Dear Healthcare Professional,

Welcome to the Cleveland Clinic Physician’s Guide to Cardiovascular Disease Prevention. This informative publication is part of the Cleveland Clinic Center for Continuing Education’s Disease Management Project, and is brought to you in collaboration with Bulletin Healthcare, the leading provider of medical news updates to healthcare professionals like yourself.

This publication, which pays special attention to cardiovascular disease risk assessment and lipid-lowering strategies, is just the beginning. Over the coming months, you also will receive valuable news updates on a range of cardiovascular issues from Bulletin Healthcare’s team of expert researchers.

We hope you will find this publication and the ongoing series of news updates both useful and educational, and we look forward to learning your thoughts about them. Just email us at mycme@ccf.org.

To good health!

William Carey, MD
Director
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Introduction

Observational studies over many decades have shown a close, direct relationship between dyslipidemia and coronary heart disease risk.\textsuperscript{1-3} Intervention trial data collected over the past 2 to 3 decades also have demonstrated that cholesterol modification, especially statin therapy (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor therapy) and its resulting reduction in low-density lipoprotein cholesterol (LDL-C) levels, is associated with favorable effects on reduction in coronary heart disease (CHD) events, especially in patients at high risk for CHD or those who already have manifested CHD.\textsuperscript{4-26}

While treatment with fibrate, niacin, or ezetimibe therapy may also result in favorable effects on the lipid profile, trials of these medications have not produced the same robust results in CHD risk reduction. The cholesterol-lowering guidelines therefore retain LDL-C as the primary target for lipid modification and statin therapy as the primary means of achieving LDL-C goals.

In 1988, the first National Cholesterol Education Program (NCEP) was begun in an effort to establish targets for cholesterol levels based on assessments of risk.\textsuperscript{27} (These guidelines were written by a panel of experts and, in subsequent publications, have been referred to as the Adult Treatment Panel [ATP], and revised as ATP II and ATP III). The NCEP guidelines were evidence based, used CHD risk assessment for the recommended LDL-C targets, and were relatively simple for healthcare providers, patients, and payers to understand.

Over the past 2 decades, the NCEP guidelines have changed in terms of lipid targets based on information obtained from clinical trials and observational studies.\textsuperscript{28-33} These guidelines have been supported by other organizations, including the American Heart Association (AHA), American College of Cardiology (ACC), American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), and American College of Physicians (ACP).\textsuperscript{34-39}

This chapter reviews the history of the guidelines, how new information has resulted in changing targets, and current approaches to CHD risk assessment. Finally, it gives a summary of approaches to lowering cholesterol.

History

The Lipid Research Clinic Coronary Primary Prevention Trial\textsuperscript{20,21} was the first large-scale, randomized, double blind, placebo-controlled clinical trial of LDL-C lowering in high-risk men aged 30-59. At baseline, LDL-C levels were typically in the 175- to 190-mg/dL range. LDL-C values in the cholestyramine-treated subjects approached the 130-mg/dL range. This trial was the foundation for the first set of NCEP guidelines published in 1988, which proposed that patients with and without CHD who had 2 or more risk factors for CHD have an LDL-C target of 130 mg/dL or lower. Lower-risk patients with fewer risk factors had correspondingly higher LDL-C targets.

The second set of NCEP guidelines, published in 1993, lowered the goal LDL-C to ≤100 mg/dL in patients with known CHD.\textsuperscript{31} Over the following years, a number of clinical end point cholesterol trials in both high-risk primary prevention (no prior known CHD) and secondary prevention (with known CHD) were carried out across a wide range of entry LDL-C levels.

In 2001, NCEP released the third set of guidelines, ATP III,\textsuperscript{32} incorporating the results of randomized, controlled clinical trials into recommendations for the management of high cholesterol levels. Since the publication of the ATP III, several additional clinical trials of statin cholesterol-lowering therapy were published, leading to updates in 2004 and 2006 suggesting a reset of treatment thresholds and targets.\textsuperscript{30}
In contrast to ATP I and II, ATP III placed greater emphasis on the prevention of CHD in patients with multiple risk factors, in addition to treatment for secondary prevention. The ATP III treatment algorithm divided patients into 3 risk categories based on clinical characteristics and the Framingham 10-year risk score:

1. Established CHD and CHD risk equivalents: High risk (10-year risk > 20%)
2. Multiple (2 or more) risk factors: Moderately high risk (10-year risk, 10% to 20%); moderate risk (10-year risk < 10%)
3. Zero to 1 (1 or none) risk factor: Lower risk (10-year risk < 10%)

ATP III greatly expanded the high-risk category by defining CHD “risk equivalents,” including noncoronary atherosclerotic disease, such as peripheral vascular and carotid disease, and abdominal aortic aneurysm; diabetes mellitus; and multiple CHD risk factors conferring an estimated 10-year risk for a cardiovascular event of > 20%.

