

# Cholesterol

## How low should we go?

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### ABSTRACT

The National Cholesterol Education Program (NCEP) has recently updated their Adult Treatment Panel (ATP) III guidelines and called for more intensive cholesterol treatment, especially in patients at high risk for coronary heart disease (CHD). The message from the updated report is that lower is better for high risk patients, with the NCEP expert panel calling for low-density lipoprotein (LDL)-cholesterol treatment targets of <100 mg/dL in patients at high risk for CHD. In very high risk patients, however, aggressively lowering LDL-cholesterol to <70 mg/dL is now a therapeutic option for clinicians. Very high risk individuals are those with cardiovascular disease plus diabetes, persistent cigarette smoking, poorly controlled hypertension, or multiple risk factors of the metabolic syndrome, and those who recently had a myocardial infarction (MI). Despite the strong clinical evidence and widely publicized treatment guidelines, many hyperlipidemic patients receive inadequate lipid-lowering treatment or leave the hospital after having a MI without a statin. Intensive therapy should be considered for all patients admitted to the hospital for acute coronary syndrome. Achieving very low levels of LDL-cholesterol often requires high doses of a statin or a combination therapy. The coadministration of ezetimibe, a new cholesterol-absorption inhibitor, further reduced LDL-cholesterol by 23% compared with those patients who remained on statin therapy alone. Recent trials with statin therapy are discussed in this review.

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Lipid-lowering therapy with statins reduces the risk of cardiovascular events, but the optimal level of low-density lipoprotein (LDL)-cholesterol is still unclear. In July, 2004, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) published updated guidelines for cholesterol management.<sup>1</sup> The updated recommendations, which are endorsed by The National Heart, Lung, and Blood Institute, the American College of Cardiology, and the American Heart Association, suggest that more intensive cholesterol treatment is an option for people at high risk for myocardial infarction (MI) and cardiovascular death. The updated report is based on new evidence derived from 5 major clinical trials with statin therapy. The recommendations in the

guidelines state that for high risk patients, those with established coronary heart disease (CHD) or cerebrovascular disease (CVD), diabetes or those with 2 or more cardiovascular risk factors (>20% risk of CHD within 10 years), the overall goal remains LDL-cholesterol levels of <100 mg/dL. In the very high risk subset, those with established CHD who also have multiple risk factors, including diabetes, metabolic syndrome, or severe or poorly controlled risk factors, and those who recently had a MI, the guidelines offer a new therapeutic option of aggressively treating LDL levels to <70 mg/dL. Even in very high risk patients with LDL levels of <100 mg/dL, the new guidelines support using drug therapy to bring LDL-cholesterol down to <70 mg/dL. In high risk patients, the update calls for

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drug therapy in those with LDL-cholesterol levels between 100-129 mg/dL. In contrast, the ATP III guidelines set the threshold for drug therapy for high risk patients at LDL-cholesterol >130 mg/dL. Drug treatment was previously optional in those patients with LDL levels between 100 and 129 mg/dL.<sup>2</sup> In moderate risk patients, those with 2 or more risk factors for CHD (10-20% risk of CHD within 10 years), the NCEP targets remain LDL-cholesterol of <130 mg/dL but give clinicians a therapeutic option to treat to <100 mg/dL. To reach this goal, drug therapy is an option to obtain LDL levels below 100 mg/dL.<sup>1</sup> Goals for drug therapy in individuals at high or moderately high risk should be a 30-40% reduction in LDL-cholesterol levels (Table 1). Recommendations for treating individuals at low or moderate risk are unchanged from the 2001 guidelines.<sup>1,2</sup> Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. The idea that you can use cholesterol lowering drugs without lifestyle changes is incorrect. Lifestyle changes have enormous benefits beyond lowering LDL-cholesterol, such as raising levels of high-density lipoprotein (HDL) cholesterol, lowering triglycerides, improving diabetes, and reducing inflammation.

