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Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines

Scott M. Grundy; James I. Cleeman; C. Noel Bairey Merz; H. Bryan Brewer, Jr; Luther T. Clark; Donald B. Hunninghake*; Richard C. Pasternak; Sidney C. Smith, Jr; Neil J. Stone; for the Coordinating Committee of the National Cholesterol Education Program

Endorsed by the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association

Abstract—The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program issued an evidence-based set of guidelines on cholesterol management in 2001. Since the publication of ATP III, 5 major clinical trials of statin therapy with clinical end points have been published. These trials addressed issues that were not examined in previous clinical trials of cholesterol-lowering therapy. The present document reviews the results of these recent trials and assesses their implications for cholesterol management. Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. The trials confirm the benefit of cholesterol-lowering therapy in high-risk patients and support the ATP III treatment goal of low-density lipoprotein cholesterol (LDL-C) <100 mg/dL. They support the inclusion of patients with diabetes in the high-risk category and confirm the benefits of LDL-lowering therapy in these patients. They further confirm that older persons benefit from therapeutic lowering of LDL-C. The major recommendations for modifications to footnote the ATP III treatment algorithm are the following. In high-risk persons, the recommended LDL-C goal is <100 mg/dL, but when risk is very high, an LDL-C goal of <70 mg/dL is a therapeutic option, ie, a reasonable clinical strategy, on the basis of available clinical trial evidence. This therapeutic option extends also to patients at very high risk who have a baseline LDL-C <100 mg/dL. Moreover, when a high-risk patient has high triglycerides or low high-density lipoprotein cholesterol (HDL-C), consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL, but an LDL-C goal <100 mg/dL is a therapeutic option on the basis of recent trial evidence. The latter option extends also to moderately high-risk persons with a baseline LDL-C of 100 to 129 mg/dL. When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels. Moreover, any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglycerides, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level. Finally, for people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy. (*Circulation*. 2004;110:227-239.)

Key Words: cholesterol ■ trials ■ lipoproteins ■ coronary disease

The Executive Summary of the 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 [ATP III]) was published in May 2001.¹ The full report of ATP III was published in December 2002.² ATP III provides evidence-based recommen-

dations on the management of high blood cholesterol and related disorders. For development of its recommendations, ATP III places primary emphasis on large, randomized, controlled clinical trials (RCTs). In the past decade, a series of large RCTs have yielded a vast body of data for these recommendations. Other lines of evidence, including prospective epidemiological studies

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and smaller clinical trials, afford additional evidence for crafting the recommendations.

All ATP reports have identified low-density lipoprotein cholesterol (LDL-C) as the primary target of cholesterol-lowering therapy. Many prospective studies have shown that high serum concentrations of LDL-C are a major risk factor for coronary heart disease (CHD). A large number of RCTs, moreover, have documented that lowering of LDL-C levels will reduce the risk for major coronary events. In ATP II,³ evidence for the benefit of LDL-lowering therapy was based on analysis and meta-analysis of RCTs that were carried out with therapies other than HMG CoA reductase inhibitors (statins). ATP III^{1,2} reviewed new data from 5 large RCTs with statins. Results of several smaller RCTs with statins and other drugs also were examined. On the basis of accumulated evidence from epidemiological studies and RCTs, ATP III proposed a treatment algorithm for LDL-lowering therapy.

Since the publication of ATP III, 5 major clinical trials with statin therapy and clinical end points have been published. These include the Heart Protection Study (HPS),⁴ the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER),⁵ Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid-Lowering Trial (ALLHAT-LLT),⁶ Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA),⁷ and the Pravastatin or Atorvastatin Evaluation and Infection—Thrombolysis in Myocardial Infarction 22 (PROVE IT—TIMI 22) trial.⁸ These trials addressed issues that had not been adequately addressed in previous statin trials. The results appear to have important implications for the management of patients with lipid disorders, particularly for high-risk patients. They further may require some rethinking of the treatment thresholds of ATP III recommendations. In addition, findings of other smaller trials or subgroup analyses of major trials have been published. The purpose of the present document is to examine the results of all of these studies and to assess their implications in relation to the ATP III report. First, we will summarize the principal elements of the ATP III treatment algorithm and the major findings of the recent trials.

According to the ATP III algorithm, persons are categorized into 3 risk categories: (1) established CHD and CHD risk equivalents, (2) multiple (2+) risk factors, and (3) zero to one (0–1) risk factor. CHD risk equivalents include noncoronary forms of clinical atherosclerotic disease, diabetes, and multiple (2+) CHD risk factors with 10-year risk for CHD >20%. All persons with CHD or CHD risk equivalents can be called *high risk*. The goal for LDL-lowering therapy in high-risk patients is an LDL-C level <100 mg/dL. According to ATP III, for a baseline or on-treatment LDL-C <100 mg/dL, no further LDL-lowering therapy was recommended. For all high-risk patients with LDL-C levels \geq 100 mg/dL, LDL-lowering dietary therapy should be initiated. When baseline LDL-C is \geq 130 mg/dL, an LDL-lowering drug should be started simultaneously with dietary therapy. However, LDL-lowering drugs were not mandated if the baseline LDL-C level is in the range of 100 to 129 mg/dL; in this range, ATP III suggested several therapeutic options. Dietary therapy should be intensified, whereas adding or intensifying an LDL-lowering drug was said to be optional. Alternatively,

if the patient has elevated triglycerides or low high-density lipoprotein cholesterol (HDL-C), a drug that targets these abnormalities may be added.

Compared with ATP II,³ ATP III added new intensity to LDL-C lowering in patients with multiple (2+) CHD risk factors. Previous ATP guidelines established the LDL-C goal for this category to be a level <130 mg/dL. This goal was retained in ATP III, but risk assessment was expanded beyond the counting of risk factors. ATP III recommended that Framingham risk scoring be carried out in individuals with 2+ risk factors so as to triage them into 3 levels of 10-year risk for hard CHD events (myocardial infarction + CHD death): >20%, 10% to 20%, and <10%. Persons with a 10-year risk >20% were elevated to the high-risk category; for them, the LDL-C goal is <100 mg/dL. For others with 2+ risk factors and a 10-year risk \leq 20%, the LDL-C goal is <130 mg/dL. LDL-lowering dietary therapy is universally advocated for patients with an LDL-C above the goal level. If the 10-year risk is 10% to 20%, drug therapy should be considered if the LDL-C level is above the goal level (ie, \geq 130 mg/dL) after a trial of dietary therapy. When 10-year risk is <10%, an LDL-lowering drug can be considered if the LDL-C level is \geq 160 mg/dL on maximal dietary therapy.

Finally, most persons with 0 to 1 risk factor have a 10-year risk <10%. For these individuals, clinical management and dietary therapy is recommended when the LDL-C level is \geq 160 mg/dL. The goal is to lower LDL-C concentrations to <160 mg/dL. If the LDL-C is \geq 190 mg/dL after an adequate trial of dietary therapy, consideration should be given to adding a cholesterol-lowering drug. When serum LDL-C ranges from 160 to 189 mg/dL, introduction of a cholesterol-lowering drug is a therapeutic option in appropriate circumstances, such as when a severe risk factor is present. ATP III outlines several factors that can be taken into consideration to guide clinical judgment for this category.