ATP III major risk factors include the following:

- Age (men, 45 years; women, 55 years)
- Cigarette smoking
- Hypertension (blood pressure = 140/90 mmHg or patient is on antihypertensive medications)
- Low high-density lipoprotein (HDL) cholesterol level (< 40 mg/dL in men, < 50 mg/dL in women; HDL cholesterol ≥ 60 mg/dL is a negative risk factor)
- Family history of premature CHD: Male first-degree relative younger than 55 years or female first-degree relative younger than 65 years

According to the ATP III, the LDL-C goal for high-risk patients is < 100 mg/dL. For all patients in the high-risk category with LDL-C > 100 mg/dL, LDL-C-lowering dietary therapy should be initiated. In addition, for patients with LDL-C > 130 mg/dL, an LDL-C-lowering drug should be started. However, in the LDL-C range of 100 to 129 mg/dL, ATP III guidelines did not mandate drug therapy; rather, therapeutic options included intensified dietary therapy, LDL-C-lowering drugs, or drug therapy for elevated triglyceride or low HDL-C levels. At the time of publication of the guidelines for ATP III, there were not enough data to recommend more intensive drug therapy for this intermediate range of LDL-C.

These recommendations were modified in the ATP III update of 2004, which recommended an LDL-C goal < 100 mg/dL for high-risk patients, with an optional goal of < 70 mg/dL for very high-risk patients (Table 1). This update also recommended initiating dietary therapy and LDL-C-lowering drugs for all patients over goal, with a planned LDL-C reduction of 30% to 40%. The rationale for these changes was based on several randomized clinical trials, the results of which were published after the release of the ATP III guidelines.

These trials included the Heart Protection Study (HPS), which evaluated the effects of simvastatin 40 mg per day versus placebo in a group of 20,536 patients aged 40 to 80 years at high risk for CHD.4-7 This included patients with coronary disease, other occlusive arterial disease, or diabetes (analogous to the ATP III CHD risk-equivalent designation), followed for a 5-year period. Patients treated with simvastatin had a 24% overall reduction in major adverse cardiovascular events compared to placebo; similar proportional risk reduction was seen even in subjects with baseline LDL-C < 100 mg/dL.
The Pravastatin or Atorvastatin Evaluation and Infection—Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) was designed to test noninferiority of a less aggressive cholesterol-lowering regimen. Ultimately, it showed that intensive LDL-C level lowering with atorvastatin 80 mg per day reduced cardiovascular risk more than standard drug therapy with pravastatin 40 mg in a group of high-risk patients hospitalized for acute coronary syndromes. The mean LDL-C level attained was 95 mg/dL with pravastatin and 62 mg/dL with atorvastatin. The study demonstrated a 16% reduction in the composite cardiovascular endpoint in the atorvastatin group compared with the pravastatin group ($P < 0.005$).

Other trials used to support these revised guidelines included the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid-Lowering Trial (ALLHAT-LLT), and Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA), a trial that evaluated 2 antihypertensive regimens and a lipid-lowering arm with atorvastatin.

Finally, in the evolution of the cholesterol guidelines, the AHA/ACC guidelines for secondary prevention of CHD released in 2006 placed more weight behind the optional goal of LDL-C < 70 mg/dL in high-risk patients with CHD, based on data accrued from the Treat to New Targets (TNT) and Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trials. It was formulated as a Class IIa recommendation and stated that it is reasonable to treat to LDL < 70 mg/dL in such (secondary prevention) patients. When the < 70-mg/dL target is chosen, it may be prudent to increase statin therapy in a graded fashion to determine a patient’s response and tolerance. Furthermore, if it is not possible to attain LDL-C < 70 mg/dL because of a high baseline LDL-C, it generally is possible to achieve LDL-C reductions of > 50% with either statins or LDL-C-lowering drug combinations.