**Major clinical trials.** The past decade witnessed the publication of several landmark trials demonstrating that statins lower the relative risk of CHD, mortality or both, by 24-37% in patients with or without prior CHD.<sup>3</sup> 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),<sup>4</sup> the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER),<sup>5</sup> Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, Lipid-Lowering Trial (ALLHAT-LLT),<sup>6</sup> Anglo-Scandinavian Cardiac Outcomes Trial, Lipid-Lowering Arm (ASCOT-LLA),<sup>7</sup> and the Pravastatin or Atorvastatin Evaluation and Infection, Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial.<sup>8</sup> These trials addressed issues that had not been adequately addressed in

previous statin trials. All 5 trials supported a log-linear relationship between LDL-cholesterol level and CHD risk, but did not identify an LDL-cholesterol level below, which no further risk reduction occurred. For every 1% reduction in LDL-cholesterol level, relative risk of CHD is reduced by 1%.<sup>4,9</sup> A 30-40% reduction in LDL-cholesterol translates into a similar CHD risk reduction of more than 5 years.

**Heart Protection Study.** The HPS<sup>4</sup> involved 20,536 volunteers aged 40-80 years who were at high risk of CHD but in whom there was little direct evidence of benefit, including those with average or below-average cholesterol, women, patients over 70 years, people with diabetes and those with non-coronary vascular disease. Patients were randomized to either 40 mg of simvastatin (Zocor, Merck and Co, Inc.) daily or placebo for an average of 5.5 years. Thirty-three percent of patients had a baseline LDL level below 116 mg/dL; 25% were between 116-135 mg/dL and the remaining 42% had levels greater than 135 mg/dL. The reduction in risk of major events was the same regardless of whether patients went from high levels to so-called normal, or from normal to even lower. 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 and 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.<sup>4</sup> Subgroup analysis of HPS suggests that simvastatin therapy produced similar reductions in relative risk regardless of the baseline levels of LDL-cholesterol, including subgroups with initial (or baseline) LDL-cholesterol levels >135 mg/dL, <116 mg/dL, or <100 mg/dL.<sup>4</sup>

**Prospective Study of Pravastatin in the Elderly at Risk.** The PROSPER trial randomized 5,804 men and women aged 70-82 years who had a history of vascular disease or cardiovascular risk factors to pravastatin (Pravachol or Lipostat, Bristol-Myers Squibb Company) 40 mg once daily or to placebo. Patients were followed up for 3.2 years. Pravastatin reduced LDL-cholesterol levels by 34%. The composite end point was reduced on pravastatin therapy by 15% ( $p=0.014$ ). Major coronary events, defined as nonfatal MI and CHD death, fell on therapy by 19% ( $p=0.006$ ), and CHD mortality by 24% ( $p=0.043$ ). However, no effect was seen on stroke, cognitive function, or disability. There was also a statistically significant increase in cancer, but

**Table 1** - Doses of currently available statins required to attain an approximate 30-40% reduction of LDL-cholesterol levels.

Drug	Dose, mg/dl	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
LDL - Low-density lipoprotein		

the investigators dismissed this as the play of chance.<sup>5</sup>

**Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial.** Patients in the ALLHAT-LLT study<sup>6</sup> were a subset of 10,355 subjects of ALLHAT subjects with hypertension, who were 55 years of age or older but were also moderately hypercholesterolemic, as well as having at least one other risk factor. Eligible patients had LDL-cholesterol between 120-189 mg/dL or between 100-129 mg/dL if CHD was already present. Patients were randomized to treatment with 40 mg of pravastatin or usual care, but the trial was not blinded. "Usual care" could include statins at the physician's discretion. The average age of the cohort was 66 years. By year 4, total cholesterol levels were reduced by 17% with pravastatin versus 8% in the usual care group. In a random sampling of subjects, LDL levels were reduced by 28% with pravastatin versus 11% with usual care. All cause mortality was similar between the 2 groups, and CHD event rates were also not significantly different. The authors attributed the failure to detect a significant reduction in risk in patients treated with pravastatin to the modest differential in total cholesterol (9.6%) between pravastatin and usual care, to the unblinded nature of the study, and to a large crossover of higher-risk subjects in the usual-care arm to lipid-lowering therapy arm.<sup>6,7</sup>