ATP III placed major emphasis on therapeutic lifestyle changes (TLC) as an essential modality in clinical management for persons at risk for cardiovascular disease (CVD). ATP III's TLC approach was designed to achieve risk reduction through both LDL-C lowering and metabolic syndrome management. Therefore, when the implications of recent LDL-lowering drug trials are considered, it must be reemphasized that the results do not in any way diminish the importance of lifestyle change for CVD risk reduction.

Review of Recent Clinical Trials With Major Cardiovascular End Points

Heart Protection Study

This clinical trial was carried out in 20 536 adults living in the United Kingdom (aged 40 to 80 years) who were at high risk for a CVD event.⁴ Entrance criteria included coronary disease, other occlusive arterial disease, or diabetes. Patients were randomly allocated to 40 mg simvastatin daily or placebo. Primary outcomes included total mortality for overall analysis and fatal or nonfatal vascular events for subcategory analyses. The incidence of cancer and other major morbidity also was determined.

Serum lipids at baseline were determined on nonfasting samples. Levels of LDL-C were measured by the direct LDL method.⁹ Average lipid values at baseline were total cholesterol 228 mg/dL, triglycerides 186 mg/dL (nonfasting), HDL-C 41 mg/dL, non-HDL-C 187 mg/dL, and direct LDL-C 131 mg/dL. In most other clinical trials of cholesterol-lowering therapy, serum lipid levels have been determined on fasting samples, and LDL-C has been calculated by the Friedewald equation [LDL-C = total cholesterol – HDL-C – VLDL-C (triglycerides/5)], where VLDL indicates very-low-density lipoprotein.¹⁰ This calculation includes intermediate-density lipoprotein in the LDL fraction. If this equation were applied to the HPS values cited above, the average calculated LDL-C would be approximately 150 mg/dL [(228–41–(186/5)]. However, because the baseline samples were nonfasting, the triglyceride levels were likely to have been at least 20 to 30 mg/dL higher than fasting; consequently, applying the Friedewald equation to baseline levels would underestimate LDL-C by 4 to 6 mg/dL [(20 to 30 mg/dL)/5] because this much cholesterol was falsely attributed to VLDL-C. Consequently, estimations of baseline fasting LDL-C, if calculated by the Friedewald equation, likely would have been in the range of 150 to 155 mg/dL, or about 15% higher than baseline LDL-C calculated by the direct method. If this difference between direct and calculated LDL-C holds at low LDL-C, a direct LDL-C level of 100 mg/dL would correspond to a calculated LDL-C of 115 mg/dL. Although this difference could be of some significance for treatment decisions, to avoid confusion the distinction will not be emphasized in the discussion to follow.

In patients allocated to simvastatin, all-cause mortality was significantly reduced by 13% ($P=0.0003$). Major vascular events were reduced by 24%, coronary death rate by 18%, nonfatal myocardial infarction + coronary death by 27%, nonfatal or fatal stroke by 25%, and cardiovascular revascularization by 24%. The reduction in the event rate was similar in each subcategory, including patients without diagnosed coronary disease who had cerebrovascular disease, or peripheral artery disease, or diabetes. Similar event reductions on simvastatin therapy occurred for men and women and for participants either under or over 70 years of age at entry. No significant adverse effects of simvastatin therapy were reported, including no significant increase in myopathy, cancer incidence, or hospitalization for any other nonvascular cause.

Subgroup analysis of HPS suggests that simvastatin therapy produced similar reductions in relative risk regardless of the baseline levels of LDL-C, including subgroups with initial (or baseline) LDL-C levels ≥ 135 mg/dL, < 116 mg/dL, or < 100 mg/dL. At least 2 issues, however, can be noted with regard to the reported subgroup analysis of HPS at low (or very low) LDL-C levels. First, LDL-C cutpoints to define these subgroups would have been higher if LDL-C had been calculated by the Friedewald equation, the method employed by ATP III for routine clinical practice. Second, the characteristics of low-LDL subgroups, ie, what portions had hypertriglyceridemia, elevated non-HDL-C, or diabetes, or were free of CVD, have not been made available. These qualifying issues must be kept in mind when generalizing HPS findings to all high-risk patients with low baseline LDL-C levels.

HPS investigators further examined their results more closely for persons with diabetes.¹¹ The study included 5963 individuals with diabetes (ages 40 to 80 years). Those subjects receiving simvastatin 40 mg/d had significant reductions of approximately one quarter in first-event rates for major coronary events, strokes, and revascularizations. Event reductions were similar to those for nondiabetic patients. In 2912 patients with diabetes and without diagnosed coronary or other occlusive arterial disease at entry, simvastatin therapy reduced risk by about one third. In 2426 participants with diabetes whose pretreatment LDL-C was < 116 mg/dL, event rates were 27% lower on simvastatin therapy. In the subgroup of patients with diabetes who were without vascular disease and whose LDL-C levels were < 116 mg/dL at baseline, a marginally significant 30% reduction in risk was observed. Efficacy of simvastatin therapy in the subgroup of patients with LDL-C < 100 mg/dL was not reported. HPS investigators concluded that, in general, cholesterol lowering with statin therapy is efficacious in patients with diabetes, including those without manifest CHD and those with relatively low LDL-C levels.

Prospective Study of Pravastatin in the Elderly at Risk

This trial examined the efficacy of pravastatin treatment in older men and women with or at high risk of developing CVD and stroke.⁵ Subjects ($n=5804$; 2804 men and 3000 women), ages 70 to 82 years, who had a history of vascular disease or CVD risk factors were randomized to pravastatin (40 mg/d) or placebo. The primary end point was a composite of coronary death, nonfatal myocardial infarction, and fatal or nonfatal stroke. Baseline total cholesterol varied widely from 150 mg/dL to 350 mg/dL. Follow-up averaged 3.2 years. Pravastatin reduced LDL-C levels by 34%. The composite end point was reduced on pravastatin therapy by 15% ($P=0.014$). Major coronary events, defined as nonfatal myocardial infarction and CHD death, fell on therapy by 19% ($P=0.006$), and CHD mortality by 24% ($P=0.043$). No reduction in stroke was observed, but transient ischemic attacks fell by 25% on therapy ($P=0.051$). The stroke rate in the trial, however, was about half of that predicted, so the effects of statin therapy on stroke must be viewed in this light. New cancer unexpectedly was found 25% more often on pravastatin treatment ($P=0.020$). This finding, however, contrasts with meta-analysis of all pravastatin and all statin trials, in which overall cancer incidence was not increased.⁵ Pravastatin therapy neither improved cognitive function nor retarded progression of disability. According to the authors, PROSPER results allow statin therapy to be extended to older persons.

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid-Lowering Trial

The primary goal of ALLHAT was to evaluate current modalities of hypertension treatment. The lipid-lowering component, which was a subset of this trial, was designed to assess whether pravastatin therapy compared with usual care reduces all-cause mortality in older, moderately hypercholes-

terolemic, hypertensive participants with at least one additional CHD risk factor.⁶ The study used 513 primarily community-based North American clinical centers. The lipid-lowering component of ALLHAT randomized 10 355 persons. Participants were over 55 years of age and had LDL-C levels ranging from 120 to 189 mg/dL and triglycerides below 350 mg/dL. Those patients with LDL-C levels \geq 120 mg/dL (100 to 129 mg/dL if known CHD) and triglycerides lower than 350 mg/dL were randomized to nonblinded arms of pravastatin (n=5170) or usual care (n=5185). Baseline mean total cholesterol was 224 mg/dL; LDL-C, 146 mg/dL; HDL-C, 48 mg/dL; and triglycerides, 152 mg/dL. Mean age was 66 years; 49% were women; 38% were black and 23% Hispanic; 14% had a history of CHD; and 35% had type 2 diabetes. The primary outcome was all-cause mortality, and secondary outcomes were nonfatal myocardial infarction or fatal CHD (CHD events) combined, cause-specific mortality, and cancer.

