

Effective Management of Patients With Dyslipidemia

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Abstract

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in the United States. A direct relationship has been demonstrated between dyslipidemia and the risk for developing CHD. Improving lipid status has been clearly demonstrated to reduce the morbidity and mortality associated with lipid disorders. The recently published National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines and revised Health Plan Employer Data and Information Set (HEDIS) performance measures have placed added emphasis on screening and treatment of lipid disorders and global risk for CHD. Current ATP III and HEDIS cholesterol screening and goal measures are targeting more Americans for cholesterol-lowering therapy. This review summarizes the implications of the HEDIS performance measures and the ATP III guidelines, reviews the economic benefits of lowering cholesterol, and identifies optimal cholesterol levels. In addition, the challenges associated with patients who have suboptimal control and patients with poor compliance are discussed, as these factors significantly increase CHD morbidity, mortality, and cost of disease. In addition, lipid-lowering drug therapies are reviewed, and a lipid-lowering agent currently in phase 3 development, rosuvastatin, is introduced.

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patients with diabetes and other coronary heart disease (CHD) risk equivalents in the highest risk category. As a result, the number of Americans who should be prescribed a lipid-modifying agent to achieve the new treatment goals is expected to be nearly 3 times greater than with previous guidelines, which will have a substantial impact on overall pharmacy costs.¹ While aggressive treatment of lipid disorders will increase pharmacy costs, it can significantly decrease total medical expenditures by reducing CHD risk and risk for CHD events, such as myocardial infarction (MI), stroke, and reduce the need for further interventions such as revascularization procedures.

The National Committee on Quality Assurance (NCQA) updated the Health Plan Employer Data and Information Set (HEDIS) measures in 2000 to provide an outcomes-based benchmark for evaluation of the effectiveness of cholesterol management strategies used by managed care organizations.² While past HEDIS cholesterol performance measures were focused solely on screening patients for dyslipidemia, the new accreditation requirements now include both screening and treatment-related outcome measures, such as achievement of predetermined low-density lipoprotein cholesterol (LDL-C) levels in selected patients. In addition, the new HEDIS performance measures require cholesterol testing and control in patients with diabetes.

This review summarizes the implications of the HEDIS performance measures and the ATP III guidelines, identifies optimal lipid levels, and reviews the economic benefits of achieving optimal lipid levels. In addition, the challenges associated with managing

In May 2001, the National Cholesterol Education Program (NCEP) released new guidelines, the Adult Treatment Panel III (ATP III) for the management of dyslipidemia.¹ These guidelines recommend more aggressive lipid management strategies than previous guidelines and significantly increase the number of individuals eligible for lipid-modification therapy by placing

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patients with suboptimal control of lipid levels and patients with poor compliance are discussed, as these factors significantly increase the morbidity, mortality, and cost of disease. Finally, lipid-lowering drug therapies are reviewed, and a lipid-lowering agent currently in phase 3 development, rosuvastatin, is introduced.

HEDIS Cholesterol Screening and Impact on Managed Care Plans

To secure NCQA accreditation, the HEDIS cardiovascular performance measures require managed care plans to provide evidence of LDL-C screening and lipid control in patients who have been diagnosed with either diabetes or CHD.² Plans must be able to demonstrate that the LDL-C is controlled at a level of 130 mg/dL or lower to meet the measurement criteria. Because the new HEDIS cholesterol screening and control measures were introduced in 1999, significant improvements in both screening and control have been noted. In 1999, only 69% of patients with either diabetes or CHD were screened. By the end of 2000, screenings increased to 77% for diabetes and 74% for CHD. Likewise in 1999, only 37% of patients with diabetes and 45% of patients with CHD achieved reduced LDL-C levels consistent with HEDIS performance measures. By 2000, 44% and 53% of patients with diabetes and CHD, respectively, had achieved reduced LDL-C levels consistent with HEDIS performance measures. Despite these gains, managed care plans will be required to expend a significant effort to improve their compliance with HEDIS performance measures.²

HEDIS performance measures are reviewed every 3 years and may be reviewed more frequently if significant new scientific evidence becomes available or if nationally recognized guidelines are updated. In addition, the NCQA retains a panel of cardiovascular and diabetes experts to evaluate whether current HEDIS cholesterol performance measures should be expanded beyond the realm of patients with CHD or diabetes and include primary prevention for patients with multiple risk factors. Inclusion of these patient groups will bring the HEDIS measures more in line with the aggressive lipid-

modification recommendations included in the ATP III guidelines and will send a consistent message to patients, providers, and health plans on the importance of identifying and treating dyslipidemia and reducing CHD risk.

NCEP ATP III Guidelines

In 2001, the NCEP ATP III guidelines were published, providing evidence-based strategies for identifying and reducing the short-term (10-year) risk for CHD.¹ Consequently, the new guidelines stratify patients into 1 of 3 risk categories according to their near-term risk of developing CHD. The first risk category includes patients with preexisting CHD or CHD risk equivalents and patients with a very high risk, defined as a greater than 20% risk for developing CHD in the next 10 years. The second category consists of patients with 2 or more risk factors but not diagnosed with CHD, and the third category includes those who are in the lowest risk category, with 0 to 1 risk factors. The new risk assessment criteria features incorporated in NCEP ATP III are summarized in **Table 1**. Treatment strategies are driven by the degree of risk for CHD; the higher the risk, the more aggressive the treatment strategy. The guidelines also propose specific cholesterol target goals that trial evidence indicates will result in significant clinical and possibly economic benefits to patients and health plans. In addition, ATP III defined the desirable triglyceride level as 150 mg/dL and set non-high-density lipoprotein cholesterol (HDL-C) treatment goals in patients with triglycerides >200 mg/dL. New classifications of LDL-C, total cholesterol (TC), and HDL-C levels are identified in **Table 2**. The ATP III guidelines also recognize the importance of patient and provider adherence to the guidelines to maximize the clinical and economic benefit of lipid-modification therapy.

CHD Risk Assessment in ATP III. ATP III recommends the use of a Framingham-based risk scoring system to quantify the 10-year risk for a coronary event.¹ Point scores are calculated according to the presence of 5 major CHD risk factors—age, gender, TC level, systolic blood pressure, HDL-C level,

and smoking status—with each risk factor worth a certain number of points. When added together, the sum yields an estimate of the 10-year risk for experiencing a coronary event. A properly conducted assessment places patients into 1 of the 3 risk categories and forms the basis for all subsequent treatment decisions.¹ Patients with documented CHD and CHD risk equivalents are automatically placed in the highest risk category. CHD risk equivalents carry a risk for a major coronary event equal to that of clinically evident CHD and include type 2 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 a level <100 mg/dL.

The first step in evaluating CHD risk is to identify patients with clinical evidence of CHD or CHD risk equivalents. All of these patients, by definition, have a >20% 10-year risk of a CHD event. The second step in assessing risk is to count the risk factors present in the remaining patients (ie, those without CHD or CHD risk equivalents). For those with >2 risk factors, the next step is to conduct a Framingham-based risk assessment to determine the most appropriate course of therapy. If the patient presents ≥2 risk factors, he/she may have a 10-year CHD risk which is >20%. If this is the case, this patient should be placed in the CHD risk equivalent category and treated to a target LDL-C goal of <100 mg/dL. Patients with a 10-year risk between 10% and 20% require more aggressive treatment, often with lifestyle modifications and drug therapy. Therapy for these patients should be sufficient to enable patients in this category to achieve an LDL-C target of <130 mg/dL. Those patients with <10% 10-year risk are candidates for lifestyle therapy and rarely, drug therapy. The target LDL-C level in this group of patients is <160 mg/dL.

Prevalence and Impact of CHD

More than 61 million Americans have cardiovascular disease (CVD). Of these, 12.6 million have CHD, 7.5 million have had an MI, and 6.4 million experience angina pectoris.³ CHD resulted in nearly 530 000

Table 1. Risk Assessment Criteria: New Features of NCEP ATP III Guidelines

<p>Focus on Multiple Risk Factors</p> <ul style="list-style-type: none"> ■ Diabetes without CHD equal to CHD risk equivalent ■ Framingham-based assessment of 10-year absolute CHD risk used to stratify patients with >2 risk factors into those with >20% risk for more intensive treatment and those with <20% risk ■ Multiple metabolic risk factors indicate candidates for intensified therapeutic lifestyle changes <p>Modifications of Lipid and Lipoprotein Classification</p> <ul style="list-style-type: none"> ■ LDL-C <100 mg/dL optimal ■ Raises categorical low HDL-C from <35 mg/dL to 40 mg/dL ■ Lowers TG classification cutpoints to give more attention to moderate elevations <p>Support for Implementation</p> <ul style="list-style-type: none"> ■ Lipoprotein analysis versus screening for TC and HDL-C alone as preferred initial test ■ Encourage dietary options (plant stanols/sterols and soluble fiber) to enhance lowering LDL-C ■ Promote adherence to therapeutic lifestyle changes and drug therapies ■ Treat to a second, non-HDL-C treatment goal in patients who have a TG ≥200 mg/dL

ATP III indicates Adult Treatment Panel III; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; TC, total cholesterol; and TG, triglycerides. Source: Reference 1.

