

## Diabetes and Cardiovascular Disease A Statement for Healthcare Professionals From the American Heart Association

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This statement examines the cardiovascular complications of diabetes mellitus and considers opportunities for their prevention. These complications include coronary heart disease (CHD), stroke, peripheral arterial disease, nephropathy, retinopathy, and possibly neuropathy and cardiomyopathy. Because of the aging of the population and an increasing prevalence of obesity and sedentary life habits in the United States, the prevalence of diabetes is increasing. Thus, diabetes must take its place alongside the other major risk factors as important causes of cardiovascular disease (CVD). In fact, from the point of view of cardiovascular medicine, it may be appropriate to say, "diabetes is a cardiovascular disease."

### Clinical Presentations of Diabetes Mellitus

The most prevalent form of diabetes mellitus is type 2 diabetes. This disorder typically makes its appearance later in life. The underlying metabolic causes of type 2 diabetes are the combination of impairment in insulin-mediated glucose disposal (insulin resistance) and defective secretion of insulin by pancreatic  $\beta$ -cells. Insulin resistance develops from obesity and physical inactivity, acting on a substrate of genetic susceptibility.<sup>1,2</sup> Insulin secretion declines with advancing age,<sup>3,4</sup> and this decline may be accelerated by genetic factors.<sup>5,6</sup> Insulin resistance typically precedes the onset of type 2 diabetes and is commonly accompanied by other cardiovascular risk factors: dyslipidemia, hypertension, and prothrombotic factors.<sup>7,8</sup> The common clustering of these risk factors in a single individual has been called the metabolic syndrome. Many patients with the metabolic syndrome manifest impaired fasting glucose (IFG)<sup>9</sup> even when they do not have overt diabetes mellitus.<sup>10</sup> The metabolic syndrome commonly precedes the development of type 2 diabetes by many years<sup>11</sup>; of great importance, the risk factors that constitute this syndrome contribute independently to CVD risk.

Recently, new criteria have been accepted for the diagnosis of diabetes.<sup>9</sup> The upper threshold of fasting plasma glucose for the diagnosis of diabetes has been lowered from  $\geq 140$  mg/dL to  $\geq 126$  mg/dL. The upper threshold for normoglycemia likewise has been reduced from  $< 115$  to  $< 110$  mg/dL. A fasting plasma glucose of 110 to 125 mg/dL is now designated IGF. These changes removed the need for oral glucose tolerance testing for diagnosis of diabetes; a diagnosis rests entirely on confirmed elevations of fasting plasma glucose. Furthermore, the terms insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus have been replaced by type 1 diabetes and type 2 diabetes, respectively.

The other form of diabetes mellitus is type 1 diabetes, which follows immunologic destruction of pancreatic  $\beta$ -cells.<sup>12</sup> Type 1 diabetes usually begins early in life and is often called juvenile diabetes. This form of diabetes frequently produces microvascular complications, nephropathy, and retinopathy,<sup>12</sup> but it also predisposes to CHD.<sup>13</sup> Because type 2 diabetes occurs much more commonly than type 1 diabetes, the present statement will emphasize type 2 diabetes. Nonetheless, type 1 diabetes will be integrated into the overall strategy of cardiovascular risk reduction.

### Scope of the Problem

At least 10.3 million Americans carry a diagnosis of diabetes mellitus.<sup>14</sup> Another 5.4 million are estimated to have undiagnosed diabetes.<sup>14</sup> Approximately 90% of patients with diabetes have the type 2 variety.<sup>14</sup> The onset of type 2 diabetes usually precedes clinical diagnosis by several years.<sup>14</sup> An increasing prevalence of type 2 diabetes cannot be divorced from the rising prevalence of obesity and physical inactivity in our society. An estimated 97 million adults in the United States are overweight or obese.<sup>15</sup> Furthermore,  $\approx 75\%$  of adult Americans have minimal physical activity or daily exercise.<sup>16</sup> Both excess body fat and physical inactivity predispose to type 2 diabetes. Several ethnic groups are particularly susceptible to type 2 diabetes: Hispanics, blacks, Native Americans, and Asians (especially South Asians).<sup>17–20</sup> The growing ethnic diversity, including these groups, contributes to the increasing prevalence of type 2 diabetes in the United States.

### Diabetes as a Major Risk Factor

A large body of epidemiological and pathological data documents that diabetes is an independent risk factor for

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CVD in both men and women.<sup>21–23</sup> Women with diabetes seem to lose most of their inherent protection against developing CVD.<sup>21,24</sup> CVDs are listed as the cause of death in ≈65% of persons with diabetes.<sup>25</sup> Diabetes acts as an independent risk factor for several forms of CVD. To make matters worse, when patients with diabetes develop clinical CVD, they sustain a worse prognosis for survival than do CVD patients without diabetes.<sup>26–28</sup> These considerations have convinced the Scientific Advisory and Coordinating Committee of the American Heart Association (AHA) that diabetes mellitus deserves to be designated a major risk factor for CVD. This formal designation commits the AHA to a greater emphasis on diabetes as a risk factor in its scientific and educational programs. This statement provides the scientific rationale for the decision to classify diabetes as a major risk factor for CVD.