Mean follow-up duration of participants was 4.8 years. Crossover of usual-care participants to lipid-lowering drugs was high (32% of usual-care participants with CHD and 29% without CHD). Follow-up of patients for lipid results was not complete. Among a nonrandom subset of participants tested, total cholesterol levels were reduced by 17% with pravastatin versus 8% with usual care at 4 years. In ALLHAT-LLT, all-cause mortality was similar for the 2 groups, with 6-year mortality rates of 14.9% for pravastatin versus 15.3% with usual care. For all participants, CHD event rates were not significantly different between the groups, with 6-year CHD event rates of 9.3% for pravastatin and 10.4% for usual care. In the African-American subgroup, however, CHD events were significantly reduced in the pravastatin arm compared with usual care. The authors speculated that the failure to detect a significant reduction in risk in hypertensive patients treated with pravastatin may be due to the modest differential in total cholesterol (9.6%) between pravastatin and usual care. Other possible explanations for the failure to observe a treatment benefit could be the unblinded nature of the study without a placebo arm and a large crossover of higher-risk subjects in the usual-care arm to active lipid-lowering therapy.

Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm

In contrast to the ALLHAT lipid-lowering component, a markedly different result was obtained in hypertensive patients in ASCOT-LLA.⁷ In this study, 19 342 hypertensive patients, 40 to 79 years old and having at least 3 other cardiovascular risk factors, were randomized to 1 of 2 antihypertensive regimens. Among these subjects, 10 305 were in addition randomly assigned atorvastatin 10 mg or placebo. Selection was made on the basis of nonfasting total cholesterol of \leq 251 mg/dL (6.5 mmol/L). LDL-C levels averaged 132 mg/dL and were reduced by an average of 42 mg/dL (29%) in the atorvastatin-treated group at the end of the study. The primary end point was nonfatal myocardial infarction and fatal CHD. The study was planned for a follow-up of an average of 5 years but was stopped after a median follow-up of 3.3 years. At that time, 100 primary

events had occurred in the atorvastatin group, compared with 154 events in the placebo group (hazard ratio 0.64, $P=0.0005$). In the atorvastatin group, incidence of fatal and nonfatal stroke was reduced by 27% ($P=0.024$), total cardiovascular events by 21% ($P=0.0005$), and total coronary events by 29% ($P=0.0005$). There was a nonsignificant trend toward a reduction in total mortality in the atorvastatin group (13%; $P=0.16$). Because of these markedly positive findings with atorvastatin therapy, the study was terminated prematurely. The authors indicated that LDL lowering with atorvastatin therapy has considerable potential to reduce risk for CVD in primary prevention in patients with multiple CVD risk factors.

Pravastatin or Atorvastatin Evaluation and Infection—Thrombolysis in Myocardial Infarction 22

This study, designated PROVE IT,⁸ was designed to determine whether intensive LDL-C lowering will reduce major coronary events, including mortality, more than “standard” LDL-C lowering with statin therapy in high-risk patients. Two statins at different doses were compared: atorvastatin 80 mg versus pravastatin 40 mg. Previous studies have shown that pravastatin 40 mg produces a reduction of LDL-C equivalent to approximately 10 mg of atorvastatin. Prior clinical trials have demonstrated that treatment of patients with established CHD with pravastatin 40 mg will reduce LDL-C levels to near 100 mg/dL and will reduce risk for major coronary events by approximately 27%.¹² In PROVE IT, 4162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days were enrolled and randomized to the 2 therapies. The primary end point of the trial was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. Mean follow-up time was 24 months. At the end of 2 years of therapy, the composite cardiovascular end point was reduced by 16% with atorvastatin compared with pravastatin ($P<0.005$). Nonsignificant trends were observed on atorvastatin therapy for total mortality ($P<0.07$) and for death or myocardial infarction ($P<0.06$). The high dose of atorvastatin was well tolerated, and no case of severe myopathy (rhabdomyolysis) was observed in either treatment group. Greater than 3-fold elevations of alanine aminotransferase were observed in 3.3% of patients treated with atorvastatin versus 1.1% on pravastatin ($P<0.003$).

The LDL-C level attained on pravastatin 40 mg was 95 mg/dL, whereas the level attained on atorvastatin 80 mg was 62 mg/dL. The difference in LDL-C thus was 33 mg/dL (35%). The results of PROVE IT suggest that more intensive LDL-C-lowering therapy reduces major cardiovascular events in patients with acute coronary syndrome compared with less intensive therapy over a period of 2 years. It must be noted, however, that 72% of the patients had LDL-C levels <125 mg/dL, and in this large subgroup, the modest trend toward benefit of atorvastatin over pravastatin was not statistically significant.

Lipid Targets of Therapy

LDL-C: The Primary Target of Lipid-Lowering Therapy

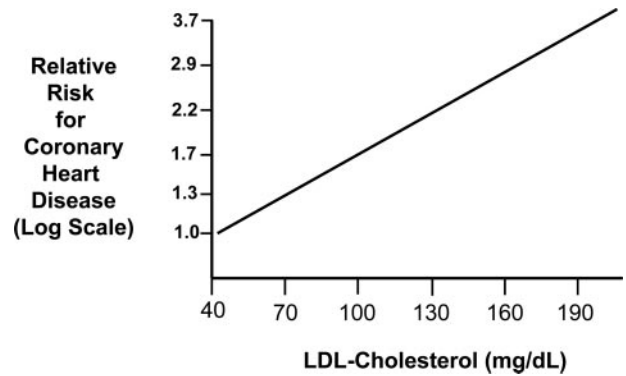
The identification of an elevated LDL-C as the primary target of lipid-lowering therapy is based on a wealth of information from basic research, animal studies, epidemiological studies, genetic forms of hypercholesterolemia, and controlled clinical trials. Recent clinical trials add further support for the NCEP priority on high serum LDL-C. Four new trials^{4,5,7,8} demonstrate that effective LDL-C reduction substantially reduces risk for CHD, whereas one trial⁶ failed to produce a sizable differential in LDL-C levels between treatment and control groups and did not yield a significant risk reduction.

Other Lipid Targets

It should be noted that ATP III introduced a new secondary target of therapy, namely non-HDL-C, in patients with elevated triglycerides (≥ 200 mg/dL). Non-HDL-C equates to VLDL + LDL-C (which, when calculated, includes intermediate-density lipoprotein). The non-HDL-C goal is 30 mg/dL higher than the LDL-C goal. Non-HDL-C was added as a secondary target of therapy to take into account the atherogenic potential associated with remnant lipoproteins in patients with hypertriglyceridemia. Because statins lower LDL-C cholesterol and non-HDL-C to a similar percentage, recent clinical trials do not differentiate between these 2 lipid measures with regard to their relative benefits in risk reduction.

