



OPTIMIZING DYSLIPIDEMIA OUTCOMES:
A Novel Pharmacotherapeutic Pathway

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Supplement

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The National Cholesterol Education Program Adult Treatment Panel III Guidelines

ROBERT J. LIPSY, PharmD, FASHP, BCPS

Summary

Coronary heart disease (CHD) persists as a major cause of morbidity and mortality in the United States, with more than 40% of all deaths each year directly attributed to the disease. Dyslipidemia is recognized as a major risk factor for the development and progression of CHD, with clinical trials clearly demonstrating the public health and economic benefits of favorable cholesterol modification. As a result of this evidence, the National Cholesterol Education Program (NCEP) has developed guidelines for the detection, evaluation, and treatment of high blood cholesterol in adults. The most recent of the NCEP recommendations, the Adult Treatment Panel III (ATP III) guidelines, were released in May 2001 and build on the earlier editions and reiterate the importance of low-density lipoprotein cholesterol (LDL-C) reduction to modify CHD risk. New features of the guidelines include the identification of CHD risk equivalents; lower treatment target goals; an emphasis on conditions conferring a higher risk for CHD, such as the metabolic syndrome; and a scoring system for calculating CHD risk. The ATP III emphasis on risk assessment will result in a substantial increase in the number of patients considered at risk for CHD and will expand the number eligible for lifestyle and drug intervention.

KEYWORDS: Atherosclerosis, Cholesterol, Coronary heart disease, Dyslipidemia, LDL-C

Target Audience

Managed care pharmacists and other health care practitioners

Learning Objectives

Upon completion of this program, the participant should be able to

1. review the issues of underidentification and undertreatment of dyslipidemia and discuss how optimal dyslipidemia therapy can improve outcomes and likely reduce comorbidity of related disease,
2. evaluate the impact of the updated NCEP guidelines on clinical practice and discuss the clinical challenges associated with reaching the ATP III goals,
3. describe how cholesterol metabolism is impacted by various lipid pathways,
4. discuss a novel therapeutic approach to lowering cholesterol and explain the rationale for the use of a new class of lipid-lowering agents,
5. review current treatment modalities and patient profiles for dyslipidemia, and
6. describe standard-of-care approaches to improving dyslipidemia treatment outcomes and describe methods for clinical pharmacists to improve therapeutic strategies that enhance overall patient outcomes.

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Coronary heart disease (CHD) persists as the single leading cause of death among Americans, and the reduction of CHD risk is a critical public health endeavor. In the United States, more than 500,000 Americans succumb to CHD-related causes each year.¹ CHD also places a significant financial burden on the U.S. economy, with the yearly direct and indirect costs of the disease estimated to be in excess of \$111 billion.¹ Dyslipidemia is recognized as a major modifiable risk factor for the development and progression of CHD. Data from epidemiological studies have indicated that lower cholesterol levels, particularly lower low-density lipoprotein cholesterol (LDL-C) levels, are associated with lower overall risk of CHD morbidity and mortality.²⁻⁵ Based on this evidence, the National Cholesterol Education Program (NCEP) released the updated Adult Treatment Panel III (ATP III) guidelines in May 2001 to provide pharmacists and other health care professionals with an up-to-date approach for the detection, evaluation, and management of dyslipidemia.⁶ Building upon ATP I (1988) and ATP II (1993), ATP III (2001) pays increased attention to the identification and quantification of risk for CHD and thereby vastly increases the number of Americans eligible for therapies designed to modify lipids and reduce risk. With these changes, ATP III will challenge pharmacists and the health care system to identify at-risk patients, implement effective therapy, and ensure that patients meet target goals.

New Features of the NCEP ATP III Guidelines

As with previous editions, ATP III provides an evidence-based approach for the detection, evaluation, and management of lipid disorders. ATP III emphasizes LDL-C reduction as the primary target of therapy and advocates that the intensity of lipid modification therapy be adjusted to the degree of risk. ATP III also reiterates the importance of lifestyle changes, such as weight loss, dietary modifications, and increased physical activity, in reducing CHD risk. New features of the guidelines include the use of a Framingham risk assessment tool to evaluate the 10-year probability of experiencing a CHD event; identification of CHD risk equivalents, such as diabetes and peripheral vascular disease; more aggressive lipid target goals; and the recognition that patients with the metabolic syndrome should be provided intensified lipid modification therapy.

One of the hallmarks of ATP III is the categorization of patients into 3 groups based on the overall risk for experiencing a CHD event in 10 years. This approach allows treatment thresholds and lipid target goals to be matched to the patient's degree of risk. Patients with CHD and CHD risk equivalents are

considered at highest risk, those with 2 or more risk factors are considered at moderate risk, and patients with 0 to 1 risk factor are at a low 10-year risk. ATP III also recognized the role played by high-density lipoprotein cholesterol (HDL-C) and triglycerides in modifying CHD risk and raised the target for HDL-C from <35 mg/dL to <40 mg/dL and lowered the target goal for triglycerides to 200 mg/dL.

■ CHD Risk Assessment

ATP III advocates the use of a Framingham risk scoring system to estimate a patient's 10-year risk for a coronary event. Point scores are calculated according to the presence of 6 major CHD risk factors (age, gender, total cholesterol, systolic blood pressure, HDL-C, and smoking status), with each risk factor worth a certain number of points. When added together, the sum yields an estimate of the risk for experiencing a coronary event in 10 years. A properly conducted assessment places patients into one of the 3 risk categories and forms the basis for all subsequent treatment decisions.

Patients with documented CHD and CHD risk equivalents are automatically placed in the highest risk category (10-year CHD risk >20%). CHD risk equivalents carry a risk for a major coronary event considered to be equal to that of patients with established CHD. CHD risk equivalents include diabetes, peripheral vascular disease, symptomatic carotid artery disease, and abdominal aortic aneurysm. The LDL-C treatment goal for patients in this high-risk category is <100 mg/dL.

In patients without documented CHD or CHD equivalents, assessment of CHD risk is essential to identify therapeutic goals. Patients with 2 or more major risk factors are considered to be at a moderately increased risk for CHD but with a 10-year risk of 10% to <20%. Therapy for these patients should be sufficient to enable patients in this category to achieve an LDL-C target of <130 mg/dL. Patients at the lowest risk are those with one or fewer major risk factors. In all but rare cases, these individuals have a 10-year risk of <10%. The target LDL-C level in this group of patients is <160 mg/dL.

■ Current Treatment Trends

With the increased emphasis on risk assessment and intensified new treatment goals, it is estimated that the number of patients eligible for CHD risk reduction through lipid modification therapy in the United States will increase to nearly 65 million. The most effective approach to CHD risk reduction is one that matches the intensity of therapy to the degree of risk. Two primary modalities advocated by ATP III for lowering LDL-C, and therefore CHD risk, are therapeutic lifestyle changes (TLC) and drug therapy.

■ Therapeutic Lifestyle Changes

First-line therapy for most patients without CHD or CHD risk equivalents and <2 risk factors is TLC. Eating a healthy diet, participating in regular physical activity, smoking cessation, and

TABLE 1 Overview of the ATP III Guidelines

- Identifies LDL-C reduction as the primary goal of lipid-modifying therapy
- Evaluates risk of experiencing CHD event in next 10 years
- Targets therapy toward patients at greatest risk, particularly those with established CHD and risk equivalents, including diabetes
- Emphasizes a multifaceted approach to therapy, including therapeutic lifestyle changes (TLC)

TABLE 2 New Features of the ATP III Guidelines

Focus on Multiple Risk Factors

- Identifies diabetes without CHD as a cardiovascular risk equivalent
- Uses Framingham projections of 10-year absolute risk to identify certain patients with >2 risk factors for more intensive treatment
- Identifies patients with metabolic syndrome as candidates for intensified TLC

Modification of Lipid and Lipoprotein Classification

- Identifies LDL-C <100 mg/dL as optimal
- Raises categorically low HDL-C from <35 mg/dL to <40 mg/dL
- Lowers triglyceride cutpoints to give attention to moderate elevations

Support for Implementation

- Recommends complete lipoprotein profile as preferred initial test (total, LDL-C, HDL-C, triglycerides)
- Encourages use of plant stanols/sterols and soluble fiber as therapeutic dietary options to enhance LDL-C lowering
- Presents strategies for promoting adherence to therapeutic lifestyle changes and drug therapies
- Once LDL-C goal is achieved, recommends treatment beyond LDL-C lowering for patients with triglycerides \geq 200 mg/dL

weight loss have all been shown to be effective in reducing LDL-C and CHD risk. Dietary changes should include a reduction of saturated fats, reduction of intake of dietary cholesterol to <200 mg/day, addition of approximately 2 grams of plant sterols/stanols each day, and incorporating approximately 10 g to 125 g/day of viscous fiber into the diet. Weight reduction can also reduce LDL-C cholesterol levels and ameliorate the risk factors associated with the metabolic syndrome. Physical activity raises HDL-C levels and decreases the concentration of very low-density lipoprotein cholesterol (VLDL-C) and triglycerides. Smoking cessation can result in an elevation of HDL-C and reduction of CHD risk.

■ Drug Therapy

ATP III recognizes the limitations of TLC and encourages the addition of drug therapy if lifestyle modifications fail to achieve goal after 3 months. Most high-risk patients (>20% chance of

CHD in 10 years) will require concomitant application of drug therapy and TLC from the onset of treatment. For patients at the highest risk for coronary events, the LDL-C threshold for initiation of therapy is >130 mg/dL (after a 3-month trial of TLC). Drug therapy is optional for patients with LDL-C between 100 mg and 129 mg/dL, and prescribers are encouraged to use professional clinical judgment in determining the most appropriate approach to risk reduction in these patients. Data from the recent Heart Protection Study have led many experts to recommend early initiation of statins in patients with CHD and CHD risk equivalents, even when the baseline LDL-C is <130 mg/dL. For patients with moderate risk without CHD or CHD risk equivalents, but with >2 major risk factors and a 10-year risk of 10% to 20%, the treatment threshold is >130 mg/dL. For patients at moderate risk, with a 10-year risk <10%, the LDL-C threshold is >160 mg/dL. For patients without CHD and with 0 to 1 major risk factor, drug treatment should be considered if LDL-C cholesterol is >190 mg/dL after 3 months of TLC, with a goal of <160 mg/dL. In all cases of drug therapy, TLC should continue to be maintained and reinforced.

■ Current Lipid-Modifying Drugs

There are currently 3 classes of lipid-modifying drugs recommended by ATP III for the reduction of LDL-C: bile acid sequestrants; nicotinic acids; and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins. A fourth class, the fibric acid derivatives (fibrates), are not recommended because they have minimal direct effect on lowering LDL-C. However, ATP III does recommend fibrates for patients with very high triglycerides to reduce the risk of acute pancreatitis and for patients with certain other types of dyslipidemia, and fibrates are, therefore, discussed below.

Statins, currently the most widely used lipid-modifying agent, decrease LDL-C by 18% to 55% in a dose-dependent manner. These agents exert their effect by inhibiting cholesterol synthesis and promoting LDL-C uptake from the circulation via activation of liver LDL-C receptors. Currently, there are 5 statins on the market. These products are primarily differentiated by the degree of LDL-C lowering elicited by each dose. Several large clinical outcome trials have demonstrated unequivocally that statin use reduces the incidence of CHD events, including myocardial infarction, coronary death, stroke, and total mortality.²⁻⁵ These agents are also highly cost effective, especially in high-risk patients. ATP III recommends statins as first-line agents when LDL-lowering drugs are indicated to achieve LDL treatment goals.