## Diabetes and Specific CVD

### Atherosclerotic CHD

Both type 1 diabetes and type 2 diabetes are independent risk factors for CHD.<sup>21–23</sup> Moreover, myocardial ischemia due to coronary atherosclerosis commonly occurs without symptoms in patients with diabetes.<sup>29</sup> As a result, multivessel atherosclerosis often is present before ischemic symptoms occur and before treatment is instituted. A delayed recognition of various forms of CHD undoubtedly worsens the prognosis for survival for many diabetic patients.

### Diabetic Cardiomyopathy

One reason for the poor prognosis in patients with both diabetes and ischemic heart disease seems to be an enhanced myocardial dysfunction leading to accelerated heart failure (diabetic cardiomyopathy).<sup>30–37</sup> Thus, patients with diabetes are unusually prone to congestive heart failure. Several factors probably underlie diabetic cardiomyopathy: severe coronary atherosclerosis, prolonged hypertension, chronic hyperglycemia, microvascular disease, glycosylation of myocardial proteins, and autonomic neuropathy. Improved glyce-mic control, better control of hypertension, and prevention of atherosclerosis with cholesterol-lowering therapy may prevent or mitigate diabetic cardiomyopathy. An early clinical trial<sup>38</sup> suggested that sulfonyl ureas used for control of hyperglycemia are cardiotoxic and may exacerbate diabetic cardiomyopathy. This side effect, however, was not confirmed in a recent large clinical trial.<sup>39</sup>

### Stroke

Mortality from stroke is increased almost 3-fold when patients with diabetes are matched to those without diabetes.<sup>40</sup> The most common site of cerebrovascular disease in patients with diabetes is occlusion of small paramedial penetrating arteries.<sup>41</sup> Diabetes also increases the likelihood of severe carotid atherosclerosis.<sup>42,43</sup> Patients with diabetes, moreover, are likely to suffer irreversible brain damage with carotid emboli that otherwise would produce only transient ischemic attacks in persons without diabetes. Approximately 13% of patients with diabetes >65 years old have had a stroke.<sup>44</sup>

### Renal Disease

Renal disease is a common and often severe complication of diabetes.<sup>45</sup> Approximately 35% of patients with type 1 diabetes of 18 years' duration will have signs of diabetic renal involvement.<sup>46</sup> Up to 35% of new patients beginning dialysis therapy have type 2 diabetes.<sup>47</sup> End-stage renal disease (ESRD) appears to be especially common among Hispanics, blacks, and Native Americans with diabetes.<sup>48–52</sup> For patients with diabetes who are on renal dialysis, mortality rates probably exceed 20% per year.<sup>47</sup> When diabetes is present, CVD is the leading cause of death among patients with ESRD.<sup>53–55</sup>

### Covariate Risk Factors

Prospective studies<sup>22–40</sup> indicate that all of the major cardiovascular risk factors—cigarette smoking, hypertension, and high serum cholesterol—continue to act as independent contributors to CVD in patients with diabetes. As already mentioned, clustering of metabolic risk factors, called the metabolic syndrome, occurs commonly in type 2 diabetes.<sup>56</sup> The onset of hyperglycemia in patients with the metabolic syndrome appears to accelerate atherogenesis, possibly by enhanced formation of glycosylated proteins and advanced glycation products<sup>57,58</sup> and/or by increasing endothelial dysfunction.<sup>59</sup> These direct consequences of hyperglycemia probably contribute to the microvascular disease underlying nephropathy and retinopathy, and they may promote macrovascular disease as well.

### Predisposing Risk Factors

Several predisposing factors simultaneously affect the development of CVD and diabetes mellitus. Among these concomitant factors are obesity, physical inactivity, heredity, sex, and advancing age. The mechanisms whereby they predispose to chronic diseases are complex and often overlapping. To some extent, these predisposing factors exacerbate the major risk factors: dyslipidemia, hypertension, and glucose tolerance; and they may cause CVD and diabetes mellitus through other pathways as well. To a large extent, both CVD and diabetes must be prevented through control of the predisposing risk factors. Modification of life habits is at the heart of the public health strategy for prevention of CVD and diabetes mellitus. High priorities are the prevention (or treatment) of obesity and promotion of physical activity. Drug therapy nonetheless may be required to control the metabolic risk factors, particularly when they arise from genetic aberration and aging. Effective drugs are currently available for treatment of hypertension and dyslipidemia. Hypoglycemic agents also are available for treatment of type 2 diabetes, but new pharmacological strategies are under investigation for more effective treatment and prevention.

### Insulin Resistance and the Metabolic Syndrome

Most patients with type 2 diabetes have insulin resistance. Indeed, insulin resistance seems to predispose to both CVD and diabetes.<sup>60</sup> Research suggests that insulin resistance is a multisystem disorder that induces multiple metabolic alterations. Factors that contribute to insulin resistance are genetics,<sup>61</sup> obesity,<sup>62</sup> physical inactivity,<sup>63</sup> and advancing age.<sup>64</sup>

**TABLE 1. Evaluation of Major Risk Factors in Diabetic Patients****Cigarette smoking**

History: Record current and past smoking habits; list smoking duration (years of use) and intensity (number of cigarettes smoked per day); determine passive smoke exposure (at work and at home)

**Blood pressure**

History: Record history of blood pressure (BP) and measures of treatment, including current and past antihypertensive agents. Also determine acquired factors affecting BP: body weight, physical activity level, sodium intake, and alcohol consumption