Table 2. NCEP ATP III Classification of Cholesterol: Total, LDL-C, HDL-C

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

ATP III indicates Adult Treatment Panel III; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and NCEP, National Cholesterol Education Program. Source: Reference 1.

Table 3. Risk of CHD: Cholesterol Levels at Various Ages

Age and Risk	Total Cholesterol Level (mg/dL)					
	<200	200-239	240+	<200	200-239	240+
	Men			Women		
Age 40	(%)	(%)	(%)	(%)	(%)	(%)
10-year risk	3	5	12	1	2	5
40-year risk	31	43	57	15	26	33
Age 50						
10-year risk	8	10	15	2	4	8
40-year risk	40	42	63	19	30	39
Age 60						
10-year risk	16	15	21	5	8	11
40-year risk	34	41	51	20	24	36
Age 70						
10-year risk	18	22	28	5	7	13
40-year risk	27	36	42	14	20	29

CHD indicates coronary heart disease.

Source: Reference 1.

deaths in the United States in 1999.³ Deaths from CHD were nearly double those from cancer and were greater than the combined number of deaths from cancer, accidents, Alzheimer's disease, and human immunodeficiency virus/acquired immune deficiency syndrome in 1999. CHD is responsible for 1 in every 5 deaths and is the dominant cause of mortality among women in the United States. Current estimates of the US annual medical costs associated with CHD exceed \$111 billion.³

Cholesterol and CHD: Prevalence of Hypercholesterolemia

TC levels, age, and the associated risk of developing CHD for both men and women are presented in **Table 3**. The 10-year risk for a man who is 40 years of age and has a TC level of <200 mg/dL is approximately 3%; the risk rises to 12% when TC level exceeds 240 mg/dL. Likewise, the 10-year risk of developing CHD for a man who is 60 years of age and

has a TC level of <200 mg/dL is 16%; this risk increases to 21% when TC level exceeds 240 mg/dL. A similar relationship is observed in women. Data from the Framingham Heart Study indicate that each 1% decrease in TC level is associated with a 2%-3% decrease in CHD.⁴ A recently published meta-analysis of 38 clinical trials found CHD mortality is reduced by 15% for each 10% decline in TC level.⁵ This analysis also confirmed that decreases in TC level were not associated with increases in noncardiac mortality.

Approximately 102.3 million US adults have TC levels >200 mg/dL. Of these, 41.3 million American adults have TC levels of ≥240 mg/dL.⁶ **Table 4** identifies the median percentages of Americans older than 18 years of age who have been told by a healthcare professional that they have high blood cholesterol. Numerous clinical trials have demonstrated that LDL-C levels of ≥130 mg/dL are associated with a higher risk of CHD. Nearly 50% of all adults in the

United States have an LDL-C ≥ 130 mg/dL (Table 5).

Cholesterol Intervention Trials

Dyslipidemia, particularly elevated LDL-C, is now widely accepted to be strongly associated with an increased risk for heart disease. Consequently, in the past few decades, more than 20 studies involving more than 100 000 person-years of participation have demonstrated the CHD risk-reducing benefits of cholesterol lowering using numerous strategies, including bile acid sequestrants, lifestyle interventions, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors (Table 6). Reductions in TC level and LDL-C have consistently shown associated reductions in morbidity and mortality in both primary and secondary prevention patient populations (Tables 7 and 8).

The West of Scotland Coronary Prevention Study (WOSCOPS) was a large primary prevention study in which cholesterol reduction elicited a decrease in CHD mortality.⁷ More than 6000 high-risk men who did not have clinically evident CHD and had a mean TC level of 272 mg/dL were randomized to receive pravastatin or placebo for 5 years. Mean TC level and LDL-C levels were reduced from baseline by 20% and 26%, respectively, with pravastatin therapy compared to no change with placebo. Patients in the active treatment group benefited from a 31% reduction in CHD death and nonfatal MI compared to the placebo group.

Table 4. Median Percentages of Americans Older than 18 Years of Age Who Have Been Told by a Healthcare Professional that They Have High Blood Cholesterol

Population Subgroup	Median Percentage Identified with Dyslipidemia
White	29.7
African American	26.0
Hispanic	25.6
Asian/Pacific Islander	27.3
Native American/Alaskan Native	26.0

Source: Reference 5.

Table 5. Percentages of Americans Older than 20 Years of Age Who Have LDL-C Levels of ≥ 130 mg/dL

Population Subgroup	Men (%)	Women (%)
Non-Hispanic white	49.6	43.7
Non-Hispanic African American	46.3	41.6
Mexican American	43.6	41.6

LDL-C indicates low-density lipoprotein cholesterol. Source: Reference 5.

Table 6. Effect of LDL-C–Lowering Therapy on CHD Outcomes

Intervention	No. Trials	No. Treated	Person-Years	Mean Cholesterol Reduction (%)	CHD Incidence (% Change)	CHD Mortality (% Change)
Bile acid sequestrants	3	1992	14 491	9	-22	-32
Diet	6	1200	6356	11	-24	-21
Statins	12	17 405	89 123	20	-30	-29

CHD indicates coronary heart disease; LDL-C, low-density lipoprotein cholesterol. Source: Reference 1.

Table 7. Evaluation of Therapies: Benefits of Therapy for Primary Prevention (Landmark Statin Trials)

Study	Year	n	Agent	Results
AFCAPS/TexCAPS*	1998	6605	Lovastatin 20/40 mg	Major coronary events—37%↓ Unstable, new-onset angina—32%↓
WOSCOPS†	1995	6595	Pravastatin 40 mg	Major coronary events—31%↓ Nonfatal MI—31%↓

AFCAPS/TexCAPS indicates Air Force/Texas Coronary Atherosclerosis Prevention Study; WOSCOPS, West of Scotland Coronary Prevention Study.

*Source: Reference 8.

†Source: Reference 7.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial randomized healthy male and female patients with average TC values, but low HDL-C levels, to lovastatin or placebo. A total of 5608 men and 997 women were followed for an average of 5.2 years. Treatment with lovastatin reduced the risk for first acute coronary events by 37% ($P < .001$). First acute coronary events were defined as fatal or nonfatal MI, unstable angina, or sudden cardiac death. Treatment with lovastatin reduced the risk of first MI by 40% (1.7% vs 2.9%), unstable angina or worsening angina by 32% (1.8% vs 2.6%), and revascularization procedures by 33%.⁸ The low HDL-C may have been the reason for the increased CHD risk in this population and the reason the lovastatin group was able to demonstrate a risk reduction.

The Scandinavian Simvastatin Survival Study (4S) trial reinforced the value of secondary prevention. More than 4000 men with previous coronary events were randomized to treatment with simvastatin or placebo for 5 years. Mean TC level was 213 mg/dL at the start of the study. Reductions in TC (25%) and LDL-C levels (35%) and an increase in HDL-C level (8%) resulted in decreases in MI, coronary artery bypass surgery, percutaneous coronary angioplasty, CHD mortality, and all-cause mortality.⁹ Simvastatin treatment significantly decreased total mortality (8% vs 12% for placebo), CVD deaths, the incidence of additional MI, and the need for revascularization procedures such as angioplasty and coronary artery

surgery. Benefits were not observed until several years into therapy, thus underscoring the importance of prolonged adherence to treatment.

Because patients with CHD often have lipid profiles that fall within the national average, the Cholesterol and Recurrent Events (CARE) trial was conducted using patients with lipid characteristics similar to those of the US population. In this trial, 3583 men and 576 women with a previous MI and TC levels <240 mg/dL were assigned to placebo or pravastatin 40 mg daily for 5 years. Mean LDL-C level decreased from 139 mg/dL to 97 mg/dL in the pravastatin group. A reduction of 10%-13% in the combined end point of death and nonfatal MI was seen when the pravastatin and placebo groups were compared.¹⁰

The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study complements the 4S and CARE studies. A total of 9000 patients with CHD and TC levels ranging from 155 to 271 mg/dL were randomized to pravastatin 40 mg daily or placebo. The primary outcome was death from CHD. Mean TC levels fell from 218 to 179 mg/dL in the active treatment group, resulting in a 24% reduction in CHD mortality and a 22% decrease in overall mortality.¹¹

The most recently completed trial that investigated the relationship between cholesterol reduction and risk reduction in CHD is the Heart Protection Study (HPS).¹² This study enrolled 20 000 primary and secondary prevention patients who were 40 to 80 years of age with CHD and CHD risk equiv-

Table 8. Evaluation of Therapies: Benefits of Therapy for Secondary Prevention

Landmark Statin Trials—Secondary Prevention				
Study	Year	n	Agent	Results
4S*	1994	4444	Simvastatin	Total mortality—30%↓ CAD mortality—42%↓ Major coronary events—35%↓
CARE†	1996	4159	Pravastatin	Major coronary events—24%↓ Fatal/nonfatal MI—25%↓ Fatal/nonfatal stroke—31%↓
LIPID‡	1998	9014	Pravastatin	Total mortality—22%↓ CAD mortality—24%↓ Major coronary events—29%↓ Fatal/nonfatal stroke—19%↓
MIRACL§	2001	3086	Atorvastatin	Recurrent events—16%↓ Stroke—50%↓

CAD indicates coronary artery disease; 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events Trial; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease Study; MI, myocardial infarction; and MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study.

