Benefits of Managing Hyperlipidemia

Coronary heart disease (CHD) is the most common cause of death in developed countries. In the United States alone, CHD accounts for approximately 500,000 deaths annually and is recognized as a major public health problem. Hyperlipidemia is an important modifiable risk factor for the development and progression of cardiovascular disease. The causal link between elevated low-density lipoprotein cholesterol (LDL-C) and CHD is now firmly established. Compelling evidence also supports an independent link between low high-density lipoprotein cholesterol (HDL-C) levels and high triglyceride levels and atherosclerosis.

Epidemiologic studies provide the largest body of evidence for the relationship between serum total cholesterol (TC) levels and CHD risk. For example, in the Multiple Risk Factor Intervention Trial, CHD rates declined progressively with lower TC levels down to a level of 150 mg/dL (3.9 mmol/L), corresponding to an LDL-C level of about 100 mg/dL (2.6 mmol/L). In fact, CHD events are rare in nonsmoking populations with TC levels < 150 mg/dL (3.9 mmol/L).

Further support for the relationship between CHD and LDL-C comes from results of several landmark primary- and secondary-prevention trials of lipid-lowering therapy. Utilizing 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins), these studies have demonstrated that coronary events, both fatal and nonfatal, can be prevented. Data from these five trials, which included 30,817 participants, were evaluated in a 1999 meta-analysis. Drug treatment with statins for a mean duration of 5.4 years was associated with a 20% reduction in TC, a 28% reduction in LDL-C, a 13% reduction in triglyceride, and a 5% increase in HDL-C. Statin therapy also led to a 31% reduction in major coronary events and a 21% reduction in all-cause mortality. The reduction in risk due to statin treatment was independent of age and sex.

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of major coronary events was similar for both men and women (31% and 29%, respectively) and between individuals ≥ 65 years and < 65 years of age (32% and 31%, respectively). There are also compelling data indicating that statins lower the risk of stroke in secondary-prevention patients.15

The best data correlating low HDL-C levels with an independent CHD event risk come from the observational Framingham Study.16,17 Every 4 mg/dL (0.1 mmol/L) decrease in HDL-C level is associated with an approximate 10% increase in CHD risk. Additionally, for patients with LDL-C levels between 100 mg/dL and 200 mg/dL (2.6 mmol/L to 5.2 mmol/L), HDL-C level is an important predictor of risk,17 especially when low HDL-C levels are associated with both a high LDL-C: HDL-C ratio (> 5) and elevated triglyceride (> 200 mg/dL [> 2.3 mmol/L]).18,19 In fact, the ratio of TC or LDL-C to HDL-C has long been considered a more sensitive marker for CHD risk than HDL-C levels alone.5 Several angiographic trials have corroborated observational findings that lower HDL-C values predict the severity of coronary atherosclerosis.20

Elevated triglyceride levels have more recently become recognized as an independent predictor of CHD risk.4,5,18 This appears especially true for women and patients with impaired glucose metabolism. The largest risk assessment of elevated triglyceride levels came from a meta-analysis of 17 studies from 1965 to 1997 involving 46,413 men and 10,864 women.4 For every 88 mg/dL (4.9 mmol/L) increase in triglyceride level, the relative risk of CHD rose 14% in men and 37% in women after adjusting for HDL-C levels. The strong association of hypertriglyceridemia with other metabolic abnormalities, including low HDL-C, insulin resistance, centripedal obesity, hypertension, small dense low-density lipoprotein (LDL) particles, and a hypercoagulable state, confounds the interpretation of cardiac risk from triglyceride alone. Nevertheless, the clustering of elevated triglyceride level with these concomitant conditions promotes a heightened risk for coronary thrombosis.19

