InetCE

Volume 8 **2004** **Number 7**

Karen J. MacKinnon, R.Ph.
Editor

Linda S. Swanson
Copy Editor

Internet Continuing Education (***InetCE***) provides free, continuing education to pharmacists and other health care providers 24 hours a day over the Internet at www.InetCE.com. Since 1997, these home study programs have assisted in keeping practitioners apprised of treatment-related topics, general pharmacy, and law in the changing health care environment.

InetCE grew out of a need for relevant, continuing education in health care, and to make it accessible to pharmacy practitioners in various practice settings. This format provides convenient instruction, on-line testing, evaluation, and certification. Continuing education examinations are graded automatically and, if successfully passed, the user can print the statement of credit.

Accreditation

ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ACPE Universal Program Number 221-999-04-096-H01 has been assigned to this home study program (initial release date November 22, 2004). This program is acceptable for 2.0 contact hours (0.20 CEUs) in states that recognize ACPE providers. The program is provided at no cost to participants. Statements of credit will be issued on-line upon successful completion (> 70% score) of the posttest.

Faculty Disclosure

It is the policy of ProCE, Inc. to ensure balance, independence, objectivity and scientific rigor in all of its continuing education programs. Faculty must disclose to program participants any significant relationships with companies that manufacture or market products discussed during their presentation. Drs. Jensen and DeKorte report having no relationships to disclose.

Please note: The opinions expressed in this program should not be construed as those of the CE provider. The information and views are those of the faculty through clinical practice and professional literature. Portions of this program may include the use of drugs for unlabeled indications. Use of drugs outside of labeling should be considered experimental, and participants are advised to consult prescribing information and professional literature.

ProCE, Inc.
850 W. Bartlett Rd., Ste. 9E
Bartlett, IL 60103-4402
www.ProCE.com

Cholesterol: How Low Should You Go?

InetCE 221-999-04-096-H01

Hanni B. Jensen, Pharm.D.
Resident
George E. Wahlen VA Medical Center
Salt Lake City, Utah

Carrie J. DeKorte, Pharm.D., BCPS
Director
Pharmacy Education and Training
George E. Wahlen VA Medical Center
Salt Lake City, Utah

PLEASE NOTE: The content of this article was current at the time it was written. The exam for this article is not valid for CE credit after November 22, 2007.

LEARNING OBJECTIVES

1. Describe the low-density lipoprotein (LDL) cholesterol goal for each risk category according to the Adult Treatment Panel III (ATP III) Guidelines.
2. Analyze the 5 recent clinical trials that led to the National Cholesterol Education Program's (NCEP) 2004 Implication statement on the ATP III guidelines.
3. Identify recommendations from the 2004 NCEP Update.
4. Discuss the possible correlation between low cholesterol levels and the increased incidence of death.

ABSTRACT: Heart disease and stroke, 2 cardiovascular disease (CVD) components, are responsible for the first and third leading causes of death in the United States. Hyperlipidemia is one major risk factor for the development of CVD. The Adult Treatment Panel III (ATP III) was published in 2001 and has provided the most up-to-date guidelines concerning the management of elevated cholesterol levels. Five recent clinical trials have led to the July 2004 publication of the National Cholesterol Education Program (NCEP) Report Implications of Recent Clinical Trials for the NCEP ATP III Guidelines. Critical evaluation of these and other clinical trials provides guidance to the implication and potential implementation of the ATP III Report with a focus on elderly patients, secondary prevention, and patients with high CVD risk. The new treatment goals for high-risk patients are optional at this point. As new studies are designed and completed, additional evidence could be forthcoming that clearly delineates a benefit in reducing low-density lipoprotein cholesterol (LDL-C) values to < 70 mg/dL in high-risk patients. Although reductions in coronary heart disease (CHD) incidence may result from more aggressive use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), it still remains to be seen whether declines in total mortality will be seen. The impact that low cholesterol levels have in other areas of a person's life is still being investigated.

ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. An on-screen statement of credit verifying participation in 0.20 CEUs (2.0 contact hours) will be displayed for printing to participants who successfully complete the examination. This article has been assigned ACPE

ID number 221-999-04-096-H01. For more information, visit http://www.InetCE.com.

CHOLESTEROL: HOW LOW SHOULD YOU GO?

Introduction

Every year over 930,000 Americans die from CVD. Heart disease and stroke are the first and third leading causes of death for males and females in the country.[1] In addition to the number of deaths arising from CVD, approximately 25% of the population live with some type of CVD. Each year, CVD is the cause of 6 million hospitalizations in the United States, contributing to total projected costs of $368 billion for the treatment of heart disease and stroke in 2004.[1] This estimate also includes costs resulting from lost productivity, death, and disability. Dyslipidemia is a major risk factor for the development of CVD, and guidelines for treatment and cardiovascular risk reduction have been established.[1] The Executive Summary of the Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, or ATP III, was published in 2001.[2] Since its publication, 5 significant clinical trials have been completed, which led to the publication in July 2004 of the NCEP Report Implications of Recent Clinical Trials for the NCEP ATP III Guidelines.[3]