*Source: Reference 9.

†Source: Reference 10.

‡Source: Reference 11.

§Source: Reference 17.

alents. Both men and women participated in this study, including healthy individuals as well as patients with diabetes and patients with noncoronary vascular disease and individuals who had average or below-average cholesterol levels as well as those with high cholesterol levels. Patients were followed for 5.5 years. Study results demonstrate that treatment with 40 mg simvastatin elicited a 24% reduction in major vascular events (MI, stroke, or revascularizations) compared to placebo. Perhaps the most important finding is that this benefit was observed for all patients receiving statin therapy independent of preexisting health status, age, gender, or baseline cholesterol level. The benefits were observed to increase throughout the study treatment period suggesting that prolonged therapy might be expected to produce greater benefits. Because of its size and the wide range of high-risk patients included, the HPS provides clear and reliable evidence that aggressive lipid-lowering therapy

reduces CHD risk and the occurrence of CHD events.

Optimal TC and LDL-C Levels

Decreasing cholesterol levels has clearly been shown to reduce the risk for CHD and CHD death. TC levels were reduced between 18% and 29% in the WOSCOPS, 4S, and LIPID studies^{7,9,11} and 10% in the Helsinki Heart Study,¹³ and all of these trials showed reductions in fatal and nonfatal CHD without increases in total mortality. However, debate continues as to what specific levels of TC and LDL-C are optimal for maximizing CHD risk reduction. There are 2 divergent schools of thought with regard to cholesterol lowering. The first supports the concept of a threshold effect, in which a certain absolute level or percentage reduction is required to maximize reduction of CHD risk. Support for this concept comes from a post-hoc analysis of the data from the CARE and WOSCOPS trials. In the CARE trial, treatment of cholesterol significantly reduced

CHD events without regard to the percent of LDL-C reduction.¹⁰ A reanalysis of the WOSCOPS data divided patients into quintiles based on the percent reduction of LDL-C and found that a 12% reduction provided benefits that were not significantly statistically different from those seen in the 3 quintiles with greater reductions in LDL-C.⁷

Alternatively, other investigators have argued that, to date, no minimum LDL-C level has been determined for which a reduction would not provide a benefit. A retrospective analysis of the 4S study data demonstrated that after 1 year, a 1.7% reduction in major coronary disease risk was seen for each 1% reduction in LDL-C level.¹⁴ This relationship was present without regard to LDL-C level, and a similar relationship is seen when plotting LDL-C reduction versus CHD data from other clinical trials.

Data from the landmark HPS provide clear evidence that lowering LDL-C has a cardioprotective effect independent of the baseline cholesterol level. CHD risk reduction and overall clinical benefit was observed in all patients receiving simvastatin regardless of their TC level. This study showed that the risk reduction observed in patients with a baseline LDL-C of 116 mg/dL was also seen in patients with baseline values of 154 mg/dL. The authors note that if a lower threshold exists, it is a much lower value than is typically seen in Western populations (eg, <80 mg/dL).¹²

Presently, at least 3 prospective, randomized trials are being conducted to address the question of what is the degree of LDL-C reduction required to realize maximal clinical benefit. The objective of one of these trials, the Treating to New Targets (TNT) trial, is to determine the lower limits of LDL-C reduction and cardiac risk.¹⁵ Subjects will receive atorvastatin 10 mg daily or 80 mg daily over 5 years with the objective to prove that lowering LDL-C from 110 mg/dL to 75 mg/dL will provide optimal reduction in CHD risk.¹⁵ Two other trials, the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) and the Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), have similar objectives. The

results of these studies will add to the observations obtained from a subanalysis of the Atorvastatin Versus Revascularization Treatments (AVERT)¹⁶ and the Myocardial Ischemia Reduction with Aggressive Lipid Lowering (MIRACL) trials.¹⁷ Data from AVERT indicates that CHD patients who had the greatest reduction in ischemic cardiovascular events also had the greatest percentage reduction in LDL-C levels.¹⁶ The subanalysis showed a 47% reduction in LDL-C levels among stable CHD patients who remained event-free following aggressive lipid-lowering therapy. By contrast, patients who did experience a cardiovascular event (eg, nonfatal heart attack, bypass surgery, revascularization and worsening angina) had only a 35% reduction in LDL-C levels.¹⁶

The MIRACL trial was conducted to determine whether statin therapy, begun within 48 hours of acute coronary syndrome, could reduce CHD events in the short term (ie, subsequent 4 months) compared to placebo.¹⁷ At the time of randomization, serum lipid levels were nearly identical in both groups, with a mean LDL-C level of 124 mg/dL. By the end of the study, the average LDL-C level had increased to 135 mg/dL in the placebo group and decreased to 72 mg/dL in the treatment group. A primary end point event occurred in 14.8% of patients in the statin group and 17.4% in the placebo group ($P = .046$). Therapy that decreased LDL-C to below 80 mg/dL in these CHD patients demonstrated a trend toward improved clinical outcomes suggesting that clinical benefits continue to be derived as LDL-C levels decrease.¹⁷

Lipid-Lowering Drug Therapies

Many drugs are available for treatment of dyslipidemia, including statins, bile acid sequestrants, niacin, fibrates, and cholesterol-absorption inhibitors. Choosing the appropriate single drug or combination of drugs is often influenced to a great degree by an individual patient's particular type of dyslipidemia, CHD risk, and preexisting comorbid conditions. Preferred drugs are those that consistently reduce LDL-C, TC, and triglyceride levels, raise HDL-C levels, and have a low incidence of adverse drug reactions. Favorable pharmacokinetics and

few drug interactions offer significant advantages. Drugs that are safe, effective, well tolerated, affordable, taken once daily, and bring a majority of patients to target lipid goals with monotherapy are the most valuable.

Currently Available Statins. The HMG-CoA reductase inhibitors, or statins, are the most widely used and arguably the most effective lipid-lowering agents currently available. These drugs work well as monotherapy and in combination with other agents. All statins lower LDL-C concentrations by upregulating hepatic LDL-C receptors after transient competitive inhibition of the reductase enzyme responsible for conversion of HMG-CoA to mevalonic acid during cholesterol synthesis. By upregulating LDL-C receptors, statins not only increase LDL-C clearance from the plasma, but also reduce circulating levels of very low-density lipoprotein cholesterol (VLDL-C) and intermediate-density lipoprotein cholesterol that serve as substrates for LDL-C synthesis. When used as monotherapy, statins reduce LDL-C by 24%-60% and triglycerides by 22%-45%. Currently available statins can also raise HDL-C up to 12%. All statins reduce serum cholesterol in a dose-related manner. Research has shown that doubling the dose of a statin above the minimal effective dose leads to an approximately 6% greater reduction in LDL-C.¹⁸

Within the class of statins, differences in absorption and metabolism can be observed for each drug. Lovastatin absorption is increased significantly in the presence of food while pravastatin is best taken on an empty stomach. Because rates of cholesterol synthesis increase between midnight and 3:00 AM, patients should be advised to take lovastatin with the evening meal, while pravastatin should be taken at bedtime. The other statins are unaffected by food and can be taken at any time during the day. The statins also differ in their metabolic pathways. Of the 5 currently available statins, 3 are metabolized through the cytochrome P450 3A4 enzyme system—atorvastatin, simvastatin, and lovastatin—while fluvastatin is metabolized through cytochrome 2C9.¹⁹ Pravastatin is not

metabolized via cytochrome P450; it undergoes hepatic sulfation.¹⁹ Metabolism via the P450 system can result in drug interactions as other agents compete or interfere with P450 enzymatic activity.

