

Cholesterol: Precursor to Many Lipid Disorders

Based on a presentation by Peter H. Jones, MD

Presentation Summary

Despite advances in treatment and prevention, coronary heart disease (CHD) remains the leading cause of death in the United States. A major risk factor for CHD is elevated low-density lipoprotein cholesterol (LDL-C). Randomized clinical trials have proven that lowering LDL-C to near target levels significantly reduces CHD risk. More aggressive LDL-C reductions would have an even greater impact on reducing CHD risk if these goal levels were applied to all patients at risk, as identified by a CHD risk prediction scoring system. In 1993 the second Adult Treatment Panel (ATP II) of the National Cholesterol Education Program issued guidelines that defined CHD risk on the basis of whether a patient qualified for primary or secondary prevention. The ATP III guidelines, issued May 2001, introduce the concept of CHD-equivalent risk in patients without known CHD, thereby expanding considerably the number of people eligible for lipid-lowering therapy. Unfortunately, many patients who are eligible for therapy are not receiving it, and among those on lipid-lowering therapy, less than half have achieved their treatment goals. As mentioned, findings from several large-scale primary- and secondary-prevention trials with statins and other lipid-lowering agents have shown that lowering LDL-C reduces the risk for fatal and nonfatal coronary events and results in fewer hospitalizations and revascularization procedures. In fact, a review of the 5 major statin trials reveals that the higher the patient's baseline CHD risk, the more striking the benefits of therapy are. Clearly, the need to lower LDL-C levels is crucial. Meeting this need involves targeting patients who are at risk, implementing appropriate treatment, and ensuring compliance with therapy.

Coronary heart disease (CHD) remains the leading cause of death in the United States, despite major advances in treatment and prevention. According to the American Heart Association, approximately 12.4 million adults in this country have established CHD.¹ By age 60, 1 in 5 men and 1 in 17 women have CHD. Each year, myocardial infarctions (MIs) occur in 1.1 million Americans and 460,000 die. The estimated price for CHD morbidity and mortality is \$100 billion, with \$53 billion attributed to direct costs and \$47 billion attributed to indirect costs.¹

A major risk factor for CHD is elevated low-density lipoprotein cholesterol (LDL-C). Elevated LDL-C, along with other lipid abnormalities and a host of other risk factors, causes atherosclerosis, a diffuse disease that results in clinical coronary events. Data from the National Health and Nutrition Examination Survey (NHANES) suggest that nearly 100 million adults in the United States may be eligible for dietary therapy, as well as drug therapy, to lower elevated total cholesterol and LDL-C levels to reduce their risk for CHD.²

Unfortunately, many of those who are eligible for therapy are not receiving it. The Lipid Treatment Assessment Project (L-TAP) showed that only 38% of patients who are receiving lipid-lowering therapy have achieved their treatment goal.³ Clearly, lowering cholesterol to target lev-

els in all patients requiring therapy is necessary to reduce CHD risk.

Approaches to Treatment

There are 2 methods used to treat lipid abnormalities. The nonpharmacologic approach consists of lifestyle modifications such as reduced dietary intake of saturated fat and cholesterol, weight control, and exercise. The pharmacologic approach consists of the use of a lipid-lowering agent such as a statin, a bile acid sequestrant, a fibrate, or nicotinic acid (niacin). To varying degrees, these interventions target not only elevated LDL-C levels, but also elevated triglyceride levels and low levels of high-density lipoprotein cholesterol (HDL-C).

Lifestyle modifications with or without pharmacologic therapy are essential to normalize lipid levels and help lessen other cardiovascular risk factors such as obesity, diabetes, impaired glucose tolerance, and hypertension. However, long-term compliance with lifestyle modifications is difficult for many patients.

National Cholesterol Education Program Guidelines

The National Cholesterol Education Program (NCEP) was established in the mid-1980s by the National Heart, Lung, and Blood Institute to help physicians identify patients with various lipid abnormalities and set treatment guidelines for both individuals and the general population. The recommendations of the first

NCEP Adult Treatment Panel (ATP I) were released in 1988; they were updated in 1993 by ATP II.⁴ The recommendations of the newly released ATP III guidelines⁵ differ from those of ATP II in several ways.*

Although both ATP II and ATP III define LDL-C as the primary target for treatment, ATP II calls for a step I or step II diet trial initially for several months, which may be followed by pharmacologic therapy to reduce LDL-C in patients at risk for CHD. In contrast, ATP III favors the use of the more stringent step II or "therapeutic" diet. This diet emphasizes a marked restriction of saturated fat and small-to-moderate restriction of total fat in addition to the administration of pharmacologic agents and dietary adjuncts (eg, fiber, soy protein, plant stanol esters) that may further lower LDL-C.