Physical examination: Define current BP from multiple measurements; measure BP supine, sitting, and standing in elderly patients; consider 24-hour automated, ambulatory BP monitoring in older patients (detects absence of nocturnal fall in BP [autonomic dysfunction], episodic hypertension, orthostatic hypertension, resistant hypertension)

**Serum lipids and lipoproteins**

History: Assess dietary habits and alcohol intake, exercise habits, efforts to modify lifestyle habits, use of medications that influence lipoprotein levels, family history of premature vascular disease and dyslipidemia, history of thyroid disorders or pancreatitis

Physical examination: Check for eruptive xanthomas and lipemia retinalis (signs of severe hypertriglyceridemia), tuberous xanthomas (sign of dysbetalipoproteinemia), xanthelasma (suggestive of hyperlipidemia), and signs of hypothyroidism

Laboratory: Measure fasting serum total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol; (optional: total apolipoprotein B\*, Lp[a], LDL size), thyroid, renal, liver function tests

**Albuminuria**

Measure serum creatinine

Test urine with a dipstick for protein: If dipstick is negative, measure urine albumin-to-creatinine ratio in the first morning urine specimen

**Glycemic status**

History: Age of onset of hyperglycemia; course of diabetes management; family history of diabetes, history of diabetic complications

Physical examination: Cardiovascular status, retinopathy, other diabetic complications

Laboratory: Fasting plasma glucose (FPG); hemoglobin A1c (periodically); diabetes=FPG>126 mg/dL ( $\times 2$ ); impaired fasting glucose=110 to 126 mg/dL ( $\times 2$ )

\*Total apolipoprotein B is especially useful if triglycerides are elevated but LDL cholesterol is in the normal range.

Patients with insulin resistance often have abdominal obesity.<sup>65</sup> Metabolic risk factors that occur commonly in patients with insulin resistance are atherogenic dyslipidemia, hypertension, glucose intolerance, and a prothrombotic state.<sup>60</sup> Each of these risk factors can be reviewed briefly.

**Atherogenic Dyslipidemia**

Atherogenic dyslipidemia is characterized by 3 lipoprotein abnormalities: elevated very-low-density lipoproteins (VLDL), small LDL particles, and low high-density-lipoprotein (HDL) cholesterol (the lipid triad). The lipid triad occurs frequently in patients with premature CHD and appears to be an atherogenic lipoprotein phenotype independent of elevated LDL cholesterol.<sup>66–69</sup> Most patients with atherogenic dyslipidemia are insulin resistant.<sup>69–71</sup> Atherogenic dyslipidemia in diabetic patients often is called diabetic dyslipidemia. Many patients with atherogenic dyslipidemia also have an elevated serum total apolipoprotein B.<sup>72</sup> Growing evidence suggests that all of the components of the lipid triad are independently atherogenic. Together they represent a set of lipoprotein abnormalities besides elevated LDL cholesterol that promote atherosclerosis.

**Hypertension**

Hypertension is a well-established major risk factor for CVD.<sup>22</sup> It increases risk for both CHD and stroke and contributes to diabetic nephropathy.<sup>73</sup> Several investigators<sup>74,75</sup> report a positive association between insulin resistance and hypertension; this finding suggests that elevated blood pressure deserves to be listed among the components of the metabolic syndrome. Hypertension nonetheless is a multifactorial disorder, and the mechanistic connections between

insulin resistance and hypertension are largely conjectural; even so, evidence for a causal link is growing.<sup>76</sup> When hypertension coexists with overt diabetes, which it commonly does, the risk for CVD, including nephropathy, is doubly increased.

**Elevated Plasma Glucose**

For several years after onset of insulin resistance, fasting and postprandial glucose levels typically are normal. During this period, pancreatic  $\beta$ -cells are able to increase insulin secretion in response to insulin resistance and thereby maintain normal plasma glucose levels. In some people, however, insulin secretion declines with aging, and elevated glucose concentrations appear. The first abnormality in plasma glucose in patients with insulin resistance is IFG (or impaired glucose tolerance).<sup>9</sup> The presence of IFG usually accompanies long-standing insulin resistance. It is currently estimated that 13.4 million adults, 7.0% of the US population, have IFG.<sup>14</sup> Many prospective studies<sup>77,78</sup> show that IFG (or impaired glucose tolerance) is a risk factor for CVD; the degree of independence as a risk factor, however, is uncertain, because IGF commonly coexists with other components of the metabolic syndrome.<sup>11</sup> A patient with IFG nonetheless must be considered at risk for both CVD and type 2 diabetes. As already indicated, once categorical hyperglycemia develops, it counts as an independent risk factor for CVD.<sup>22</sup>

**Prothrombotic State**

A newly recognized component of the metabolic syndrome is a prothrombotic state.<sup>76</sup> Patients with insulin resistance frequently manifest several alterations in coagulation mechanisms that predispose them to arterial thrombosis. These alterations include

**TABLE 2. Evaluation of Predisposing Risk Factors in Diabetic Patients**

**Body weight and fat distribution**

History: Assess history of body weight, age at onset of overweight, history of weight loss and weight gain; assess eating and exercise habits, social and occupational factors affecting body weight, family support, history of body weights in family members in childhood and adulthood, attitudes and motivation for weight control