ATP III Background

The NCEP develops recommendations to assist providers in managing hypercholesterolemia, according to evidence-based medicine. The ATP I report focused on primary prevention of CHD in patients who had either high or borderline high LDL-C combined with at least 2 risk factors. High LDL-C was defined as $\geq$ 160 mg/dL, and borderline high LDL-C ranged from 130-159 mg/dL.[2] ATP II agreed that primary prevention was important, but also noted that LDL-C needed to be better controlled in people with CHD for secondary prevention. At this point the goal for CHD patients was set at $\leq$ 100 mg/dL. The ATP III guidelines that are currently being used confirm the importance of ATP I and II, but note that additional groups also need rigorous LDL-C control for both primary and secondary prevention. These groups are considered to have CHD risk equivalents. In each ATP Guideline, LDL-C has been identified as an independent risk factor for CHD and a primary focus in treatment of hypercholesterolemia.[2,3]

The relationship between LDL-C and CHD risk is well-known, leading experts to try to quantify it. Although a continuous relationship can be seen between the two, the relationship is direct. As LDL-C increases the CHD risk also climbs, but at an accelerated rate. This results in a log-linear relationship. Consequently, those people who are at a higher risk of developing CHD because of co-existing risk factors, but who have a lower LDL-C, will experience a similar reduction in risk as those who have fewer risk factors but a higher LDL-C when similar reductions in LDL-C are seen.[3,4] This also means that those patients who have a lower risk with low LDL-C will not experience as great a number of benefits from decreases in LDL-C levels.

The National Institute of Health National Heart, Lung and Blood Institute's website

www.nhlbi.nih.gov provides a quick reference for the ATP III guidelines. One of the primary steps in assessing an individual's risk of CHD is to establish the patient's risk category. Risk is split into the following groups:

1. CHD or CHD Risk Equivalents (high risk: LDL Goal < 100 mg/dL
2. Two or more risk factors, but 10-year risk ≤ 20% (moderate risk): LDL Goal < 130 mg/dL
3. Zero to one risk factor (low risk): LDL Goal < 160 mg/dL

Pharmacotherapy: HMG CoA Reductase Inhibitors (Statins)

The most effective class of medication for reducing LDL-C, which is also the group of medications tested in recent trials, is the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, more commonly referred to as statins.[5] The ability to lower LDL-C is dependent on statin dose and potency, with resulting decreases ranging from 20% to 65%.[6] Statins are not as potent at decreasing triglycerides or increasing HDL-C, 7% to 45% and 2% to 25%, respectively.[6,7]

One worrisome side effect associated with statin use is development of myalgias. Myalgias may be experienced by 1% to 6% of patients on statins, but severe myopathy is unusual, affecting perhaps 0.1% of patients.[8] Pravastatin appears to have the lowest risk of myopathy.[9] Routine monitoring of serum creatine kinase (CK) is not recommended, but patients should be counseled to report the new onset of myalgias or muscle weakness.

Another side effect is an elevation in the serum amino transferases—aspartate aminotransferase [previously SGOT] (AST) and alanine aminotransferase (ALT). This also occurs in a small percentage of patients, primarily within the first 3 months of therapy, and is dose-dependent.[5] In a review of recent clinical trials, it appears that the elevated AST and ALT may not be statistically significantly different from placebo, and many experts do not recommend routine monitoring beyond baseline levels,[10,11] although manufacturers of the statins still recommend routine monitoring of AST and ALT.

Recent Trials of Statins since Publication of ATP III in 2001

The 5 trials referenced in the 2004 NCEP Report are the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid-Lowering Trial (ALLHAT-LLT), the Heart Protection Study (HPS), the Pravastatin or Atorvastatin Evaluation and Infection-Thombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22), and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER).[3] These trials have yielded additional information about cholesterol and its connection to CHD. A risk reduction relationship that is independent from baseline LDL-C seemed to be apparent in these trials. None of the trials reached an LDL-C level at which no further CHD reduction was seen.[3] Patient characteristics from each of the studies are listed in the table below.

	ASCOT-LLA	ALLHAT-LLT	HPS	PROVE IT 22	PROSPER
Age	64% over 60 y/o	Mean 55 y/o	28% ≥ 70 y/o	Mean 58 y/o	Mean 75 y/o
Percentage Males	81.2%	51%	75.3%	78%	48.3%
Mean TC (mg/dL)	213	224	228	180.5	221
Mean LDL-C (mg/dL)	131	146	131	106	147
Mean HDL-C (mg/dL)	50	48	41	38.5	50

Key: Total Cholesterol (TC); years old (y/o)

ASCOT-LLA

This primary prevention trial evaluated over 10,000 hypertensive patients who had more than 3 additional risk factors for CHD. All participants had non-fasting serum cholesterol levels less than 251 mg/dL. Patients were randomized to either placebo or atorvastatin 10 mg daily.

The primary endpoint was the combined incidence of non-fatal myocardial infarctions (MIs) and fatal coronary heart disease. Although the lipid-lowering arm was initially designed for 5 years of data gathering, the trial was stopped prematurely with a median 3.3-year follow-up, as a result of significant benefit in the atorvastatin arm in the primary combined endpoint (hazard ratio 0.64 [95% CI 0.50 to 0.83], $P = 0.0005$). In secondary endpoints, there was a statistically significant 27% decrease in fatal and non-fatal stroke, 21% decrease in total cardiovascular events, and 29% decline in total coronary events in those patients taking atorvastatin over placebo. There was not a statistically significant reduction in all-cause mortality, however, (hazard ratio 0.87 [95% CI 0.71 to 1.06]) or cardiovascular mortality (hazard ratio 0.90 [95% CI 0.66 to 1.23]).[4,12] The primary prevention of non-fatal MI and fatal coronary disease results from ASCOT-LLA confirm the findings of previous primary prevention studies (WOSCOPS, AFCAPS/TexCAPS). The statistically significant reduction in stroke adds more evidence to the positive benefits of statin therapy.