Two randomized-controlled prospective trials have demonstrated significant improvements in cardiovascular clinical outcomes using fibrates in the treatment of patients with a low HDL-C, a high LDL-C to HDL-C ratio, or hypertriglyceridemia. The primary prevention Helsinki Heart Study randomized 4,081 asymptomatic male subjects to treatment with either gemfibrozil or placebo and reported 34% fewer cardiac events and a 26% reduction in CHD mortality in the treated cohort after 5 years of follow-up.21 Patients with triglyceride level > 200 mg/dL (2.3 mmol/L) and LDL-C/HDL-C ratios > 5:1 benefited the most. These individuals carried a 3.8-fold higher risk of cardiac events and experienced an impressive 71% risk reduction with gemfibrozil use.19 The secondary-prevention Veterans Affairs HDL Cholesterol Intervention Trial enrolled 2,531 patients and reported after 5.1 follow-up years that gemfibrozil conferred a 22% reduction in the incidence of CHD-related death and myocardial infarction (MI; p = 0.006) and a nonsignificant 10% reduction in all-cause mortality (p = 0.23).22 This occurred in the presence of no change in LDL-C, a 6% rise in HDL-C, and a 31% reduction in triglyceride levels. It remains unclear from these two trials whether improvements in HDL-C or triglyceride levels imparted more of the cardiovascular benefit; it is likely that both of these changes in lipid fractions contributed to the clinical benefits observed.

Elevations in noncardiac mortality from gemfibrozil in the Helsinki Heart Study21 and clofibrate in the World Health Organization Cooperative Study23 provide partial explanations for the relatively infrequent use of fibrates in treating dyslipidemia. Moreover, a 1999 systematic meta-analysis24 involving > 85,000 treated and 87,000 control patients compared the efficacy of currently available lipid-lowering interventions and reported that only statins showed a large and statistically significant reduction in all-cause (risk ratio, 0.75; 95% confidence interval [CI], 0.65 to 0.86) and CHD (risk ratio, 0.66; 95% CI, 0.54 to 0.79) mortality. For this reason, statins are the agents of choice in treating most high-risk patients with hyperlipidemia.

Guidelines for the Treatment of Dyslipidemia

The National Cholesterol Education Program Adult Treatment Panel II (NCEP ATP-II), published in 1993, recommends using CHD risk status as a guide to the intensity of therapy.25 Patients are categorized into one of three categories according to their perceived level of CHD risk. NCEP ATP-II identifies LDL-C as the primary target of lipid-lowering therapy.25 The LDL-C cut-off values for treatment decisions are presented in Table 1. Although pooling of data from early clinical trials revealed a definite trend toward decreased total mortality in patients with CHD, no clinical trial or meta-analysis had yet shown a reduction in total mortality in patients without established CHD (ie, primary prevention). NCEP ATP-II also designates low HDL-C as a negative risk factor and high HDL-C as a protective risk factor.25 However, given the lack of prospective trial data on how to best
mortality appears to be directly proportional to the degree to which they lower lipids. This analysis estimated that for every 10% reduction in TC, CHD mortality and total mortality risk would be reduced in a consistent fashion. A post hoc analysis of the Scandinavian Simvastatin Survival Study (4S trial) also suggested that a reduction in major coronary events was highly correlated with lower posttreatment LDL-C levels and greater changes in LDL-C levels from baseline. It was estimated that for each additional 1% reduction in LDL-C, there was a 1.7% reduction in major coronary events (CI, 1 to 2.4%; p = 0.00001).

Further support for the concept of lower LDL goals comes from the Post Coronary Artery Bypass Graft trial. Aggressive lipid-lowering treatment (lovastatin, 80 mg, plus cholestyramine if needed) to reduce LDL-C levels to < 100 mg/dL slowed atherosclerotic progression in bypass grafts to a greater extent than less aggressive lipid lowering (lovastatin, 5 mg) to a range of 132 to 136 mg/dL (3.4 to 3.5 mmol/L). The rate of revascularization over 4 years was 29% lower in the aggressively treated group vs the group receiving low-dose lovastatin treatment (6.5% vs 9.2%; p = 0.03). However, it should be noted that in the Cholesterol and Recurrent Events trial utilizing pravastatin, an on-treatment LDL-C of 80 mg/dL did not appear to confer any additional risk reduction over that obtained with an LDL-C of 120 mg/dL, though this analysis was limited by wide CIs. Two ongoing trials will attempt to clarify these divergent data in patients with documented coronary artery disease. The Treating to New Targets study is comparing treatment with 10 mg vs 80 mg of atorvastatin, and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine is comparing 20 mg vs 80 mg of simvastatin. In 2004, these results will indicate the necessary degree of LDL-C reduction in the secondary-prevention setting for optimal outcome benefit. They will also provide data on the cost-effectiveness of aggressive lipid lowering.