Physical examination: Measure body weight (kg) and height (m); calculate body mass index (BMI) ( $\text{kg/m}^2$ ); categorize body weight (BMI 25 to 29.9=overweight;  $>30$ =obesity); measure waist circumference (abdominal obesity= $>40$  in [102 cm] in men or  $>36$  in [88 cm] in women; borderline abdominal obesity in men, 88 to 102 cm)

**Physical activity**

History: Assess past and current levels of physical activity; ascertain activity on the job, participation in sports, regular walking, jogging, or swimming. In women, ask about activity in housework, child care; determine opportunities and available facilities for regular exercise

Physical examination: Assess level of cardiovascular fitness in cardiac rehabilitation facilities

**Family history**

History: Assess family history for CVD or sudden death. (Family history is positive if CVD or sudden death occurred in first-degree male relatives before age 55 years or first-degree female relatives before age 65 years.) Determine presence or absence of other risk factors—high cholesterol levels, cigarette smoking, hypertension, diabetes—in first-degree relatives (biological parents, siblings, offspring). If possible, expand family tree to second-degree relatives (grandparents, uncles, aunts). Create a simple family tree

Laboratory: Measure glucose and lipids (cholesterol, triglycerides, and HDL cholesterol) in first-degree relatives

increased fibrinogen levels,<sup>79</sup> increased plasminogen activator inhibitor-1,<sup>80</sup> and various platelet abnormalities.<sup>81</sup>

**LDL Cholesterol and Atherogenesis in Diabetic Patients**

An elevated concentration of serum LDL cholesterol is a major risk factor for CHD.<sup>82</sup> In fact, some elevation of LDL cholesterol appears to be necessary for the initiation and progression of atherosclerosis. In populations having very low LDL cholesterol levels, clinical CHD is relatively rare, even when other risk factors—hypertension, cigarette smoking, and diabetes—are common.<sup>83</sup> In contrast, severe elevations in LDL cholesterol can produce full-blown atherosclerosis and premature CHD in the complete absence of other risk factors.<sup>84</sup>

The view has been expressed that most patients with diabetes do not have an elevated serum LDL cholesterol; if not, a high LDL serum cholesterol would not be a common risk factor in patients with diabetes. It is true that most patients who have diabetes do not have marked elevations of LDL cholesterol, but these patients nonetheless carry high enough levels to support the development of atherosclerosis.<sup>85</sup> A role for LDL in hyperglycemic patients became apparent in recent clinical trials, eg, the Scandinavian Simvastatin Survival Study (4S),<sup>86,87</sup> the Cholesterol and Recurrent Events (CARE) trial,<sup>88,89</sup> and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID).<sup>90</sup> In all of these trials, aggressive LDL-lowering therapy reduced recurrent CHD events in patients with diabetes.

**Cigarette Smoking**

Cigarette smoking is a leading risk factor for CVD. Patients with diabetes who are smokers are doubly at risk. Unfortunately, many patients continue to smoke despite having diabetes; for these patients, the benefits that can be derived from modifying other risk factors are mitigated.

**Diabetic Nephropathy**

Diabetic nephropathy can be divided into 4 phases: microalbuminuria, macroalbuminuria, the nephrotic syndrome, and

chronic renal failure.<sup>45</sup> Microalbuminuria (urine albumin 30 to 300 mg/d or  $<300$  mg/g creatinine) is the first clinical sign of diabetic damage to the kidney.<sup>91,92</sup> Not only is microalbuminuria a harbinger of progressive kidney damage, but its presence also reflects a higher risk for CVD.<sup>92–95</sup> Macroalbuminuria (urine albumin  $>300$  mg/d or  $>300$  mg/g creatinine) usually denotes significant diabetic nephropathy and will be followed by a decline in glomerular filtration rate (GFR). The majority of patients with diabetes who have macroalbuminuria also have hypertension<sup>96,97</sup>; in these patients, control of hypertension slows the decline in GFR.<sup>98–100</sup> Some patients with diabetes develop the nephrotic syndrome (urine protein  $>3$  g/d); diabetic dyslipidemia in such patients often is compounded by nephrotic dyslipidemia, most notably by higher cholesterol levels. The nephrotic syndrome usually heralds progressive renal insufficiency; thereafter, ESRD ensues and dialysis and/or transplantation become necessary to sustain life.

**Risk Assessment in the Diabetic Patient**

Risk assessment must take into account the major risk factors (cigarette smoking, elevated blood pressure, abnormal serum lipids and lipoproteins, and hyperglycemia) and predisposing risk factors (excess body weight and abdominal obesity, physical inactivity, and family history of CVD). Identification of risk factors is a major first step for developing a plan for risk reduction in persons with diabetes. Specific steps in the evaluation of the major risk factors in such persons are presented in Table 1. These steps include a thorough medical history, careful physical examination, and appropriate laboratory measurements. Specialized testing may be particularly useful, eg, 24-hour monitoring of ambulatory blood pressure by automated techniques. Lipoprotein analysis should draw a clear distinction between elevated LDL cholesterol concentrations and atherogenic dyslipidemia (or diabetic dyslipidemia) as manifested by elevated triglycerides and small LDL and low HDL cholesterol levels. Even borderline-high-risk LDL cholesterol levels (130 to 159 mg/dL) are of concern in patients with diabetes and call for aggressive intervention.



