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Impending Epidemic of Obesity, Metabolic Syndrome and Diabetes Mellitus-the Role of Prevention

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Introduction

Alan S. Brown, MD

The incidence of diabetes mellitus and obesity has been increasing at an alarming rate over the last 5 decades. This combination has the potential to reach epidemic proportions in our lifetime. In the fall of 2004, thought leaders from around the United States convened a symposium entitled “Role of Prevention in the Impending Epidemic of Obesity, Metabolic Syndrome, and Diabetes” at the Midwest Heart Foundation Seventh Annual Lipids in the Desert symposium in Tucson, Arizona. New clinical trial data regarding more aggressive goals for the lowering of plasma low-density lipoprotein (LDL) cholesterol levels in patients at high risk were also reviewed and discussed in detail.

The faculty agreed that there is a need to expand the number of physicians and other healthcare professionals who are familiar with the diagnosis and treatment of obesity and diabetes as well as a critical need for better understanding of strategies for behavioral modification. The articles in this supplement to The American Journal of Cardiology are based on lectures regarding the metabolic syndrome, diabetes, and aggressive lowering of elevated plasma LDL cholesterol levels. It is hoped that the information herein will assist practitioners in the diagnosis and management of patients at high risk for coronary events.

In the first article, Dr. Matthew J. Sorrentino describes the implications, diagnosis, and epidemiology of the metabolic syndrome. He suggests that diagnosis of the metabolic syndrome can help determine whether patients at intermediate risk should be considered for more aggressive risk-factor reduction and that measurement of novel factors, such as inflammatory markers, can identify patients who are at high intermediate risk. Treatment strategies to prevent or delay the development of diabetes and thus reduce risk for cardiovascular disease (CVD) are also explored.

Dr. Robert S. Rosenson then discusses assessment of risk across the spectrum of patients who have the metabolic syndrome, highlighting the importance of individual risk factors. The metabolic syndrome is a constellation of interrelated risk factors that are associated with increased risk for the development of type 2 diabetes and CVD events. Dr. Rosenson believes that CVD risk assessment in individuals with the metabolic syndrome is improved with measurement of LDL particle numbers, inflammatory markers such as C-reactive protein, and circulating levels of plasminogen activator inhibitor–1.

In his article, Dr. John P. Foreyt points out the critical need for lifestyle intervention in the prevention and treatment of the metabolic syndrome. He gives advice on how the clinical practitioner can initiate appropriate lifestyle interventions—most notably, preventive weight management or therapeutic weight loss—in patients with obesity and the metabolic syndrome. Keys to long-term success in lifestyle modification—setting reasonable goals, raising awareness, confronting barriers to change, managing stress, cognitive restructuring, preventing relapse, and providing support—are delineated.

Dr. Neil J. Stone and David Saxon follow with an approach to treatment of the patient with the metabolic syndrome, specifically emphasizing dietary and lifestyle interventions. They focus on the syndrome’s root causes—atherogenic diet, sedentary lifestyle, and overweight or obesity—and highlight the results of recent studies that demonstrate the effectiveness of therapeutic lifestyle change in preventing or improving components of the metabolic syndrome. These authors offer a practical approach that encompasses the patient, physician, and healthcare professionals as well as the overall healthcare system.

Dr. Michael H. Davidson explains the management of dyslipidemia in individuals with complicated metabolic syndrome, including those with the challenging comorbidities of hepatic steatosis and human immunodeficiency virus (HIV) lipodystrophy. Dyslipidemia in patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis may benefit from treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), fibric acid...
derivatives (fibrates), niacin, and thiazolidinediones. Because HIV lipodystrophy is associated with a marked risk for coronary artery disease (CAD), Dr. Davidson posits that more aggressive management may be required to improve prognosis for this dyslipidemia.

Next, I discuss findings from several new studies assessing the utility of aggressive lipid management in patients with diabetes. These studies indicate that statin therapy reduces the CAD risk in patients with diabetes, regardless of baseline LDL cholesterol levels.

Dr. Steven Haffner reviews the rationale for the new American Diabetes Association (ADA) guidelines and how they compare to the National Cholesterol Education Program (NCEP) guidelines for patients with diabetes. Both the ADA and the NCEP consider type 2 diabetes to carry CVD risk equivalent to that of existing CAD, requiring the lowering of plasma LDL cholesterol levels to <2.59 mmol/L (<100 mg/dL). Dr. Haffner describes the even lower LDL cholesterol goal of <1.81 mmol/L (<70 mg/dL), which is suggested for patients at very high risk for CVD events, including individuals with diabetes with or without existing CVD, and adjustment to therapy that may further reduce CVD event rates.

The increasing potential for complications of diabetes consequent to the impending epidemic of this disease is examined in the article by Dr. Mark A. Deeg, who describes for nonendocrinologists a basic approach to the management of hyperglycemia and its complications that encompasses control of multiple risk factors, including hypertension, dyslipidemias, and hyperglycemia. He focuses on the therapeutic options for managing hyperglycemia, from lifestyle modification to oral antidiabetic agents and insulin.

Dr. Falguni Vasa presents a protocol for aggressive glucose management in the critically ill, hospitalized patient with diabetes. He discusses the results of several landmark studies that challenge the widely held belief that stress hyperglycemia is beneficial and describes in detail the insulin infusion protocol developed to maintain euglycemia—and improve outcomes—in patients undergoing cardiac surgery.

Next, Dr. Gregg C. Fonarow outlines the pharmacologic approach to countering the neurohormonal activation that plays an essential pathophysiologic role in insulin resistance, diabetes, CVD events, and progression of heart failure. Pharmacologic intervention has been shown to decrease the morbidity and mortality associated with diabetes and heart failure, and thus the combination of β-adrenergic receptor blockade, angiotensin-converting enzyme inhibition, and aldosterone antagonism should be standard therapy for patients with diabetes and heart failure.

Dr. Neil J. Stone and his colleagues then take an in-depth look at the recent amendments to the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines for decision making in patients at high or very high risk for CVD. These authors suggest a process that encompasses risk assessment, therapeutic lifestyle change, use of statins as first-line pharmacotherapy (except in cases of severe hypertriglyceridemia), and combination therapy with a fibrate or niacin for other dyslipidemias after the plasma LDL cholesterol goal is achieved.

The penultimate article by Dr. James M. McKenney discusses pharmacologic approaches and options available for the achievement of aggressive plasma lipid–lowering goals. Because a significant reduction in coronary events is most often associated with ≥30% reduction in plasma levels of LDL cholesterol, starting more aggressive therapy with a potent statin (or higher dose of a less potent statin) is recommended. For an additional 10% to 15% lowering of LDL cholesterol, combination therapy can be instituted with colesevelam, ezetimibe, or niacin added to the stable statin regimen. Few data exist regarding the safety of lowering plasma LDL cholesterol levels to ≤1.81 mmol/L (≤70 mg/dL); however, a recent 2-year trial found no untoward effects at progressively lower levels in patients whose treatment achieved LDL concentrations as low as 0.67 mmol/L (26 mg/dL).

Finally, Dr. Paul Ziajka discusses the utility of LDL apheresis and its role in clinical practice. He points out that apheresis can reduce the plasma levels of total cholesterol, LDL cholesterol, and lipoprotein(a). Additional benefits associated with LDL apheresis, including induction of atherosclerosis regression; improvement in myocardial perfusion and endothelial function; and the potential for reduction in CVD event rates, are described.

Acknowledgment

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The MHF is also grateful for the efforts of the faculty of the 2004 Lipids in the Desert meeting for their outstanding presentations and their contributions to this supplement.

I would like to thank Lynn A. Cofer, MSN, RN, Guest Assistant Editor, for her outstanding effort and insight with regard to the preparation of this supplement.
Implications of the Metabolic Syndrome: the New Epidemic

Matthew J. Sorrentino, MD

On the basis of traditional risk factors, a large number of individuals in the United States can be classified as at intermediate risk for the development of ischemic heart disease. The diagnosis of the metabolic syndrome can help determine whether patients at intermediate risk should be considered for more aggressive risk-factor reduction. The measurement of novel risk factors, such as inflammatory markers, can identify a group of patients at high intermediate risk. The Adult Treatment Panel of the National Cholesterol Education Program suggests considering a more aggressive low-density lipoprotein cholesterol treatment goal in this group of individuals. In addition, the presence of the metabolic syndrome is highly predictive of the development of diabetes mellitus. A treatment strategy focusing on aerobic exercise and weight loss can help delay or prevent the development of diabetes and can help reduce cardiovascular risk. For significant risk reduction to be achieved, treatment strategies must focus on therapy for all risk factors, including dyslipidemia, hypertension, and insulin resistance. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:3E–7E)

Coronary artery disease (CAD) remains the leading cause of death for men and women in this country. The identification of cardiovascular risk factors can determine the risk of developing heart disease and lead to beneficial preventive measures. A large number of individuals in the United States, however, can be classified as at intermediate risk for the development of CAD; more precise ways are needed to measure risk in this group. The designation of the metabolic syndrome as well as the use of novel risk markers can help to identify a cohort at higher risk within the intermediate risk category who may benefit from more aggressive risk-reduction therapies.

Determination of Risk

The standard method for calculating a patient’s risk is the counting of traditional independent CAD risk factors (Table 1) and use of an algorithm based on a large data set, such as that of the Framingham study. The Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) suggests categorizing individuals into 3 risk groups: high risk, defined as a >20% 10-year risk for patients with documented CAD or CAD risk equivalent disease; intermediate risk, defined as a 10% to 20% 10-year risk for patients with multiple risk factors; and low risk, defined as a <10% risk for individuals with ≤1 risk factor.1 The 10-year risk assessment is carried out using a simplified version of the Framingham scoring system. Certain individuals are considered to be at high risk regardless of Framingham score. These individuals are classified as having CAD risk equivalent disease (Table 1). This category includes patients with diabetes mellitus and/or atherosclerotic disease in other vascular beds, such as peripheral arterial disease, abdominal aortic aneurysm, or symptomatic carotid artery disease. These patients have a >2% 1-year or >20% 10-year risk of having a coronary event.

There are a number of shortcomings to the Framingham scoring system for determination of cardiac risk. The scoring system does not include family history of premature CAD even though family history has been designated a major risk factor. The scoring system does not include risk factors that were not independent predictors of risk in this data set, such as obesity, sedentary lifestyle, and elevated triglyceride values. The metabolic syndrome is likewise not included as a component of the current scoring system. The Framingham scoring system does not discriminate risk very well in women aged <60 years and in the elderly. With this data set, women need to be 10 to 20 years older than men to achieve the same level of risk. In addition, the Framingham scoring system may not be applicable to all populations. Among Japanese American and Hispanic men, Native American women,2 and a large Chinese cohort,3 the Framingham functions overestimated CAD risk. The risk associated with hypertension, especially in black women, may be underestimated by the largely white Framingham population.2

The Framingham scoring system can be used as an initial estimate of risk, however. Evaluation of emerging risk factors can then be done to modify the initial prediction. This will be most important for the large group of individuals who are included in the intermediate risk category. After their basal risk is assessed by means of traditional risk factor
analysis, individuals can be evaluated for criteria of the metabolic syndrome, novel risk factors such as inflammatory markers can be measured, and assessment for the presence of subclinical atherosclerotic disease can be performed. The presence of these additional factors may change an individual’s risk calculation from low-intermediate to high-intermediate risk or even high risk. These patients can then be treated with more aggressive risk-reduction modalities to modify their future CAD risk. This type of analysis can help to identify the patient who is likely to be vulnerable to plaque rupture and acute coronary events.

The Metabolic Syndrome

The metabolic syndrome as defined by the NCEP1 is described in Table 2. The metabolic syndrome is a constellation of risk factors that develop in individuals who have abdominal (visceral) obesity, an increased prevalence of insulin resistance, and an increased risk of diabetes. The presence of abdominal obesity is more highly correlated with the development of insulin resistance than is body weight or body mass index (BMI), so measurement of waist circumference is recommended for diagnosis of the metabolic syndrome. The development of insulin resistance leads to many of the metabolic abnormalities associated with this syndrome. Patients with insulin resistance tend to have an increased prevalence of small, dense, more atherogenic low-density lipoprotein (LDL) particles; below average plasma levels of high-density lipoprotein (HDL) cholesterol; elevated plasma levels of triglyceride-containing particles; endothelial dysfunction that can lead to hypertension; and impaired fasting plasma glucose levels.

Measuring the presence of novel risk factors can further modify the estimate of risk. This may be useful in determining the risk associated with the metabolic syndrome. The presence of inflammatory markers correlates with an increased risk of acute coronary events and thus may be a predictor of the existence of vulnerable plaques. C-reactive protein (CRP), one of the best-studied inflammatory markers, is associated with a number of medical conditions (Table 3).4 Serum CRP levels correlate with the Framingham risk score5 and, in a cohort of men aged 45 to 74 years, gave a significant contribution to coronary event prediction.

Table 1
Major risk factors* for coronary artery disease (CAD) and CAD risk equivalent diseases

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Defining level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>Hypertension (≥ stage 1, or using antihypertensive medication)</td>
<td></td>
</tr>
<tr>
<td>Low plasma levels of HDL cholesterol (&lt;1.03 mmol/L [&lt;40 mg/dL])</td>
<td></td>
</tr>
<tr>
<td>Family history of premature CAD (CAD in male first-degree relative &lt;55 yr, CAD in female first-degree relative &lt;65 yr)</td>
<td></td>
</tr>
<tr>
<td>Age (men aged ≥45 yr, women aged ≥55 yr)</td>
<td></td>
</tr>
<tr>
<td>CAD risk equivalent diseases</td>
<td></td>
</tr>
<tr>
<td>Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Multiple risk factors, conferring a 10-yr risk for CAD &gt;20%</td>
<td></td>
</tr>
</tbody>
</table>

*Exclusive of low-density lipoprotein cholesterol.
HDL = high-density lipoprotein.
Adapted with permission from JAMA.1

Table 2
Clinical identification of the metabolic syndrome*

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Defining level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (waist circumference)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥1.69 mmol/L (≥150 mg/dL)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;1.03 mmol/L (&lt;40 mg/dL)</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;1.29 mmol/L (&lt;50 mg/dL)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>≥6.11 mmol/L (≥110 mg/dL)</td>
</tr>
</tbody>
</table>

*Diagnosis requires the presence of ≥3 risk factors.
Adapted with permission from JAMA.1
that was independent of the Framingham score. CRP levels can further modify risk associated with the metabolic syndrome. In women, the presence of ≥3 features of the metabolic syndrome is associated with high levels of CRP, and CRP measurement added prognostic value to the risk predicted by the metabolic syndrome alone. A risk gradient has been shown between CRP values and all levels of the Framingham risk score, suggesting that a CRP-modified CAD risk score can be calculated to improve prediction of cardiac events.

Finally, the single most useful piece of information in patients at intermediate risk is knowledge of whether subclinical atherosclerotic disease is present. Table 4 lists the available modalities that may measure subclinical disease. Exercise stress testing has been the standard screening test; however, it will reveal only occlusive lesions and cannot identify nonocclusive but vulnerable plaques. The ankle-brachial index (the ratio of systolic blood pressure in the posterior tibialis artery and the brachial artery) is easily determined in the office setting. A ratio of <0.9 indicates the likely presence of peripheral arterial disease and correlates with an increased risk of cardiovascular events. Calcium scoring by electron-beam computed tomography (EBCT) can quantify the burden of atherosclerotic disease. The higher the score, the more likely vulnerable plaques are present. EBCT and magnetic resonance imaging, however, are not universally available. Carotid intimal-medial thickness correlates with the incidence of coronary events, but the technology for determining this measurement is not readily available and accurate values may be difficult to reproduce outside of a research setting. Therefore, the optimal test to measure subclinical atherosclerotic disease has not yet been determined.

The metabolic syndrome has become common, with >22% of Americans fulfilling the criteria for this syndrome. Not all of these individuals are at high cardiovascular risk. Risk-factor assessment—beginning with traditional risk-factor analysis and including determination of the risk elements of the metabolic syndrome, measurement of inflammatory markers or novel lipid parameters, and an assessment of subclinical atherosclerotic disease—has the potential of dividing this large group of individuals into low-intermediate and high-intermediate risk cohorts. Risk-reduction therapy can then be tailored to the risk group.

An underlying cause of the metabolic syndrome and diabetes, obesity has markedly increased in prevalence in this country. A number of studies have correlated increasing weight with cardiovascular risk. For example, the Nurses’ Health Study showed a correlation between body weight and mortality among middle-aged women. Women in the highest weight category (BMI ≥32.0) had a >4-fold risk of death due to cardiovascular disease compared with lean women.

The metabolic syndrome is a precursor to the development of diabetes. Identifying individuals with the metabolic syndrome is a way to find a large number of patients who are destined to develop diabetes if no intervention is begun at an earlier stage in their disease. Patients who are euglycemic but insulin resistant with hyperinsulinemia may already have developed endothelial dysfunction and many of the metabolic abnormalities (eg, dyslipidemia, inflammation, prothrombotic state, oxidative stress) that may lead to the development of vascular disease. Intervention at this earlier stage may help prevent the development of diabetes and the vascular sequelae associated with this disease.
Treatment of the Metabolic Syndrome

Treatment of the metabolic syndrome should focus on the underlying causes. Since the obesity epidemic is a major cause of the metabolic syndrome, weight loss and exercise is the cornerstone of any treatment plan. Regular physical exercise may reduce plasma LDL and very-low-density lipoprotein cholesterol levels, raise plasma levels of HDL cholesterol, lower blood pressure, and improve insulin sensitivity. Studies have proved a cardiovascular benefit to exercise. For example, 1 recent survey showed a strong protective effect of cardiovascular fitness against all-cause and cardiovascular mortality in men with the metabolic syndrome.

Weight loss may also improve plasma lipid levels, lower blood pressure, improve insulin sensitivity, and reduce levels of inflammatory markers. Weight loss combined with an exercise program can delay and possibly prevent the development of diabetes in insulin-resistant individuals. The Diabetes Prevention Program examined a large cohort of individuals with insulin resistance. A subset of participants began a lifestyle modification program with a goal of ≥7% weight loss and 150 minutes of physical activity per week. After an average follow-up of 2.8 years, the lifestyle intervention group achieved a nearly 60% reduction in the incidence of diabetes compared with the placebo group.

In addition to a therapeutic lifestyle program, it is necessary to address both the lipid and nonlipid factors in the metabolic syndrome to reduce cardiac risk. Lipid-lowering therapy across the spectrum of cardiovascular risk has been shown to be effective in preventing major cardiovascular events. LDL cholesterol should be the primary target of therapy. The Heart Protection Study showed that lipid-lowering therapy with simvastatin 40 mg/day in patients at high risk, including individuals who are in the CAD risk equivalent disease category, reduced the risk of major vascular events regardless of initial plasma cholesterol concentrations. The Collaborative Atorvastatin Diabetes Study (CARDS) verified that lipid-lowering therapy with atorvastatin 10 mg/day for the primary prevention of cardiovascular disease is effective in a diabetic population even when plasma LDL cholesterol levels are not high. The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) demonstrated that lipid-lowering treatment with atorvastatin 10 mg/day in a cohort of patients with hypertension substantially reduced the incidence of major cardiac events, with benefit emerging within the first year of therapy.

Since patients with the metabolic syndrome typically have a mixed hyperlipidemia, there has been interest in lipid-lowering modalities that may reduce plasma levels of triglycerides and raise plasma levels of HDL cholesterol as well as lower plasma levels of LDL cholesterol or change LDL cholesterol particles to a less atherogenic subfraction. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) used gemfibrozil 1,200 mg/day in a group of patients with CAD and low values for plasma HDL cholesterol. Treatment reduced plasma levels of triglycerides by about 31% and increased plasma levels of HDL cholesterol by about 6% with no significant change in LDL cholesterol levels. The treatment group achieved a 24% reduction in cardiovascular events, a risk reduction similar to that achieved in the Heart Protection Study. Results of primary prevention trials with fibrates, such as the Helsinki Heart Study, suggest that the subset of patients with high plasma levels of triglycerides and low levels of HDL cholesterol may achieve the greatest risk reduction with this class of agents. This describes the patient with the metabolic syndrome.

Additional studies on the optimal treatment of insulin resistance and hypertension in the metabolic syndrome are needed. There is interest in using agents such as the thiazolidinediones, currently prescribed for diabetes, for patients with the metabolic syndrome, in part because of possible favorable effects on cardiovascular risk factors. Optimal goals for hypertensive therapy are needed for patients with the metabolic syndrome. There is emerging evidence suggesting that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may reduce the incidence of new-onset diabetes, as seen recently in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial. These findings will require further study so that guidelines for the treatment of risk factors in patients with the metabolic syndrome can be formulated.

The metabolic syndrome represents a constellation of interrelated risk factors that identify individuals at increased risk for the development of type 2 diabetes mellitus and cardiovascular events. The definitions for the metabolic syndrome differ in that the World Health Organization (WHO) and American College of Endocrinology definitions require the presence of insulin resistance, whereas the criteria of the Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) are satisfied by a combination of any 3 of 5 criteria that include central obesity, hyperglycemia (fasting plasma glucose $\geq 6.11$ mmol/L [$\geq 110$ mg/dL]), high plasma levels of triglycerides (fasting triglycerides $\geq 1.69$ mmol/L [$\geq 150$ mg/dL]), and a low value for plasma high-density lipoprotein (HDL) cholesterol ($<1.03$ mmol/L [$<40$ mg/dL] in men and $<1.29$ mmol/L [$<50$ mg/dL] in women). Clearly, these definitions that mandate insulin resistance will more accurately identify individuals at increased risk for type 2 diabetes. However, these definitions are equally valid in the assessment of cardiovascular risk. Yet the major components of the metabolic syndrome, in conjunction with plasminogen activator inhibitor–1 (PAI–1) levels, account for no more than 50% of the cardiovascular risk associated with the metabolic syndrome. This overview discusses the utility of lipoprotein particle number, inflammatory mediators, and hemostatic variables in risk-assessment models for patients with the metabolic syndrome (Table 1).

Lipids and Lipoproteins

Two major criteria for the metabolic syndrome include abnormalities in plasma lipid levels (eg, high levels of fasting triglycerides and low levels of HDL cholesterol); however, lipoprotein subclass abnormalities that accompany the metabolic syndrome provide important insights regarding cardiovascular risk and approaches to treatment.

Lipoprotein abnormalities in insulin resistance are characterized by increased levels of large very-low-density lipoprotein particles, high levels of small cholesterol-deplete low-density lipoprotein (LDL) particles, and low levels of large cholesterol-enriched HDL particles. In the Framingham Offspring Study, increasing numbers of metabolic risk factors were associated with progressively higher concentrations of small LDL particles and progressively lower concentrations of large LDL particles. Although there were no associations between LDL cholesterol levels and components of the metabolic syndrome, the numbers of LDL particles increased as the number of metabolic factors increased. LDL particle number is more strongly related to coronary atherosclerosis and cardiovascular events than either calculated or direct measures of LDL cholesterol. In the Women’s Health Study, LDL particle number was associated with a 4.17 (95% confidence interval [CI], 1.96 to 8.87) increased risk of a major cardiovascular event in multivariate analyses that included major lipid and nonlipid risk factors.

In patients with the metabolic syndrome, LDL particle number is an especially important measure. In the Framingham Offspring Study, 73% of patients with the metabolic syndrome and a plasma LDL cholesterol level $<2.59$ mmol/L ($<100$ mg/dL, lower 20th percentile) had elevated LDL particle numbers (above the 20th percentile). Because small LDL particles carry less cholesterol than do large...
Inflammatory Markers

Vascular inflammation is a central process that leads to instability of atherosclerotic plaques. The inflammatory pathways responsible for the recruitment and retention of T cells and mononuclear cells, transformation of mononuclear cells into macrophages, and synthesis of matrix-degrading proteolytic enzymes that weaken the fibrous cap of the plaque are activated by multiple pathways operant in the metabolic syndrome. The metabolic stimuli that activate the redox-sensitive transcription factor nuclear factor–κB (NF-κB) include oxidized LDL, angiotensin II, and the receptor for advanced glycosylation end products (RAGE). In human carotid endarterectomy specimens isolated from patients with diabetes, there were concentration-dependent associations between hyperglycemia, RAGE, NF-κB activation, inflammatory cell infiltrates (T cells and macrophages), and expression of matrix metalloproteinases.

Visceral adipocytes release tumor necrosis factor (TNF)–α and interleukin (IL)–1β that in turn induce hepatic synthesis of C-reactive protein (CRP). TNF–α binds to cellular receptors R1 and R2. Ligation of the TNF-R2 receptor has a dual effect on insulin resistance through inhibition of the cellular uptake of glucose and phosphorylation of the insulin receptor. In a cross-sectional analysis, the atherogenic dyslipoproteinemia (high plasma levels of triglycerides, low levels of HDL, small LDL particles) of insulin resistance was more highly correlated with increased levels of TNF-R2 receptor than were concentrations of IL-6 or high-sensitivity (hs)–CRP.

Although several inflammatory markers have been shown to indicate individuals at heightened risk for an initial or recurrent cardiovascular event, 3 proinflammatory markers identified healthy women at increased risk of type 2 diabetes. New-onset type 2 diabetes incidence was highest in women with the highest levels of hs-CRP (multivariate odds ratio [OR], 4.36; 95% CI, 2.80 to 6.80 for the uppermost quintile: ≥4.05 mg/L) versus the lowest quintile (≤0.55 mg/L) and to a lesser extent by IL-6 (OR, 1.91; 95% CI, 1.27 to 2.86) and TNF-R2 (OR, 1.64; 95% CI, 1.10 to 2.45). Several prospective studies have demonstrated that increasing numbers of metabolic syndrome factors were accompanied by higher levels of hs-CRP as well as increased rates of type 2 diabetes onset and cardiovascular events. Further, elevated hs-CRP levels identified patients with diabetes at particularly high risk for cardiovascular events.

Adiponectin is involved in the regulation of insulin sensitivity, lipid oxidation, and inhibition of NF-κB activation. Thus it may lower circulating concentrations of NF-κB, IL-6, and hs-CRP. High levels of adiponectin are associated with a reduced risk of type 2 diabetes and myocardial infarction (multivariate relative risk 0.41; 95% CI, 0.24 to 0.70).

Hemostatic Abnormalities

The hemostatic abnormality most closely linked to insulin resistance is elevation of circulating PAI-1. Other abnormalities less consistently associated with insulin resistance include high levels of plasma fibrinogen and vitamin K-dependent coagulation factors. Using factor analyses, high levels of fibrinogen cluster with body mass index, and coagulation factors cluster with fasting and postprandial triglyceride levels. In the Insulin Resistance Atherosclerosis Study, high PAI-1 levels identified overweight individuals at high risk for type 2 diabetes. However, variability of PAI-1 measurements has limited its clinical utility.