Although the potential benefit of HDL-raising therapy has evoked considerable interest, current documentation of risk reduction through controlled clinical trials is not sufficient to warrant setting a specific goal value for raising HDL-C. Recent lipid-lowering drug trials provide no new evidence in this regard.¹³ New drugs that effectively raise serum HDL-C levels are currently under development, and it is likely that these drugs will be tested for efficacy for clinical event reduction in the future. One class of drugs that modestly raises HDL-C is the fibrates. Post-hoc analysis^{2,14} of several clinical trials with fibrates indicates that they reduce risk for CHD events in patients with high triglycerides and low HDL-C, especially when the patients have diabetes or characteristics of the metabolic syndrome.¹⁵ Although the evidence base to support fibrate therapy is not as strong as that for statins, fibrates may have an adjunctive role in the treatment of patients with high triglycerides/low HDL, especially in combination with statins. Concern about development of myopathy with this combination has been lessened somewhat by the recent finding that one fibrate, fenofibrate, does not interfere with catabolism of statins and thus likely does not substantially increase the risk for clinical myopathy in patients treated with moderate doses of statins.^{16,17}

Another drug that raises HDL-C is nicotinic acid. Several clinical trials support the efficacy of nicotinic acid for reduction of CHD risk, both when used alone^{18,19} and in combination with statins.^{20,21} The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C.²² As a result of these studies, the US Food and Drug Administration has approved one



Log-linear relationship between LDL-C levels and relative risk for CHD. This relationship is consistent with a large body of epidemiological data and with data available from clinical trials of LDL-lowering therapy. These data suggest that for every 30-mg/dL change in LDL-C, the relative risk for CHD is changed in proportion by about 30%. The relative risk is set at 1.0 for LDL-C=40 mg/dL.

statin/nicotinic acid combination. Although the majority of patients can tolerate nicotinic acid therapy, a sizable minority are intolerant because of a variety of side effects.

Relation of Serum LDL-C Concentrations to CHD Risk

Epidemiological surveys have shown that serum total cholesterol levels are continuously correlated with CHD risk over a broad range of cholesterol values. This relationship has been observed in many populations throughout the world.²³⁻²⁵ Because serum LDL-C levels correlate highly with total cholesterol in populations, the same relation must exist between LDL-C concentrations and CHD risk. Although the association between LDL-C levels and CHD risk is continuous, it is not linear; risk rises more steeply with increasing LDL-C concentrations. This results in a curvilinear, or log-linear, relationship (Figure). This means that when the relationship between LDL-C levels and CHD risk is plotted on a log scale, the relationship becomes linear. Thus, at any level of LDL-C, for a given milligram-per-decimeter change in the LDL-C level, the change in relative risk is the same as at any other LDL-C level. This relationship has 2 important implications. First, when persons with low LDL-C have the same absolute risk (because of other risk factors) as those with high LDL-C, the same absolute benefit is attained for a given milligram-per-decimeter lowering of LDL-C. Second, when persons with low LDL-C have a lower absolute risk than those with higher LDL-C, less absolute benefit is attained for a given LDL-C lowering in the low LDL-C group. Clinical trials of cholesterol-lowering therapy have generally confirmed this log-linear relation. In fact, epidemiological studies and clinical trials have produced congruent results by showing an almost identical pattern of association.²³⁻²⁵ Until recently, however, cholesterol-lowering clinical trials in high-risk patients failed to conclusively recapitulate the relationship observed in epidemiological studies in the lower ranges of LDL-C, ie, below 125 mg/dL.¹² This lack of hard evidence of benefit from further reducing already low LDL-C concentrations made it impossible for ATP III to

make unequivocal recommendations on LDL-lowering therapy for persons with lower levels of serum LDL-C.

The results of HPS help to confirm the congruence of epidemiology and clinical trials at low LDL-C levels. HPS provides strong new evidence to support the log-linear relationship between LDL-C levels and CHD risk, even at low LDL-C concentrations. In fact, HPS results suggest that reducing serum LDL-C from any baseline level further lowers risk in high-risk patients. In HPS, absolute risk reductions for major vascular events were smaller at lower LDL-C levels because the risk imparted by higher LDL-C itself was lacking. Nonetheless, the association between LDL-C levels and CHD risk seemingly remains log-linear at low LDL-C levels (Figure). The recent trials did not identify a threshold LDL-C level below which no further reduction in risk occurs.

Implications of Log-Linear Relationship Between LDL-C and CHD Risk for ATP III's Categorical Goals of Therapy in High-Risk Patients

Rationale for Recommended Low LDL-C

Goal (<100 mg/dL)

ATP III set the goal for LDL-C lowering in high-risk patients to be <100 mg/dL. This goal is consistent with the observed log-linear relationship between LDL-C levels and CHD risk observed in epidemiological data.^{23–25} It was as low as could be supported by clinical-trial evidence at the time of ATP III release. It also was a goal that could be achieved through LDL-C lowering in a sizable proportion of high-risk patients by standard doses of drugs used in clinical trials. The latter point is important. Doses of statins used in most secondary prevention trials will achieve an LDL-C level <100 mg/dL in little more than half of high-risk patients.^{4,26–28} To attain an LDL-C <100 mg/dL in the remaining patients, either the statin dose must be increased or a second LDL-lowering drug must be added to therapy. Thus, in ATP III, the LDL-C goal of <100 mg/dL was considered to be not only the limit of efficacy supported by available clinical trial data but also the practical limit that could be achieved in most high-risk patients with standard therapy as informed by clinical trials.

Rationale for Optional Very Low LDL-C

Goal (<70 mg/dL)

A question raised by HPS and PROVE IT is whether an LDL-C goal of <100 mg/dL is sufficiently low in high-risk patients who already have a low LDL-C level at baseline. In HPS, patients whose LDL-C levels at baseline were <116 mg/dL, and even the subgroup with LDL-C concentrations <100 mg/dL, exhibited significant risk reduction when statin therapy was introduced. In PROVE IT, intensive LDL-C-lowering therapy with high-dose statin (atorvastatin) reduced major cardiovascular events in only 2 years as compared with standard-dose statin (pravastatin 40 mg). Pravastatin 40 mg reduced the median LDL-C from 106 mg/dL to 95 mg/dL, which achieved the ATP III goal of <100 mg/dL; atorvastatin 80 mg lowered LDL-C to a median of 62 mg/dL. Thus, on the basis of both HPS and PROVE IT, an LDL-C level of 100 mg/dL does not appear to be a threshold below which no further benefit could be achieved by still more LDL-C

lowering. It is important to note that ATP III considered an LDL-C level of 100 mg/dL to be a *minimal* goal of treatment for high-risk patients. This level was not viewed as the level of maximal benefit of LDL lowering. A goal of less than 100 mg/dL was explicitly established by ATP III to indicate that the level of 100 is a minimal goal of therapy. Both HPS and PROVE IT indeed suggest that additional benefit may be obtained by reducing LDL levels to substantially below 100 mg/dL. This likelihood is enhanced by the finding that intensive lowering of LDL-C to well below 100 mg/dL will reduce progression of coronary atherosclerotic lesions compared with LDL-C reductions to approximately 110 mg/dL.²⁹ If HPS is taken at face value, reducing LDL-C by 30% starting at 100 mg/dL will produce another 20% to 30% lowering in relative risk for CHD. In PROVE IT, the somewhat smaller reduction of 16% in major cardiovascular events on atorvastatin 80 mg compared with pravastatin 40 mg may be related to the relatively short duration of the trial. Thus, in terms of absolute risk, an LDL-C of 70 mg/dL seems preferable for high-risk patients compared with a level of 100 mg/dL. At present, however, HPS and PROVE IT cannot be taken as the final word on the benefit of reducing LDL levels to well below 100 mg/dL. Several other clinical trials (reviewed in Waters et al³⁰) are underway to probe the efficacy of lowering LDL to very low levels.