**TABLE 3. Detection of Clinical and Subclinical Cardiovascular Disease in the Diabetic Patient****Stress testing for coronary heart disease**

Consult AHA guidelines for exercise treadmill testing

Special considerations for exercise testing in diabetic patients

Blood pressure and heart rate responses often blunted (due to elevated resting heart rate)

Painless ST-segment depression common in diabetic patients

Diagnostic specificity of ST-segment depression often reduced (due to previous silent myocardial infarction, conduction abnormalities, and increases in LV mass)

Exercise or pharmacological stress  $^{201}\text{Tl}$  (or  $^{99}\text{Tc}$ ) perfusion scintigraphy favorable alternative for exercise testing in diabetic patients

Ambulatory ECG monitoring for silent ischemia: may be helpful in some diabetic patients, but not recommended routinely

**Noninvasive evaluation of cardiac function**

Echocardiography (with Doppler) and radionuclide ventriculography

Special considerations for diabetic patients

Diastolic dysfunction common in asymptomatic diabetic patients

Diastolic dysfunction often precedes systolic dysfunction

LV wall motion abnormalities: suggests diabetic cardiomyopathy

**Evaluation of autonomic dysfunction**

Bedside evaluation of autonomic dysfunction

Two or more of the following tests are abnormal

Resting heart rate (supine)  $\geq 100$  bpm

Excess diastolic blood pressure response to hand-grip exercise

Abnormal expiratory/inspiratory RR-interval ratio

Postural hypotension

Significance of autonomic dysfunction in diabetic patients

Carries poor prognosis (50% mortality in 5 years)

Sudden death common; consider electrophysiological study for syncope workup

Enhanced complications after elective surgical procedures

Increased danger with general anesthesia

**Detection of subclinical cardiovascular disease**

History: Assess carefully for claudication, angina, dyspnea on exertion, cerebrovascular disease

Physical exam: routine cardiovascular examination; assess for carotid and femoral artery bruits; evaluate peripheral artery pulses; ratio of ankle-to-brachial artery systolic blood pressure (marker of subclinical peripheral vascular disease)

Laboratory: check for microalbuminuria (see Table 1)

ECG: LV hypertrophy strong predictor of CHD morbidity and mortality

Electron beam CT: coronary calcium score highly correlated with total coronary atherosclerosis burden (role in risk assessment currently under investigation)

Carotid ultrasound: detects subclinical carotid atherosclerosis (role in risk assessment currently under investigation)

LV indicates left ventricular.

The quality of glycemic control can best be assessed by periodic measurement of hemoglobin A1c. Furthermore, because hyperglycemia per se confers increased risk for CVD, the presence of other risk factors—smoking, hypertension, even borderline-high-risk LDL cholesterol, and atherogenic dyslipidemia—signifies enhanced risk and signals the need for more aggressive intervention on all risk factors.

Risk assessment in the diabetic patient is not complete until predisposing risk factors—obesity, physical inactivity, and family history of premature CVD—have been evaluated (Table 2). Identification of predisposing risk factors will provide insight into the causation of the major risk factors. The finding of abdominal obesity, as evidenced by an increased waist circumference, usually indicates the presence of insulin resistance. A careful assessment of the status of the predisposing risk factor sets the stage for therapeutic modification of life habits. A genetic basis for risk, as revealed by

a positive family history of CVD or diabetes, may point to the need for pharmacological control of risk factors. Moreover, a positive family history often uncovers family members who also need risk-factor intervention.

## Clinical Evaluation

### Detection of Clinical and Subclinical CVD

Prospective studies<sup>101</sup> document an increased likelihood of sudden cardiac death and unrecognized myocardial infarctions in patients with diabetes. Moreover, acute ischemic syndromes, peripheral arterial disease, and advanced CVD complications occur more commonly in patients with diabetes than in those without.<sup>101</sup> Because the typical cardiac symptoms often are masked in patients with diabetes, the diagnosis of myocardial infarction commonly is missed or delayed. Effective strategies for earlier detection of clinical

**TABLE 4. Evaluation of Renal Status**

Urine albumin and protein

Yearly screen for microalbuminuria 7 years after onset of types 1 and 2 diabetes and in all hypertensive patients with diabetes; thereafter, test urine for albumin yearly

Microalbuminuria: urine albumin 30 to 300 mg/d or 30 to 300 mg/g creatinine in the first morning urine specimen\*

Rule out other kidney diseases that cause proteinuria

Detect increased urine albumin and protein

Macroalbuminuria: urine protein >300 mg/d (or >300 mg/g creatinine) in the first morning urine specimen\*

Nephrotic syndrome: urine protein >3 g/d

If either present, further renal evaluation is necessary

Patients with microalbuminuria or proteinuria and those with high serum creatinine or the nephrotic syndrome should be evaluated by a nephrologist to detect other causes of kidney disease and to develop a treatment strategy

Urinalysis

The presence of hematuria, pyuria, and a large number of casts (eg, red blood cell casts, white blood cell casts, or >2 granular casts per high-power field) is often an indication that a nondiabetic disease is also affecting the kidney. Such patients should be evaluated by a nephrologist to develop a treatment strategy if needed

Blood pressure evaluation

If hypertension is present, exclude secondary causes, including advancing renal insufficiency

