In patients with diabetes, a high priority must be given to modification of the major risk factors for cardiovascular disease (CVD). There is growing evidence that control of these risk factors will reduce the likelihood of developing CVD and its complications in patients with diabetes. In clinical management of patients with diabetes, attention must be given to the following risk factors: smoking, hypertension, prothrombotic state, low-density lipoprotein (LDL) cholesterol and diabetic dyslipidemia, hyperglycemia, overweight/obesity, physical inactivity, and adverse nutrition.

Specific considerations of Writing Group IV will be reviewed. They will be discussed in light of current recommendations for management of risk factors in diabetes as presented by the American Diabetes Association (ADA), the American Heart Association (AHA), and the national education programs sponsored by the National Heart, Lung, and Blood Institute (NHLBI). These recommendations are summarized in the Table.

**Cigarette Smoking**

In addition to being a cause of many forms of cancer and chronic lung disease, cigarette smoking is a major cardiovascular risk factor. When a smoking patient also has diabetes, this patient is doubly at risk for CVD. Thus, every effort must be made to convince patients with diabetes who smoke to give up the smoking habit. This need is strongly reinforced by a position statement from the ADA.

**Hypertension**

Elevated blood pressure is a major independent risk factor for multiple cardiovascular end points: coronary heart disease (CHD), stroke, chronic renal failure, and heart failure. Patients with diabetes have an increased prevalence of hypertension. Multiple factors undoubtedly contribute to hypertension in patients with diabetes, eg, obesity, insulin resistance, hyperinsulinemia, and renal disease. Systolic hypertension appears to be the main blood pressure–related risk factor in patients with diabetes. Microalbuminuria often is associated with hypertension and may represent an independent risk factor, as well as a target of therapy.

Treatment of hypertension in patients with diabetes should be appropriately intensive to achieve targets recommended by recent guidelines. The Sixth Joint National Commission (JNC VI) guidelines for hypertension management singled out diabetes as a high-risk state deserving of aggressive blood pressure control. When diabetes is present, the blood pressure goal in JNC VI is a level of <130/<85 mm Hg (Table). The ADA goes further and recommends a goal of <130/<80 mm Hg. Therapeutic lifestyle changes (weight reduction, increased physical activity, low salt intakes, increased fruit and vegetable consumption, and higher potassium intakes) will facilitate blood pressure control. Nonetheless, antihypertensive drugs often will be required. In fact, multiple drugs commonly are necessary to achieve the goal of therapy. The common drugs used to treat hypertension (diuretics, β-blockers, angiotensin converting enzyme [ACE] inhibitors, and calcium channel blockers) are generally effective in patients with diabetes. Thiazide diuretics in high doses can worsen glucose tolerance, but at lower doses, which are similarly efficacious, they do not significantly accentuate hyperglycemia. β-Blockers may worsen insulin resistance and may mask symptoms of hyperglycemia; even so, they are generally well tolerated by patients with diabetes and are indicated in those with recent myocardial infarction. Moreover, in the United Kingdom Prospective Diabetes Study (UKPDS), β-blockers rivaled ACE inhibitors in overall efficacy for prevention of diabetic complications. Assiduous treatment of hypertension in patients with diabetes will delay progression of diabetic nephropathy and retinopathy. ACE inhibitors and angiotensin II receptor inhibitors are efficacious for slowing progression of diabetic nephropathy and may be indicted in the presence of microal-
buminuria. A recent clinical trial further observed that ACE inhibitor therapy reduces CHD events in patients with established CHD; the possibility that the same result would be obtained specifically in patients with diabetes has not been tested adequately.

**LDL Cholesterol and Atherogenic Dyslipidemia**

Patients with diabetes have 2 lipid disorders that must be addressed. One is an LDL cholesterol level higher than optimal, which contributes to atherogenesis and coronary plaque rupture. The other is a condition called atherogenic dyslipidemia, which is characterized by a triad of lipid disorders: elevated triglycerides, small LDL particles, and low high-density lipoprotein (HDL) cholesterol. This lipid triad is especially common in patients with type 2 diabetes. Both LDL cholesterol and atherogenic dyslipidemia deserve attention.