Bile acid sequestrants are another commonly used agent that can be used as monotherapy or as add-on therapy to statins. Monotherapy with sequestrants can lead to attainment of treatment goal when moderate reductions in LDL-C are required. However, when more aggressive LDL-C reduction is required, sequestrants must be used in combination with statins. Although generally safe, adherence to a therapeutic regimen

containing sequestrants is limited because of poor tolerability and inconvenient dosing.

A third class of agents is nicotinic acid or niacin. Niacin provides a moderate LDL-C-lowering action, but the primary utility of these agents is in combination with statins for patients who have elevated triglycerides and/or low HDL-C. Niacins are also limited in their effectiveness because of compliance issues resulting from poor tolerability. However, the tolerability of niacin therapy can be improved by using either sustained release formulations of the drug or by slowly increasing the dose and providing patients with instructions on how to minimize side effects.

Fibric acids or fibrates are a fourth class of lipid-modifying agents. They are not recommended as primary therapy for LDL-C reduction but are recommended for persons with very high triglycerides to reduce the risk of acute pancreatitis. They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-VLDL). Fibrate therapy should be considered an option for treatment of persons with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. They also should be considered in combination with statin therapy in persons who have elevated LDL-C and atherogenic dyslipidemia. While ATP III does not recommend fibrates in patients who require LDL-C reduction, these agents are useful in patients with combined forms of hyperlipidemia and are especially effective in patients who have severe hypertriglyceridemia. Poor tolerability with fibrates, such as gemfibrozil, can limit adherence to fibrate therapy and therefore reduce the effectiveness of these agents. Limited data suggest that the risk of myopathy may be lowered by substituting the newer fibric acid derivative fenofibrate for gemfibrozil. However, the incidence of myopathy with fenofibrate-statin therapy has not been well studied.

Statins remain the first-line choice of therapy for lipid modification. In most cases, they are safe, effective, and well tolerated, particularly at low doses. However, despite the success of statins in favorably modifying lipids and reducing coronary events, alternative agents are needed for patients unable to tolerate statins. In these cases, prescribers have been forced to use bile acid sequestrants, niacin, or fibrates. However, these alternative agents vary in their effectiveness in reducing LDL-C due to low efficacy of the agent or poor compliance because of undesired side effects.

A promising new alternative therapy has recently received U.S. Food and Drug Administration approval. Phase 2 data suggest that ezetimibe, the first selective inhibitor of intestinal cholesterol absorption, appears to have significant potential for use as monotherapy in patients at low risk for CHD who require only a modest reduction in their LDL-C or for those who do not tolerate statin therapy.⁷ In addition, ezetimibe, when used in combination with a low-dose statin in patients at moderate to high risk for CHD, can elicit a reduction in LDL-C comparable to those seen at the highest statin doses.⁸ Furthermore, ezetim-

ibe has a safety profile similar to placebo.

Implementation of the ATP III Guidelines

Implementation of the ATP III guidelines will present an enormous challenge to pharmacists and the health care system. Adherence to previous guidelines suggests that achieving the aggressive new detection and treatment goals will be difficult. The ATP II guidelines, although much less complex, were rarely followed in patients with CHD, let alone in a patient with sub-clinical disease. Data from the Lipid Assessment Treatment Project demonstrated that only 18% of patients with CHD achieved ATP II goals and that <40% of all patients on lipid-modification therapy receive sufficient lipid lowering to reduce CHD risk.⁹ Because overall adherence and goal achievement was low with previous guidelines, the inherent challenge in achieving ATP III goals is clear.

In an attempt to improve cholesterol management, many institutions have developed multidisciplinary lipid clinics with physicians, nurses, pharmacists, and dietitians working together to target, treat, and manage patients at highest risk for CHD. These clinics have been successful in increasing the number of patients achieving NCEP target goals and reducing CHD risk when compared to patients receiving usual care.

Summary and Conclusion

The NCEP ATP III report updates the clinical guidelines for the detection and treatment of lipid disorders. While the emphasis remains on reducing long-term CHD risk by lowering LDL-C, new features of the guidelines include a scoring system for calculating CHD risk as well as the identification of CHD risk equivalents. The ATP III emphasis on risk assessment will substantially increase the number of individuals considered to be at risk for CHD and will expand the number who will be eligible for lifestyle and drug intervention. Pharmacists have the opportunity to impact patient care by positively encouraging cholesterol evaluation screening and treatment upon patient admission to the hospital and in the clinic. In addition, pharmacists can assist patients through education on the need for risk-factor interventions and achieving target goals and by encouraging adherence and persistence to therapy.

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Underidentification and Undertreatment Issues

MICHAEL B. BOTTORFF, PharmD, FCCP

Summary

Despite the Adult Treatment Panel (ATP) guidelines and strong evidence that reduction of blood cholesterol levels favorably decreases the morbidity and mortality associated with coronary heart disease (CHD), a significant number of patients remain undiagnosed and untreated. With the aggressive detection and evaluation methods ATP III advocates, more than 65 million Americans are now eligible for lipid modification through lifestyle changes and/or drug therapy. Recent data suggest, however, that as many as 50% of all patients do not have their cholesterol assessed and less than 45% receive lipid-modifying therapy. Additionally, more than 75% of patients who receive therapy fail to achieve their National Cholesterol Education Program (NCEP) target low-density lipoprotein cholesterol goal. Persistence with therapy is another challenge, as less than 30% of patients continue with therapy beyond one year. If a realistic attempt is to be made to reduce the CHD risk among Americans, diagnosis of dyslipidemia and treatment to therapeutic targets must be improved.

KEYWORDS: ATP III, Compliance, Cholesterol, Dyslipidemia

The American Heart Association estimates that 70 million adults in the United States have total cholesterol levels >200 mg/dL, and at least 40% of these individuals have cholesterol levels in excess of 240 mg/dL.¹ Based on low-density lipoprotein cholesterol (LDL-C) targets recommended in Adult Treatment Panel III (ATP III), an estimated 12.7 million Americans are eligible for drug therapy but are currently not receiving it.² This number reflects the increased emphasis in the new guidelines for treating not only patients with established coronary heart disease (CHD) but also patients who are at increased risk for CHD, including those with diabetes or 2 or more major risk factors. In addition, ATP III identifies significantly lower LDL-C target goals for all patients and includes treatment recommendations for conditions that predispose patients to higher risk, such as the metabolic syndrome. The net result of the new guidelines is that pharmacists and other health care professionals are challenged to implement systems that target the appropriate patients, identify therapies capable of achieving LDL-C target goals, and ensure that patients adhere to their therapeutic regimen so they can reap the CHD risk-reduction benefits of lipid-modification therapy.

Unmet Needs: Underdiagnosis

The National Cholesterol Education Program (NCEP) ATP III guidelines² increase to more than 65 million the number of adult Americans eligible for lipid-modifying therapy. This results from an increased emphasis on CHD risk assessment, identification of CHD risk equivalents, and new, lower LDL-C treatment thresholds. However, despite an increased awareness of the relationship between dyslipidemia and CHD risk, lipid disorders are significantly underdiagnosed in the United States. Data from the Lipid Treatment Assessment Project (L-TAP) illustrates the extent of the underdiagnosis of lipid disorders.³ This study identified that 50% of all patients do not have their cholesterol assessed when they visit the office of their primary care physician. Similarly, a survey of the cholesterol management practices of U.S. physicians indicated that only 1 in 12 physicians routinely provide cholesterol screening to patients who may be at risk.⁴

ATP III advocates a 9-step process to determine CHD risk and the need for lipid-modification therapy in patients. Screening is recommended when the patient reaches 20 years of age and every 5 years thereafter, with measurement of a fasting LDL-C and lipid panel, followed by a physical evaluation to determine the presence or absence of CHD and CHD risk equivalents such as diabetes, peripheral arterial disease, abdominal aortic aneurism, or symptomatic carotid artery disease. The presence of the major risk factors should then be identified to determine the Framingham risk score. Major risk factors for CHD include cigarette smoking, hypertension, low high-density lipoprotein cholesterol (HDL-C), family history of premature CHD, and age. The Framingham risk score provides an estimation of the 10-year risk of experiencing a CHD-related event. Patients with CHD or CHD risk equivalents have a

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>20% chance of experiencing a CHD event in the next 10 years and are considered at highest risk. Patients at moderate risk have a 10-year event risk of 10% to 20%, while those at lowest risk have a <10% chance of experiencing an event in 10 years. Thus, the usefulness of the Framingham risk score is 2-fold: the measure identifies patients who require lipid modification, and it provides a guide to LDL-C treatment thresholds and targets.

Detection of CHD risk is also enhanced in ATP III by the inclusion of type 2 diabetes as a CHD risk equivalent (ATP II classified this condition as a risk factor). In addition, ATP III identifies the metabolic syndrome as a condition potentially requiring treatment and advocates new treatment thresholds for triglycerides and HDL-C. By identifying type 2 diabetes as a CHD risk equivalent, patients with this condition are considered at the same 10-year risk as those with clinically evident CHD. Diabetics are now clearly candidates for aggressive lipid-lowering therapy. The metabolic syndrome, which impacts more than 70 million Americans, is also recognized as a potential contributor to CHD risk. This condition is characterized by obesity, hypertension, dyslipidemia, and type 2 diabetes. ATP III considers elevated triglycerides and decreased HDL-C as contributory to the CHD disease process, and both are now included as targets of therapy.

■ Unmet Needs: Undertreatment

A diagnosis of lipid disorder does not guarantee treatment. Less than 45% of patients who qualify for therapy receive treatment⁵ and >70% of patients who initiate lipid-lowering therapy persist with it for more than a year.⁶ Receiving therapy does not necessarily mean a patient will receive the full risk-reducing benefits of the regimen as more than 75% of patients who do receive therapy fail to reach their NCEP target LDL-C goal.³ Data collected in the primary care setting indicated that only 9% of dyslipidemic patients with >2 CHD risk factors achieved their ATP II target level (Table 1).³ Even less encouraging is the number of patients with CHD who receive therapy. Fonarow and colleagues⁷ studied the medication records of 138,000 patients hospitalized for an acute myocardial infarction and noted that only 31.7% of patients were receiving lipid-lowering therapy at the time of discharge.

These studies suggest that dyslipidemic patients at all risk levels are not receiving optimal therapy or are being prescribed therapy inconsistent with their CHD risk. This perspective is supported by the observation that high doses of drugs and combination therapies of lipid-modifying drugs are not being used.³ Data from numerous outcome trials indicate that aggressive lipid lowering in the context of a tightly monitored clinical trial setting can result in a predictable reduction of CHD events.⁸⁻¹⁰ In many clinical settings, lipid-lowering therapy is not properly titrated and progress toward lipid goals is poorly monitored. Consequently, patients risk the possibility of forfeiting the significant risk-reduction benefits inherent with aggressive lipid treatment. Therefore, a more aggressive approach to LDL-C reduction is required.

TABLE 1 Percentage of Adults Achieving ATP II Target LDL-C Goals

| CHD Risk Level | Percentage of Patients Achieving LDL-C Goal |
|------------------------|---|
| Low (0-1 risk factor) | 68 |
| High (>2 risk factors) | 37 |
| CHD patients | 18 |
| TOTAL | 37 |

Data from the L-TAP Study. Pearson TA et al. *Arch Intern Med.* 2000;160:459-67.