Treatment with an ACE inhibitor may be preferred unless there is hyperkalemia or other complications

Blood urea nitrogen, serum creatinine, and glomerular filtration rate

The blood urea nitrogen is affected by both the degree of renal insufficiency and dietary protein and therefore is not a satisfactory estimate of renal function

The serum creatinine becomes high only after >50% of kidney function is lost and therefore is not useful for detecting early renal insufficiency. A rising serum creatinine indicates progressive renal failure, and a plot of the reciprocal of serum creatinine vs time is useful for tracking the progressive decline in renal function

The glomerular filtration rate is the most accurate estimate of the degree of renal dysfunction, but it generally requires administration of a radioisotope and  $\geq 4$  hours of the patient's time. The loss of glomerular filtration rate also provides the most accurate estimate of the rate of loss of kidney function

\*Urine collections must be done when there is no complicating condition that can elevate protein excretion; this includes fever, heavy exercise, poor glucose control, heart failure, and urinary tract infection. Also, certain drugs can depress albumin excretion; these include nonsteroidal anti-inflammatory drugs and ACE inhibitors.

CVD could reduce morbidity and mortality in patients with diabetes. In addition, detection of subclinical atherosclerosis and early clinical manifestation of CVD could lead to more effective primary prevention in some patients with diabetes.

Table 3 outlines a general approach to the detection of clinical and subclinical CVD in the hyperglycemic patient. Stress testing for myocardial ischemia and dysfunction should be performed in accord with general American College of Cardiology (ACC)/AHA guidelines<sup>102</sup>; Table 3 lists further special considerations for exercise testing in patients with diabetes. Noninvasive evaluation of cardiac function in hyperglycemic patients suspected of having myocardial dysfunction may be a useful guide to cardiovascular management in some of these patients. Many patients with diabetes suffer from an autonomic dysfunction that impairs quality of life and predisposes to life-threatening cardiovascular complications. Finally, the finding of subclinical CVD signals the need for institution of more aggressive preventive measures.

### Evaluation of Renal Status

Chronic renal failure is a major clinical outcome in patients with diabetes. It is more likely to develop in type 1 diabetes than in type 2 diabetes. However, the high prevalence of type 2 diabetes makes it a major cause of ESRD. The renal status of patients with diabetes therefore must be appropriately monitored so that effective intervention can be introduced early in the course of renal disease. Table 4 outlines the steps in evaluation. Testing for urine albumin and protein is the

first step. Microalbuminuria is indicative of early diabetic nephropathy. In patients with type 1 diabetes, it is a harbinger of ongoing renal damage; in type 2 diabetes, it signifies enhanced risk for CVD. Macroalbuminuria and/or nephrotic-range proteinuria predicts a decline in renal function. Patients with macroalbuminuria should be referred to a nephrologist who can rule out another kidney disease and who can help to plan a strategy for preventing progression to ESRD. This strategy should include aggressive management of hypertension to blood pressure levels of <130/85 mm Hg. Although the serum creatinine is not a sensitive indicator of the degree of loss of GFR, a rising serum creatinine plotted as changes in the reciprocal of serum creatinine versus time provides a means of determining the rate of decline in renal function. Direct measurement of GFR is the most reliable estimate of the amount of residual kidney function but is more expensive and technically demanding.

### Cardiovascular Clinical Management

#### Medical (Noninvasive) Management of Diabetic Patients With Clinical CVD

Compelling evidence, including data from recent clinical trials, demonstrates that comprehensive medical intervention in patients with established atherosclerotic CVD has the

**TABLE 5. Guide to Comprehensive Risk Reduction for Patients With Coronary and Other Vascular Disease Who Have Diabetes**