For many years, it was believed that LDL cholesterol concentrations were not “elevated” in patients with diabetes. However, recent clinical trials of LDL-lowering therapy in patients with type 2 diabetes demonstrate a substantial reduction in CHD risk. This observation documents the importance of even moderate elevations of serum LDL cholesterol for increasing risk of CHD in patients with diabetes. For this reason, the National Cholesterol Education Program’s recently updated clinical guidelines have set an optimal LDL cholesterol level (ie, LDL cholesterol <100 mg/dL) as a goal of therapy in patients with diabetes. This goal of therapy is supported by the ADA. The National Cholesterol Education Program further recommends that LDL-lowering drugs should be started simultaneously with dietary therapy when baseline LDL cholesterol levels are =130 mg/dL in patients with diabetes. When LDL cholesterol levels are near optimal (100 to 129 mg/dL), several therapeutic options are available, eg, intensification of dietary and/or drug therapies for LDL lowering or more aggressive control of other lipid or nonlipid risk factors. The need for intensive LDL-lowering therapy for patients with diabetes is being increasingly recognized and accepted.

The lipid triad (atherogenic dyslipidemia) is common in patients with type 2 diabetes and long was considered the “primary” lipid abnormality in this disorder. Clinical trials of fibrate therapy provide suggestive evidence for benefit from modification of atherogenic dyslipidemia in patients with type 2 diabetes and the metabolic syndrome. Clinical trials in nondiabetic patients suggest that favorable modification of atherogenic dyslipidemia with fibric acids will reduce risk for CHD to about half that which can be achieved by aggressive LDL-lowering therapy. This observation raises the possibility that combined drug therapy with fibrates and statins will offer a greater risk reduction than can be achieved with LDL lowering alone. Many patients with diabetes have elevated levels of triglycerides. Adult Treatment Panel (ATP) III recommends a secondary target of therapy, beyond LDL cholesterol goals, in patients with atherogenic dyslipidemia. When triglyceride levels are in the range of 200 to 499 mg/dL, the non-HDL cholesterol goal is 30 mg/dL, the non-HDL cholesterol goal is 40 mg/dL in patients with diabetes whose LDL cholesterol goal is <100 mg/dL, this would translate into a non-HDL cholesterol goal of <130 mg/dL.

**Prothrombotic State**

Patients with insulin resistance and type 2 diabetes harbor a prothrombotic state. The latter is characterized by elevated plasma levels of plasminogen activator inhibitor-1 and other defects of coagulation. Platelet abnormalities also have been reported to accompany diabetes. A prothrombotic state

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### Goals for Risk Factor Management in Patients With Diabetes

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Goal of Therapy</th>
<th>Recommending Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Complete cessation</td>
<td>ADA</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;130/85 mm Hg</td>
<td>JNC VI (NHLBI)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>&lt;100 mg/dL</td>
<td>ATP III (NHLBI)</td>
</tr>
<tr>
<td>Triglycerides 200–499 mg/dL</td>
<td>Non-HDL cholesterol &lt;130 mg/dL</td>
<td>ATP III (NHLBI)</td>
</tr>
<tr>
<td>HDL cholesterol &lt;40 mg/dL</td>
<td>Raise HDL (no set goal)</td>
<td>ATP III (NHLBI)</td>
</tr>
<tr>
<td>Prothrombotic state</td>
<td>Low-dose aspirin therapy (patients with CHD and other high-risk patients)</td>
<td>ADA</td>
</tr>
<tr>
<td>Glucose</td>
<td>Hemoglobin A1c &lt;7%</td>
<td>ADA</td>
</tr>
<tr>
<td>Overweight and obesity (BMI ≥25 kg/m²)</td>
<td>Lose 10% of body weight in 1 year</td>
<td>OEI (NHLBI)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Exercise prescription dependent on patient status</td>
<td>ADA</td>
</tr>
<tr>
<td>Adverse nutrition</td>
<td>See text</td>
<td>ADA, AHA, and NHLBI's</td>
</tr>
</tbody>
</table>