■ The Challenge of Reaching ATP III Goals

Achieving target cholesterol goals results in favorable clinical and economic outcomes. Data from landmark clinical trials involving both primary and secondary prevention have demonstrated that lipid modification to treatment goals results in significant reductions in morbidity and mortality as well as a reduced need for clinical procedures. Data from these trials suggest that for every 1% reduction in LDL-C, there is a 1% decrease in CHD-related mortality.^{8,9} Pharmacoeconomic analyses have demonstrated that statins are the treatment of choice and that lipid reduction with these agents results in cost-effective outcomes. However, to achieve optimal clinical and economic effectiveness, managed care organizations must adopt programs designed to reduce overall CHD risk by achieving LDL-C targets and addressing other independent risk factors.

There are many challenges to the implementation of the ATP III guidelines, including overcoming the gap between awareness of the guidelines and the actual practice of achieving LDL-C goals. The L-TAP study noted that 64% of primary care physicians indicated that cholesterol reduction had a great impact on reducing CHD risk, and 36% thought it had only a moderate effect. In addition, 63% of primary care physicians indicated that they follow NCEP lipid treatment guidelines "quite a bit," 31% stated they followed the guidelines "somewhat," and 2% did not follow the guidelines at all.³ Despite the awareness of primary care physicians of the NCEP guidelines, a significant number of their patients failed to reach LDL-C goals. This discrepancy may be caused by the fact that physicians used inappropriately low doses of drugs, used drugs with limited effectiveness, failed to choose the correct drug for a specific lipid disorder, and failed to consider tolerability and/or side effect profiles of the drug.³

With their historical emphasis on prevention, managed care organizations are in a strong position to implement CHD risk reduction through pharmacologic and nonpharmacologic therapies, including dietary modification, weight loss, regular physical activity, and drug therapy if indicated. Although nonpharmacologic interventions have frequently been maligned as an ineffective or inefficient way to alter the lipid profile, the L-TAP study suggests that lifestyle advice provided by health care professionals and patient compliance with this advice were independent predictors

of success in reaching LDL-C goals. These results underscore the influence of health care professionals on patient behaviors and suggest that even a minimal amount of education and encouragement can have a favorable impact on CHD risk reduction.

■ Summary and Conclusion

Achieving ATP III goals is a step-by-step process involving risk assessment, designing and implementing the appropriate therapy, monitoring and adjusting the therapy as required, and encouraging patient adherence to the prescribed interventions. The health care providers and their patients share the responsibility for treatment and management of lipid disorders. Patient involvement is essential to achieve target goals and reduce risk. Managed care organizations are strongly positioned to implement the ATP III guidelines by instituting disease management and outcome programs designed to treat eligible patients, achieve LDL-C target goals, and reduce overall CHD risk.

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Overview of Pharmacologic Therapy for the Treatment of Dyslipidemia

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Summary

Although the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines stress the importance of nonpharmacologic lipid modification interventions such as diet and exercise, the guidelines also recognize that many patients will require drug therapy to achieve low-density lipoprotein cholesterol (LDL-C) target goals. Currently available lipid-modifying drugs include bile acid sequestrants (or resins), fibrates, nicotinic acid, and statins, with each class exerting different effects on the lipid profile. In addition, nonprescription agents such as plant stanols and sterols have been shown to be effective in modifying plasma lipids. Of these agents, the statins are the most effective, most widely prescribed, and best-tolerated form of lipid-lowering drug therapy. New formulations of other drugs, such as niacin and bile acid sequestrants, can also improve treatment regimes and reduce side effects, thereby improving patient compliance with these therapies. In patients who have high levels of LDL-C and triglycerides together with low concentrations of high-density lipoprotein cholesterol (HDL-C), combination therapy may be required. Ezetimibe, a selective cholesterol absorption inhibitor, is the first of a new class of lipid-lowering agents and provides a new agent for the management of patients with dyslipidemia. Data from the ezetimibe clinical development program suggests that this agent can be used alone or in combination with statins to reduce LDL-C, improve compliance, and bring more patients to ATP III target goal.

KEYWORDS: Atherosclerosis, Cholesterol, Coronary heart disease, Drug therapy, Dyslipidemia

Adult Treatment Panel III (ATP III) stresses the importance of initiating therapeutic lifestyle changes (TLC) and reiterates that TLC forms the foundation for all drug therapy. However, diet modification and regular physical activity are often not adequate to achieve the aggressive new treatment goals outlined by the guidelines. In addition, long-term patient compliance with TLC is often poor. Consequently, ATP III encourages the addition of drug therapy if TLC fails to reduce low-density lipoprotein cholesterol (LDL-C) to goal after 3 months. For patients at high risk, ATP III recommends that drug therapy may be initiated along with TLC from the onset of treatment. Utilization of appropriate drug therapy offers a real chance for patients to reduce LDL-C and can significantly decrease the risk for coronary heart disease (CHD). Numerous clinical trials completed in the past several decades have demonstrated the effectiveness of lipid-lowering agents in decreasing the need for percutaneous transluminal coronary angioplasty and decreasing coronary events and stroke, arterial stenosis, and cardiovascular and overall mortality.¹⁻³

The treatment goals and lipid thresholds for initiating drug therapy are based on the presence of CHD or CHD risk equivalents, the number of major risk factors, and the estimated 10-year risk of CHD.⁴ For patients with the highest risk for coronary events, ATP III identified an LDL-C threshold of >130 mg/dL for initiation of drug (after a 3-month trial of TLC) and a goal of <100 mg/dL. For patients with a baseline LDL-C between 100 mg/dL and 129 mg/dL, ATP III recommends that drug therapy is optional, and physicians are encouraged to use their professional clinical judgment to determine the nature of therapy required to reduce CHD risk.

Results of the Heart Protection Study have subsequently demonstrated benefit with statins for patients at high risk, even when the baseline LDL-C is <130 mg/dL. For patients with moderate risk without definite CHD or CHD risk equivalents but with >2 major risk factors and a 10-year risk of 10% to 20%, the threshold is >130 mg/dL and the target is also <130 mg/dL. For patients at moderate risk but with a 10-year risk <10%, the LDL-C threshold is >160 mg/dL and the target is <130 mg/dL. For patients without CHD and with 0 to 1 major risk factor, drug treatment should be considered if LDL-C cholesterol is >190 mg/dL after 3 months of TLC, with a goal of <160 mg/dL. In all cases, TLC should be encouraged and supported (Table 1).

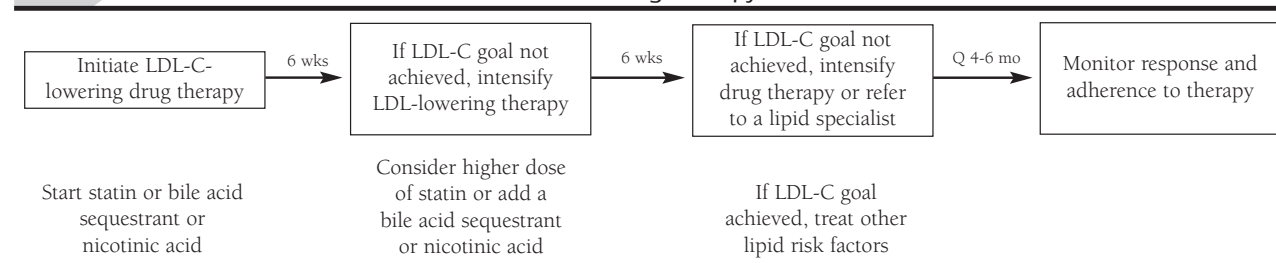
At any level of LDL-C, the risk for CHD may be increased by the presence of the metabolic syndrome. Consequently, this syndrome is a secondary therapeutic target after the LDL-C goal is achieved. The metabolic syndrome is characterized by the presence of at least 3 of the following risk factors: abdominal obesity, elevated triglycerides, low high-density lipoprotein cholesterol (HDL-C), hypertension, and elevated fasting glucose. The meta-

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FIGURE 1 ATP III Treatment Recommendations for Drug Therapy⁴



bolic syndrome may also be characterized by elevated levels of lipoprotein(a) and homocysteine, and a prothrombotic and pro-inflammatory state. These emerging risk factors suggest the existence of subclinical atherosclerotic disease and indicate the need for a more aggressive strategy in patients who appear healthy based on traditional risk factors.⁴

Once the decision has been made to initiate drug therapy, patients should be provided with the agent that offers the greatest opportunity to achieve target LDL-C levels with minimal titration (Table 2). Several classes of agents are currently available for the pharmacologic treatment of lipid abnormalities, including fibrates, nicotinic acids, bile acid sequestrants, and statins (Figure 1). In addition, plant stanols and sterols have been used to effectively modify lipid levels.

Current Lipid-Modifying Drugs—Statins

Of the 4 classes of lipid-modifying drugs the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, are the most widely prescribed, best tolerated, and most effective agents. Statins decrease LDL-C by competitively inhibiting HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol synthesis. The resultant reduction in hepatocyte cholesterol concentration stimulates increased expression of hepatic LDL-C receptors, which remove LDL-C from the circulation. Several large clinical trials with statins have demonstrated their efficacy in lowering LDL-C by 24% to 60% in hypercholesterolemic patients in a dose-dependent manner and in reducing triglycerides by 10% to 29%.⁵ In addition, statins may increase HDL-C by up to 12%.⁵ The currently available statins are differentiated by the LDL-C lowering potency elicited at a given dose. Large clinical outcome trials have demonstrated unequivocally that statins reduce the incidence of CHD events, including myocardial infarction, coronary death, stroke, and total mortality.¹⁻³

Although statin monotherapy is well tolerated and associated with few adverse effects, the most serious side effect is hepatic and skeletal muscle toxicity. Elevated transaminase levels occur in approximately 1% of patients regardless of dose.⁶ Myopathy is less common than increases in liver enzymes, but can in rare instances lead to rhabdomyolysis and acute renal failure. With statin monotherapy, myopathy occurs in approximately 1 in 1,000 patients and is dose-related. This issue is particularly pertinent

with the recent withdrawal of cerivastatin and the U.S. Food and Drug Administration's delay of the approval of rosuvastatin. Hence, there remains some debate as to whether clinicians should up-titrate statins to their highest dose. It should be noted, however, that statin monotherapy rarely causes myopathy and rhabdomyolysis, and these conditions are more common when statins are combined with gemfibrozil or when used in patients with hepatic or renal failure, acute infection, and hypothyroidism.⁷

Bile Acid Sequestrants

Bile acid sequestrants have been in clinical use for more than 30 years. These agents bind bile acids in the intestine and thereby interrupt the process by which nearly 90% of bile acids are returned to the liver for reuse. Since bile acids are formed from cholesterol, sequestrants reduce total body cholesterol. When the bile acid pool is depleted due to sequestrant-induced excretion, hepatic synthesis of bile acids is increased, leading to a reduction in hepatic cholesterol. This reduction also triggers a secondary activation of HMG-CoA reductase, however, that causes an increased cholesterol production that can attenuate the cholesterol-lowering effect of bile acid sequestrants. The addition of a statin to bile acid sequestrant therapy can block the secondary activation of HMG-CoA reductase.

Bile acid sequestrants can be used as monotherapy when moderate reductions in LDL-C are required to achieve goal or as add-on therapy to statins, particularly in patients with severe dyslipidemia. Although effective in reducing LDL-C by 15% to 30% over the dose range, compliance is limited because many patients consider bile acid sequestrants to be unpalatable, and their use may be associated with undesirable GI side effects.⁵ Colesevelam, a high-capacity polymer that selectively binds bile acids in the intestine, is the newest bile acid sequestrant. Because of its selectivity, colesevelam may help reduce the bothersome side effects, although compliance remains an issue, as patients are required to take up to 6 tablets at a time.

