Prevention Conference VI: Diabetes and Cardiovascular Disease

Executive Summary

Conference Proceeding for Healthcare Professionals From a Special Writing Group of the American Heart Association

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The American Heart Association (AHA) sponsored a scientific conference entitled “Prevention VI: Diabetes and Cardiovascular Disease” on January 18 to 20, 2001, in Orlando, Fla. The purpose of this conference was to create a report that would assist the AHA in the development of an agenda to reduce cardiovascular diseases (CVDs) that are associated with diabetes. The report has been developed by working group sections. The topics to be covered by each working group were introduced by a series of presentations, and this was followed by an extensive discussion of a team of working group members. The primary objectives of this meeting were as follows:

- To review the scope of CVD in patients with diabetes
- To review current concepts of the pathophysiology of cardiovascular complications in patients with diabetes
- To review recent clinical trials demonstrating the control of cardiovascular risk factors for the prevention of complications in patients with diabetes
- To review approaches to the assessment of cardiovascular risks associated with diabetes
- To review current evidence for efficacy of medical management of the cardiovascular complications accompanying diabetes
- To review efficacy and safety of standard invasive (or surgical) procedures for the treatment of the cardiovascular complications of diabetes

The key findings of each working group are presented in this Executive Summary of the conference. The full conference report with references is available online at http://www.circulationaha.org in the May 7, 2002, issue of Circulation.

Writing Group I: Epidemiology

The prevalence of diabetes in the United States is increasing rapidly, and individuals with diabetes are at high risk for cardiovascular disorders that affect the heart, brain, and peripheral vessels. Although CVD accompanying diabetes is on the rise, many unanswered questions remain concerning the temporal relations between diabetes and CVD, the contributions of conventional risk factors, and the role of diabetes-specific risk factors.

Almost 35 million Americans—20% of all people in the middle-adult years and 35% of the entire older population—have some degree of abnormal glucose tolerance; this higher-risk group will account for a significant portion of CVD and premature mortality in the United States. The increasing frequency of obesity and sedentary lifestyles, major underlying risk factors for type 2 diabetes in both developed and developing countries, portends that diabetes will continue to be a growing clinical and public health problem. This is true both for the United States and worldwide.

The prevalence of, incidence of, and mortality from all forms of CVD are 2- to 8-fold higher in persons with diabetes than in those without diabetes. The proportion of new-onset CVD attributable to diabetes or impaired glucose tolerance ranges from ≈14% in whites to 50% to 80% in American Indians. Diabetes, notably type 2 diabetes, is on the rise in children and adolescents, thereby increasing the likelihood that they will develop premature coronary heart disease (CHD). The major CVD risk factors—elevated low-density lipoprotein (LDL) cholesterol, hypertension, smoking, and sex—remain important determinants of CVD in patients with diabetes. In addition, the emerging risk factors—albuminuria, fibrinogen, degree of glycemia, extent of insulin resistance, and presence of subclinical atherosclerosis—further appear to affect risk in individuals with diabetes.

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Early detection of CVD risk factors in patients with established diabetes and early intervention should delay onset of CVD in this population. Determinants of progression of coronary atherosclerosis and development of clinical events in patients with diabetes need to be better defined. Detection and intervention with regard to the atherogenic metabolic abnormalities and glucose intolerance that precede development of diabetes would be even more beneficial. Gene-environment interactions should also be explored as they relate to diabetes and CVD; in particular, the impact of sociocultural factors must be considered in risk assessment and prevention strategies. Improved measures to identify individuals at risk for diabetes and CVD must be evaluated; in particular, in risk assessment, the American Diabetes Association (ADA) category of impaired fasting glucose and the post–glucose-challenge level in older individuals may be underused. Whether methods of measuring atherosclerosis and vascular disease, such as carotid ultrasound, echocardiography, magnetic resonance imaging, and ankle-brachial index, will augment risk assessment in patients with diabetes requires additional evaluation.

Writing Group I recommends, on the basis of the ominous rise of diabetes and its associated CVD, that the AHA institute programs to achieve the following: monitor the burden of CVD attributable to diabetes; monitor temporal changes in glucose homeostasis; test and target CVD prevention strategies with regard to diabetic children, adolescents, and those with impaired glucose tolerance; develop diet and exercise programs to mitigate CVD risk in diabetic patients; with an aggressive focus on the newly diagnosed; continue research into lifestyle and biochemical CVD risk factors in diabetes; and elucidate the economic burden of diabetes-associated CVD.