Another key difference between ATP II and ATP III is the approach to risk assessment. Although aggressive LDL-C reduction in secondary prevention is a given in both sets of guidelines, ATP III places a greater emphasis on primary prevention by expanding the criteria for defining CHD risk and thus the eligibility for therapy. ATP III introduces the concept of CHD risk equivalents; that is, a 20% or higher risk for a first coronary event within the next 10 years. Patients without known CHD who are considered to be CHD risk equivalent to those with known CHD are those with noncoronary atherosclerosis (eg, transient ischemic attacks, cerebrovascular accidents, peripheral artery disease), type 2 diabetes, and multiple risk factors that confer, in combination, a 10-year risk of 20% or higher. The ATP III guidelines recommend that these risk-equivalent patients be treated just as aggressively with lipid-lowering agents as patients with known CHD.

In ATP II, risk was assessed in terms of primary or secondary prevention, and

Table. NCEP ATP III Guidelines for LDL-C

Patient Risk Status	LDL-C Goal
Without CHD or <10% 10-year risk	<160 mg/dL
Without CHD or 10% to 20% 10-year risk	<130 mg/dL
With CHD or CHD risk equivalents (>20% 10-year risk)	<100 mg/dL

ATP = Adult Treatment Panel; CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program.

Source: Reference 5.

*ATP III guidelines were officially released on May 15, 2001, less than a month after the symposium upon which this supplement is based was held. Dr. James M. McKenney, who chaired the symposium, served as a member of ATP III.

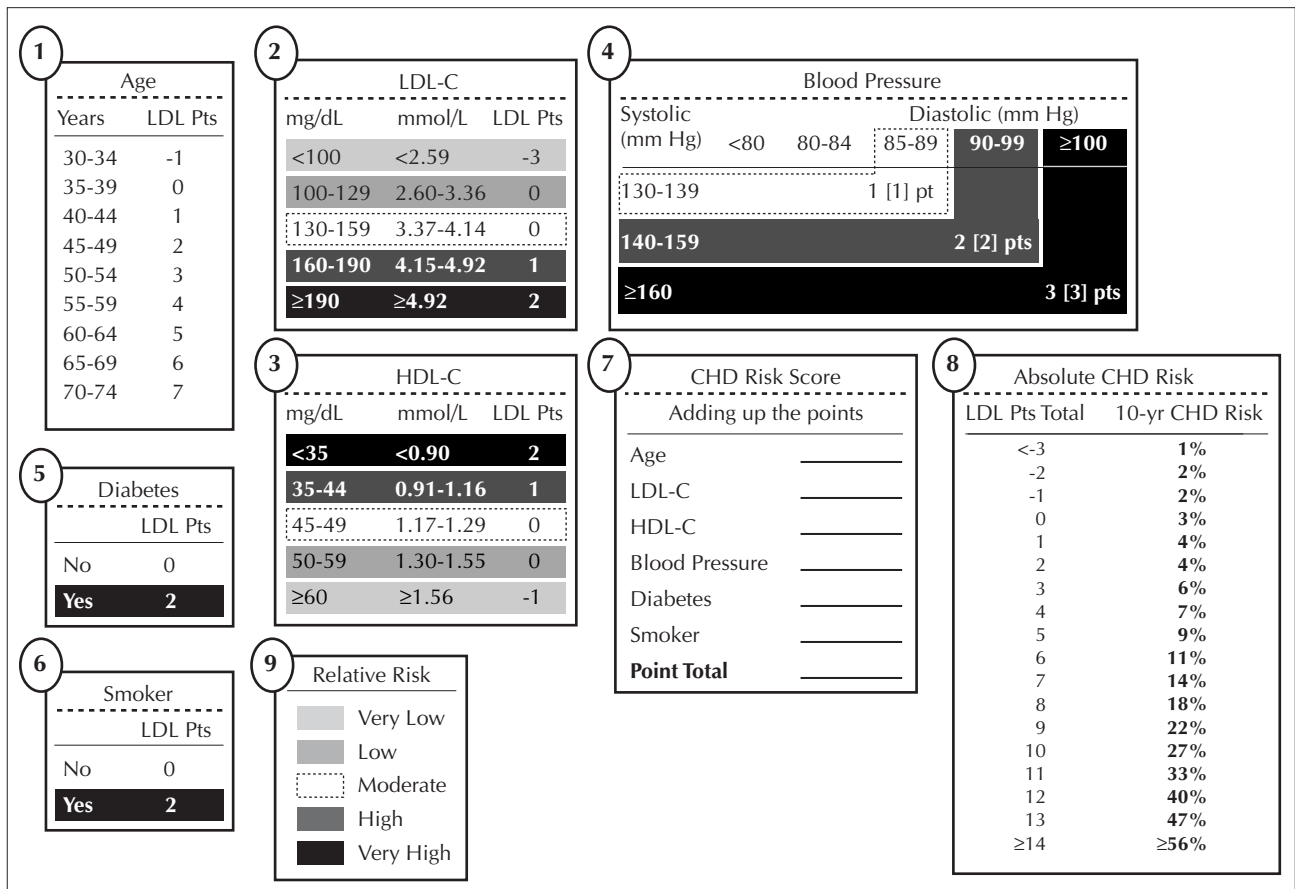
LDL-C treatment goals were established for each category. ATP II categories and LDL-C goals for patients with known CHD are low-risk primary prevention (< 160 mg/dL), higher-risk primary prevention (< 130 mg/dL), or secondary prevention (≤ 100 mg/dL).