Nicotinic Acids

Nicotinic acid (niacin) is the oldest lipid-lowering drug available, having first been used in the 1950s. Nicotinic acids are most commonly used in their rapid-release form and provide an LDL-C reduction in the range of 10% to 20% at doses of 1,500 mg/day to 4,000 mg/day.⁵ It is also the most powerful agent for elevating

HDL-C, with increases of 10% to 15% even at modest doses.⁵ In addition, niacin is effective in lowering triglycerides and is a helpful agent in the management of patients with mixed dyslipidemia. Nicotinic acid reduces hepatic synthesis of triglycerides and limits secretion of triglyceride-rich, very-low-density lipoprotein cholesterol (VLDL-C) by inhibiting the mobilization of free fatty acids from the peripheral tissues. In addition, niacin may also inhibit the conversion of VLDL-C to LDL-C and initiate a shift in LDL-C from the small, dense particles to large, buoyant, less atherogenic LDL-C particles.

The primary drawback with niacin is tolerability. Patients experience GI upset, flushing, itching, and skin irritation in the face and neck with initial dosing.⁵ Most of these bothersome side effects can be overcome with proper initiation, titration, and patient education; however, nicotinic acids remain underused. More serious side effects are evident at higher doses. Although rare, high doses of niacin can elicit gout, clinical hepatitis, hypertriglyceridemia, and negatively impact glycemic control.⁵

Newer, extended-release preparations of niacin have been developed to overcome many of these undesirable side effects. Studies utilizing the newer preparations as monotherapy demonstrated favorable dose-related effects on LDL-C and HDL-C; the trials also demonstrate that the agents are generally well tolerated.⁵ Extended-release niacin has also been shown to be effective in improving lipid parameters when used in combination with statins, particularly for patients who have elevated triglycerides and/or low HDL-C.⁸ An older formulation of sustained-release niacin given in combination with simvastatin has also been shown to increase HDL-C 26%, reduce LDL-C 42%, retard stenosis, and reduce the combined endpoints of death, myocardial infarction, stroke, and revascularization in patients with known coronary disease, low HDL-C, and normal LDL-C.⁹

■ Fibrates

Fibric acid derivatives gemfibrozil and fenofibrate possess minimal LDL-C-reducing capacity but are especially effective in patients who have severe hypertriglyceridemia and in patients with combined forms of hyperlipidemia.¹⁰ Although the mechanism by which fibrates reduce triglycerides is poorly understood, it is believed that these agents work to increase fatty acid oxidation in the liver, resulting in decreased secretion of VLDL-C and increased lipoprotein lipase activity in skeletal muscle. Thus, the lipid-modifying effects of fibrates are secondary to changes in these LDL-C precursors. In patients with very high triglycerides, fibrates may increase LDL-C levels.

Fibrates may be used in combination with niacins or bile acid sequestrants since these drugs appear to be additive in lowering LDL-C and raising HDL-C. When fibrates are given in combination with a sequestrant, the administration of the 2 drugs must be separated by at least 2 hours to ensure full bioavailability of the fibrate. Combinations of fibrates with statins are very effective in lowering LDL-C and increasing HDL-C, particularly in patients with mixed hyperlipidemia, characterized by elevated triglyceride

TABLE 1 ATP III Classification of Normal and Abnormal Lipid Levels⁴

| Total Cholesterol | |
|-------------------|----------------------------|
| <200 | Desirable |
| 200-239 | Borderline high |
| ≥240 | High |
| LDL Cholesterol | |
| <100 | Optimal |
| 100-129 | Near optimal/above optimal |
| 130-159 | Borderline high |
| 160-189 | High |
| ≥190 | Very high |
| HDL Cholesterol | |
| <40 | Low |
| ≥60 | High |

TABLE 2 Effects of Each Drug Class on Lipids

| | LDL-C | HDL-C | Triglyceride |
|-----------------------------------|-----------------|-----------|--------------|
| Nicotinic acid | ↓ 5%-25% | ↑ 10%-25% | ↓ 20%-50% |
| Fibrates | Variable effect | ↑ 10%-25% | ↓ 20%-50% |
| Statins | ↓ 27%-55% | ↑ 5%-10% | ↓ 10%-25% |
| Bile acid resins | ↓ 15%-30% | ↑ 3%-5% | ↓ 0%-20% |
| Cholesterol absorption inhibitors | ↓ 18%-20% | ↑ 3%-5% | ↓ ~5% |

and LDL-C. Statin-fibrate combinations have been historically limited by fear of the increased risk of myopathy. However, the absolute risk has been estimated to be as low as 0.12%. The combination of a statin with gemfibrozil has been most often reported although this may be due to much greater use of this fibrate to date. When the choice is made to use a statin and fibrate in combination, these drugs should be used only in the lowest effective doses and only in patients who have normal liver and kidney function.

■ Plant Stanols

Plant stanols decrease LDL-C by approximately 10% in modestly hypercholesterolemic patients. These compounds reduce cholesterol absorption from the intestine by competing for the limited space available in mixed micelles that deliver lipids for absorption into the intestinal mucosal cell.¹¹ Plant stanols are nonprescription, and their use should be encouraged for patients at low risk, requiring only modest LDL-C reductions. These agents are not recommended as primary therapy for moderate- to high-risk patients requiring more aggressive lipid lowering. Plant stanols are generally well tolerated, and the LDL-C-lowering effect appears to be additive to statin or fibrate therapy.¹¹

Despite the efficacy of statins and other lipid-modifying agents in reducing coronary events, the issues of tolerability, untoward side effects, and safety remain concerns with many agents, particularly when administered at high doses or in combination. This

problem restricts use when patients cannot tolerate statins or when statin up-titration is limited due to safety concerns. In these cases, physicians and patients are limited to agents such as bile acid sequestrants, niacin, or other less-effective therapies.

A promising new alternative therapy is the recently approved selective inhibitor of intestinal cholesterol absorption, ezetimibe. Ezetimibe appears to have significant potential for use as monotherapy for patients at low risk for CHD who require a modest reduction in their LDL-C or for those who do not tolerate statin therapy.¹² In addition, when ezetimibe is used in combination with a low-dose statin in patients at moderate to high risk for CHD, the drug can elicit a reduction in LDL-C comparable to that seen at the highest statin doses, with a safety profile similar to placebo.¹² Thus, ezetimibe appears to be a safe and effective lipid-modifying agent that can help patients achieve target while minimizing tolerability and safety concerns that lead to poor adherence and reduced clinical and economic effectiveness.

■ Pharmacoeconomic Outcomes of Lipid-Lowering Therapies

The assessment of the economic impact of drug treatment is complex and involves the consideration of many factors, including drug costs, costs related to the diagnosis, treatment, and management of CHD events, and direct and indirect costs associated with lost productivity and quality of life. Most of the direct and indirect costs of CHD are related to the cost of hospitalization, invasive procedures such as angioplasty, and loss of quality of life. Therefore, the real cost benefits of lipid-modification therapy are related not only to the reduction in morbidity and mortality but also to the reduction of direct and indirect costs. Now that several clinical trials have clearly shown the benefit of cholesterol lowering on cardiovascular morbidity and mortality, the debate surrounding lipid drugs may shift from their efficacy and safety to that of their cost and cost-effectiveness. Of course, safe and efficacious drugs cannot improve cost-effectiveness without a commitment on the part of patients and physicians to implement and adhere to treatment in order to realize the clinical and economic outcome benefits observed in clinical trials.

The Scandinavian Simvastatin Survival Study (4S) demonstrated that statin use in a high-risk secondary prevention population is cost effective in all subgroups analyzed.¹ Furthermore, 4S data indicated that cost-effectiveness increases as the number of CHD risk factors increases. When certain indirect costs such as loss of job productivity and disability are taken into consideration, statin therapy provides a cost saving, particularly in young men.¹³ The West of Scotland Coronary Prevention Study (WOSCOPS) suggested that in a primary prevention cohort, the use of pravastatin was relatively cost effective in those patients at highest risk.¹³

The cost-effectiveness of providing statin therapy to high-risk patients for the reduction of CHD is supported by these pharmacoeconomic analysis of WOSCOPS and 4S. However, when the usual starting dose of most statins is doubled, the result is only about a 6% additional LDL-C reduction while the increase

in cost can be as much as 2-fold. This illustrates the reality that the greater the need to achieve LDL-C target goals, the greater the cost. Multiple upward titrations of statins have the potential to significantly increase the overall cost of treatment as drug costs, office visits, and patient monitoring costs are added with each move from the starting dose. In addition, undesirable side effects of many statins are dose-related; use of high statin doses may lead to added costs for intensified monitoring. Novel therapies currently in development have the potential to minimize costs associated with multiple statin titrations and side-effect monitoring. Safe and effective new agents that can be used either as monotherapy or in combination with low-dose statins hold promise to provide additional cost-effective strategies for the reduction of LDL-C.

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A Novel Therapeutic Approach

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Summary

Since 1988, the National Cholesterol Education Program has identified low-density lipoprotein cholesterol (LDL-C) as the target of therapy; the new Adult Treatment Panel III (ATP III) guidelines continue the tradition of matching the aggressiveness of LDL-lowering therapy according to the risk of coronary heart disease (CHD). A significant change in the new guidelines is the definition of "CHD risk equivalents" and the inclusion of a modified Framingham global risk score. These revisions significantly raise the number of patients who qualify for lipid-lowering therapy. ATP III recognizes statins as the drug of first choice for LDL-C lowering. Statins are proven to be safe and effective for LDL-C reduction and are proven to reduce CHD event rates and mortality. Some patients are not candidates for statin therapy, however, and must rely on nonstatin agents that are less effective in reducing LDL-C, less safe, or poorly tolerated. Consequently, new cholesterol-lowering therapies are needed. Ezetimibe, approved by the U.S. Food and Drug Administration (FDA) in October 2002, is the first in a new class of selective cholesterol absorption inhibitors and offers a novel approach to the treatment of dyslipidemia. Phase 2 data demonstrated that ezetimibe lowers LDL-C by 18% and has a tolerability and short-term safety profile similar to placebo. This paper reviews the cholesterol metabolic pathways and the mechanism of action of the currently available lipid-modifying agents and introduces ezetimibe, the first selective cholesterol absorption inhibitor.

KEYWORDS: Cholesterol, Combination therapy, Dyslipidemia, Ezetimibe, Monotherapy

Hypercholesterolemia is a well-established risk factor for coronary heart disease (CHD).^{1,2} The Adult Treatment Panel III (ATP III) emphasis on both aggressive therapy for patients at high risk and long-term, less aggressive therapy for patients at high lifetime risk, contributes to the growing need to identify new approaches to combat lipid abnormalities. Of great interest is the development of new drugs that can favorably alter the lipid profile through mechanisms that differ from currently available drugs. Based on the overwhelming evidence of benefit, statins are currently recommended by ATP III as first-line agents for the reduction of low-density lipoprotein cholesterol (LDL-C). Because of the intensified LDL-C targets recommended by ATP III, combination therapy may be required by significant numbers of patients to achieve goal. Agents that target novel pathways of cholesterol metabolism may enable a greater number of patients to attain these LDL-C targets.