Conclusion

In individuals with the metabolic syndrome, those markers that impart clinically useful information concerning risk of developing type 2 diabetes or cardiovascular disease are LDL particle number and hs-CRP. LDL particle number is a robust predictor of cardiovascular events, and the importance of LDL particle number is particularly relevant in the metabolic syndrome, where “optimal” plasma LDL cholesterol levels generally do not reflect optimal numbers of LDL particles. Moreover, LDL particle number serves as a rational guide to therapeutic decisions. Although there has been much discussion concerning small LDL particle size, LDL particle size is a weak or nonsignificant predictor of cardiovascular events in models that include LDL particle numbers.

CRP is the most extensively studied inflammatory predictor of type 2 diabetes and cardiovascular events among individuals with the metabolic syndrome. Although the
studies that have included soluble TNF-R2 and adiponectin are limited, these inflammatory markers require further investigation because they are integral to the pathogenesis of the insulin resistance syndrome.


The metabolic syndrome is the fastest growing disease entity in the world. Prevention and effective treatment emphasize lifestyle intervention, including healthful diet, physical activity, and pharmacologic agents to target specific risk factors. Weight loss improves all aspects of the metabolic syndrome and is a primary intervention target. Effective weight management also helps prevent the development of the metabolic syndrome. Lifestyle change strategies—including setting reasonable goals, raising awareness, confronting barriers to change, managing stress, cognitive restructuring, preventing relapse, and providing support—are the keys to long-term success. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:11E–14E)

The metabolic syndrome is the fastest growing disease entity in the world. It is the disease of the new millennium. In the United States, almost 25% of adults have the metabolic syndrome.1 By the time they become 60 years old, almost 50% of adults have the syndrome, which is characterized by a group of metabolic risk factors, including central obesity, atherogenic dyslipidemia (high plasma levels of triglycerides and low plasma levels of high-density lipoprotein cholesterol), raised blood pressure, and impaired glucose tolerance.2 The metabolic syndrome will soon overtake cigarette smoking as the number 1 risk factor for heart disease in the US population. Its prevalence is increasing dramatically worldwide because of increasing obesity and inactivity. The syndrome is also afflicting an increasing number of children and adolescents.

Effective treatment emphasizes lifestyle intervention, including diet, physical activity, and pharmacologic agents to target specific risk factors. Weight loss significantly improves all aspects of the metabolic syndrome and is a primary intervention target. An effective way of reducing insulin resistance in obese patients with the metabolic syndrome is weight loss and increase in physical activity. Effective lifestyle intervention will also help prevent the development of the metabolic syndrome.

How to Begin

Most patients with or at risk for the metabolic syndrome will need to make some changes in their diet, increase their physical activity, and lose weight. For the physician to be most effective in guiding lifestyle changes, it is helpful to have a “toolbox” of strategies available. No two patients are alike, and being able to tailor interventions to the unique needs of each patient increases the likelihood of long-term success. This article outlines a number of toolbox strategies that have shown some success in helping patients achieve and maintain a healthful lifestyle. Physicians are busy and do not have much time to spend with patients, so the critical elements of a brief lifestyle-counseling approach are summarized.

Patient assessment: Patient assessment typically includes a patient’s degree of obesity, diet, exercise, emotional problems, and motivation to change.3 The degree of obesity helps define the most useful intervention. For example, lifestyle-change strategies are typically most helpful with patients who are overweight to moderately obese, with a body mass index (BMI) ranging from 25 to 40. With patients whose BMIs exceed 40, much more intensive strategies, even involving bariatric surgery, may be indicated. Registered dietitians are best for helping evaluate patients’ diets and dietary patterns. If referral to a dietitian is not practical, a brief assessment tool, such as the MEDFICTS (Meats, Eggs, Dairy, Fried Foods, Fat in Baked Goods, Convenience Foods, Fats Added at the Table, and Snacks) Dietary Assessment Questionnaire, can be helpful.4 The standard diet for weight loss includes a balanced, reduced-calorie plan, based on US Department of Agriculture guidelines, with a deficit of 500 to 1,000 calories/day, leading to a safe, recommended loss of 1 to 2 lb/wk (0.45 to 0.90 kg/wk).5 Physical activity can be assessed by asking patients the number of minutes per day they spend in activities such as brisk walking or, better yet, having them complete the brief 7-day Physical Activity Recall Questionnaire.6 Emotional problems tend to complicate weight-loss interventions. The Beck Depression Inventory for Primary Care or some similar brief questionnaire can help identify patients who may need referral to counselors before beginning lifestyle intervention.7 Unfortunately, not all patients are sufficiently motivated to make changes in their lifestyles.
Understanding a patient’s willingness to adopt a more healthful diet and exercise plan can help the physician select the most appropriate intervention. For patients who do not appear motivated to change, setting goals—either by having the patient identify and modify the barriers to their lifestyle change, or by increasing awareness—can sometimes be helpful. For patients who appear interested in making a few changes, basic education about some simple steps to improve their health is often useful. Encouragement from physicians can make a major difference in the lives of many patients. For patients who are motivated to change, the lifestyle change strategies described below are extremely helpful. Patients who are already eating healthfully, exercising, and managing their weight are usually encouraged and sustained by a few words of moral support and recognition from their physician.

**Lifestyle Intervention Strategies**

To help patients develop healthful lifestyles, a number of strategies that are especially efficacious can be part of a physician’s toolbox. These strategies include setting goals, raising awareness, confronting barriers, managing stress, cognitive restructuring, preventing relapse, providing support, and contracting.

**Setting goals:** Patients frequently have unrealistic goals regarding weight loss. Many patients express a desire to lose ≥30% of their current weight when, in reality, the average patient will lose about 8% to 10% of baseline weight. Even though this modest weight loss will lead to improvement in metabolic syndrome risk factors, it is often disappointing to the patient. Setting easy-to-achieve short-term goals, such as increasing the number of steps per day or the number of minutes that a patient walks during the day, can lead ultimately to weight regain and feelings of failure.

**Raising awareness:** The most important of all lifestyle intervention strategies for achieving and maintaining a healthful lifestyle is self-monitoring, or raising awareness. It is essential that patients know what they are eating and how much they are exercising. Self-monitoring involves self-observation, self-recording, and feedback. Food and exercise diaries are the best way to achieve this. Patients are required to write down what they eat and how many minutes they exercise. They then look up the calories that they ate during the day and estimate how many calories they burned during exercise, calculating about 6 calories per minute for walking. Inexpensive pedometers are also helpful, figuring about 100 calories burned for each 2,000 steps. Accuracy is not crucial in their recording, as most patients tend to underestimate their energy intake by about one third and overestimate their expenditure by about one half. Food and exercise diaries are critical not for their accuracy but because they help raise awareness. Patients do not like to keep diaries. Yet diaries are considered to be the most important of all lifestyle-change strategies, and if physicians encourage their use, they will increase significantly patients’ chances of long-term success. Diaries thus are an essential component of a physician’s toolbox. To increase awareness of body weight, weighing daily during the weight loss phase and weekly during long-term maintenance is also needed.

**Confronting barriers:** Why is the patient not eating healthfully and exercising regularly? Problem solving involves helping the patient identify and modify the barriers contributing to the diet and physical activity lapses. The food and exercise diaries, or a brief discussion with the patient, can be used to identify problems faced since the last appointment. Eating away from home, extensive traveling, and eating late in the evening are common barriers to staying on course. Asking patients what they can do to overcome these problems can be helpful. Encouraging the patient to figure out strategies to deal with the behavioral issue is usually better than the physician solving the problem for the patient. Calling restaurants ahead of time and asking for healthful menu suggestions; carrying meal replacements or prepackaged, calorie-controlled meals when traveling; and planning sensible evening snacks ahead of time are some strategies that patients can be encouraged to implement.

**Managing stress:** Stress will interfere with the development or maintenance of a healthful lifestyle. A brief discussion of stressful life events that patients need to address can help them manage their diets more successfully. Physical activity is a particularly useful strategy for managing stress because it raises psychological well-being. Daily meditation can be helpful. Progressive muscle relaxation, a strategy involving tensing and relaxing muscles, also can be easily learned and can lead to a significant reduction in stress.

**Cognitive restructuring:** Unfortunately, some patients seem to believe that by losing weight their lives will be forever changed and that all their problems will magically disappear. Cognitive restructuring involves helping patients change the way they think about themselves in a more positive, realistic manner. Patients can develop self-enhancing, self-affirming thoughts and beliefs to help them stay focused. Having patients come up with their own self-affirmations, such as “I will walk for at least 30 minutes before dinner today,” and having them repeat it daily can be a strong impetus to continue their lifestyle program.
**Preventing relapse:** Everyone strays from time to time. Helping patients handle their transgressions by understanding that lapses are to be expected and learning to deal with them are particularly important.\(^{14}\) When patients learn to expect lapses (such as during holiday or vacation periods) and practice coping strategies, they may avoid a total collapse.

**Providing support:** Strong support from family members, close friends, colleagues, physicians, and others can be powerful for patients losing weight and maintaining a healthful lifestyle.\(^{14}\) A family that eats and exercises together can be an ideal support system. Friends and colleagues who exercise together can often encourage each other to stay the course. Support systems are successful because they provide good role models, help in overcoming barriers to change, and allow for self-acceptance.

**Contracting:** Contracting involves having patients verbalize ≥1 healthful behavior that they agree to perform between visits.\(^{14}\) The behavior should be realistic, simple, and achievable. Increasing the number of days walked during the week from 3 to 4, increasing the minutes walked per day from 20 to 30, adding a vegetable to the evening meal, or cutting desserts to twice a week are probably achievable. Having patients write down the behavior change and sign the page seems to formalize the agreement and may thus help in achieving the goal. Contracts can be especially useful in motivating short-term change. A new contract each visit is recommended.

**Adding pharmacotherapy:** Sometimes behavioral change strategies are not enough. Adding pharmacotherapy to the patient’s lifestyle-change program can be helpful.\(^{15}\) The US Food and Drug Administration (FDA) has approved 2 weight-loss drugs for long-term use: sibutramine hydrochloride monohydrate (Meridia; Abbott Laboratories, North Chicago, IL) and orlistat ( Xenical; Roche Laboratories Inc., Nutley, NJ). Sibutramine is a selective serotonin and noradrenaline reuptake inhibitor, with its primary mechanism of action being enhanced satiety. It has good evidence of efficacy at the approved doses of 10 to 15 mg/day.\(^{16}\) It does increase blood pressure and pulse in some patients, so careful monitoring is required. It may not be applicable for those with significant cardiovascular disease. Orlistat is a lipase inhibitor that reduces the body’s absorption of about 30% of dietary fat. It also has good efficacy at approved doses of 120 mg 3 times a day (at each main meal).\(^{17}\) Its expected effects include oily or loose stools, oily spotting, and the urge to have a bowel movement quickly. With a diet including <30% fat, these effects tend to be minimal. Orlistat also works as a behavioral-change strategy because it encourages patients to eat a lower-fat diet to avoid the gastrointestinal effects. A multivitamin supplement is required because orlistat reduces the absorption of fat-soluble vitamins.

### Streamlining Lifestyle Intervention

Because physicians do not have the time to assist with all of the lifestyle issues that their patients face in their daily lives, an efficacy assessment was undertaken of a tailored, brief intervention for weight reduction that involved monthly 15- to 20-minute sessions (unpublished data). The key elements included a brief review of food and exercise diaries, review of goals from the previous session, discussion of additional problems, setting of new goals, and having the patients sign a behavioral contract for which they agreed to make ≥1 new change in their lives. The patients were given positive feedback and encouragement, and all successes were congratulated. Lack of progress was not criticized. Table 1 summarizes the elements of this streamlined lifestyle-intervention session.

### Conclusion

Weight loss is essential for most individuals with or at risk for the metabolic syndrome. Lifestyle-change strategies—including setting reasonable goals, raising awareness, confronting barriers, managing stress, cognitive restructuring, preventing relapse, and providing support—are keys to long-term success. A streamlined approach for physicians involving brief discussion of food and exercise diaries, review of previous goals, problem solving, setting new goals, and use of behavioral contracts may help patients achieve and maintain a healthful lifestyle.


Approach to Treatment of the Patient with Metabolic Syndrome: Lifestyle Therapy

Neil J. Stone, MD*, and David Saxon, BA

The National Cholesterol Education Program’s Adult Treatment Panel III definition of the metabolic syndrome identifies those at high risk for diabetes mellitus and/or a cardiac event by clustering a number of easily measured clinical findings, including abdominal obesity, elevated plasma levels of triglycerides, low plasma levels of high-density lipoprotein cholesterol, elevated fasting blood glucose, and elevated blood pressure. The presence of \( \geq 3 \) of these 5 risk factors justifies a diagnosis of the metabolic syndrome. This article focuses on root causes of the syndrome (atherogenic diet, sedentary lifestyle, and overweight/obesity) and highlights recent studies that demonstrate the effectiveness of therapeutic lifestyle changes in improving or preventing the components of the metabolic syndrome. We offer a practical approach with a focus that embraces not only patients, but also physicians and healthcare professionals as well as the larger healthcare system. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:15E–21E)

The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) offered an evidence-based approach to management of the patient with high plasma levels of cholesterol.\(^1\) Due to the strong causal relation between elevated plasma values for low-density lipoprotein (LDL) cholesterol and coronary artery disease (CAD), the primary focus of the ATP III algorithm was on LDL cholesterol. Knowledge of LDL cholesterol plasma level alone, however, is not enough to describe individual risk for CAD. Risk factors increase the likelihood of CAD at every level of LDL cholesterol, and individuals with multiple or severe risk factors are found to have CAD at low plasma levels of LDL cholesterol. An important syndrome of multiple metabolic risk factors, the metabolic syndrome was operationally defined in the ATP III report by requiring \( \geq 3 \) of 5 easily measured clinical and laboratory parameters.\(^2\) The components and the diagnostic criteria for the metabolic syndrome are given in Table 1.

Subsequent to the ATP III report, studies have shown that metabolic syndrome enhances the risk of CHD, not only in those with elevated plasma levels of LDL cholesterol, but also in those with average or below-average levels.\(^3,4\) Even individuals with 1 or 2 risk factors of the metabolic syndrome are at increased risk. Moreover, presence of the metabolic syndrome predicts CAD risk more strongly than each of the individual risk factors does alone. This accentuated CAD risk likely involves not only the dyslipidemia (high plasma levels of triglycerides and low plasma levels of high-density lipoprotein [HDL] cholesterol), hypertension, and hyperglycemia, but also other clinically unmeasured risk factors such as prothrombotic (eg, fibrinogen, plasminogen activator inhibitor–1) and proinflammatory (eg, ultrasonic reactive C-reactive protein) markers. Whereas each risk factor can be dealt with individually, the initial therapeutic approach to the metabolic syndrome should focus on reversing its root causes of atherogenic diet, sedentary lifestyle, and overweight or obesity. This article reviews those studies that have focused on what ATP III called therapeutic lifestyle change as the nonpharmacologic approach to management of the metabolic syndrome.

**Atherogenic Diet**

Currently, the diet of the United States is characterized by being high in calories, saturated fat, and dietary cholesterol. Because of the key role of saturated fat intake in raising plasma cholesterol levels and eventual CAD death rates,\(^5\) national organizations have recommended a restriction in saturated fat intake for several decades. For many years, the NCEP and the American Heart Association (AHA) advocated an intake of \(<7\%\) of energy as saturated fats and \(<30\%\) of total energy as fat. In the 2001 ATP III report, total fat was allowed to range from 25% to 35% of total energy because it was recognized that some groups may benefit from a higher intake of unsaturated fat and less carbohydrate. Willet and Leibel\(^6\) reviewed randomized dietary trials lasting \( \geq 1 \) year and concluded that fat consumption had little, if any, effect on body fatness. They also noted that the substantial decline in total dietary fat was associated with an increase, not a decrease in the prevalence of obesity.

To treat the metabolic syndrome, a diet should lower saturated fat intake but also promote weight loss. A review of popular American diets shows that regardless of whether
carbohydrate intake is high or low, short-term weight loss is possible. However, there is no compelling evidence supporting long-term weight loss with low-carbohydrate diets, despite their popularity.\(^7\) Shortly after the publication of this meta-analysis, 2 studies compared carbohydrate-restricted diets against standard advice (not the ATP III diet) (Table 1). The study by Samaha and colleagues\(^8\) had a high dropout rate (only 79 of 132 subjects completed the study), but its results indicated that people assigned to the low-carbohydrate diet as compared with a low-fat diet lost more weight, had a greater decrease in plasma triglyceride levels, and exhibited improved insulin sensitivity. At 1-year follow-up, the low-carbohydrate group showed a number of positive metabolic changes, including a greater decrease in plasma levels of triglycerides as well as a lesser decrease in plasma HDL cholesterol and, for the small group of participants with diabetes (n = 54), improved hemoglobin A\(_{1c}\) levels.\(^9\) The study by Foster and associates\(^10\) assigned subjects to a low-carbohydrate, high-protein, high-fat (Atkins) diet or a low-calorie, high-carbohydrate, low-fat (conventional) diet. Weight-loss results were encouraging for the Atkins-like diet at 3-month and 6-month follow-ups; however, after 12 months, the difference in weight loss between the 2 groups was insignificant (p = 0.26). This lack of success with weight loss is problematic, owing to the putative long-term consequences of low-carbohydrate diets, including hypercalciuria and the effects of a high-protein diet on the kidneys.\(^11\)

A low-energy regimen that appeared to promote dietary adherence consisted of moderate fat intake (35% of energy) that emphasized sources of monounsaturated fats. McManus and colleagues\(^12\) randomized 101 men and women to either the Mediterranean-style diet that had unsaturated oils, peanut butter, and nuts or to a low-fat diet with 20% of energy as fat. All subjects in this randomized trial were instructed to consume between 1,200 and 1,500 daily calories that were low in saturated fat and cholesterol. Weight loss was modest but more sustained in the moderate-fat diet group. Drop-out rates over the course of the 18-month trial were lower in the moderate-fat, low-energy group than in the low-fat, low-energy group.

Although the promise for weight loss and improved risk factor profile is touted for very-low-fat diets, an ongoing concern is that only a highly selected group of subjects participate in available clinical trials, limiting the ability to generalize the findings to the broader population. Ornish and colleagues\(^13\) examined the effects of a very-low-fat diet on a small group of patients with CAD. Patients were randomized to an AHA diet or to a multiple risk factor reduction program that included exercise, stress management, and smoking cessation and a diet that offered <10% of total calories as fat. As expected, dietary cholesterol and saturated fat intake were very low. At the end of the first year, the intervention group had lost 10 kg (22.2 lb) of weight and had convincing improvements in clinical angina and angiographic progression in contrast with the control group. This weight loss was maintained at 5 years. In addition, in 440 subjects who had both CAD and multiple metabolic risk factors, the Ornish program resulted in significant weight loss and improved risk factor profiles.\(^14\) Despite the favorable results in the small numbers of studies to date, there have been concerns regarding adherence rates in study subjects with a dietary fat restriction of <25% of calories.\(^15\) Moreover, certain patients, especially those with the metabolic syndrome, can exhibit lower HDL cholesterol and higher triglyceride plasma levels\(^16\) or their lipid profiles can shift from large LDL particles to smaller, dense LDL particles with such low-fat diets.\(^17\)

**Exercise**

Exercise is a key component of effective treatment of the metabolic syndrome. It can improve the plasma lipid profile as well as other risk factors and provide the added bonus of increased fitness. It has been noted that sedentary lifestyles exact a heavy medical and economic toll in our society.\(^18\) The US Behavioral Risk Factor Surveillance System defined sedentary lifestyle as “one in which demanding physical activity does not exceed 20-minute sessions or when such activity occurs fewer than 3 times per week.” Most importantly, great benefits accrue to the persons who can go from sedentary to fit. Blair and colleagues\(^20\) found that men who maintained or improved adequate physical fitness were less likely to die of any cause or of cardiovascular disease during follow-up than were persistently unfit men. Indeed, their observational cohort study of 19,173 men aged 20 to 83 years, from the Aerobics Center Longitudinal Study, not only confirmed that obesity and the metabolic syndrome are associated with an increased risk of cardiovascular disease mortality and all-cause mortality, but their data also argued

### Table 1

<table>
<thead>
<tr>
<th>Lifestyle risk factors</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>&lt;1.03 mmol/L (&lt;40 mg/dL)</td>
</tr>
<tr>
<td>Men</td>
<td>&lt;1.29 mmol/L (&lt;50 mg/dL)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥1.69 mmol/L (≥150 mg/dL)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥6.11 mmol/L (≥110 mg/dL)</td>
</tr>
</tbody>
</table>

* 40 mg/dL is only about the 15th percentile for women; in the United States, the mean value for women is about 55 mg/dL.

The American Diabetes Association recently changed the definition of impaired fasting glucose from ≥110 mg/dL to ≥100 mg/dL.
<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Duration (yr)</th>
<th>Subjects</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N (Women</td>
<td>Characteristics (Wt Change, TG, HDL-C) Mean BMI:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(%)</td>
<td>Age (yr)</td>
</tr>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Samaha et al⁸</td>
<td>Low carbohydrate diet: &lt;30 g/day</td>
<td>1</td>
<td>132 (79</td>
<td>Mean BMI: 42.9</td>
</tr>
<tr>
<td></td>
<td>Conventional diet: restrict caloric intake by 500 calories/day with &lt;30% fat</td>
<td></td>
<td>completed</td>
<td>MS: 44</td>
</tr>
<tr>
<td></td>
<td>calories</td>
<td></td>
<td>20</td>
<td>DM: 42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>53</td>
<td>TG: –5.1 + 8.7; p = 0.20</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>HDL-C: –8.7; p = 0.044</td>
</tr>
<tr>
<td>Foster et al¹⁰</td>
<td>Low carbohydrate diet: 4-phase program*</td>
<td>1</td>
<td>63 (37</td>
<td>Mean BMI: 33.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>completed</td>
<td>63</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>44</td>
<td>MS: 44</td>
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<td></td>
<td>DM: 40</td>
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<td></td>
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<td></td>
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<td>TG: –4.4 ± 6.7; p = 0.26</td>
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<td>HDL-C: –17.0 ± 23.0; p = 0.04</td>
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<td></td>
<td>Wt: –2.5 ± 6.3; p = 0.04</td>
</tr>
<tr>
<td></td>
<td>Conventional diet: 60% carbohydrates, 25% fat, 15% protein; low-calorie</td>
<td></td>
<td>73</td>
<td>Mean BMI: 34.4</td>
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<tr>
<td></td>
<td>(women, &lt;1,500/day; men, 1,500–1,800/day)</td>
<td></td>
<td>44.2</td>
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<tr>
<td>DPP²⁵</td>
<td>Placebo</td>
<td>2.8 (mean)</td>
<td>3,234</td>
<td>Mean BMI: 31</td>
</tr>
<tr>
<td></td>
<td>Metformin (850 mg bid)</td>
<td></td>
<td>with IGT</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Life-style intervention: goals = 7% weight loss and exercise 150 min/wk</td>
<td></td>
<td>51</td>
<td>DM: 11.0</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Finnish Diabetes</td>
<td>Control</td>
<td>3.2 (mean)</td>
<td>522</td>
<td>Mean BMI: 31.0</td>
</tr>
<tr>
<td>Prevention Study²⁶</td>
<td>Life-style intervention: reduct weight, total and saturated fat intakes; increase fiber intake and exercise</td>
<td></td>
<td>with IGT</td>
<td>67</td>
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<td></td>
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<td>55</td>
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BMI = body mass index; DM = progression to diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; IGT = impaired glucose tolerance; MS = metabolic syndrome; TG = triglycerides; Wt = weight.
that these risks were largely explained by cardiorespiratory fitness.\textsuperscript{21} The same appears to hold true for women. Among 936 women enrolled in the National Heart, Lung, and Blood Institute–sponsored Women’s Ischemia Syndrome Evaluation (WISE) prospective cohort study, higher self-reported physical fitness scores were shown to be an important consideration in predicting good CAD outcomes.\textsuperscript{22} In these women, who underwent coronary angiography for suspected ischemia, higher self-reported physical fitness scores were independently associated with fewer CAD risk factors, less angiographic coronary disease, and a lower risk for adverse cardiovascular events.

How does exercise-induced weight loss compare with that obtained through diet? Ross and associates\textsuperscript{23} found that exercise-induced weight loss and diet-induced weight loss provide similar reductions in abdominal obesity, visceral fat, and insulin resistance. Two reasons to include exercise are the improvements in fitness (vide supra) and the fact that exercise without dieting was found to reduce abdominal fat while effectively maintaining body weight.

Finally, exercise can normalize the elevated triglyceride and lowered HDL cholesterol plasma levels seen in the metabolic syndrome. In the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study,\textsuperscript{24} the effect of exercise training after 20 weeks was only beneficial in subjects with baseline plasma levels high in triglycerides and low in HDL cholesterol (as may be seen in the metabolic syndrome) in contrast to its lack of effect on isolated low levels of HDL cholesterol.

### Lifestyle-Change Programs

Three studies, the Diabetes Prevention Program,\textsuperscript{25} the Finnish Diabetes Prevention Study,\textsuperscript{26} and the Da Qing Trial,\textsuperscript{27} have illuminated the benefits of therapeutic lifestyle change in individuals with impaired glucose tolerance (IGT). In the Diabetes Prevention Program,\textsuperscript{25} 3,234 obese subjects with IGT but without type 2 diabetes mellitus were randomized to regimens of metformin, lifestyle modification, or placebo. The lifestyle-modification group had goals of 7% weight loss and 150 minutes of physical activity per week. This intervention resulted in a 58% reduction in the incidence of type 2 diabetes when compared with placebo and was significantly more effective than metformin (31% reduction versus placebo). The Finnish Diabetes Prevention Study\textsuperscript{26} consisted of 522 men and women with IGT who were randomized to either lifestyle intervention or placebo. Subjects in the intervention group received individualized counseling aimed at reducing both weight and intake of total and saturated fats while increasing fiber consumption and physical activity. After a mean follow-up of 3.2 years, the lifestyle-modification group achieved a greater weight loss and a 58% reduction in the incidence of type 2 diabetes (p <0.001) with the greatest benefit for those who exercised the most.

The Da Qing Trial\textsuperscript{27} consisted of 577 men and women with IGT. The cumulative incidence of diabetes at 6 years was 67.7% (59.8% to 75.2%) in the control group versus 43.8% (35.5% to 52.3%) in the diet group, 41.1% (33.4% to 49.4%) in the exercise group, and 46.0% (37.3% to 54.7%) in the diet-plus-exercise group. Taken together, these studies provide strong evidence for lifestyle recommendations in those with IGT.