In the Atorvastatin Versus Revascularization Treatments study, patients with stable coronary artery disease achieved significant benefit by aggressive LDL-C lowering to < 100 mg/dL (2.6 mmol/L). Over 18 months, there was a 36% reduction in the incidence of cardiovascular events (eg, nonfatal MI, revascularization, and/or worsening angina) in the high-dose atorvastatin (80 mg) arm (13%) compared to the angioplasty/usual-care arm (21%). Patients treated with atorvastatin achieved a mean LDL-C level of 77 mg/dL (2.0 mmol/L), compared to 119 mg/dL (3.1 mmol/L) in those treated with angioplasty/usual care. Unfortunately, a minimal amount of lipid-lowering therapy was not mandated for all of the subjects randomized to angioplasty in the Atorvastatin Versus Revascularization Treatments trial. Also, it is likely that many patients in the usual-care arm did not even receive a starting dose of a statin during most of the follow-up period. Future trials will determine the incremental benefit of percutaneous coronary intervention over optimal medical management initiated at the time of the revascularization procedure. To date and to our knowledge, no prospective trials of lipid-lowering therapy before and following percutaneous intervention and stenting have demonstrated a lowering of in-stent restenosis rates in patients receiving treatment. Although in-stent restenosis rates were not affected, the investigators in the Fluvastatin Angiographic Restenosis Trial did find that the patients in the fluvastatin arm experienced fewer deaths and MIs (1.5% vs 4%; p < 0.025). An ongoing follow-up study will assess whether this outcome will be reproducible.

The above trials emphasize the importance of treating LDL-C to targets as set forth by the NCEP ATP-II. Additionally, given the low incidence of serious statin-related side effects, these trials strongly support statin use as first-line therapies for most cases of hyperlipidemia. Unfortunately, the majority of pa-

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**Table 1—NCEP ATP-II Recommendations for Treatment Based on LDL-C Level**

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Initiation LDL-C Level, mg/dL (mmol/L)</th>
<th>Goal LDL-C Level, mg/dL (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary therapy</td>
<td>Without CHD and &lt; 2 risk factors</td>
<td>≥ 160 (4.1) &lt; 160 (4.1)</td>
</tr>
<tr>
<td></td>
<td>With CHD</td>
<td>&gt; 100 (2.6) &gt; 100 (2.6)</td>
</tr>
<tr>
<td>Drug treatment</td>
<td>Without CHD and &lt; 2 risk factors</td>
<td>≥ 190 (4.1) &lt; 160 (4.1)</td>
</tr>
<tr>
<td></td>
<td>With CHD</td>
<td>&gt; 130 (2.6) &gt; 100 (2.6)</td>
</tr>
</tbody>
</table>

*From Gould et al.26 Risk factors include age (≥ 45 years in men and ≥ 55 years in women), family history of premature CHD, cigarette smoking, hypertension, low HDL-C levels (< 35 mg/dL), and diabetes mellitus.

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patients with CHD are not treated to appropriate LDL-C levels. In fact, many adults with multiple CHD risk factors do not even have their lipid levels screened. It has been estimated that only 1 in 12 adults undergo routine cholesterol screening.