Ezetimibe, approved by the U.S. Food and Drug Administration (FDA) in October 2002, is the first in a new class of selective cholesterol absorption inhibitors. Ezetimibe monotherapy blocks cholesterol and bile acid absorption from the intestine and results in up to an 18% reduction in LDL-C with once-daily dosing and a short-term safety profile similar to placebo.³ When 10 mg of ezetimibe is combined with a low-dose statin, the complementary mechanisms of action of the 2 agents produces LDL-C reductions typically seen only with high-dose statin therapy.^{4,5}

Cholesterol Pathways

Developing clinically effective therapies requires an understanding of the basic principles of cholesterol balance. Cholesterol is a ubiquitous sterol that plays a vital role in cell membranes, bile and bile acid production, and steroid hormones. The total body pool of cholesterol is controlled by 3 main factors that determine cholesterol balance. On the input side, cholesterol can be produced endogenously or can be obtained from absorption of dietary or biliary sources of cholesterol. In an otherwise healthy person, endogenous cholesterol synthesis contributes approximately 900 mg of cholesterol to the total cholesterol pool each day, while an additional 300 mg is added by intestinal absorption. Endogenous cholesterol synthesis results from numerous enzymatically mediated reactions, the most important being the conversion of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) to mevalonic acid. This step is catalyzed by the HMG-CoA reductase enzyme, which is tightly controlled by the flow of intestinal cholesterol to the liver. Newly synthesized hepatic cholesterol is released into the circulation in the form of a triglyceride-rich, very-low-density lipoprotein cholesterol (VLDL-C) particle. Although it was previously suspected that the hepatic production of cholesterol was the primary source

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of endogenously synthesized cholesterol, hepatic production of cholesterol accounts for only 10% of the total daily production. Peripheral tissues synthesize the majority of cholesterol. As VLDL-C circulates in the blood, the triglyceride component is removed and the lipoprotein particle accumulates cholesterol from peripheral tissues, resulting in the formation of intermediate-density lipoproteins (IDL). The IDL, which is depleted of triglycerides but rich in cholesterol, has 2 possible fates: it is either taken up by receptors on the liver or it remains in the circulation and is converted to LDL-C. Ultimately, the IDL-derived LDL-C may be removed from the circulation by hepatic LDL-C receptors or it can penetrate arterial walls to develop atheromas, precursors to atherosclerotic plaques. High-density lipoprotein (HDL-C) cholesterol is an additional carrier lipoprotein for moving peripherally synthesized cholesterol back to the liver for transfer.

The exogenous pathway altering total body cholesterol balance involves a complicated processing of both dietary and biliary cholesterol by the intestine. The first step in this process is the absorption of cholesterol by the enterocytes that line the intestinal lumen. Once inside the enterocyte, cholesterol is ultimately packaged into a triglyceride-rich chylomicron particle. Chylomicrons are released into the circulation, where the triglyceride component is stripped away, resulting in a remnant particle. Chylomicron remnants are cholesterol-rich particles that are removed from the circulation by remnant receptors found on the surface of the liver. In the liver, exogenously derived cholesterol is mixed with the endogenously synthesized cholesterol and used to form bile acids or incorporated into VLDL-C and returned to the circulation.

Cholesterol balance is achieved by regulating the amount of cholesterol synthesis. Reduced delivery of intestinal cholesterol to the liver increases HMG-CoA reductase activity and enhances cholesterol synthesis, whereas high intestinal uptake of cholesterol inhibits HMG-CoA activity, reduces hepatic synthesis, decreases LDL-C uptake, and increases plasma LDL-C. Because the liver and intestine are critical centers for cholesterol balances, they are prime targets for cholesterol modification therapies. Thus, statin therapy, by its action of reducing total body cholesterol synthesis, has a secondary effect of increasing LDL-receptor activity. The liver is the primary target of the secondary effect of statins, as the liver is the organ that contains most of the body's LDL receptors. The intestine is the target of therapy designed to limit exogenous cholesterol intake (e.g., the novel cholesterol absorption inhibitor, ezetimibe).

■ Mechanism of Action of Currently Available Drugs

Statins exert their effects largely by inhibiting the activity of the HMG-CoA reductase enzyme. Reduced enzyme activity decreases the amount of free hepatic cholesterol and stimulates an up-regulation of LDL receptors located on the surface of the hepatocytes. Up-regulation of liver LDL-C receptors stimulates an increased LDL-C uptake from the circulation to restore the hepatic cholesterol balance. Thus, statins exert both direct and indirect effects that result in a lowering of LDL-C: they directly decrease cholesterol synthesis, which, in turn, increases the uptake of cholesterol from

the blood, thereby decreasing blood LDL-C levels. Statins also have moderate HDL-raising and triglyceride-lowering effects.

A decline in LDL-C levels can also be achieved by directly increasing cholesterol loss from the body. Augmentation of cholesterol loss has been achieved for many years using bile acid sequestrants. A significant portion of the cholesterol entering the liver is eventually converted into bile acids. Bile acids are secreted into the lumen of the small intestine and are responsible for the absorption of dietary fatty acids as well as fat-soluble vitamins. The total body biliary pool is quite small and is rapidly excreted and reabsorbed 2 to 3 times during a single meal and up to 10 times during a typical day. This significant recycling of biliary acids is accomplished by highly specific transporter proteins in the intestinal wall that can rapidly return bile acids back to the liver in the enterohepatic circulation. Bile acid sequestrants prevent this recycling by interfering with the ability of the transporter to move bile acids back to the liver. Sequestrants sequester bile acids so that they cannot be reabsorbed and must be excreted in stool. Because bile acid synthesis requires cholesterol as a precursor, disruption of bile acid reabsorption creates a major perturbation of cholesterol balance, lowering the total body cholesterol pool size.

The effectiveness of this approach is limited because the liver has a remarkable capacity to up-regulate its own rate of cholesterol synthesis in order to produce more bile in the face of a deficit. This compensatory increase in cholesterol synthesis by the liver consequently blunts the cholesterol-lowering action of the sequestrant, limiting its ability to significantly lower plasma LDL-C.

Nicotinic acid is another drug option for the treatment of dyslipidemia; nicotinic acid can produce reductions in LDL-C, as well as reductions in triglycerides and increases in HDL-C. Nicotinic acids work primarily by inhibiting the transport of free fatty acids from the peripheral tissues to the liver. This action reduces both the hepatic synthesis of triglycerides and the hepatic secretion of VLDL-C. Nicotinic acid may also limit the conversion of VLDL-C to LDL-C and initiate a shift in LDL-C from the small, dense, atherogenic type to large, buoyant, less atherogenic LDL-C particles. Fibrates have limited LDL-C-lowering capacity and are most useful in the treatment of isolated hypertriglyceridemia and combined hypercholesterolemia with elevated triglycerides. These agents primarily lower triglycerides and raise HDL-C. Plant stanols and sterols block cholesterol absorption from the intestinal lumen by interfering with the formation of lipid-rich chylomicrons and chylomicron remnants. Although relatively effective in reducing LDL-C, these agents must be taken primarily during meals to be effective.

Given the limitations of currently available lipid-lowering approaches, a therapy or combination of therapies that is tolerable; offers safe, convenient dosing; and removes cholesterol from the body without triggering compensatory hepatic mechanisms may achieve superior LDL-C reductions.

■ The Novel Cholesterol Absorption Inhibitor: Ezetimibe

Approximately half the total cholesterol found in the gut after a meal is absorbed by the intestinal enterocyte; the remainder is

excreted in the stool. Absorbed cholesterol is packaged by the enterocyte into triglyceride-rich chylomicrons. Restricting dietary intake of cholesterol can reduce the pool of cholesterol available for intestinal absorption, but the impact on LDL-C levels is highly variable, with some patients having little or no response to dietary restriction alone. Blocking the absorption of cholesterol from the intestinal lumen has a greater effect on cholesterol balance because the block inhibits not only dietary cholesterol absorption but also biliary cholesterol absorption. The search for an effective, convenient, safe, and better-tolerated drug for the reduction of cholesterol and prevention of CHD has led to the development of a novel class of lipid-reducing agents, the selective cholesterol absorption inhibitors.

Ezetimibe, the first in a new class of selective cholesterol absorption inhibitors, reduces plasma cholesterol by selectively inhibiting the absorption of dietary and biliary cholesterol from the intestine.³ Early studies in animals show that ezetimibe lowers both serum and liver cholesterol concentrations in a dose-dependent manner.⁶ Ezetimibe is rapidly glucuronidated in the gut and liver and the glucuronidated derivative is the active, more potent form of the drug. Both ezetimibe and its glucuronide derivative undergo extensive enterohepatic circulation and are ultimately secreted into the bile. Glucuronidated ezetimibe is returned to the intestinal lumen when bile is secreted in response to a high-fat meal and localizes to the brush border membrane of the intestinal mucosal cell. Glucuronidated ezetimibe appears to specifically inhibit free cholesterol uptake into the enterocyte by interacting with a cholesterol transporter protein, however, its exact mechanism of action remains to be elucidated.⁷

Ezetimibe was recently approved by the FDA, and many of the results of the phase 2 development program are available.^{8,9} The goals of the phase 2 trials were to describe the dose-response relationship of ezetimibe, investigate the existence of any food interactions, determine if differences existed between morning and evening dosing, and determine dosing regimens for phase 3 trials. The phase 2 trials also investigated the pharmacokinetic and pharmacodynamic interaction between ezetimibe and several statins as well as the magnitude of LDL-C reduction when administered in combination with statins.

Patients included in phase 2 trials are representative of those seen by primary care physicians. Total cholesterol and LDL-C levels at randomization were >250 mg/dL and >130 mg/dL, respectively, and triglycerides were below 300 mg/dL. Patients with diabetes were excluded. The first phase 2 trials were small, placebo-controlled trials that randomized patients into groups that received ezetimibe at doses between 1 mg and 40 mg for approximately 8 weeks. One group received 40 mg lovastatin as a benchmark against which to assess the lipid-lowering actions of ezetimibe. The results of these studies indicated a small, dose-dependent effect for ezetimibe with the maximum LDL-C reduction achieved at once-daily dosing of 10 mg to 20 mg. Tolerability, side effects, and biochemical abnormalities were no different than those seen with placebo.¹⁰ This small pilot trial was followed by a 12-week,

placebo-controlled, dose-ranging study. Approximately 50 patients were randomized to each study arm using a dose range of 1 mg to 10 mg of ezetimibe per day. The results confirmed the findings of the smaller dose-ranging trial and demonstrated a peak LDL-C reduction of 18% from baseline at 10 mg/day.¹⁰

To determine if LDL-C reduction was impacted by the timing of dosing or by the presence of food, another phase 2 study evaluated the lipid-lowering effects of 5 mg and 10 mg/day administered to 189 patients in the morning and in the evening, with and without food. These studies found no significant differences between morning and evening dosing with 10 mg of ezetimibe, with LDL-C reductions of 17.5% and 18.2% for morning and evening dosing, respectively. LDL-C reductions were also unaffected by the presence or absence of food.^{9,10}

In total, the phase 2 monotherapy studies included 124 patients who received 5 mg ezetimibe, 118 who received 10 mg, and 87 who received placebo. Pooling the data reveals a consistent dose-response effect with a peak LDL-C reduction of 18.5% at 10 mg/day. Ezetimibe showed essentially no effect on triglyceride levels and a small, but statistically significant increase of 3.5% in HDL-C.⁹

A second arm of the phase 2 program was designed to test the effectiveness, tolerability, and safety of ezetimibe in combination with currently available agents. Each trial included 32 patients with elevated LDL-C and tested the cholesterol-lowering effect of 10 mg/day of ezetimibe in monotherapy and in combination with atorvastatin 10 mg/day, fluvastatin 20 mg/day, and fenofibrate 200 mg/day. Ezetimibe monotherapy reduced LDL-C cholesterol by 22.7% from baseline compared to 40% with atorvastatin 10 mg/day. Combination therapy with atorvastatin decreased LDL-C by 55%.⁴ Ezetimibe, when compared to fluvastatin, reduced LDL-C by 20.2% versus 12.8% for fluvastatin 20 mg/day. When taken together, the combination achieved a reduction of 32% from baseline.¹¹ The trial that compared ezetimibe with fenofibrate demonstrated that ezetimibe decreased LDL-C by 22.3% from baseline versus 13.5% with the fenofibrate 200 mg/day. The 2 drugs in combination produced a 36.3% reduction in LDL-C.¹²

From the results of these small, well-designed studies, it can be concluded that ezetimibe, when used as monotherapy, produces clinically significant reductions in LDL-C. In addition, these trials suggest that combination therapy of ezetimibe with atorvastatin, fluvastatin, or fenofibrate leads to LDL-C reductions greater than that observed when the agents are administered alone. The overall results of the phase 2 development program indicated that the selective cholesterol absorption inhibitor, ezetimibe, is effective both as monotherapy and in combination with several statins. The short-term coadministration trials also found that the combination of ezetimibe with statins or fenofibrate was safe and that ezetimibe did not alter the pharmacokinetics of the other agents or vice versa. The phase 2 trials established that ezetimibe achieved maximum cholesterol lowering at doses between 10 mg and 20 mg/day. These studies also demonstrated that ezetimibe was well tolerated, with a side-effect profile no different from placebo.