Another important use for lifestyle intervention is in prevention of weight gain, especially in high-risk groups such as perimenopausal women. A 5-year randomized clinical trial known as the Women’s Healthy Lifestyle Project\textsuperscript{28} assigned 535 healthy, premenopausal women aged 44 to 50 years to either a lifestyle-intervention group receiving a 5-year behavioral, dietary, and physical activity program or to an assessment-only control group. The lifestyle-intervention group was given modest weight-loss goals (5 to 15 lb [2.25 to 6.75 kg]); a low-calorie, 25% total fat, 7% saturated fat eating pattern; and an increase in energy expenditure per week. After 4.5 years, significantly more subjects in the lifestyle-intervention group (55%) were at or below baseline weight contrasted with control subjects (26%), and beneficial effects on mean weight change and waist circumference were seen. Participants in the lifestyle-intervention group were consistently more physically active and reported eating fewer calories and less fat than controls.

Other periods that may be appropriate for weight-gain prevention include the ages between 25 and 35 years; the year following successful weight loss; and during interventions that often result in weight gain, such as smoking cessation, use of steroids for disease control, and use of certain antidiabetic, antidepressant, or antipsychotic medications. Wing\textsuperscript{29} suggested that such weight-gain prevention efforts include exercise, changes in quality and quantity of food consumed, behavior modification, and some degree of therapist contact.

### How Are These Goals Accomplished?

One approach to the hurdles of implementation in clinical practice is to consider 3 elements of the problem:

- The patient: How to overcome internal and external barriers to adhering to the diet and exercise prescription
- The physician/healthcare provider: How to determine the level of patient motivation and how to prescribe an appropriate diet and exercise regimen
- The system: How to use a multidisciplinary approach using an array of healthcare professionals to translate the physician’s orders into the patient’s acquisition of the proper knowledge and skills for needed change

The patient: For each patient, there are internal and external hurdles to lifestyle change. A crucial internal barrier is lack of motivation. Thus, an important first step a
physician can take is to query patients on their desire to change. Manson and colleagues adapted the stages-of-change model for weight loss and physical activity. They suggested that the stages for the intended behaviors of weight loss and increased physical activity are (1) precontemplation, in which desired behaviors are not occurring and the patient does not intend to initiate them; (2) contemplation, in which desired behaviors are not occurring and the patient intends to initiate them; (3) preparation, in which the patient is exploring options; (4) action, in which the patient has begun lifestyle modification and engaged in it for <6 months; and (5) maintenance, in which the patient has engaged in lifestyle modification for ≥6 months.

One way to initiate this discussion is to ask the patient to rate their willingness to change on a scale of 1 to 10, with 10 indicating certainty and lower numbers less certainty that behavioral change will occur. For those in precontemplation, it is useful to provide an empowering comment such as the statement, “I have patients like you who have successfully changed; let me know when you are ready to change.”

It may be useful to point out that many people finally are ready to change after a serious cardiac event occurs either to themselves or to a close relative, a friend, a coworker, or even a national figure. When motivation is the result of such events, it is consistent with the Health Belief Model that desired behaviors are not occurring and the patient intends to initiate them; (3) preparation, in which the patient is exploring options; (4) action, in which the patient has begun lifestyle modification and engaged in it for <6 months; and (5) maintenance, in which the patient has engaged in lifestyle modification for ≥6 months.

The ATP III report noted several external barriers to lifestyle modification for patients:

- Increased consumption of foods prepared away from home
- Lack of time to both eat right and exercise
- Lack of third-party reimbursement for nutritional counseling
- Lack of adequate strategies for referral to registered dietitians and exercise trainers
- Perception that drug therapy is easier and, in all cases, more effective.

Good examples of these points have recently appeared in the literature. For example, the Coronary Artery Risk Development in Young Adults (CARDIA) study examined dietary habits and metabolic parameters in 3,031 young adults (aged 18 to 30 years at enrollment). During the 15-year study, subjects who visited fast-food restaurants more than twice per week both at baseline and follow-up gained an extra 4.5 kg (9.9 lb) of body weight and exhibited a significant 2-fold greater increase in insulin resistance compared with individuals who visited fast-food restaurants infrequently. A way to remove an external barrier is with home exercise equipment. In a small, carefully conducted study in obese women, multiple short bouts of exercise with home equipment improved long-term weight and fat loss compared with the same regimen without home exercise equipment.

To prevent childhood obesity, the limiting of children’s television, videogame, and video game use holds great promise as a population-based approach.

The physician/healthcare provider: ATP III commented on survey data showing that many physicians had little confidence in the patient’s ability to adhere to dietary change. This may reflect several factors. One important concern that can be easily remedied is the lack of availability of a brief, validated dietary assessment tool. ATP III included a detailed dietary questionnaire in their full report. This can be filled out by the patient before the visit and serve as a useful source of dietary information for the physician and the health-care team. A simpler tool that provides useful feedback is the use of a diet diary that the patient brings to the visit. Asking the patient to identify areas that can be improved can be a valuable learning experience or at least indicate areas where professional guidance with a dietitian can be useful. Also, physicians can provide suggestions for patients to incorporate more physical activity into their daily lives.

Physicians concerned about improving adherence should also be aware of the findings of the Obesity Guidelines panel that reviewed 36 randomized clinical trial reports to determine potential benefits of behavioral therapy. Key findings from these studies to improve adherence include multimodal strategies; more frequent contact with the healthcare team; greater intensity of intervention, especially initially; and setting achievable goals from the outset.

The system: ATP III noted that the use of a multidisciplinary team in the management of patients with high plasma cholesterol levels, and especially in individuals with the metabolic syndrome, was an important factor in the successful implementation of their recommendations. ATP III recommended the use of nurses, dietitians, nurse practitioners, pharmacists, and health educators whenever possible. Alternatively, referral to commercial weight-loss programs can be considered, but a systematic review noted that “with the exception of 1 trial of Weight Watchers, the evidence to support the use of the major commercial and self-help weight-loss programs is suboptimal.” Of interest, a small study showed that a combination of a commercial program (Weight Watchers) and individualized counseling proved to be the best for achieving weight loss in obese women with breast cancer.

Although smoking cessation counseling per se is beyond the scope of this article, it is worth noting that the effectiveness of the Agency for Health Care Policy and Research clinical practice recommendations of “ask, advise, assist, and arrange” to facilitate quitting smoking can be improved with appropriate individual and team feedback. It may be appropriate for clinics and private practices periodically to
Conclusion

Several determinants of the metabolic syndrome, especially in young adults, are fatness, fitness, and lifestyle. We believe that clinics or practices that focus not only on the patient, but also on the providers and the system will manage the metabolic syndrome most effectively. We reemphasize that the benefits of either preventing weight gain during vulnerable periods in the life cycle or encouraging and supporting small amounts of weight loss brought about by lifestyle changes are crucial. Losing weight over the short term is not a comprehensive enough goal for patients with the metabolic syndrome, and thus neither they nor healthcare providers should be satisfied with short-term improvements. How to accomplish long-term improvement in features of the metabolic syndrome by means of lifestyle changes—in a cost-effective manner that extends to the entire population—remains an important challenge.

Acknowledgment

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Management of Dyslipidemia in Patients with Complicated Metabolic Syndrome

Michael H. Davidson, MD

As the prevalence of the metabolic syndrome increases, 2 comorbid conditions—hepatic steatosis and human immunodeficiency virus (HIV) lipodystrophy—have become difficult clinical challenges. Dyslipidemia in patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis may improve with use of statins, fibrates, niacin, and thiazolidinediones, but the data are presently very limited. HIV lipodystrophy is associated with a marked risk of coronary artery disease (CAD), and more aggressive management of the dyslipidemia is likely necessary to improve the prognosis. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:22E–25E)

Treatment of dyslipidemia in the patient with the metabolic syndrome is frequently complicated by comorbid conditions. The majority of patients with the metabolic syndrome have hypertension and/or diabetes mellitus, requiring medications to treat these important coronary artery disease (CAD) risk factors. Therefore, in managing dyslipidemia in patients with the metabolic syndrome, the efficacy and safety of combining lipid-altering drugs with antihypertensive and hypoglycemic agents must be considered. In particular, 2 comorbid conditions associated with the metabolic syndrome—hepatic steatosis and human immunodeficiency virus (HIV) lipodystrophy—provide unique challenges for the clinician in the management of dyslipidemia. These conditions are rapidly increasing in prevalence as the epidemic of obesity continues to expand and as drug therapy for HIV infection is markedly prolonging the life expectancy of affected individuals. Management of dyslipidemia in these patient populations is therefore becoming increasingly more important.

Nonalcoholic Fatty Liver Disease

The prevalence of nonalcoholic fatty liver disease (NAFLD), according to the Third National Health and Nutrition Examination Survey, ranges from 16% to 23%. NAFLD is a spectrum of disorders that range from simple steatosis (fat accumulation within liver cells) to steatohepatitis (fat accumulation and liver cell injury) or nonalcoholic steatohepatitis (NASH). NASH can progress to cirrhosis (fibrosis, scarring, and nodule formation), especially if other insults to the liver occur, such as excessive alcohol intake, hepatitis C infection, or a toxic insult to the liver. The prevalence of NASH is between 2% and 6%, depending on the diagnostic method. NAFLD is commonly associated with the metabolic syndrome and obesity, with 21% to 55% of patients with NAFLD having diabetes. In patients with morbid obesity, the prevalence of NAFLD is >95%.

Fat accumulation in the liver is associated with several features of insulin resistance even in individuals whose weight is normal or who are moderately overweight. At present, it is unclear whether the extent of hepatic steatosis is a cause rather than a consequence of the metabolic syndrome.

Hepatic triglyceride content is balanced by the activities of cellular molecules that facilitate hepatic triglyceride uptake, fatty acid synthesis and esterification (input), fatty acid oxidation, and the export of triglycerides by the secretion of low-density lipoprotein (LDL) (output). Hepatic steatosis appears when input exceeds output. In the presence of insulin resistance, free fatty acid (FFA) levels are increased, causing an increase in input to the liver. Other factors such as high-fat diets and leptin or adiponectin deficiencies may result in excessive amounts of fatty acid delivery to the liver. There are also examples of intrahepatic causes of steatosis such as high sucrose feeding, which induces fat accumulation by increased de novo lipogenesis. Factors that impair hepatic triglyceride output include a decrease in β-oxidation of hepatic free fatty acids or drugs that inhibit microsomal transfer protein, which is involved in very-low-density lipoprotein (VLDL) assembly. Therefore, as input exceeds output of free fatty acids, hepatic steatosis occurs.

Clinically, hepatic steatosis may result in elevation of the liver enzymes aspartate aminotransferase and alanine aminotransferase. Active liver disease is a contraindication for the use of most lipid-lowering drugs and, consequently, many patients with hepatic steatosis may not receive the appropriate therapy to treat dyslipidemia because of safety concerns. There are little data regarding the safety of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) and other lipid-lowering drugs in patients with...
NAFLD, but based on the pathogenesis of the hepatic steatosis, there is a rationale suggesting that lipid therapies may not exacerbate hepatic damage in patients with NAFLD while they may provide significant clinical benefits.

On the basis of their potential mechanism of action, drugs that decrease circulating free fatty acid should improve hepatic steatosis. Niacin decreases free fatty acid movement from the peripheral cells, and fibrates as well as peroxisome proliferator-activated receptor (PPAR)–γ agonists increase lipoprotein lipase activity to enhance clearance of free fatty acid. Fibrates also increase hepatic β-oxidation of free fatty acid. Niacin trials for the treatment of NAFLD are ongoing, and a randomized controlled trial of gemfibrozil in 46 patients with NASH demonstrated a significant decrease in serum ALT, but histologic data were unavailable.5 Statins also may be useful. In a small pilot study, 7 patients with NASH treated with atorvastatin for 1 year had significant improvement in ballooning degeneration and inflammatory scores on liver biopsy.6

Because the majority of patients with NAFLD have the metabolic syndrome, drugs that improve insulin resistance and therefore decrease free fatty acid flux to the liver may prove clinically helpful. In a small study with the thiazolidinedione troglitazone, 7 of 10 patients with NASH exhibited normalized serum alanine aminotransferase levels, but follow-up liver biopsies did not show significant improvement after 6 to 10 months of therapy.7 Both rosiglitazone and pioglitazone have been shown to induce biochemical and histologic improvement in patients with hepatic steatosis. Larger trials are under way, but because thiazolidinedione use has a history of hepatotoxicity, further data are warranted to justify more widespread recommendations. Metformin also improved biochemical markers in 14 patients with NAFLD.8

Nonpharmacologic therapy may also be clinically useful. Small trials have demonstrated benefits with vitamin E, which as an antioxidant protects cellular damage from oxygen free radicals and reactive products of lipid peroxidation.9 Other dietary supplements such as betaine and N-acetyl cysteine have shown biochemical improvement in small studies.10

Weight loss is probably the best therapeutic approach for hepatic steatosis. Because low-carbohydrate diets11 appear to lower levels of circulating triglycerides and improve insulin resistance markers to a greater degree than do low-fat diets, at least in the short term, this dietary approach may prove to be more clinically useful in alleviating the biochemical and histologic effects of hepatic steatosis. Further research is needed to verify this dietary approach.

### Dyslipidemia in Patients with HIV

The management of dyslipidemia in patients infected with HIV has become an increasingly more important issue owing to the markedly improved survival associated with the advent of highly active antiretroviral therapy (HAART). On the basis of recent statistics, there is a 25% increase in CAD risk in the first 4 to 6 years of HAART, and 76% of patients with HIV who have acute myocardial infarction are aged <55 years.12 Of the patients with HIV and premature CAD, 58% have no other risk factors. In patients infected with HIV, there is marked progression of carotid intimal-medial thickness compared with age-matched control subjects.13 The metabolic syndrome induced by HAART, therefore, represents a significant clinical challenge for clinicians involved in the treatment of patients with HIV (Table 1).14

The etiology of the metabolic syndrome and lipodystrophy associated with HAART is uncertain. Before the use of HAART, patients with HIV developed the metabolic syndrome more frequently than did age-matched controls. However, once the protease inhibitors became available, the incidence of the metabolic syndrome sig-

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**Table 1**

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<th>Possible signs and symptoms of the HIV-associated lipodystrophy syndrome*</th>
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*AIDS = acquired immunodeficiency syndrome; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus.

*At least 1 condition in each section (A through D) must be present.

Adapted with permission from Lancet.
significantly increased. As opposed to the “traditional” metabolic syndrome, which involves high free fatty acid levels due to the inability for appropriate storage into fat cells in the presence of insulin resistance, patients receiving HAART develop a lipotoxicity due to mitochondrial dysfunction resulting in the excess release of free fatty acid. Protease inhibitors may also induce the lipoatrophy by inhibiting sterol regulatory enhancer-binding protein 1 and PPAR-γ, which are both involved in lipogenesis. Free fatty acid levels are increased, resulting in increased production of VLDL and small, dense LDL as well as low plasma levels of high-density lipoprotein (HDL) (Figure 1). This increase in lipolysis appears to cause the characteristic subcutaneous lipoatrophy in the face, legs, and buttocks with accumulation of fat in the visceral area and the back of the neck (buffalo hump).

The management of dyslipidemia in patients taking HAART is complicated by the risk of combining a statin with protease inhibitors that are potent cytochrome P450 3A4 (CYP 3A4) inhibitors (Table 2). Therefore, statin doses should not exceed 10 mg/day in combination with a protease inhibitor unless a statin that is not metabolized by CYP 3A4 (eg, pravastatin, fluvastatin, or rosuvastatin) is used. Because these patients usually have moderate to severe hypertriglyceridemia, a fibrate is frequently necessary to achieve the appropriate National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) non-HDL targets. Gemfibrozil should be avoided in combination with a statin (except for fluvastatin) because of the inhibition of glucuronidation metabolism resulting in markedly higher statin levels and, therefore, increasing the risk of myopathy. Fenofoibrate, which does not impair statin glucuronidation and does not adversely affect statin levels, is the preferable fibrate option to maximize the safety of combination therapy. Niacin, which reduces the release of peripheral free fatty acid, may also be useful in improving the dyslipidemia but may exacerbate insulin resistance if the doses exceed 1,000 to 1,500 mg/day. The thiazolidinediones, as PPAR-γ agonists, do not appear to improve the lipodystrophy significantly and have not been shown to modify the dyslipidemia beneficially.

Table 2
Therapeutic options for HIV-associated lipodystrophy and related metabolic complications

| Lifestyle changes (reduce saturated fat and cholesterol intake, increase physical activity, stop smoking) |
| Change antiretroviral therapy (replacement of protease inhibitor, replacement of stavudine) |
| Statins (eg, atorvastatin, pravastatin) |
| Fibrates (eg, gemfibrozil or bezafibrate) |
| Metformin |
| Recombinant human growth hormone |
| Surgical intervention |

Adapted with permission from HIV Medicine 2003.

Figure 1. Human immunodeficiency virus infection and the insulin resistance syndrome. FFA = free fatty acids; VLDL = very-low-density lipoprotein.
Because HIV infection frequently occurs in young individuals, long-term HAART is necessary and, therefore, risk-factor modification is increasingly important to prevent the development of CAD. On the basis of the markedly increased risk of CAD associated with relatively short HAART therapy, lifestyle changes and lipid-lowering therapy will likely be necessary to prevent CAD. Low-carbohydrate diets have been shown to improve the dyslipidemia associated with the metabolic syndrome and, therefore, may also be useful. Use of the nucleoside analog abacavir and lamivudine with the non-nucleoside analog efavirenz appears to result in less lipoatrophy. Tenofovir combined with lamivudine and efavirenz improves the lipid profile compared to stavudine therapy. However, these modifications of HAART should not be used at the expense of successful treatment of the underlying HIV disease. Because the risk of CAD is markedly elevated, patients with HIV receiving HAART should most likely be considered at high risk according to the NCEP ATP III guidelines even though their age may give them an adapted Framingham score for 10-year risk of ~20%.

Lipoprotein therapy for these patients and further development of a team approach by the medical community to optimize care despite limited resources. © 2005 Elsevier Inc.

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The incidence of diabetes mellitus has increased at a dramatic rate over the last 4 decades; there has been a 5-fold increase in prevalence in the United States between 1958 and 1994. This increase in glucose intolerance is closely associated with a similar increase in obesity. The rise in obesity has been attributed to several factors, including an increase in caloric intake for the average American as well as a decrease in physical activity. It has also been suggested that as parents become more protective of their children in a more dangerous world, children are allowed to do less leisure-time outdoor athletic activity out of the sight of their parents. Television and video games may have also contributed to the less active lifestyle of children and an increase in obesity in the young.

As diabetes became more prevalent in our society, several new studies and initiatives emerged to guide prevention and treatment. With regard to lipid management, the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, ATP III) guidelines established diabetes as a risk equivalent to coronary artery disease (CAD) for the probability of experiencing a cardiac event. The basis for this CAD equivalency stratification is epidemiologic evidence that patients with diabetes who do not have CAD have a 7-year incidence of fatal and nonfatal cardiac events relatively similar to that of patients without diabetes who have established CAD (Figure 1). Figure 1 demonstrates this equivalency: the lowest risk is seen in patients with no diabetes and with no prior CAD; a substantial intermediate risk—about 20% over 7 years—is associated with the absence of diabetes but with a prior myocardial infarction (MI); and a similar 20% 7-year event rate is seen in patients with diabetes but with no known (CAD). Of course, the individuals at highest risk are those who have concomitant diabetes with established CAD: these patients have almost a 50% incidence of MI over 7 years.

Of interest, patients often present with macrovascular disease (such as CAD) prior to manifesting insulin resistance as full-blown type 2 diabetes. Most patients with type 2 diabetes will first have normal results on glucose tolerance testing and then progress to impaired glucose tolerance or impaired fasting plasma glucose values. These patients then present with dyslipidemia, such as low plasma levels of high-density lipoprotein (HDL) cholesterol and high plasma levels of triglycerides, and often manifest their first cardiac event. It is only later that they show elevated values for fasting plasma glucose and then manifest microvascular disease associated with diabetes, such as retinopathy, nephropathy, and neuropathy. This progression from normal glucose tolerance to full-blown type 2 diabetes was well described by Haffner and colleagues as the “ticking clock phenomenon.” This is particularly pertinent for cardiologists, who while monitoring patients after angioplasty or bypass surgery may often observe diabetes developing in the patient. Thus the cardiovascular caregiver, such as the cardiologist or practitioner managing the dyslipidemia, will often be the first to recognize that the patient has glucose intolerance and, later, type 2 diabetes.

Unfortunately, complications of atherosclerosis are responsible for the vast majority of diabetic mortality. In
diabetic individuals, 80% of all deaths are due to atherosclerotic disease, and 75% of those are due to CAD. Over 75% of all hospitalizations for diabetic complications are related to atherosclerotic vascular disease, and about 50% of patients with so-called non–insulin-dependent diabetes have preexisting diagnosed atherosclerotic heart disease. The unfortunate reality is that the diagnosis of CAD often comes too late: in all patients with undiagnosed CAD, the initial presentation is an acute MI rather than angina pectoris in approximately 62% of men and a MI without warning symptoms in approximately 46% of women.

The risk of CAD mortality is directly proportional to the degree of insulin resistance. Those patients who have a normal glucose tolerance test enjoy the lowest CAD mortality rates, whereas those with impaired glucose tolerance are at intermediate risk and those with established type 2 diabetes have the highest risk of a fatal cardiac event (Figure 2).

Not only is the risk of a fatal event higher with worsening glucose intolerance, but diabetic individuals also have a higher initial mortality while hospitalized after an MI than do their nondiabetic counterparts. The death rate in patients with diabetes in their first 28 days after MI is substantially greater than in nondiabetic patients, as is the postdischarge late mortality. When long-term survival was evaluated, 5-year survival after MI was also substantially worse in diabetic than in nondiabetic individuals (Figure 3).

From the standpoint of cardiovascular risk, another concern-causing phenomenon has emerged in patients with diabetes. This phenomenon is related to the effect of other risk factors—such as cigarette smoking, hypertension, and
dyslipidemia—on patients with and without diabetes. As shown in Figure 4, with the addition of each concomitant cardiovascular risk factor, the age-adjusted cardiovascular death rate is impacted to a much greater extent in diabetic than in nondiabetic individuals.\(^\text{10}\)

In summary, all patients with diabetes are more likely to have a coronary event by virtue of being diabetic. They are also much more likely to experience a fatal coronary event than are patients without diabetes. Finally, and to a greater extent than expected in similar patients without diabetes, the impact of other cardiovascular risk factors exponentially increases the risk in patients with diabetes.

In addition to the value of glucose tolerance testing as a predictor of cardiovascular events, the baseline level of glycosylated hemoglobin (HbA\(_1c\)) also predicts cardiac mortality and the incidence of nonfatal cardiac events (Figure 5).\(^\text{11}\) As can be seen in Figure 5, CAD mortality is highest when the baseline HbA\(_1c\) is \(\geq 7.9\)% and lowest when HbA\(_1c\) is \(< 6\)%. This predictive value of HbA\(_1c\) may lead one to believe that tight control of glucose substantially reduces the cardiovascular event rate. Although it is believed that tight control of plasma glucose levels in the patient with diabetes should reduce the incidence of cardiovascular events, the United Kingdom Prospective Diabetes Study (UKPDS) results suggest that the reduction in MI risk by aggressive glucose control was not statistically significant, whereas reduction in other diabetic end points (eg, retinopathy, microalbuminuria, and neuropathy) were highly dependent on tight plasma glucose control (Figure 6).\(^\text{12}\)

With regard to dyslipidemia and diabetes, plasma values for low-density lipoprotein (LDL) cholesterol are also a clear predictor of cardiovascular events in patients with diabetes. The patient with a plasma level of LDL cholesterol of approximately 3.89 mmol/L (150 mg/dL) is at 2-fold greater risk for experiencing a cardiovascular event than is the diabetic patient whose plasma value for LDL cholesterol is 1.81 mmol/L (70 mg/dL).\(^\text{13}\) Unlike the relatively low impact on the incidence of cardiovascular events with tight plasma glucose management, tight control of dyslipidemia has been shown to reduce cardiovascular events remarkably in the diabetic population.

Until recently, the majority of data related to lipid management in patients with diabetes was confined to the secondary prevention studies in these patients who had concomitant CAD. In the Scandinavian Simvastatin Survival Study (4S),\(^\text{14}\) there were a substantial number of patients with diabetes; these patients were predominantly not insulin.
dependent. In the diabetic patients in the placebo group, in whom elevated plasma values for LDL cholesterol were not treated, the 5-year mortality was approximately 25%. With treatment using a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) in this trial, mortality was reduced by almost 50%. The actual impact on reduction of cardiovascular mortality was significantly greater in diabetic patients with dyslipidemia than in nondiabetic patients. This again emphasizes that the patients at the highest risk will most likely receive the most benefit from a preventive intervention. Apparently, in the 4S study, for approximately every 4 diabetic patients with CAD who used statin therapy, 1 major cardiovascular event was prevented over the next 5 years.

As previously stated, few studies examined the benefit of lipid management in patients with diabetes without established coronary disease until the publication of the Heart Protection Study (HPS). The HPS was a study in 20,000 men and women with cardiovascular risk factors who were randomized to receive 40 mg of simvastatin or placebo daily. Of this cohort, almost 6,000 patients had diabetes, and 4,000 of these patients had no evidence of prior CAD. The HPS, therefore, provided a substantial amount of additional information regarding the importance of plasma LDL-cholesterol lowering in those with diabetes. The study helped to establish that in addition to sharing the same level of risk as nondiabetic individuals with coronary disease, diabetic patients share the same benefit from treatment of their dyslipidemia. The data from the HPS confirmed that all patients with diabetes older than 40 years received benefit from lipid lowering regardless of their baseline levels of plasma LDL cholesterol and, specifically, in the subgroup of diabetic patients in the trial, there was a 25% event reduction. This event reduction occurred regardless of the patient’s age or gender, presence or absence of hypertension, baseline measurements of plasma lipids, or duration of diabetes. In addition, the number needed to treat to save a cardiovascular event (between 10 and 14 patients) was virtually the same for patients with diabetes without coronary disease as for patients without diabetes with established CAD. These data
strongly support the ATP III guidelines that not only established diabetes as a CAD risk equivalent but also established LDL goals to be the same for diabetic patients without CAD as for secondary prevention in patients without diabetes with established CAD.