Statins are well tolerated by most people. The most common adverse effects of the statins include gastrointestinal upset, abdominal pain, flatulence, constipation, myalgia (defined as muscle ache or weakness without elevations in creatine kinase), flu-like symptoms, and headache. Less common problems are an asymptomatic elevation of liver enzymes (defined as >3 times the upper limit of normal) and myositis (defined as muscle pain, soreness, or weakness with serum creatine kinase concentrations of >10 times the upper limit of normal), rash, insomnia, unpleasant or vivid dreams, and difficulty sleeping or concentrating.¹⁹ Elevated hepatic transaminases generally occur in 0.5%-2.0% of cases and are dose-dependent.²⁰ Whether transaminase elevation with statin therapy constitutes true hepatotoxicity has not been determined and progression to liver failure specifically due to statins is exceedingly rare. Reversal of transaminase elevation is frequently noted with a reduction in dose, and elevations rarely return when challenged with the same or different statin.²¹ Furthermore, no direct evidence suggests that statins exacerbate liver disease.²² The incidence of elevated liver enzymes can be increased in patients receiving drugs metabolized by the cytochrome P450 system. In patients exhibiting elevated liver enzymes, aminotransferase levels usually are elevated 3 times the upper limit of normal.¹⁹ An LDL-C level that suddenly declines despite stable dosing is also a sign of toxicity regardless of aminotransferase levels.²²

The ability of statins to produce myopathy (defined as any disease of the muscles) under some circumstances is well established. A common complaint is myalgia or nonspecific muscle aches or joint pains that are generally not associated with significant increases in creatine kinase. In placebo-controlled trials, the incidence of these complaints is generally similar to that reported with placebo. Myositis is even less common, occurring in 0.8%-0.9% of patients taking

Table 9. Trials Comparing Efficacy of Rosuvastatin With Other Statins

Study	Patient Population	Design	Active Treatment Groups,* mg/day	% LDL-C Reduction From Baseline	Overall % of Patients at Target LDL-C	High-Risk Patients at Target LDL-C
Davidson et al ¹⁸	519 patients with hypercholesterolemia	MC, R, DB, PC, PG, 12 weeks	Rosuvastatin 5	40 [†]	83	42
			Rosuvastatin 10	43 [‡]	84	47
			Atorvastatin 10	35	73	19
Olsson et al ²⁹	412 patients with hypercholesterolemia	MC, R, DB, PG, 52 weeks	Rosuvastatin 5	47 [§]	88	65
			Rosuvastatin 10	53 [§]	98	97
			Atorvastatin 10	44	87	61
Brown et al ³¹	477 patients with hypercholesterolemia	MC, R, DB, PG, 52 weeks	Rosuvastatin 5	42	88	84
			Rosuvastatin 10	48 [†]	88	71
			Pravastatin 20	32	60	6
			Simvastatin 20	38	73	30
Stein et al ³⁶	622 patients with heterozygous familial hypercholesterolemia	MC, R, DB, PG, FT, 18 weeks	Rosuvastatin [‡]	58 [‡]	61	24
			Atorvastatin [‡]	50	46	3

*Dosage was titrated to between 12-52 weeks to meet NCEP ATP III LDL-C goals (except for Stein et al³⁶).

[†] $P < .01$ vs atorvastatin.

[‡] $P < .001$ vs atorvastatin.

[§] $P < .05$ vs atorvastatin.

^{||} $P < .05$ vs pravastatin.

^{††} $P < .05$ vs simvastatin.

[‡]Force titration to next dose level every 6 weeks.

LDL-C indicates low-density lipoprotein cholesterol; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; MC, multicenter trial; R, randomized trial; DB, double-blind trial; PC, placebo-controlled trial; PG, parallel group; and FT, forced titration.

statins as monotherapy.^{22,23} Myositis is most likely to occur in people with multiple morbidities and/or those taking several medications. The incidence has been reported to be 0.2% in patients on high-dose lovastatin monotherapy (80 mg daily)²³ but may be higher in patients who are also taking cyclosporine or erythromycin,²⁴ niacin, macrolide antibiotics, and certain antifungal drugs.²² When lovastatin is given in combination with fibrates, myositis occurs in approximately 1% of patients.²⁴ Small-framed, older patients with impaired renal function are at the highest risk for myositis when given this combination.²⁵

Rosuvastatin: A New Statin. Rosuvastatin is a potent HMG-CoA reductase inhibitor currently in phase 3 development. The drug does not induce or act as a sub-

strate for hepatic enzymes to any significant degree, therefore, little if any drug interactions are expected. In phase 2 and phase 3 trials, rosuvastatin has been well tolerated with reported adverse reactions equal to other HMG-CoA inhibitors and similar to placebo.

Pharmacokinetics. Rosuvastatin is both hepatoselective and hydrophilic and exhibits minimal metabolism (<5%) via the cytochrome P450, 2C9, and 2C19 systems. This compound is highly absorbed following oral administration and has a half-life of approximately 20 hours. Peak serum levels are reached in 3 to 5 hours. Ninety percent of a single oral dose undergoes biliary excretion and is recovered in the feces.²⁶ Ten percent of an oral dose is recovered in the urine.²⁷ The pharmacokinetics of rosu-

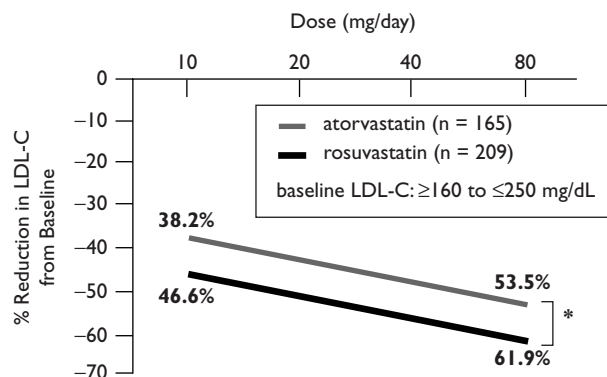
vastatin are not significantly altered in the elderly, and the drug can be safely administered at any time in the day.²⁸

Efficacy. Rosuvastatin has been studied in more than 5000 patients enrolled in phase 2 and phase 3 studies, including several head-to-head trials with currently available statins^{18,29-31} as well as in combination with niacin,³² cholestyramine,³³ and fibrates.³⁴ In addition, rosuvastatin has been studied in patients with diabetes,³⁴ patients with hypertriglyceridemia,³⁵ and patients with familial hypercholesterolemia.³⁶ Rosuvastatin lowers LDL-C levels by 34%-65% across a dose range of 1 mg to 80 mg daily. A starting dose of 10 mg daily will reduce LDL-C by approximately 50%, which should treat most patients to within NCEP ATP III goals.¹⁸

Several head-to-head trials comparing the efficacy of rosuvastatin and atorvastatin are summarized in **Table 9**. A 6-week randomized, double-blinded study was conducted to compare the LDL-C-lowering effect of rosuvastatin and atorvastatin across a dose range of 10-80 mg daily (**Figure 1**).³⁷ The overall percent reduction in LDL-C from baseline for rosuvastatin was from 46.6%-61.9% across the dose range compared to 38.2%-53.5% for atorvastatin.³⁷ Rosuvastatin was compared to atorvastatin in a 52-week study of patients with LDL-C between 160 and 250 mg/dL.²⁹ During the first 12 weeks, subjects were randomized to rosuvastatin 5 mg or 10 mg daily or atorvastatin 10 mg daily. Over the next 40 weeks, doses could be sequentially doubled to allow subjects to reach NCEP ATP III goals for LDL-C levels. Rosuvastatin produced greater reductions in LDL-C at both 12 and 52 weeks when compared to atorvastatin. At 52 weeks, 98% of subjects on rosuvastatin 10 mg daily had reached goal LDL-C levels versus 87% with atorvastatin. Eighty-two percent of subjects taking rosuvastatin 10 mg daily reached goal without a dose escalation versus 59% with atorvastatin.²⁹

Rosuvastatin 5 mg and 10 mg daily were compared to pravastatin 20 mg daily and simvastatin 20 mg daily. Patients with LDL-C levels between 160 and 250 mg/dL and triglyceride levels <400 mg/dL were ran-

Figure 1. Rosuvastatin vs Atorvastatin: 6-Week Dose-Response Comparison



*Mean % change = -8.4%, $P < .001$.

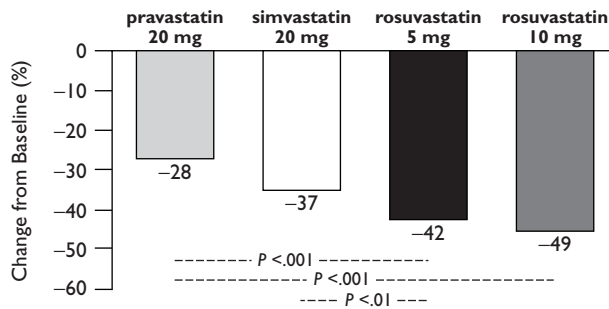
LDL-C indicates low-density lipoprotein cholesterol.