**Adherence to NCEP ATP-II Guidelines**

Although the National Cholesterol Education Program and European guidelines on management of lipids have been widely distributed, management of hyperlipidemia is less than optimal in our current health-care system. Results from the recent Lipid Treatment Assessment Project indicate that the majority of patients with hypercholesterolemia are undertreated according to NCEP ATP-II guidelines and are, thus, at unnecessarily increased risk for developing CHD events. Among 4,888 primary-care patients receiving lipid-lowering treatment for hypercholesterolemia, treatment intensity was sufficient to achieve the LDL-C target level in only 39% overall. Among patients at highest risk for an event, (ie, those with CHD), only 18% achieved LDL-C levels at the NCEP ATP-II target of < 100 mg/dL (2.6 mmol/L).

While it is estimated that approximately 28% of the US population is eligible for at least dietary treatment according to NCEP ATP II guidelines, almost two thirds receive no such instruction. Furthermore, in a primary-care study of 603 patients with CHD, 33% were not screened with lipid panels, 45% did not receive dietary counseling, and 67% were not receiving lipid-lowering medication. Of those who were treated, only 14% achieved the recommended LDL-C levels of < 100 mg/dL (< 2.6 mmol/L). There were no significant differences in efficacy between physicians of different specialties.

Evidence also points to gender bias regarding utilization of lipid-lowering treatment among individuals with CHD. During the 3-year Prospective Evaluation of the Vascular Effects of Norvasc trial, the use of lipid-lowering therapy was prospectively evaluated in 825 men and women with documented CHD recruited from 16 centers throughout the United States and Canada. Between 1994 and 1997, the proportion of patients with LDL-C of > 130 mg/dL (> 3.4 mmol/L) was reduced by 42% in men but by only 6% in women. At study completion, the NCEP ATP-II LDL-C target goal of < 100 mg/dL (< 2.6 mmol/L) was achieved by nearly three times as many men as women (31% vs 12%; p = 0.001). Nevertheless, the overall adherence rate to established guidelines was low in both men and women. Surprisingly, this occurred despite instructions received by all investigators recommending the institution of lipid-lowering therapy to a target of ≤ 100 mg/dL (2.6 mmol/L) following publication of the 4S trial results.

There are many possible explanations for the poor compliance with lipid-lowering therapy in these studies. Difficulties in extrapolating clinical trial data to everyday practice, insufficient knowledge of disease pathophysiology, time constraints, and economic issues are but a few examples of the proposed barriers to adequate physician diagnosis, treatment initiation, and drug titration.

**Patient Compliance With Lipid-Lowering Therapy**

In addition to physician nonadherence with cholesterol treatment guidelines, patient compliance with lipid-lowering therapy is far from optimal. Noncompliance with drug therapy is endemic; data suggest that only one third of patients consistently take their prescribed medication, one third take it inconsistently, and one third never take it. The consequences of noncompliance with treatment in patients with CHD are immense in terms of morbidity, mortality, and health-care costs. Compliance with prescribed drug regimens is particularly important among the elderly with documented cardiovascular disease because of their increased vulnerability to progressive atherosclerosis and high prevalence of chronic disorders such as diabetes and hypertension. Factors that appear to be major determinants of compliance with lipid-lowering medications include patient education and cost. Other important factors involve patients’ attitudes toward treatment, differences dosing regimens, and the side effect profiles among the available drugs. In a recent study of 622 patients hospitalized with acute MI who met National Cholesterol Education Program criteria for lipid-lowering therapy, only 37% of the patients were actually receiving an agent. One nonclinical factor that increased the likelihood of receiving lipid-lowering therapy was participation in a managed-care plan.

Of the currently available classes of lipid-lowering drugs, statins are associated with the lowest incidences of adverse effects. Bile acid sequestrants can be unpalatable and cause intolerable GI effects at dosages of cholestyramine (≥ 16 g/d) or colestipol (≥ 20 g/d) required to achieve a 15 to 30% reduction in LDL-C levels. Thus, these agents are now largely relegated to use as adjuncts to statin therapy when further lowering of TG or LDL-C is indicated. Bile acid sequestrants may be used in primary therapy when patients are intolerant of statins or when systematic therapy with statins is undesirable.