Until these trials are completed, prudence requires that setting an LDL-C goal of <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. Factors that favor a decision to reduce LDL-C levels to <70 mg/dL are those that place patients in the category of *very high risk*. Among these factors are the presence of established CVD plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high triglycerides ≥ 200 mg/dL plus non-HDL-C ≥ 130 mg/dL with low HDL-C [<40 mg/dL]), and (4) on the basis of PROVE IT, patients with acute coronary syndromes. To avoid any misunderstanding about cholesterol management in general, it must be emphasized that the optional goal of <70 mg/dL does not apply to individuals who are not high risk.

Potential Side Effects of Very Low LDL Cholesterol

In the past, concern has been raised about potential dangers of reducing LDL to very low levels. Some epidemiological studies^{31–33} suggest that very low serum cholesterol levels are associated with an increase in total mortality. In particular, an association with cerebral hemorrhage has been reported. In these studies, a causal link between low cholesterol levels and morbidity or mortality has not been established. Some investigators attribute the association to confounding factors. In recent clinical trials with statin therapy, no significant side effects from LDL lowering per se have been identified. For these reasons, the decision to achieve very low LDL levels in very high-risk patients should be based on evidence of benefit and recognition that there appears to be only a remote possibility of side effects from LDL lowering per se.

TABLE 1. Doses of Currently Available Statins Required to Attain an Approximate 30% to 40% Reduction of LDL-C Levels (Standard Doses)*

Drug	Dose, mg/d	LDL Reduction, %
Atorvastatin	10†	39
Lovastatin	40†	31
Pravastatin	40†	34
Simvastatin	20–40†	35–41
Fluvastatin	40–80	25–35
Rosuvastatin	5–10‡	39–45

*Estimated LDL reductions were obtained from US Food and Drug Administration package inserts for each drug.

†All of these are available at doses up to 80 mg. For every doubling of the dose above standard dose, an approximate 6% decrease in LDL-C level can be obtained.⁴⁵

‡For rosuvastatin, doses available up to 40 mg; the efficacy for 5 mg is estimated by subtracting 6% from the Food and Drug Administration–reported efficacy at 10 mg.⁴⁵

Limitations in Efficacy of LDL-Lowering Therapy

In spite of growing evidence for benefit of reducing LDL-C levels to <70 mg/dL in very high-risk patients, many such patients may not be able to achieve such low levels with currently available drugs. This will be the case particularly when baseline LDL-C levels are relatively high. For example, even with high-dose statins³⁴ or LDL-lowering drug combinations,^{35,36} LDL-C reductions >50% often cannot be achieved. Thus, when baseline LDL-C is >150 mg/dL, it may not be possible to achieve an LDL-C <70 mg/dL in very high-risk patients.

Relation of Percentage Reduction in LDL to CHD Risk: Implications for Therapy

ATP III recommendations on therapy placed higher priority on reaching the LDL-C goals than on achieving a given percentage lowering of LDL-C levels. ATP III guidelines also identified characteristics of persons in whom cholesterol-lowering drugs should be considered. The guidelines, however, were not explicit on how much LDL-C lowering should be sought from drug therapy beyond achieving the LDL-C goal. Recent clinical trials nonetheless have documented how much reduction in relative risk for major coronary events can be achieved from a given lowering of LDL-C.^{4–7,26–28,37,38} They indicate that for every 1% reduction in LDL-C levels, relative risk for major CHD events is reduced by approximately 1%. HPS data suggest that this relationship holds for LDL-C levels even below 100 mg/dL (Figure). Currently available statins at doses typically used in these trials will lower LDL-C levels by 30% to 40%, which translates into a similar percentage reduction in CHD risk over a 5-year period. In the present document, the statin doses that produce such reductions are called *standard doses*. Table 1 lists these standard doses for currently available statin drugs. Similar reductions in LDL-C of 30% to 40% can likewise be attained by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, nicotinic acid, ezetimibe, plant stanols/sterols). Because of the availability of a variety

of relatively safe LDL-lowering options, when ATP III indicates that drug therapy should be considered, it is reasonable to employ doses adequate to achieve a reduction in risk for major coronary events of 30% to 40%. To use minimal drug therapy just to produce a small LDL reduction that will barely attain the LDL-C goal would not be a prudent use of LDL-lowering drugs. These comments must not be taken to mean that NCEP is recommending a 30% to 40% reduction of LDL-C levels as a goal of therapy. The comments simply recognize that 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.

Because of the success of statin trials, some investigators have suggested that guidelines can be simplified by merely recommending that high-risk patients be treated with the doses of statins used in clinical trials. In the view of NCEP, this suggestion represents an oversimplification that will lead to undertreatment of many patients. It does not take advantage of the strong database supporting the log-linear relationship between LDL levels and CHD risk (Figure). As shown in HPS, if a high-risk patient has a relatively low LDL concentration at baseline, a standard dose of statin may achieve the minimal LDL-C goal of <100 mg/dL or even the more stringent optional goal of <70 mg/dL. For persons with higher LDL levels at baseline, standard doses of statins may fail to achieve an LDL-C level <100 mg/dL and thus may not achieve the full potential of benefit from LDL lowering. As the number of LDL-lowering options increases, the initiation of more intensive therapies becomes feasible. NCEP recommends that such therapies be employed within the bounds of safety and tolerability to at least achieve an LDL-C level of <100 mg/dL.

Implications of HPS and PROVE IT for Clinical Management of Elevated LDL-C in High-Risk Patients

HPS in general supports ATP III guidelines for high-risk patients. The introduction of the concept of *CHD risk equivalents* in ATP III expanded the definition of *high risk* beyond established CHD to include other types of high-risk patients. Because the LDL-C treatment goal for all of these categories is a level <100 mg/dL, the majority of high-risk patients will require intensive LDL-lowering therapy. By coincidence or design, HPS included several different types of high-risk patients that would qualify as CHD risk equivalents according to ATP III. The benefit of LDL-lowering therapy in such high-risk patients was amply demonstrated by HPS. Importantly, HPS provides support for the use of intensive LDL-C lowering in most high-risk patients. The implications of HPS for different levels of LDL-C in high-risk patients thus can be considered.

Baseline LDL-C Levels ≥130 mg/dL

For high-risk persons, ATP III recommended that LDL-lowering drugs begin simultaneously with dietary therapy when LDL-C is ≥130 mg/dL. HPS supports this recommendation; those HPS subjects with higher LDL-C levels had the greatest reduction in absolute risk from statin therapy. As shown in several clinical trials,^{26–28} including HPS, however,

when LDL-C levels are well above 130 mg/dL, eg, ≥ 160 mg/dL, standard doses of statins may not be sufficient to achieve the goal of <100 mg/dL. When they do not, the dose of statin may have to be increased or a second agent (eg, ezetimibe, bile acid sequestrant, or nicotinic acid) may be needed. Alternatively, a maximizing of dietary therapy (including the use of plant stanols/sterols) combined with a standard dose of statin may be sufficient to attain the ATP III goal in some patients. A recent report indicates that maximal dietary therapy can achieve LDL-C reductions of up to 25% to 30%.³⁹ Combined with standard doses of statins, such dietary therapy should lower LDL-C levels by well above 40%, which often will achieve the recommended target of therapy.