Source: Reference 37.

domized to 1 of 4 active drug therapies. In this trial, rosuvastatin 5 mg and 10 mg reduced LDL-C levels by 42% and 49%, respectively, compared with a 28% reduction with pravastatin and 37% with simvastatin (**Figure 2**).³⁰ A greater proportion of rosuvastatin-treated patients (5 mg, 71%; 10 mg, 87%) with known CHD reached ATP III goals for LDL-C levels compared with 64% of simvastatin-treated patients and 53% of pravastatin patients.³⁰ These results were supported by a 52-week trial comparing the same drugs and dosages in 477 patients. All the rosuvastatin doses produced greater statistically significant reductions in LDL-C at weeks 12 and 52 ($P < .05$), with the exception of rosuvastatin 5 mg at 52 weeks compared to simvastatin ($P = .053$). After 52 weeks, rosuvastatin 5 mg and 10 mg reduced LDL-C levels by 42% and 48%, respectively, compared to 32% for pravastatin and 38% for simvastatin.³¹

Safety. A review of phase 2 and phase 3 trials suggests that rosuvastatin has an excellent safety profile. Analysis of data from rosuvastatin-treated patients representing over 3000 patient-years of continuous drug exposure found a similar incidence of adverse reactions (55%) with rosuvastatin and placebo (53.3%). The most commonly

Figure 2. LDL-C Reductions—Rosuvastatin vs Pravastatin vs Simvastatin at Week 12



LDL-C indicates low-density lipoprotein cholesterol.
Source: Reference 30.

reported adverse events were constipation (1%), diarrhea (2%), dyspepsia (1%), and abdominal pain (1.5%). Clinically significant increases in alanine aminotransferase, defined as an increase of >3 times the upper limit of normal on 2 occasions 4 to 10 days apart, occurred in 0.5% of patients. Myositis, defined as creatine kinase elevation of >10 times the upper limit of normal accompanied by muscle symptoms, occurred in 0.2% of patients all of whom were on the 80-mg dose of rosuvastatin. These data indicate that these adverse events are similar to those associated with currently available statins.²⁸

Future Studies. A comprehensive, long-term, and evolving global research initiative called the GALAXY program will investigate the impact of rosuvastatin on the reduction of cardiovascular risk and improving patient outcomes. The GALAXY program is slated to include at least 16 studies involving more than 80 000 subjects with high, moderate, and low risk of CHD in more than 30 countries. Currently, 10 ongoing studies have enrolled more than 9000 subjects in 20 countries.³⁸

Niacin

Niacin (nicotinic acid) is a safe, effective, low-cost, lipid-lowering therapy that has

been used to treat dyslipidemia since 1955. Niacin inhibits the mobilization of free fatty acids from peripheral tissues, reducing hepatic synthesis of triglyceride and secretion of VLDL-C and inhibiting conversion of VLDL-C to LDL-C. The expected maximum reduction in LDL-C and VLDL-C concentrations is 30% and 40%, respectively. Niacin also increases serum HDL-C levels by up to 30%, surpassing all other drugs in this regard.

The most common adverse reactions associated with niacin result from prostaglandin-mediated vasodilation and include flushing, tingling, itching, rash, and headaches. Although these adverse events cannot be completely avoided, they can be minimized by slowly titrating the daily dose upward or with pretreatment using aspirin or nonsteroidal anti-inflammatory drugs. Gastrointestinal adverse reactions, such as dyspepsia, diarrhea, flatulence, and nausea, are also seen with niacin. At high doses of sustained-release niacin (>2 g daily), elevations in hepatic enzymes and uric acid can occur, although this phenomenon is not observed with high doses (up to 6 g daily) of the immediate-release formulation of niacin. Impaired glucose tolerance has been associated with niacin therapy. However, treatment with niacin has been shown to be an appropriate treatment option for patients with diabetes. A recently published 16-week, placebo-controlled study randomized patients with diabetes into 2 groups: one receiving 1000 or 1500 mg daily of extended-release niacin and the other, placebo. In addition to noting dose-dependent increases in HDL-C and reductions in triglyceride levels, hemoglobin A_{1c} levels were unchanged by niacin therapy compared to placebo. The authors concluded that low-dose extended-release niacin therapy was a safe and effective treatment for patients with type 2 diabetes.³⁹

The extended-release form of niacin does not appear to cause the hepatotoxicity associated with previous sustained-release forms of the drug. Niacin can be dosed once, or, more commonly, twice daily. However, flushing can still be a bothersome side effect with this product. At the maximum recommended dose of 2 g daily, extended-release

niacin reduces LDL-C levels by 16.7%, triglyceride levels by 34.5%, and raises HDL-C levels by 25.8%.

A new fixed-dose combination of lovastatin and extended-release niacin recently became available in the US market. This medication is indicated for use as a replacement for lovastatin monotherapy when patients require additional reductions in triglyceride or elevations in HDL-C are needed and as a replacement for niacin monotherapy when additional LDL-C reductions are required. The product is available as a combination of 500, 750, and 1000 mg of niacin with 20 mg of lovastatin. Results of a forced titration study indicate that the 1000/20-mg combination of the 2 agents reduced LDL-C levels by 32% and triglyceride levels by 32%, while increasing HDL-C levels by 30%.⁴⁰

Fibrates

Fibrates (fibric acid derivatives) gemfibrozil and fenofibrate possess minimal LDL-C reducing capacity, but are especially effective in patients who have severe hypertriglyceridemia and low HDL-C levels. Fibrates are also useful in patients with combined forms of hyperlipidemia. Although the mechanism by which fibrates reduce triglycerides is poorly understood, it is believed 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 as these drugs appear to be additive in lowering LDL-C levels and triglycerides and raising HDL-C levels. When fibrates are given in combination with a bile acid sequestrant, the administration of the 2 drugs must be separated by at least 2 hours to ensure full bioavailability of the fibrates. Combinations of fibrates with statins are very effective in lowering LDL-C levels and increasing HDL-C levels, particularly in patients with mixed hyperlipidemia characterized by elevated triglyceride and LDL-C levels. Combinations

of statins and fibrates have been historically limited by the increased risk for myopathy. This is particularly true for the combination of a statin and gemfibrozil. This risk appears to be minimized by substituting one of the newer fibrates, fenofibrate, for gemfibrozil. When the choice is made to use a statin and fibrates in combination, these drugs should be used only in the lowest effective doses and only used in patients who have normal liver and kidney function.

Bile Acid Sequestrants

Bile acid sequestrants, or resins, are now used primarily as adjuncts to statins or niacin. The resins bind to bile acids in the intestine, impeding their reabsorption. The interruption of the enterohepatic bile circulation causes the liver to convert more of the hepatic cholesterol pool into bile acids. It also stimulates cholesterol synthesis, resulting in increased VLDL-C production. Reduction in hepatic cholesterol pools results in an up-regulation of hepatic LDL-C receptors and increased LDL-C clearance from the circulation. Bile acid sequestrants reduce LDL-C levels by 15%-27%. When used in combination with a statin, additional lowering of LDL-C levels of 9%-16% can be seen with as little as 4 g twice daily. Caution should be used when treating patients who have mixed hyperlipidemias, as bile acid sequestrants can increase triglyceride levels by 7%.

Currently available bile acid sequestrants include cholestyramine and colestipol, which are both supplied as powdered products that require mixing with juices or food to make them more palatable. The most common adverse reactions are gastrointestinal effects, including abdominal pain, belching, bloating, constipation, gas, heartburn, and nausea. These resins should be administered 2 hours before or 6 hours after warfarin, theophylline, digoxin, and levothyroxine. Colesevelam is a new bile acid binding resin available in tablet form. Compliance may be improved with this formulation, and no drug interactions have been noted between colesevelam and the agents known to interact with cholestyramine and colestipol, which are listed above.

Cholesterol-Absorption Inhibitors

A new class of cholesterol-lowering agents, the selective cholesterol-absorption inhibitors, recently entered the market. Ezetimibe, the first agent available in this class, reduces plasma cholesterol by selectively inhibiting the absorption of dietary and biliary cholesterol from the intestine. Ezetimibe appears to specifically inhibit free cholesterol uptake into the intestinal enterocyte by interacting with a cholesterol transporter, however its exact mechanism of action remains to be elucidated.⁴¹ Treatment of 820 patients who have hypercholesterolemia with 10 mg daily of ezetimibe reduced LDL-C levels by 18%, elicited a 12% decrease in TC levels, a 4% decrease in triglyceride levels, and a 1% increase in HDL-C levels. 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, α -carotene, and β -carotene. The most common side effects in both the active treatment and placebo groups were headache, upper respiratory tract infections, and back pain, although the back pain was not believed to be related to either ezetimibe or placebo.⁴²

The combination of ezetimibe and a low-dose statin inhibit both the endogenous and exogenous production of cholesterol. Subjects with hypercholesterolemia treated with simvastatin 10 mg daily for 14 days achieved a 35% reduction in LDL-C levels, while those treated with simvastatin 10 mg plus ezetimibe 10 mg achieved a reduction of 52%, which is a decrease expected from the much higher simvastatin dose of 80 mg.⁴³ 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.