Following the completion of the phase 2 trials, it was decided to

test the LDL-C-lowering effect of ezetimibe in larger and longer trials. The third phase of the development program was designed to determine whether ezetimibe could provide consistent and predictable reductions in LDL-C when used as monotherapy, to evaluate the drug's efficacy as an adjunct to dietary therapy, to determine whether the drug could provide consistent LDL-C lowering when coadministered with a statin at any dose, and to further describe its safety and tolerability profile.

The purpose of the first phase 3 study was to evaluate the efficacy of ezetimibe versus placebo. This double-blinded, randomized, parallel group trial included 820 patients with LDL-C between 130 mg/dL and 250 mg/dL and triglyceride levels below 350 mg/dL. Prior to randomization, all patients completed 6 to 12 weeks of drug washout and diet, followed by 3:1 randomization and 12 weeks of active treatment. The primary efficacy endpoint was the percentage reduction in LDL-C from baseline, with changes in total cholesterol, triglycerides, and HDL-C as secondary endpoints. Ezetimibe treatment reduced LDL-C by 18%, with a 12% decrease in total cholesterol, a 4.1% decrease in triglycerides, and a 1% increase in HDL-C. The safety profile of ezetimibe was similar to placebo, with no clinically significant changes in creatine kinase or hepatic transaminase levels, and no effect on the absorption of fat soluble vitamins A, D, E, or alpha carotene and beta carotene. The most common side effects in both the active treatment and placebo groups were headache, upper respiratory tract infections, and back pain not believed to be related to either ezetimibe or placebo.³

At the conclusion of the 12-week study period, all patients were enrolled in an open-label extension trial designed to provide confirmatory data of the stability of the lipid response and to assess long-term safety. In this extension study, the investigators will consider adding a statin to ezetimibe monotherapy in those patients not achieving the LDL-C targets recommended in ATP III.

A series of randomized, double-blind, placebo-controlled, factorial design phase 3 trials investigating coadministration of ezetimibe 10 mg with most available doses of simvastatin, lovastatin, pravastatin, and atorvastatin are ongoing, but are available in abstract form only at the time of preparation of this manuscript. In addition to confirming the efficacy and safety of using ezetimibe 10 mg in combination with currently available statins, these studies are designed to assess whether a 3-step statin titration—from 10 mg to 20 mg, 20 mg to 40 mg, and 40 mg to 80 mg—is better than, as good as, or not as good as a 1-step administration of a low-dose statin and ezetimibe 10 mg in patients classified by ATP III as having a 10-year risk of CHD >10% and with LDL-C >130 mg/dL, despite low-dose statin monotherapy.

Summary and Conclusion

ATP III has increased the number of patients qualifying for aggressive LDL-C reduction, and statins remain the drugs of first choice for LDL-C reduction. Ezetimibe monotherapy at 10 mg/day offers an excellent alternative therapy to statins for patients who require modest LDL-C lowering or patients who are statin-intolerant. Coadministration of ezetimibe and a statin offers additional LDL-C

reduction and is associated with an excellent tolerability and safety profile and ease of use. Taken as a whole, the phase 2 and 3 studies indicated that ezetimibe, the first in a new class of selective cholesterol absorption inhibitors, is effective as monotherapy and complements the LDL-C-lowering effects of statins. Ezetimibe at a once-daily dose of 10 mg lowers LDL-C by 18% to 20% as monotherapy, and when coadministered with a low-dose statin, produces LDL-C reductions usually observed only with high doses of statins. Furthermore, the ezetimibe and low-dose statin combination maximizes LDL-C reductions with a safety profile similar to placebo. Although ezetimibe has been shown to reduce LDL-C levels, its effectiveness in reducing cardiovascular morbidity and mortality remains to be proven. It is not certain whether lowering LDL-C by ezetimibe therapy alone versus statin plus ezetimibe will have the same cardiovascular benefits as statin therapy.

DISCLOSURES

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Combination Therapy

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Summary

Adult Treatment Panel III (ATP III) guidelines recommend specific treatment targets for low-density lipoprotein cholesterol (LDL-C) levels according to an individual's short-term and long-term risk for coronary heart disease (CHD). Therapeutic lifestyle changes are recommended for all patients at any level of risk for CHD. Although most patients will achieve some LDL-C lowering with lifestyle modification, ATP III recognizes that a majority of patients with dyslipidemia will require drug therapy to reach their LDL goal. Surveys of physicians' practices suggest that only a small percentage of patients enrolled in an active treatment program actually achieve their LDL-C target. In addition, other surveys suggest that not all patients who are treatment candidates are receiving assessment. From a medication perspective, either up-titration of statin dose or the use of drug combinations should further enhance the likelihood of achieving target lipid levels. Combination therapies that target both the endogenous and exogenous pathways of cholesterol synthesis are particularly attractive. This paper reviews the pharmacotherapeutic effects of combination therapy, summarizes the strengths and weaknesses of current lipid-lowering drug combinations, and identifies the potential contribution of the novel cholesterol absorption inhibitor, ezetimibe, to the LDL-C treatment algorithm.

KEYWORDS: Cholesterol, Combination therapy, Dyslipidemia, LDL-C

Similar to the prescription practices in the treatment of hypertension, combination therapies are often required for optimal lipid management. Despite the fact that combination therapy can be effective, well tolerated, and safe, surveys suggest that only a few patients are receiving combination therapies for dyslipidemia. For patients, combination therapy may offer the only effective means to achieve desired lipid targets. As with the treatment of hypertension, the combination of 2 low-dose drugs can achieve lipid reductions that exceed those observed with high-dose monotherapy. When combination therapy employs 2 different drug classes with complementary mechanisms of action, the effectiveness is additive. Achieving target low-density lipoprotein cholesterol (LDL-C) goals using a combination that includes a statin can be particularly effective. Some combinations may prove to be better tolerated than high-dose monotherapy with statins, particularly when the lipid-lowering capacity of the add-on drug allows for reduction in the dose of the original therapy and offers a favorable side-effect profile. Examples of currently available combination therapies are described below.

Currently Available Combination Therapies

Statins are identified as the drug of first choice for lowering of LDL-C by Adult Treatment Panel III (ATP III). Consequently, the most logical combination strategy would be to add a drug from another class to statin therapy. Combination therapy with statins has some distinct advantages. In general, lower doses of each drug can be used, minimizing the risk of side effects. Additionally, combining a drug with a mechanism of action different from that of a statin typically achieves at least an additional 10% reduction in LDL-C, whereas doubling the dose of a statin will achieve only a 6% additional lowering of LDL-C.¹ Bile acid resins and niacin are common add-on therapy to a statin. Other statin combinations, while effective in favorably modifying lipid profiles, must be used with caution due to an increased possibility of side effects.

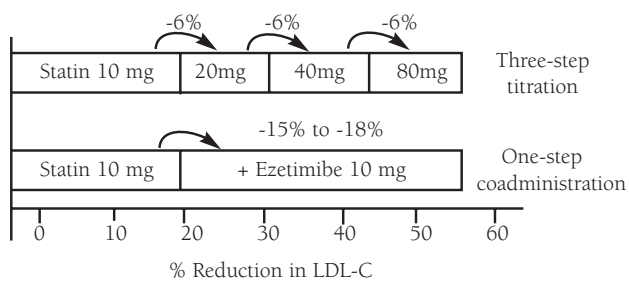
Statins and bile acid resins are the most common combination. Adding a statin to bile acid resin monotherapy overcomes the compensatory increase in cholesterol synthesis that occurs during bile acid resin therapy. This combination has been shown to reduce LDL-C by as much as 50%, an amount equivalent to that achieved by high-dose statin alone.¹ The inconvenience of multiple daily dosing of bile acid resins and their accompanying GI side effects limits the effectiveness of these agents in either monotherapy or combination regimens.

The combination of low-dose statins and fibrates appears to have complementary effects on triglycerides and LDL-C and proves to be especially attractive for patients with mixed hyperlipidemia characterized by elevated triglyceride and LDL-C. However, caution must be exercised when using statins and fibrates together because this combination has an increased risk of myopathy beyond what is normally observed with either drug

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FIGURE 1 One-Step Titration of Ezetimibe and Statin Combination

class alone. Appropriate precautions, such as using the combination with the lowest effective doses in patients who have normal liver and kidney function, been educated regarding the signs and symptoms of myopathy, and been instructed to stop drugs if symptoms occur, should help minimize the risk. Some research has suggested that the combination of fenofibrate and statin is associated with a lower rate of myopathy than gemfibrozil and statin. Given the low incidence of myopathy, however, far larger studies would be required to confirm this observation.²

The combination of statin and niacin is an effective combination for patients with mixed hyperlipidemia as well as for patients with simple hypercholesterolemia. For example, 2 grams of niacin added to a stable dose of statin achieved an additional 31% LDL-C lowering.³ Unfortunately, similar to the combination of fibrates and statins, the combination of niacin and statin is associated with an increased risk of myopathy. Similar to bile acid resins, niacin as a single agent or as part of combination therapy is associated with vasodilatory side effects that are difficult for some patients to tolerate. Additional notes of caution are required—niacin can unmask glucose intolerance and worsen glycemic control in patients with diabetes; niacin can raise uric acid levels and precipitate an attack of gout.

Not all combination therapies employ the use of a statin. The combination of bile acid resins and nicotinic acids was used extensively before statins were even developed. This combination achieves LDL-C reductions of 32% to 43% with high-density lipoprotein cholesterol (HDL-C) increases of 37% to 43%.⁴ The use of this combination is limited by the gastrointestinal and vasodilatory side effects of the drugs. Lowering the dose of each drug can reduce the side effects and achieve reasonably good improvement in LDL-C and HDL-C, although improvement is not as significant as with higher doses.⁴

Although used infrequently, the fibrate-niacin combination may have some synergy with respect to the individual effects of the drugs on triglyceride and HDL-C levels and may prove useful in patients with very high triglyceride levels.⁵ The addition of fish oil supplements can also be employed to lower triglyceride levels.