Writing Group II: Pathogenesis of Atherosclerosis in Diabetes

This writing group found that the pathogenesis of atherosclerosis in diabetes is complex and multifactorial. Five general areas of mechanism were defined. The first, metabolic factors, exists on a foundation of hyperglycemia that results from both insulin deficiency and insulin resistance. The insulin resistance syndrome is a composite of numerous covariates that include increased flux of free fatty acids, dyslipidemia (increased very-low-density lipoprotein and decreased high-density lipoprotein and small dense lipoproteins), hyperinsulinemia, and hypertension. Importantly, hyperglycemia results in increased rates of glycation and oxidation. Excessive oxidation/glucosilation is a consequence of abundant protein glycation in the setting of increased oxygen radicals with subsequent advanced glycation end-product accumulation. An increase in lipid and lipoprotein peroxidation also occurs, a process that likely contributes to foam cell formation within the arterial wall. Endothelial dysfunction is associated with hyperglycemia, dyslipidemia, hypertension, and atherosclerosis. Although endothelial dysfunction is not atherosclerosis, it may be an important pathophysiological precursor. Insulin resistance may be a contributor to endothelial dysfunction. Moreover, the process of inflammation probably is increased in diabetes. This in part relates to the excessive amount of adipose tissue, an important source of interleukin-6, a precursor for C-reactive protein generation. Cytokines not only contribute to oxidative metabolism in tissues but also generate growth factors that are important to the response of the arterial wall to injury. These growth factors stimulate the proliferation and migration of smooth muscle cells and induce platelet aggregation. Diabetes is also considered to be a prothrombotic state. This is an imbalance in prothrombotic mechanisms and antifibrinolytic processes. Debates remain as to differences in the plaque in type 1 versus type 2 diabetes. Overall, a better understanding of the pathophysiological mechanisms of atherosclerosis may provide a better understanding of the process in general.

Writing Group III: Risk Assessment

Writing Group III reviewed all of the current data on risk assessment techniques for CVD with special reference to the data for patients with diabetes. It was first established that the goal of risk assessment would be to identify subclinical CVD in patients with diabetes, which would lead to a change in management that would result in an improvement in morbidity and/or mortality. This group reviewed existing guidelines, then evaluated the data on office-based risk factor assessment, as well as diagnostic imaging techniques.

Patients with diabetes are known to be at increased risk of CVD; moreover, patients with diabetes have an increased risk of cardiac events once the diagnosis of CVD has been established. Because of this increased risk, the AHA designates diabetes as a “coronary risk equivalent” and indicates that patients with diabetes belong in the same risk category as patients with known CVD. Thus, Writing Group III began with the premise that all patients with diabetes should be treated with aggressive risk factor modification.

Principles of Screening

Screening is defined here as the detection of disease in asymptomatic persons. Because screening tests are intended for widespread application, they are should be rapid and inexpensive. In addition, to be useful, the results of testing should lead to a change in management, and the results of testing should improve outcome.

Current Clinical Practice Guidelines

There are several existing published guidelines for risk assessment in patients with CVD or those at risk for CVD. The French Guideline for Detection of Silent Myocardial Ischemia in patients with diabetes suggests that screening for silent myocardial ischemia should be performed in patients with diabetes and 1 additional factor: peripheral arterial disease, proteinuria, or the presence of major CVD risk factors. They specifically mention the use of exercise treadmill testing or thallium stress testing. The American College of Cardiology (ACC)/AHA Guidelines for Exercise Testing give screening by exercise treadmill testing in patients with diabetes a data quality rating of IIb, ie, its usefulness or efficacy is less well established by evidence or opinion. They add that exercise testing “might be useful in people with heightened pretest risk.” The ADA/ACC Consensus State-
Ankle-Brachial Blood Pressure Index

Ankle-brachial blood pressure index (ABI) is performed by measuring blood pressure in both arms and the posterior tibial and dorsalis pedis arteries and computing an ankle/average arm blood pressure ratio. An ABI of 0.90 constitutes a diagnosis of peripheral arterial disease. A low ABI has been shown to provide incremental independent predictive power for CVD risk in population-based studies. These latter studies provide convincing evidence that the ABI is a useful noninvasive measure for the detection of subclinical peripheral arterial disease; moreover, a low ABI provides incremental information beyond that provided by standard CVD risk factors, especially in people aged 50 years and older with increased risk for CVD, such as those with diabetes. Thus far, studies have included too few subjects with diabetes to allow reliable estimations of the contribution of this noninvasive test to the prediction of the future risk of CVD mortality and morbidity among asymptomatic subjects with diabetes. Moreover, because the presence of diabetes counts as a CHD risk equivalent, the management of risk factors will not be modified by the detection of a low ABI.

Ankle-Brachial Blood Pressure Index

Risk Assessment Strategy

Risk assessment should begin with a careful medical history, with special attention paid to elicit symptoms of atherosclerotic disease, such as angina, claudication, or erectile dysfunction. A dietary assessment and questions on physical activity level must be included. Next is a careful physical examination and an ECG to look for evidence of left ventricular hypertrophy and ST-T changes, both of which are accompanied by increased cardiovascular risk.

There are many noninvasive tests that are being evaluated to determine their ability to predict cardiac risk. Writing Group III considered that any noninvasive test should provide risk prediction beyond that obtained by office-based risk assessment. Because diabetes is considered a risk equivalent for CHD by the AHA, a negative test result in a patient would not remove the patient from this high-risk category; conversely, a positive test would not change the already recommended aggressive approach to risk factor modification. The writing group nonetheless recognized that there may be special situations in which noninvasive testing would be beneficial, such as for patients with type 1 diabetes. The writing group did examine carefully all data on the following noninvasive tests; however, most of these data were not obtained in patients with diabetes.

