Improving clinical outcomes in patients at high risk for coronary heart disease (CHD) requires a multimodal approach. This is especially important in patients with the constellation of metabolic risk factors that constitute the metabolic syndrome, which is associated with an elevated risk of CHD at all levels of low-density lipoprotein cholesterol (LDL-C). Achieving optimal clinical outcomes requires a comprehensive and aggressive therapeutic plan that includes pharmacotherapy and lifestyle changes. Effective pharmacotherapy for components of the metabolic syndrome (eg, hypertension, elevated LDL-C levels, prothrombotic state) is important in improving clinical outcomes, as is pharmacotherapy for glycemic control in patients with diabetes. Therapeutic lifestyle changes recommended for treatment of metabolic syndrome include smoking cessation, exercise programs, nutritional counseling, and weight control. Patient questionnaires are an effective way to help tailor recommendations to individual patients and thereby increase compliance. Clinicians can also help motivate patients by offering practical tips for modifying diet and eating habits and explaining all the benefits of exercise. These combined approaches can be used to help more patients achieve their lipid goals, and new pharmacologic therapies currently under investigation may further expand available treatment options.

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optimal medical therapy. The results underscored the importance of targeting components of the metabolic syndrome with pharmacologic therapy and therapeutic lifestyle changes (TLC).

Pharmacotherapeutic Considerations
Effective pharmacotherapy for the components of the metabolic syndrome is important in improving clinical outcomes. In particular, lowering blood pressure with antihypertensive agents, lowering LDL-C levels with statins, and managing the prothrombotic state with aspirin are well-established methods of reducing the risk of CHD. Although a full review of pharmacologic management of the metabolic syndrome is beyond the scope of the present review, a few general considerations are important.

For the management of hypertension in patients with diabetes mellitus, agents that target the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors (ACEIs), are preferred (or angiotensin receptor blockers when ACEIs are not tolerated). When combination therapy is required, combining an ACEI with a calcium channel blocker is a reasonable choice. This recommendation is based partly on the results of the Avoiding Cardiovascular Events in Patients Living With Systolic Hypertension (ACCOMPLISH) trial, in which the combination of benazepril plus amlodipine was superior to benazepril plus hydrochlorothiazide for reducing cardiovascular events in patients with diabetes and hypertension.

Pharmacotherapy for glycemic control in patients with diabetes is another important component of care and is associated with a decreased risk of diabetes-related complications. Guidelines from the American Diabetes Association recommend the initiation of metformin therapy in combination with TLC at diagnosis and supplementation with additional agents to achieve the target glycated hemoglobin level of less than 7% in most patients. These guidelines state that the choice of specific glucose-lowering agents should be individualized for each patient, taking into account the ability of the agent to lower glycated hemoglobin, safety and tolerability, ease of use, long-term adherence, cost, and nonglycemic effects. Metformin remains the cornerstone of therapy and is one of the few agents that has been clearly shown to be effective for diabetes prevention. Several classes of drugs are associated with weight loss (eg, glucagon-like peptide-1 agonists, pramlintide) or to be weight neutral (metformin, dipeptidyl peptidase-4 inhibitors). In contrast, other agents, such as thiazolidinediones, sulfonylureas, and insulin, are associated with weight gain (Table 1). In addition, thiazolidinediones are associated with fluid retention, increased risk of congestive heart failure, and possibly myocardial infarction (rosiglitazone).

Based on their proven ability to substantially lower LDL-C levels and to reduce the risk of clinical events, statins are the drug of choice for patients with hyperlipidemia. Patients who do not achieve lipid treatment goals with initial statin therapy, there are a number of options (Table 2). Doubling the dose of the statin produces a modest additional improvement in lipid parameters, but the benefit may not be sufficient to get patients to their goal. Bile acid sequestrants lower LDL-C levels additively in combination with statins and lack systemic toxicity, but they are associated with gastrointestinal symptoms and tend to raise serum triglyceride levels. Niacin produces a favorable effect across the entire lipid profile, raising high-density lipoprotein cholesterol levels and decreasing levels of LDL-C, lipoprotein(a), and triglycerides. However, compliance is a problem because of adverse effects (eg, flushing, gastrointestinal symptoms). Fibrates are especially effective for lowering triglyceride concentrations. The addition of ezetimibe to a statin is also an effective option. For example, the combination of rosuvastatin plus ezetimibe significantly increases the likelihood of achieving LDL-C goals. However, because such combinations are associated with increased costs and might decrease compliance, the use of a fixed-dose statin combination (eg, simvastatin-ezetimibe) is a reasonable option.