ALLHAT-LLT

ALLHAT-LLT is another primary prevention trial that included over 10,000 hypertensive patients of at least 55 years of age, with LDL-Cs ranging from 120-189 mg/dL. ALLHAT-LLT was designed to determine pravastatin's effect on all-cause mortality.[13] Participants were randomized to 40 mg of pravastatin each day or usual care. Usual care is the care that the participant's primary care provider would normally select, although vigorous cholesterol lowering was discouraged, unless warranted by clinical circumstances. This study did not produce similar results to the other trials reviewed in the recent NCEP statement. A difference was not found between the 2 groups in either all-cause mortality [95 % CI 0.89 to 1.11] or in the number of CHD events [95% CI 0.79 to 1.04]. African-Americans were the only subgroup to show an improvement in CHD events attributable to pravastatin treatment ($P = 0.03$).[13]

Investigators hypothesized that reductions in mortality were not seen from pravastatin use because of the high rate of statin use in the usual care group. This study was not blinded, and 8% of participants in the usual care group were using a statin by year 2 of the study. This crossover rate increased to 17% by the end of year 4, and continued to slightly

increase through the completion of the trial in year 6.[13]
Study participants were also encouraged to follow the NCEP step 1 diet. Following this diet may have contributed to the lack of significant differences in mortality seen between the 2 groups. In a study by Jenkins et al., participants were randomized to a control diet that was low in saturated fat, the use of lovastatin, or to a dietary portfolio group.[13] The dietary portfolio group ate a diet that had high levels of plant sterols, soy protein, viscous fibers, and almonds. When all of the groups were compared at the end of the study, the control diet group had an 8.0% reduction in LDL-C ($P = 0.002$). The group receiving lovastatin experienced a 30.9% decline in LDL-C values ($P < 0.001$), and the dietary portfolio group displayed a 28.6% decrease in LDL-C ($P < 0.001$). The latter 2 groups' change in LDL-C was significantly different from the control dietary group, but a statistical difference did not exist when they were compared with one another.[14] Although the NCEP step 1 diet does not correspond precisely to the dietary portfolio group, the recommendations to lower saturated fat are similar, and could impact LDL-C values. One other possible reason that differences in mortality were not seen could be that the control group was allocated to usual care. Usual care would be more effective at reducing CHD than a placebo, which is what the control groups were assigned to in the other 4 studies.[3]

ASCOT-LLA and the ALLHAT-LLT are the only studies that investigated the effects of medications for hypertension and hypercholesterolemia simultaneously. The former study showed a benefit in patients whose blood pressure was controlled and were using a statin, but the latter trial did not.[13] Because hypertension and hyperlipidemia are both risk factors for the development of CHD, more investigation may need to be performed to determine whether a synergistic effect was responsible for some of the decline in CHD. Even if synergy was seen, this still does not explain the difference in outcomes between the 2 studies.

HPS

This secondary prevention trial limited inclusion to high-risk patients with treated hypertension, diabetes, coronary or cerebrovascular disease, and peripheral artery disease. Approximately twice the number of participants were involved in this study compared with ASCOT and ALLHAT, with 20,536 United Kingdom citizens enrolled, aged 40 to 80 years.[4] Study participants were randomized to 40-80 mg per day using simvastatin or placebo.

The primary outcome of this study was also total mortality. In the simvastatin group, 12.9% of participants died compared with 14.7% in the placebo group ($P = 0.0003$).[4] This difference primarily resulted from a decline in deaths attributable to vascular causes. Rates of death attributable non-vascular causes were 5.3% and 5.6% ($P = 0.4$) for simvastatin and placebo use, respectively.[4] Significant risk reductions from simvastatin use were also seen in rates of vascular events (95% CI 19 to 28), coronary death rates (95% CI 30 to 46), stroke (95% CI 19 to 40), and cardiovascular revascularization (95% CI 17 to 30).[4]

Similar to ALLHAT-LLT, participants in the control group were allowed to use non-study statins if prescribed by their

primary care provider. As expected, the control group was more likely to be prescribed a non-study statin. After 5 years of the study had been completed, 32% of control patients were using a non-study statin.[4] This is of note, as the authors of ALLHAT-LLT, along with others who have analyzed the ALLHAT-LLT, hypothesized that the reason a difference in CHD mortality was not seen in that trial was because of the high use of non-study statins in the control group. In reality, the percentage of usual care patients who used a non-study statin was almost half as few as those who used one in the HPS, but the HPS still detected a difference between the 2 groups.[4,15] Counseling was also provided to HPS participants regarding risk factors and dietary changes.[4]

The investigators of the HPS performed a subgroup analysis to determine baseline LDL-C's relationship to outcomes. The results suggest that the baseline LDL-C level does *not* predict the amount of risk reduction that will be seen in patients taking simvastatin. The decreased risk seen in the trial was similar among those with baseline LDL-C values of $\geq$ 135 mg/dL, < 116 mg/dL, or < 100 mg/dL.[4]