Baseline LDL-C Levels of 100 to 129 mg/dL

By setting an LDL-C goal of <100 mg/dL, ATP III favored institution of LDL-lowering therapy in this LDL-C range. Still, for patients having low HDL levels as the predominant lipoprotein abnormality, fibrates or nicotinic acid were acknowledged as alternatives to statin therapy. Recent clinical trials with fibrate therapy are consistent with this option.⁴⁰ HPS results, on the other hand, reinforce the ATP III-preferred option, ie, institution of LDL-lowering drug therapy. The HPS finding of a substantial benefit from use of a standard dose of statin further implies that for those with baseline LDL-C close to 100 mg/dL, therapy should be intensive enough to achieve a 30% to 40% reduction in LDL-C levels, and not merely enough statin to attain an LDL-C level just below 100 mg/dL. A small lowering of LDL-C just to achieve the goal will not yield much additional risk reduction. Standard doses of statins, in contrast, are sufficient to attain a substantial risk reduction. If nicotinic acid or fibrates are considered an option for this LDL-C range, it may be preferable to use them in combination with an LDL-lowering drug and not as a sole agent.

Baseline LDL-C Levels <100 mg/dL

ATP III did not recommend institution of LDL-lowering therapy in high-risk patients when the serum LDL-C is <100 mg/dL. HPS, however, found that such patients had a significant lowering of risk for CVD events when they were treated with a standard dose of statin. On the basis of HPS, some authorities recommend the use of statin therapy in virtually all high-risk patients whose LDL-C is <100 mg/dL. Indeed, further risk reduction through LDL lowering in patients with high baseline risk is consistent with the log-linear relationship between LDL-C levels and CHD risk shown in the Figure. However, a global recommendation to lower LDL-C in high-risk patients with LDL-C <100 mg/dL cannot be based on HPS alone in light of the limitations discussed before (page 229). Ongoing clinical trials may provide additional support for recommending an LDL-C goal well below 100 mg/dL. In the meantime, initiation of an LDL-lowering drug in high-risk patients when baseline serum LDL-C is <100 mg/dL, eg, to reduce LDL-C to the range of <70 mg/dL, is a reasonable therapeutic decision on the basis of clinical judgment that the patient is still at very high absolute risk for future CVD events. This therapeutic strategy is supported by

the results of HPS and PROVE IT. For LDL-C <100 mg/dL, other lipid-lowering drugs (eg, fibrates, nicotinic acid) can be considered for patients with elevated triglycerides and/or low HDL-C; these drugs can be used, either as alternatives to statin therapy, as shown by the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT),⁴⁰ or in combination with statins.

On-Treatment LDL-C <100 mg/dL

Again, ATP III did not recommend further LDL-lowering therapy for this group. A log-linear relationship between LDL-C level and CHD risk implies that further reduction in risk could be achieved by still more LDL lowering (Figure). HPS results are consistent with this possibility, and so are those of PROVE IT, but these results cannot be considered definitive. Several clinical trials are currently underway (see Waters et al³⁰) in which standard-dose and high-dose statin therapy are being compared. Moreover, to achieve the LDL-C goal of <100 mg/dL, many patients may already have been treated with either high doses of statins or combined drug therapy. In such patients, achieving a yet lower LDL goal (eg, <70 mg/dL) will not be a practical option. For those patients who attain an LDL-C <100 mg/dL on standard doses of statins, physicians can consider intensifying LDL-C reduction. Intensified therapy might be reserved for those patients deemed to be at very high risk. PROVE IT reported 2-year benefit from intensified LDL lowering in patients with acute coronary syndromes, and it will be important to confirm these results through several other ongoing clinical trials (see Waters et al³⁰) of similar design before making global recommendations for high-risk patients with on-treatment LDL-C <100 mg/dL.

Patients With Acute Coronary Syndromes

These patients are at very high risk for suffering recurrent coronary events in the near term. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial⁴¹ previously suggested that intensive LDL-lowering therapy would reduce risk for recurrent cardiovascular events in the first 18 months after acute coronary syndromes. PROVE IT greatly strengthens the evidence for benefit of intensive LDL lowering in the first 2 years after acute coronary syndromes. For this reason, intensive therapy should be considered for all patients admitted to the hospital for acute coronary syndromes. A strong case is made by PROVE IT for achieving the optional LDL-C goal of <70 mg/dL. Choice of drug and dosage should be guided in part by measurement of LDL-C within 24 hours of admission to the hospital. Modification of therapy can be made at follow-up if necessary to achieve the desired LDL-C level. If the baseline in-hospital LDL-C is relatively low, even an LDL-C level of <70 mg/dL may be achieved by a standard dose of statin. If the baseline LDL-C level is higher, a high dose of statin or the combination of a standard dose of statin with ezetimibe, bile acid sequestrant, or nicotinic acid may be required. In choice of therapy, consideration should be given to safety of the regimen for the individual patient as well as to efficacy of treatment.

Implications of HPS Results for Patients With Diabetes

ATP III identified diabetes as a high-risk condition. This designation was based on evidence that the majority of patients with diabetes in higher-risk populations have a relatively high 10-year risk for developing CVD. In addition, the onset of CVD in patients with diabetes carries a poor prognosis, both at the time of an acute CVD event and in the post-event period. Moreover, clinical trials^{42,43} before HPS provided moderately strong evidence that LDL-lowering therapy is efficacious in patients with diabetes. HPS investigators recently carried out and reported a detailed analysis of their results in patients with diabetes.¹¹ The results of this analysis can be considered in relation to ATP III recommendations.

Diabetes Plus CVD

In HPS, patients who had both diabetes and CVD were at very high risk for future CVD events. In terms of absolute risk reduction, this category of patient obtained the greatest benefit from statin therapy. Therefore, patients with the combination of diabetes and CVD deserve intensive lipid-lowering therapy. On the basis of HPS, the presence of this combination appears to support initiation of statin therapy regardless of baseline LDL-C levels. For patients with diabetes plus CVD, it is reasonable to attempt to achieve a very low LDL-C level (eg, <70 mg/dL).

Diabetes Without CVD

ATP III indicated that most patients with diabetes are at high risk even in the absence of established CHD. Most patients with hyperglycemia have type 2 diabetes, are older, and have multiple risk factors. Epidemiological studies and clinical trials demonstrate that in higher-risk populations these patients have a risk for CVD events approximately equal to that of nondiabetic patients with established CVD. HPS data found both a high risk in this group and benefit from LDL-lowering therapy, supporting the LDL-C goal of <100 mg/dL. On the other hand, in those diabetic patients without CVD who had an LDL-C at baseline of <116 mg/dL, risk reduction accompanying statin therapy was only marginally significant for first coronary event. Thus, whether to start an LDL-lowering drug when LDL-C is <100 mg/dL in this category of patient must be left to clinical judgment.