Table 1. Summary of ATP III Guidelines Update, 2004

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>&lt; 100 mg/dL; optional goal, &lt;70 mg/dL</td>
<td>≥100 mg/dL</td>
<td>≥100 mg/dL</td>
</tr>
<tr>
<td>CHD or CHD-risk equivalent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10-year risk &gt;20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately high risk</td>
<td>&lt; 130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥130 mg/dL</td>
</tr>
<tr>
<td>≥2 risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10-year risk = 10%-20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>&lt; 130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td>≥2 risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10-year risk &lt;10%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>&lt; 160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL</td>
</tr>
<tr>
<td>1 or no risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


ATP, adult treatment panel; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; TLC, therapeutic lifestyle changes
Risk Assessment

Several variables have been taken into consideration to determine CHD risk. Any patient who has had a CHD event is at markedly increased risk for a subsequent event. Risk models such as the Framingham risk score\(^1\) are used in risk assessment. Any patient who has a > 20% risk for a CHD event based on the Framingham risk score is considered to be at equivalent risk to a patient with established CHD. The Framingham risk score does not take into account family history because of difficulty obtaining this measure in all patients. Furthermore, it does not include some of the newer markers such as high-sensitivity C-reactive protein (hsCRP) or microalbuminuria\(^{43-45}\) or the components of the metabolic syndrome such as waist circumference and triglycerides.\(^{46}\) Current guidelines and many clinical studies consider diabetes mellitus as a CHD risk equivalent (> 20% risk over 10 years) in setting targets for LDL-C and non–HDL-C levels.\(^{4,6,8,10,11,15,34,35,37,39,47-53}\)

Although many diabetic patients are not CHD risk-equivalent based on models such as the United Kingdom Prospective Diabetes Study (UKPDS) risk engine, this approach does ensure that high-risk diabetic patients are treated aggressively. Low HDL-C concentrations are associated with increased CHD risk. Studies such as AFCAPS/TEXCAPS have demonstrated that aggressive LDL-C lowering attenuates much of the adverse risk associated with low HDL-C.\(^{25,26}\)

There are also extensive data showing that hsCRP is associated with increased risk for CHD, even when adjustments are made for other risk factors. Current guidelines suggest that hsCRP be used to help in ongoing risk assessment in patients judged to be at intermediate risk for CHD.\(^{43,45,54}\) In fact, the Reynolds Risk score is one such risk assessment tool that incorporates hsCRP as well as family history of CHD in parents at aged < 60 years, in addition to the traditional risk factors. This risk calculator is modeled to project lifetime CHD risk, and may be useful for assessment of risk in women, for whom the Framingham score often tends to underestimate risk.

Other markers of risk have not been consistently included in guidelines but should be considered in clinical practice. Renal dysfunction is associated with an increased risk for CHD. This is true for markers of renal disease such as albuminuria, but several studies have shown that impaired renal function is associated with marked increases in CHD risk, especially when associated with the need for renal-replacement therapy (dialysis or renal transplantation). Peripheral vascular disease and cerebrovascular disease also are associated with increased risk for CHD events. Furthermore, most statin trials have shown a reduction in risk for stroke, although stroke event rates are consistently lower than CHD event rates in most studies.

Several observational studies have suggested that patients who have systemic inflammatory disorders such as rheumatoid arthritis and systemic lupus erythematosus, especially if they are treated with glucocorticoids, are at increased risk for CHD. Similarly, organ transplant recipients, especially renal, heart, and lung transplants, may be at increased risk for CHD. Many CHD risk-prevention clinics, including the Preventive Cardiology Clinic at the Cleveland Clinic, have set more aggressive LDL-C targets for such patients. This approach extends the general concept of more aggressive lipid lowering in patients at increased risk of disease.
Lipid-Lowering Treatment

Diet and Lifestyle

All patients, whether in secondary or primary prevention categories, are urged to implement lifestyle and dietary strategies to prevent cardiovascular disease. Healthy eating habits, starting in childhood, are the cornerstone for cardiovascular risk reduction and, together with lifestyle goals, including maintenance of healthy body weight, avoidance of tobacco products, and adherence to a regimen of physical activity, may be termed elements of primordial prevention.