Contribution of Cholesterol Absorption Inhibitors to Combination Therapy

Several alternatives to currently available combination therapies are in development. Ezetimibe, the first of a new class of selective cholesterol absorption inhibitors, was recently approved by the U.S. Food and Drug Administration; it offers a mechanism of action distinct from statins and other agents. Cholesterol absorption inhibitors significantly reduce intestinal absorption of both dietary and biliary cholesterol from the intestine. The combination of ezetimibe and a low-dose statin results in a decrease of the absorption of cholesterol from the intestine as well as a decrease in the synthesis of cholesterol in the body. The net effect is an up-regulation of LDL receptor activity in the liver and a reduction in plasma LDL concentrations. The additive nature of these 2 effects explains the synergy of the combination (Figure 1).

Phase 2 and 3 studies from the ezetimibe development program have demonstrated that combining selective cholesterol absorption inhibition with statins is an effective strategy for optimizing cholesterol-lowering effects. For example, subjects with hypercholesterolemia treated with simvastatin 10 mg daily for 14 days achieved a 35% reduction in LDL-C while those treated with simvastatin 10 mg plus ezetimibe 10 mg achieved a reduction of 52%⁶—a decrease in LDL-C expected from a simvastatin dose of 80 mg. Additionally, ezetimibe has virtually no effect on statin pharmacokinetics. Thus, combining ezetimibe with a statin may reduce the dose of the latter drug required to achieve target levels, or, in patients who respond poorly to statins, may improve the lipid-lowering effect.

A similar phase 2 coadministration study found that the decrease in LDL-C was 40% for 10 mg atorvastatin alone, 23% for 10 mg ezetimibe alone, and 56% for both drugs given together. Consistent with the findings of the simvastatin coadministration studies, the additional reduction in LDL-C cholesterol seen with the combination of 10 mg/day ezetimibe and 10 mg/day atorvastatin was equivalent to the reduction expected with 80 mg/day atorvastatin monotherapy.⁷

Conclusion

For the majority of patients with dyslipidemia, statins remain the treatment of choice. Despite their efficacy, evidence from clinical trials and clinical practice demonstrates that the majority of dyslipidemic patients do not achieve ATP III target LDL-C goals. This is especially true for high-risk patients where lower LDL targets are recommended. Multiple factors contribute to the failure to achieve lipid goals with statin therapy. Some failures occur because high-risk patients who are excellent candidates for therapy are not identified. Other failures occur because the prescribed dose of statin is insufficient to achieve the recommended LDL lowering. For the most part, statins have been proven to be exceptionally safe drugs. However, some patients clearly experience side effects such as muscle pain and elevated liver enzymes, particularly at higher doses. If high doses of statins are poorly tolerated, niacin and bile acid resins are typical alternative or add-on agents. The use of

Combination Therapy

these agents is limited by their side-effect profile. Ezetimibe is a promising new alternative in phase 3 development. Ezetimibe holds the potential to become a viable agent for either monotherapy or as an add-on to a statin.

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Strategies for Optimizing Treatment Outcomes

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Summary

The relationship between increased levels of cholesterol and elevated risk for coronary heart disease (CHD) has been described in many epidemiological and well-designed prospective trials. Additionally, since first being elucidated by the Coronary Primary Prevention Trial, numerous trials have demonstrated that reducing blood cholesterol levels results in a corresponding reduction in risk for CHD. The evidence now indicates that cholesterol reduction confers up to a 35% reduction in total mortality, coronary mortality, coronary artery procedures, stroke, and other CHD-related events. This article reviews data that demonstrate that cholesterol reduction decreases CHD risk, discusses current and emerging treatment modalities, describes methods by which health care practitioners can enhance lipid treatment outcomes, and identifies educational tools that can be used to empower patients to improve their compliance and become actively involved in reducing their CHD risk.

KEYWORDS: Adherence, Cholesterol, Coronary heart disease, Dyslipidemia, LDL-C, Compliance, Outcomes

Based on the decline of the death rate from coronary heart disease (CHD) over the past 10 to 15 years, it appeared as if public health efforts aimed at reducing cigarette smoking and implementing lipid modification through dietary changes and statin use were having a positive effect on cardiovascular health. However, the data can be misleading because despite the reduction in CHD mortality, hospitalization rates for myocardial infarction (MI) and other CHD events continues to rise.¹ Upon closer inspection, it appears the decline in CHD deaths is attributable to an improvement in peri-event procedures and care such as coronary artery bypass graft surgery and angioplasty. Furthermore, the increasing number of CHD-related hospitalizations may be associated with a rapid increase in the prevalence of other CHD risk factors such as an aging population, the growing number of overweight Americans, the increased prevalence of diabetes, and hypertension. These observations may explain the persistence of CHD as the leading cause of death among Americans and suggest that renewed effort is required to reduce the cardiovascular risk burden within the U.S. population. Data from the Framingham Heart Study demonstrate a direct correlation between cholesterol levels and 40-year survival among adults younger than 50 years.² Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for the development of CHD, and clinical trials have demonstrated a reduction in risk with LDL-C-lowering therapy.

Cholesterol and CHD Risk

Atherosclerosis results from the accumulation of LDL-C in the subendothelial space of the arterial walls. Over time, this accumulation leads to the formation of atherosclerotic lesions. Large lesions are relatively stable but can cause obstructive symptoms such as angina pectoris. These lesions can be effectively treated with coronary artery bypass graphs, angioplasty, or stents. Surprisingly, it is the small newer lesions that are more prone to rupture and can result in the formation of a thrombus that can lead to MI, unstable angina, sudden death, stroke, or occlusion of a peripheral artery.

The Framingham Heart Study³ was the first to propose that the risk of developing CHD was linked to cholesterol, a concept that has been subsequently confirmed in numerous trials. The Framingham study was a prospective epidemiological trial that monitored blood lipids, blood pressure, smoking, and exercise habits in men and women over a period of time, up to 28 years. A continuous, graded relationship between increasing cholesterol levels (total and LDL) and CHD risk was observed. Moreover, the results proposed that high-density lipoprotein cholesterol (HDL-C) levels were inversely associated with CHD risk. Data from the Framingham study forms the basis of the CHD risk assessment advocated by Adult Treatment Panel III (ATP III).

The hypothesis that cholesterol levels are associated with risk of CHD was further confirmed in the Multiple Risk Factor Intervention Trial (MRFIT). MRFIT demonstrated a curvilinear relationship between rising cholesterol levels and CHD risk. Risk

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increased slightly as total cholesterol levels rose from 150 mg/dL to 200 mg/dL, at which point, risk increased 2-fold at cholesterol levels of 250 mg/dL, and 4-fold at levels >300 mg/dL.⁴

Outcome Trials

The first large study demonstrating that interventions that reduce cholesterol lead to a reduction in CHD morbidity and mortality was the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT). The LRC-CPPT randomized men with primary hypercholesterolemia to receive cholestyramine or placebo daily for an average of 7.4 years. The cholestyramine group showed a 9% reduction in CHD mortality and nonfatal MI. These benefits were most strongly linked to a decrease in total and LDL cholesterol. LRC-CPPT also provided one of the earliest demonstrations of the principle that every 1% reduction in LDL-C leads to a 2% reduction in CHD risk.⁵ Since publication of the LRC-CPPT results, numerous clinical trials have added evidence from a variety of patient populations using several different lipid-lowering therapies (Table 1). The Scandinavian Simvastatin Survival Study (4S) study showed a reduction in mortality and morbidity in CHD patients with high total and LDL-C levels. This trial was also the first to show a reduction in overall mortality with lipid-lowering therapy.⁶ The West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated a reduction in CHD risk in patients with elevated cholesterol but with no CHD at enrollment.⁷ Subsequently, the Cardiac and Recurrent Events (CARE) trial and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed that CHD risk could be reduced in patients who had normal or near-normal cholesterol levels.⁸ CARE provided evidence of benefit in a secondary prevention setting whereas AFCAPS/TexCAPS was in a primary prevention population. The Heart Protection Study demonstrated a significant reduction of the CHD risk in a large population of patients with CHD and CHD risk equivalents and only moderately elevated LDL-C (Table 2).⁹

Although the bulk of recent evidence that demonstrates the benefits of lipid-lowering therapy on CHD outcomes is derived from statin intervention trials, other drugs have also proven beneficial. The Helsinki Heart Study showed a reduction in CHD risk with gemfibrozil.¹⁰ More recently, the Veterans Affairs High-Density Lipoprotein Intervention Trial demonstrated a benefit with gemfibrozil in patients who did not have elevated total cholesterol or LDL-C but had low levels of HDL-C. Patients receiving gemfibrozil showed no significant change in LDL-C although their HDL-C was raised by 6%.¹¹

Current Treatment Modalities

The ATP III recommendations retain the historical endorsement of therapeutic lifestyle changes (TLC), primarily dietary modification, and regular exercise, as essential elements of risk-reduction therapy. ATP III advocates a 3-month trial of TLC before initiating drug therapy, although some high-risk patients will require pharmacologic intervention from the outset. TLC is intended to reduce CHD risk by helping to decrease LDL-C and triglyceride levels and

TABLE 1 Landmark Primary Prevention Cholesterol-Lowering Trials

| Study | Year | n* | Agents Used | Results |
|----------------|------|-------|----------------|--|
| LRC-CPPT | 1984 | 1,906 | cholestyramine | CHD incidence ↓ 18.9% |
| HHS | 1987 | 2,051 | gemfibrozil | CHD incidence ↓ 34% |
| WOSCOPS | 1995 | 3,302 | pravastatin | Death from all CVD ↓ 32% Non-fatal MI ↓ 31% |
| AFCAPS/TexCAPS | 1998 | 3,304 | lovastatin | First acute major event ↓ 37% |

*n = number of patients in the treatment group.

LRC-CPPT = Lipid Research Clinics Coronary Primary Prevention Trial; HHS = Helsinki Heart Study; WOSCOPS = West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study.

TABLE 2 Landmark Secondary Prevention Cholesterol-Lowering Trials

| Study | Year | n* | Agents Used | Results |
|--------|------|--------|--------------|--|
| 4S | 1994 | 2,221 | simvastatin | CHD mortality ↓ 42% |
| CARE | 1996 | 2,081 | pravastatin | CHD death or nonfatal MI ↓ 24% |
| LIPID | 1998 | 4,512 | pravastatin | CHD death ↓ 24% |
| MIRACL | 2001 | 1,538 | atorvastatin | Recurrent events ↓ 16% Stroke ↓ 50% |
| HPS | 2002 | 10,269 | simvastatin | Coronary death rate ↓ 18% |

*n = number of patients in the treatment group

4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events Trial; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease Study; MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study; HPS = Heart Protection Study.

raise HDL-C.

Diet modification is the cornerstone of therapy for mild to moderate dyslipidemia. ATP III recommends a TLC diet that includes a reduction of saturated fats to <7% of total calories, reduction of intake of dietary cholesterol to <200 mg/day, addition of plant sterols/stanols at a level of 2 g/day (plant sterols/stanols are commercially available in special margarines), and incorporating viscous fiber into the diet at a level of 10 g to 25 g/day.¹²

If followed faithfully, dietary therapy can result in a reduction in total cholesterol of 12% to 18%.¹³ There is no clear evidence that demonstrates a diet low in saturated fat and cholesterol will improve CHD outcomes. Systematic reviews of observational studies have found that increased consumption of fruits and vegetables is associated with a lower incidence of MI and stroke; however, these data are limited. Patients who do not respond to the recommended diet changes or who have difficulty complying with recommendations should be referred to a dietician or nutritionist for medical nutrition therapy.

TABLE 3 Elements of a Successful Lipid Management Program

- Target and enroll at-risk patients
- Reduce patient noncompliance
- Address patients on multidrug regimens who still fail to reach goals
- Manage existing comorbid conditions that prevent prescription of optimal lipid-lowering therapy
- Enhance adherence to guidelines
- Well-conceived, managed and operated cost-effective clinics

Cabana et al., JAMA. 1999;282:1458-65.