Diabetic patients were also examined as a subgroup in HPS. These patients experienced almost a 25% reduction in revascularization, stroke, and major coronary events ($P < 0.0001$).[4] This reduction was similar to those seen for non-diabetic patients, leading to the conclusion that statin therapy is effective for patients with diabetes, even if they begin with relatively low cholesterol (< 116 mg/dL). Similar reductions were also seen when participants with cerebrovascular disease ($P = 0.001$) and peripheral vascular disease ($P < 0.0001$) were examined separately.[4]

PROVE IT-TIMI 22

The PROVE IT-TIMI-22 study was a secondary prevention trial that involved participants who had been hospitalized within the last 10 days for an acute coronary syndrome (ACS).[15] Over 4000 patients with total cholesterol levels $\leq$ 240 mg/dL or $\leq$ 200 mg/dL on current use of a cholesterol-lowering medication, when checked within 24 hours of ACS onset were included in the study.

The primary outcome investigated in PROVE IT-TIMI 22 was reduction in major coronary events. To determine if a greater reduction in events would be seen with intensive LDL-C–lowering therapy compared with standard treatment, participants were assigned to receive pravastatin 40 mg each day (standard therapy) or atorvastatin 80 mg per day (intensive treatment).[3,15] Use of other statins was not permitted by either group in this study, but dietary counseling was provided at regular intervals to participants.

Major coronary events occurred in 26.3% of the pravastatin group and 22.4% in the atorvastatin group. This difference equates to a 16% risk reduction in the atorvastatin group ($P = 0.005$). Death attributable to CHD, revascularization, or MI was the secondary endpoint in the study. This endpoint was reduced by 14% from use of atorvastatin ($P = 0.029$). When individual causes of death were examined, no difference was seen in total mortality ($P = 0.07$) or in death from MIs ($P = 0.06$) between the groups. The data seemed to show a trend favoring atorvastatin, but did not reach statistical significance.[15] It is important to

remember that statistical significance was not seen in overall mortality. The authors state in this continuing pharmacy education article that use of the more intensive regimen decreased the risk of death from any cause and decreased major cardiac events. In reality, only a trend towards reduction in all-cause mortality or fatal MIs was seen, whereas a statistical difference, favoring atorvastatin, was only seen when all cardiovascular endpoints were combined.[15] Benefits of atorvastatin therapy appeared by day 30 and continued throughout the trial. Greater reductions in LDL-C were seen from the use of atorvastatin, which is understandable as it is more potent. Another possible contributing factor would be that additional differences might exist between the statins that cause varied declines in risk, beyond just the reduction in LDL-C.[15] One way to determine this would be to conduct a study that compared atorvastatin 80 mg per day with atorvastatin at a dose equipotent to pravastatin 40 mg.

One other significant difference seen between the 2 groups in the PROVE IT-TIMI 22 study was an increased rate of elevated liver enzymes in the atorvastatin group. No difference was seen in the rates of severe myopathy or stroke between the 2 groups, but patients who were using other medications that potently inhibited cytochrome P-450 3A4 were excluded from participation in the trial.[3,15] Inhibitors of this system do not affect pravastatin, so the rate of myopathies between the 2 medications may vary in real-world settings.[15]

PROSPER

PROSPER is the final study that was considered to have major significance on the ATP III guidelines. The PROSPER study was also a primary prevention trial that included 5804 elderly participants (aged 70-82 years), who were at high risk of developing a stroke or CVD. Participants were randomized to 40 mg of pravastatin or placebo.[16]

The primary combined endpoint of the PROSPER study was death from CHD, non-fatal MI, and fatal or non-fatal stroke. A statistically significant reduction was seen in the combined rates of coronary death, non-fatal MIs, and either fatal or non-fatal strokes in the pravastatin group. When these categories were examined individually, statistical significance was still achieved in the coronary events (19% reduction), but no difference was seen in stroke rate between 2 groups. Transient ischemic attacks declined in the pravastatin group by 25%, but this reduction was not statistically significant. The study did not have enough power to evaluate if an overall reduction in mortality would be seen from the use of pravastatin. A 34% reduction in LDL-C was seen along with a 13% decrease in triglycerides and a 5% increase in HDL-C.[16]

One unusual finding in this study was that cancer was found 25% more frequently in the group taking pravastatin compared with those using placebo.[3,16] The authors were surprised by this finding, so they conducted a meta-analysis of 7 trials, which compared statins with placebo, and found no increased frequency of cancer overall (95% CI 0.96 to 1.09) or from use of pravastatin alone (95% CI 0.96 to 1.17).[16] The ASCOT-LLA and HPS trials also mentioned that no significant differences were seen in cancer rates between

patients using a statin and those on placebo.[4,13]

2004 NCEP/ATP Recommendations as a Result of Recent Trials

The NCEP developed 6 implications that resulted from the trials published since the advent of the ATP III guidelines. The resulting recommendations stem from one of the following implications and will be discussed below:

1. Implications of log-linear relationship between LDL-C and CHD risk for ATP III's categorical goals of therapy in high-risk patients
2. Relation of percentage reduction in LDL to CHD risk: implications for therapy
3. Implications of HPS and PROVE IT-TIMI 22 for clinical management of elevated LDL-C in high-risk patients
4. Implications of HPS results for patients with diabetes
5. Implications of HPS, PROSPER, and ASCOT for cholesterol management in older persons
6. Implications of the ASCOT-LLA and ALLHAT-LLT trials for patients at moderately high risk