Specifically, the American Heart Association recommends a diet low in fat, particularly saturated and trans fats, enriched in fruits, vegetables, whole grains, and fish, and low in added sugar and salt (Table 2).\textsuperscript{53} This approach, especially regarding fat intake, is supported by other nutrition guidelines.\textsuperscript{47,56,57} Controversies regarding the superiority of the Mediterranean diet (including higher proportions of monounsaturated fats and omega-3 fatty acids) over the traditional AHA step II diet may have been settled recently by a study showing their relative equivalence in lipid lowering and risk reduction. In addition, a study of a diet enriched in plant sterols, soy protein, viscous fiber, and almonds has shown comparable reductions in LDL-C and CRP as compared with lovastatin 20 mg.\textsuperscript{58} These findings all highlight the importance of dietary intervention in prevention.

\textit{Table 2. Therapeutic Lifestyle Changes: Diet Recommendations}\textsuperscript{53}

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat</td>
<td>25%-35% of total calories</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>&lt; 7% of total calories</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>\leq 10% of total calories</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>\leq 20% of total calories</td>
</tr>
<tr>
<td>Trans fat</td>
<td>&lt; 1% of total calories</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt; 300 mg/day</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>50%-60% of total calories</td>
</tr>
<tr>
<td>Fiber</td>
<td>20-30 g/day</td>
</tr>
<tr>
<td>Protein</td>
<td>~ 15% of total calories</td>
</tr>
<tr>
<td>Total calories (energy)</td>
<td>Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain.</td>
</tr>
<tr>
<td>Other</td>
<td>• Consume a diet rich in fruits and vegetables</td>
</tr>
<tr>
<td></td>
<td>• Choose whole-grain, high-fiber foods</td>
</tr>
<tr>
<td></td>
<td>• Consume fish, especially oily fish, at least twice a week</td>
</tr>
<tr>
<td></td>
<td>• Avoid fish with potential for mercury contamination</td>
</tr>
<tr>
<td></td>
<td>• Minimize intake of beverages and foods with added sugars</td>
</tr>
<tr>
<td></td>
<td>• Choose and prepare foods with little or no salt</td>
</tr>
<tr>
<td></td>
<td>• Consume alcohol in moderation. Men, 2 drinks/day; women, 1 drink/day</td>
</tr>
<tr>
<td></td>
<td>• When eating food prepared outside the home, follow the American Heart Association diet and lifestyle recommendations</td>
</tr>
</tbody>
</table>


Smoking cessation may have beneficial effects on the lipid profile by increasing HDL-C (mean, 4 mg/dL). Exercise, physical activity, and weight loss may also increase HDL-C and lower triglyceride levels. The AHA recommends 30 minutes of moderate-intensity aerobic exercise on most days of the week. Moderate alcohol intake (1 or 2 drinks per day) is associated with a lower risk of myocardial infarction, possibly because of alcohol’s ability to raise the HDL-C level (1 oz/day increases the HDL-C level by a mean of 4 mg/dL). Many studies have been devoted to other potential mediators found in alcoholic beverages, such as polyphenols in red wine. Excessive alcohol consumption is associated with elevations in triglyceride levels as well as the potential for hepatic dysfunction and addiction; therefore, the recommendation that patients increase or begin consumption is given with several caveats.

**Medications**

Various medications are currently available for lowering lipid levels; a summary is given in Table 3.

**Table 3. Summary of Lipid-Lowering Medications and Side Effects**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Change in Level (%)</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDL-C</td>
<td>HDL-C</td>
</tr>
<tr>
<td>Statins</td>
<td>↓20-60</td>
<td>↑5-15</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓10-15</td>
<td>↑10-15</td>
</tr>
<tr>
<td>BARs</td>
<td>↓15-30</td>
<td>↑3-5</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓10-25</td>
<td>↑15-35</td>
</tr>
<tr>
<td>HRT</td>
<td>↓10-15</td>
<td>↑2-8</td>
</tr>
<tr>
<td>CAI</td>
<td>↓15-20</td>
<td>No change</td>
</tr>
</tbody>
</table>

**Statins**

The introduction in the 1980s of the HMG-CoA reductase inhibitors, also known as the statins, has markedly improved the ability to treat hyperlipidemia and decrease future risk for CHD. The statins are the most effective drugs available for lowering LDL-C and are generally well-tolerated, with an acceptable side-effect profile. They are the first line of therapy for lipid lowering and attaining ATP III goals.