Risk Intervention	Recommendations				
Smoking Goal: complete cessation	Strongly encourage patient and family to stop smoking Provide counseling, nicotine replacement, and formal cessation programs as appropriate				
Blood pressure control  Goal: ≤135/85 mm Hg	Initiate lifestyle modification—weight control, physical activity, alcohol moderation, and moderate sodium restriction—in all patients with blood pressure >135 mm Hg systolic or 85 mm Hg diastolic  Add blood pressure medication, individualized to other patient requirements and characteristics (ie, age, race, need for drugs with specific benefits) if blood pressure is not <140 mm Hg systolic or <90 mm Hg diastolic in 3 months or if initial blood pressure is >160 mm Hg systolic or >100 mm Hg diastolic				
Lipid management Primary goal: LDL≤100 mg/dL  Secondary goals: HDL>35 mg/dL; TG<200 mg/dL	Start AHA Step II Diet in all patients: ≤30% fat, <7% saturated fat, <200 mg/d cholesterol				
	Assess fasting lipid profile. Immediately start cholesterol-lowering drugs when baseline LDL>130 mg/dL				
	LDL<100 mg/dL No drug therapy	LDL 100 to 129 mg/dL Consider adding drug therapy to diet, as follows		LDL≥130 mg/dL Add drug therapy to diet, as follows	HDL<35 mg/dL Emphasize weight management and physical activity Advise smoking cessation
		Suggested drug therapy			
		TG<200 mg/dL	TG 200 to 400 mg/dL	TG>400 mg/dL	
±	Statin Resin	Statin Fibrate	Consider combined drug therapy (statin+fibrate)		
Glucose control Goal: near normal fasting glucose Goal: HbA1c≤1% above normal	First-step therapy: weight reduction and exercise  Second-step therapy: oral hypoglycemic agents (sulfonylureas and/or metformin; ancillary: acarbose, glitazone)  Third-step therapy: insulin therapy				
Physical activity: Goal: minimum goal 30 minutes 3 to 4 times per week	Assess risk, preferably with exercise test, to guide prescription Encourage minimum of 30 to 60 minutes of moderate-intensity activity 3 or 4 times weekly (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, using stairs, gardening, household work) Maximum benefit 5 to 6 hours a week Advise medically supervised programs for moderate- to high-risk patients				
Weight management	Start intensive dietary therapy and appropriate physical activity, as outlined above, in patients whose BMI is ≥25 kg/m <sup>2</sup> Particularly emphasize need for weight loss in patients with hypertension, elevated triglycerides, or elevated glucose levels				
Antiplatelet agents/ anticoagulants	Start aspirin 80 to 325 mg/d if not contraindicated  Manage warfarin to international normalized ratio 2 to 3.5 for post-MI patients not able to take aspirin				
ACE inhibitors in post-MI patients	Start early post-MI in stable high-risk patients (anterior MI, previous MI, Killip class II [S <sub>3</sub> gallop, rales, radiographic congestive heart failure]) Continue indefinitely for all with LV dysfunction (ejection fraction ≤40%) or symptoms of failure Use as needed to manage blood pressure or symptoms in all other patients				
β-Blockers	Start in high-risk post-MI patients (arrhythmia, LV dysfunction, inducible ischemia) at 5 to 28 days. Continue 6 months minimum. Observe usual contraindications. Appropriate use of β-blockers not contraindicated in patients with diabetes Use as needed to manage angina, rhythm, or blood pressure in all other patients				
Estrogen	Observational studies (but not clinical trials) suggest benefit. Limited data in diabetic women Individualize recommendation consistent with other health risks				

TG indicates triglycerides; MI, myocardial infarction; and LV, left ventricular.

following benefits: it extends overall survival; improves quality of life; decreases the need for intervention procedures, such as angioplasty and coronary artery bypass graft surgery; and reduces the incidence of subsequent myocardial infarction.<sup>103</sup> In many patients with CHD, aggressive risk reduction with medical therapy will delay or eliminate the need for revascularization procedures. Treatment of risk factors in patients with established CHD or other clinical atherosclerotic disease has been called secondary prevention. Although the number of patients with diabetes included in clinical trials has been limited, the available results suggest that these patients respond to secondary prevention interventions at least as well as those without diabetes.<sup>86–90</sup> Consequently, the general guidelines for noninvasive, medical management in secondary prevention can be applied when patients with diabetes have clinical atherosclerotic CVD. Table 5 summarizes the AHA/ACC guide<sup>103</sup> to comprehensive risk reduction in patients with clinical coronary and other vascular disease, as modified for CVD patients with diabetes.

A few general comments can be made about application of these guidelines to patients with diabetes. Because cigarette smoking remains a powerful risk factor in patients with diabetes, a major effort must be made to overcome the smoking habit. The AHA has recently published practical guidelines for assisting patients in smoking cessation.<sup>104</sup> For lipid management, the primary goal of therapy is to reduce LDL-cholesterol levels to  $\leq 100$  mg/dL.<sup>103</sup> This goal should be achieved by addition of drug therapy (when necessary) to maximal dietary therapy. Statins are first-line therapy to achieve an LDL cholesterol of  $\leq 100$  mg/dL. When triglycerides remain  $>200$  mg/dL in patients receiving statin therapy, consideration should be given to adding a fibrate to achieve the secondary goal of lipid management, ie, a triglyceride  $<200$  mg/dL. Although nicotinic acid effectively lowers triglycerides and raises HDL levels in patients with type 2 diabetes, its tendency to worsen hyperglycemia causes it to be relatively contraindicated. The goal of blood pressure control is to reduce blood pressure to  $<135/85$  mm Hg in hypertensive patients<sup>105</sup>; this goal often will require antihypertensive drug therapy.

Treatment of hyperglycemia is stepwise and typically dependent on duration of disease. To prevent microangiopathy, neuropathy, and perhaps macrovascular disease, a prudent therapeutic goal is to reduce the glycohemoglobin to  $\leq 1\%$  above the upper limit of normal.<sup>39,106</sup> Weight loss and increased exercise are first-line therapy for reducing hyperglycemia. If hyperglycemia persists, a sulfonylurea or metformin can be used next. The recent UK Prospective Diabetes Study<sup>39</sup> revealed the safety and efficacy of sulfonylureas in control of hyperglycemia in diabetic patients. Metformin also proved efficacious, although an apparent increase in death rates on the combination of metformin and sulfonylureas calls for more study on the safety of this combination.<sup>107</sup>

Another promising group of agents for treatment of type 2 diabetes includes the thiazolidenediones. These agents lower glucose levels by reducing insulin resistance. The first drug in this class to be approved for clinical use was troglitazone. This agent is approved for use in combination with insulin therapy to improve glycemic control. Unfortunately, troglita-