A second study was recently published regarding the treatment of patients who had type 2 diabetes without established coronary disease and the potential benefit from statin therapy. This study was called the Collaborative Atorvastatin Diabetes Study (CARDS). It was designed to evaluate the effectiveness and safety of atorvastatin 10 mg daily compared with placebo for primary prevention of cardiovascular disease events—including major coronary events, revascularization, and stroke—in patients with type 2 diabetes who had "normal" plasma cholesterol levels. This randomized study included just over 2,800 patients. The baseline measurement of plasma LDL cholesterol had to be $\leq 4.14$ mmol/L ($\leq 160$ mg/dL) for inclusion in the study and the patients had to have 1 of the following: hypertension, based on either receiving antihypertensive treatment or having a blood pressure $>140/90$ mm Hg; retinopathy; either microglobulinemia or macroglobulinuria; or current cigarette smoking. The goal of the trial was to determine whether statin use would reduce the incidence of cardiovascular events, the rate of CAD death, and total mortality in patients who had type 2 diabetes without established CAD. The average age of the patients randomized in this trial was approximately 61 years. The mean values for plasma LDL cholesterol at baseline in the placebo and atorvastatin groups were 3.06 mmol/L (118 mg/dL) and 3.08 mmol/L (119 mg/dL), respectively. The mean baseline values for HDL cholesterol were 1.37 mmol/L (53 mg/dL) in the placebo group and 1.35 mmol/L (52 mg/dL) in the atorvastatin-treated group. The mean plasma triglyceride levels at baseline were 1.70 mmol/L (150 mg/dL) in both groups. Approximately 80% of the patients in the atorvastatin treatment group achieved their target plasma level of LDL cholesterol based on the ATP III guidelines: $<2.59$ mmol/L ($<100$ mg/dL). In contrast, approximately 25% of the placebo group achieved a plasma level of LDL cholesterol below that same target. At the end of the trial (just under 5 years), there was a 37% relative risk (RR) reduction in cardiovascular events associated with the active treatment, atorvastatin 10 mg daily. This benefit in the statin-treated group was apparent regardless of the baseline plasma values for LDL cholesterol, HDL cholesterol, or triglycerides. The data confirmed that at all lipid levels in the treatment group, a similar benefit was incurred by statin therapy. Overall in the trial, one would need to treat 27 patients to save 1 cardiovascular event over 4 years. This "number needed to treat" is similar to that determined by secondary prevention trials in patients with similar lipid levels at baseline in the absence of diabetes. In conclusion, the CARDS trial was terminated 2 years earlier than anticipated because of a highly significant reduction in the primary end points observed at the second interim analysis of the trial. There was a 37% RR reduction in the incidence of major cardiovascular events, a 48% RR reduction in the incidence of stroke, and a 27% RR reduction in all-cause mortality, which achieved only borderline statistical significance. This benefit was noted regardless of age, sex, plasma lipid levels, or additional complications such as hypertension, smoking, or retinopathy at baseline. The CARDS trial, again, confirmed the importance not only of plasma lipid management but also of statin therapy in adult patients with type 2 diabetes, regardless of comorbidity.

With the remarkable increase in the incidence of diabetes in the US population, attention has been appropriately focused on the potential for prevention of diabetes. Preventive approaches to diabetes can focus on lifestyle modification such as weight reduction, exercise, and appropriate diet alteration as well as on use of emerging agents to enhance insulin sensitivity. The Diabetes Prevention Program was designed to evaluate these options. In this program, patients at high risk for development of diabetes were randomized to a placebo group, a group receiving metformin, and a group undergoing aggressive lifestyle modification. The results of the study (Figure 7) show a significant reduction in the incidence of type 2 diabetes in the patients treated with metformin. These data suggest that insulin-sensitizing agents can postpone or prevent the development of type 2 diabetes in patients at high risk for the disease. An even
more striking finding was that the group receiving aggressive lifestyle modification had, by far, the best outcomes—with an even greater reduction in risk of developing diabetes than in those treated with metformin. A similar study called the Finnish Diabetes Prevention Study included 522 middle-aged overweight individuals whose average body mass index was 31. The participants were 172 men and 350 women and the duration of the study was 3.2 years. These individuals at high risk for developing type 2 diabetes were randomized into 2 groups. The intervention group received individualized counseling with an attempt at weight reduction, a reduction in total intake of fat and saturated fat, and an increase in fiber intake as well as an increase in physical activity. The control group followed a normal lifestyle. The first important result was that the patients receiving aggressive counseling were successful in losing weight and reducing their fat and saturated fat intake. They also were more successful in incorporating exercise, >4 hours per week, into their routine (Table 1). The final outcome of the Finnish Diabetes Prevention Study showed that in the group with intervention and counseling, only 11% went on to develop full-blown type 2 diabetes, whereas in the placebo group, 23% went on to develop the disease. This translated into a RR reduction of developing diabetes of approximately 52% (Figure 8).

The results of these 2 lifestyle intervention studies emphasize the importance of an approach to diabetes that includes aggressive lifestyle modification. Unfortunately, even though many healthcare professionals are well versed in the use of statin therapy for dyslipidemia and the use of insulin-sensitizing agents for patients with type 2 diabetes, far fewer are well versed in lifestyle modification and even fewer yet have found a way to be successful in large numbers of patients.

The majority of the recent data for lipid management in patients with diabetes centers around statin therapy despite the fact that most patients with type 2 diabetes have a more complex dyslipidemia, with high plasma levels of LDL cholesterol, low plasma levels of HDL cholesterol, and elevated values for plasma triglycerides. The statin trials have repeatedly demonstrated that patients with this type of lipid profile are the ones with the most benefit from statin therapy. More work is necessary to establish the role of combination therapy with statins and niacin or fibrates to see whether further risk reduction is possible. A reasonable clinical approach is to initiate statin therapy to achieve the plasma LDL cholesterol goal and then re-measure plasma triglyceride levels. If the triglyceride plasma level remains elevated, calculate the plasma value for non-HDL cholesterol (total cholesterol value minus HDL value). The plasma value for non-HDL cholesterol should be ≤3.37 mmol/L (≤130 mg/dL) in diabetic patients. If the plasma value for non-HDL cholesterol is elevated, the practitioner may either increase the statin dose or initiate combination therapy by adding agents such as niacin or a fibrate to
achieve the lipid goal. If the diabetes is not well controlled, niacin should be used with caution to avoid aggravation of hyperglycemia. Studies comparing statin therapy with combination therapy will be necessary for further evaluation of safety versus benefit in patients with diabetes.

If the goal is reduction of the incidence of diabetes in the population to reduce the incidence of future cardiovascular events, a large-scale intervention to increase exercise and reduce caloric intake will be required. One such intervention is being initiated this year via a collaboration between the Midwest Heart Foundation and the American College of Cardiology. This diabetes initiative will be an attempt to teach cardiologists about lifestyle modification as well as the identification and prevention of diabetes; it will also attempt to familiarize cardiologists with the initial therapy for hyperglycemia. In addition, a systematic approach to adding appropriate preventive therapies—such as statins, aspirin, and angiotensin-converting enzyme inhibitors or aldosterone receptor blockers—for all patients with diabetes has been incorporated into the project. In 2006, the project will be repeated for primary care specialists through several meetings around the country provided by the American College of Cardiology. In addition to these projects, as well as others sponsored by the American Diabetes Association and the American Heart Association, among other societies, public policy changes will be necessary to stem the tide of obesity and insulin resistance. These policies will likely include mandating aerobic exercise in schools as well as incentives by employers to employees to improve overall cardiovascular health, reduce excessive weight, and embrace an active lifestyle. In the interim, the individual practitioner can have a major impact on reducing the incidence of cardiovascular events and mortality in their patients by identifying those who have the metabolic syndrome and who are insulin resistant, including those with type 2 diabetes, and aggressively treating not only their hyperglycemia but also all of their comorbidities.


3. [East West Study – source of figure 1].


5. Lewis GF. Diabetic dyslipidemia: a case for aggressive intervention in the absence of clinical trial and cost effectiveness data. Can J Cardiol 1995;11(suppl C):24C–28C.


Rationale for New American Diabetes Association Guidelines: Are National Cholesterol Education Program Goals Adequate for the Patient with Diabetes Mellitus?

Steven Haffner, MD

Both the American Diabetes Association (ADA) and the National Cholesterol Education Program (NCEP) consider type 2 diabetes mellitus to be a coronary artery disease (CAD) risk equivalent and thus suggest that patients with either diabetes or CAD should have their plasma levels of low-density lipoprotein (LDL) cholesterol lowered to <2.59 mmol/L (<100 mg/dL). Recently the NCEP issued a white paper suggesting an even lower plasma LDL cholesterol goal of <1.81 mmol/L (<70 mg/dL) for patients at high cardiovascular risk, including patients with diabetes. This rationale was based partly on the higher risk of future cardiovascular disease seen in patients who have diabetes with or without preexisting cardiovascular disease than in nondiabetic subjects with preexisting cardiovascular disease. Additionally, as reported in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study, high-dose lipid-lowering therapy has been shown to further reduce CAD event rates compared with conventional therapy. © 2005 Elsevier Inc.

This article covers 3 aspects of the treatment of diabetic dyslipidemia: (1) current recommendations for treatment; (2) the rationale for treating patients with diabetes mellitus as if they were at a level of risk equivalent to coronary artery disease (CAD), as currently recommended by the American Diabetes Association (ADA)¹ and the National Cholesterol Education Program (NCEP)²; and (3) a theoretical rationale for even more aggressive treatment of dyslipidemia in some patients with diabetes.

Current Recommendations for Therapy of Diabetic Dyslipidemia

Currently both the ADA¹ and the NCEP² recommend that normalization of elevated plasma low-density lipoprotein (LDL) cholesterol is the first criterion for treating diabetic dyslipidemia (Table 1). However, the choice of secondary and tertiary targets differs slightly between the NCEP and the ADA. The NCEP recommends that after the primary target for LDL cholesterol is met, if the plasma triglyceride level is ≥2.26 mmol/L (≥200 mg/dL), the healthcare provider may consider non–high-density lipoprotein (non-HDL) as a secondary target. The non-HDL cholesterol goal is set 0.78 mmol/L (30 mg/dL) above the LDL goal. Thus, the non-HDL cholesterol goal in patients with diabetes is ≤3.37 mmol/L (≤130 mg/dL). The ADA secondary target is to raise plasma levels of HDL cholesterol. The tertiary target is to lower plasma triglyceride levels. Both the ADA and the NCEP have the same LDL cholesterol goal of ≤2.59 mmol/L (≤100 mg/dL).

The 2004 ADA recommendations¹ suggest that healthcare providers should aim for an LDL reduction of 30% to 40%. Thus, if a patient has a plasma LDL cholesterol level of 2.85 mmol/L (110 mg/dL), the healthcare provider might aim for an LDL cholesterol level considerably below 2.59 mmol/L (100 mg/dL). There is no equivalent recommendation by the NCEP,² but the new NCEP white paper³ suggests a reduction of 40%.

Diabetes As a Coronary Artery Disease Risk Equivalent

Both the ADA¹ and the NCEP² recommend treatment of dyslipidemia in patients with diabetes to the same degree of intensity as that for patients with CAD. Three criteria are generally necessary for diabetes to be accepted as a CAD risk equivalent: (1) the risk of vascular disease should be similar in patients with diabetes or CAD, (2) intensive glycemic control should not be sufficient to eliminate the excess risk of cardiovascular disease in patients with diabetes, and (3) lipid-lowering therapy should be equally effective in individuals with and without diabetes. Diabetes has long been recognized as an important cardiovascular risk factor. Using data from the Framingham study, Kannel⁴ suggested that diabetes was associated with a 2-fold in-
creased risk for cardiovascular disease in men and a 3-fold to 4-fold increased risk for cardiovascular disease in women. In studies in the general population, nondiabetic patients with prevalent CAD have a risk of future vascular disease similar to that of patients with diabetes but without prevalent CAD (Figure 1). Traditional cardiovascular risk factors such as elevated plasma LDL cholesterol, low plasma levels of HDL cholesterol, elevated systolic blood pressure, and tobacco smoking, as well as elevated levels of glycosylated hemoglobin (HbA1c), predict the development of cardiovascular disease in patients with diabetes.6

Table 1

<table>
<thead>
<tr>
<th>Target</th>
<th>NCEP ATP III</th>
<th>ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>LDL cholesterol</td>
<td>LDL cholesterol</td>
</tr>
<tr>
<td>Secondary</td>
<td>Non-HDL cholesterol</td>
<td>HDL cholesterol</td>
</tr>
<tr>
<td>Tertiary</td>
<td>NA</td>
<td>TG</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein cholesterol; NA = not applicable; TG = triglycerides.
Adapted from Diabetes Care1 and Circulation.2
* Both guidelines recommend statins as the drug of choice for treating elevated LDL cholesterol levels.

Why is it likely that intensive glycemic control will not fully eliminate the excess risk of cardiovascular disease in patients with type 2 diabetes? Cardiovascular risk factors have been shown to be elevated in subjects with normal glucose tolerance that later converts to type 2 diabetes.7 This is believed to be due to the increased insulin resistance in prediabetic subjects. Additionally, there may be an increase in the risk of cardiovascular disease before the onset of clinical diabetes, as has been recently shown in the Nurses Health Study.8 This latter observation suggests that diabetes prevention may be an important strategy for reducing the risk of cardiovascular disease in patients with type 2 diabetes. It is likely that these prediabetic individuals may have the metabolic syndrome.

There is ample evidence that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy has an equally large effect on reducing CAD in patients with and without diabetes, as seen in the Scandinavian Simvastatin Survival Study (4S)9 and the Cholesterol and Recurrent Events (CARE) trial.10 The 4S and CARE studies, however, were secondary prevention studies in which patients with diabetes constituted a fairly small subgroup in the overall study. Until recently, there were little data available on the effect of statin therapy in patients with diabetes but without preexisting cardiovascular disease. The Heart Protection Study (HPS)11 was a large study in approximately 20,000 subjects, of which about 6,000 individuals had diabetes. Of these 6,000 patients, half did not have previous vascular disease. Simvastatin 40 mg/day was effective in reducing vascular events in these patients both with and without vascular disease. In addition, statin therapy was equally effective in individuals with high and low plasma LDL cholesterol levels, which led to the idea that statin therapy may be prescribed to patients with vascular disease or diabetes regardless of their plasma LDL cholesterol level. Thus the clinician may treat a patient with either CAD or diabetes whose plasma LDL cholesterol is 2.33 mmol/L (90 mg/dL) with a statin even if the LDL cholesterol is below the ADA1 and NCEP2 goal of <2.59 mmol/L (<100 mg/dL). Such a concept is now included in the NCEP white paper.3 The effect of statin therapy in reducing the incidence of vascular events was similar in the 600 patients with type 1 diabetes and in the larger group of patients with type 2 diabetes; however, the results were not statistically significant for the patients with type 1 diabetes, probably because of statistical power. Recently in the Collaborative Atorvastatin Diabetes Study (CARDS),12 atorvastatin 10 mg/day significantly reduced the risk of vascular disease in patients with diabetes but without preexisting vascular disease (Figure 2). As in the HPS, the statin was equally effective in individuals with high and low levels of plasma LDL cholesterol. In CARDS, atorvastatin significantly reduced the incidence of both stroke and CAD.

Is there a rationale for even more aggressive treatment of dyslipidemia in some diabetic subjects? In the NCEP guidelines3 the intensity of therapy is geared to the degree of risk. (This is not always the case for treatment of chronic diseases. For instance, the ADA1 suggests that HbA1c be <7.0% in all patients with diabetes regardless of comorbid conditions.) Clearly individuals with diabetes and preexisting vascular disease are at higher risk of future vascular disease than are nondiabetic patients with previous vascular disease.5 Thus, it may be logical to suggest more aggressive therapy either by having lower plasma LDL goals or increased use of combination therapy with fibric acids or niacin in such patients. The white paper recently issued by the NCEP3 suggests that in some patients with cardiovascular disease who are at high risk, a goal for plasma LDL cholesterol of <1.81 mmol/L (<70 mg/dL) may be indicated (Table 2). The 4 categories of patients identified as at high risk are those who have cardiovascular disease plus ≥1 of the following: diabetes, multiple risk factors (especially current cigarette smoking), the metabolic...
syndrome, and acute coronary syndrome. The strongest support for the NCEP white paper comes from the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study, in which 4,000 patients with acute coronary syndrome were randomized to receive either atorvastatin 80 mg/day or pravastatin 40 mg/day for an average of 1.5 years. Patients randomized to atorvastatin 80 mg/day had a 16% lower risk of a cardiovascular disease composite end point (p < 0.01). Patients with type 2 diabetes, who constituted about 25% of the group with acute coronary syndrome in the PROVE-IT study, appeared to receive the same cardiovascular benefit from aggressive LDL cholesterol lowering as did the nondiabetic subjects. More definitive data on whether such aggressive LDL lowering is indicated in the broader range of patients with prevalent CAD (who have a much lower risk of future CAD than do patients with acute coronary syndrome) comes from the Treating to New Targets (TNT) trial. In this trial, atorvastatin 10 mg/day was compared with atorvastatin 80 mg/day in 10,001 patients followed up for an average of 5 years.

This study is likely to be a good test of whether a plasma LDL cholesterol level of 1.94 mmol/L (75 mg/dL) is better than a level of 2.59 mmol/L (100 mg/dL) for cardiovascular end points. Almost 15% of the participants in this trial have type 2 diabetes. Cardiovascular disease was reduced by 22% (p < 0.001) in the atorvastatin 80 mg/day group.

**Conclusion**

Strong evidence exists to support the idea that all patients with diabetes be treated to the same lipid goals as are patients with CAD. The first priority for treating dyslipidemia in type 2 diabetes is to lower plasma levels of LDL cholesterol. There is a consensus that a minimal goal should be a plasma level of LDL cholesterol of <2.59 mmol/L (<100 mg/dL). Although definitive data do not yet exist, a still lower plasma LDL cholesterol goal (<1.81 mmol/L [<70 mg/dL]) may be considered in some patients with type 2 diabetes.
Table 2
National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) goals for low-density lipoprotein (LDL) and cutpoints for therapeutic lifestyle changes (TLC) and drug therapy in different risk categories and proposed modifications based on recent clinical trial evidence

<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</td>
<td>4.92 mmol/L (190 mg/dL) (optional goal: &lt;4.14 mmol/L [160 mg/dL]; LDL-lowering drug option)</td>
<td>=4.14 mmol/L (160 mg/dL)</td>
<td>=4.92 mmol/L (190 mg/dL)</td>
</tr>
<tr>
<td>(10-yr risk &gt;20%)</td>
<td>3.37 mmol/L (130 mg/dL)</td>
<td>=3.37 mmol/L (130 mg/dL)</td>
<td>=4.14 mmol/L (160 mg/dL)</td>
</tr>
<tr>
<td>Moderately high</td>
<td>4.14 mmol/L (160 mg/dL)</td>
<td>=4.14 mmol/L (160 mg/dL)</td>
<td>=4.92 mmol/L (190 mg/dL)</td>
</tr>
<tr>
<td>≥2 risk factors</td>
<td>3.37 mmol/L (130 mg/dL)</td>
<td>=3.37 mmol/L (130 mg/dL)</td>
<td>=4.14 mmol/L (160 mg/dL)</td>
</tr>
<tr>
<td>(10-yr risk 10% to 20%)</td>
<td>2.59 mmol/L (100 mg/dL) (optional goal: &lt;1.81 mmol/L [70 mg/dL])</td>
<td>≥2.59 mmol/L (100 mg/dL)</td>
<td>≥2.59 mmol/L (100 mg/dL); consider drug options</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.59 mmol/L (100 mg/dL) (optional goal: &lt;1.81 mmol/L [70 mg/dL])</td>
<td>≥2.59 mmol/L (100 mg/dL)</td>
<td>≥2.59 mmol/L (100 mg/dL); consider drug options</td>
</tr>
<tr>
<td>≥2 risk factors</td>
<td>3.37 mmol/L (130 mg/dL)</td>
<td>=3.37 mmol/L (130 mg/dL)</td>
<td>=4.14 mmol/L (160 mg/dL)</td>
</tr>
<tr>
<td>(10-yr risk &lt;10%)</td>
<td>2.59 mmol/L (100 mg/dL)</td>
<td>≥2.59 mmol/L (100 mg/dL)</td>
<td>≥2.59 mmol/L (100 mg/dL); consider drug options</td>
</tr>
<tr>
<td>Low</td>
<td>3.37 mmol/L (130 mg/dL)</td>
<td>=3.37 mmol/L (130 mg/dL)</td>
<td>=4.14 mmol/L (160 mg/dL)</td>
</tr>
<tr>
<td>≤1 risk factor</td>
<td>4.14 mmol/L (160 mg/dL)</td>
<td>=4.14 mmol/L (160 mg/dL)</td>
<td>=4.92 mmol/L (190 mg/dL)</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; LDL-C = LDL cholesterol.
Adapted with permission from *Circulation.*

2 diabetes who are at high risk, such as those with prevalent cardiovascular disease.

The prevalence of type 2 diabetes mellitus is growing rapidly worldwide. Reducing the complications of diabetes requires aggressive management of multiple risk factors, including elevated blood pressure, abnormal plasma lipid levels, and elevated plasma glucose. Fortunately, numerous agents are available to control these risk factors. This review discusses the therapeutic options in managing hyperglycemia, including lifestyle, oral agents, and insulin. © 2005 Elsevier Inc. All rights reserved.

The current prevalence of type 2 diabetes mellitus in the US population is 7% and it is increasing in all age groups. Moreover, the total number of individuals with type 2 diabetes is expected to reach 300 million worldwide by 2025.1,2 Approximately 25% of individuals aged >65 years have diabetes or prediabetes.3 The prevalence of diabetes in the United States will continue to grow owing to the aging of the population, the increasing prevalence of obesity, and changes in racial and ethnic composition. The complications of diabetes can be devastating. Diabetes is the leading cause of blindness and end-stage renal disease in United States. Over 70% of patients with type 2 diabetes die of cardiovascular disease.4

In 1996, the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) along with >200 public and private partners launched the National Diabetes Education Program. The National Diabetes Education Program initiated a public campaign to raise the awareness of and promote the aggressive treatment of risk factors for diabetic complications. The “ABCs” of managing diabetes are hemoglobin A1c (HbA1c), blood pressure control, and cholesterol management. The importance of glycemic control in preventing the microvascular complications of diabetes, including retinopathy and nephropathy, is well established. However, the effect of glycemic control for decreasing macrovascular complications remains unproved.5 Fortunately, the number of therapeutic options available to providers for controlling glycemia has increased over the past few years. This article reviews the therapeutic options and glycemic goals for managing glycemia in patients with type 2 diabetes.

Natural History of Type 2 Diabetes

Insulin resistance may be identified at an early age,6–8 but plasma glucose levels remain normal as long as the islet β-cell is capable of increasing insulin production to overcome the insulin resistance. With time, β-cell function deteriorates and hyperglycemia ensues. Loss of glycemic control in patients with diabetes is gradual and occurs over the course of years. Hence, the onset of hyperglycemic symptoms is often insidious and sometimes manifests as vague complaints such as fatigue or sleepiness. At the time of diagnosis, only 50% of islet function may be remaining.9 Fortunately, at least some β-cell dysfunction is reversible by lowering plasma glucose by means of lifestyle changes or use of hypoglycemic agents.10,11 However, the duration of remission is unknown. Current research efforts are aimed at preserving and maximizing β-cell function in patients with diabetes.

Glycemic Goals

Treatment targets for glycemic control from the American Diabetes Association (ADA)12 and the American College of Endocrinology13 are summarized in Table 1. Both preprandial and postprandial plasma glucose levels should be monitored. A level of HbA1c of 6.5% to 7.0% is the target. Achieving normal glycemia (ie, HbA1c <6%) will likely come at the expense of an increased risk of significant hypoglycemic events. Early diabetes may manifest itself as postprandial hyperglycemia while fasting plasma glucose measurements and HbA1c levels may be normal or slightly elevated. The importance of postprandial hyperglycemia in overall glycemic control increases as the HbA1c percentage improves. For example, in patients whose HbA1c is 7.3% to 8.3%, postprandial hyperglycemia accounts for 50% of the elevated HbA1c.14 Targeting postprandial glucose control has taken on additional importance with evidence that elevated postprandial plasma glucose is an independent risk factor for cardiovascular disease.15

For critically ill hospitalized patients with diabetes, intensive insulin therapy to achieve a plasma glucose level of
Weight loss is the primary goal. Even a modest changes are discussed by Foreyt elsewhere in this supplement.17) Other hospitalized patients with diabetes have a maximal plasma glucose goal of <9.99 mmol/L (<180 mg/dL) at all times to maximize wound healing, fighting of infections, and maintenance of metabolic control.

Although these goals are aggressive, it is important to keep in mind that individualized management for each patient may dictate less aggressive goals. Limitations in access to healthcare, the patient’s ability to self-monitor, comorbidities, or severe or frequent hypoglycemia may modify the glycemic goals in individual patients.

### Treatment of Hyperglycemia

The cornerstone of managing insulin resistance and the metabolic abnormalities of diabetes involves adjusting caloric intake and expenditure. Lifestyle changes, including caloric restriction and exercise, can have significant benefit in reducing plasma levels of glucose and improving insulin resistance and dyslipidemia. (Approaches to lifestyle changes are discussed by Foreyt elsewhere in this supplement.17) Weight loss is the primary goal. Even a modest weight loss of 5 to 10 lb (2.25 to 4.5 kg) is associated with reductions in plasma glucose.18 In patients with prediabetes, this amount of weight loss produces a nearly 70% reduction in the risk for progressing to type 2 diabetes regardless of age, sex, and racial or ethnic background.19 Agents available for lowering plasma glucose include insulin secretagogues, α-glucosidase inhibitors, thiazolidinediones, biguanides, and insulin.

Insulin secretagogues can be divided into sulfonylureas and nonsulfonylureas. Sulfonylureas (glipizide, glyburide, and glimepiride) have been the mainstay of managing glycemia in patients with type 2 diabetes for several decades. These agents bind the sulfonylurea receptor in the β-cell and stimulate insulin secretion from the islet β-cell. As monotherapy, the sulfonylureas produce an average HbA1c reduction of 0.8% to 2.0%.20 Weight gain and hypoglycemia are common side effects. The average incidence of significant hypoglycemia is 1% to 2% per year. Because sulfonylureas are metabolized in the liver and renally excreted, they should be used with caution in patients with liver impairment or renal insufficiency since these conditions increase the risk of hypoglycemia.

Nonsulfonylureas (repaglinide and nateglinide) also stimulate insulin secretion. These agents differ from sulfonylureas by their quicker onset, shorter duration of action, and nonrenal excretion. Hence, these agents are administered with meals and control postprandial glycemia well. These characteristics make these agents useful for the elderly, patients with renal insufficiency, or those who need mealtime flexibility. The average HbA1c reduction is 0.5% to 2.0%.20 Weight gain and hypoglycemia also occur with these agents.