JNC VI indicates 6th report of the Joint National Committee on Prevention, Evaluation, and Treatment of High Blood Pressure; NHLBI, National Heart, Lung, and Blood Institute; ATP III, National Cholesterol Education Program Adult Treatment Panel III; HDL, high-density lipoprotein; and OEI, Obesity Education Initiative Expert Panel on Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.
may interfere with endothelial function, promoting atherogenesis; furthermore, when coronary plaques rupture, it may enhance propagation of thrombi and thereby worsen acute coronary syndromes.

The most readily available means to counteract the prothrombotic state is chronic use of aspirin. When patients with diabetes have established CHD, aspirin therapy is almost always indicated. Use of aspirin probably is prudent even when patients with diabetes do not have manifest CHD because they nonetheless are at increased risk for acute coronary syndromes.

**Hyperglycemia**

The presence of hyperglycemia is the defining component in the diagnosis of diabetes. By current definition, diabetes is present when the fasting plasma glucose is confirmed to be ≥126 mg/dL. Fasting plasma glucose of 110 to 125 mg/dL is called impaired fasting glucose and often denotes the presence of the metabolic syndrome. Patients with impaired fasting glucose are at increased risk for type 2 diabetes and macrovascular disease (CHD), although not microvascular disease. The majority of patients with impaired fasting glucose have the metabolic syndrome, and consequently the specific contribution of glucose levels in the range of 110 to 126 mg/dL to CHD risk has been difficult to determine.

Risk for CHD rises even more when fasting glucose exceeds 126 mg/dL; moreover, when levels are persistently above 126 mg/dL, microvascular disease begins to make its appearance.

Control of hyperglycemia is mandatory for the prevention of microvascular disease (diabetic nephropathy, neuropathy, and retinopathy). Clinical trials in patients with diabetes of both types 1 and 2 confirm the benefit of good glycemic control in the prevention of diabetic microvascular complications. Whether glycemic control will reduce the risk of macrovascular complications has not been proved definitively through controlled clinical trials. Nonetheless, available clinical trial evidence is suggestive of benefit, even though it is not definitive.

Current recommendations for glycemic control in patients with diabetes include reducing fasting glucose to near normal with a hemoglobin A1c of <7%. Such control will largely prevent the development of microvascular disease. Furthermore, it may reduce the risk of macrovascular disease. For patients with type 1 diabetes, insulin therapy will always be required to achieve good glycemic control. In contrast, the majority of patients with type 2 diabetes are treated first with oral hypoglycemic agents. Many authorities favor initial therapy with metformin. This drug has the advantage of reducing insulin resistance, one of the underlying causes of type 2 diabetes. Some diabetologists prefer to start with sulfonylureas. Ultimately, a large portion of patients with type 2 diabetes will be treated with combined oral agents so as to delay use of insulin. After several years of therapy with oral agents, insulin therapy usually will be required to achieve the goals of hypoglycemic control.

The introduction of thiazolidinediones (TZDs) provides another hypoglycemic agent to delay the initiation of insulin therapy. The TZDs reduce insulin resistance. In fact, the TZDs or metformin can sometimes be used along with insulin therapy to achieve even better glycemic control. Whether reducing insulin resistance independent of glucose control will reduce risk for CHD is an important but unresolved question.

The action of drugs to control hyperglycemia in patients with type 2 diabetes can be enhanced by weight loss and increased physical activity. Indeed, if these lifestyle therapies are introduced early enough, it may be possible to delay introduction of hypoglycemic drugs for several years before hemoglobin A1c and fasting glucose levels indicate the need for drug therapy.

Finally, there is preliminary but growing evidence that aggressive glucose lowering during acute CVD events and procedures is beneficial. The mechanisms for such benefit are still under investigation.