Log-Linear Relationship Implication

The LDL-C goal of < 100 mg/dL for high-risk patients was designed from determining that as LDL-C decreased the risk of CHD also decreased. Researchers knew that this trend was followed at least until an LDL-C of ≤ 100 mg/dL was reached. This value also seemed to be one that was attainable through use of standard statin doses.[3]

PROVE IT-TIMI 22 and HPS used intensive LDL-C–lowering therapy in study participants, and the results indicate that CHD risk continues to decline as LDL-C levels fall below 100 mg/dL. As a result of these findings, a new optional LDL-C goal of < 70 mg/dL has been set for certain high-risk patients.[3] This group of patients includes those with known CVD plus multiple risk factors, the most important of which is diabetes. Serious uncontrolled risk factors, particularly cigarette smoking or a strong risk of developing the metabolic syndrome would also place a person in this group. Those with acute coronary syndromes fall into the final group that may benefit from intensive LDL-C lowering, as this was the group studied in PROVE IT-TIMI 22. This new goal is currently listed only as a therapeutic option, while the goal of < 100 mg/dL is still a strong recommendation. As a greater number of studies examine the effects of intensive LDL-C lowering, additional information may be available to develop a more solid recommendation. Regardless of the final recommendation on the goal for LDL-C in the highest-risk patients, one point to remember is that many patients may not be able to achieve LDL-C levels of < 70 mg/dL, as reductions in baseline LDL-C over 50% are very difficult to achieve.[3]

Percentage Reduction in LDL to CHD Risk-Relation Implication

The ATP III recommendations focused on attainment of a goal LDL-C level dependent upon a person's risk factors. Apart from simply reaching an LDL-C goal, the guidelines did not address the desired degree of LDL-C lowering. Recent trials demonstrated that each 1% reduction in LDL-C levels is associated with a 1% decrease in CHD events.

Standard statin doses decrease CHD events by 30%-40%.[3] Current evidence indicates that simply decreasing LDL-C by a small amount to reach a set goal may not be the wisest use of cholesterol-lowering medications, as a greater decrease in CHD events could be seen with a larger percent LDL-C reduction. The recommendation is *not* to have all patients with high cholesterol undergo a 30%-40% decrease in LDL-C with a corresponding decrease in CHD events. Instead, consider seeking at least a moderate risk reduction in CHD event rate through use of lipid-lowering medication, instead of simply focusing on a set goal that may only decrease risk slightly.[3]

HPS and PROVE IT-TIMI 22 Recommendations for High-Risk Patients

The results seen from HPS and PROVE IT-TIMI 22 can be applied to 5 groups of high-risk patients. The first group is those with a *baseline LDL-C ≥ 130 mg/dL*. According to ATP III, high-risk patients with this baseline LDL-C should begin drug therapy at the same time as lifestyle modifications. HPS supports this conclusion as participants who experienced the greatest absolute risk reduction were those with higher initial LDL-C levels.[3]

The second group of high-risk patients studied had *baseline LDL-C levels between 100-129 mg/dL*. According to ATP III, pharmacotherapy would be indicated in this group if lifestyle modifications were not sufficient to reach the LDL-C goal of < 100 mg/dL. This LDL-C level could be achieved through use of statins, or if the primary concern was a low HDL-C level, through fibrates or nicotinic acid.[3] HPS results support the use of a statin with the primary focus of lowering LDL-C, and as discussed above attaining a significant percentage reduction in LDL-C.[3]

Patients with *baseline LDL-C levels < 100 mg/dL* at high risk were in the third group that the study results have been likened to. These patients were at the goal LDL-C level according to ATP III. HPS and PROVE IT-TIMI 22 both demonstrated a persistent decline in risk as LDL-C level continued to decrease below 100 mg/dL. As discussed before, this does not mean that all high-risk patients should have a LDL-C goal of < 70 mg/dL, but benefits may be seen for those at the highest CHD risk.[3]

The risk reduction seen from these studies indicate that benefits may also be seen in people with *LDL-C values of < 100 mg/dL who are already on lipid-lowering therapy*. Unfortunately, achieving greater reductions in this group may be more difficult as many patients may already be on high-dose statins or combination therapy to have reached this level. Once again, changing the goal LDL-C to < 70 mg/dL would most likely be of use in those patients at the highest risk.[3]

The final group of high-risk patients the evidence from these studies is applied to is those with *acute coronary syndrome*. PROVE IT-TIMI 22 indicates that these patients may experience a greater decline in CHD event risk if LDL-C values are lowered to < 70 mg/dL.[3]

Implications of HPS for Patients with DiabetesDiabetes was designated as a CHD risk equivalent in ATP III, and evidence showed that LDL-C–lowering therapy is efficacious in diabetic patients. HPS participants with both CVD and

diabetes attained the greatest absolute risk reduction from statin therapy, supporting more intensive lipid-lowering regimens to achieve LDL-C levels of < 70 mg/dL. [3]

Diabetic patients without established CVD also benefit from statin therapy, but the relationship is not as well defined. Diabetic patients in HPS who had baseline LDL-C values of < 116 mg/dL, and no known CVD, only experienced a marginal risk reduction for first coronary events. Clinical judgment should be used when evaluating whether to begin statin therapy in people with diabetes, no CVD, and whose LDL-C is < 100 mg/dL initially. [3]