α-Glucosidase inhibitors (acarbose and miglitol) slow down the digestion of complex carbohydrates in the gut. These agents reduce primarily the postprandial rise in glucose and must be taken with every meal. The average HbA1c reduction is 0.7% to 1.0%.20 Side effects include flatulence, abdominal pain, and diarrhea.

Thiazolidinediones (pioglitazone and rosiglitazone) improve skeletal muscle insulin sensitivity and to a lesser extent hepatic insulin sensitivity. Since thiazolidinediones do not increase plasma insulin levels, hypoglycemia is rare when an agent of this drug class is used as monotherapy. The average HbA1c reduction with a thiazolidinedione was 0.5% to 1.5% in clinical studies.20 Weight gain and edema are common side effects. Because thiazolidinedione-induced congestive heart failure is rare but may occur, these agents are contraindicated in patients with New York Heart Association (NYHA) class III or IV congestive heart failure.21 Interestingly, with the use of thiazolidinediones, visceral adiposity is reduced and subcutaneous fat mass increases. Thiazolidinediones have additional effects that may benefit patients with type 2 diabetes, including improvements in lipid profile, reduction of C-reactive protein levels, lowering of elevated blood pressure, and decrease in levels of plasminogen activator inhibitor–1.20

### Table 1

Summary of glycemic targets

<table>
<thead>
<tr>
<th>American Diabetes Association</th>
<th>American College of Endocrinology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatients</strong></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>&lt;7.0%</td>
</tr>
<tr>
<td>Fasting/per-meal glucose</td>
<td>5.00–7.22 mmol/L (90–130 mg/dL)</td>
</tr>
<tr>
<td>Postprandial glucose</td>
<td>&lt;9.99 mmol/L (&lt;180 mg/dL)</td>
</tr>
<tr>
<td><strong>Hospitalized patients</strong></td>
<td></td>
</tr>
<tr>
<td>Intensive care</td>
<td>&lt;6.11 mmol/L (&lt;110 mg/dL)</td>
</tr>
<tr>
<td>Noncritical care</td>
<td>&lt;6.11 mmol/L (&lt;110 mg/dL)</td>
</tr>
<tr>
<td>Preprandial</td>
<td>&lt;6.11 mmol/L (&lt;110 mg/dL)</td>
</tr>
<tr>
<td>Maximal</td>
<td>&lt;9.99 mmol/L (&lt;180 mg/dL)</td>
</tr>
</tbody>
</table>

* At peak.
† At 2 hours.

<6.11 mmol/L (<110 mg/dL) at all times is recommended. (This topic is discussed in more detail in the article by Vasa elsewhere in this supplement.16) Other hospitalized patients with diabetes have a maximal plasma glucose goal of <9.99 mmol/L (<180 mg/dL) at all times to maximize wound healing, fighting of infections, and maintenance of metabolic control.
Metformin improves hepatic insulin sensitivity with a modest reduction in skeletal muscle insulin resistance. The average HbA1c reduction with metformin in clinical studies was 1.5% to 2.0%. Additional benefits of metformin include a low incidence of hypoglycemia when used alone and weight loss or stabilization when used alone or in combination with other oral agents. This latter property makes use of metformin alone or in combination an attractive option in obese patients with type 2 diabetes. Metformin also is the first oral hypoglycemic to demonstrate a reduction in all-cause mortality. Gastrointestinal side effects of metformin include diarrhea, flatulence, nausea, vomiting, and abdominal discomfort. These events usually subside after a few weeks, and it is helpful to start with 500 mg daily after meals and slowly titrate upward to the maximal dose. Lactic acidosis, the most serious side effect of metformin use, is rare. Contraindications for metformin that increase the risk of lactic acidosis include renal insufficiency (serum creatinine >132.6 mmol/L [≥1.5 mg/dL] for men or ≥123.8 μmol/L [≥1.4 mg/dL] for women), acute renal or hepatic dysfunction, congestive heart failure, use of intravenous contrast, and hypoxia.

Insulin is the oldest agent used for glycemic control. Higher doses of insulin will almost always result in lower plasma glucose levels. To achieve glycemic control in patients with type 2 diabetes, typical doses of insulin are 0.5 to 1.5 U/kg of body weight. In clinical situations with extreme insulin resistance, eg, after surgery or in the setting of myocardial infarction, insulin requirements may be as high as 30 or 40 U/hr to maintain euglycemia! The risks of insulin therapy include weight gain and hypoglycemia. Numerous insulin preparations are available with differences in time of onset and duration of action. Ultra-short-acting insulin has an effect within minutes and lasts <4 hours. These agents are best for controlling postprandial hyperglycemia and offer flexibility for patients skipping meals. Rapid-acting insulin works within 30 to 60 minutes and has a duration of 4 to 8 hours. Intermediate-acting and long-acting insulins have durations of action of 8 to 14 hours and 18 to 24 hours, respectively. The latter preparations can be used once or multiple times a day to achieve sufficient nighttime and fasting glycemic control.

Strategies for Achieving Glycemic Control

The traditional approach to treating hyperglycemia has been to start with lifestyle modifications. The importance of education and lifestyle changes in managing glycemia and dyslipidemia cannot be overstated. Then, monotherapy is introduced with an oral agent, progressing to combination therapy with drugs from different classes, then finally adding insulin, advancing each step as glycemic control worsens. The failure-based approach can be a long and frustrating process for both the healthcare provider and the patient. Type 2 diabetes is a progressive disease and the failure rate of sulfonylurea or metformin monotherapy is typically >5% per year. In the UK Prospective Diabetes Study, a large trial in patients with type 2 diabetes, only 50% of patients had adequate glycemic control with sulfonylureas or metformin after 3 years. Hence, combination therapy addressing the multiple defects in type 2 diabetes may be a more practical and effective approach than monotherapy in newly diagnosed patients or patients with glycemic levels higher than desired goals.

Numerous combinations of oral agents or oral agents and insulin have been studied. Combinations have proved to be more effective than either drug alone. Generally, the incidence of adverse events resulting from use of a combination of oral agents is similar to the profile of the more problematic drug. Insulin can be introduced at any time. Even if insulin is being added to therapy with oral agents, maintaining the oral agents will likely reduce the total amount of insulin required for glycemic control. Aggressive glycemic control at the time of diagnosis may preserve and even restore β-cell function by reducing glucotoxicity.

The approach to management will depend greatly on the degree of hyperglycemia. In patients with mild to moderate hyperglycemia (HbA1c <9.0%), lifestyle and monotherapy may be sufficient to achieve the glycemic goal. If the patient is overweight, with a body mass index ≥25, metformin should be strongly considered as the starting pharmacotherapy. Adjustments should be made in a timely fashion to achieve the glycemic goals within 6 to 12 months. In patients with more severe hyperglycemia (HbA1c ≥9.0%), pharmacologic measures should be started immediately. Combination therapy will likely be required and, if there is marked hyperglycemia (HbA1c ≥11.0%), insulin therapy should be instituted.

8. Paulsen EP, Richenderfer L, Ginsberg-Fellner F. Plasma glucose, free fatty acids, and immunoreactive insulin in sixty-six obese children:


Systematic Strategies for Improved Outcomes for the Hyperglycemic Hospitalized Patient with Diabetes Mellitus

Falguni Vasa, MD

Diabetes mellitus is reaching epidemic proportions in the United States. It is now the fourth most common comorbid condition complicating hospital discharges. There is a rapidly evolving body of literature assessing the short-term and long-term effects of strict glycemic control in the hospital setting. Results from several landmark studies have challenged the long-held notion that stress hyperglycemia is beneficial. This article will focus on these studies, postulated mechanisms of action, and finally, description of an insulin infusion protocol developed at a community hospital for patients undergoing cardiac surgery. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:41E–46E)

Insulin Therapy and Acute Myocardial Infarction

The benefits of insulin were first described in the setting of acute myocardial infarction (MI) in the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. This multicenter trial randomized 620 patients with acute MI. A total of 306 patients received an insulin-glucose infusion for ≥24 hours followed by multiple daily subcutaneous injections for ≥3 months (infusion group). The remaining 314 patients (control group) did not receive insulin unless it was felt to be clinically necessary. Both groups received standard coronary therapy.

At randomization, patient profiles were similar with regard to levels of glycosylated hemoglobin (HbA1c). This value significantly declined in the infusion group at 3 and 12 months. After 1 year, mortality in the infusion group was 18.6% versus 26.1% in the control group (p = 0.0273). This corresponds to a relative reduction of 30%, an effect that seems to extend to ≥3.4 years. The most significant decrease was seen in patients classified as having low cardiovascular risk who had no prior insulin therapy. In this group the relative reduction was 51% (p = 0.004). In addition, hospital stay was reduced from 11.3 ± 13.3 days in the infusion group to 9.5 ± 9.4 days in the control group (p = 0.043).

The benefit of a glucose-insulin-potassium (GIK) infusion was challenged in a recent study. The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation combined with Estudios Cardiológicas Latinoamérica (the CREATE-ECLA trial) used a partial 2×2 factorial design to determine the effect of GIK infusion in patients with acute ST-segment elevation MI. The first randomization was to GIK infusion versus control and the second to double-blind therapy with reviparin or placebo. The primary outcome was death from any cause at 30 days. Secondary outcomes included nonfatal cardiac arrest, cardiogenic shock, death, or reinfarction. Overall 20,201 patients were randomized. Of those, 10,088 received GIK infusion in addition to usual care. The 2 groups were similar with regard to age, gender, blood pressure, time to randomization, and Killip class at randomization. Approximately 17% of patients in each group had a known history of diabetes. At baseline, mean blood glucose levels were 8.99 mmol/L (162 mg/dL) in both the GIK infusion group and the control group. At 6 hours after randomization, the blood glucose level in the GIK infusion
patients with a diagnosis of diabetes were evaluated. Primary end points were in-hospital mortality, length of hospital stay, and infection. From 1987 to 1991, patients were treated with subcutaneous insulin (SQ group) every 4 hours to maintain blood glucose levels at <11.10 mmol/L (<200 mg/dL). From 1991 to 2003, patients received an insulin infusion titrated to maintain glucose levels within defined targets. From 1991 to 1998 the goal was 8.33 to 11.10 mmol/L (150 to 200 mg/dL); in 1999 it decreased to between 6.94 and 9.71 mmol/L (125 and 175 mg/dL); and in 2000, it decreased further to between 5.55 and 8.33 mmol/L (100 and 150 mg/dL). Until January 1995, the protocol was used postoperatively only and discontinued on transfer to telemetry. After 1995, the protocol was initiated in the operating room and continued until the third postoperative day regardless of patient location. The study groups were heterogeneous, with the continuous insulin infusion (CII)

Insulin Therapy and Critical Illness

Van den Berghe and colleagues\(^6\) performed a prospective, randomized controlled study in 1,548 patients in the surgical ICU who were receiving mechanical ventilation. Some 60% had undergone cardiac surgery. The remaining patients were admitted for noncardiac surgery, neurologic disease, trauma, burns, or transplantation. Approximately 13% were known to be diabetic prior to admission. Patients were randomized to receive either intensive insulin therapy (IIT) via an insulin infusion to maintain blood glucose levels between 4.44 and 5.55 mmol/L (80 and 110 mg/dL), or conventional therapy to maintain blood glucose values between 9.99 and 11.10 mmol/L (180 and 200 mg/dL). Insulin infusion was begun in the conventional group only if the blood glucose measurement exceeded 11.93 mmol/L (215 mg/dL). Once discharged from the ICU they received standard care in the hospital, keeping glucose levels between 9.99 and 11.10 mmol/L (180 and 200 mg/dL).

Patients in the intensive and conventional groups were well matched for age, sex, body mass index, reason for admission, Acute Physiology and Chronic Health Evaluation (APACHE) scores, and history of diabetes. Ninety-nine percent of those in the IIT group received an insulin infusion versus 39% in the conventional group. Mean blood glucose levels were 5.72 ± 1.05 mmol/L (103 ± 19 mg/dL) in the IIT arm compared with 8.49 ± 1.83 mmol/L (153 ± 33 mg/dL) in the conventional arm. IIT reduced ICU mortality from 8.0% in the conventional group to 4.6% in the intensive group (p <0.04). The benefit was seen in patients with an ICU stay of >5 days. IIT also reduced in-hospital mortality by 34%. The greatest reduction was seen in deaths attributable to multiple organ failure with a septic focus. The mortality benefit was seen across almost all levels of APACHE II scores and was similar for cardiac versus noncardiac surgery. Conventional insulin treatment, but not a history of diabetes or hyperglycemia, was found to be an independent predictor of mortality. Hospital and ICU survival were linearly associated with ICU glycemic control, with the highest survival rates occurring in patients in whom the average blood glucose values were ≤6.11 mmol/L (<110 mg/dL). In a subsequent analysis, the authors found that each 1.11-mmol/L (20 mg/dL) increase in blood glucose above 5.55 mmol/L (100 mg/dL) increased the risk of ICU death by 30% (p <0.0001).\(^7\)

Furthermore, IIT improved morbidity in ICU-hospitalized patients. The rate of sepsis was decreased by 46%, acute renal failure by 41%, transfusions by 50%, and critical illness polyneuropathy by 44%. These striking improvements in morbidity and mortality were found regardless of a history of diabetes.

Insulin Therapy and Cardiac Surgery

Furnary and colleagues\(^8\) performed a prospective, nonrandomized, interventional study to evaluate the effect of glycemic control on patients undergoing cardiac surgery; 3,554 patients with a diagnosis of diabetes were evaluated. Primary end points were in-hospital mortality, length of hospital stay, and infection. From 1987 to 1991, patients were treated with subcutaneous insulin (SQ group) every 4 hours to maintain blood glucose levels at <11.10 mmol/L (<200 mg/dL). From 1991 to 2003, patients received an insulin infusion titrated to maintain glucose levels within defined targets. From 1991 to 1998 the goal was 8.33 to 11.10 mmol/L (150 to 200 mg/dL); in 1999 it decreased to between 6.94 and 9.71 mmol/L (125 and 175 mg/dL); and in 2000, it decreased further to between 5.55 and 8.33 mmol/L (100 and 150 mg/dL). Until January 1995, the protocol was used postoperatively only and discontinued on transfer to telemetry. After 1995, the protocol was initiated in the operating room and continued until the third postoperative day regardless of patient location. The study groups were heterogeneous, with the continuous insulin infusion (CII)
group having a greater percentage of tobacco use, hypertension, renal insufficiency, and obesity. The admission values for blood glucose, however, were similar in both groups.

Average blood glucose value was $11.88 \pm 2.28$ mmol/L ($214 \pm 41$ mg/dL) in the SQ group compared with $9.83 \pm 1.67$ mmol/L ($177 \pm 30$ mg/dL) in the CII group ($p < 0.001$). Length of stay decreased from $10.4 \pm 6.6$ days in the SQ group to $8.0 \pm 5.3$ days in the CII group ($p < 0.001$). Mortality was almost cut by 50%, with 5.3% in the SQ group compared with 2.5% in the intensive treatment arm ($p < 0.001$). The reduction in mortality was entirely due to a reduction in cardiovascular deaths. Furthermore, a linear relation was found between cardiac mortality and blood glucose levels, suggesting a myocardial mechanism of action. External risk adjustment revealed a 50% decrease in risk-adjusted mortality attributable solely to CII on days 0 to 2 (odds ratio [OR] = 0.5; $p = 0.005$).

Recent data (reported in 2003) indicate that 4,864 patients with diabetes have undergone cardiac surgery. The blood glucose average value on days 0 to 2 (known as the 3-BG value) has now emerged as an independent predictor of death. In addition, mortality after coronary artery bypass grafting was found to double for every 2.78 mmol/L (50 mg/dL) increase in 3-BG. Implementation of the protocol intraoperatively independently reduced mortality by 60%, with patients with diabetes now having a lower mortality than that of the nondiabetic population. Multivariate analysis also showed that CII reduced the risk of deep sternal wound infection (DSWI) by 66% ($p < 0.005$). Furthermore, length of stay was decreased by 1 day for every 2.78 mmol/L (50 mg/dL) reduction in blood glucose value.

The authors conducted an actual cost analysis, which revealed that 1 case of DSWI was prevented for every 31 patients treated with the protocol, resulting in a cost savings of $2,613 per patient. The reduced length of stay saves $3,105 per patient. Thus, the total savings per patient is $5,718. The direct and indirect costs of the insulin infusion were approximately $138, resulting in a net savings of $5,580 per patient. The mortality reduction translates into 1 life saved for every 38 treated patients, saving the healthcare industry $212,040 per life saved. Each year, an estimated 102,950 patients with diabetes undergo coronary artery bypass surgery. If the above calculations are applied, the Portland Protocol would save 1,959 cases of DSWI; 2,676 lives; and 278,000 hospital days. The healthcare industry would realize a savings of between $70 million and $574 million dollars annually.

**Proposed Mechanisms of Action**

The striking improvement in outcomes with achievement of euglycemia has spurred the development of several candidate mechanisms by which insulin imparts its protective effects. It is becoming evident that benefits of insulin therapy may result from multiple pathways, including the effects on glycemic control as well as insulin itself. At a very basic level, insulin appears to modulate the body’s stress response.

The physiologic response to stress involves proinflammatory cytokines such as interleukin-6 (IL-6) and tissue necrosis factor–α (TNF-α). TNF-α induces insulin resistance, which increases lipolysis. The resultant rise in free fatty acids further enhances insulin resistance, which ultimately raises blood glucose levels. Elevated free fatty acid levels have also been associated with an increase in oxidative stress in individuals with type 2 diabetes, endothelial dysfunction, and increased plasminogen activator inhibitor–1 transcription. In addition, TNF-α itself can cause endothelial dysfunction by generating free radicals. This damages endothelial cells, resulting in fibrin deposition and a procoagulable state.

The modulation of inflammatory cytokines is intricate (Figure 1). Insulin is thought to be beneficial via 3 main mechanisms. First, insulin is known to reduce the transcription of proinflammatory genes, chemokines, adhesion molecules, and nuclear factor–κB (NF-κB). NF-κB regulates the enzymes responsible for the generation of reactive oxygen species; it also increases production of TNF-α, IL-6, intercellular adhesion molecule–1 (ICAM-1), vascular cell adhesion molecule–1 (VCAM-1), monocyte chemoattractant protein–1 (MCP-1), and C-reactive protein (CRP). Second, insulin increases the synthesis of nitric oxide (NO) via stimulation of NO synthase, resulting in an acute vasodilative effect as well as an antiaggregative effect on platelets. Finally, insulin therapy corrects the hyperglycemia, but it also suppresses free fatty acid generation, thus reversing the “lipotoxicity.”

**The Edward Hospital Open Heart Insulin Protocol**

The compelling nature of the data prompted us to develop an insulin infusion protocol for patients who have undergone heart surgery (Table 1). It is initiated if the postoperative blood sugar measurement exceeds 6.66 mmol/L (120 mg/dL) and is titrated to maintain blood glucose levels at <6.11 mmol/L (<110 mg/dL). It is adapted and revised from a published algorithm created by researchers led by Braithwaite at the University of North Carolina-Chapel Hill. Once the protocol is begun, blood glucose is measured hourly, and the drip rate of the infusion changed according to the columns in a treatment grid that dictate the insulin infusion rate and reflect the degree of insulin resistance. The higher the column, the higher the infusion rate necessary to maintain the current blood glucose value. Most patients start at column 2 and move up to the next column if target blood glucose levels are not attained. Parameters for titration and discontinuation of the drip are delineated. Once the patient is eating, transition to a subcutaneous regimen is performed according to a weight-based calculation, and monitoring of blood glucose is decreased to every 6 hours.
Endocrinology insulin standing order for adult hyperglycemic patients (postoperative heart standing order)

- All patients on insulin drip from OR continue IV insulin, drip rate standing order as follows:

<table>
<thead>
<tr>
<th>FSBG</th>
<th>Drip Rate</th>
<th>Insulin order</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8.33 mmol/L (&lt;150 mg/dL) or ≥8.33 mmol/L (≥150 mg/dL) and ≥8.33 mmol/L (≥150 mg/dL) and ≥8.33 mmol/L (≥150 mg/dL) and ≥8.33 mmol/L (≥150 mg/dL) and ≥8.33 mmol/L (≥150 mg/dL) and ≥8.33 mmol/L (≥150 mg/dL) and ≥8.33 mmol/L (≥150 mg/dL)</td>
<td>&lt;4 U/hr 4–5.9 U/hr 6–7.9 U/hr 8 U/hr</td>
<td>Go to column 2 in grid Go to column 3 in grid Go to column 4 in grid Go to column 5 in grid</td>
</tr>
</tbody>
</table>

- From OR, no insulin drip, do stat postoperative FSBG.
  - If blood glucose is ≥6.66 mmol/L (≥120 mg/dL), recheck in 6 hours and follow standing order.
  - Blood glucose may be rechecked PRN if the patient is symptomatic and/or suspected of having hypoglycemia.
  - If >6.66 mmol/L (≥120 mg/dL), initiate IV endocrinology insulin standing order (postoperative heart standing order). Assign to column 2.

- To begin IV insulin drip, go to “To begin IV insulin drip.”
  - If patient advances to column 4, call endocrinologist Drs.
  - If blood glucose is <3.86 mmol/L (<70 mg/dL) or >22.20 mmol/L (>400 mg/dL), call endocrinologist Drs.

- To begin IV insulin drip:
  - Bolus 0.1 U/kg IV regular human insulin and immediately begin regular insulin drip of 100 U/100 mL 0.9% NS based on FSBG above.
  - FSBG hourly.
  - Adjust drip according to column recommendations.

- Managing the insulin drip:
  - For FSBG ≥8.33 mmol/L (≥150 mg/dL) for 2 hours, advance to next higher column.
  - Notify endocrinology if patient has FSBG ≥14.99 mmol/L (≥270 mg/dL) for 2 hours or if patient has advanced to column 4.
  - Patients in columns 4 or 5 for 8 hours and FSBG <6.66 mmol/L (<120 mg/dL), proceed to next lower column.

- To interrupt or discontinue the insulin drip:
  - If FSBG is <5.55 mmol/L (<100 mg/dL), temporarily suspend the insulin drip for no longer than 60 minutes, then repeat FSBG.
  - Do FSBG hourly × 3. If <5.55 mmol/L (<100 mg/dL) or in column 1, then discontinue the insulin drip. Proceed to Cardiac Subcutaneous (SQ) Sliding Scale.
  - If FSBG is >6.66 mmol/L (≥120 mg/dL), resume insulin drip at next lower column.

Postoperative Day 1
If transferring to surgical floor on insulin drip, endocrinologist must be notified.
On insulin drip >2 U/hr
  - Continue with endocrinology insulin standing order.
  - If insulin drip >2 U/hr on postoperative day 2, call consulting endocrinologist.
On insulin drip <2 U/hr
  - If the patient is eating, not nauseated, then perform FSBG.
  - Begin Cardiac SQ Sliding Scale.
  - Give insulin based on the Cardiac SQ Sliding Scale.
  - After subcutaneous insulin injection is given, turn the insulin drip off.
  - If the insulin drip is >2 U/hr and the patient is NPO, then consult endocrinologist.

Intended for postoperative use, open heart surgery

<table>
<thead>
<tr>
<th>Intravenous insulin drip rate (total units of insulin per day)</th>
<th>31–50 units/day</th>
<th>51–70 units/day</th>
<th>71–90 units/day</th>
<th>≥91–120 units/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column 1 (for patients whose estimated rate is ≥1 U/hr for maintenance)</td>
<td>Column 2 (for patients whose estimated rate is 1.1–1.5 U/hr for maintenance)</td>
<td>Column 3 (for patients whose estimated rate is 1.6–2 U/hr for maintenance and who failed column 2)</td>
<td>Column 4 (for patients whose estimated rate is &gt;2 U/hr for maintenance and who failed column 3)</td>
<td>Column 5 (for patients whose estimated rate is &gt;4 U/hr for maintenance and who failed column 4)</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>IV</td>
<td>Blood glucose</td>
<td>IV</td>
<td>Blood glucose</td>
</tr>
<tr>
<td>≤119 mg/dL Off 100–119 0.5 120–149</td>
<td>≤119 mg/dL Off 100–119 1</td>
<td>≤119 mg/dL Off 100–119 1.5 120–149</td>
<td>≤119 mg/dL Off 100–119 2</td>
<td>≤119 mg/dL Off 100–119 2.5</td>
</tr>
<tr>
<td>120–149 0.5 120–149</td>
<td>≤119 mg/dL Off 100–119 1.5</td>
<td>≤119 mg/dL Off 100–119 2</td>
<td>≤119 mg/dL Off 100–119 2.5</td>
<td>≤119 mg/dL Off 100–119 3</td>
</tr>
<tr>
<td>150–179 1</td>
<td>≤119 mg/dL Off 100–119 2</td>
<td>≤119 mg/dL Off 100–119 2.5</td>
<td>≤119 mg/dL Off 100–119 3</td>
<td>≤119 mg/dL Off 100–119 3.5</td>
</tr>
<tr>
<td>180–239 1.5</td>
<td>≤119 mg/dL Off 100–119 3</td>
<td>≤119 mg/dL Off 100–119 3.5</td>
<td>≤119 mg/dL Off 100–119 4</td>
<td>≤119 mg/dL Off 100–119 4.5</td>
</tr>
<tr>
<td>240–299 2</td>
<td>≤119 mg/dL Off 100–119 4</td>
<td>≤119 mg/dL Off 100–119 5</td>
<td>≤119 mg/dL Off 100–119 6</td>
<td>≤119 mg/dL Off 100–119 7</td>
</tr>
<tr>
<td>300–359 2.5</td>
<td>≤119 mg/dL Off 100–119 5</td>
<td>≤119 mg/dL Off 100–119 6</td>
<td>≤119 mg/dL Off 100–119 8</td>
<td></td>
</tr>
<tr>
<td>≥360 3</td>
<td>≤119 mg/dL Off 100–119 6</td>
<td>≤119 mg/dL Off 100–119 8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FSBG = finger-stick blood glucose measurement; IV = intravenous; NPO = nothing by mouth; NS = normal saline; OR = operating room; PRN = as needed; stat = immediately. Adapted with permission from Endocrin Pract.12
Despite the convincing nature of the data, there were several barriers to implementation, the foremost of which was fear of hypoglycemia. The nursing staff had concerns regarding the aggressive nature of the insulin infusion rates and glycemic targets. Repeated education sessions were required, and continue to be required, to overcome the long and widely held belief that stress-engendered hyperglycemia is acceptable. Ease of use of the protocol was another issue, although this concern has almost disappeared as the comfort level has increased. The protocol was initiated on September 15, 2004. Since then, nearly all patients have required insulin infusion to maintain acceptable glycemic targets after cardiac surgery. A significant percentage of those with stress hyperglycemia did not have a history of diabetes. As expected, patients with a history of diabetes prior to surgery required titration to more aggressive columns, occasionally necessitating the creation of column 6 and beyond. Continued use has brought to light necessary small revisions, which are ongoing.