The mechanism of action of statins has been well characterized. They inhibit HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis, thus decreasing the hepatic formation of cholesterol. Hepatic LDL-C receptors are upregulated, resulting in further clearance of LDL-C from the systemic circulation.

Statins use results in a 20%-60% decrease in LDL-C levels, with more modest increases in HDL-C and decreases in triglyceride levels. Specifically, atorvastatin 10-80 mg per day was associated with decreases in LDL-C of from 27%-42%, decreased triglycerides levels of 10%-35%, and a 4%-8% increase in HDL-C levels. Fluvastatin 40 mg and 80 mg per day decreased LDL-C by 22% and 27%, increased HDL-C by 4%-8%, and reduced triglycerides by 10%-20%. Lovastatin, 20 mg, 40 mg, and 80 mg per day were linked to 22%-32% reductions in LDL-C, 4%-8% increases in HDL-C, and 10%-25% decreases in triglycerides. Similarly, pravastatin 20 mg and 40 mg, reduced LDL-C by 22% and 27% and triglycerides by 10%-20%, and increased HDL-C by 4%-8%. Rosuvastatin, in daily doses of 5 mg to 40 mg, reduced LDL-C by 38%-56% and triglycerides by 7%-32%, and increased HDL-C by 5%-11%. Simvastatin 10 mg to 80 mg reduced LDL-C by 22%-37% and triglycerides by 10%-5%.
The early landmark trials of statin use in primary and secondary prevention, such as the Scandinavian Simvastatin Survival Study (4S) \(^{14,43}\) and the West of Scotland Coronary Prevention Study (WOSCOPS),\(^{16}\) have shown that cholesterol lowering resulted in a decreased CHD risk and mortality of approximately 25% to 35%.

The CARE (n = 4159) and LIPID (n = 9014) trials examined the efficacy of pravastatin 40 mg per day for secondary prevention through reduced LDL-C. Patients began the CARE trial with a baseline LDL-C of 139 mg/dL and saw a mean 32% reduction by the end of the trial. This translated to a 24% reduction in coronary events and a number needed to treat (NNT) of 33. Patients began the LIPID trial with a mean LDL-C of 150 mg/dL and saw a mean 25% reduction during the course of the trial. This reduced coronary events by 24% for an NNT of 28.

The 4S trial (n = 4444) looked at secondary prevention with simvastatin 20 mg to 40 mg per day. Patients started the study at a mean baseline LDL-C of 188 mg/dL and saw a mean 35% reduction over the course of the trial. Coronary events were reduced by 34% for an NNT of 33.

The WOSCOPS trial (n = 6595) examined primary prevention with lovastatin 40 mg per day. Patients began the trial with a mean LDL-C or 192 mg/dL which was reduced by a mean 26%. Coronary events were reduced by 31% for an NNT of 42.

Similarly, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) (n = 6605) looked at primary prevention withLovastatin 20 mg to 40 mg per day. Patients started the study with a mean baseline LDL-C of 150 mg/dL and saw a 25% reduction in LDL-C and a 37% reduction in coronary events for an NNT of 24.\(^{63}\)

Later trials, such as the Heart Protection Study (HPS)\(^{7}\) and PROVE-IT TIMI-22,\(^{40}\) have shown that risk reduction occurs all along the continuum of cholesterol lowering, including the lower end, although to a lesser absolute degree. The curve of cholesterol lowering versus risk reduction is therefore probably best understood as a direct logarithmic relationship (Figure 1).\(^{30,60}\) To date, the lower limit of cholesterol that still results in risk reduction is unknown, although many experts have theorized that it may be at an LDL-C level of 40 mg/dL.