Economic Benefits of Cholesterol-Lowering Therapy

Reductions in cardiovascular morbidity and mortality are obvious benefits of cholesterol-lowering therapy. However these bene-

fits come at a cost. Currently, agents used for the management of dyslipidemia account for approximately 7% of per-patient-per-month drug costs in managed care plans. In 2000, statins were ranked third in overall expenditures by therapeutic category as they accounted for more than \$8 billion in sales and 6.2% of pharmaceutical utilization. Three of the top 15 drugs prescribed in 2000 were statins. In an environment of escalating pharmacy and medical costs, rigorous economic analyses are needed to demonstrate the impact of statins on total medical costs and their cost effectiveness.

Using data from the WOSCOP study, Shepard et al⁷ analyzed the economic impact of pravastatin-associated reductions in coronary events. In the primary prevention population studied in WOSCOPS, statin therapy was calculated to prevent 318 events per 10 000 patients at a discounted cost per life-year gained of \$31 818. The ATP III guidelines also provide an estimate of the cost effectiveness of lipid-lowering drugs based on cost of therapy and estimated risk of CHD. Estimates of cost effectiveness per quality-adjusted life-year ranged from \$1250 to \$200 000 (Table 10). Cost effectiveness declined as the cost of drug therapy increased or the risk for CHD decreased. Additional studies are needed that demonstrate the cost effectiveness of lipid-lowering drugs in specific populations, such as primary prevention of patients with low risk, women, patients with diabetes, and minorities.

Detection and Treatment of Dyslipidemia

Despite the known benefits of cholesterol reduction, the medical community has failed to identify and appropriately treat many patients who require lipid-modification therapy. Despite the availability and widespread use of pharmacologic agents, patients frequently fail to achieve target lipid levels and gain the clinical and economic benefits of CHD risk reduction. This can be attributed to a number of factors, including inadequate patient identification, ineffective evaluation, and suboptimal treatment.⁴⁴

The ATP III guidelines estimate that 33% of adult Americans require cholesterol-low-

Table 10. Dependence of Cost Effectiveness on Cost of LDL-Lowering Drugs

Estimated Cost Effectiveness of LDL-Lowering Therapy—Costs per QALY Gained—at Different Cost of LDL-Lowering Drugs				
10-Year Risk (%)	\$1000 Yr	\$500 Yr	\$250 Yr	\$125 Yr
35	10 000	5000	2500	1250
25	25 000	12 500	6250	3125
15	50 000	25 000	12 500	6250
10	100 000	50 000	25 000	12 500
5	200 000	100 000	50 000	25 000

LDL indicates low-density lipoprotein; QALY, quality-adjusted life-years.

Source: Reference 1.

ering therapy. In addition, 18% of adult Americans have cholesterol levels sufficiently high to warrant drug therapy.¹ However, the National Health and Nutrition Examination Survey III (NHANES III) found that only 65% of all people who should be undergoing cholesterol-lowering therapy actually receive treatment.⁴⁵ National estimates indicate that 20%-25% of patients with CHD are on therapy and less than 33% of primary prevention patients needing therapy are receiving it. In addition, of those patients on cholesterol-reducing therapy, <10% are at goal. In response to these findings, the American Heart Association has established a nationwide program designed to increase the detection and treatment of lipid disorders. Objectives of the program include increasing detection and appropriate referrals, raising public consciousness, providing information about cholesterol management, and reaching patients who might not receive cholesterol screening as part of their routine healthcare. This program, and the NCQA HEDIS performance measures, the ATP III guidelines, and other national, regional, and local initiatives, are all designed to increase the detection and appropriate treatment of lipid disorders to reduce the risk of CHD in Americans.

Even when diagnosed, dyslipidemia often goes untreated or the condition is undertreated. A review of 4888 patients who

received a lipid-lowering agent for 3 months determined that LDL-C goal was reached in 68% of patients with <2 risk factors and no CHD, in 37% of patients with 2 or more risk factors and no CHD, and in only 18% of patients with known CHD.⁴⁴ A second study of 1252 patients in a secondary prevention population found that 57% continued to have an LDL-C above 130 mg/dL. Surprisingly, 13% of these CHD patients had undiagnosed dyslipidemia.⁴⁶

Appropriate treatment and LDL-C goal achievement have been shown to be elusive in the managed care setting. One study conducted in a managed care primary care setting identified 358 patients who had been screened for cholesterol, 68 of whom had documented CHD and were therefore eligible for the most aggressive therapy. In the CHD group, only 19.6% of patients with LDL-C greater than 130 mg/dL received therapy. In the non-CHD group, the percentage was approximately 10%.⁴⁷ Similar results were reported by a study conducted in a Veterans Affairs medical center population. These authors report that only 36.2% of patients with CHD risk factors and 35.4% of patients with known CHD had reached goal cholesterol levels while on drug therapy.⁴⁸ An earlier Veterans Affairs study evaluated 90 patients (73% with documented CHD) who had been on a single cholesterol-lowering drug for at least 1 year. Only 33% of all

patients, and 24% of secondary prevention patients, were at NCEP goal LDL-C levels.⁴⁹

Treatment: The Impact of Suboptimally Controlled Patients

The impact of suboptimal cholesterol control and noncompliance was analyzed using WOSCOPS data.⁵⁰ Patients who had a greater than 75% compliance rate in taking active drug had a 33% lower risk for CHD death compared to those with a compliance

rate of less than 75%. Reductions in all-cause mortality, MI, and revascularization procedures were also seen in compliant patients. The relationship between compliance to therapy and clinical outcomes was also studied in the Coronary Disease Project-Niacin Study. This study identified a 10% difference in fatal and nonfatal events in compliant patients. Similarly, patients who were >75% compliant with their therapy in the β -Blocker Heart Attack Trial demonstrated a 2% lower mortality rate compared to their less compliant peers.⁵¹ A third small study of 41 non-CHD patients assigned to a specialty cholesterol clinic demonstrated that patients with compliance rates of >75% resulted in greater LDL-C reductions (26% vs 6%), and attainment of LDL-C goals.⁵² Data from these small studies suggest that failure to identify and appropriately treat patients with lipid disorders often results in a forfeiture of the clinical and economic benefits, which could be achieved with proper lipid therapy.

Poor Compliance: A Significant Barrier to Appropriate Therapy

Despite appropriate screening, diagnoses, and therapeutic recommendations, attainment of goal cholesterol levels can remain elusive. Studies have shown that one of the major impediments to achieving target goals is inappropriate compliance. Reasons for noncompliance are listed in **Table 11**.⁵³ Patients discontinue medications because of cost, fear of adverse reactions, denial, or the feeling that the condition has been cured or sufficiently improved. Identifying the reason for inappropriate compliance is a key step in correcting this problem.

A number of investigators have studied discontinuation rates of lipid-lowering agents. One study reviewed 12 months of prescription-dispensing data collected on 610 patients receiving cholesterol-lowering drugs. Sixty percent of the patients discontinued their drug within 1 year, 50% within 3 months, and 25% within 1 month. Patients indicated that the reasons for their discontinuation of the drug included the perception that the drug was not needed any longer (32%), poor efficacy (32%), and adverse

Table 11. Reasons for Patient Noncompliance With Drug Therapy

Noncompliant Behavior	Reasons Cited
Refusal to take medication	<ul style="list-style-type: none"> ■ Patient not convinced of need for drug ■ Fear of adverse effects ■ Acquisition expense ■ Dislike of taking drugs
Discontinuation	<ul style="list-style-type: none"> ■ Patient not convinced of the drug's benefit ■ Intolerance of side effects ■ Patient cannot remember to take the drug ■ Drug is too expensive ■ Perception that health problem has been fixed
Reducing dosage	<ul style="list-style-type: none"> ■ Patient not convinced of the drug's benefit ■ Intolerant to side effects ■ Drug is too expensive
Increasing dosage	<ul style="list-style-type: none"> ■ Perception that more is better ■ Perception that the drug makes the patient feel good ■ To hurry the cure or treatment process
Drug holiday	<ul style="list-style-type: none"> ■ Patient not convinced of the drug's benefit ■ To achieve some sort of effect perceived as enjoyable ■ To accommodate a transient life event ■ Perception that the drug interferes with certain events ■ Inability to remember
White-coat compliance	<ul style="list-style-type: none"> ■ Patient not convinced of the drug's benefit ■ To procure approval from the clinician or avoid rebuke

Source: Reference 53.

reactions (7%). Only 50% of patients who discontinued because of poor efficacy received a second drug.⁵⁴ Similar discontinuation rates were reported in managed care populations by Sung et al⁵⁵ (37% in 3 months) and Andrade et al⁵⁶ (32% in 6 months). Andrade et al also evaluated the discordance between discontinuation rates of various lipid-lowering agents reported in clinical trials and those observed in 2369 managed care patients. This study found higher rates of discontinuation with bile acid sequestrants, niacin, and gemfibrozil in the health maintenance organization setting. However, rates of discontinuation with HMG-CoA reductase inhibitors were similar between clinical trials and real-world practice.⁵⁷ A study of nearly 8000 American and Canadian patients found that maintenance lipid-lowering prescriptions were filled 40% of the time over a 1-year period, with 52% of these patients continuing to fill their prescriptions after 5 years. Persistence was better in patients when statins versus cholestyramine were prescribed for lipid lowering.⁵⁸

Interventions to Improve Compliance and Outcomes

A number of strategies have been demonstrated to improve compliance to drug therapy. Successful interventions include the following elements identified in **Table 12**.¹ Both healthcare providers and patients require training on strategies to improve drug compliance. Reviews of interventional trials aimed at improving healthcare performance reveal that healthcare professionals are particularly receptive to academic detailing by experts or opinion leaders and by individual patient-mediated strategies, such as chart reminders. Programs that use only a single intervention experience a lower success rate than those that implement >1 strategy. Programs incorporating 3 different interventions were the most successful. The most successful programs for individual patients employ a multidisciplinary team that provides patient education supported by written or audiovisual aids, encourage multiple clinic visits, and regularly follow-up by phone.