Conclusion

Diabetes is reaching epidemic proportions in the United States. Diabetic individuals suffer increased frequency and duration of hospitalizations, higher surgical complication rates, and greater morbidity and mortality than their nondiabetic counterparts. Until recently, stress hyperglycemia was felt to be not only acceptable but beneficial. Growing evidence now supports the contrary. Strict glycemic control has been shown to improve both morbidity and mortality in acute MI as well as after cardiac surgery. The mortality benefit ranges from 30% to 60%, depending on the setting. Historically, in a population that has generally done poorly, few interventions have been shown to improve outcomes to such a remarkable degree. Consequently, we have created and implemented an insulin infusion protocol for patients undergoing cardiac surgery that is based on the Braithwaite algorithm. Patients with stress hyperglycemia postoperatively are managed by means of this protocol, regardless of history of diabetes. Despite the resistance of healthcare workers at first, this has resulted in better glycemic control postoperatively. Evaluation of the protocol as well as its effect on outcomes is ongoing.

4. Malmberg K, for the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study group. Prospective randomized study of intensive insulin treatment on long term survival


An Approach to Heart Failure and Diabetes Mellitus

Gregg C. Fonarow, MD

Diabetes mellitus is a chronic progressive disease that results in microvascular and macrovascular complications. Diabetes is a significant independent risk factor for heart failure, and there are a substantial number of patients with diabetes and heart failure. Neurohormonal activation plays an important pathophysiologic role in insulin resistance, diabetes, cardiovascular events, and progression of heart failure. Pharmacologic intervention in these neurohormonal systems (ie, angiotensin-converting enzyme [ACE] inhibition, aldosterone antagonism, and β-adrenergic blockade) has been shown to decrease the morbidity and mortality of diabetes and of heart failure. Despite this knowledge, ACE inhibitors, aldosterone antagonists, and β-blockers are grossly underutilized, and deaths and hospitalizations due to heart failure have steadily increased. Guidelines for the management of heart failure recommend the use of ACE inhibitors and β-blockers in patients with mild, moderate, and severe heart failure with or without diabetes. Aldosterone antagonists are recommended in severe heart failure and recent data also support their use in mild to moderate heart failure. Concerns about increased incidence of hypoglycemia, worsening dyslipidemia, and decreased insulin sensitivity with β-blockers may be preventing physicians from prescribing these agents for their patients with diabetes who have heart failure. β-Blockade, in conjunction with ACE inhibition and aldosterone antagonism, should be standard therapy for all patients with diabetes and heart failure. Furthermore, every effort should be made to ensure that eligible patients are treated with these evidence-based, guideline-recommended, life-prolonging therapies. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:47E–52E)

Heart failure is a common disorder associated with high rates of mortality and morbidity. Heart failure affects nearly 5 million Americans and is the primary cause of or a contributory factor in approximately 300,000 deaths each year. Despite advances in treatment, deaths and hospitalizations due to heart failure have increased steadily over the past several years. Heart failure is more prevalent in certain patient populations, including patients with diabetes mellitus. Diabetes is a significant independent risk factor for heart failure and there are a substantial number of patients with both diabetes and heart failure. Neurohormonal activation plays an important pathophysiologic role in insulin resistance, diabetes, cardiovascular events, and progression of heart failure. Several clinical trials have shown that specific pharmacologic interventions (ie, angiotensin-converting enzyme [ACE] inhibition, aldosterone antagonism, and β-blockade) reduce mortality and morbidity due to heart failure and diabetes. The role of these interventions in the optimal management of the patient with diabetes and heart failure will be reviewed.

Diabetes and Heart Failure

Diabetes is an independent risk factor for the development of heart failure. The Framingham study revealed a 2.4-fold increase in symptomatic heart failure in men and a 5.0-fold increase in women with diabetes, independent of coexisting hypertension or ischemic heart disease. Several mechanisms have been postulated to explain the correlation between diabetes and heart failure. Risk factors for heart failure, including hypertension, hyperlipidemia, premature atherosclerosis, and left ventricular hypertrophy, occur with increased frequency in the diabetic population and may directly contribute to the development of heart failure. Both heart failure and diabetes are believed to share pathophysiologic processes, including neurohormonal activation, endothelial dysfunction, and increased oxidative stress. Diabetes accelerates the development of atherosclerosis and increases the risk of myocardial infarction (MI) and ischemic heart failure. Diabetes may act synergistically with other risk factors such as hypertension to increase the risk of heart failure.

Diabetes may also affect cardiac structure as well as systolic or diastolic function independent of other established risk factors for heart failure. Experimental and clinical studies support the existence of a specific diabetic cardiomyopathy, independent of atherosclerosis, that is related to microangiopathy, metabolic factors, and/or myocardial fibrosis, which may also contribute to the increased
incidence of heart failure in individuals with diabetes. The extent of metabolic impairment has been shown to be related to the risk of developing heart failure. In the United Kingdom Prospective Diabetes Study (UKPDS) poor glycemic control was associated with increased risk of heart failure in patients with type 2 diabetes. A US health maintenance organization study demonstrated that every 1% increase in baseline glycosylated hemoglobin level correlates with a 15% increased risk of developing heart failure. Thus, diabetes may contribute to heart failure both by promotion of atherosclerosis and coronary artery disease (CAD) as well as by engendering independent diabetes-induced cardiomyopathy.

More recently, heart failure itself has been shown to be associated with the development of insulin resistance and new-onset diabetes. Over 8 years of follow-up, patients with CAD and moderate to severe heart failure were found to have a 1.7-fold (95% confidence interval [CI], 1.1 to 2.6) increase in the rate of development of diabetes compared with patients who have CAD without heart failure. Diabetest predisposes patients to development of heart failure, and heart failure predisposes patients to development of diabetes.

The prevalence of diabetes in the adult US population is 4% to 6%. The reported range of patients with heart failure who have concomitant diabetes is substantially higher, ranging from 15% to 25% among patients enrolled in randomized clinical heart failure trials. The prevalence of diabetes is even higher in registries of patients hospitalized with heart failure, ranging from 26% to 44%. With an overall heart failure prevalence of 5 million, there are thus an estimated 1 to 2 million patients with heart failure and diabetes in the United States.

**Diabetes, Heart Failure, and Mortality**

Diabetes has been demonstrated to increase mortality risk in patients with heart failure. Analysis of the prevention and treatment arms of the Studies of Left Ventricular Dysfunction (SOLVD) identified diabetes as a modest independent predictor of increased mortality in both symptomatic and asymptomatic heart failure. A subsequent analysis of the same database revealed that the increased risk with diabetes was confined to patients with an ischemic heart failure cause (relative risk [RR], 1.37; 95% CI, 1.21 to 1.55; p <0.0001). In contrast, for patients with heart failure of nonischemic origin, diabetes conferred no increase in risk (RR, 0.98; 95% CI, 0.76 to 1.32; p = 0.98). In the Rotterdam study, among a community cohort of patients found to have heart failure, diabetes was an independent predictor of mortality, along with renal insufficiency and atrial fibrillation. In an analysis of a national cohort of 170,239 elderly patients newly hospitalized with heart failure in 1986 and followed up over the next 6 years, diabetes was an independent predictor of mortality.

**Pathophysiologic Role of Neurohormonal Activation in Diabetes and Heart Failure**

There is substantial evidence that activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system plays an important pathophysiologic role in diabetes and heart failure. Factors that have been shown to contribute to cardiac and vascular injury and subsequent activation of these neurohormonal systems include hypertension, hyperlipidemia, the metabolic syndrome, diabetes, atherosclerosis, acute MI, and heart failure. Activation of neurohormonal systems leads to insulin resistance, and insulin resistance leads to activation of neurohormonal systems.

Injury to the heart and blood vessels as a result of hypertension, insulin resistance, diabetes, and MI activates the renin-angiotensin system, resulting in prolonged expression of angiotensin II. Angiotensin II acts both as a circulating hormone and as a locally acting paracrine/autocrine/intracrine factor. Angiotensin II has a multiplicity of adverse effects on the heart, blood vessels, and kidneys. Increased levels of angiotensin II produce elevated resistance to the pumping function of the myocardium, vasoconstriction, increased cardiac preload and afterload, remodeling, vascular inflammation, impaired vascular compliance, sympathetic activation, baroreceptor dysfunction, and sodium retention.

Activation of the SNS has been demonstrated in diabetes and heart failure. Excessive activation of the SNS produces a variety of deleterious cardiovascular effects. Injury to the heart results in activation of the SNS. This activation produces a variety of negative effects in the heart, vasculature, and kidneys. In the heart, sympathetic activation promotes ongoing cardiac injury, hypertrophy, and adverse remodeling and increases the risk for life-threatening arrhythmias. SNS activation also produces arterial and venous vasoconstriction, increasing cardiac preload and afterload. Catecholamines are also proatherogenic, playing a role in the initiation and propagation of atherosclerosis. Renal effects of SNS activation include vasoconstriction, salt and water retention, and increased renin release, all of which elevate the activity of the renin-angiotensin-aldosterone system. Sympathetic activation can also increase platelet activation and precipitate a procoagulant state. All of these
actions contribute to the progression of cardiovascular disease in patients with diabetes and heart failure.\textsuperscript{15,18}

**Metabolic Abnormalities in Patients with Diabetes and Heart Failure**

In diabetes, significant changes in myocardial energy metabolism can occur and contribute to progressive ventricular dysfunction. Myocardial glucose transport, glycolysis, and glucose oxidation are all impaired in diabetes.\textsuperscript{19} Hyperinsulinemia is associated with increased free fatty acid levels in patients with type 2 diabetes.\textsuperscript{20} In addition, activation of the SNS in patients with diabetes results in increased myocardial utilization of free fatty acids.\textsuperscript{5,20} Increases in fatty acid oxidation accompanied by decreases in glucose metabolism can result in the myocardium becoming almost entirely reliant on fatty acid oxidation as a source of energy. This increased fatty acid metabolism causes increased myocardial oxygen consumption, which can lead to myocardial ischemia, reduced cardiac function, and cardiac arrhythmias.\textsuperscript{20} This switch in energy metabolism contributes to heart failure by increasing the severity of injury following an acute MI and by having direct negative effects on contractile function.\textsuperscript{20}

Diabetes has also been shown to induce changes in myocardial gene expression of key regulators in cardiac energy metabolism and calcium homeostasis.\textsuperscript{21} Animal models of diabetes and diabetic human myocardium have been shown to exhibit abnormalities in metabolic gene expression. In the failing human heart, decreased levels of sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2a) are associated with impaired cardiac function.\textsuperscript{21} In patients with nonischemic heart failure, diabetes further decreases levels of SERCA2a. Studies have also shown impaired sarcoenodplasmic calcium uptake in the diabetic heart. Myosin heavy chain (MHC)–\(\alpha\) expression is decreased in the failing human heart when compared with the nonfailing human heart. Downregulation of MHC–\(\alpha\) in the failing human heart is augmented by diabetes.\textsuperscript{22} Together, the decrease in SERCA2a and MHC–\(\alpha\) gene expression observed in the failing hearts of humans with diabetes may contribute to progressive cardiac dysfunction. Improved glycemic control may limit these switches in energy metabolism and transcriptional changes in contractile proteins that contribute to the contractile dysfunction in patients with heart failure who have diabetes.

**Neurohormonal Antagonists in the Management of Heart Failure**

There is compelling clinical trial evidence that the standard of care for all patients with heart failure due to left ventricular systolic dysfunction, regardless of severity or etiology, should include pharmacotherapy with an ACE inhibitor and a \(\beta\)-blocker unless the patient has a contraindication to their use or cannot tolerate treatment with these agents.\textsuperscript{1,15} Compelling clinical evidence of cardiovascular protection, fewer hospitalizations, and reduced mortality in patients who receive \(\beta\)-blocker therapy in conjunction with ACE inhibitor therapy has resulted in these therapies being recommended as standard therapy for heart failure in numerous practice guidelines.\textsuperscript{1} The mechanisms of benefit for ACE inhibitors and for \(\beta\)-blockers are highlighted in Table 1.

**Benefits of Angiotensin-Converting Enzyme Inhibition in the Patient with Diabetes**

The Heart Outcomes Prevention Evaluation (HOPE) study\textsuperscript{23} demonstrated the significant benefits of ACE inhibition in patients with documented coronary disease. This study assessed the effects of treatment with the ACE inhibitor ramipril versus placebo in 9,297 patients who had evidence of vascular disease or diabetes plus 1 additional cardiovascular risk factor and who did not have left ventricular dysfunction or heart failure. Treatment with ramipril resulted in reduced rates of death from cardiovascular causes, MI, stroke, death from any cause, revascularization procedures, cardiac arrest, heart failure, and complications related to diabetes. In terms of heart failure, ramipril treatment reduced the risk of new-onset heart failure by 23%.\textsuperscript{23}

A substudy of the HOPE trial, the microalbuminuria, cardiovascular, and renal outcomes (MICRO)–HOPE study\textsuperscript{24} examined whether ramipril can lower the risks of cardiovascular disease and renal disease in patients with diabetes. The analysis included 3,577 patients with diabetes who had been included in the HOPE study. The independent safety and monitoring board stopped the MICRO-HOPE study early (after 4.5 years) because ramipril therapy demonstrated a consistent benefit compared with placebo in this patient population. Specifically, it reduced the risk of total mortality by 24\%, MI by 22\%, stroke by 33\%, cardiovascular death by 37\%, and revascularization by 17\%.\textsuperscript{24} The HOPE and MICRO-HOPE studies provide convincing evidence that ACE inhibition can lower the risk of new-onset heart failure in patients with diabetes.

In patients with symptomatic heart failure, there is a wealth of data demonstrating the benefits of ACE inhibitor therapy. Garg and Yusuf\textsuperscript{25} analyzed 32 randomized, controlled trials of ACE inhibitor therapy in patients with symptomatic congestive heart failure and found that ACE inhibitor treatment resulted in a 23\% reduction in mortality. A more recent analysis of major clinical trials of ACE inhibitors further shows that patients with heart failure who have diabetes experience a benefit from therapy with ACE inhibitors similar to that of their nondiabetic counterparts.\textsuperscript{26}

**Aldosterone Blockade**

Aldosterone promotes myocardial and vascular fibrosis and has a number of other deleterious effects in heart failure.
Aldosterone production is incompletely suppressed by ACE inhibitor therapy. Thus, aldosterone blockade in patients with heart failure theoretically may provide benefit in addition to ACE inhibitor therapy. The Randomized Aldactone Evaluation Study (RALES) was designed to determine whether the aldosterone antagonist spironolactone, when added to standard heart failure therapy, would improve prognosis in patients with severe heart failure. The trial randomized 1,663 patients with left ventricular ejection fraction <0.35 and New York Heart Association (NYHA) functional class IV heart failure in the prior 6 months. All patients at the time of enrollment were being treated with an ACE inhibitor and a loop diuretic. After a mean follow-up period of 24 months, mortality in the spironolactone treatment arm was significantly less than that in the placebo arm, representing a relative reduction of 30%. In addition, patients benefited from treatment in RALES without a significant increase in the risk of serious hyperkalemia. In routine clinical practice, however, it is necessary to monitor patients for hyperkalemia after initiating therapy with a low dose of spironolactone to avoid this adverse effect.

RALES did not report separate data for patients with diabetes and heart failure. However, a more recent study of aldosterone blockade, the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), did look at these patients as a specific subgroup. All-cause mortality was reduced by 15% in patients treated with eplerenone. Patients with diabetes (n = 2,122) also benefited from aldosterone blockade, and there was no significant heterogeneity with respect to mortality benefit between diabetic and nondiabetic individuals. Thus, the use of aldosterone blockade lowers mortality beyond that achieved with standard therapy in patients with mild to moderate or severe heart failure.

Benefits of β-Blockade in the Patient with Diabetes

The UKPDS demonstrated that β-blockade can prevent heart failure in the patient with diabetes. Although this was primarily a study of the effects of tight control of blood pressure in patients with diabetes (goal: <150 mm Hg), patients enrolled in the study received either a β-blocker or an ACE inhibitor as their main treatment. The reduction in risk of heart failure in patients whose blood pressure was tightly controlled with either of these therapies was a remarkable 56%.

β-Blockade has also been shown to reduce mortality in patients with established heart failure. β-Blockers have been evaluated in >10,000 patients with heart failure in >20 published clinical trials and have demonstrated a ≥34% reduction in the risk of mortality in mild, moderate, and severe heart failure (Table 2). The safety and efficacy of β-blockade in patients with or without diabetes who had symptoms of severe heart failure were demonstrated in the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS). This study enrolled >2,200 patients with heart failure symptoms at rest or on minimal exertion (NYHA class IV) and an ejection fraction of <0.25 to assess the effects of β-blockade in patients with severe heart failure symptoms. The study was stopped early because carvedilol therapy in this population resulted in a dramatic reduction in all-cause mortality (35%) and a significant reduction in the combined risk of death or hospitalization. Furthermore, benefits of carvedilol were seen within the first 8 weeks across all patient subgroups, including the patients at highest risk.

Some studies of β-blockade in heart failure have provided data comparing therapy in diabetic and nondiabetic populations. In COPERNICUS and the US Carvedilol Heart Failure Evaluation Study (CIBIS II), benefits of carvedilol were seen in subgroups of patients with diabetes (goal: <150 mm Hg).

### Table 1
Cardiovascular benefits of angiotensin-converting enzyme (ACE) inhibition and β-adrenergic blockade

<table>
<thead>
<tr>
<th>ACE Inhibition</th>
<th>β-Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevents ischemia</td>
<td>Reverses cardiac remodeling</td>
</tr>
<tr>
<td>—Stimulates endothelial nitric oxide production</td>
<td>Prevents sudden death</td>
</tr>
<tr>
<td>—Reduces myocardial oxygen consumption</td>
<td>Prevents ischemia</td>
</tr>
<tr>
<td>Opposes atherogenesis</td>
<td>—Decreases heart rate and blood pressure</td>
</tr>
<tr>
<td>Lowers systemic vascular resistance and mean blood pressure</td>
<td>—Prolongs diastole (filling of coronary arteries)</td>
</tr>
<tr>
<td>Reduces cardiac afterload and systolic ventricular wall stress</td>
<td>Decreases myocardial wall stress, which reduces risk of cardiac rupture due to decrease in heart rate and blood pressure</td>
</tr>
<tr>
<td>Attenuates remodeling in heart failure</td>
<td>Opposes atherogenesis</td>
</tr>
<tr>
<td></td>
<td>Reduces shear stress and endothelial dysfunction</td>
</tr>
</tbody>
</table>

### Table 2
Effect of β-adrenergic blockade on mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Heart Failure Severity</th>
<th>Target Dosage (mg)</th>
<th>Effect on Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol HF Study</td>
<td>Carvedilol</td>
<td>Mild/moderate/severe</td>
<td>6.25–25 bid</td>
<td>↓ 65% (p &lt; 0.001)</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>Bisoprolol</td>
<td>Moderate/severe</td>
<td>10 qd</td>
<td>↓ 34% (p &lt; 0.0001)</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>Metoprolol succinate</td>
<td>Mild/moderate</td>
<td>200 qd</td>
<td>↓ 34% (p = 0.0062)</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>Carvedilol</td>
<td>Severe</td>
<td>25 bid</td>
<td>↓ 35% (p = 0.0014)</td>
</tr>
</tbody>
</table>

CIBIS II = Cardiac Insufficiency Bisoprolol Study II; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Study; HF = heart failure; MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure.
Failure Study, there was a significant reduction in all-cause mortality in patients with diabetes who received carvedilol therapy.\textsuperscript{31,33} In fact, in COPERNICUS, the relative risk reduction in all-cause mortality was exactly the same for patients with or without diabetes who were treated with carvedilol: 35%.\textsuperscript{33} In the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF),\textsuperscript{30} there was a trend toward improvement in all-cause mortality in patients with diabetes who received metoprolol therapy; however, this improvement was not statistically significant.

**Conclusion**

Individuals with diabetes are at elevated risk for heart failure, and the risk of morbidity and mortality in patients with both diabetes and heart failure is high. Clinical trials have demonstrated that combined neurohormonal blockade with the use of ACE inhibitors, aldosterone antagonists, and \( \beta \)-blockers is essential in the treatment of patients with heart failure. Combined neurohormonal blockade is especially important in patients with diabetes because they are at increased risk for MI and death. ACE inhibitors and \( \beta \)-blockers have been shown to be useful in these patients across the cardiovascular disease continuum: before a cardiovascular event, for secondary prevention, and in heart failure. ACE inhibitors, aldosterone antagonists, and \( \beta \)-blockers for the treatment of heart failure in the patient with diabetes represent a major therapeutic advance. Every effort should be made to apply these life-saving therapies in all patients with heart failure, including those with diabetes, in the absence of contraindications or intolerance.


Recent National Cholesterol Education Program Adult Treatment Panel III Update: Adjustments and Options

Neil J. Stone, MD,* Sarah Bilek, and Sara Rosenbaum

In the summer of 2004, an evidence-based update of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines for management of hypercholesterolemia was published. This detailed assessment of 5 major clinical trials, published since the ATP III report in 2001, was designed to provide guidance for physicians in decision making for patients at high risk and very high risk. We have tried to summarize this assessment by suggesting the following to clinicians: (1) Calculate global risk of coronary artery disease (CAD) to determine an overall strategy for cholesterol management. (2) Emphasize the benefits of diet, exercise, and weight control or therapeutic lifestyle change, especially in those with lifestyle risk factors. (3) Use 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) as first-line drugs to reduce risk of CAD and stroke in those at moderate to high risk. (4) If statins are prescribed, use moderate doses that reduce plasma levels of low-density lipoprotein (LDL) cholesterol by ≥30% to 40%. (5) Strongly consider statin therapy in those with diabetes (with the exception of severe hypertriglyceridemia). (6) Consider LDL cholesterol-lowering drug therapy for lipids in older patients at risk. (7) Consider adding either a fibrate or nicotinic acid in high-risk patients with elevated plasma triglyceride values or low levels of plasma high-density lipoprotein cholesterol after statin therapy has achieved the LDL cholesterol goal. (8) Continue to treat those at low risk in similar fashion as before. This update is to inform current physician judgment in this area. Further clinical trial data that may modify or extend these recommendations are eagerly awaited. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:53E–59E)

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) was a detailed, evidence-based approach to the diagnosis and management of hypercholesterolemia.1 It placed a strong emphasis on each patient’s risk of developing coronary artery disease (CAD). Indeed, determining risk of CAD was a crucial part of the algorithm for managing hypercholesterolemia that was presented to clinicians (Table 1).2 The major target of treatment was low-density lipoprotein (LDL) cholesterol. Important secondary targets were both the non–high-density lipoprotein (HDL) cholesterol for those with plasma triglyceride values ≥2.26 mmol/L (≥200 mg/dL) and the metabolic syndrome. The latter was defined as being present when ≥3 of the following criteria were met:

- Increased abdominal circumference, >102 cm (>40 in) for men and >90 cm (>35 in) for women
- Low plasma level of HDL cholesterol, <1.04 mmol/L (<40 mg/dL) for men and <1.30 mmol/L (<50 mg/dL) for women; the level for men is only the 15th percentile for women
- Increased values for plasma triglycerides, ≥1.70 mmol/L (≥150 mg/dL)
- Elevated blood pressure, ≥130/85 mm Hg
- Elevated level of blood sugar, ≥6.11 mmol/L (≥110 mg/dL). The American Diabetes Association (ADA)3 has recently suggested adjusting this value to ≥5.55 mmol/L (≥100 mg/dL).