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

ATP III recommends that people with elevated cholesterol should not be denied lipid-lowering therapy solely upon the basis of age. Statin use was investigated in persons over 65 years of age in HPS. This group achieved similar absolute risk reductions as the other high-risk groups studied in HPS. Elderly patients without established CVD were also studied in the PROSPER and ASCOT studies. These studies demonstrated that elderly patients were able to tolerate statin doses that decrease the rate of coronary events. [3]

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

The ATP III goal for persons at moderately high risk is an LDL-C < 130 mg/dL. Results from ASCOT-LLA illustrated a reduction in CVD risk for patients in this group who were started on a statin, even when they had an initial LDL-C < 130 mg/dL. A goal LDL-C of < 100 mg/dL is now a therapeutic option for these patients dependent upon clinical judgment and a person's risk factors for CVD development. The following are risk factors to consider when deciding to lower LDL goal for moderate risk persons: [3]

- Elderly
- More than 2 risk factors
- Severe risk factors (smoking status or positive family history of premature atherosclerotic CVD)
- Triglycerides ≥ 200 mg/dL in conjunction with non-HDL-C ≥ 160 mg/dL
- HDL-C < 40 mg/dL
- Metabolic syndrome
- Presence of risk factors currently under study, such as elevated C-reactive protein

The ALLHAT-LLT did not demonstrate significant improvement between participants in the 2 groups, except among African-Americans. The primary implication resulting from this trial is that races other than white males (the majority of participants in these studies) will benefit from LDL-C lowering. [3]

Trials Since the 2004 NCEP Update

A meta-analysis of 25 studies comparing the effectiveness of statins in adults with CHD was also published this year.[17] This study provides additional information to help evaluate the recent recommendations found in the 2004 NCEP implications. Studies included in the meta-analysis enrolled participants with CHD or who were at risk of CHD owing to diabetes, hypertension, smoking status, and cerebrovascular disease. At least 100 patients were in each treatment arm of the trials, individuals were randomly assigned to a treatment, and the

studies reported clinical outcomes. The goals of the meta-analysis were to evaluate if statin use decreased CHD, vascular events, revascularization procedures, and all-cause mortality.[17] The secondary outcomes were to determine the effectiveness of statins at lowering LDL-C, the LDL-C level at which pharmacotherapy should be started, and if aggressive LDL-C reduction is more effective than moderate reductions.

CHD, Vascular Events, Revascularization Procedures, and All-Cause Mortality

Statin use produced a 25% relative risk reduction in CHD mortality and non-fatal MIs (95% CI 0.71 to 0.79), and a 16% relative risk reduction in all-cause mortality (95% CI 0.79 to 0.89). When the individual reports were analyzed, only a small number actually demonstrated statistical significance, but when analyzed together, a benefit was seen from the use of these agents.[17]

Statin Effectiveness, LDL-C to Start Pharmacotherapy, and Aggressive vs. Moderate LDL-C Reductions

Significant declines in LDL-C levels were seen with the use of a statin (-22% to -38%) compared with placebo or usual care (19% to 37%).[17] Only the HPS has shown that a benefit is seen when cholesterol is further reduced once it is already at the goal of < 100 mg/dL.[17] Overall risk reductions were seen in all patients who had initial LDL-C levels of at least 130 mg/dL.[17] No relationship was found between pretreatment LDL-C and the percentage reduction in LDL-C, but a direct association between absolute decreases in LDL-C and preliminary readings was seen.[19] This is understandable as similar relative risk reductions would equate to larger absolute risk reductions with increased initial LDL-C. [17] The authors did not find sufficient evidence to conclude that intensive therapy was more beneficial in decreasing mortality, non-fatal CHD events, or revascularizations.[17]

Implications of Meta-Analysis to 2004 NCEP Update

One item of significance reported in the meta-analysis is only 2 trials had control groups that achieved LDL-C values of < 130 mg/dL.[17] Consequently, when reductions in mortality from statin use are reported, they are primarily reductions compared with groups of patients who have not reached the goal LDL-C for high-risk persons.

The meta-analysis results coincided with the NCEP conclusion that treating elderly patients with hyperlipidemia is beneficial. Death from all causes was reduced by 15% (95% CI 0.71 to 0.81) and CHD death plus nonfatal MI declined by 24% (95% CI 0.71 to 0.81) in those patients who were at least 60 years old.[17] Some studies suggest that in patients older than 85 years of age, increased cholesterol levels may actually be associated with greater rates of survival, but the majority of the evidence does not indicate this.[18]

Trials currently underway that may shed additional light on the NCEP recommendations include the Treating New Targets trial (TNT) and the Incremental Decrease in Endpoints through Aggressive Lipid Lowering trial (IDEAL). The TNT trial will randomize patients to receive daily doses of either atorvastatin 10 mg (goal LDL-C of 100 mg/dL) or atorvastatin 80 mg (goal LDL-C of 75 mg/dL). The TNT trial will help

delineate if reductions in risk continue to decline as LDL-C levels drop and will also eliminate confounding variables from using different statins. Patients in the IDEAL study will receive either atorvastatin 80 mg or simvastatin 20-40 mg daily. Both studies will investigate fatal CAD and non-fatal MI frequency.[19]