Therapeutic Lifestyle Changes
Therapeutic lifestyle changes (TLC) are important elements of treatment for patients with most major components of the metabolic syndrome (eg, dyslipidemia, hypertension, insulin resistance). Therapeutic lifestyle changes have 4 major constituents, as follows:

- smoking cessation
- exercise programs
- nutritional counseling
- weight control

These components can be simplified for patients into an easy-to-remember sound bite: “Eat smart, eat less, and move more.” Weight loss achieved through TLC is associated with improvements in diabetes control, hypertension, and lipid parameters. “Eating smart” also means eating the right kinds of food, and the Mediterranean diet is a good option for decreasing cardiovascular risk. For example, the Lyon Diet Heart Study was a secondary prevention study designed to evaluate whether a Mediterranean-type diet could reduce the rate of recurrence after a first myocardial infarction, compared with a prudent Western-style diet. After a mean follow-up of approximately 4 years, patients in the Mediterranean diet group achieved statistically significant reductions in all-cause and cardiovascular mortality (P=.01) and in the combination of recurrent myocardial infarction and cardiac death (P=.0001). There was an absolute 32% reduction (14 vs 44 events) for the combined end point of recurrent myocardial infarction and cardiac death. This dramatic reduction in risk exceeds that achieved in statin trials and underscores the value of TLC in the therapeutic regimen.

Figure 1 illustrates the differences between the Mediterranean diet pyramid and the United States Department of Agriculture food pyramid. The most important difference between these pyramids is the increased importance of fish consumption in the Mediterranean pyramid. In addition, there is a big emphasis in the Mediterranean pyramid on increasing the intake of fruits and vegetables. This increase is supported by results from the Nurses’ Health Study.
and the Health Professionals’ Follow-up Study, which evaluated 84,251 women aged 34 to 59 years, followed for 14 years, and 42,148 men aged 40 to 75 years, followed for 8 years. Increased intake of fruits and vegetables was associated with a progressive decrease in the risk for CHD, with a 20% risk reduction in the highest quintile compared with the lowest quintile. Each serving of fruits or vegetables was associated with a 4% lower risk for CHD, with green leafy vegetables and vitamin C–rich fruits and vegetables having the greatest benefit. Dietary whole grains and fiber have also been demonstrated to reduce CHD events. A pooled analysis of 10 clinical trials found that each 10-g incremental increase in total dietary fiber intake was associated with a 14% decreased relative risk for all coronary events and a 27% decreased risk of coronary death.

Achieving Maximal Reductions in Cardiovascular Risk

Achieving optimal clinical outcomes requires a comprehensive and aggressive therapeutic plan. In other words, pharmacotherapy and TLC both need to be used, with both components being approximately equally important. Failure to implement all the components of the plan will result in failure to achieve maximal reductions in future cardiovascular events.

Despite the conservative recommendations of the National Cholesterol Education Program ATP III, treatment should be considered in all men older than 45 years and all women older than 55 years. Treatment goals should also be aggressive because, as discussed earlier, there is a clear relationship between lower concentrations of LDL-C and improved clinical outcomes. Another major impetus for overcoming the clinical inertia for initiating aggressive therapy is the likelihood that insurance and governmental reimbursement rates in the future will be tied to quality-of-care markers. Physician reimbursements will be affected by the ability of clinicians to get their patients to targets established by national guidelines.

Enhancing the Likelihood of Successful TLC Implementation

Questionnaires

Persuading patients to embrace an effective TLC program is challenging; simply telling them to eat better and exercise more is usually not effective. Patient questionnaires are an effective way to increase patient acceptance of TLC programs by allowing the recommendations to be tailored to individual patients. Potential questions to be asked of patients are listed in Figure 2.

Patient Education: Clinical Pearls

It is important to discuss the patient’s eating schedule and to emphasize the value of eating breakfast. Skipping breakfast drives nighttime eating, which can cause patients to skip breakfast. When breakfast is skipped, lunch becomes breakfast, dinner becomes lunch, and the late-night snack becomes dinner, causing the cycle to continue. The importance of

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<tr>
<th>Table 1. Risk Factor Goals From the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial</th>
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<tr>
<td><strong>Variable</strong></td>
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<td>Smoking</td>
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<td>Total dietary fat/saturated fat</td>
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<td>Dietary cholesterol</td>
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<td>LDL-C (primary goal)</td>
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<td>HDL-C (secondary goal)</td>
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<td>Triglycerides (secondary goal)</td>
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<td>Physical activity</td>
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<td>Body mass index (BMI)</td>
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<td>Initial, 25-27</td>
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<tr>
<td>Initial, &gt;27.5</td>
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<tr>
<td>Blood pressure</td>
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<td>Diabetes</td>
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*Abbreviations:* HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