Guidelines are written to reflect a consensus, an evidence-based approach at a single point in time. They can be expected to change with the emergence of new evidence that meets the same standards of evidence used in the original report. With the publication of 5 large-scale, randomized trials of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins),4–8 it seemed reasonable to provide an update to the ATP III 2001 report.9 Titled “Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines,” this update took a critical look at the Heart Protection Study (HPS), the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid Lowering Trial (ALLHAT-LLT), the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA), and the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT). As noted in the ATP III update, “These trials addressed issues that were not examined in
Table 1
Summary of National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) recommendations

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Obtain fasting plasma lipoprotein profile</td>
</tr>
<tr>
<td></td>
<td>Calculate LDL by formula: Total cholesterol − HDL-C − TG/5, as long as TG &lt;4.52 mmol/L (&lt;400 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Major goal is LDL-C levels: Optimal: ≤2.59 mmol/L (&lt;100 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Near/above optimal: 2.59–3.34 mmol/L (100–129 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Borderline high: 3.36–4.11 mmol/L (130–159 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>High: 4.14–4.89 mmol/L (160–189 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Very high: ≥4.91 mmol/L (≥190 mg/dL)</td>
</tr>
<tr>
<td>2.</td>
<td>Identify presence of CAD or risk equivalent</td>
</tr>
<tr>
<td></td>
<td>Presence of clinical atherosclerotic disease associated with high risk for CAD events (&gt;20% over 10 yr)</td>
</tr>
<tr>
<td></td>
<td>Clinical CAD</td>
</tr>
<tr>
<td></td>
<td>Symptomatic or significant carotid artery disease</td>
</tr>
<tr>
<td></td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td></td>
<td>Abdominal aortic aneurysm</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>3.</td>
<td>Determine presence of major risk factors (other than elevated LDL)</td>
</tr>
<tr>
<td></td>
<td>Hypertension (BP ≥140/90 mm Hg or taking antihypertensive medication)</td>
</tr>
<tr>
<td></td>
<td>Low HDL-C: &lt;1.04 mmol/L (&lt;40 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Family history of premature CAD (CAD in male first-degree relative &lt;55 yr or female first-degree relative &lt;65 yr)</td>
</tr>
<tr>
<td></td>
<td>Age (men ≥45 yr, women ≥55 yr)</td>
</tr>
<tr>
<td>4.</td>
<td>Assess 10-year CAD risk</td>
</tr>
<tr>
<td></td>
<td>Only necessary if ≥2 risk factors (other than elevated LDL) are present without CAD or CAD risk equivalent</td>
</tr>
<tr>
<td></td>
<td>Levels of risk: &gt;20% (CAD risk equivalent) 10%–20% &lt;10%</td>
</tr>
<tr>
<td>5.</td>
<td>Determine risk category to establish LDL-C goal of therapy</td>
</tr>
<tr>
<td></td>
<td>Determine need for TLC</td>
</tr>
<tr>
<td>6.</td>
<td>Initiate TLC if LDL-C is above goal</td>
</tr>
<tr>
<td></td>
<td>TLC includes: Diet: saturated fat &lt;7% of calories, cholesterol &lt;200 mg/day, increased viscous fiber (10–24 g/day) to enhance LDL lowering)</td>
</tr>
<tr>
<td></td>
<td>Weight management</td>
</tr>
<tr>
<td></td>
<td>Increased physical activity</td>
</tr>
<tr>
<td>7.</td>
<td>Consider adding drug therapy if LDL-C exceeds recommended levels</td>
</tr>
<tr>
<td></td>
<td>Consider drug simultaneously with TLC for patients at high risk</td>
</tr>
<tr>
<td></td>
<td>For other risk categories, consider adding lipid-lowering drug to TLC after 3 mo</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
</tr>
<tr>
<td></td>
<td>Bile acid sequestrants</td>
</tr>
<tr>
<td></td>
<td>Nicotinic acid</td>
</tr>
<tr>
<td></td>
<td>Fibrate</td>
</tr>
<tr>
<td>8.</td>
<td>Identify the metabolic syndrome and treat if present after 3 mo of TLC</td>
</tr>
<tr>
<td></td>
<td>Metabolic syndrome is identified by 3 of the following: Abdominal obesity (increased waist circumference: men &gt;101.6 cm [≥40 in], women &gt;88.9 cm [≥35 in])</td>
</tr>
<tr>
<td></td>
<td>High TG ≥1.70 mmol/L (≥150 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Low HDL (men, &lt;1.04 mmol/L [&lt;40 mg/dL], women, &lt;1.30 mmol/L [&lt;50 mg/dL])</td>
</tr>
<tr>
<td></td>
<td>High blood pressure (≥130/85 mm Hg)</td>
</tr>
<tr>
<td></td>
<td>High fasting plasma glucose, ≥6.11 mmol/L (≥110 mg/dL)*</td>
</tr>
<tr>
<td></td>
<td>Treat underlying causes by intensifying weight management and increasing physical activity</td>
</tr>
<tr>
<td>9.</td>
<td>Treat elevated plasma TG (≥1.70 mmol/L [≥150 mg/dL])</td>
</tr>
<tr>
<td></td>
<td>Intensity weight management</td>
</tr>
<tr>
<td></td>
<td>Increase physical activity</td>
</tr>
<tr>
<td></td>
<td>Primary aim is to reach LDL-C goal: If TG ≥2.26 mmol/L (≥200 mg/dL) after LDL goal is reached, set secondary goal for non-HDL-C at 0.78 mmol/L (30 mg/dL) higher than LDL-C goal If TG 2.26–5.64 mmol/L (200–499 mg/dL) after LDL-C goal is reached, consider adding drug to reach non-HDL-C goal If TG &gt;5.65 mmol/L (≥500 mg/dL), first lower TG with very-low-fat diet to prevent pancreatitis</td>
</tr>
<tr>
<td>10.</td>
<td>Consider treatment of low HDL-C (a component of step 9 in ATP III algorithm, but separated here for clarity)</td>
</tr>
<tr>
<td></td>
<td>First reach LDL goal, then: Intensity weight management and increase physical activity</td>
</tr>
<tr>
<td></td>
<td>If TG = 2.26–5.64 mmol/L (200–499 mg/dL), achieve non-HDL-C goal</td>
</tr>
<tr>
<td></td>
<td>If TG &lt;2.26 mmol/L (&lt;200 mg/dL) in patients with CAD or CAD equivalent, consider nicotinic acid or fibrate</td>
</tr>
</tbody>
</table>

BP = blood pressure; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; TLC = therapeutic lifestyle change.
* The American Diabetes Association has suggested lowering this threshold to 5.55 mmol/l (100 mg/dL).
Adapted from ATP III Guidelines At-a-Glance Quick Reference.
previous clinical trials of cholesterol-lowering therapy. The present document [implications paper] reviews the results of these recent trials and assesses their implications for cholesterol management.” The design and results of these trials are summarized in Table 2.4–8 There are no changes to the ATP III report (Table 1). ATP III recommended the all strategy for cholesterol management.

In an attempt to summarize the essential points of this update (which is not a new set of guidelines), we recommend the following 8 considerations for clinicians in their approach to management of the patient with hypercholesterolemia:

1. **Calculate global risk of CAD to determine an overall strategy for cholesterol management.**

   This recommendation remains unchanged from the initial ATP III report (Table 1). ATP III recommended the Framingham risk score to stratify individuals with ≥2 risk factors who may, depending on their risk factor burden, have a 10-year risk for “hard” CAD that is <10%, 10% to 20%, or ≥20%. This stratification approach emphasizes a key management dictum that intensity of therapy should be proportional to near-term CAD risk. Table 3 emphasizes this point.

2. **Emphasize the benefits of diet, exercise, and weight control (called therapeutic lifestyle change [TLC]), especially in individuals with lifestyle risk factors.**

   In patients with risk factors that can be related to lifestyle, such as obesity, sedentary lifestyle, elevated plasma glucose levels, high plasma triglyceride values, or low levels of plasma HDL cholesterol, TLC deserves major emphasis. In the ATP III initial report, TLC was designed to achieve reduction of CAD risk through improvement of both plasma LDL cholesterol levels and metabolic syndrome management. Even though statin drugs have proved effective in lowering CAD risk, in patients at moderate or high risk for CAD, TLC should be emphasized as an important component of therapy regardless of plasma LDL cholesterol level. For example, in those with the metabolic syndrome, individualized counseling for weight loss, regular exercise, and therapeutic diet may be particularly effective in helping to improve plasma triglyceride and HDL cholesterol values while offering promise for reducing the burden of medication required to improve the risk factor profile.

3. **Use statins as first-line drugs to reduce CAD and stroke risk in those at moderate to high risk.**

   Table 3 indicates threshold LDL cholesterol levels for statin use. However, clinical judgment is required to decide to whom statin therapy should be given. There are several instances for which drug therapy—or for those at very high risk, intensive drug therapy—is a reasonable management option. Two examples were given in the ATP III update. The presence of diabetes mellitus, multiple metabolic syndrome risk factors, and persistent risk factors such as smoking in those with established cardiovascular disease (CVD) or acute coronary syndrome, argue for consideration of a lower plasma LDL cholesterol threshold, such as 1.81 mmol/L (70 mg/dL). This goal is optional because the benefits and negative aspects of additional drug therapy should be weighed carefully in this patient group. In addition, there are trials underway whose results may modify this recommendation in the future.
Table 3
Clinical risk categories, low-density lipoprotein cholesterol (LDL-C) goals, and thresholds for therapeutic lifestyle change (TLC) and drug therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal, mmol/L (mg/dL)*</th>
<th>LDL-C Cut-Point, mmol/L (mg/dL)†</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established CVD and 1 of the following:</td>
<td>Optional goal of 1.81 (&lt;70) Also: If TG &gt;2.26 (&gt;200) despite LDL-C &lt;2.59 (&lt;100), non–HDL-C goal is &lt;2.59 (&gt;100)</td>
<td>≥70</td>
<td>This is a new, optional strategy for certain groups with established CAD that was suggested by data from the 5 new trials since ATP III. The writing group of the implications paper noted that further ongoing trials may modify this suggestion in the future</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent risk factors (such as cigarette smoking)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD or CAD risk equivalent (&gt;20% risk)</td>
<td>&lt;2.59 (&lt;100)</td>
<td>≥2.59 (≥100)</td>
<td>This is the guideline from the 2001 ATP III report</td>
</tr>
<tr>
<td>Moderately high</td>
<td>≥2 risk factors (10-yr risk of 10%–20%)</td>
<td>3.37 (≤130)</td>
<td>≥3.37 (≤130)</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>≥2 risk factors (10-yr risk of &lt;10%)</td>
<td>&lt;3.37 (&lt;130)</td>
<td>≥4.14 (≥160)</td>
</tr>
<tr>
<td>Low</td>
<td>≤1 risk factor</td>
<td>&lt;4.14 (&lt;160)</td>
<td>≥4.92 (≥190)</td>
</tr>
</tbody>
</table>

ATP III = Adult Treatment Panel III; CAD = coronary artery disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.

* Initiate TLC if above the LDL-C goal.
† Level of LDL-C at which to consider drug therapy.
‡ Factors that may favor the use of drug therapy include advancing age; >2 CAD risk factors; severe risk factors, such as continued cigarette smoking or a strongly positive family history of premature atherosclerotic CVD; high TG (≥200 mg/dL) plus elevated non–HDL-C (≥160 mg/dL); low HDL-C (<40 mg/dL); the metabolic syndrome; and/or the presence of emerging risk factors, such as high-sensitivity C-reactive protein (> 3 mg/L) or coronary calcium score > 75th percentile for the person’s age and sex.

Table 3 outlines factors that can help the clinician decide whether to use LDL cholesterol–lowering drug therapy in those at moderately high risk (≥2 risk factors and a 10% to 20% CAD risk over 10 years).

4. If statins are prescribed, use at least moderate doses that reduce plasma LDL cholesterol levels by ≥30% to 40% (Table 4).

A review of statin trials shows that when doses of statins achieve an LDL cholesterol reduction of 30% to 40%, the best results are obtained. When a lesser LDL cholesterol reduction is obtained, significant differences between intervention and control groups are not seen. For instance, ALLHAT-LLT found only an 18% difference between control and intervention groups.

5. Statin therapy is advised in those with diabetes.

In the HPS trial, those with diabetes (either type 1 or type 2) and CVD were at very high risk for future CAD events and stroke. This large study (20,000 participants) showed convincingly that the benefit of statin therapy in patients at high risk, including individuals with diabetes, extended to those who had an initial plasma LDL cholesterol value of <2.59 mmol/L (<100 mg/dL). It should be noted that...
plasma LDL cholesterol levels in the HPS were measured in nonfasting blood samples by a direct LDL method.\textsuperscript{10} This gives a different result than if the samples had been fasting and plasma levels of LDL cholesterol calculated by the Friedewald formula (Table 1, step 1), which uses the values for total cholesterol, triglycerides, and HDL cholesterol.\textsuperscript{11} The ATP III update pointed out that the HPS cut-points would have been about 15% higher had they used the calculated rather than the measured method for determining the value for LDL cholesterol. Nonetheless, the HPS database argues persuasively for more intensive statin therapy in patients with diabetes and established CVD, and it supports a new optional plasma LDL cholesterol goal of $<181 \text{ mmol/L}$ ($<70 \text{ mg/dL}$) for these patients at very high risk.

For those with diabetes and no evidence of established CAD, risk is still high, particularly in those who are older and who have multiple risk factors. In the HPS, those subjects with diabetes and plasma levels of LDL cholesterol $<3.00 \text{ mmol/L}$ ($<116 \text{ mg/dL}$) had only a marginally significant reduction in CAD events with statin therapy. However, subsequent to publication of the ATP III update, the Collaborative Atorvastatin Diabetes Study (CARDS) examined the effects of atorvastatin 10 mg/day in 2,838 adults with type 2 diabetes who had an average plasma value for LDL cholesterol of 3.06 mmol/L (118 mg/dL) and no evidence of established CAD.\textsuperscript{12} The trial was terminated at 3.9 years, 2 years earlier than planned, because statin therapy resulted in significant 48% reductions in acute CAD events, coronary revascularizations, and rate of stroke. Statin therapy reduced the death rate by 27% (confidence interval [CI 95%], -48 to 1; $p = 0.059$). Additionally, no excess of adverse events was noted in the atorvastatin group.

It is important to understand that the patient with diabetes who presents with a plasma triglyceride value $>11.3 \text{ mmol/L}$ ($>1,000 \text{ mg/dL}$) and features of the chylomicronemia syndrome (eruptive xanthomas, lipemia retinalis, and acute pancreatitis) should not be given a statin initially. The severe hypertriglyceridemia characteristic of this syndrome is best controlled with a regimen that includes a fibric acid drug, a low-fat diet, fish oil supplementation, tight blood sugar control (usually with insulin), and weight loss if obese.

6. Consider LDL cholesterol–lowering drug therapy in older patients at risk.

Although PROSPER\textsuperscript{3} looked exclusively at CVD risk in older persons (aged 70 to 82 years), it is not the only data set that pertains to the benefit of statin therapy in this age group. More than 50% of the 20,000 subjects in the HPS were $>65$ years.\textsuperscript{4} Moreover, 28% were between the ages of 70 and 80 years at the time of enrollment. The ATP III update noted, “HPS explicitly documented risk reduction with statin therapy in older persons (aged 65 to 80) at high risk.” In the ASCOT-LLA\textsuperscript{7} trial, 64% of participants were $>60$ years, and atorvastatin 10 mg/day had a significant effect on stroke reduction in this primary prevention trial of hypertensive subjects. Also, although noted on post hoc analysis, the benefit of statin therapy in reducing the incidence of fatal and nonfatal stroke was maintained in those subjects $>70$ years.\textsuperscript{7}

Safety of statin therapy is especially important in older age groups. Statin-induced problems such as significant increases in liver transaminase values and development of myopathy must be watched for in this group: older patients may be taking multiple medications that increase the risk for drug-drug interactions, and they may also have underlying renal or hepatic abnormalities. In the HPS, however, there was no significant increase in risk of myopathy or significant hepatic transaminase problems between drug and placebo groups. It should be noted that patients with a prior intolerance of statins, an alanine aminotransferase value $>1.5$ times the upper limit of normal, or a serum creatinine level $>203.32 \text{ mmol/L}$ ($>2.3 \text{ mg/dL}$) were not entered into this trial. The investigators also had potentially eligible subjects enter a prerandomization “run-in” phase to ensure long-term involvement in the study. The run-in treatment involved 4 weeks of placebo (to allow review of baseline parameters) followed by 4 to 6 weeks of a fixed dose of 40 mg of simvastatin daily. We believe that clinicians should not only avoid extrapolating conclusions from this study to patients who would not qualify, they should also consider emulating a careful assessment of who qualifies for intensive statin therapy and perform a thorough assessment after 4 to 6 weeks of therapy, especially in their older patients.

One concern that emerged from the PROSPER trial\textsuperscript{8} was the excess of cancer occurrences in the treated group. Gastrointestinal cancers were more common in the pravastatin-treated group (65 versus 45 cases in the placebo cohort). Overall, a new cancer diagnosis was 25% more frequent in the pravastatin group. However, to put this finding into context, the investigators performed a meta-analysis of cancer rates in previously done randomized placebo-controlled trials lasting $>3$ years and using either pravastatin or other statins. This check on external validity is important because cancer is prevalent in the older age group and a consistent finding of an increased cancer occurrence among different studies would make it less likely that this observation was due to chance. The hazard ratios for pravastatin (1.06; 95% CI, 0.96 to 1.17; $p = 0.20$) or all statins taken together (1.02; 95% CI, 0.96 to 1.09; $p = 0.32$) in this meta-analysis showed that the total experience with statins was not associated with an excess incidence of cancer.

The older person at high risk but without established CVD is also a candidate for drug therapy. Women tend to be overrepresented in older age groups because they experience fewer cardiovascular events at an earlier age than do their male counterparts, according to the Framingham study.\textsuperscript{13} However, after menopause, risk markers such as high ratios of total cholesterol to HDL cholesterol, left ventricular hypertrophy, and diabetes become more prevalent and tend to eliminate the female advantage with regard to CAD risk. Indeed, CAD is a prime suspect in older decades of life as CVD becomes the leading cause of death both in women and in men. Nonetheless, the decision to use drug therapy for hypercholesterolemia is not simple because
of the lack of good risk-assessment tools. The Framingham risk score is generally not as useful after the age of 70 years, owing to the dominant effect of age on the score. In those with ≥2 risk factors for CAD, other considerations such as the presence of low plasma levels of HDL cholesterol, a positive ankle-brachial index, abnormal findings on carotid ultrasonography, or an elevated coronary artery calcium score can provide support for more intensive therapy. Yet, in addition to therapeutic efficacy, the ATP III update emphasized the importance of factors such as safety, tolerability, and patient preference that should be considered before therapy is undertaken in this age group.

7. Consider adding either a fibrate or nicotinic acid to an LDL cholesterol-lowering drug in patients at high risk who have elevated plasma triglycerides (≥2.26 mmol/L [≥200 mg/dL]) or a low plasma value for HDL cholesterol (<1.04 mmol/L [<40 mg/dL]) after statin therapy has achieved the LDL cholesterol goal.

The data supporting this role for drug therapy in improving these components of the metabolic syndrome is not as well defined as the data supporting drug therapy for lowering plasma LDL cholesterol. Nonetheless, there are compelling data to consider. Fibrates were shown to be effective in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), in those men with CAD who had an average plasma LDL cholesterol of only 2.87 mmol/L (111 mg/dL) and a low HDL cholesterol of 0.83 mmol/L (32 mg/dL). Moreover, most of the benefit of fibrate therapy in this study appeared to occur in those with high fasting insulin levels or diabetes. Nicotinic acid is the most effective lipid drug for raising values of plasma HDL cholesterol. In an informative angiographic clinical trial in men and women with low values for plasma HDL cholesterol, nicotinic acid and simvastatin were effective in significantly reducing coronary angiographic progression compared with placebo. Of note, antioxidant vitamins diminished the beneficial response seen with nicotinic acid. These studies suggest the benefit of combination therapy in those at highest risk.

8. Continue to treat those at low risk in similar fashion as before.

Patients at low risk should be evaluated and treated as previously indicated by the ATP III (Table 3).

Conclusion

The ATP III update is a carefully written summary of the evidence that can be used to improve the care of patients at highest risk for CVD events. Those interested in a more detailed discussion of the above points should read the ATP III update in its entirety. The basic ATP III algorithm for treating hypercholesterolemia remains intact, with the addition of the modifications implicated by more recent clinical trials. The emphasis on physician judgment in both the original and the updated versions of the ATP III guidelines cannot be overstressed. Drug therapy is a long-term proposition with significant costs that include not only drug purchase but also the expense of monitoring and treatment of potential side effects. Thus, the decision of when to start should be based on thoughtful consideration of compelling factors.

Continuing advances in both diagnosis and therapy will mandate future revisions of the guidelines for the management of hypercholesterolemia. However, certain essential principles are likely to remain, including the following 3 points: (1) Intensity of management is based on overall cardiovascular risk. (2) Treatment takes into account the importance of the added risk of metabolic syndrome if present. (3) Additional data may be needed for those at intermediate risk (such as those with other risk markers and/or measures of subclinical atherosclerosis) to determine intensity of therapy.

Finally, until we have clinical trial data to guide every therapeutic decision that arises in clinical practice, informed physician judgment will still be most important in providing the best treatment for patients.


Lessons from recent end point trials of lipid-lowering drugs indicate that patients at very high risk for coronary artery disease (CAD) benefit from treatment that lowers low-density lipoprotein (LDL) cholesterol plasma levels to ≤1.81 mmol/L (≤70 mg/dL), that patients with ≥2 risk factors benefit from treatment that lowers plasma LDL cholesterol to <2.59 mmol/L (<100 mg/dL), and that a significant reduction in CAD event rates is most often associated with a minimum plasma LDL cholesterol reduction of 30%. Recently, the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) recommendations were amended to incorporate these lessons. To reach these more aggressive goals and plasma LDL cholesterol reductions, more aggressive therapies will be required. The best way to implement more aggressive therapy is to start with one of the more potent statins, especially atorvastatin or rosuvastatin, or higher doses of other statins. This approach alone is likely to achieve treatment goals in 50% to 80% of patients. For patients needing additional plasma LDL cholesterol lowering, combination therapies will be required. Adding colestevam, ezetimibe, or niacin to a stable statin regimen will generally provide an additional 10% to 15% lowering of plasma LDL cholesterol. These more potent statins, even when used in higher doses, appear to be safe. The incidence of myopathy and rhabdomyolysis, as documented in long-term clinical trials, is <0.1% and <0.01%, respectively, except for simvastatin, which has a higher incidence of these problems. Less information is available about the safety of lowering levels of plasma LDL cholesterol to ≤1.81 mmol/L (≤70 mg/dL), but an analysis of a recent 2-year-long clinical trial, in which patients had on-treatment plasma LDL cholesterol levels as low as 0.67 mmol/L (26 mg/dL), reported no signals of untoward effects in patients with progressively lower levels. © 2005 Elsevier Inc. All rights reserved.

We are fortunate to have dozens of randomized clinical trials comparing the impact of lipid-lowering treatments with placebo or active controls on coronary artery disease (CAD) event rates (Table 1).1–15 Collectively, they give us many important insights into the effective management of CAD risk. As may be seen in Table 1, some of these insights are:

- Lowering plasma levels of low-density lipoprotein (LDL) cholesterol lowers CAD event rates.
- For every 1% lowering in value for plasma LDL cholesterol, there is roughly a 1% lowering in the incidence of CAD events.
- The baseline plasma level of LDL cholesterol is closely correlated to the rate of CAD events. The higher the plasma LDL cholesterol level, the higher the placebo CAD event rate; this is especially evident in secondary prevention studies.
- Every treatment that effectively lowers the plasma level of LDL cholesterol leads to a significant reduction in incidence of CAD events. This is so whether the treatment is an oral 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) with systemic activity, a nonabsorbed bile acid sequestrator, or nonpharmacologic treatment such as ileal bypass surgery. This suggests that an important component in reducing CAD risk is the lowering of plasma LDL cholesterol levels, regardless of the method. Other mechanisms may be involved, as the many pleiotropic effects of current therapies suggest, but these mechanisms track LDL cholesterol lowering.
- The level of the patient’s risk for CAD in part determines the degree of CAD risk reduction. The higher the CAD risk, the greater the benefit from risk-reducing therapy. This is especially true for absolute risk; the higher the CAD risk, the greater the number of events that will be prevented with treatment. However, interestingly, the relative risk reduction with the lowering of plasma LDL cholesterol is about the same whether the patient has high or moderate CAD risk.
Table 1

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Reduction in LDL Cholesterol, % (Placebo minus Treatment)</th>
<th>Treatment LDL Cholesterol Values at Baseline and End Point, mmol/L (mg/dL)</th>
<th>Placebo Rate of CAD Death/Nonfatal MI* (%)</th>
<th>Treatment Reduction in Rate of CAD Death/Nonfatal MI (%)</th>
</tr>
</thead>
</table>

Patients with multiple CAD risk factors

- ALLHAT-LLT4: Pravastatin –16 3.78–2.69 (146–104) 3.78–2.69 (146–104) 10.4 –9 (NS)

Patients with CAD or CAD risk equivalent

- GREACE8: Atorvastatin –41 4.66–2.51 (180–97) 4.66–2.51 (180–97) 18.5† –54†
- CARE11: Pravastatin –32 3.60–2.54 (139–98) 3.60–2.54 (139–98) 13.2 –24
- HPS12: Simvastatin –32 3.39–2.31 (131–89) 3.39–2.31 (131–89) 11.8 –24

Patients with acute coronary syndrome

- MIRACL13 (4 wk): Atorvastatin vs placebo –47 (135 vs 72) 3.31–1.94 (151–87) 3.31–1.94 (151–87) 10.9 –8
- PROVE-IT14 (24 mo): Atorvastatin vs placebo –35 (95 vs 62) 2.75–1.61 (106–62) 2.75–1.61 (106–62) 8.3 –16
- A to Z15 (24 mo): Simvastatin 80 vs 20 mg 2.90–1.71 (112–66) 2.90–1.71 (112–66) 7.4 –4

A to Z = Phase Z in the A to Z Trial; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm; CAD = coronary artery disease; CARE = Cholesterol and Recurrent Events Trial; GREACE = Greek Atorvastatin and Coronary Heart-Disease Evaluation; HPS = Heart Protection Study; LDL = low-density lipoprotein cholesterol plasma levels; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; POSCH = Program on the Surgical Control of Hyperlipidemias; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy; 4S = Scandinavian Simvastatin Survival Study; WOSCOPS = West of Scotland Coronary Prevention Study.

* Extrapolated to 5-year rate.

† Extrapolated to 5-year rate.

§ Values in parentheses are LDL cholesterol levels at end of study for simvastatin 20 mg vs simvastatin 80 mg.

‡ Values in parentheses are LDL cholesterol levels at end of study for atorvastatin vs placebo.

Table 1: Major end point trials with lipid-lowering therapy

- By doubling the 5-year event rates reported for placebo groups in studies in patients with CAD or CAD risk equivalents, the estimated 10-year event rates are 24% to 60%. In the Heart Protection Study (HPS),12 in which patients with CAD and CAD risk equivalent conditions were evaluated, the CAD event rate was >20% even in those patients with baseline plasma LDL cholesterol levels <2.59 mmol/L (<100 mg/dL). The 10-year CAD event rates among placebo-treated patients with multiple risk factors were 6% to 30%.

- No on-treatment level of plasma LDL cholesterol has been identified for which the CAD event rate is zero. Even the most aggressive LDL cholesterol lowering, producing very low plasma LDL cholesterol levels, is associated with CAD events, albeit few. Even patients with an acute coronary syndrome treated to plasma levels <1.81 mmol/L (<70 mg/dL) have high 2-year event rates: 7.2% with CAD death or nonfatal myocardial infarction (MI) in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)14 and 7.1% with an MI in the A to Z Trial.15 Extrapolation of curves plotting plasma LDL cholesterol levels versus CAD event rates suggest that the “zero” CAD event rate is reached at a level of about 1.42 mmol/L (55 mg/dL) in patients with multiple risk factors and about 0.78 mmol/L (30 mg/dL) in patients with CAD or CAD risk equivalents.

- A certain minimal plasma LDL cholesterol reduction appears to be required to produce a significant CAD risk reduction. Studies that achieved ≥1 mmol/L greater reduction in plasma level of LDL cholesterol (approximately 40 mg/dL or about 30%) with the primary therapy versus that with the placebo or active comparator resulted in a significant CAD event reduction; studies with a lesser difference between groups in end point plasma LDL cho-
Table 2

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Consider Drug Therapy</th>
<th>LDL Cholesterol Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD or CAD risk equivalent (&gt;20% 10-yr risk)</td>
<td>LDL &gt; 2.59 mmol/L (&gt;100 mg/dL) Consider drug option: &lt; 2.59 mmol/L (&lt;100 mg/dL)</td>
<td>&lt; 2.59 mmol/L (&lt;100 mg/dL) Optional goal for patients at very high risk: &lt; 1.81 mmol/L (&lt;70 mg/dL)</td>
</tr>
<tr>
<td>No. of risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 (10%–20% 10-yr risk)</td>
<td>LDL &gt; 3.37 mmol/L (&gt;130 mg/dL) Drug option: 2.59–3.34 mmol/L (100–129 mg/dL)</td>
<td>&lt; 3.37 mmol/L (&lt;130 mg/dL) Optional goal: &lt; 2.59 mmol/L (&lt;100 mg/dL)</td>
</tr>
<tr>
<td>≥2 (&lt;10% 10-yr risk)</td>
<td>LDL &gt; 4.14 mmol/L (&gt;160 mg/dL)</td>
<td>&lt; 3.37 mmol/L (&lt;130 mg/dL)</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>LDL &gt; 4.92 mmol/L (&gt;190 mg/dL) Drug option: 4.14–4.90 mmol/L (160–189 mg/dL)</td>
<td>&lt; 4.14 mmol/L (&lt;160 mg/dL)</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; LDL = low-density lipoprotein cholesterol plasma levels.
Adapted with permission from JAMA16 and Circulation.17

Cholesterol levels were more likely to have an insignificant CAD risk reduction.