Up to 50% of patients discontinue treatment with short-acting nicotinic acid because of adverse events. Nicotinic acid can cause bothersome flushing, and management of this effect often requires the
additional administration of aspirin, 325 mg, 30 to 60 min before each dose or the ingestion of niacin during or after meals. Nicotinic acid can also cause hyperuricemia, aggravate peptic ulcer disease, and worsen hyperglycemia in patients with glucose intolerance or overt diabetes. Despite these potential adverse events, nicotinic acid formulations are the most effective pharmacologic agents for raising depressed HDL-C levels. Additionally, the recent introduction of the US Food and Drug Administration approved controlled-release niacin has led to considerably improved compliance and better tolerability among patients in need of niacin therapy. Fibrates are generally well tolerated but can occasionally cause GI discomfort or promote gallstone formation. Its use is reserved for the treatment of hypertriglyceridemia and may require the addition of another lipid-lowering agent, such as statins, to augment reduction in LDL-C.

A review of the large clinical trials confirmed anecdotal clinical experience that drug therapy discontinuation rates were lowest with statins (6 to 12%), intermediate with fibrates (7 to 31%) and resins (27 to 34%), and highest with niacin (11 to 45%). Moreover, in a cohort study of 2,369 new users of lipid-lowering therapy in a primary-care health maintenance organization setting, the 1-year probability of drug therapy discontinuation was 15% for statins (95% CI, 11 to 19%), 37% for fibrates (95% CI, 31 to 43%), 41% for bile acid sequestrants (95% CI, 38 to 44%), and 46% for niacin (95% CI, 42 to 51%).

The importance of medication compliance with lipid-lowering therapy cannot be overstated. In a post hoc analysis of the West of Scotland Coronary Prevention Study, patients with compliance ≥75% showed a 38% (95% CI, 23 to 50%) risk reduction for CHD events, a 46% (95% CI, 19 to 64%) reduction in risk of coronary revascularization, and a 32% (95% CI, 7 to 51%) risk reduction (p = 0.015) for all-cause mortality compared with values of 31% (95% CI, 17 to 43%), 37% (95% CI, 11 to 56%), and 22% (95% CI, 0 to 40%) for the intention-to-treat population mortality. Additionally, the absolute clinical benefit of statin therapy over placebo treatment increased progressively with each year of follow-up in the 4S trial.

TREATING HYPERLIPIDEMIA IN THE MILIEU OF CONCOMITANT DISEASE

Selection of a lipid-lowering drug predominantly involves consideration of the magnitude of LDL-C reduction needed to achieve the recommended target level. Further merits include the coexistence of low HDL-C and high triglyceride or other dyslipidemias, the simplicity of regimen (eg, once-daily monotherapy), the presence of concomitant illnesses and medications, and the adverse event and cost profile of the intended drug. Each of the currently available classes of lipid-lowering agents (eg, statins, nicotinic acid, fibrates, and bile acid sequestrants) exerts different mechanisms of action. Their clinical advantages and limitations are recognized in the context of hyperlipidemia and concomitant medical conditions.

It should be noted that since the publication of NCEP ATP-II, certain medical conditions should be recognized as CHD equivalents, including peripheral arterial disease manifestations of thrombotic stroke, transient ischemic attacks, claudication, and vascular bruises. At the time of NCEP ATP-II publication, patients with type II diabetes and type I diabetes for >10 years duration were only considered CHD risk factors, but they have since been recognized as CHD equivalents. Figure 1 represents a comprehensive treatment algorithm based on the initial NCEP ATP-II guidelines and data from prospective lipid intervention trials. According to a patient’s prescribed CHD risk status and considers how the several concomitant medical conditions discussed below might influence dyslipidemia treatment decisions.