Telephone-based patient interventions have produced favorable results. In a secondary prevention study, dietitians called or sent postcards in an effort to improve the percentage of patients achieving their LDL-C goal of either <100 mg/dL or <130 mg/dL. At baseline, 34% and 66% of patients had LDL-C levels of <100 mg/dL and less than 130 mg/dL, respectively. After 2 years, the program had increased these percentages to 61% and 89%. Mean LDL-C levels declined by 38%, and statin use had increased from 47% to 85%.⁵⁹

Two nurse-managed programs demonstrated significant increases in the number of patients screened for dyslipidemia, achieved reductions in LDL-C levels, and reached lipid target goals. The first study involved 140 patients with CHD.⁶⁰ At the end of 1 year of prospective management, 97% of the patients had been screened for LDL-C levels, 100% were on treatment if needed, and 71% had reached LDL-C goal. In comparison, NCQA data collected from several similar health plans during the same time period indicated that only 44% of patients with known CHD had been screened for lipid abnormalities and only 11% of the screened patients were at their target goal.⁶⁰ Another study compared nurse-managed lipid outcomes versus management by primary care physicians who had received

Table 12. Strategies to Improve Compliance to Drug Therapy

- Convey a clear need for the drug
- Provide both verbal and written instructions
- Tailor regimen to the patient's needs when possible
- Ask patients frequently about adherence
- Consider cost of medications being prescribed
- Foster a provider-patient partnership in drug therapy management
- Provide regular follow-up contact
- Provide cognitive aids concerning the drug and medical condition

Source: Reference 1.

training on the national guidelines.⁶¹ Goal LDL-C level was either 130 mg/dL or 160 mg/dL, depending on patient risk factors. By the conclusion of the 2-year study, 26% of nurse-managed patients met goal versus 10% for enhanced physician care. Greater reductions in mean LDL-C level and increases in the number of patients receiving appropriate drug therapy were noted with the nurse-managed patients.⁶¹

Kaiser Permanente of Ohio produced dramatic increases in LDL-C goal achievement by instituting computer-generated chart reminders for patients with CHD. At the completion of the study, the percentage of patients with CHD at goal LDL-C (<100 mg/dL) had risen from 10%-36%.⁶²

The Role of Pharmacists in the Treatment of Dyslipidemia and CHD

Pharmacists often have more frequent contact with patients compared with other healthcare professionals. Numerous studies have demonstrated pharmacy-based intervention programs have improved patient outcomes in hypertension, asthma, diabetes, congestive heart failure, and other conditions. More specifically, several studies have also documented improved outcomes in cholesterol management with pharmacist interventions. A randomized, controlled clinical trial involving 675 patients conducted in 54 community Canadian pharmacies demonstrated the benefits of pharmacist-physician collaboration. The study found that 57% of patients randomized to the collaborative monitoring and follow-up group received a cholesterol screening and the appropriate cholesterol-lowering medication compared with 31% of those randomized to usual care.⁶³ Another study reported that 12 weeks of postsurgical intervention in revascularization patients increased compliance and lipid reductions over a 2-year period.⁶⁴ O'Donnell et al⁶⁵ reported that pharmacist-coordinated lipid clinics improved cholesterol management and cholesterol goal attainment. However, this study also noted that 39% of successful patients failed to maintain goal cholesterol levels after discharge from the clinic, demonstrating the need for continued intervention.⁶⁵

Conclusion

CHD is the leading cause of morbidity and mortality in the United States. A direct relationship has been demonstrated between elevated cholesterol and CHD morbidity and mortality. Appropriate treatment that results in decreased LDL-C levels has been clearly shown to decrease CHD risk and improve clinical and economic outcomes. The new ATP III guidelines and HEDIS performance measures place added emphasis on risk factor screening and lipid control. Achievement of these objectives will require appropriate lipid-modification therapy. In addition, lipid-lowering drug therapy has been shown to be cost effective. Despite this emphasis and the availability of a growing number of safe and effective drugs that favorably modify the lipid profile, dyslipidemia remains underidentified and undertreated in millions of Americans. A multidisciplinary effort is needed to improve this situation. Physicians, nurses, and pharmacists all play an important role in these efforts.

REFERENCES

- 1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.** Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
- 2. National Committee on Quality Assurance.** Cholesterol Management and Screening Control. Available at: http://www.ncqa.org/somc2001/CHOLESTEROL/SOMC_2001_CHM.html. Accessed November 10, 2002.
- 3. American Heart Association.** 2002 Heart and Stroke Statistical Update. Dallas, Texas: American Heart Association; 2001.
- 4. Castelli WP.** Epidemiology of coronary heart disease: The Framingham Study. *Am J Med*. 1984;76:4-12.
- 5. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD.** Cholesterol reduction yields clinical benefit: impact of statin trials. *Circulation*. 1998;97:946-952.
- 6. American Heart Association.** Biostatistical fact sheet—risk factors; high blood cholesterol and other lipids. Available at: <http://www.americanheart.org/downloadable/heart1017696825613chollip.pdf>. Accessed November 7, 2002.
- 7. Shepard J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group.** Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307.