Although the LDL-C target levels established by ATP III are almost the same as those established by ATP II, the risk categories have been redefined to include the 10-year CHD risk (Table). ATP III assesses global risk by evaluating risk factors as a continuous variable over a 10-year period, using a coronary prediction model.⁶ This model was based on pooled data

from 2489 men and 2856 women who participated in the Framingham Heart Study or the Framingham Offspring Study. Risk prediction score sheets were developed for men (Figure 1) and for women (Figure 2).

The Framingham risk prediction score sheets take “hard” risk factors into account (eg, age, LDL-C or total cholesterol, HDL-C, blood pressure [systolic or diastolic, whichever is higher], diabetes, and smoking). Each risk factor is worth a certain number of points which, when added together, yields an absolute CHD risk at 10 years. The total point score that indicates high risk (ie, a 20% risk for a

Figure 1. Framingham CHD Risk Prediction Chart (Men)



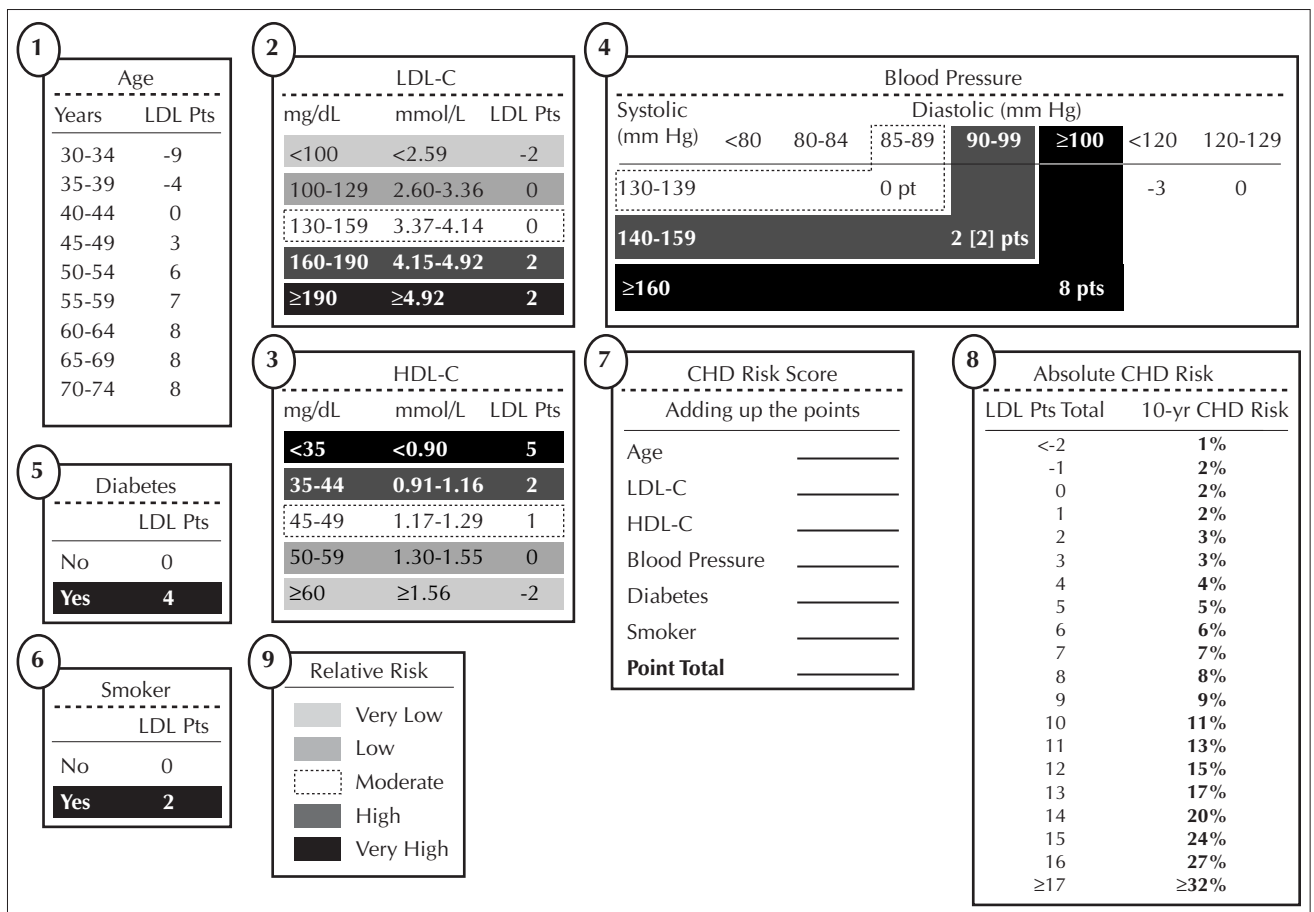
CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Pts = points. Source: Wilson PWF, D’Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-1847. Reprinted with permission.

coronary event over the next 10 years) is 9 for men (Figure 1) and 14 for women (Figure 2).⁶