**Anglo-Scandinavian Cardiac Outcomes Trial, Lipid-Lowering Arm (ASCOT-LLA).** The lipid part of the ASCOT-LLA trial<sup>8</sup> involved 10,305 hypertensive patients aged 40-79 years with at least 3 other cardiovascular risk factors and with total cholesterol below 6.5 mmol/L (250 mg/dL). They were randomized to 10 mg atorvastatin (Lipitor, Pfizer) or placebo. Follow-up was planned for 5 years, but treatment was stopped after 3.3 years because of significant benefits in the atorvastatin group. There was a significant 36% reduction in the primary end point of fatal CHD/nonfatal MI in the atorvastatin group after a median follow-up of 3.3 years ( $p=0.0005$ ). 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% ( $p=0.0005$ ). The study showed that LDL lowering with atorvastatin therapy has considerable potential to reduce risk of cardiovascular events in patients with multiple CVD risk factors.<sup>8</sup>

**The Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22 trial (PROVE IT-TIMI 22).** The PROVE IT-TIMI 22 study<sup>9</sup> enrolled 4,162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days. Patients were randomized to receive standard therapy with 40 mg pravastatin daily or intensive therapy with 80 mg of atorvastatin daily. The primary end point was a composite of death from any cause, MI, unstable

angina requiring rehospitalization, revascularization performed at least 30 days after randomization, and stroke. Mean follow-up was 24 months. In the standard therapy group that received 40 mg of pravastatin, LDL was lowered to a median of 95 mg/dL (2.46 mmol/L) at follow-up and thus met current NCEP guidelines. The intensive therapy group treated with 80 mg of atorvastatin showed even greater improvement, achieving a median LDL of 62 mg/dL (1.60 mmol/L) with an interquartile range of 50-79 mg/dL ( $p<0.001$ ). At 2 years, rates of the primary end point of death or major cardiovascular event were 26.3% in the pravastatin group and 22.4% in the atorvastatin group. These rates corresponded to a 16% reduction in the hazard ratio favoring atorvastatin ( $p=0.005$ ; 95% confidence interval, 5-26%). Most interestingly, the benefit was seen to emerge after only 30 days, when there was already a 17% reduction in the risk of the primary endpoint. In addition, this relative benefit stayed constant throughout the treatment period, so that at any given time point, there was always a 16% lower risk in the primary endpoint. Abnormal liver function tests occurred in 3.3% of patients in the atorvastatin group compared with 1.1% in the pravastatin arm ( $p<0.003$ ).<sup>9</sup> It must be noted that 72% of the patients had LDL-cholesterol levels of <125 mg/dL, and in this large subgroup, the modest trend toward benefit of atorvastatin over pravastatin was not statistically significant.<sup>1</sup>

In an editorial accompanying publication of PROVE IT-TIMI 22, Topol<sup>1</sup> notes that the trial has confirmed the idea that aggressive lipid lowering is more beneficial, as first suggested by the results of the Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, which, although it was not designed to detect differences in clinical outcomes, used the same statin regimens. Nissen et al<sup>10</sup> demonstrated that atorvastatin at a dose of 80 mg reduced coronary atheroma volume compared with pravastatin at a dose of 40 mg. The REVERSAL trial randomized patients with stable coronary disease who had at least a 20% intravascular ultrasound (IVUS) documented stenosis in an artery that had not been subjected to intervention. After an 8-week washout period, patients were randomized to atorvastatin 80 mg ( $n=253$ ) or pravastatin 40 mg ( $n=249$ ). The achieved LDL levels were 79 versus 110 mg/dL for the atorvastatin and pravastatin treatment groups. The primary endpoint, total plaque volume, showed a significant progression with pravastatin (2.7% increase,  $p=0.001$ ), but no difference with atorvastatin (-0.4 compared with baseline,  $p=0.98$ ). Interestingly, the C-reactive protein levels decreased 35% with atorvastatin and just 5% with pravastatin ( $p=0.001$ ).<sup>10</sup>

**Why a new optional goal (<70 mg/dL)?** A question raised by HPS and Pravastatin or Atorvastatin Evaluation and Infection Therapy

