of total coronary events ($P < .0005$), a 21% lower rate of total cardiovascular events ($P < .0005$), a 48% lower rate of stroke, and a lower mortality rate that was not

statistically significant.

Older patients benefitted from treatment as much as younger patients: there was a 36% relative risk reduction in the primary end point (nonfatal myocardial infarction and fatal coronary heart disease) in subjects older than 60 years ($N = 6,570$), comparable to the 34% relative risk reduction in subjects age 60 and younger ($N = 3,735$).

■ BETTER UNDERSTANDING OF LDL-C AND RISK

The 2004 update reflects our growing understanding about the relation between LDL-C and cardiovascular risk.

For decades, observational studies such as the Framingham Heart Study showed that the relationship between LDL-C concentration



and the risk of coronary heart disease was curvilinear, ie, the higher the LDL-C concentration, the more steeply the risk rises—and the more the risk falls with therapy.¹⁰ Now, clinical trials are confirming the observational findings that the relationship is curvilinear, (FIGURE 2).

Although there are differences in study duration over the past 2 decades, the following examples help to demonstrate the curvilinear relationship between LDL-C and reduction in coronary disease risk.

In the 1984 Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT),¹¹ the mean entry LDL-C concentration was 216 mg/dL, which was reduced with therapy by 11%, resulting in a 19% relative reduction in events. Thus, in this trial, for every 1% reduction in LDL-C the event rate was reduced by 2%.

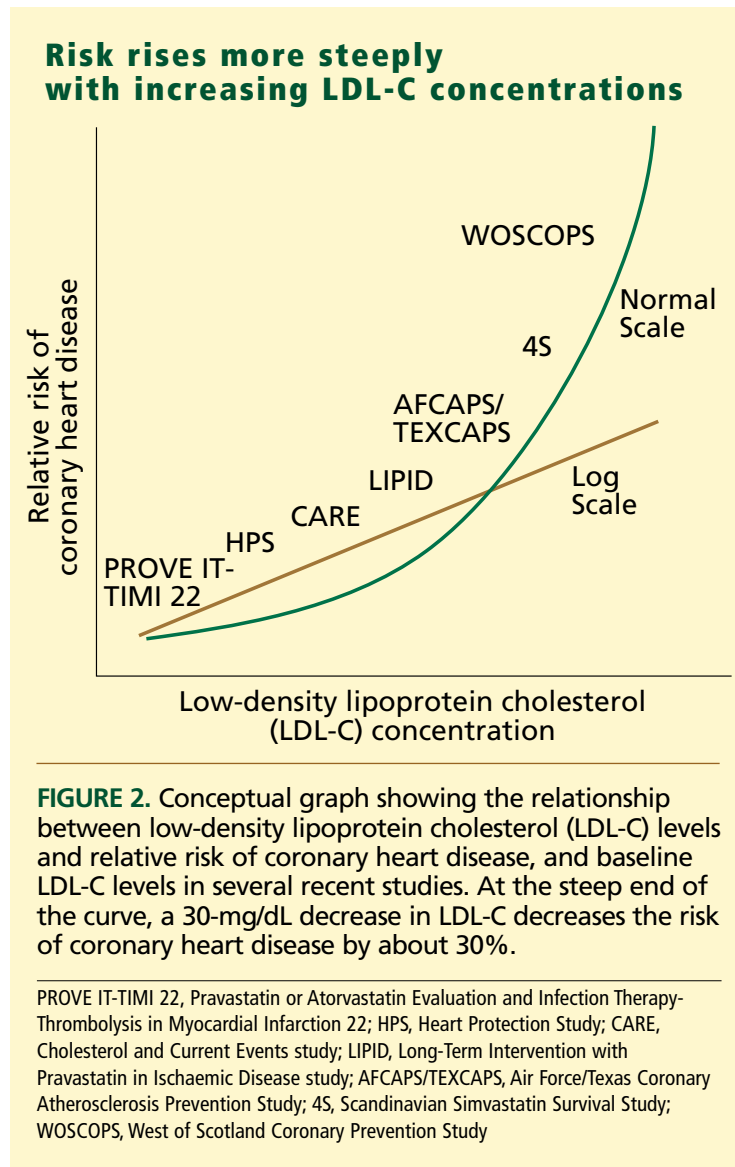
In trials in the mid-1990s,¹² baseline LDL-C levels were in the mid-100 mg/dL range and were reduced by 25% to 40% with therapy. For every 1% reduction in LDL-C, events were reduced by about 1%.

In 2001, not enough data from clinical trials were available to determine whether reducing LDL-C to levels well below 100 mg/dL would be similarly beneficial.¹³ Thus, the 2001 guidelines set the LDL-C goal for patients at high risk at less than 100 mg/dL as a minimal goal of treatment. However, the panel recognized that this level of 100 mg/dL did not necessarily provide maximal risk reduction.