The points add up quickly, as illustrated by the point scores for age: a 70-year-old man is given 7 points for age alone; another 2 points puts him into the high-risk primary-prevention category. By contrast, a 45-year-old man (2 points for age) who smokes (2 points) and also has diabetes (2 points), elevated LDL-C (2 points), and high blood pressure (135/88 mm Hg, 1 point) has the same total point score of 9 (Figure 1).⁶ For women (Figure 2), the risk for CHD increases rapidly past the 45 to 49 age bracket, which reflects

menopause and the loss of cardioprotection associated with endogenous estrogen. Indeed, women past the age of 60 receive 8 points for age alone, and they need only 6 points more to be classified as high risk. In addition, the point score given for HDL-C levels below 35 mg/dL is higher for women (5 points) than for men (2 points). Thus, a 65-year-old woman with an HDL-C level below 35 mg/dL but no other risk factors already has a total point score of 13 and a 10-year CHD risk of just under 20%.⁶ The actual risk scoring system in ATP III has been modified from what is presented here; for example, diabetes has been removed because it is a

Figure 2. Framingham CHD Risk Prediction Chart (Women)



CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Pts = points. Source: Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-1847. Reprinted with permission.

CHD-equivalent risk and systolic blood pressure alone is a risk factor instead of either systolic or diastolic blood pressure.⁵ Thus, it is clear that aggressive lipid therapy, along with attention to glucose control, blood pressure, and smoking cessation, are essential to reduce CHD risk.