Ankle-Brachial Blood Pressure Index

Ankle-Brachial Blood Pressure Index

Electron-Beam Computed Tomography

Electron-beam computed tomography measures coronary artery calcium, which is a marker for coronary atherosclerosis. It appears to be capable of detecting coronary artery calcification (CAC) in many asymptomatic patients with either type 1 or type 2 diabetes. Many asymptomatic subjects with diabetes, however, have been reported to have CAC scores of 0. CAC scores in some studies appear to have predictive power for likelihood of developing clinical CVD. Whether CAC scores predict future clinical events in asymptomatic patients with diabetes is not yet known, and such data are needed to help define a role for electron-beam computed tomography in asymptomatic patients with diabetes. The predictive value for clinical events in patients with diabetes is not well defined.

Exercise Tolerance Testing

In subjects without diabetes, exercise testing appears to be predictive of prognosis, ie, prediction of likelihood of experiencing major coronary events. In the same way, exercise single photon emission computed tomography (SPECT) has independent predictive power. However, there is a paucity of data on the predictive power of exercise testing in patients with diabetes. Limited data nonetheless suggest that whereas symptoms may be unreliable for detection of ischemic heart disease in patients with diabetes, ischemic findings on exercise ECG appear to be at least as predictive of prognosis in patients with diabetes (and possibly indicative of even worse outcome) than in nondiabetic patients. However, there are few outcome data that document the utility of early identification of asymptomatic CVD in patients with diabetes. This may not be true, however, for asymptomatic persons without diabetes. For example, in the Lipid Research Clinics–Coronary Primary Prevention Trial, exercise testing in asymptomatic, hypercholesterolemic subjects identified a high-risk group, and cholesterol-lowering therapy significantly lowered their risk.

Magnetic Resonance Imaging

High-resolution magnetic resonance imaging can differentiate plaque components, and under some circumstances, it may be able to identify vulnerable plaque. Although this technique appears promising, there are few data on its power to predict future CVD events at this time. The assessment of atherosclerotic plaques by imaging techniques may prove valuable for the identification of vulnerable plaques. In vivo high-resolution, multicontrast magnetic resonance imaging holds promise for noninvasively imaging vulnerable plaques and characterizing the different components in all arteries, including the coronary arteries. Magnetic resonance allows serial evaluation assessment of the progression and regression of atherosclerosis over time. Recommendation of this technique for risk assessment awaits more data.

Carotid Intima-Media Thickness

Carotid intima-media thickness measurements use B-mode ultrasound to measure the lumen and wall of the carotid artery. Prospective population-based studies have shown that in asymptomatic subjects, intima-media thickness provides incremental predictive information on the future risk of CVD. However, these observations cannot be directly extrapolated to subjects with diabetes, in whom intima-media thickness has been found to be greater than in nondiabetic subjects.
Outcomes and Risk Assessment

Taken together, the data suggest that several measures may be useful predictors of CVD events; however, their incremental value to office-based risk assessment and cost-effectiveness for screening of patients with diabetes have not been evaluated fully. Currently, there are no data to show benefit of early identification of subclinical atherosclerotic disease in the asymptomatic stage in patients with diabetes. Because patients with diabetes are already considered to be at high risk for future CVD events, routine risk assessment by noninvasive testing is not recommended for the purpose of determining intensity of risk factor reduction. Furthermore, few data are available to justify noninvasive testing for subclinical disease for the purpose of invasive intervention in asymptomatic patients.

Future Research

Research is necessary to investigate the incremental value of noninvasive tests over office-based risk assessment for prediction of future risk for developing CVD. The role of noninvasive risk assessment in lifestyle changes (such as a heart-healthy diet and increased physical activity), medication use (prescription rates and compliance), and outcomes (both hard events, such as nonfatal myocardial infarction or death, and soft events, such as angina and revascularization) is essential. Cost-effectiveness analysis of various strategies is essential to make informed medical and policy decisions.

Conclusions: Noninvasive Risk Assessment in Patients With Diabetes

For patients with diabetes, office-based assessment of risk factors is useful to define targets for intervention to reduce cardiovascular risk; additional noninvasive testing is not recommended on a routine basis at this time because it would not change management or lead to improvement in outcomes. However, there may be special considerations, such as patients with type I diabetes or elderly people with type 2 diabetes, in whom noninvasive testing would be useful for making management decisions. The realization of this possibility awaits further investigation.

Writing Group IV: Lifestyle and Medical Management of Risk Factors

A high priority must be given to modification of the major risk factors for CVD in patients with diabetes. Increasing evidence indicates that controlling CVD risk factors will reduce onset of CVD and its complications in patients with diabetes. In the clinical management of patients with diabetes, attention must be given both to major risk factors (cigarette smoking, hypertension, elevated LDL cholesterol and diabetic dyslipidemia, and hyperglycemia) and to underlying risk factors (overweight/obesity, physical inactivity, and adverse nutrition). Writing Group IV reviewed these risk factors in light of current recommendations for management of risk factors in diabetes as presented by the ADA, the AHA, and the national education programs sponsored by the National Heart, Lung, and Blood Institute (Table).