**Overweight/Obesity**

Overweight and obesity contribute importantly to type 2 diabetes, the most common form of diabetes. Excess body fat raises insulin resistance and may accelerate the decline in insulin secretion that is required for development of clinical diabetes. After onset of type 2 diabetes, weight reduction will still reduce insulin resistance and mitigate the metabolic risk factors associated with diabetes. Nonetheless, because of loss of β-cell function, hyperglycemia may persist in spite of weight loss. In spite of these limitations, weight management in patients with type 2 diabetes must remain one component of risk factor management.

A reasonable clinical approach to weight reduction is made available in the 1998 clinical guidelines of the NHLBI and the National Institute of Digestive Disease, Diabetes, and Kidney. The guidelines were developed under the auspices of the Obesity Education Initiative. According to the rationale for therapy reviewed in these guidelines, overweight (body mass index 25 to 29.9 kg/m²) and obesity (body mass index ≥30 kg/m²) are major underlying causes of insulin resistance, the metabolic syndrome, and type 2 diabetes. Among body weight parameters, abdominal obesity, which is denoted by increased waist circumference (male ≥103 cm; female ≥88 cm), is closely associated with development of metabolic risk factors and type 2 diabetes. Once type 2 diabetes develops, overweight/obesity contributes to persistent hyperglycemia and to a worsening of the metabolic risk factors. Body weight, body mass index, and waist circumference should be measured and monitored during the management of patients with diabetes.

In clinical practice, attention must be paid to several basic principles for weight management in patients with diabetes. A team approach that makes use of the expertise of physicians, nurses, registered dietitians, or other health professionals and pharmacists is required to achieve and maintain acceptable weight reduction. The first goal of weight reduction therapy is to prevent further weight gain. Moreover, it must be recognized that any weight loss is beneficial to the patient. In general, “crash diets” to achieve rapid weight loss have been unsuccessful; weight regain has been the rule. Instead, slow weight reduction, with the aim to lose 10% of body weight over a period of 1 year, is more likely to produce long-term success.
Physical Inactivity

Physical inactivity has several adverse effects on CVD risk. It contributes importantly to the development of overweight/obesity, as reflected in the rising prevalence of obesity in our sedentary society. Physical inactivity impairs insulin sensitivity and worsens the metabolic syndrome. It also raises risk for CVD through other mechanisms that may be mediated through cardiovascular fitness and function. Through its enhancement of insulin resistance and worsening of metabolic risk factors, physical inactivity is especially detrimental in patients with diabetes.

Thus, in the management of patients with diabetes, increased physical activity constitutes a prime goal. If possible, it should become a coequal partner with weight reduction both to achieve better glycemic control and to lessen the metabolic syndrome. The physical activity prescription for the patient with diabetes depends on clinical judgment. At a minimum, however, when regular physical activity is not contraindicated, the usual prescription of 30 minutes of moderate-intensity exercise daily can be recommended. If more intense exercise can be tolerated without harm, it will provide a still greater benefit. The AHA provides an exercise prescription that can be recommended for clinical practice. Moreover, consideration can be given to taking advantage of existing professionally assisted programs in exercise (eg, cardiac rehabilitation) for appropriately selected patients with diabetes. In these patients, appropriate attention must be paid to the dangers of hypoglycemia related to strenuous exercise and to trauma-induced diabetic foot disease through inappropriate foot protection.

Adverse Nutrition

Few topics related to management of patients with diabetes have received more attention than dietary therapy (medical nutrition therapy). Although it is widely accepted that most patients with type 2 diabetes need to lose weight, there is not universal agreement on what the desirable diet prescription is for these patients. The pendulum of opinion has moved back and forth between low-fat diets and low-carbohydrate diets. In recent years, most investigators have agreed that the diet of patients with diabetes should be low in saturated fatty acids and cholesterol; curtailing intakes of these factors will help to keep LDL cholesterol levels low. Whether the remaining calories should be relatively high in unsaturated fats or carbohydrates, however, has been debated. The primary argument in favor of a low-fat, high-carbohydrate diet is that it may promote weight reduction. On the other hand, the case against such a diet is that it can produce an exaggerated postprandial response in glucose and insulin; moreover, it often results in a higher level of serum triglycerides and a lower level of HDL cholesterol.