As noted in ATP III, not all patients with clinical diabetes have a 10-year risk >20%. Many of those who do not nonetheless deserve to be classified as high risk because of poor prognosis once CHD becomes manifest, as mentioned before. On the other hand, a portion of patients with diabetes can be considered to be at only moderately high risk because of young age or lack of other risk factors. Such patients were not studied in HPS. For the category of moderately high risk (10-year risk 10% to 20%), ATP III guidelines favored institution of LDL-lowering drugs along with dietary therapy when LDL-C levels are \geq 130 mg/dL. Thus, if a patient with diabetes is considered to be at lower risk, an LDL-lowering drug might not be started if the LDL-C level is <130 mg/dL. Maximal TLC clearly is indicated, but clinical judgment must

be exercised with regard to when to initiate an LDL-lowering drug.

Implications of HPS, PROSPER, and ASCOT for Cholesterol Management in Older Persons

ATP III counseled that, on the basis of considerations of age alone, older persons should not be denied the benefits of LDL-lowering therapy accorded to other age groups. Although several epidemiological studies found that elevated cholesterol levels confer a smaller relative risk in older compared with younger persons, the absolute risk attributable to increased cholesterol levels remains high. Moreover, subgroup analysis of several previous trials with statins strongly suggested that LDL-lowering therapy significantly reduces risk for CHD in older persons. HPS and PROSPER results add support for benefit of LDL-lowering therapy in older persons. The implications for 2 groups of older persons can be examined briefly.

Older Persons With Established CVD

HPS explicitly documented risk reduction with statin therapy in older persons (65 to 80 years) at high risk. Absolute risk reduction was just as great in this group as in other high-risk groups. Older persons tolerated statin therapy well. Although PROSPER had fewer older persons with established CVD, and they were treated for a shorter time than in HPS, a strong trend toward reduction in CHD was noted. The results of HPS and PROSPER, taken together with the findings of other statin trials, provide a strong justification for intensive LDL-lowering therapy in older persons with established CVD.

Older Persons at High Risk Without Established CVD

Absolute risk rises with age because of progressive accumulation of coronary atherosclerosis.^{1,2} Women are at lower risk, but if they have multiple risk factors, they too are at relatively high risk. Older patients with diabetes certainly must be considered to be at high risk. Unfortunately, risk assessment in older persons is not highly reliable. Other tests in older persons without clinical CVD hold promise for improving risk estimates, but so far, additional testing has not been integrated into quantitative risk assessment. Therefore, beyond use of Framingham risk scoring in older persons, clinical judgment is required as to when to initiate intensive LDL-lowering therapy in older persons without CVD. Efficacy alone is not the key issue in this group. A host of factors must be weighed, including efficacy, safety, tolerability, and patient preference, in this age group. The results of both PROSPER and ASCOT support the efficacy of statin therapy in older, high-risk persons without established CVD.

Implications of the ASCOT-LLA and ALLHAT-LLT Trials for Patients at Moderately High Risk

ATP III identified a specific risk category that includes people with 2+ risk factors and a 10-year risk of 10% to 20% (moderately high risk). Individuals in this category were considered to be candidates for LDL-lowering drugs if their serum LDL-C after TLC is \geq 130 mg/dL. The LDL-C goal for

TABLE 2. ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy**
<i>High risk:</i> CHD* or CHD risk equivalents† (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)‖	≥100 mg/dL#	≥100 mg/dL†† (<100 mg/dL: consider drug options)**
<i>Moderately high risk:</i> 2+ risk factors‡ (10-year risk 10% to 20%)§§	<130 mg/dL¶	≥130 mg/dL#	≥130 mg/dL (100–129 mg/dL; consider drug options)‡‡
<i>Moderate risk:</i> 2+ risk factors‡ (10-year risk <10%)§§§	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
<i>Lower risk:</i> 0–1 risk factor§	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

†CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.

‡Risk factors include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥55 years).

§§Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

§Almost all people with zero or 1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.

‖Very high risk favors the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.

¶Optional LDL-C goal <100 mg/dL.

#Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

**When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

††If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

‡‡For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.

these persons was set at a level of <130 mg/dL. If LDL-lowering drugs are employed to achieve the LDL-C goal recommended by ATP III, presumably the dose of drug should be sufficient to reduce LDL-C levels by 30% to 40%.

ATP III did not recommend LDL-lowering therapy in moderately high-risk patients in whom serum LDL-C is <130 mg/dL. However, a significant portion of the subjects in the ASCOT study, who had LDL-C <130 mg/dL and were at moderately high risk by ATP III criteria, had a significant lowering of risk for CVD when they were treated with a standard dose of a statin. Thus, ASCOT supports use of an LDL-lowering drug in persons with a 10-year risk of 10% to 20% and LDL-C level of 100 to 129 mg/dL, at baseline or on lifestyle changes, to achieve an LDL-C level <100 mg/dL, as a therapeutic option on the basis of clinical judgment of the patient's absolute risk and potential benefit of an LDL-lowering drug. Initiation of TLC also is recommended. Factors that might favor use of an LDL-lowering drug in this category include advancing age, more than 2 risk factors, severe risk factors (eg, continued cigarette smoking, a strongly positive family history of premature atherosclerotic CVD), high triglycerides (≥200 mg/dL) plus elevated non-HDL-C (≥160 mg/dL), low HDL-C (<40 mg/dL), the metabolic syndrome, and/or the presence of emerging risk factors (eg, serum high-sensitivity C-reactive protein >3 mg/L^{2,44} or coronary calcium >75th percentile for a person's age and sex²).

ALLHAT-LLT recruited a heterogeneous group of subjects that on average appear to fall into the moderately

high-risk category. The results in ALLHAT were disappointing because of the small difference in cholesterol levels between usual-care and statin-therapy groups. It should be noted, however, that a significant reduction in risk for major cardiovascular events was obtained in the African-American subgroup treated with pravastatin; this finding supports the ATP III recommendation that goals of LDL-lowering therapy should not be modified on the basis of ethnicity.

For people in lower risk categories (2+ risk factors and 10-year risk <10%, or 0 to 1 risk factor), the results of recent clinical trials do not modify the goals and cutpoints of therapy.

Summary of Implications of Recent Clinical Trials for ATP III Treatment Algorithm

From the evidence of previous statin trials, the ATP III panel was able to expand both the scope and intensity of LDL-lowering therapy for higher-risk individuals beyond that recommended in ATP II. The number of Americans for whom LDL-lowering drugs are considered was significantly increased by ATP III. Recent statin trials have provided new information on benefits of LDL-lowering therapy applied to persons in categories in which ATP III could not make definitive recommendations about drug therapy. In general, these new trials have strongly reinforced ATP III recommendations. In particular, they support ATP III recommendations for the benefit of LDL-lowering therapy for patients with diabetes and in older persons. Moreover, they provide new information on the efficacy of risk reduction in high-risk

TABLE 3. Recommendations for Modifications to Footnote the ATP III Treatment Algorithm for LDL-C

- Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.
- In high-risk persons, the recommended LDL-C goal is <100 mg/dL.
 - An LDL-C goal of <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk.
 - If LDL-C is \geq 100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.
 - If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug to achieve an LDL-C level <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
 - If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When triglycerides are \geq 200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.
- For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL; an LDL-C goal <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence. When LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
- Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.
- When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy.

persons with relatively low LDL-C levels. Although the full benefit of LDL-C reduction in higher-risk patients with low or very low LDL-C levels is still under investigation, the recent results open the door to use of cholesterol-lowering drugs in such patients with very high absolute risk who are most likely to benefit from added therapy.