(PROVE IT) is whether an LDL-cholesterol goal of <100 mg/dL is sufficiently low in high risk patients who already have a low LDL-cholesterol level at baseline. Thus, on the basis of both HPS and PROVE IT, an LDL-cholesterol level of 100 mg/dL does not appear to be a threshold below which no further benefit could be achieved by still more LDL-cholesterol lowering.<sup>1</sup> Factors that favor a decision to reduce LDL-cholesterol 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 with low HDL-C [ $<40$  mg/dL]), and (4) on the basis of PROVE IT, patients with acute coronary syndromes. To avoid any misunderstanding on cholesterol management generally, it must be emphasized that the optional goal of <70 mg/dL does not apply to individuals who are not high risk.<sup>1</sup> To achieve the LDL-cholesterol goal of <100 mg/dL, many patients might have been treated with either high doses of statins or combined drug therapy. In such patients, achieving a yet lower LDL goal (for example, <70 mg/dL) will not be a practical option. For those patients who attain an LDL-cholesterol of <100 mg/dL on standard doses of statins, physicians can consider intensifying LDL-cholesterol reduction. Intensified therapy might be reserved for those patients deemed to be at very high risk.<sup>1</sup> An LDL-cholesterol reduction of greater than 50% often cannot be achieved. Thus, a high risk patient with a baseline LDL-cholesterol level of more than 150 mg/dL would not be able to achieve an LDL-cholesterol level of less than 70 mg/dL. The expert panel stated that until further trials are completed, HPS and PROVE-IT should not be taken as the final word on the benefit of reducing LDL-cholesterol levels to well below 100 mg/dL. Until further studies are completed, such as Treating to New Targets trial (TNT), Study of the Effectiveness of Additional Reduction in Cholesterol and Homocysteine with Simvastatin and Folic Acid/Vitamin B12 (SEARCH), and Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL), prudence requires that setting an LDL-cholesterol goal of <70 mg/dL must be left as an option, whereas a goal of <100 mg/dL can be retained as a strong recommendation.<sup>1</sup>

**On going trials.** The publication of several major statin therapy trials in stable CHD patients is anxiously awaited. The large clinical-end-point trials are each comparing high dose versus moderate or low dose statin treatment: The TNT trial enrolled approximately 10,000 CHD patients, and will likely

be presented at the 2005 American College of Cardiology Scientific Sessions. In this trial, patients are treated to different goals to compare the conventional NCEP guideline of an LDL-cholesterol goal of less than 100 mg/dL with a more aggressive LDL-cholesterol goal of less than 75 mg/dL.<sup>11</sup> The SEARCH study compares the intensity of lipid lowering, rather than specific goals, in 12,000 subjects who have had a prior MI. The lipid lowering interventions tested are simvastatin 20 mg versus simvastatin 80 mg. In addition, SEARCH is testing the homocysteine hypothesis by the use of 2 mg of folic acid and 1 mg of vitamin B12.<sup>12</sup> The IDEAL trial is a 7,600 patient study investigating whether additional clinical benefits can be achieved by greater percentage reductions in LDL-cholesterol levels with atorvastatin 80 mg than those seen with usual care (simvastatin 20-40 mg) in patients with existing CHD.

**Are there any 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 suggest that very low serum cholesterol levels are associated with an increase in total mortality. In recent clinical trials with statin therapy, no significant side effects from LDL lowering have been identified. The NCEP expert panel believes that 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.<sup>1</sup>

**Combination therapy.** Doses of statins used in most secondary prevention trials achieve LDL-cholesterol lowering to less than 100 mg/dL in just more than half of patients, and the statin dose may need to be increased and a second agent such as a bile acid sequestrant, nicotinic acid or ezetimibe may be added for the remaining half. Concern on development of myopathy with the combination therapy 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.<sup>1,13</sup> In statin treated patients who failed to reach NCEP cholesterol targets, the coadministration of ezetimibe (Zetia, Merck/Schering-Plough Pharmaceuticals) further reduced LDL-cholesterol by 23% compared with those patients who remained on statin therapy alone.<sup>14</sup> The Ezetimibe Add-on to Statin for Effectiveness (EASE) trial,<sup>14</sup> examined whether patients could reach their NCEP goal cholesterol levels on statin therapy alone, or whether the addition of ezetimibe to statin therapy was needed to achieve these goals. The EASE trial included