The ADA notes that there is no “diabetic diet” or “ADA diet.” Medical nutrition therapy in patients with diabetes is best performed by a registered dietitian or other qualified nutrition specialist. Nonetheless, the ADA does offer a series of principles that should be followed when dietary therapy is designed for individuals with diabetes. Particularly for those with type 2 diabetes, the primary aims are to achieve and maintain goals for plasma glucose, lipids, and blood pressure. Weight reduction is needed for many patients, and moderate caloric restriction (250 to 500 fewer calories per day) is appropriate for most patients. For patients with evidence of diabetic nephropathy, a reduction of protein intake to <10% of calories may retard progression of kidney disease. Saturated fat should be reduced to ≤7% of total calories in accordance with ATP III guidelines. These guidelines also indicate that total fat can range between 25% and 35% of total calories. Higher intakes of unsaturated fat (up to 35% of calories) will guard against the putative adverse metabolic effects of higher carbohydrate intakes. The desirable types of carbohydrate for the diet continue to be debated. Some investigators contend that foods with a “high glycemic index” should be avoided, but the ADA does not recognize the priority of such a change. Nonetheless, high intakes of fruits and vegetables are advocated, as recommended by the Dietary Guidelines for Americans 2000. The ADA discourages large intakes of fructose because of a possible adverse effect on diabetic dyslipidemia.

Hormone-Replacement Therapy in Postmenopausal Women

Before the results of the Heart and Estrogen/progestin Replacement Study (HERS) trial became available, institution of hormone-replacement therapy (HRT) in high-risk postmenopausal women was widely recommended. One group of high-risk women is those with diabetes. In fact, several studies have shown that HRT will improve risk factors, including glycemic control, in women with diabetes. The fact that no benefit of HRT has been shown for reducing cardiovascular events in postmenopausal women with established CHD has led to a striking decline in enthusiasm for HRT in high-risk women. Currently, strong recommendations are not being made for HRT in postmenopausal women with diabetes.

Recommendations for AHA Programs

Writing Group IV made the following recommendations for AHA programs:

- The AHA and ADA should coordinate their efforts to develop a joint position statement on prevention of CVD in patients with diabetes. This statement should establish goals of therapy for each of the risk factors for CVD.
- The AHA Council on High Blood Pressure should develop new initiatives for improved management of hypertension in patients with diabetes. The AHA, ADA, and JNC should work together to establish common goals for the treatment of hypertension.
- Specific guidelines should be developed for the routine measurement of urinary protein in patients with diabetes. Appropriate management of different categories of microalbuminuria should be specified.
- The AHA and ADA should promote improved treatment of lipid disorders in patients with diabetes. The need to achieve LDL cholesterol goals for such patients should be emphasized. Moreover, guidance is needed on use of lipid-lowering drugs in combination drug therapies.
• The AHA and ADA should review and coordinate their recommendations for aspirin prophylaxis in patients with diabetes who are without established CHD. The AHA’s Council on Arteriosclerosis, Thrombosis, and Vascular Biology further should consider initiatives to better understand the nature of the prothrombotic state in patients with diabetes. This improved understanding may uncover new targets of antithrombotic therapy. Whether new antiplatelet drugs have a role in the prevention of acute coronary syndromes in patients with diabetes deserves consideration and study.

• The Council on Nutrition, Physical Activity, and Metabolism (NPAM) should ensure that each of its 4 major committees—Diabetes, Obesity, Physical Activity, and Nutrition—pays attention to the problem of diabetes. Each should be sensitive to opportunities to extend their areas of concern both within NPAM and throughout all the scientific councils of the AHA.

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