Achieving LDL-C Goals: Room for Improvement

In addition to expanding the number of patients eligible for lipid management, and especially those eligible for aggressive therapy, the revised guidelines are expected to positively impact the number of patients achieving LDL-C target goals. To some degree, the expected improvement will be prompted by the performance measures for total cholesterol and LDL-C instituted in 2000 by the Health Plan Employer Data and Information Set (HEDIS) of the National Committee for Quality Assurance (NCQA). The HEDIS performance measure is based on the achievement of an LDL-C < 130 mg/dL within 60 to 365 days after hospital discharge following a major coronary event.⁷ Managed care organizations (MCOs) must report LDL-C levels of these patients within the time frame as a requirement for NCQA accreditation. Both the HEDIS performance measure (LDL-C < 130 mg/dL) and the ATP III target (LDL-C < 100 mg/dL for patients with known CHD) are expected to encourage physicians to use more aggressive lipid-modification therapy and improve MCOs' compliance with NCQA requirements.

The need to increase the proportion of patients achieving LDL-C targets is evident. Data from NHANES III, covering the years 1988 to 1991, revealed that only 43% of the adult population with 2 or more traditional risk factors for cardiovascular disease (high-risk primary prevention) achieved LDL-C target levels < 130 mg/dL.² The same survey showed that only 15% of adults with CHD achieved LDL-C target levels < 100 mg/dL.² Clearly, there is much room for improvement.

Findings from the more recent L-TAP study were only slightly better. L-TAP sur-

veyed 606 primary care physicians and assessed the achievement of LDL-C target levels in 4888 patients who were receiving drug and nondrug therapy to lower cholesterol. Although 95% of the physicians, who practiced in 5 different geographic regions of the United States, said they knew the NCEP target goals for LDL-C, only 63% followed the guidelines and treated patients until they achieved target levels.³

Overall, only 38% of patients in the L-TAP study achieved LDL-C target goals. Broken down by risk category, 68% of the 1143 patients at low risk achieved an LDL-C < 160 mg/dL, and 37% of 2285 high-risk patients achieved an LDL-C < 130 mg/dL. Of the 18% of CHD patients who did not achieve the LDL-C goal of ≤ 100 mg/dL, 45% still had LDL-C levels > 130 mg/dL, including nearly 17% with levels > 160 mg/dL.³ In other words, of those study patients with CHD who did not achieve goal, the 45% with LDL-C levels > 130 mg/dL would have failed to meet the HEDIS/NCQA performance measure.⁷

Of the 38% of L-TAP patients who did achieve their LDL-C targets, most were treated with fluvastatin, pravastatin, lovastatin, or simvastatin. Among those at low risk, all 4 statins were relatively equal in their efficacy to achieve goal. However, among those at high risk and those with CHD, simvastatin was most effective in lowering LDL-C to target levels,³ indicating that a more potent statin increases the likelihood of achieving goal. Atorvastatin was not evaluated in L-TAP because it was not available at the time of the study. However, had atorvastatin been included in the evaluation, it is likely that more patients would have achieved goal.

Identifying and Treating Patients at High Risk

Identifying patients at high risk for CHD and treating them appropriately begins with the recognition that atherosclerosis, the underlying cause of most CHD and other cardiovascular diseases, is a progressive, diffuse process that represents a continuum of risk. The ability to intervene with effective lipid-lowering

therapy at an early point along the continuum keeps the patient in the primary-prevention arena, before an acute coronary event can occur.

Although many physicians have long recognized that multiple risk factors and diabetes increase the risk for CHD, and many of them initiate therapy to reduce this risk, very few physicians prescribe treatment to lower the LDL-C level to < 100 mg/dL in patients with noncoronary atherosclerosis (eg, transient ischemic attack, completed stroke, peripheral vascular disease, intermittent claudication, diminished peripheral pulses, and femoral or carotid bruits). Clearly, these patients are CHD risk equivalents and should be treated aggressively to reduce their risk for a coronary event. At present, there are several noninvasive methods to detect noncoronary atherosclerosis, including electron beam computed tomography scans that identify coronary calcium, carotid ultrasound, and ankle/brachial indexes.

Evidence That Lowering LDL-C Reduces Risk

Several large-scale primary- and secondary-prevention trials have provided compelling evidence that lowering LDL-C reduces CHD risk. A 1984 multicenter study, the Lipid Research Clinics Coronary Primary Prevention Trial, tested the efficacy of cholestyramine versus placebo in 3806 asymptomatic middle-aged men with total cholesterol levels > 265 mg/dL. Cholestyramine, a powdered bile acid resin, reduced LDL-C levels by a modest 13% and over 5 years reduced the risk of CHD death and/or nonfatal MI, CHD death, and nonfatal MI by 19%, 24%, and 19%, respectively.⁸

Poor compliance in the treatment group was the reason given for the small reduction in LDL-C levels. The protocol called for 6 doses a day of the powdered resin, and many patients in the treatment group found it difficult to comply with the full dose. This is perhaps why cholesterol-lowering therapy with bile acid resins, which are capable of lowering LDL-C more than 13%,⁸ were not prescribed more

frequently in the mid-1980s, when bile acid resins were one of the indicated pharmacologic agents available to lower cholesterol.