Major Risk Factors

Cigarette Smoking

Cigarette smoking is a major risk factor for CVD, and 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.
Hypertension

Elevated blood pressure is a major independent risk factor for CHD, stroke, chronic renal failure, and heart failure. The prevalence of hypertension is increased in patients with diabetes. Factors that contribute to hypertension in these patients include obesity, insulin resistance, hyperinsulinemia, and in many cases, renal disease. Microalbuminuria often accompanies hypertension but probably is an independent risk factor for CVD. The Sixth Report of the Joint National Committee for the Detection, Evaluation, and Treatment of Hypertension (JNC VI) singled out diabetes as a high-risk state deserving of more aggressive blood-pressure control. It set the blood pressure goal as a level of <130/<85 mm Hg (Table). The ADA recommends a goal of <130/<80 mm Hg. Therapeutic lifestyle changes (weight reduction, increased physical activity, lower salt intakes, increased fruit and vegetable consumption, and higher potassium intakes) are first-line therapy. Nonetheless, antihypertensive drugs, often in combination, commonly are required to achieve the goal of therapy. Most of the major drugs used to treat hypertension (diuretics, β-blockers, angiotensin converting enzyme [ACE] inhibitors, and calcium channel blockers) are effective in patients with diabetes. Thiazide diuretics preferably are used at lower doses. Although β-blockers may worsen insulin resistance and may mask symptoms of hyperglycemia, they are generally well tolerated by patients with diabetes and are indicated in those with recent myocardial infarction. Assiduous treatment of hypertension in patients with diabetes will delay progression of diabetic nephropathy and retinopathy. ACE inhibitors and angiotensin II receptor inhibitors will slow progression of diabetic nephropathy; they may be indicated in the presence of microalbuminuria.

LDL Cholesterol and Diabetic Dyslipidemia

Patients with diabetes commonly have 2 lipid disorders. First, a higher than optimal level of LDL cholesterol contributes to atherosclerosis and coronary plaque rupture. The second disorder is a condition called diabetic dyslipidemia, which is characterized by a triad of lipid disorders: elevated triglycerides, small LDL particles, and low levels of high-density lipoprotein cholesterol. This lipid triad is especially common in patients with type 2 diabetes. Both LDL cholesterol and diabetic dyslipidemia deserve attention. The recently updated clinical guidelines of the National Cholesterol Education Program have set an optimal LDL cholesterol level (<100 mg/dL) as a goal of therapy in patients with diabetes. This goal for LDL cholesterol is advocated by the ADA. These guidelines further recommend 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 LDL-lowering diet and/or drug therapy or more aggressive control of other lipid or nonlipid risk factors.

For patients with diabetic dyslipidemia, LDL lowering, usually with statins, is the primary target. However, recent clinical trials of fibrate therapy provide suggestive evidence for benefit by modification of diabetic dyslipidemia in patients with type 2 diabetes and the metabolic syndrome. This observation raises the possibility that the combination of drug therapy with fibrates and statins will offer a greater risk reduction than can be achieved with LDL lowering alone.

Prothrombotic State

Most patients with insulin resistance harbor a prothrombotic state, which is characterized by elevated plasma levels of plasminogen activator inhibitor-1 and other defects of coagulation. A prothrombotic state may interfere with endothelial function, promoting atherogenesis; furthermore, in cases of coronary plaque rupture, it can promote propagation of thrombi and thereby worsen acute coronary syndromes. The most readily available means to counteract the prothrombotic state is use of low-dose aspirin therapy. For patients with diabetes who have established CHD, aspirin therapy is almost always indicated. Aspirin therapy probably is prudent even for patients with diabetes without manifest CHD because of increased risk for acute coronary syndromes.

Hyperglycemia

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, or impaired fasting glucose, often denotes the presence of the metabolic syndrome. Impaired fasting glucose carries increased risk for the individual to develop type 2 diabetes and macrovascular disease (CHD) but not microvascular disease. The specific contribution of impaired fasting glucose to CHD risk is uncertain. Risk for CHD rises even more when fasting glucose exceeds 126 mg/dL, and 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 for macrovascular complications has not been proved definitively through controlled clinical trials.

The primary goal for glycemic therapy is to achieve a near-normal fasting glucose level and a hemoglobin A1c level <7% (Table). Glycemic therapy for type 2 diabetes usually begins with oral hypoglycemic agents (eg, metformin, sulfonylureas, or glitazones). After several years of therapy with oral agents, insulin therapy usually will be required to achieve the goals of hypoglycemic control.

Underlying Risk Factors

Overweight and Obesity

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. Weight management in patients with type 2 diabetes must remain one component of risk factor management.
In clinical practice, attention should be given 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. 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 contributes importantly to development of overweight/obesity, as reflected in the rising prevalence of obesity in our sedentary society. Physical inactivity impairs insulin sensitivity, worsens the metabolic syndrome, and enhances risk for CVD through other mechanisms that are mediated through cardiovascular fitness and function. In the management of patients with diabetes, increased physical activity constitutes a prime goal. The physical activity prescription 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. Consideration should be given to taking advantage of existing professionally assisted programs in exercise (eg, cardiac rehabilitation) for appropriately selected patients with diabetes. For these patients, appropriate attention must be paid to the dangers of hypoglycemia related to strenuous exercise and initiation of diabetic foot disease through inappropriate foot protection.