TABLE 4 Steps to Improve the Cost-Effectiveness of Lipid-Modifying Therapy

- Identify and aggressively treat high-risk patients
Treat to ATP III risk-related LDL-C treatment goals
- Reduce treatment costs
Maximize therapeutic lifestyle changes (TLC)
Use most cost-effective drugs
- Increase effectiveness of treatment
Increase compliance
Aggressively lower LDL-C

Persistent physical inactivity is now recognized by the American Heart Association as an independent risk factor, raising the risk of CHD by 2-fold. Physical activity raises HDL-C levels and decreases the concentration of very-low-density lipoprotein cholesterol (VLDL-C) and triglycerides. When exercise results in weight loss, it contributes to LDL-C reduction. Weight reduction can reduce LDL-C levels and ameliorate the risk factors associated with the metabolic syndrome by improving insulin sensitivity and serum glucose uptake and thus reducing the risk of diabetes. Cigarette smoking remains a CHD risk factor and smoking cessation can contribute to an increased HDL-C.

Failure of TLC to modify LDL-C or the presence of high CHD risk warrants the use of pharmacologic therapy. However, TLC should be maintained and continually reinforced by the physician even after the initiation of drug therapy. Treatment goals and lipid thresholds for initiating drug therapy are dependent on the patient's risk category that is calculated using the Framingham risk assessment tool advocated by ATP III.

Risk category 1 includes patients with a 10-year risk >20% (e.g., definite CHD or CHD risk equivalents). For these patients, the LDL-C threshold for initiating therapy is >130 mg/dL (after a 3-month trial of TLC) and the treatment goal is <100 mg/dL. For patients whose LDL-C cholesterol level is 100 mg/dL to 129 mg/dL, drug therapy is optional and physicians are encouraged to use their clinical judgment to determine if drug therapy is appropriate. Recently published data from the Heart Protection Study, however, have led many experts to reduce the threshold for drug therapy in patients with established CHD and CHD risk equivalents to >100 mg/dL.

Risk category 2 encompasses patients without definite CHD or CHD risk equivalents but with at least 2 major risk factors that

confer a 10-year risk of <20%. For patients with a 10-year risk of <10%, the LDL-C threshold is >160 mg/dL and the target is <130 mg/dL. In those patients that present with a 10-year risk of 10% to 20%, the treatment threshold is >130 mg/dL and the target is <130 mg/dL. In both instances, lipid-modifying drug treatment may not be necessary after a 3-month trial of TLC.

Risk category 3 includes patients without CHD who have 0 to 1 major risk factor. Drug treatment should be considered for these patients if their LDL-C is >190 mg/dL after 3 months of TLC. For patients in this category, the LDL-C goal is <160 mg/dL.

When setting therapeutic goals in patients with metabolic syndrome, physicians must consider up to 3 lipoprotein abnormalities, including increased LDL-C, increased triglycerides, and low HDL-C. These patients should be provided a 3-month trial of TLC. If the lipid profile is not favorably altered by TLC, an agent that reduces LDL-C and possibly triglycerides should be added to the lifestyle therapy. For high-risk patients with elevated triglycerides (>200 mg/dL), drug therapy can be added if weight reduction and increased physical activity fail to have a triglyceride-lowering effect.

LDL-C-lowering drug therapy should be monitored at 6-week intervals to determine if progress is being made toward goal, evaluate patient tolerability and adherence to the therapy, and provide patient education. If the LDL-C goal is not achieved, therapy should be intensified, with an increase in the drug dose or the addition of a second LDL-C-lowering drug with a different mechanism of action. Even if the LDL-C goal is attained, physicians and patients are encouraged to identify and treat other CHD risk factors such as hypertension or diabetes. Once the LDL-C levels are within a desirable range, patients should be monitored every 6 to 12 months for any event that may impact compliance to therapy.

Improving Lipid-Therapy Outcomes

The ATP III guidelines offer the opportunity to take significant steps in reducing the risk of CHD among Americans. However, the challenge is in the implementation of the guidelines. Successful implementation leads to increased adherence and, ultimately, better clinical and economic outcomes. In general, physicians recognize the importance of lipid control and are familiar with the basics of the guidelines. However, fewer than 40% of dyslipidemic patients are being treated, and many who are being treated are not reaching their target goals. Fewer than half of primary prevention patients have LDL <130 mg/dL, and fewer than 20% of patients with CHD who receive treatment have an LDL-C <100 mg/dL. Persistence with therapy is another challenge, as 70% of patients do not maintain therapy beyond one year.¹⁴

Noncompliance is not always the result of patient misunderstanding or intransigence. Health care professionals share the responsibility for assisting patients in their attempts to reach therapeutic goals. Among the reasons physicians do not adhere to guidelines are lack of awareness; disagreement with the guidelines; a perception of uncertain outcomes; a practice setting not conducive to implementation; and environmental factors, including lack of reminders and ineffective educational materials. Managed care

pharmacists can assist in the effort to promote lipid screening and effective lipid management as a priority by assisting in the development of clinical programs designed to identify and track high-risk patients, providing educational seminars on the benefits of lipid-lowering therapies, communicating to physicians the nature of the pharmacy benefit design and the cost-effectiveness of different therapies, and educating patients to prompt their doctors to screen for CHD (Table 3).

Patients who need lipid-lowering therapy are likely to need it long-term, perhaps for a lifetime. Yet, many patients do not adhere to their lipid-modification regimen even when prescribed an effective, well-tolerated agent. Improving adherence to therapy requires empowering patients, encouraging physicians, and establishing new ways to deliver lipid-modifying care. Clearly, there are numerous reasons patients discontinue therapy. Consequently, there is no single strategy that will improve adherence in all patients.

Perhaps the best strategy may be to employ a systematic approach of providing education about the disease and encouraging patients to take increased responsibility for their own care. Pharmacists can work closely with physicians to provide educational opportunities that teach patients about cardiovascular risk factors and explain the potential benefits of therapy. In addition, pharmacists are instrumental in increasing adherence through refill reminders, answering questions about drug interactions and side effects, and encouraging patients to follow up with their physicians on a regular basis. Tools that can support this effort include the Internet, videos, informational brochures, and telemedicine. Additionally, pharmacists should encourage the involvement of family and friends in the treatment plan, schedule more frequent visits, strive to keep the treatment regimen as simple as possible, provide clear instructions, and discuss adherence for at least a few minutes at each visit. Special attention should be given to those patients who do not reach goals, who miss appointments, or who require complex therapeutic regimens to reach treatment goals.

Adherence is also improved by devising new avenues of CHD risk screening, therapy, and patient education. Targeting inpatients during hospitalization for either an acute coronary event or an interventional procedure is an effective way to identify the highest-risk patients and initiate appropriate therapy prior to discharge. Multidisciplinary lipid-management clinics that address many aspects of CHD have proven to be effective in increasing adherence and improving both clinical and economic outcomes, particularly when treating patients at highest risk (Table 4). Hospital- and clinic-based pharmacists can also collaborate with community pharmacists to identify, educate, and treat high-risk patients.

Summary and Conclusions

The ongoing challenge in health care is to encourage pharmacists, physicians, and patients to employ strategies that lead to improved clinical and economic outcomes. Adherence to the ATP III guidelines is critical to reproducing the magnitude of CHD risk-reduction benefit demonstrated in clinical trials of lipid lowering. A significant effort must be made to maximize compliance in order to

attain the highest possible level of CHD risk reduction. Pharmacists can impact patient care at all levels by encouraging cholesterol screening and management. Whether in the clinic, hospital, or in the pharmacy, pharmacists have the opportunity to assist patients in achieving their lipid targets, encouraging risk factor intervention, monitoring therapies, and encouraging both adherence and persistence with treatment.

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|--|--|-------------------------------------|-------------------------------------|
| 1. | 6. | 11. | 16. |
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| 3. | 8. | 13. | 18. |
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Optimizing Dyslipidemia Outcomes: A Novel Pharmacotherapeutic Pathway

Please indicate the correct answers on the Record of Completion.

1. NCEP ATP III advocates that the intensity of lipid-modification therapy be adjusted to the patient's level of risk for CHD.
 - A. True
 - B. False
2. ATP III recommends using a Framingham risk assessment tool to quantify a patient's ____ -year risk for developing CHD.
 - A. 15
 - B. 20
 - C. 10
 - D. 5
3. CHD risk equivalents identified by ATP III include
 - A. Diabetes
 - B. Peripheral vascular disease
 - C. Abdominal aortic aneurysm
 - D. All the above are CHD risk equivalents
4. An estimated ____million American adults who are eligible for lipid-lowering drug therapy are not receiving adequate treatment based on the LDL-C targets recommended by ATP III.
 - A. 12.7
 - B. 3.9
 - C. 45.1
 - D. 22.3
5. Major risk factors for CHD as identified in the ATP III include
 - A. Cigarette smoking
 - B. Hypertension
 - C. Metabolic syndrome
 - D. A and B only
6. Data from the 4S and WOSCOPS trials suggest that for every 1% reduction in LDL-C, there is a 1% decrease in CHD mortality.
 - A. True
 - B. False
7. Which of the following are characteristics of the metabolic syndrome?
 - A. Abdominal obesity
 - B. Elevated levels of lipoprotein (a)
 - C. Low HDL-C cholesterol
 - D. All the above are characteristic of the metabolic syndrome
8. Statin use has been demonstrated to reduce the incidence of CHD events, including myocardial infarction, total mortality, and coronary death.
 - A. True
 - B. False
9. The real cost benefits of lipid-modification therapy are related not only to the improvement of morbidity and mortality but also to the reduction of direct and indirect costs.
 - A. True
 - B. False
10. Cholesterol is obtained by the body from both endogenous and exogenous sources.
 - A. True
 - B. False
11. Cholesterol absorption by the gut can be reduced by which of the following pharmacologic agents?
 - A. Plant stanols and sterols
 - B. Fibrates
 - C. Ezetimibe
 - D. Both A and C
12. Ezetimibe 10 mg/day as monotherapy reduces LDL-C by approximately 18%.
 - A. True
 - B. False

13. Which of the following describes the features of ezetimibe?
- A. Time of dosing has no effect on clinical efficacy
 - B. Can be taken with or without food
 - C. Safety profile similar to placebo
 - D. All of the above are features of ezetimibe
14. The proper combination of 2 lipid-lowering drugs with different mechanisms of action has proven effective in achieving lipid reductions that exceed those observed with most monotherapy.
- A. True
 - B. False
15. The combination of low-dose statins and fibrates appears to have complementary effects on _____ and _____.
- A. Triglycerides, LDL-C
 - B. HDL-C, lipoprotein (a)
 - C. LDL-C, HDL-C
 - D. Apoprotein a, triglycerides
16. The combination of a cholesterol absorption inhibitor and a statin reduces cholesterol derived from both endogenous and exogenous sources.
- A. True
 - B. False
17. Statins, when used in combination with bile acid resins, result in a compensatory increase in LDL-C production.
- A. True
 - B. False
18. Which of the following outcome trials was the first to demonstrate that lowering cholesterol reduced the risk for CHD?
- A. MRFIT
 - B. 4S
 - C. WOSCOPS
 - D. LRC-CPPT
19. ATP III advocates a ___ -month trial of therapeutic lifestyle changes prior to beginning drug therapy in most low- to moderate-risk patients.
- A. 6
 - B. 2
 - C. 3
 - D. 1
20. Multidisciplinary lipid management clinics have proven to be clinically and economically effective.
- A. True
 - B. False



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