Table 2 shows the ATP III goals and cutpoints and proposed modifications in the treatment algorithm for LDL cholesterol based on evidence from recent clinical trials. Essential modifications are highlighted in footnotes to Table 2 and are summarized in Table 3. Several modifications offer therapeutic options with regard to LDL-C goals lower than those in ATP III and choice of therapies. Recent clinical trials provide greater rationale for more intensive LDL-lowering therapy, but they do not resolve all issues surrounding very low LDL levels. At these levels, physicians must ultimately rely on clinical judgment to weigh patient risk and the efficacy, safety, and cost of different therapies. These issues can be discussed in the following context.

For high-risk patients, the recommended LDL-C treatment goal remains at <100 mg/dL. However, a target of <70 mg/dL represents a therapeutic option, ie, a reasonable clinical strategy, for persons considered to be at very high risk, on the basis of emerging clinical trial data. TLC is recommended in high-risk patients whenever the LDL-C level is \geq 100 mg/dL. Furthermore, any person at high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglycerides, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level. As before, whenever the baseline LDL-C concentration is \geq 130 mg/dL, simultaneous initiation of an LDL-lowering drug and dietary therapy is recommended. If LDL-C is 100 to 129 mg/dL, the same now holds. If baseline LDL-C is <100 mg/dL and the patient is considered to be at very high risk, initiation of an LDL-lowering drug to achieve an LDL-C level of <70 mg/dL is a therapeutic option that has clinical trial support. For those high-risk patients who have elevated triglycerides or low HDL-C

levels, addition of a fibrate or nicotinic acid to LDL-lowering therapy can be considered.

For patients at moderately high risk (10-year risk 10% to 20%), the LDL-C goal remains <130 mg/dL. However, a goal of <100 mg/dL represents a therapeutic option on the basis of evidence of efficacy in risk reduction from primary-prevention trials. TLC should be initiated in all such persons whose LDL-C level is \geq 130 mg/dL. Again, any person at moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglycerides, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level. If the LDL-C concentration is \geq 130 mg/dL after TLC, consideration should be given to initiating an LDL-lowering drug, to achieve and sustain the LDL-C goal of <130 mg/dL. For LDL-C levels of 100 to 129 mg/dL at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of clinical trial evidence of additional efficacy.

When initiating LDL-lowering therapy in a person at high risk or moderately high risk, the efficacy of therapeutic lifestyle change both to lower LDL-C levels and to reduce risk through other mechanisms must not be overlooked. Lifestyle change must be an integral part of risk reduction therapy. When an LDL-lowering drug is employed in a person at high risk or moderately high risk, a reduction in LDL-C levels of at least 30% to 40% beyond dietary therapy should be achieved if feasible. For people in lower risk categories, there are no proposed changes to the treatment goals and cutpoints.⁴⁵

References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the 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). *JAMA*. 2001;285:2486–2497.
2. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cho-

- olesterol 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. 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.
 4. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360(9326):7–22.
 5. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG; PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. PROSpective Study of Pravastatin in the Elderly at Risk. *Lancet*. 2002;360:1623–1630.
 6. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. 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.
 7. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, 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.
 8. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM; 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.
 9. McNamara JR, Cole TG, Contois JH, Ferguson CA, Ordovas JM, Schaefer EJ. Immunoseparation method for measuring low-density lipoprotein cholesterol directly from serum evaluated. *Clin Chem*. 1995;41:232–240.
 10. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
 11. Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005–2016.
 12. Sacks FM, Tonkin AM, Shepherd J, Braunwald E, Cobbe S, Hawkins CM, Keech A, Packard C, Simes J, Byington R, Furberg CD. Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project. *Circulation*. 2000;102:1893–1900.
 13. Dean BB, Borenstein JE, Henning JM, Knight K, Bairey Merz CN. Can change in HDL-cholesterol reduce cardiovascular risk? *Am Heart J*. 2004;147:966–976.
 14. Rubins HB. Triglycerides and coronary heart disease: implications of recent clinical trials. *J Cardiovasc Risk*. 2000;7:339–345.
 15. Robins SJ, Rubins HB, Faas FH, Schaefer EJ, Elam MB, Anderson JW, Collins D; Veterans Affairs HDL Intervention Trial (VA-HIT). Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes Care*. 2003;26:1513–1517.
 16. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos*. 2002;30:1280–1287.
 17. Pan WJ, Gustavson LE, Achari R, Rieser MJ, Ye X, Gutterman C, Wallin BA. Lack of a clinically significant pharmacokinetic interaction between fenofibrate and pravastatin in healthy volunteers. *J Clin Pharmacol*. 2000;40:316–323.
 18. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975;231:360–381.
 19. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245–1255.
 20. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, Zhao XQ, Bisson BD, Fitzpatrick VF, Dodge HT. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med*. 1990;323:1289–1298.
 21. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583–1592.
 22. Bays HE, Dujovne CA, McGovern ME, White TE, Kashyap ML, Hutcheson AG, Crouse JR; ADVICOR Versus Other Cholesterol-Modulating Agents Trial Evaluation. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADVICOR Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol*. 2003;91:667–672.
 23. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ*. 1994;308:367–372.
 24. Law MR, Wald NJ. An ecological study of serum cholesterol and ischaemic heart disease between 1950 and 1990. *Eur J Clin Nutr*. 1994;48:305–325.
 25. 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.
 26. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
 27. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels: Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335:1001–1009.
 28. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
 29. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, et al; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291:1071–1080.
 30. Waters DD, Guyton JR, Herrington DM, McGowan MP, Wenger NK, Shear C; 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.
 31. Stemmermann GN, Chyou PH, Kagan A, Nomura AM, Yano K. Serum cholesterol and mortality among Japanese-American men: the Honolulu (Hawaii) Heart Program. *Arch Intern Med*. 1991;151:969–972.
 32. Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, Shih J, Stamler J, Wentworth D. 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.
 33. Iso H, Naito Y, Kitamura A, Sato S, Kiyama M, Takayama Y, Iida M, Shimamoto T, Sankai T, Komachi Y. Serum total cholesterol and mortality in a Japanese population. *J Clin Epidemiol*. 1994;47:961–969.
 34. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, Cain VA, Blasetto JW; STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol*. 2003;92:152–160.
 35. Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, Suresh R, Sun S, Veltri EP. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol*. 2002;40:2125–2134.
 36. Ballantyne CM, Houry J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, Sun S, LeBeaut AP, Sager PT, Veltri EP; Ezetimibe Study Group. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation*. 2003;107:2409–2415.
 37. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301–1307.
 38. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Krueyer W, Gotto AM Jr. Primary prevention of acute coronary events with lovastatin in men and women with average

- cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615–1622.
39. Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, de Souza R, Emam A, Parker TL, Vidgen E, Lapsley KG, Trautwein EA, Josse RG, Leiter LA, Connelly PW. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *JAMA*. 2003;290:502–510.
 40. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999;341:410–418.
 41. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285:1711–1718.
 42. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. *Circulation*. 1998;98:2513–2519.
 43. Haffner SM, Alexander CM, Cook TJ, Bocuzzi SJ, Musliner TA, Pedersen TR, Kjekshus J, Pyorala K. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study. *Arch Intern Med*. 1999;159:2661–2667.
 44. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F; Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499–511.
 45. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol*. 1998;81:582–587.