more than 3,000 patients who were on a stable dose of a statin but who were not at their NCEP ATP-III LDL-cholesterol goal. Patients were randomized in a 2:1 fashion to "add on" therapy with statin plus ezetimibe 10 mg or continuation of their current statin regimen plus placebo for a period of 6 weeks. Within the trial, patients were treated with atorvastatin, simvastatin, pravastatin, fluvastatin, and lovastatin, with 62% on the starting dose of the drugs. The investigators observed that by adding ezetimibe, they could get an additional 23% reduction in LDL, which compares favorably with data from other trials that have shown a 6-8% reduction in LDL when the statin dose is doubled. Most importantly, by the end of the treatment period, approximately 70% of patients on ezetimibe plus statin had in fact, reached the NCEP ATP-III goal, compared with only 17% of those on standard statin therapy.<sup>14,15</sup>

**Acute coronary syndrome (ACS).** The findings of PROVE IT indicates that patients recently hospitalized for an ACS event benefit from early and continued use of intensive therapy to lower LDL-cholesterol to substantially low levels. Nevertheless, despite the strong clinical evidence and widely publicized treatment guidelines, many hyperlipidemic patients receive inadequate lipid-lowering treatment. A survey of nationwide hospitals in the United States of America (USA) shows that only approximately one third of post-MI patients leave the hospital with a prescription for statin therapy, although over 90% could be expected to benefit from treatment. Fonarow et al<sup>16</sup> used data on 138,001 MI patients treated in 1,407 hospitals, taken from the National Registry of Myocardial Infarction 3 (NRMI 3) a prospective, observational study, and they found only 31.7% of patients had a prescription for a statin when they were discharged. Statin therapy was prescribed still less often among women, African-Americans, and more elderly patients.<sup>16</sup> Lipid lowering therapy initiated during hospitalization for an acute coronary event should become part of the initial treatment plan and thus, less likely to be overlooked later by prescribing physicians, or to be considered less important by the patients. This strategy should reduce the unjustifiable under treatment problem that still exists for patients with coronary disease.<sup>17</sup>

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial previously suggested that intensive LDL-lowering therapy would reduce risk for recurrent cardiovascular events in the first 18 months after ACS.<sup>18</sup> The trial found that patients given 80 mg of atorvastatin between 24-96 hours after admission to hospital for ACS had a 16% reduction in the primary endpoint - death, nonfatal acute MI, resuscitated cardiac arrest, or worsening unstable angina, compared with those on placebo. However,

this reduction in events only just reached statistical significance ( $p=0.048$ ) and most of the benefit of atorvastatin was attributed to a significant reduction in symptomatic ischemia requiring rehospitalization. However, there was no reduction in revascularization rates.<sup>18</sup>

The PROVE IT trial greatly strengthens the evidence for benefit of intensive LDL lowering in the first 2 years after ACS. For this reason, intensive therapy should be considered for all patients admitted to the hospital for ACS. A strong case is made by PROVE IT for achieving the optimal LDL-cholesterol goal of <70 mg/dL.<sup>19</sup> A substudy of the Platelet Receptor Inhibitor in Ischemic Syndrome Management (PRISM) trial has found pretreatment with statins in patients with ACS significantly reduces cardiac risk during the first 30 days after onset of symptoms. But stopping statin therapy after onset of ACS symptoms not only eliminates this protective effect, it results in a three-fold higher risk of death or non-fatal MI.<sup>19</sup> Of the original PRISM participants, 465 patients were pretreated with statins before onset of symptoms; of these, 86 had statin therapy withdrawn while 379 continued to take them. At 30-day follow-up, statin therapy was associated with a 51% reduction in death and nonfatal MI compared with patients who did not receive statins throughout the study period (adjusted hazard ratio 0.49;  $p=0.004$ ). All statins appeared to provide a similar protective effect when patients were pretreated for at least 6 months.<sup>19</sup> If statin therapy was withdrawn during or after admission for ACS, the incidence of death and nonfatal MI significantly increased compared with those who continued to receive statins (adjusted HR 2.93;  $p=0.005$ ).<sup>19</sup> The ATP III considers hospitalization for a coronary event a unique opportunity to initiate LDL-cholesterol-lowering therapy. Clinicians were urged to measure LDL levels in such patients within 24 hours of admission and discharge them with orders for both therapeutic lifestyle changes and LDL-lowering drug to lower the LDL-cholesterol levels to <70 mg/dL as a "therapeutic option, while the definitive recommendation is to lower LDL-cholesterol levels to a target of <100 mg/dL.<sup>1</sup>