Diabetes

Diabetes is perhaps the most important concomitant condition in terms of its impact on CHD. The dyslipidemia that is commonly associated with type II diabetes is believed to be a major source of increased risk in these individuals. Recent data indicate that patients with type II diabetes and without a history of MI have the same risk of MI as nondiabetic patients with CHD. Given the magnitude of this risk, diabetic dyslipidemia must be managed aggressively. Accordingly, the most recent American Diabetes Association clinical guidelines for the treatment of dyslipidemia recommend that lipid-lowering therapy be strongly considered in all patients with type II diabetes and LDL-C levels ≥130 mg/dL, with a goal to lower LDL-C level ≤100 mg/dL. The typical lipid profile found in most diabetics consists of high triglyceride levels combined with low HDL-C levels and moderately increased LDL-C levels. The first priority in treating this dyslipidemia should generally be to lower the elevated LDL-C levels. Once this goal has been accomplished, attention can then be turned to raising HDL-C levels and lowering triglyceride levels.

Statins should be considered first-line therapy for the majority of diabetic patients with dyslipidemia who do not have severe hypertriglyceridemia. In diabetic subgroups in the 4S trial and Cholesterol
and Recurrent Events study, statins significantly reduced the incidence of major CHD events (by 55% and 25%, respectively). Niacin may increase insulin resistance and potentially worsen glycemic control in higher doses. Bile acid sequestrants may raise triglyceride levels and cause constipation that can be problematic for elderly patients with diabetes. Fibrates are useful to lower triglyceride levels and raise...
HDL-C levels, but they may sometimes raise LDL-C levels. Caution must be exercised when combining fibrates with statins due to possible, but infrequent, adverse events of hepatitis or myositis. Statins are generally employed initially to reach the LDL-C goal and if triglyceride and/or HDL-C levels remain suboptimal despite lifestyle improvements, fibrates can be cautiously added to the regimen. Good glycemic control is also important for improving triglycerides, even though it does not always lead to satisfactory LDL-C reductions.

Hypertension

Hypertension and hyperlipidemia commonly coexist. Forty percent of the 51 million hypertensive persons in the United States have elevated cholesterol (>240 mg/dL) levels and 46% of those with elevated cholesterol levels have hypertension.25 There is also a high prevalence (5 to 25%) of low HDL-C levels and a higher prevalence of elevated triglyceride levels in hypertensive individuals compared to normotensive individuals.51 Untreated hypertension increases the incidence of cardiovascular events by twofold to fourfold compared with age-matched normotensive individuals.51 Elevated cholesterol levels augment the risk of cardiovascular disease associated with hypertension. In fact, a large proportion of the CHD risk in patients with hypertension can be attributed to dyslipidemia.51 The typical management of hyperlipidemia does not appreciably differ in hypertensive patients from those in the general population. However, the high attendant CHD risk when these two conditions coexist warrants a strict emphasis on dietary and pharmacologic therapy to successfully achieve NCEP ATP-II goals.

Postmenopausal State

Premenopausal women have a considerably lower risk of CHD compared with similarly aged men. Below the age of 55 years, the incidence of CHD in women is approximately one third that of men. However, this “protection” is progressively lost after menopause and a nearly equivalent CHD rate exists among men and women by the age of 75 years.52 This is likely due to a steady increase in the plasma concentration of atherogenic lipoproteins after menopause even though HDL-C remains at approximately premenopausal levels.53 Decreases in endogenous estrogen levels, weight gain, and decreases in physical activity after menopause are likely responsible for these changes. Observational studies54,55 have usually reported lower rates of CHD in women receiving postmenopausal estrogen replacement therapy than in those not receiving estrogen replacement therapy. However, results from more recent studies, including the Heart and Estrogen/progestin Replacement Study, showed that estrogen plus progestin (in the form of medroxyprogesterone acetate) did not reduce the overall rate of CHD events in postmenopausal women with established CHD (average follow-up of 4.1 years).56

Based on the results of Heart and Estrogen/progestin Replacement Study, the regimen of conjugated equine estrogen plus continuous combined medroxyprogesterone acetate should not be started for the sole purpose of secondary prevention of CHD. The selection of a lipid-lowering agent in postmenopausal women should be based on the predominant abnormality found in the lipoprotein profile. Statins are a good initial choice for women with elevated LDL-C levels, either with or without moderate elevations in triglyceride levels. CHD risk reduction with statins has also been shown to similarly benefit both men and women irrespective of age.11,57,58 Hormone replacement therapy will improve HDL-C and LDL-C levels, but it may increase triglyceride levels. Additionally, hormone replacement therapy remains the preferred treatment to delay the progression of osteoporosis and reduce vasomotor symptoms. If cost is a substantial patient issue, hormone replacement therapy is much less expensive than statin therapy. Ongoing studies will determine the efficacy of hormone replacement therapy in the primary prevention of CHD.59