Adverse Effects of Low Cholesterol

Two longitudinal trials and one ongoing, randomized controlled trial have addressed the issue of low cholesterol level and the potential association with increased mortality from cancer, hemorrhagic stroke, and violent death.[20-22] The MRFIT trial was a randomized study designed to determine the impact of cholesterol, blood pressure, and cigarette smoking on CHD incidence. Baseline cholesterol, blood pressure, and smoking status were all assessed. Participants were grouped according to total cholesterol < 160 mg/dL, 160-199 mg/dL, 200-239 mg/dL, and ≥ 240 mg/dL. Diabetic persons and patients who had been hospitalized for more than 2 weeks for a MI were excluded from participation. The study followed 350,977 men for 12 years.[20]

Over the 12 years, 21,499 deaths were noted. The largest proportion of deaths (43%) resulted from CVD, three quarters of which were attributable to CHD. Cancer was responsible for 36% of deaths, and 20% of deaths resulted from miscellaneous causes.[20] The risk of CVD death was adjusted for diastolic blood pressure, smoking status, race, age, income, and season of the year. After adjustments, a direct relationship was noted between cholesterol level and CVD death. When deaths from the CHD subset were compared with cholesterol levels, an even stronger correlation was observed.[20]

Strokes accounted for 7% of the CVD deaths. An association was not found between cholesterol levels and deaths from strokes. This is because the risk of death from non-hemorrhagic stroke was elevated as cholesterol increased, but hemorrhagic strokes occurred more frequently in the lowest cholesterol level group (< 160 mg/dL).[20] The latter result may have been linked to increased blood pressure, as the increased risk of intracranial hemorrhage was only seen in those participants who had a baseline diastolic blood pressure of > 90 mm Hg ($P < 0.001$).[20] No difference was seen in rate of hemorrhagic stroke among the 3 higher cholesterol groups ($P = 0.90$).[20]

Cancer deaths were similar to hemorrhagic strokes in that a difference in the incidence was not seen between the upper 3 cholesterol groups. Cancer deaths did increase for the group with total cholesterol levels < 160 mg/dL. This risk decreased as the trial progressed, but was still significant after 10 years.[20]

The association between cholesterol and cancer varied depending upon the type of cancer. No relationship between cholesterol and colon cancer was seen (95% CI 0.88 to 1.02).[20] A difference was also not present in the rate of liver and pancreatic cancers in the upper 3 cholesterol strata ($P = 0.85$), but each of these groups experienced a lower occurrence than did patients with total cholesterol values of < 160 mg/dL (95% CI 0.48 to 1.0). Lymphatic cancers also occurred less frequently as cholesterol levels increased ($P = 0.002$).[20]

A total of 4281 deaths did not result from CVD or cancer. Thirty-nine percent of these deaths resulted from homicides, suicides, or accidents. Respiratory and digestive diseases accounted for another 35% of these deaths. When these miscellaneous causes of death were combined, an increased rate of death was once again seen in those patients with the lowest total cholesterol values (95% CI 0.59 to 0.71), with the strongest inverse relationship found in patients who died from chronic obstructive pulmonary disease ($P < 0.001$).[20] Subgroup analysis showed that suicide, homicide, and accidental deaths alone also occurred more frequently in the low cholesterol level group, but cirrhosis resulted in death more often in that same group.[22] Statistical significance in deaths rates was only found with the link between cholesterol levels and suicide (95% CI 0.46 to 0.84).[20]

A similar study to MRFIT was performed in the Honolulu (Hawaii) Heart Program. This study also only included males, but limited inclusion to American men of Japanese ancestry. The study followed 7961 participants for 18 years.[21] The results corresponded to that seen in MRFIT, with a direct, significant relationship between total cholesterol and both CHD and non-hemorrhagic stroke. An inverse relationship was also apparent between cholesterol levels and cancer.[21]

Baseline cholesterol levels of those who died (218.2 mg/dL) were similar to those who survived (218.4 mg/dL). The baseline cholesterol for patients who died from cancer in the first 6 years was 203.1 mg/dL, compared with 212.2 mg/dL for those dying between year 7 and 12, and 215.5 mg/dL for any cancer patients who died after 12 years.[21]

A conference was held to evaluate numerous studies that examined the effects of low cholesterol.[22] They found that all cause death was the lowest in participants with total cholesterol levels ranging from 160-199 mg/dL, and rates increased by 14%-22% in those participants who had total cholesterol levels < 160 mg/dL or ≥ 240 mg/dL. The risk for total CVD death was also the lowest in the 160-199 mg/dL group.[22]

The UCSD trial is an ongoing, randomized controlled trial that is examining the impact of lower cholesterol levels. This trial will randomize 1000 participants to receive daily doses of pravastatin 40 mg, simvastatin 20 mg, or placebo for 6 months. The hypothesis being investigated in this study is that the statins will reduce cognitive function and cause increased irritability.[23] The investigators of this study acknowledge that statins are very effective at reducing CHD, but desire to test the link between low cholesterol levels and increased rates of violent behavior, including suicide, in patients seen through observational trials.[23]

Discussion

The new treatment goals for high-risk and moderate-risk patients are optional at this point. As new studies are designed and completed, additional evidence could be forthcoming that clearly delineates a benefit in further reducing LDL-C in these patients who have the additional risk factors discussed above.