**Post-percutaneous coronary intervention (PCI).** The Lescol Intervention Prevention Study (LIPS)<sup>20</sup> showed that patients undergoing angioplasty significantly reduced their risk of major adverse cardiovascular events (MACE) by 22% and delayed the time to next serious cardiac event by taking fluvastatin (Lescol, Novartis company) over the 4 years of follow-up. Over the 4 years, LDL levels in fluvastatin patients, a mean of 131 mg/dL at baseline, dropped by 27% but increased by 11% in placebo-treated patients. The investigators also saw striking results in particular patient subsets. In both diabetic patients and those with multivessel disease, fluvastatin treatment lowered the risk of MACE by

47% and 34%.<sup>20</sup> In an accompanying editorial, Dr. George Sopko<sup>21</sup> stated that the LIPS findings suggest that routine early use of statins (median of 2 days between PCI and initiation of therapy) provided benefit regardless of baseline cholesterol level, as well as for patients with increased CHD risk.

**Diabetes.** Data from the diabetes subgroup of HPS (5,963 patients) revealed a reduction of one third in MI, strokes, or revascularizations among diabetics taking 40 mg of simvastatin a day for 5 years, benefits similar to those observed in the entire HPS population.<sup>22</sup> Use of statins in patients with type 2 diabetes is not currently widespread, as most of them tend to have average or below-average LDL-cholesterol. 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-cholesterol levels. The 2004 NCEP recommendations support the inclusion of patients with diabetes in the high risk category. In patients with diabetes plus CVD, the panel notes that it is reasonable to attempt to achieve very low LDL levels (<70 mg/dL). In diabetic patients without CVD, the data supports the recommendation of lowering LDL to <100 mg/dL, although whether to start lipid-lowering therapy when the baseline LDL levels are already below 100 mg/dL remains to clinical judgment. Similarly, if a patient with diabetes is considered to be low risk (young age, lack of other risk factors) then the decision to initiate drug therapy when LDL is <130 mg/dL is left to clinical judgment. However, in both types of patients, lifestyle modifications are clearly recommended.<sup>1</sup>

**Stroke prevention.** The HPS<sup>23</sup> recently demonstrated significant cerebrovascular protective benefits of statin therapy in a large number of patients with (n=3280) and without (n=17,256) a history of CVD. Compared with controls, who had a mean LDL-cholesterol level of 128 mg/dL after 5 years on placebo, the simvastatin 40 mg group achieved a mean LDL-cholesterol level of 89 mg/dL and had a 25% lower risk of stroke and 17% lower risk of transient ischemic attack ( $p<0.02$  versus placebo for both risk values). The decline in stroke rate reached statistical significance within the second year of treatment. In the ASCOT-LLA trial, the incidence of stroke was also reduced by 27% ( $p=0.024$ ) in the atorvastatin group.<sup>8</sup> A prior meta-analysis of randomized primary and secondary coronary prevention trials demonstrated that lowering total cholesterol below a threshold of 232 mg/dL, significantly reduced the incidence of stroke.<sup>24</sup>

**Elderly.** Elderly patients who are at highest risk of cardiovascular events are least likely to be prescribed statins. Using multiple linked health

administrative databases, Ko et al<sup>25</sup> surveyed almost 400,000 patients aged 66 or older who had a history of CVD or diabetes while undergoing medical treatment. Only 19.1% of this secondary prevention cohort were prescribed statins (75,617 of 396,077 patients). The HPS documented risk reduction with statin therapy in older persons (65-80 years) at high risk. Although PROSPER trial 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 with the findings of other statin trials, provide a strong justification for intensive LDL lowering therapy in older persons with established CVD. Beyond use of Framingham risk scoring in older persons, clinical judgment is required 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-LLA support the efficacy of statin therapy in older, high risk persons without established CVD.<sup>1,8,9</sup>