Adverse Nutrition
Although it is widely accepted that most patients with type 2 diabetes need to lose weight, there is not universal agreement on what is the best diet composition for patients with diabetes. The ADA notes that there is no “diabetic diet” or “ADA diet.” Medical nutrition therapy for diabetes is best performed by a registered dietitian or other qualified nutrition specialist. For type 2 diabetes, the primary goals are to achieve and maintain goals for plasma glucose, lipids, and blood pressure. 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 accord with guidelines of the National Cholesterol Education Program’s Adult Treatment Panel III. These guidelines also indicate that total fat can range between 25% and 35% of total calories. High intakes of fruits and vegetables are advocated by all recommending groups.

Writing Group V: Management of Cardiovascular-Renal Complications

Progressive Renal Insufficiency in Diabetes
Diabetes has emerged as the leading cause of end-stage renal disease in the United States. Largely because of the high incidence of CHD in diabetic patients with end-stage renal disease, the 5-year survival of these patients is only 20%. Causes of excess CVD prominently include hypertension, dyslipidemia, and anemia. Major goals of management include early recognition of diabetic nephropathy and institution of measures to prevent progressive loss of renal function.

Nephropathy develops similarly in the 2 types of diabetes. First, ≈10 years of supranormal glomerular filtration rate is followed by ≈5 years of microalbuminuria; finally, macroalbuminuria and loss of glomerular filtration rate occur. Macroalbuminuria identifies substantial histological damage that heralds a predictable, linear decline in glomerular filtration rate. To monitor progression of nephropathy, yearly testing for albuminuria is required at the onset of type 2 diabetes and after 7 years of type 1 diabetes. Macroalbuminuria not only predicts loss of renal function, it also is a risk marker for CVD. The first-line test for microalbuminuria is the simple spot, early-morning-urine sample for determining the microalbumin to creatinine ratio.

Writing Group V outlined the following steps in management of patients with diabetic nephropathy. Once diabetes is detected, blood pressure should be strictly controlled. After microalbuminuria makes its appearance, dietary salt should be restricted, and ACE inhibition should be considered. Although the United Kingdom Prospective Diabetes Study found β-blockers to be as efficacious in slowing progression of renal disease as ACE inhibitors, many investigators still favor ACE inhibition as primary antihypertensive therapy. Some recommend use of ACE inhibitors even in the absence of hypertension when microalbuminuria appears. If blood pressure control is not achieved or there is a complication from ACE inhibitor use, β-blockers, diuretics, calcium channel antagonists, or other drugs should be added. Often, patients with diabetic nephropathy require multiple antihypertensive agents to achieve adequate blood pressure control. Treatment should also include strict control of blood glucose to hemoglobin A1c <7.0%, which has been successful in clinical trials in controlling the progression of nephropathy in patients with both types of diabetes. In patients with diabetes who have LDL-cholesterol levels above optimal (≥100 mg/dL), cholesterol-lowering drugs (eg, statins) should be considered. If increasing macroalbuminuria occurs or if renal insufficiency is progressive despite these measures, the patient should be referred to a nephrologist. Dietary protein restriction in patients who have progressive renal insufficiency will reduce accumulation of nitrogen-containing waste products and can have a beneficial influence on progression of renal insufficiency.

Diabetes and Left Ventricular Dysfunction
Abundant evidence indicates that diabetes predisposes to impaired left ventricular (LV) systolic and diastolic function. Mechanisms underlying impaired LV function in patients with diabetes have been variously attributed to several factors: (1) concomitant coronary atherosclerotic disease, (2) concomitant hypertension, (3) LV hypertrophy, (4) disease of the coronary microvasculature, (5) endothelial dysfunction, (6) obesity, (7) autonomic dysfunction, and (8) metabolic abnormalities that contribute to the diabetic cardiomyopathy. Endothelium-derived substances may have profound effects on myocardial structure and function, and endothelial dysfunction is characteristic of diabetes. Both endothelin and angiotensin II cause myocardial hypertrophy and increased...
interstitial connective tissue, and both may promote myocardial apoptosis. Several experimental models of diabetes show altered myocyte gene expression, disorders of calcium ion homeostasis, and abnormal systolic and diastolic function accompanying high plasma glucose levels. Moreover, the early cardiovascular manifestations of diabetes include increased LV mass and hyperdynamic LV function, both related to a hyperadrenergic state. These changes, combined with hypertension and coronary atherosclerotic disease, probably account for the common occurrence of heart failure with normal systolic function, especially in older persons with diabetes.

To date, however, the pathophysiology, management, and outcomes of persons with diabetes who have heart failure and preserved systolic function have not been specifically addressed. β-Blockers and ACE inhibitors are generally recommended for this condition, although there is a paucity of data supporting such practice in patients with diabetes.

Several longitudinal community-based studies (eg, the Framingham Study, the Glasgow MONICA [Monitoring Trends and Determinants in Cardiovascular Disease] cohort, the New Haven cohort, and the Cardiovascular Heart Study) have identified diabetes as a major risk factor for development of clinical heart failure. Also, among 14 multicenter heart failure treatment trials or data registries that reported diabetes as a comorbidity of the study population, diabetes was present in 7974 of 32 649 patients, representing an overall prevalence of 24%. The prevalence of diabetes ranged from 14% to 28% in these studies.