Out of the 5 trials that led to the Implications of Recent Clinical Trials for the NCEP ATP III Guidelines, only HPS showed a decrease in total mortality, and this decrease was primarily owing to a

reduction in CHD deaths. The ASCOT-LLA, ALLHAT-LLT, and PROVE IT-TIMI 22 did not detect any difference in overall mortality or in deaths from cardiovascular causes. The PROSPER study did not have adequate power to detect if a difference in all-cause mortality was apparent between the 2 groups, but CVDs decreased. All of the studies except for the ALLHAT-LLT found reduced rates of CHD events, which is significant, as medical costs are apparent not only in those who die from CHD, but also in those who live with the effects of CHD.[1] Both the meta-analysis and HPS, PROSPER, and ASCOT-LLA show a positive impact from statin use in the elderly population.

One possible reason for the lack of impact in overall mortality in these studies could be that low cholesterol increases the risk of other causes of death. The evidence for the reduction of CHD events is stronger than the observational trials evaluating the risks of low cholesterol. Some of the controlled trials examined the purported causes of increased deaths from low cholesterol, but few saw any differences in the incident rates between statin use and placebo, although they may not have had adequate power to detect this. On the other hand the MRFIT and Honolulu Heart program trials took place over a longer period of time, the type of study design used in these trials may be necessary to determine the long-term consequences of low cholesterol levels. The need for a long-term study to identify mortality from other causes is just one possibility, since in the MRFIT trial, rate of deaths attributable to cancer actually decreased throughout the trial.

Conclusion

Little argument exists that elevated cholesterol levels, especially LDL-C, contribute to the development of CHD. Unfortunately, more still remains to be learned not only about reducing the incidence of CHD events, but also about decreasing overall mortality. Current studies are investigating the benefits of intensive lipid-lowering therapy and the cognitive impact of low cholesterol. Evidence now exists that may impact LDL-C–lowering therapy in patients at the highest risk of developing CHD, but the optimal level is still unknown.

References

1. Robertson, RM. CDC Preventing Heart Disease and Stroke Addressing the Nation's leading Killers. 2004. http://www.cdc.gov.
2. 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.
3. Grundy SM, Cleeman JI, Bairey CN, Bairey Merz CN, Brewer B, Clark LT, et al. Implications of the recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *Circulation*. 2004;110:227-239.
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;360:7-22.
5. Gluckman TJ, Baranowski B, Ashen MD, Henrikson CA, McAllister M,

Braunstein JB, et al. A practical and evidence-based approach to cardiovascular disease risk reduction. *Arch Intern Med.* 2004;164:1490-1500.
6. Jones, PH, Davidson, MH, Stein, EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol*. 2003;92:152.
7. Brown WV, Chitra RR, Zedler BK et al: Long-term efficacy and safety of rosuvastatin; results of a 52-week comparator-controlled trial versus pravastatin and simvastatin. *Eur Heart J*. 2001;22:270.
8. Grundy, SM. Can statins cause chronic low-grade myopathy? *Ann Intern Med*. 2002;137:617.
9. Pfeffer, MA, Keech, A, Sacks, FM, et al. Safety and tolerability of pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) Project. *Circulation.* 2002;105:2341.
10. Weismantel, D. What laboratory monitoring is appropriate to detect adverse drug reactions in patients on cholesterol-lowering agents? *J Fam Pract*. 2001;50:927.
11. Gotto, AM Jr. Safety and statin therapy: reconsidering the risks and benefits. *Arch Intern Med*. 2003;163:657.
12. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. 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 randomized controlled trial. *Lancet.* 2003;361:1149-58.
13. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT-LLT). *JAMA.* 2002;288:2998-3007.
14. Jenkins DJA, Kendall CW, Marchie A, Faulkner DA, Wong JMW, Souza R de, et al. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *JAMA*. 2003;290:502-510.
15. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495-1504.
16. Shepherd J, Blauw GJ, Murphy MB, Bollen ELEM, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *Lancet*. 2002;360:1623-1630.
17. Wilt TJ, Bloomfield HE, MacDonald R, Nelson D, Rutks I, Ho M, et al. Effectiveness of statin therapy in adults with coronary heart disease. *Arch Intern Med*. 2004;164:1427-1436.
18. Weverling-Rijnsburger, Annelies W. E., Blauw, Gerard J. Total cholesterol and risk of mortality in the oldest old. *Lancet*. 1997;350:1119-1123
19. Deanfield JE Clinical trials: evidence and unanswered questions—hyperlipidaemia. *Cerebrovasc Dis*. 2003;16(suppl 3):25-32.9.
20. Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, Shih J. Serum cholesterol level and mortality findings for men screened in the multiple risk factor intervention trial. *Arch Intern Med*. 1992;152:1490-1499.

21. Stemmermann GN, Chyou PH, Kagan A, Nomura AMY, Yano K. Serum cholesterol and mortality among Japanese-American men the Honolulu (Hawaii) heart program. *Arch Intern Med*. 1991;151:969-972.
22. Jacobs D, Blackburn H, Higgins M, Reed D, Iso H, McMillan G, et al. Report of the conference on low blood cholesterol: mortality associations. *Circulation*. 992;86:1046-1060.
23. Golomb BA, Criqui MH. White H. Dimsdale JE. Conceptual foundations of the UCSD statin study – a randomized controlled trial assessing the impact of statins on cognition, behavior, and biochemistry. *Arch Intern Med*. 2004;164:153-159.