**Are we doing enough?** A comparison of 2 large surveys highlighted the failure of European cardiologists to reduce coronary risk factors in their patients with established CHD.<sup>26</sup> European cardiologists do not appear to have carried out much to implement measures proven to decrease cardiovascular risk. The first European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) survey, which was carried out among patients with established CHD in 9 European countries in 1995-96, showed that there was a substantial potential for risk reduction. However, the EUROASPIRE II results, drawn from the same countries 5 years later, indicate the potential for risk reduction has largely been squandered. Just as many CHD patients continue to smoke (20.8% versus 19.4%), obesity has increased (from 25.3-32.8%), hypertension incidence is virtually the same (53.9%), and although many more patients are on lipid-lowering drugs than before, cholesterol levels are still uncontrolled in 58.8% of the population surveyed.<sup>26</sup> In an accompanying commentary,<sup>27</sup> Dr. Jerome D. Cohen<sup>27</sup> from St. Louis University School of Medicine, notes that the EUROASPIRE findings are consistent with coronary prevention data in the USA, and that they are by no means unique to Europe. Cohen put forth his suggestions for improving the situation. First and foremost would be to adopt a simple "ABCDE" checklist for use on each patient at the time of their diagnosis, or before they leave the hospital. Dr. Cohen's<sup>27</sup> ABCDE checklist involves the following questions: A. Are you on aspirin? ACE Inhibitors? B. Are you on beta

blockers? C. Are you on cholesterol lowering drugs? D. Don't smoke. Diet. E. Exercise. We believe that patients do really well when they're on their ABC's. We've got to treat the basic disease process of atherosclerosis. That's not with a bypass, that's not with percutaneous transluminal coronary angioplasty, and it's not with stents. It is by changing the natural history of the disease, which we can do with modification of the risk factors.<sup>27</sup> This point became clearly evident with the publication of the Cardiac Hospitalization Atherosclerosis Management Program (CHAMP) study.<sup>28</sup> This study, which looked at treatment rates, repeat hospitalizations, and risk factor lowering in patients with CAD discharged from hospital, provides dramatic evidence that initiating secondary prevention therapies prior to hospital discharge can have a profound impact on patient outcomes. In their study, Fonarow et al<sup>28</sup> compared treatment rates and clinical outcome in patients discharged from hospital during the 2 years before CHAMP was implemented and in the 2-year period afterwards. The use of beta blocker, statin, and ACE inhibitors increased from 12%, 6% and 6% to 62%, 86% and 58%. Almost 6 out of 10 CHAMP patients were able to achieve LDL-cholesterol levels of <100 mg/dL, compared to only 6 out of 100 pre-CHAMP patients. Patients in the CHAMP program were also significantly less likely to have a MI (7.8% versus 3.1%), hospitalization (14.8% versus 7.6%), cardiac death (5.1% versus 2.0%), or death from any cause (7% versus 3.3%). This study shows that the key to keeping heart disease patients alive is providing them with immediate and thorough treatment before they walk out of the hospital.<sup>28</sup> Finally, evidence-based medicine strongly supports clinical benefit from the treatment of hypercholesterolemia in men and women with and without known CAD, and the main goal should be to ensure that patients who could benefit from lipid lowering therapy are effectively treated and followed to ensure long term compliance, efficacy, and safety.

In conclusion, 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. Several modifications were made in the recent update of ATP III to offer therapeutic options regarding LDL-cholesterol goals lower than those in ATP III and choice of therapies. Lifestyle change must be an integral part of risk reduction therapy and should be initiated in all such persons. When an LDL-lowering drug is employed in a person at high risk or moderately high risk, a reduction in LDL-cholesterol levels of at least

30-40% beyond dietary therapy should be achieved if feasible. These guidelines will probably be updated further based on the results of ongoing clinical trials scheduled for completion in the next 18 months.

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