The leading cause of LV systolic dysfunction and congestive heart failure in developed countries in the current era is CHD. Most likely, the majority of persons with diabetes and heart failure are also those with CHD, with the expected worse prognosis of coronary disease patients with diabetes compared with persons without diabetes. This underscores the importance of primary and secondary prevention measures, including control of blood pressure, use of statins and aspirin, smoking cessation, and implementation of ACE inhibitors in persons with diabetes and CVD risk factors. Unfortunately, the multicenter heart failure trials and registries have not fully described the diabetic populations regarding presence or severity of underlying CHD (or hypertension); furthermore, few trials have reported the outcome of patients with diabetes relative to the nondiabetic populations. Nonetheless, available data do uniformly demonstrate that persons with diabetes and heart failure represent an unusually high-risk group with a substantially worse prognosis than those without diabetes. Although the therapeutic benefit of ACE inhibitors appears well established in patients with diabetes and heart failure, the beneficial effects attributed to β-blocker therapy in patients with heart failure have not been confirmed for patients with diabetes. Whether greater efficacy may be achieved in patients with diabetes with use of a nonselective β blocker with α1-blocking properties, such as carvedilol, will be determined only by future trials, or perhaps by further analysis of existing trial data.

There are very limited data regarding the impact of myocardial revascularization on survival and quality of life in patients with diabetes, CHD, and LV dysfunction. A retrospective analysis of data from the SOLVD (Studies of Left Ventricular Dysfunction) treatment and prevention trials has demonstrated a significant improvement in survival, symptoms, and rehospitalization with myocardial revascularization plus medical therapy compared with the results of medical therapy alone.

### Acute Myocardial Infarction

In-hospital and long-term mortality rates after acute myocardial infarction (AMI) are twice as high among individuals with diabetes as among those without diabetes. Approximately 30% of hospitalized patients with AMI have diabetes, compared with a diabetes prevalence of 6% to 8% in the general population. Diabetes is also a major risk factor for adverse outcomes in patients with unstable angina. There are numerous factors responsible for this increased risk. Persons with diabetes, particularly in the setting of autonomic neuropathy, have impaired angina recognition and may not consider shortness of breath, nausea, vomiting, unexplained fatigue or diaphoresis, or disturbances of glycemic control as symptoms of cardiac ischemia. Atypical symptoms could also prevent recognition of AMI by caretakers and be a cause of treatment delay. Because thrombolytic trials show improved outcomes with reduction in the time to presentation and to institution of treatment, delay in recognition undoubtedly is one factor that contributes to the worse prognosis. Too often, AMI is the first clinical expression of CHD in the patient with diabetes, who may have experienced prior, unheeded symptoms of cardiac ischemia. Furthermore, one should not assume that the absence of angina in the post–myocardial infarction (MI) patient is a reliable index of CHD stability. Surveillance with noninvasive testing may be of benefit in some persons with diabetes.

Factors specific to diabetes may not only increase the risk of MI but also adversely affect its outcome. Sympathovagal imbalance lowers the threshold for life-threatening arrhythmia and increases the risk of hemodynamic instability. Elevated fibrinogen levels, elevated plasminogen activator inhibitor-1 levels, and platelet abnormalities may increase the risk of thrombosis at the site of plaque disruption and possibly increase the risk of reinfarction after thrombolytic therapy. The diabetic ventricle is more prone to maladaptive remodeling that increases the risk of heart failure and cardiogenic shock. The status of the noninfarct zone, an important determinant of the remodeling process, may be affected by silent infarction, autonomic nervous system–related diastolic and/or systolic dysfunction, diabetic and/or hypertensive cardiomyopathy, impaired microvascular perfusion, and more extensive epicardial CHD. Furthermore, a higher prevalence of comorbidities, including dyslipidemia, hypertension, renal insufficiency, and peripheral and cerebral vascular disease, often worsens outcome in patients with diabetes. There is a higher rate of previous MI, an excess risk of heart failure before and at presentation, and more extensive epicardial CHD. Patients with diabetes present at a younger age; women are affected as often as men.

In almost all respects, the management of AMI is similar for patients with and without diabetes. However, hyperkalemia and renal insufficiency may preclude the use of ACE...
inhibitors. Targets for treatment include reestablishment of coronary flow and myocardial perfusion, plaque stabilization, prevention of recurrent ischemia, limitation of LV remodeling, arrhythmia suppression, and initiation of a lifelong program of secondary prevention. Persons with diabetes derive the same or greater relative survival benefit from fibrinolytic therapy. Previous concerns about the hemorrhagic risk associated with diabetic retinopathy have not been substantiated. Similarly, acute success rates with primary percutaneous coronary intervention are comparable in the presence or absence of diabetes, although restenosis and long-term mortality rates remain higher. Aspirin is the mainstay of antithrombotic therapy for all patients with acute coronary syndromes and should be provided as first-line therapy. The glycoprotein IIb/IIIa inhibitors improve outcomes for high-risk patients with unstable angina and non-ST elevation, especially those undergoing percutaneous coronary intervention. Intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin should be provided as clinically indicated, independent of diabetic status.