Conclusion

Data from epidemiologic and observational studies form the basis for the NCEP ATP-II guidelines. Over the past few years, a number of large prevention studies8–10,12,13 with statins have confirmed that lowering elevated levels of LDL-C can reduce CHD risk. In most of these studies, this reduction in CHD events and mortality was proportional to the baseline CHD risk and to the extent of the LDL-C reduction. To date and to our knowledge, all of the large clinical event trials with the statins have employed pravastatin, simvastatin, or lovastatin. However, it is likely that these benefits represent a class effect attributable to the degree of LDL lowering. There are now large randomized, placebo-controlled clinical event trials underway with fluvastatin, atorvastatin, and cerivastatin in a variety of patient populations.

Strategies employed predominantly to target HDL-C and triglyceride have invoked more controversy in terms of their suggested impact on patient outcomes. Fibrates likely impart cardiovascular improvements in patients with elevated triglyceride and
low HDL-C levels. Additionally, while nicotinic acid is the most effective agent for elevating isolated low HDL-C levels, only the Coronary Drug Project showed a decrease in total mortality in the niacin treatment group after 15 years of follow-up.25

Recent studies34,39 have shown that the lipid-lowering treatment given to most patients is not sufficient to reduce LDL-C to NCEP ATP-II target levels. Of particular concern are the large numbers of patients at the highest risk for cardiovascular events who receive inadequate treatment or none at all. There is evidence to suggest that women at similar risk for CHD events are treated less aggressively than men. Physicians who care for patients at high risk for cardiovascular disease should take responsibility for appropriate screening and management of dyslipidemic patients. This is especially true for patients with the coronary risk factors of smoking, hypertension, diabetes, and/or a family history of premature CHD. The ultimate challenge for improving the treatment of dyslipidemia is to combine the efforts of all healthcare professionals with those of patients and their families. This approach maximizes the likelihood of proper initiation and adherence to lipid-lowering treatments. Providers should also assess each patient’s global risk of CHD in determining the aggressiveness of the prescribed intervention.47

Dietary and lifestyle interventions are the cornerstone of successful clinical management of hyperlipidemia. Drug therapy is added when patients do not achieve target lipid levels with dietary therapy within 6 months or when the short-term risk of future CHD events is sufficiently high to embark on prompt lipid lowering. When selecting drug therapy, it is important to match the lipid profile with the drug or class of drugs most likely to produce the desired changes.

Of the available lipid-lowering agents, statins most effectively lower LDL-C and also reduce triglyceride proportional to the patient’s baseline triglyceride levels. Therefore, these drugs are the first agents of choice for most patients with elevated LDL-C levels. Ongoing trials will determine if the reduction in CHD events seen in trials with pravastatin, simvastatin, and lovastatin can be replicated by the newer statin agents that are generally less expensive. Ideally, statin selection should be based primarily on (1) the ability of the drug to effectively lower LDL-C levels (preferably obtaining NCEP ATP-II target lipid levels at or near the initially prescribed drug dose), and (2) documentation of efficacy in prospective trials powered to show a reduction in clinical events.

### Addendum

A major new focus in Adult Treatment Panel III is to determine the absolute 10-year CHD risk in primary prevention with at least two risk factors. The term CHD risk equivalent is defined as 10-year risk of developing a MI or a coronary death of >20%. Diabetes in primary prevention is termed a CHD risk equivalent. A revised Framingham risk score has been created to determine the 10-year absolute risk for hard CHD events. An optimal LDL level is now classified as <100 mg/dL and an optimal triglyceride level is classified as <150 mg/dL. A low HDL-C level is now defined categorically as <40 mg/dL.60

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