8. **Downs JR, Clearfield M, Weis S, et al, for the AFCAPS/TexCAPS Research Group.** Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA*. 1998;279:1615-1622.
9. **Scandinavian Simvastatin Survival Study Group.** Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.
10. **Sacks FM, Pfeffer MA, Moye LA, et al.** The effects of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001-1009.
11. **The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group.** Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349-1357.
12. **Heart Protection Study Collaborative Group.** MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.
13. **Frick MH, Elo O, Haapa K, et al.** Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237-1245.
14. **Pedersen TR, Olsson AG, Færgeman O, et al.** Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation*. 1998;97:1453-1460.
15. **Brown WV.** Cholesterol lowering in atherosclerosis. *Am J Cardiol*. 2000;24;86(4B):29H-32H.
16. **Pitt B, Waters D, Brown WV, et al.** Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus revascularization treatment investigators. *N Engl J Med*. 1999;341:70-76.
17. **Schwartz GG, Olsson AG, Ezekowitz MD, et al.** Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285:1711-1718.
18. **Davidson M, Ma P, Stein E, et al.** Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *Am J Cardiol*. 2002;89:268-275.
19. **Knopp RH.** Drug treatment of lipid disorders. *N Engl J Med*. 1999;341:498-511.
20. **Hsu I, Spinler SA, Johnson NE.** Comparative evaluation of the safety and efficacy of HMG-CoA reductase inhibitor monotherapy in the treatment of primary hypercholesterolemia. *Ann Pharmacother*. 1995;29:743-759.
21. **Cressman MD, Hooquewerf BJ, Moodie DS, Loin JW, Weinstein CE.** HMG-CoA reductase inhibitors. A new approach to the management of hypercholesterolemia. *Clev Clin J Med*. 1988;55:93-100.
22. **Pasternak RC, Smith S, Bairey-Merz CN, et al.** ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation*. 2002;106:1024-1028.
23. **Bradford RH, Shear CL, Chremos AN, et al.** Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. *Arch Intern Med*. 1991;151:43-49.
24. **Illingworth DR, Tobert JA.** A review of clinical trials comparing HMG-CoA reductase inhibitors. *Clin Ther*. 1994;16:366-385.
25. **Pierce LR, Wysowski DK, Gross TP.** Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. *JAMA*. 1990;264:14-17.
26. **Simonson SG, Martin PD, Mitchell PD, et al.** Pharmacokinetics and pharmacodynamics of rosuvastatin in hepatically impaired subjects [abstract]. *Clin Pharmacol Ther*. 2001;69:P86. Abstract PIII-88.
27. **Martin PD, Dane AL, Schneck DW, et al.** Disposition of new HMG-CoA reductase inhibitor ZD4522 following dosing in healthy subjects [abstract]. *J Clin Pharmacol*. 2000;40:1056. Abstract 48.
28. **Chong PH, Yim BT.** Rosuvastatin for the treatment of patients with hypercholesterolemia. *Ann Pharmacother*. 2002;36:93-101.
29. **Olsson A, Southworth H, Wilpshaar JW.** Long-term efficacy and safety of rosuvastatin: results of a 52-week comparator-controlled trial versus atorvastatin. *Eur Heart J*. 2001;22(suppl):253. Abstract 1410.
30. **Paoletti R, Fahmy M, Mahla G, Mizan J, Southworth H.** Rosuvastatin demonstrates greater reduction of low-density lipoprotein cholesterol compared with pravastatin and simvastatin in hypercholesterolaemic patients: a randomized, double-blind study. *J Cardiovas Risk*. 2001;8:383-390.
31. **Brown WV, Chitra RR, Zedler BK, Bays HE, Hassman H.** Long-term efficacy and safety of rosuvastatin: results of a 52-week comparator-controlled trial versus pravastatin and simvastatin [abstract]. *Eur Heart J*. 2001;22(suppl):270.
32. **Morgan JM, Cressman MD, Hutchinson HG, Capuzzi DM.** Beneficial effects of combination therapy with rosuvastatin and extended-release niacin in patients with mixed dyslipidemia [abstract]. Presented at: International Symposium on Drugs Affecting Lipid Metabolism (DALM); September 9-13, 2001; New York, NY.
33. **Ballantyne C, Miller E, Chitra R.** Rosuvastatin alone produces similar lipid benefits compared with rosuvastatin plus cholestyramine in patients with primary hypercholesterolemia. Paper presented at: International Symposium on Drugs Affecting Lipid Metabolism (DALM); September 9-13, 2001; New York, NY.
34. **Durrington P, Hamann A, Tuomilehto J, Smith K, Kallend D.** Rosuvastatin alone and in combination with fenofibrate in hyperlipidaemic patients with type 2 diabetes. *Diabetologia*. 2001;44(suppl 1):A165. Abstract 631.
35. **Hunninghake DB, Chitra RR, Simonson SG, Schneck DW.** Effects of rosuvastatin on serum lipids and lipid subfractions in patients with hypertriglyceridemia [abstract]. Presented at: International Symposium on Drugs Affecting Lipid Metabolism (DALM); September 9-13, 2001; New York, NY.
36. **Stein E, Strutt KL, Miller E, Southworth H, for the HEFH Study Group.** ZD4522 is superior to atorvastatin in the treatment of patients with heterozygous familial hypercholesterolemia [abstract]. *J Am Coll Cardiol*. 2001;37(suppl A):292A. Abstract 1261-176.
37. **Knopp RH, Ballantyne CM, McPherson R, et al.** Comparing rosuvastatin and atorvastatin across their dose ranges in patients with hypercholesterolemia [abstract]. *Eur Heart J*. 2002;4(suppl):19.

- 38. Rosuvastatin Outcomes Program.** Presented at: Annual Congress of the European Society of Cardiology Meeting (ESC); August 31-September 4, 2002, Berlin, Germany.
- 39. Grundy SM, Vega GL, McGovern ME, et al.** Diabetes Multicenter Research Group. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type-2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. *Arch Intern Med.* 2002;162:1568-1576.
- 40. Advicor [package insert].** Miami, FL: Kos Pharmaceuticals, Inc; 2002. Available at: <http://www.advicor.com/hcp.html>. Accessed November 7, 2002.
- 41. van Heek M, Farley C, Compton DS, et al.** Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235 and its glucuronide, SCH60663. *Br J Pharmacol.* 2000;129:1748-1754.
- 42. Knopp RH, Gitter H, Truitt T, et al.** Ezetimibe reduces low-density lipoprotein cholesterol: results of a phase III randomized, double blind, placebo-controlled trial [abstract]. *Atherosclerosis.* 2001;2:38.
- 43. Kosoglou T, Meyer I, Musiol B, et al.** Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor SCH 58235 and simvastatin [abstract]. *Atherosclerosis.* 2000;151:135.
- 44. Pearson TA, Laurora I, Chu H, Kafonek S.** The Lipid Treatment Assessment Project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med.* 2000;160:459-467.
- 45. Hoerger TJ, Bala MV, Bray JW, et al.** Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment eligible United States adults. *Am J Cardiol.* 1998;82:61-65.
- 46. Qureshi AI, Suri MFK, Guterman LR, Hopkins LN.** Ineffective secondary prevention in survivors of cardiovascular events in the US population. Report from the Third National Health and Nutrition Examination Survey. *Arch Intern Med.* 2001;161:1621-1628.
- 47. Lai LL, Poblet M, Bello C.** Are patients with hyperlipidemia being treated? Investigation of cholesterol treatment practices in an HMO primary care setting. *South Med J.* 2000;93:283-286.
- 48. Williams ML, Morris MT II, Ahmad U, Yousseff M, Li W, Ertel N.** Racial differences in compliance with NCEP-II recommendations for secondary prevention at a Veterans Affairs medical center. *Ethnic Dis.* 2002;12: S58-S62.
- 49. Marcelino JJ, Feingold KR.** Inadequate treatment with HMG-CoA reductase inhibitors by health care providers. *Am J Med.* 1996;100:605-610.
- 50. Caro J, Klittich W, McGuire A, et al.** The West of Scotland Coronary Prevention Study: economic benefit analysis of primary prevention with pravastatin. *BMJ.* 1997;315:1577-1582.
- 51. B-blocker Heart Attack Study Group.** A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA.* 1982;247:1707-1714.
- 52. Horwitz RI, Horwitz SM.** Adherence to treatment and health outcomes. *Arch Intern Med.* 1993;153:1863-1868.
- 53. LaRosa JH, LaRosa JC.** Enhancing drug compliance in lipid-lowering treatment. *Arch Fam Med.* 2000;9:1169-1175.
- 54. Simons LA, Lewis G, Simons J.** Apparent discontinuation rates in patients prescribed lipid-lowering drugs. *Med J Aust.* 1996;164:208-211.
- 55. Sung JCY, Nichol MB, Venturini F, Bailey KL, McCombs JS, Cody M.** Factors affecting patient compliance with antihyperlipidemic medications in an HMO population. *Am J Manag Care.* 1998;4:1421-1430.
- 56. Andrade SE, Walker AM, Gottlieb LK, et al.** Discontinuation of antihyperlipidemic drugs: do rates reported in clinical trials reflect rates in primary care settings? *N Engl J Med.* 1999;333:1125-1131.
- 57. Andrade SE, Saperia GM, Berger ML, Platt R.** Effectiveness of antihyperlipidemic drug management in clinical practice. *Clin Ther.* 1999;21:1973-1987.
- 58. Avorn J, Monette J, Lacour A, et al.** Persistence of use of lipid-lowering medications. A cross-national study. *JAMA.* 1998;279:1458-1462.
- 59. Robinson JG, Conroy C, Wickemeyer WJ.** A novel telephone-based system for management of secondary prevention to a low-density lipoprotein cholesterol < 100 mg/dL. *Am J Cardiol.* 2000;85:305-308.
- 60. Brown AS, Cofer LA.** Lipid management in a private cardiologist practice (the Midwest heart experience). *Am J Cardiol.* 2000;85(suppl):18A-22A.
- 61. Becker DM, Raqueno JV, Yook RM, et al.** Nurse-mediated cholesterol management compared with enhanced primary care in siblings of individuals with premature coronary disease. *Arch Intern Med.* 1998;158:1533-1539.
- 62. The Kaiser Foundation Health Plan and the Permanente Medical Group of Ohio.** Improvement of cardiac outcomes in Kaiser Permanente of Ohio. *Permanente J* [serial online]. Spring 2000;4(2). Available at: <http://www.kaiserpermanente.org/medicine/permjournal/spring00pj/cad.html>. Accessed September 3, 2002.
- 63. Tsuyuki RT, Johnson JA, Teo KK, et al.** A randomized trial of the effect of community pharmacist intervention on cholesterol risk management: the Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP). *Arch Intern Med.* 2002;162:1149-1155.
- 64. Faulkner MA, Wadibia EC, Lucus BD, Hilleman DE.** Impact of pharmacy counseling on compliance and effectiveness of combination lipid-lowering therapy in patients undergoing coronary artery revascularization, a randomized controlled clinical trial. *Pharmacotherapy.* 2000;20:410-416.
- 65. O'Donnell DC, Chen WT, Piziak VK.** Goal attainment and maintenance of serum cholesterol level in a pharmacist-coordinated lipid clinic. *Am J Health Syst Pharm.* 2001;58:325-330.