The advent of the statins in the late 1980s and early 1990s revolutionized the treatment of hypercholesterolemia. As a class, these drugs are safe and well tolerated, formulated for once-a-day dosing, and can reduce LDL-C levels by 25% to 35%.⁹⁻¹³ Two large, randomized, placebo-controlled, primary-prevention trials, the West of Scotland Coronary Prevention Study (WOSCOPS) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), demonstrated the safety and effectiveness of statins in 2 different populations. Whereas the WOSCOPS included only men with high LDL-C levels, the AFCAPS/TexCAPS expanded the primary-prevention population and is the only primary-prevention study to involve women. AFCAPS/TexCAPS included older men and postmenopausal women with modestly elevated LDL-C levels (150 mg/dL) and low HDL-C levels (40 mg/dL for women, 37 mg/dL for men). Although the participants are representative of the general population, only 17% would have been eligible for drug therapy under NCEP ATP II guidelines. Thus, the study demonstrated that the benefits of lipid-lowering therapy—namely, a reduction in CHD risk of 35% to 40% after 5 years of therapy—extend to generally healthy individuals across all risk groups.¹⁰

Three large, randomized, secondary-prevention trials have demonstrated the benefits of statin therapy in CHD patients.¹¹⁻¹³ However, it is interesting to note that at least half of the patients in the trials failed to achieve the LDL-C goal of ≤ 100 mg/dL.¹¹⁻¹³ It would be interesting to know how much more beneficial the trials would have been had LDL-C been reduced to < 100 mg/dL in the majority of the treatment groups.

In the Scandinavian Simvastatin Survival Study, the baseline LDL-C level of 188 mg/dL was reduced to 122 mg/dL with the use of simvastatin over 5 years of treatment. At least 60% of the study patients failed to reach the goal level,

however.¹¹ Similarly, in the Long-Term Intervention with Pravastatin in Ischemic Disease trial, the baseline LDL-C level of 150 mg/dL was lowered to an average of 113 mg/dL over 5 years, but at least 55% of the study patients did not reach the goal level.¹² Likewise, in the Cholesterol and Recurrent Events trial, in which the baseline LDL-C level of 139 mg/dL was reduced to a mean level of 98 mg/dL over 5 years, 50% of the study patients did not reach goal.¹³

The statin trials have clearly shown that the higher the patient's risk at study entry, the more striking the benefits are over time, both in primary and secondary prevention. Additionally, all 5 trials have shown that risk reduction with lipid-lowering drug therapy is highly cost effective. Targeting primary-prevention patients at greatest risk (ie, those with diabetes and those with multiple risk factors) is likely to reduce risk even further, and result in even greater cost effectiveness.

Although the efficacy of statins has been clearly demonstrated, statin therapy is not appropriate for all patients or tolerated by all. Moreover, there are other effective lipid-lowering drugs that are available to help patients reach their LDL-C goals. These drugs can be considered for the following patients: those who are not achieving their LDL-C goals on maximum tolerated statin doses; those who are intolerant to statins at the initiation of therapy or who develop adverse effects on dose escalation; those who are ineligible for statin therapy because of active liver disease or unexplained elevations in liver function tests; and those who are interested in nonsystemic therapy (eg, young adults, those requiring only modest reductions in LDL-C, and women of childbearing potential).

... DISCUSSION HIGHLIGHTS ...

Effects of Statins

Member of the Audience: I appreciate that you referred to statin usage as a whole class, but one of the things we try

to teach is the ability of all statins to lower overall cholesterol. There seems to be evidence of other effects and differences among the statins as well. Could you comment?