More recent clinical trials included patients with lower baseline LDL-C levels and are beginning to fill in the missing data points.

The Heart Protection Study⁵ suggested that lowering LDL-C to well below 100 mg/dL in patients at high risk and very high risk could further decrease risk, even if their baseline LDL-C levels are already below 100 mg/dL.

The PROVE IT-TIMI 22 trial⁶ confirmed the benefit, as the incidence of cardiovascular end points was 16% lower in the intensive therapy group (which achieved a mean LDL-C concentration of 62 mg/dL) than in the standard therapy group (in which the mean LDL-C concentration achieved was 95 mg/dL). This translates into



just a 0.5% reduction in events for every 1% reduction in LDL-C.

Thus, although the Heart Protection Study and PROVE IT-TIMI 22 show that reducing LDL-C to less than 100 mg/dL can be beneficial, the relative risk reduction in this part of the curve is incrementally less for the same absolute change in LDL-C. However, as yet, researchers have not identified an LDL-C level below which no further risk reduction will occur. The results of ongoing trials such as the Treating to New Targets study (comparing atorvastatin 10 mg vs 80 mg) may be instructive.¹⁴

■ SUMMARY OF THE UPDATE

Below is a summary of the key changes outlined in the 2004 update.

Optional LDL-C goal: < 70 mg/dL for patients at 'very high risk'

The update states: "An LDL-C goal < 70 mg/dL for high-risk patients must be left as a therapeutic option on the basis of clinical trial evidence, whereas a goal of < 100 mg/dL can be retained as a strong recommendation."¹

An LDL-C goal of < 70 mg/dL should be considered in patients at "very high risk," eg, those with known cardiovascular disease plus any of the following:

- Multiple major risk factors, especially diabetes mellitus
- Severe and poorly controlled risk factors, especially cigarette smoking
- Multiple risk factors of the metabolic syndrome, including elevated triglycerides (≥ 200 mg/dL), elevated non-HDL-C (≥ 130 mg/dL), and low HDL-C (< 40 mg/dL)
- Acute coronary syndromes.

This new category of very high risk includes all patients with acute coronary syndromes, most patients with multiple risk factors associated with substantially increased coronary risk based on the presence of known coronary heart disease plus other risk factors (eg, with diabetes or low HDL-C) or, in the absence of known coronary heart disease, multiple risk factors for it.

Although not all of these subgroups of patients at very high risk were represented in the clinical trials in which LDL-C levels lower than 70 mg/dL were achieved, it is reasonable to set the target LDL-C at less than 70 mg/dL for all such patients. However, even with aggressive therapy, this target may not be achievable in all patients, as some of them may not tolerate the high medication doses or combinations that are necessary to achieve this new target.

Should all patients at high risk aim for LDL-C < 70?

What about patients at high risk but not "very high risk," eg, those with diabetes mellitus but no other risk factors? For these patients the goal is less well defined and has been the

source of some uncertainty. Data from clinical trials support an LDL-C goal of less than 100 mg/dL, but there is not yet evidence to recommend a goal of less than 70 mg/dL.

The 2001 guidelines identified diabetes mellitus as a coronary heart disease risk equivalent and placed patients with diabetes in the high-risk category. In the Heart Protection Study, patients with diabetes plus known cardiovascular disease derived the greatest benefit from statin therapy of all the subgroups, and thus this group warrants aggressive therapy with the optional goal LDL-C concentration less than 70 mg/dL.

Patients with diabetes without known cardiovascular disease also benefit from LDL-lowering therapy. But not all diabetic patients have risk equivalent to that of coronary heart disease, especially if they do not have hypertension, albuminuria, or low HDL-C concentrations. The 2001 guidelines acknowledged that some younger diabetic patients may not be "CHD risk equivalent," but did not make special recommendations for this group.

After the guidelines were updated, the Collaborative Atorvastatin Diabetes Study (CARDS), a primary prevention study in 2,838 diabetic patients, showed that those who received atorvastatin 10 mg daily (and achieved a mean LDL-C concentration of approximately 80 mg/dL) had a 37% lower rate of coronary events than did those receiving placebo (whose mean LDL-C concentration was 120 mg/dL).¹⁵ These data further support the guidelines.

In older people, elevated cholesterol levels confer a lower relative risk for mortality than in younger people, but the risk remains high. The Heart Protection Study specifically showed a benefit of statin therapy in patients 65 to 80 years old with known cardiovascular disease, and results of PROSPER and ASCOT-LLA likewise showed benefit in older patients without known cardiovascular disease.

Clinicians are left to make some assessment of risk and the ease of achieving LDL-C concentrations well below 100 mg/dL in these situations.