Trials performed in the pre-reperfusion era established conclusively that β-blockers confer early and late survival benefit in patients with diabetes that exceeds that seen among persons without diabetes. Relative concerns regarding alterations in lipid profiles/glycemic control and the masking of symptoms of hypoglycemia do not pertain in this setting. The standard contraindications related to pump function, atrioventricular conduction, and active bronchospasm should apply. ACE inhibitors may be more effective in diabetics than in persons without diabetes after AMI and should be given early to all diabetic AMI patients unless contraindications are present. Substantial evidence points to the admission glucose level as an independent predictor of early and late mortality after MI in patients with and without diabetes.

AMI should prompt a meticulous search for CHD risk factors, including diabetes. For patients with newly recognized diabetes, this provides an opportunity for prompt referral to a diabetes management team, in addition to a program of cardiac rehabilitation.

**Writing Group VI: Revascularization in Patients With Diabetes**

About 25% of the nearly 1.5 million surgical and percutaneous coronary revascularization procedures performed annually in the United States occur in patients with diabetes. Typically, patients with diabetes have increased comorbidities associated with cardiovascular risk and experience a greater than usual morbidity and mortality during and after revascularization. Comorbidities among diabetic patients that contribute to a worse outcome include hypertension, dyslipidemia, systolic and diastolic heart failure, autonomic dysfunction, peripheral vascular disease, cerebrovascular disease, microvascular disease, a prothrombotic state, and nephropathy.

Immediate success rates for patency after balloon coronary angioplasty (percutaneous transluminal coronary angioplasty [PTCA]) are similar for patients with and without diabetes; however, the incidence of major adverse cardiac events generally is higher among patients with diabetes. Moreover, long-term mortality is much higher for patients with diabetes. For example, the National Heart, Lung, and Blood Institute registry reported a 9-year mortality rate after PTCA of 39.9% for patients with diabetes versus 17.9% for those without diabetes. The increased incidence of restenosis and associated need for revascularization among diabetic patients after PTCA has been of particular concern. Speculation has turned to potential advantages of coronary bypass grafting (CABG) and novel percutaneous coronary intervention techniques for this group.

This latter speculation was reinforced by the results of the Bypass Angioplasty Revascularization Investigation (BARI) trial. This trial reported a highly significant difference in survival for randomized patients with treated diabetes and 2- or 3-vessel disease undergoing CABG compared with PTCA (76% versus 56%, \(P=0.0011\)). However, the benefits of CABG were seen only for those patients receiving at least 1 arterial conduit during CABG. In BARI, subsequent revascularization rates among the PTCA group were much higher in patients with diabetes than in nondiabetic controls (60% versus 13%, respectively; \(P<0.001\)). Whether BARI results can be generalized to all patients with diabetes is uncertain. For example, in the BARI registry, patients with diabetes who underwent revascularization did not differ significantly in long-term survival after PTCA compared with CABG. Differences in patient characteristics may account for differences in outcome. The treated diabetic patients in the BARI registry had a higher educational level, were more physically active, were less likely to smoke cigarettes, and had a higher level of quality of life than their randomized counterparts. Moreover, they were also less likely to have 3-vessel disease than randomized patients in the BARI trial or those in the registry who were undergoing CABG. Thus, physician selection for patients undergoing revascularization based on clinical considerations may be more important for determining outcomes with different procedures than an across-the-board generalization about patients with diabetes.

If patients with diabetes do in fact have a worse prognosis after PTCA, what might be the reasons? Several mechanisms have been postulated: decreased endothelial function, a prothrombotic state, increased intimal hyperplasia, increased negative remodeling, and increased protein glycosylation and vascular matrix deposition. Furthermore, hyperglycemia and hyperinsulinemia appear to potentiate these adverse mechanisms. Coronary intravascular ultrasound and histological analysis of atherectomy specimens suggest that the poor prognosis may be due to both a heightened proliferative response and an increased vascular matrix deposition, which accelerates restenosis among patients with diabetes. Serial intravascular ultrasound assessment in hyperinsulinemic patients revealed increased neointimal tissue proliferation after coronary stent implantation, which suggests a causative role for insulin. Although reduction in insulin resistance and tighter control of diabetes might improve outcomes, confirmatory studies are lacking. Still, in one study, administration of troglitazone in a small number of patients with type 2 diabetes after stent implantation showed reduced neointimal tissue proliferation.

Intracoronary stents could improve outcomes for patients with diabetes undergoing PTCA, as they have done for...
nondiabetic patients. To date, results of stenting in patients with diabetes are retrospective, and studies have been small in patient number. Limited reports indicate variable restenosis rates when stents are used in patients with diabetes; although outcomes generally are improved compared with PTCA alone, restenosis rates remain higher than those observed in persons without diabetes. Whether tight control of hyperglycemia will reduce restenosis rates after stenting has not been determined. Nonetheless, the IIb/IIIa platelet receptor antagonist abximab has been shown to significantly reduce major cardiac events and target-vessel revascularization at 6 months among patients with diabetes who have undergone stenting. These findings suggest abximab may exert beneficial effects on the diabetic prothrombotic state and neointimal proliferation. Intracoronary vascular irradiation has been reported to reduce restenosis after PTCA and also when used as part of therapy for in-stent restenosis among patients with diabetes. Thus, several newer therapies may give better outcomes for patients with diabetes than those reported by the randomized BARI trial. Examples include intracoronary stents, adjunct acute therapy with the platelet IIb/IIIa receptor antagonist abximab, intracoronary vascular irradiation, tight control of diabetic hyperglycemia, pharmaco-coated stents, and aggressive medical therapies with statins and ACE inhibitors.