Dr. Jones: You always like to have evidence-based medicine, and you like to go with treatments that have been proven to do what a study says they will do. I believe, however, that the ability of the statins to lower LDL-C has the most benefit. All the statins have the ability to do that, regardless of the unique properties of an individual statin, the duration of its half-life, or whether it is lipid soluble. As data accumulate, and as we look at markers and measures that we believe are related to the benefits of statin therapy, that is, the effects on the endothelium, the effects on inflammation within the artery wall, and the changes responsible for vulnerable plaques and rupture that cause acute coronary syndromes, we still see that lowering LDL-C has the most benefit. There might be a small amount of systemic statin that circulates and may act directly on the artery wall, but it's a very small concentration because all statins undergo a high degree of first-pass extraction in the liver. Very little of the active metabolites get into the systemic circulation, and there really isn't much difference among the various statins in that regard.

Looking at all mechanisms that might be involved in LDL-C lowering, I believe it is a class effect. Although trials are in progress with some of the other statins, it is clear that very early and aggressive treatment with atorvastatin is beneficial in patients with acute coronary syndromes. That was shown in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial, which was recently reported in *JAMA*.¹⁴ I believe in the next few years the data will demonstrate that it is a class effect.

Member of the Audience: Will there be any way to differentiate the class effects among the newer statins in raising HDL-C, for example?

Dr. Jones: One of the advances with the newer statins is going to be more aggressive LDL-C lowering at reasonable doses. There may be some differences in the metabolism of the newer drugs, which won't be important in monotherapy but may be important in combination therapy, where you use a statin plus a fibrate or a statin plus niacin.

The newer statins might also have some differences with regard to interaction with other medications, such as immunosuppressive agents in high-risk transplant patients, where drug-drug interactions might be important in the risk of myositis. Statins do increase HDL-C somewhat. They all tend to raise it by about the same amount, except for high-dose atorvastatin, which doesn't seem to raise HDL-C levels as well. However, none of the statins will ever raise HDL-C as much as niacin can. Niacin is the best drug to raise HDL-C. Regular physical activity is another excellent way to raise HDL-C; it probably produces an even greater increase than you can get with statins.

Triglyceride levels tend to decrease somewhat with statin therapy. Triglyceride lowering is not going to be as important with the statins, however, or much different among the statins. Niacin and fibrates will still be the drugs of choice for triglyceride control in high-risk individuals, including those with diabetes. Although there will be differences in some of the new statins in the future, I think the differences may be more in their metabolism and in their concomitant use with other drugs.

Cost Issues

Dr. McKenney: Let's assume you are the director of a pharmacy benefits management company. You have a million lives you're responsible for and a fixed budget for taking care of those patients. Their mean age is 65. How are you going to make decisions about allocating resources to the older population with expensive statin therapy?

Dr. Jones: The hard part is that the pharmacy budget sometimes tends to be in

one part of the total healthcare budget and the expenditures for other related things such as hospitalization are included in another area. I have seen this in the Veterans Administration and other hospitals where the pharmacy budget is separate from what the hospital spends. The 2 budgets should be interrelated because whatever the pharmacy spends to prevent disease and other adverse events should be reimbursed from the saved hospital expenditures. Both hospitalizations and utilization of services will be reduced by treating some of these CHD risks more aggressively. Whatever is spent on smoking cessation is an expenditure that will yield benefits in the future. The same thing is true for diabetes management and lipid treatment. I don't think anybody's going to have a problem with cost and resource allocations for secondary prevention. However, the new cholesterol guidelines are going to pull in a lot of older patients for primary prevention. If you're older but otherwise healthy, you are at high risk for future coronary events because it's most likely that you're going to have a coronary or vascular event in the next 10 years.

Physicians should be able to identify these high-risk patients for primary prevention, perhaps by some algorithm or using the Framingham risk prediction charts. How long does it take to fill out that chart? As long as you have the information, about 15 seconds. How long does it take to show the patient what his or her risk is? Another 15 seconds. You can tell the patient, "Your risk for a major heart attack is 1 in 4 in the next 10 years." That's pretty straightforward. The educational process isn't that difficult, and it doesn't take a lot of effort.

Whatever you do in terms of prevention will have to include lipid-lowering therapy. Statins will be the first line of treatment and should be administered based on risk, using these kinds of algorithms. Choose those patients who are otherwise healthy. Convince the managed benefits group you work with that this is going to benefit them in the long run, even though the expenditure is up front.

The difficult thing about prevention is that the money is spent first with the hope that there will be benefit later on. As consumers, that's the exact opposite of what we do. We get something up front and pay for it later. This is a whole different concept and it is very difficult for MCOs to understand.