- The lowest plasma LDL cholesterol level achieved in patient populations with multiple risk factors has been <2.59 mmol/L (<100 mg/dL), which supports the new recommendation of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III) for these patients (see below). Likewise, the lowest study finding of on-treatment plasma LDL cholesterol level in patients with CAD or CAD risk equivalents is <2.59 mmol/L (<100 mg/dL), which supports the current ATP III recommended goal. The on-treatment levels of plasma LDL cholesterol in patients with acute coronary syndromes are generally <1.81 mmol/L (<70 mg/dL), supporting a new, more aggressive treatment goal in this patient population.

- In patients with the highest CAD risk (eg, patients with acute coronary syndrome), benefit from statin therapy can be seen in as little as 4 weeks.

On the basis of these insights, ATP III published its treatment recommendations in 200116 and updated them in 2004.17 The revised guidelines are illustrated in Table 2 and important changes are summarized below:

- Patients with CAD or CAD risk equivalent conditions who have an LDL cholesterol plasma level >2.59 mmol/L (>100 mg/dL) can be considered for simultaneous lipid-lowering drug therapy and lifestyle modification, and they are assigned a plasma LDL cholesterol treatment goal of <2.59 mmol/L (<100 mg/dL). On the basis of the HPS results,12 patients with CAD or CAD risk equivalents who have a plasma level of LDL cholesterol <2.59 mmol/L (<100 mg/dL) may also be considered for lipid-lowering drug therapy, which lowers plasma LDL cholesterol by ≥30%.

- Patients experiencing an acute coronary syndrome may be considered for an optional plasma LDL cholesterol goal of <1.81 mmol/L (<70 mg/dL). These patients are at very high risk for CAD. Other patients who have a similar very high CAD risk may, at the discretion of the treating health professional, be considered for a similar optional plasma LDL cholesterol goal of <1.81 mmol/L (<70 mg/dL). Examples of groups that may be considered at very high risk are patients with diabetes who have stable CAD, patients with stable CAD who have multiple uncontrolled risk factors, and patients with CAD who have multiple risk factors for the metabolic syndrome.

- Patients with ≥2 risk factors have a plasma LDL cholesterol goal of <3.37 mmol/L (<130 mg/dL). Because of the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) findings, patients with multiple risk factors, including hypertension, may be considered for a plasma LDL cholesterol goal of <2.59 mmol/L (<100 mg/dL) at the treating health professional’s discretion.

- Finally, when a commitment is made to reduce CAD risk by lowering plasma levels of LDL cholesterol with drug therapy, the lowering should be ≥30% to 40%.

What Therapies Should Be Considered for Treating Patients to the New Adult Treatment Panel III Goals?

Treatment for most patients was not changed appreciably by the updated ATP III recommendations. For most patients, plasma LDL cholesterol–lowering therapy will begin with prescription of a statin. However, to meet the new recommendation that the plasma LDL cholesterol reduction should be ≥30% to 40%, one of the more potent statins or a high dose of a less potent statin must be deployed (Table 3).18 If the patient does not tolerate a statin, none of the remaining plasma LDL cholesterol–lowering therapies—including bile acid sequestrants, cholesterol absorption inhibitors, and niacin—can meet this new standard alone; thus, the therapist is forced to consider combination therapy. Once the
A patient has achieved his or her plasma LDL cholesterol goal, if the plasma triglyceride level is >2.26 mmol/L (>200 mg/dL), adjusting existing therapy to achieve a more aggressive plasma LDL cholesterol lowering or adding a triglyceride-lowering agent (eg, fibrate, niacin) are options to reach the non–high-density lipoprotein cholesterol goal.

A patient at very high CAD risk or having multiple risk factors may be considered for the new, more aggressive plasma LDL cholesterol goals of <1.81 mmol/L (<70 mg/dL) and <2.59 mmol/L (<100 mg/dL), respectively. The key is first identifying patients who may benefit from these more aggressive goals and then building a lifestyle/drug regimen that is most likely to reach these goals. Here the potent statins have a dominant role (Table 3). However, many patients still will not achieve their new, lower goals and so combination therapy will have to be used.

Among the statins, the most potent are atorvastatin and rosuvastatin. They can lower levels of plasma LDL cholesterol the recommended 30% to 40% with starting doses, thus allowing higher doses to be used when needed to achieve greater plasma LDL cholesterol lowering in patients who do not achieve their goal.\(^1\) In the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR) trial,\(^1\) rosvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and pravastatin 20 mg achieved the plasma LDL cholesterol goal of <2.59 mmol/L (<100 mg/dL) in 53%, 44%, 14%, and 3% of patients, respectively. At their top doses, rosuvastatin 40 mg, atorvastatin 80 mg, simvastatin 80 mg, and pravastatin 40 mg daily achieved the plasma LDL cholesterol level of <2.59 mmol/L (<100 mg/dL) in 80%, 70%, 53%, and 8% of patients, respectively. This study illustrates that the less potent statins, while demonstrating the ability to reduce CAD risk in randomized clinical trials, have a limited role in meeting these more aggressive treatment recommendations. This study also demonstrates that not all patients reach the plasma LDL cholesterol goal of <2.59 mmol/L (<100 mg/dL), even with the highest doses of the most potent statins, and so logically even fewer will reach the goal of <1.81 mmol/L (<70 mg/dL) with statin monotherapy.

Thus combination therapy will have to be used in a large number of patients at high or very high CAD risk to achieve their treatment goals. The plasma LDL cholesterol–lowering drugs that are candidates for combination therapy include statins, colestevelam, ezetimibe, and niacin. Fibrates are not effective plasma LDL cholesterol–lowering therapies and thus are not preferred for combination therapy. In most instances, a statin will be initiated, and a second agent will be subsequently added. The additional plasma LDL cholesterol lowering that can be anticipated with a second agent has been studied (Table 4). In general, colestevelam 3.8 g/day will provide an additional 10% to 16% lowering of plasma LDL cholesterol when added to a constant dose of a statin, ezetimibe will provide 7% to 17% additional lowering, and niacin will cause about 8% additional lowering with 1 g/day and 24% additional lowering with 2 g/day.\(^20\)–\(^24\) These added therapies may be used with starting doses of statins to create a 2-drug, low-dose combination or they may be added to top doses of statins to create a maximal plasma LDL cholesterol–lowering combination. The latter can achieve a mean lowering of plasma LDL cholesterol as great as 60% to 65%. Information on the efficacy of a triple-drug combination regimen is limited. The combination of a moderate dose of a statin together with a maximum dose of niacin and a bile acid sequestrant is reported to reduce plasma LDL cholesterol levels an average of 60%.\(^26\) It is not clear why 60% to 65% appears to be the maximum mean lowering of plasma LDL cholesterol achieved with these combination therapies; it may represent what can be maximally achieved pharmacologically or physiologically. Reductions beyond what can be achieved with combination drug regimens can be achieved with LDL cholesterol apheresis.

### How Safe Is It to Lower Levels of Plasma LDL Cholesterol Aggressively?

Arguably the most important and potentially serious toxicity associated with statin therapy is muscle damage, manifested as myopathy (symptoms of muscle weakness, soreness, or pain and an elevation of serum creatinine kinase [CK] >10 times the upper limit of normal) or rhabdomyolysis (myopathy with worsening serum creatinine concentrations). The incidence of these problems is generally very low, as illustrated in the major clinical trials involving statins (Table 5).\(^2,3,5,6,8,9,11–15\) This method of documenting adverse events with drugs has the advantage of providing a defined population of subjects who are randomly assigned to receive blinded study drugs and are followed up by experienced investigators. A disadvantage of this method is that it often includes a study population in which many of the risk factors for muscle toxicity have been excluded (eg, advanced age, renal dysfunction, and interacting drugs). With that in mind, the incidence of muscle toxicity in clinical trials of most statins is very low. A total of 11 cases of myopathy (0.1%) and no case of rhabdomyolysis were recorded among nearly 10,000 patients administered pravastatin 40 mg/day for 5 years (Table 5). No case of myop-

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**Table 3**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean LDL Cholesterol Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 10–80 mg</td>
<td>39–60</td>
</tr>
<tr>
<td>Fluvastatin XL 80 mg</td>
<td>36</td>
</tr>
<tr>
<td>Lovastatin 40–80 mg</td>
<td>32–42</td>
</tr>
<tr>
<td>Pravastatin 40 mg</td>
<td>34</td>
</tr>
<tr>
<td>Simvastatin 20–80 mg</td>
<td>38–47</td>
</tr>
<tr>
<td>Rosuvastatin 5–40 mg</td>
<td>45–63</td>
</tr>
</tbody>
</table>

Reprinted from Physician’s Desk Reference.\(^18\)
atherosclerosis Prevention Study; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARE = Cholesterol and Recurrent Events trial; GREACE = Greek Atorvastatin and Coronary Heart Disease Evaluation; HPS = Heart Protection Study; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy; 4S = Scandinavian Simvastatin Survival Study; statin = 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor.

A to Z = Phase Z in the A to Z Trial; AFCAPS/Texcaps = Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARE = Cholesterol and Recurrent Events trial; GREACE = Greek Atorvastatin and Coronary Heart Disease Evaluation; HPS = Heart Protection Study; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; MIRACL = Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; PROVE-IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy; 4S = Scandinavian Simvastatin Survival Study; statin = 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor; WOSCOPS = West of Scotland Coronary Prevention Study.

A final safety question not directly related to the drug itself: How safe is lowering of plasma LDL cholesterol to ≤1.81 mmol/L (≤70 mg/dL), regardless of the drug or method? The answer to this question is not straightforward, nor are there abundant data upon which to draw definitive conclusions. Here is what we know: First, small groups of humans who live primitively as hunters and gatherers are reported to have plasma total cholesterol levels of 2.46 to 3.10 mmol/L (95 to 120 mg/dL), ie, a plasma LDL cholesterol level of 1.30 to 2.07 mmol/L (50 to 80 mg/dL). Wild primates (eg, baboons, monkeys) and mammals (eg, horses, elephants) have similar plasma total cholesterol and LDL levels. CAD in these groups is rare or nonexistent.

Another issue that has arisen with rosuvastatin is renal toxicity. A 2+ or greater proteinuria was recorded in 3,300 patients receiving lovastatin 20 to 40 mg daily for 5 years (0.03%); likewise, 1 patient in nearly 10,000 patients receiving atorvastatin 10 or 80 mg/day for 2 to 5 years experienced rhabdomyolysis (0.01%). The story with simvastatin is different. The incidence of both myopathy and rhabdomyolysis with this statin increases in a dose-dependent manner; among patients receiving simvastatin 80 mg for 2 years in the A to Z Trial, the incidence of myopathy was 0.3% and of rhabdomyolysis 0.1% (Table 5).

Data for rosuvastatin, the newest statin, come from randomized clinical trials in about 10,500 patients that were completed during the drug development program. The incidence of myopathy with doses of 10 to 40 mg is 0.1%, in keeping with the other statins; no cases of rhabdomyolysis and no deaths were reported with the drug at these doses, although several cases of rhabdomyolysis occurred in patients receiving the 80-mg dose and a number of cases have been reported at all doses since the drug has been on the market (in common with other statins). The 80-mg dose was not approved for the market because of an increased incidence of side effects.

Another issue that has arisen with rosuvastatin is renal toxicity. A 2+ or greater proteinuria was recorded in 1.2% of patients treated with rosuvastatin 40 mg who initially had a negative or trace reading; the incidence of a 2+ or greater proteinuria was ≤0.6% in patients receiving placebo or 5-, 10-, and 20-mg doses of rosuvastatin. Further analysis of this patient subset reveals that serum creatinine values and calculated glomerular filtration rates improved over the course of the study, including in the 1,100 patients who received 10 to 40 mg of rosuvastatin for as long as 96 weeks. These data suggest that there is no renal impairment associated with rosuvastatin therapy.

A final safety question not directly related to the drug itself: How safe is lowering of plasma LDL cholesterol to ≤1.81 mmol/L (≤70 mg/dL), regardless of the drug or method? The answer to this question is not straightforward, nor are there abundant data upon which to draw definitive conclusions. Here is what we know: First, small groups of humans who live primitively as hunters and gatherers are reported to have plasma total cholesterol levels of 2.46 to 3.10 mmol/L (95 to 120 mg/dL), ie, a plasma LDL cholesterol level of 1.30 to 2.07 mmol/L (50 to 80 mg/dL). Wild primates (eg, baboons, monkeys) and mammals (eg, horses, elephants) have similar plasma total cholesterol and LDL levels. CAD in these groups is rare or nonexistent.
Second, the average plasma LDL cholesterol level in the newborn human is about 1.48 mmol/L (57 mg/dL), with a range of 0.67 to 3.19 mmol/L (26 to 123 mg/dL); this at a point when cells are dividing and the need for cholesterol is high. The incidence of CAD in newborns is also very low and does not become manifest until years later, when their plasma total cholesterol level has risen to the population mean of 5.26 mmol/L (203 mg/dL).

Third, patients with hypobetalipoproteinemia have plasma LDL cholesterol levels below the fifth percentile (approximately <2.33 mmol/L [<90 mg/dL]) and have a reduced risk of CAD. In fact, this heritable disorder is associated with longevity.

A few clinical trials have been analyzed for the relation between adverse events and low on-treatment plasma LDL cholesterol levels. The results are encouraging but generally contain too few subjects to allow a definitive statement on safety to be made. Among 2,502 patients who participated in rosvastatin clinical trials, 319 had plasma LDL cholesterol levels <2.07 mmol/L (<80 mg/dL), and 21 had levels <1.30 mmol/L (<50 mg/dL). Results of liver function tests (LFT), serum CK levels, myalgia, and withdrawals due to adverse events were not different between the groups. Among 2,579 patients who participated in rosuvastatin clinical trials, 971 had a plasma LDL cholesterol level <2.07 mmol/L (<80 mg/dL) and 149 had levels <1.30 mmol/L (<50 mg/dL). Again, there were no differences between these groups with regard to elevated LFT results, elevated levels of serum CK, myalgias, or any other adverse event. Recently, patients enrolled in the PROVE-IT study who took atorvastatin 80 mg or pravastatin 40 mg for 2 years were analyzed for their on-treatment plasma levels of LDL cholesterol and adverse events; no significant differences were found in terms of total and non-CAD mortality and elevations of LFT results or serum CK levels (Table 6). Adapted from "Can LDL Be Too Low? A Safety Analysis of the Intensive Treatment Arm of PROVE-IT–TIMI 22."

Table 6
Incidence of adverse events in patient groups arranged by on-treatment low-density lipoprotein (LDL) cholesterol levels in Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)

<table>
<thead>
<tr>
<th>End Point Value for LDL</th>
<th>LDL Cholesterol</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.07–2.59 mmol/L</td>
<td>1.55–2.07 mmol/L</td>
</tr>
<tr>
<td>n = 256</td>
<td>n = 566</td>
<td>n = 625</td>
</tr>
<tr>
<td>Death</td>
<td>1.2%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Non-CAD death</td>
<td>0.8%</td>
<td>1.4%</td>
</tr>
<tr>
<td>ALT &gt;3× ULN</td>
<td>3.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>CK &gt;3× ULN</td>
<td>2.0%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

ALT = alanine transferase; CAD = coronary artery disease; CK = creatine kinase; ULN = upper limit of normal.

Conclusion

The ATP III cholesterol treatment guidelines as revised have presented new challenges to health professionals, especially the more aggressive plasma LDL cholesterol goals recommended in patients at very high risk for CAD and the greater absolute LDL cholesterol lowering recommended in all patients who are committed to lipid-lowering drug therapy. These changes support a greater utilization of the more potent statins or high doses of other statins, and more combination therapies with a statin plus colestevam, ezetimibe, or niacin. The clinical trial literature suggests that statins have a strong safety profile and that lowering of plasma LDL cholesterol to ≤1.81 mmol/L (≤70 mg/dL) with pharmacologic intervention appears to be safe, although more experience is needed to fully embrace this statement.


Role of Low-Density Lipoprotein Apheresis

Paul Ziajka, MD, PhD

Low-density lipoprotein (LDL) apheresis has been shown to reduce plasma levels of total cholesterol, LDL cholesterol, and lipoprotein(a). In addition to these lipoprotein changes, LDL apheresis induces atherosclerosis regression, improves myocardial perfusion and endothelial function, and may reduce cardiovascular event rates. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]:67E–69E)

Patients with familial hypercholesterolemia who cannot tolerate, or whose condition is unresponsive to, conventional lipid-lowering interventions have limited therapeutic options: ileal bypass surgery, liver transplantation, or low-density lipoprotein (LDL) apheresis.1 The present review focuses on LDL apheresis.

The LDL apheresis procedure involves several distinct steps: (1) Blood is removed from the patient via an intravenous catheter usually placed in a cubital vein. (2) Plasma is separated from the cellular elements of the blood via an automated cell separator. (3) Plasma is physically treated to remove apolipoprotein B (apo-B)–containing lipoproteins. (4) Blood cells and the now LDL-depleted plasma are recombined. (5) Finally, blood is infused back into the patient via another intravenous catheter usually placed in a contralateral cubital vein. There are 2 techniques approved for clinical use by the US Food and Drug Administration (FDA) to remove the apo-B containing lipoproteins from the serum: heparin-mediated extracorporeal LDL fibrinogen precipitation (HELP system; B. Braun Melsungen AG, Melsungen, Germany) and apo-B adsorption via charge attraction to dextran sulfate cellulose columns (Liposorber system; Kaneka Corporation, Osaka, Japan).2 Both techniques are approved for use in patients with familial hypercholesterolemia who cannot tolerate, or whose condition is unresponsive to, pharmacologic treatment and who have either known cardiovascular disease and a plasma level of LDL cholesterol >5.18 mmol/L (>200 mg/dL) or no known cardiovascular disease and a plasma level of LDL cholesterol >7.77 mmol/L (>300 mg/dL). LDL apheresis also can be approved on an individual basis for patients with known cardiovascular disease who do not have familial hypercholesterolemia but who have a very high plasma level of LDL cholesterol or lipoprotein(a) and who cannot tolerate, or whose condition is unresponsive to, conventional therapy.

Both LDL apheresis techniques acutely lower plasma levels of total cholesterol by 60% to 70%, LDL cholesterol by 70% to 80%, very-low-density lipoprotein (VLDL) triglycerides by 65% to 75%, and lipoprotein(a) by 60% to 70%.3,4 However, as soon as the procedure is stopped, the lipoproteins begin to reaccumulate at a rate dependent on their rate of production. VLDL triglycerides have a very rapid turnover time and usually return to pretreatment levels within 24 to 36 hours after the procedure. LDL and lipoprotein(a) have much slower turnover times and increase more gradually. Time-averaged lipoprotein levels can be calculated, as illustrated in Figure 1. LDL apheresis is usually scheduled to lower the time-averaged plasma values for total cholesterol by 45% to 55%, for LDL by 40% to 60%, and for lipoprotein(a) by 40% to 60%. The frequency of treatments is calculated to keep the time-averaged lipoprotein concentration at or below the patient’s therapeutic goal. The typical patient with heterozygous familial hypercholesterolemia requires an LDL apheresis treatment once every 2 to 3 weeks. A treatment session lasts approximately 3 hours, during which time about 150% of the patient’s plasma volume is processed. The procedure is generally well tolerated. The most common adverse event is transient hypotension, which occurs in 3% of patients undergoing LDL apheresis.5

Low-Density Lipoprotein Apheresis and Angiographic Trials

Several studies have examined the effects of LDL apheresis on angiographically documented coronary and carotid artery atherosclerosis. Schuff-Werner and colleagues6 followed up 39 patients with known coronary artery disease (CAD) who were managed with drug and lifestyle therapy and had a plasma level of LDL cholesterol >5.18 mmol/L (>200 mg/dL). The patients received LDL apheresis an average of once every 7.8 days. Over the 2-year study, the combined drug plus LDL apheresis treatments reduced average coronary stenosis from 32.5% to 30.6%. Kroon and associates7 followed up 42 men with known CAD and plasma total cholesterol levels >7.77 mmol/L (>300 mg/dL). All patients had baseline atherosclerosis documented by carotid ultrasonography. Patients were randomized to receive simvastatin 40 mg once daily or simvastatin 40 mg once daily plus LDL apheresis every 2 weeks. The groups were followed up for 2 years. Plasma values for LDL cholesterol dropped from 7.80 mmol/L (301 mg/dL) to 4.09 mmol/L (156 mg/dL), and lipoprotein(a) dropped from 2828 Casa Aloma Way, Suite 600, Winter Park, Florida 32792.
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(158 mg/dL) in the simvastatin-alone group and to 3.00 mmol/L (116 mg/dL) in the simvastatin plus LDL apheresis group. Carotid intima-media thickness increased by 0.06 mm in the simvastatin-alone group and decreased by 0.05 mm in the simvastatin plus LDL apheresis group. For a mean of 2.3 years, Nishimura and colleagues followed up 36 patients with familial hypercholesterolemia and angiographically documented baseline CAD. The patients were randomized to drug therapy alone versus drug therapy plus LDL apheresis. The group managed with drug therapy alone had an on-treatment plasma level of LDL cholesterol of 4.40 mmol/L (170 mg/dL) versus a time-averaged LDL cholesterol plasma level of 3.63 mmol/L (140 mg/dL) in the group receiving the drug plus LDL apheresis. At the end of the study, the group receiving the drug alone had disease progression, with a decrease in minimal lumen diameter of 0.44 mm, whereas the drug plus LDL apheresis group experienced regression, with an increase in minimal lumen diameter of 0.19 mm. In a similar study designed by Matsuzaki and associates, 19 patients with familial hypercholesterolemia underwent a series of assessments by means of coronary angiography and intravascular ultrasonography. Patients were randomized to receive therapy with drugs alone or drugs plus LDL apheresis every 2 weeks for 1 year. The group managed with drugs alone had progression of disease, with a decrease in minimal lumen diameter of 0.08 mm and an increase in plaque area of 0.017 mm². The group managed with drugs plus LDL apheresis demonstrated regression, with an increase in minimal lumen diameter of 0.12 mm and a decrease in plaque area of 0.69 mm².

Taken together, these studies demonstrate a difference in quantitative angiographic changes in the coronary arteries between drug-only and drug-plus-LDL apheresis of 0.15 to 0.65 mm. To put this difference into perspective, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) quantitative angiographic trials such as the Canadian Coronary Atherosclerosis Intervention Trial and the Reversal of Atherosclerosis with Aggressive Lipid Lowering study demonstrated a 0.04 to 0.10 mm difference between the end points in the treatment and placebo groups.

Low-Density Lipoprotein Apheresis and Myocardial Perfusion Studies

Using positron emission tomography (PET), Mellwig and colleagues measured myocardial perfusion in 9 patients with familial hypercholesterolemia immediately before and 18 to 20 hours after an LDL apheresis treatment. The baseline value for plasma LDL cholesterol was 5.02 mmol/L (194 mg/dL), which decreased to an immediate posttreatment value for plasma LDL cholesterol of 2.10 mmol/L (81 mg/dL). Myocardial blood flow increased 30% after the LDL apheresis, from 173 mL/min per 100 g pretreatment to 226 mL/min per 100 g posttreatment. Similarly, Sampietro and associates determined myocardial perfusion by means of PET in 7 patients with heterozygous familial hypercholesterolemia immediately before and after an LDL apheresis treatment. Immediately posttreatment, the plasma values for LDL cholesterol decreased 91%, for apo-B decreased 87%, and for lipoprotein(a) decreased 89%. Myocardial blood flow increased 72.5% after the apheresis, from a baseline of 131 mL/min per 100 g to 226 mL/min per 100 g.

Low-Density Lipoprotein Apheresis and Endothelial Reactivity Studies

Tamai and colleagues performed a trial that addressed the question of how rapidly endothelial function can be improved by LDL apheresis. In that study in 7 patients with familial hypercholesterolemia, brachial artery blood flow responses to sodium nitroprusside and acetylcholine influ-
sions were measured before and immediately after a single 2-hour LDL apheresis treatment. Plasma values for LDL cholesterol acutely dropped 70%. Sodium nitroprusside has effects on blood flow independent of endothelial function, and there was no difference in blood flow response to sodium nitroprusside before or after the apheresis treatment. Acetylcholine, on the other hand, affects blood flow via a mechanism dependent on endothelial function, and there was a 200% increase in brachial flow in response to the acetylcholine infusion after LDL apheresis.

Low-Density Lipoprotein Apheresis and “Outcomes” Studies

Because of the relative rarity of patients with familial hypercholesterolemia and the large number of subjects needed for cardiovascular and mortality reduction studies, it is doubtful that there will ever be an LDL apheresis trial comparable to such “mega-trials” as the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study and the Scandinavian Simvastatin Survival Study (4S). However, the findings of 2 observational studies suggest that there may be an event-reduction benefit associated with LDL apheresis therapy. Mabuchi and associates monitored the clinical outcomes of 130 nonrandomized patients with familial hypercholesterolemia who received either drug therapy alone or drug therapy plus LDL apheresis. Over the 6-year observation, the patients receiving drug therapy alone experienced a 36% cardiovascular event rate, whereas those managed with drug plus LDL apheresis therapy had a 10% event rate (p = 0.0088). In another retrospective study, Gordon and colleagues followed up 29 patients with familial hypercholesterolemia managed with LDL apheresis therapy for 5 years. In the 5 years before LDL apheresis was initiated, the 29 patients had experienced 24 cardiovascular events. In the subsequent 5 years, during LDL apheresis therapy, the same 29 patients experienced 7 cardiovascular events (not statistically significant).

Conclusion

When diet, lifestyle modification, and drug therapy fail to achieve plasma LDL cholesterol goals in patients with familial hypercholesterolemia, who are at extremely high risk, LDL apheresis offers an additional therapeutic option. LDL apheresis has been demonstrated to lower plasma levels of LDL cholesterol and lipoprotein(a), induce regression of atherosclerosis in the coronary and carotid vascular beds, improve myocardial perfusion and endothelial function, and possibly reduce the incidence of cardiovascular events.