![Figure 1. Conceptual graph showing the relationship between low-density lipoprotein cholesterol (LDL-C) levels and relative risk of coronary heart disease, and baseline LDL-C levels in several recent studies. At the steep end of the curve, a 30-mg/dL decrease in LDL-C decreases the risk of coronary heart disease by about 30%.)](image-url)
Not all the cardiovascular risk reduction seen with statin use is attributable to LDL-C lowering. Studies of the pleiotropic effects of statins have suggested that they may also improve endothelial function, have antioxidant and anti-inflammatory effects, and stabilize atherosclerotic plaque. High-dose statin therapy has become part of standard care for patients presenting with acute coronary syndrome, based in part on the results of the PROVE-IT trial. 40

In addition, the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) (2008) showed significant reductions in cardiovascular events and all-cause mortality in apparently healthy patients with elevated hsCRP \( \geq 2.0 \text{ mg/L} \) treated with rosuvastatin 20 mg compared to placebo. This study suggests a benefit to statin use in a widely expanded primary prevention population with levels of increased inflammation.

Statins are among the most widely prescribed medications in the United States and have a remarkably good record of safety that is based on the large number of patients taking them. One statin, cerivastatin (Baycol), was removed from the market in 2001 because of excessive muscle toxicity; however, the other statins remain available and safe. The most commonly described side effects are transaminitis, occurring in < 3% of patients, and myopathy or myositis. Liver enzyme abnormalities are usually reversible when the dose of statin is decreased or the medication is discontinued. The occurrence of adverse side effects increases with concurrent use of the lipid-lowering agents fibrates and niacin, with cyclosporine, antifungal agents, antiretroviral protease inhibitors, daptomycin, verapamil, amiodarone, and grapefruit juice, and in patients with hepatic or renal insufficiency.

Reports of the prevalence of muscular side effects have described muscular aching that varies in degree of severity from mild aching or cramps, with or without associated elevations in the creatinine kinase level, to frank rhabdomyolysis, with creatinine kinase elevations \( > 40 \times \) the upper limit of normal and associated renal dysfunction. Unfortunately, these effects are idiosyncratic and may occur at any point during therapy. In the largest statin trial to date, the HPS, which included 20,536 patients randomized to either simvastatin 40 mg daily or placebo, the incidence of muscle complaints at any time during the study was 32.9% in the drug group and 33.2% in the placebo group; rhabdomyolysis occurred in 0.05% of those in the simvastatin group. 7

The choice of statin may depend on the degree of LDL-C lowering needed to attain ATP III goals, side-effect profile, and cost. Among the statins, pravastatin, fluvastatin, and rosuvastatin are hydrophilic and may be associated with fewer muscle side effects. It is commonly noted that side effects encountered with one of the medications in this class may not necessarily be reproduced with another. Therefore, we recommend a trial of another statin whenever possible. We also have found that intermittent statin dosing, from every other day to once weekly, may reduce symptoms.

Ubiquinone (coenzyme Q10 \([\text{CoQ}_{10}]\)) supplementation, 100 to 400 mg daily, is widely used to reduce muscle symptoms, but no robust placebo-controlled trials have confirmed the benefits of this approach.

**Fibrates**

The lipid-lowering medications known as the fibrates (eg, gemfibrozil, fenofibrate, bezafibrate, clofibrate) are an important part of the armamentarium for lipid lowering but are rarely used as monotherapy, except in cases of primary prevention with metabolic syndrome profile, in which the goal of the LDL-C level has already been attained.

Fibrates activate the peroxisome proliferator-activated receptor-\( \alpha \) (PPAR-\( \alpha \)), which ultimately results in increased lipolysis and elimination from plasma of triglyceride-rich particles and increased synthesis of apolipoproteins A-I, A-II, and HDL-C. Fibrates can therefore lower triglyceride levels by 20% to 50% and increase HDL-C levels by 10% to 15%, along with a possible 10% to 15% decrease in LDL-C levels.
Although no large randomized clinical trial to date has shown an improvement in mortality with use of the fibrates, the HHS, using gemfibrozil in primary prevention, and VA-HIT, using gemfibrozil in secondary prevention, have shown a significant risk reduction in cardiovascular events, especially in subgroups with high triglyceride and low HDL-C levels. The FIELD study in more than 9,000 people with diabetes could not confirm these data, but the trial results were confounded by very high rates of statin drop-in.

Safety concerns regarding fibrates include the possibility of transaminitis or cholelithiasis and caution must be used when combining a fibrate with a statin (increased risk of myopathy, especially with gemfibrozil) or warfarin (increased risk of bleeding). Because fibrates are primarily excreted renally, caution must be used in the patient with renal insufficiency. If fibrate therapy is indicated, dose reduction with decreased renal function is advisable.