Risk Factors

Member of the Audience: The risk prediction charts seem to have dropped family history and genetics. Could you comment on that?

Dr. Jones: We try to use the risks that are easy to quantify, and family history is very difficult to quantify. A family history of premature CHD is a risk factor; Aunt Tillie's dying of a heart condition at age 90 is not. Yes, it's in the family, but it's not premature.

Genetic factors are also very hard to quantify. We don't know all of the risk factors for heart disease. Family history is considered a predisposing risk factor. Part of the predisposition may be factors that we can measure, such as cardiovascular metabolic syndrome, diabetes, hypertension, central obesity, and dyslipidemia. However, there may be other genetic factors that we don't know about, so they're hard to quantify.

The same thing is true of obesity. Although obesity increases the risk for cardiovascular disease, most people feel its risk potential is manifested through other identifiable and modifiable factors such as diabetes and dyslipidemia. Therefore, obesity is considered a predisposing risk factor.

There is also a whole list of conditional factors that we think are risks, but because we don't really know, they're listed as conditional. These include homocysteine levels, high sensitivity C-reactive protein, and the presence of clotting factors V and VII as well as fibrinogen.

We don't know how to quantify these factors. The Framingham study doesn't know how to quantify them, and other

observational studies don't know how to quantify them. The net result is that the Framingham charts underestimate the risk of heart disease because they can't include all factors. Therefore, if you have a high score on the Framingham chart, your risk is at least that high, if not higher, because of additional factors that have not even been considered. If a patient has risk factors such as a positive family history, central obesity, or a sedentary lifestyle, along with a 20% risk on the chart, then that patient's risk is actually much higher than 20%.

Statin Intolerance

Member of the Audience: How common is intolerance to the statins, and would tolerance develop with long-term use?

Dr. Jones: Intolerance as a result of side effects occurs in about 10% of patients. Myalgia is probably the most common complaint, but it resolves if the statin is discontinued.

Mild elevations of alanine aminotransferase and aspartate aminotransferase, which can be a problem, are seen in perhaps 10% of patients. Elevations that are 3 times the upper limit of normal and persistent would be a reason for decreasing the dose or discontinuing the statin.

Usually a patient can tolerate at least 1 of the statins at some reasonable dose. Don't give up if a patient has myalgia with 1 statin. Try another or change the dose.

There is no tendency for tachyphylaxis with long-term statin use. You may get what I call a short honeymoon period with a statin, where the liver doesn't quite recognize what's going on, and there is a sudden drop in LDL-C, more than you expect. Then, over the next year, the LDL-C level slowly drifts upward, flattens out, and stabilizes.

What the liver is actually doing is compensating for the competitive inhibition. It's trying to remake enzyme to overcome that inhibition, but because the LDL-C level drops a lot during that first honeymoon period, then drifts

slightly, flattens out, and stays there, there really is no tachyphylaxis.

... REFERENCES ...

1. **American Heart Association.** *2001 Heart and Stroke Statistical Update.* Dallas, TX: American Heart Association; 2001.
2. **National Center for Health Statistics.** *National Health and Nutrition Examination Survey III (1988-1991).* Hyattsville, MD: National Center for Health Statistics; 1994.
3. **Pearson TA, Laurora I, Chu K, Kafonek S.** The Lipid Treatment Assessment Project (L-TAP): A multi-center survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000;160:459-467.
4. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993;269:3015-3023.
5. 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.
6. **Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB.** Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-1847.
7. **Lee TH, Cleeman JI, Grundy SM, et al.** Clinical goals and performance measures for cholesterol management in secondary prevention of coronary heart disease. *JAMA* 2000;283:94-98.
8. **The Lipid Research Clinics Coronary Primary Prevention Trial** results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351-364.
9. **Shepherd J, Cobbe SM, Ford I, et al.** 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.
10. **Downs JR, Clearfield M, Weis S, et al.** 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.
11. **Scandinavian Simvastatin Survival Study Group.** Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-1389.
12. **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.
13. **Sacks FM, Pfeffer MA, Moyé LA, 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.
14. **Schwartz GG, Olsson AG, Ezekowitz MD, et al.** Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: The MIRACL study: A randomized controlled trial. *JAMA* 2001;285:1711-1718.