Aim for a percent reduction in LDL-C?

Although the relationship between LDL-C and coronary risk is continuous and graded, the

Low cholesterol may be due to cancer, not the cause of it



2001 guidelines were based on absolute target LDL-C levels: 100, 130, or 160 mg/dL. This approach was easy to communicate to patients and physicians. However, most clinical trials aimed for a percent reduction in LDL-C. Therefore, the updated guidelines also emphasize the goal of a 30% to 40% reduction from baseline LDL-C to achieve a corresponding 30% to 40% reduction in coronary risk.

This recommendation applies to patients with LDL-C levels at or near the targets. For example, under the 2001 guidelines, a patient at high risk presenting with a baseline LDL-C concentration of 110 mg/dL might need only minimal drug therapy to achieve the goal of 100 mg/dL. The updated guidelines now say: "...if drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction."¹

Other targets of therapy

Metabolic syndrome. The 2001 guidelines identified the features of the metabolic syndrome (abdominal obesity, hypertension, glucose intolerance, high triglycerides, low HDL) as conferring high risk for coronary heart disease. Therapeutic lifestyle changes are recommended, including a low-fat diet and exercise.


Low HDL-C is a significant risk factor for coronary heart disease, but no specific goal value for raising HDL-C is specified in the 2001 guidelines or the update, nor is there a goal for lowering high triglycerides. Fibrates or

nicotinic acid are endorsed for their effects on triglycerides and HDL-C, but the focus of therapy is on reducing LDL-C to goal levels.

■ POTENTIAL SIDE EFFECTS OF THERAPY

In large epidemiologic studies,¹⁶ very low serum cholesterol levels were linked to higher total mortality rates, though no definite causal links to cancer or cerebral hemorrhage have been identified. Furthermore, the association was even less robust when results were adjusted for cancers diagnosed within 1 year of detection or the beginning of cholesterol-lowering therapy.

These findings suggest that a low cholesterol concentration might be due to pre-existing cancer (which causes cholesterol levels to drop) rather than the cause of cancer. Recent statin trials with low LDL-C levels have not reported trends toward higher incidences of cancer or total mortality, thus allaying earlier fears about aggressive cholesterol-lowering.

In clinical practice, many patients stop taking statins because of muscular complaints. However, the Heart Protection Study showed no significant difference in reports of muscle pain or weakness between the simvastatin-treated and placebo-treated groups (32.9% vs 33.2%); there was an annual excess risk of myopathy of only 0.01%. In addition, there does not appear to be any significant difference in the rate of serum aminotransferase elevations between statin-treated and placebo-treated groups. 

■ REFERENCES

1. Grundy SM, Cleeman JI, Merz CN, et al; Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol* 2004; 44:720-732.
2. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106:3143-3421.
3. The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Arch Intern Med* 1988; 148:36-69.
4. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994; 89:1333-1445.
5. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360:7-22.
6. Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; 350:1495-1504.
7. Shepherd J, Blauw GJ, Murphy MB, et al; PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360:1623-1630.
8. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002; 288: 2998-3007.
9. Sever PS, Dahlof B, Poulter NR, et al; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361:1149-1158.
10. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003; 326:1423-1427.
11. Lipid Research Clinics Program. The Lipid Research Clinics Coronary



- Primary Prevention Trial results I. Reduction in incidence of coronary heart disease. *JAMA* 1984; 251:351–364.
12. **Shepherd J, Cobbe SM, Ford I, et al for the West of Scotland Coronary Prevention Study Group.** Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1994; 333:1301–1307.
 13. **Sacks FM, Tonkin AM, Shepherd J, et al.** Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project. *Circulation* 2000; 102:1893–1900.
 14. **Waters DD, Guyton JR, Herrington DM, et al; TNT Steering Committee Members and Investigators.** Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *Am J Cardiol* 2004; 93:154–158.
 15. **Colhoun HM, Betteridge DJ, Durrington PN, et al; CARDS investigators.** Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; 364:685–696.
 16. **Neaton JD, Blackburn H, Jacobs D, et al.** Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. *Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med* 1992; 152:1490–1500.
 17. **Ridker PM.** High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* 2001; 103:1813–1818.
 18. **Ridker PM, Rifai N, Rose L, Buring JE, Cook NR.** Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; 347:1557–1565.
 19. **Stampfer MJ, Manilow MA, Willett WC, et al.** A prospective study of plasma homocyst(e)ine and risk of myocardial infarction in US physicians. *JAMA* 1992; 268:877–881.
 20. **Gerstein HC, Mann JF, Yi Q, et al.** Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; 286:421–426.
-
- ADDRESS:** Julie Huang, MD, Section of Preventive Cardiology, C51, Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail huangj1@ccf.org.