Niacin

One of the older lipid-lowering medications, niacin is commonly prescribed for its ability to raise HDL-C levels by up to 35%. It also lowers triglyceride levels by 20% to 50% and lowers LDL-C levels by 10% to 25%, making it a useful medication for monotherapy or in combination with statins or fibrates. It decreases hepatic production of very low-density lipoproteins (VLDLs) and apolipoprotein (apo) B-100, inhibits free fatty acid release from adipose tissue, and stabilizes apo A-I from HDL-C, maintaining the structure and function of HDL-C.

In addition to the lipid modifications noted earlier, niacin is one of the few medications available to lower the lipoprotein (a) (Lp(a)) level, a modified and highly atherogenic form of LDL-C. The usefulness of this capability is unclear, however. Although an elevated Lp(a) level is associated with increased cardiovascular mortality and morbidity, no randomized clinical trials have shown a benefit in targeting its lowering.

The use of niacin has increased with the introduction of the long-acting forms (eg, Niaspan), designed to attenuate the most bothersome side effect associated with niacin, an intense feeling of warmth or flushing occurring shortly after ingestion of the medication. A niacin formulation with laropiprant, a prostaglandin D2 blocker designed to reduce flushing, is available in Europe, but not in the United States. Other potential side effects include hyperglycemia, hyperuricemia, and the risk of interaction with statins, causing hepatotoxicity or myopathy.

Bile Acid Resins

Bile acid resins (BARs) act in the small intestine to block the reabsorption of bile acids, thereby decreasing their enterohepatic circulation and upregulating hepatic LDL-C receptors. Although long-term use is considered to be safe because they are not systemically absorbed, the bile acid resins are rarely used in the current era of lipid lowering. This is due to their inferiority compared with statins in LDL-C-lowering capability, approximately 15% to 30%, as well as in their reduction of CHD. They may be useful in patients who cannot tolerate statins because of side effects or in patients in whom the risk of statin therapy might outweigh the benefit—for example, during pregnancy when statins are contraindicated because of concerns about a possible teratogenic effect. Whereas bile acid resins are usually well tolerated, they may be associated with gastrointestinal side effects, such as constipation or bloating, and long-term use may cause malabsorption of the fat-soluble vitamins A, D, E, and K. They require administration 2-4 times daily.
Cholesterol Absorption Inhibitor

Ezetimibe is currently the only available drug in the class of cholesterol absorption inhibitors. It localizes to the epithelial brush border of the small intestine to block uptake of cholesterol, resulting in decreased delivery of cholesterol to the liver and subsequent upregulation of LDL-C receptors. Ezetimibe’s glucuronide metabolite is also active and results in a long half-life as the 2 are circulated enterohepatically. It is usually administered in conjunction with a statin, and may lower LDL-C levels by an additional 15% to 20%, slightly less when used with a statin. Because there is little systemic absorption, ezetimibe is generally well tolerated and side effects are rare. Gastrointestinal symptoms and muscle aches have been reported. Enthusiasm for use of ezetimibe has decreased since publication of ENHANCE (Effect of combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) (2008) showing no difference in progression of carotid intimal-medial thickness between groups treated with simvastatin with and without ezetimibe.64

Summary

Guidelines for cholesterol lowering are based on assessment of cardiovascular risk with progressively lower LDL-C goals in patients at higher risk. Currently, patients with CHD or CHD risk equivalents (eg, stroke, aortic aneurysm, peripheral arterial disease, diabetes mellitus, metabolic syndrome) or multiple CHD risk factors conferring an estimated 10-year risk for a cardiovascular event > 20% have a recommended target LDL-C of < 100 mg/dL, and optimally < 70 mg/dL.

Framingham risk score, family history, and lifestyle factors are important in the assessment of cardiovascular risk. Additional risk markers, such as microalbuminuria and hsCRP, may be helpful to establish LDL-C targets.

Statin medications are the most effective and widely used agents for cholesterol lowering and have the most robust clinical trial data to support their use in lowering cardiovascular risk. Statins are generally well tolerated but use may be limited by hepatotoxicity or muscle side effects.

Lifestyle and dietary interventions are integral parts of primary and secondary cardiovascular prevention and are recommended for all patients.