New clinical trials thus are needed. The BARI 2D trial, which has a 2×2 factorial design, will compare tight diabetic control with insulin-providing versus insulin-sensitizing therapy with and without a revascularization procedure of choice and should contribute significantly to our understanding of the appropriate revascularization strategy for patients with diabetes.

The Diabetic State and Protection of Ischemic Myocardium

Pharmacological approaches to increase the tolerance of myocardium to ischemia and to limit injury in reperfused ischemic myocardium represent opportunities to preserve ventricular function and improve clinical outcome. As new clinical strategies are developed to prevent the loss of ventricular muscle in coronary syndromes and as they are applied to the general population, the unique physiological response of the diabetic heart must be considered. For example, in the diabetic state, substrates used for energy production and mechanisms of ionic homeostasis differ from the nondiabetic state. Utilization of fatty acids increases; glycolysis, Na `/H` exchange (NHE), and Na `/Ca` exchange activity decrease; and the Na`-dependent bicarbonate co-transporter contributes more significantly to extrude protons from the cell. Free fatty acids increase, and the capacity to scavenge reactive oxygen species increases. Such metabolic and physiological changes are predicted to increase the tolerance of the diabetic heart to ischemia, but they may also influence 2 important mechanisms that have the potential to preserve ischemic myocardium, ie, ischemic preconditioning and inhibition of NHE. Although in animal studies, preconditioning and NHE inhibition are equivalent in their capacity to limit ischemia/reperfusion injury, limited data are available describing the efficacy of preconditioning and NHE inhibition to prevent ischemia/reperfusion injury in the diabetic heart.

Preconditioning and NHE Inhibition in Diabetic Heart

Preconditioning represents an adaptation of cardiac cells to a previous ischemic event, thereby increasing the tolerance of the heart to subsequent ischemic events. Preconditioning delays the time to onset of irreversible ischemic/reperfusion injury and limits cellular injury when reperfusion is achieved in a timely manner. Benefits of preconditioning include a decrease in infarct size, ischemic contracture, cell-to-cell electrical uncoupling, postischemic contractile dysfunction, and arrhythmia. The cellular mechanism of preconditioning appears to involve protein kinase C and the opening of the ATP-dependent K channel (K_ATP), which is the same channel modified by diabetes and blocked by sulfonylureas. Preconditioning occurs in human heart, yet there are few data to address the capacity of diabetic heart to precondition, and what data do exist suggest that human diabetic myocardium preconditions poorly. The limited capacity of diabetic myocardium to precondition might account for some of the increased risk of ischemia in the diabetic state. Whether sulfonylureas further attenuate ischemic preconditioning in the diabetic heart remains to be determined.

Metabolic and physiological changes associated with the diabetic state are predicted to increase the tolerance of the diabetic heart to ischemia. Experimental data tend to support this hypothesis, although this point is controversial and may depend on the experimental model of diabetes and the species studied. Because NHE activity is already reduced in the diabetic state, it is not known whether inhibitors of NHE will benefit diabetics when used in coronary syndromes, before CABG, or as adjuvant therapy during primary revascularization to prevent ischemia/reperfusion injury. Currently, clinical studies assessing the role of NHE inhibition in the treatment of ischemic events have not been powered to answer this question. In the future, basic and clinical studies will be necessary to determine the influence of the diabetic state on the magnitude of ischemia/reperfusion-induced injury as mediated by NHE.

In summary, ionic regulation and metabolism during ischemia are modified by the diabetic state. The diabetic heart may be more tolerant of ischemia in certain experimental animal models, but comparable data do not exist in humans. Although this review has emphasized the role of preconditioning and NHE inhibition to protect ischemic and reperfused diabetic hearts, other strategies are also being investigated. Adenosine receptor agonists, K_ATP channel openers, anti-integrins, antiselectins, and anticomplement molecules that target the preconditioning mechanism or inflammation are currently being assessed or planned. Additional work is necessary to define the role of these modalities in the treatment of patients with diabetes. More basic science is needed to more fully understand the effect of the prediabetic and diabetic state on metabolism, cellular energetics, gene expression, signal transduction, and channel function. Likewise, clinical studies should be designed to include, when possible, sufficient subjects with diabetes to have the statistical power to assess the influence of the diabetic state on the clinical end points.

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The members of the Writing Groups who contributed to the content of the Executive Summary and the six online reports from Prevention VI Proceedings should be included as an Appendix to the Executive Summary published in the May 7, 2002, issue of the journal (Circulation. 2002;105:2231–2239).

Appendix

Prevention VI: Diabetes and Cardiovascular Disease

Executive Summary: Conference Proceeding for Healthcare Professionals From a Special Writing Group of the American Heart Association

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