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<tr>
<th>Table 2. Drug Effects of Therapeutic Options for Patients Who Do Not Achieve Lipid Goals With Statin Monotherapy</th>
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<tr>
<td><strong>Drug Class</strong></td>
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<td>Double statin dose</td>
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<tr>
<td>Ezetimibe</td>
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<td>Niacin</td>
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<td>Bile acid sequestrant</td>
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<td>Fibrate</td>
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*Abbreviations:* HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, not significant.
breakfast should be stressed—based on my expertise, eating breakfast is clearly associated with weight loss. It is also important to educate patients on the role of visceral obesity in the development of metabolic manifestations. Patients should understand that visceral fat cells are involved in the production of inflammatory proteins and the development of insulin resistance, elevated blood sugar, hypertension, and dyslipidemia and that, based on my expertise, relatively modest reductions in weight (eg, 10%) can result in a 33% reduction in visceral fat and have a very positive effect on the lipid profile and insulin resistance.

Patients also need to understand that the calories consumed in liquids can often be substantial. A dietary diary that lists the time, location, portion size, and calories of everything consumed—including liquids—can be an excellent approach. Downloadable Internet applications (eg, www.myplate.com) can also be used to determine the caloric content of specific food portions.

Specific eating tips for patients include having an apple before lunch, which will decrease the number of calories consumed during the meal. Fiber intake can be increased by sprinkling a high-fiber breakfast cereal (eg, Fiber One) on low-fat yogurt as a bedtime snack. Patients should also be encouraged to eat only in a designated spot. Refraining from eating in other places can help break a number of bad eating habits.

Explaining the benefits of exercise to patients can help motivate them. Most patients are aware of the benefits of exercise for reducing cardiovascular risk, but emphasizing other benefits can be helpful. The effect of exercise on metabolic abnormalities—rather than as the key to weight reduction—should be stressed. Most patients do not know that, beginning at about age 45 years, they lose almost 1% in muscle mass per year.14 Patients should also be reminded of the potential benefits of exercise for maintaining cognitive function and reducing the risk of osteoporosis. Furthermore, exercise is helpful for maintaining flexibility and is a good stress reducer.

It is important to discuss pharmacotherapy and TLC at each office visit to underscore the importance of these treatments, and there are a number of specific things patients can be told to help improve their compliance with therapy. Patients should be reminded that their medications are not necessarily prescribed to make them feel better but to reduce their risk potential for heart attack and stroke. The establishment of target levels and the use of “report cards” (with smiley face stickers for good results) are important morale boosters. Relating personal experiences with successful therapy and stressing that the benefits of pharmacotherapy far outweigh the risk are also useful ways to motivate patients. Finally, recognize that cost is an important factor in patient compliance.

Future Therapies

A wide range of pharmacologic therapies are currently under clinical investigation. These include agents that work at different points in cholesterol synthesis (eg, squalene synthase inhibitors), affect intestinal lipid transport (eg, microsomal triglyceride transfer protein inhibitors), stimulate hepatic LDL receptors and potentially amplify several steps in reverse cholesterol transport (eg, thyromimetics), or target apolipoprotein B production genetic determinants (eg, antisense oligonucleotides), as well as bile acid transport inhibitors, anti-inflammatory agents, immunizations against oxidized LDL, and selective D prostanoid 1 inhibitors.

Figure 1. Dietary recommendations from United States Department of Agriculture (USDA) food pyramid (A) vs the Mediterranean food pyramid (B).
development of these newer agents will increase the available treatment options and may help more patients achieve their lipid goals.

Conclusion
The benefit and importance of lowering LDL-C levels is increasingly clear; therefore, LDL-C target goals should be aggressive. To achieve these goals, multifactorial interventions—not just a pharmacologic approach—are required to realize maximal reductions in cardiovascular risk. However, getting patients to their goals requires a concerted and systematic effort. Patient education is the key to changing behavior and improving compliance with prescribed therapeutic regimens. Questionnaires are a useful tool to help create individualized plans for patients to successfully implement TLC, and using easy-to-remember “sound bites” at every patient visit can also help drive home important concepts. By incorporating these approaches into everyday clinical practice, the attainment of target LDL-C concentrations can be improved, helping to optimize clinical outcomes.

References