**TABLE 6. Management of Diabetic Nephropathy**

Control of hyperglycemia
Slows progression of proteinuria and nephropathy
Treatment of hypertension
Blood pressure reduction slows progression of nephropathy
Maintain blood pressure at $<130/85$ mm Hg
ACE inhibitors preferred antihypertensive agent
ACE inhibitors
Probably slow progression of nephropathy even in normotensive patients
Carry danger of hyperkalemia (in patients with type 4 renal tubular acidosis or hyporenin/hypoaldosteronism)
Sodium restriction
Reduces blood pressure (which slows progression of nephropathy)
Dietary protein restriction
Slows progression of nephropathy
Adjust diet to $0.8 \text{ g protein} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ (add 1 g dietary protein for each 1 g proteinuria $>5$ g/d)

zone produces rare but severe liver toxicity<sup>108–110</sup>; the possibility of this adverse reaction requires close monitoring of patients. Nonetheless, despite its potential hepatotoxicity, troglitazone is currently being widely used to treat hyperglycemia. New drugs of the same class, rosiglitazone and pioglitazone, may have less potential hepatotoxicity. A different type of drug available for glucose control is acarbose; this agent partially blocks glucose absorption. In patients who fail to achieve glucose control and near-normal hemoglobin A1c levels by changes in life habits and oral hypoglycemic agents, insulin should be initiated.

Other risk-reduction strategies in patients with diabetes deserve attention equal to that given glucose control. Patients with type 2 diabetes should increase physical activity and eliminate excess body weight; both may be facilitated with the help of professional guidance. Antiplatelet agents have become almost routine in patients with atherosclerotic CVD, and their use can be extended to patients with diabetes who have established atherosclerotic disease.  $\beta$ -Blockers reduce cardiovascular mortality after myocardial infarction. They may be particularly effective in patients with diabetes, who are at risk for symptomatic ischemic episodes secondary to increased sympathetic activity.<sup>111</sup>  $\beta$ -Blockers are often mentioned as being contraindicated for patients with diabetes because of their blocking of hypoglycemic symptoms in the presence of a hypoglycemic regimen. Clinicians should be aware of this potential danger, although this side effect need not preclude use of  $\beta$ -blockers when CHD patients have diabetes. Angiotensin-converting enzyme (ACE) inhibitors are widely prescribed in the post-myocardial infarction period to favorably influence myocardial remodeling and fibrosis, and they should be continued indefinitely in all patients with reduced left ventricular ejection fraction or symptoms of heart failure. Unfortunately, limited data are available on use of estrogen replacement therapy in postmenopausal women with diabetes; a recent clinical trial calls into question its putative benefit in postmenopausal, nondiabetic women with established CHD.<sup>112</sup>



**TABLE 7. Guide to Primary Prevention of Cardiovascular Diseases in Patients With Diabetes**

Risk Intervention	Recommendations			
Smoking  Goal: complete cessation	Ask about smoking status as part of routine evaluation. Reinforce nonsmoking status Strongly encourage patient and family to stop smoking Provide counseling, nicotine replacement, and formal cessation programs as appropriate			
Blood pressure control  Goal: <130/85 mm Hg	Measure blood pressure at each visit. Consider home blood pressure monitoring  Promote lifestyle modification: weight control, physical activity, moderation in alcohol, moderate sodium restriction  Consider blood pressure medication: If blood pressure ≥140/90 mm Hg after 3 months of life habit modification or if initial blood pressure >160/100 mm Hg: individualize therapy to patient's other requirements and characteristics			
Cholesterol management  Primary goal: LDL <130 mg/dL  (Some authorities recommend LDL ≤100 mg/dL for diabetic patients with multiple risk factors)  Rule out secondary causes of high LDL (liver function tests, thyroid function tests, urinalysis)  Secondary goals: HDL >35 mg/dL; TG <200 mg/dL	Ask about dietary habits as part of routine evaluation Measure total and HDL cholesterol and TG; estimate LDL			
	Start AHA Step II Diet (≤30% fat, <7% saturated fat, <200 mg/dL cholesterol) and weight control		Risk factors to consider for more aggressive LDL-lowering therapy, ie, LDL goal ≤100 mg/dL: age (men ≥45 y, women ≥55 y or postmenopausal), hypertension, diabetes, smoking, HDL <35 mg/dL, family history of CHD in first-degree relatives (in male relatives <55 y, female relatives <65 y)	
	Consider adding drug therapy to diet therapy for LDL levels >130 mg/dL			
	Suggested drug therapy for LDL levels >130 mg/dL (drug selection priority modified according to TG level)		HDL<35 mg/dL: Emphasize weight management and physical activity, avoidance of cigarette smoking	
	TG<200 mg/dL	TG 200–400 mg/dL		TG>400 mg/dL
	Statin Resin	Statin ±Fibrate		Consider combined drug therapy (statin+fibrate)
	If LDL goal not achieved, consider combination drug therapy			
Glucose control  Near normal fasting glucose  HbA1c≤1% above normal	First-step therapy: weight reduction and exercise Second-step therapy: oral hypoglycemic agents (sulfonylureas and/or metformin; ancillary: acarbose, glitazone)  Third-step therapy: insulin therapy			
Antiplatelet agents	Some authorities recommend aspirin 80 to 325 mg/d if not contraindicated for primary prevention in high-risk diabetic patients			
Physical activity  Goal: Increase amount; exercise regularly 3–4 times per week for 30 minutes	Ask about physical activity status and exercise habits as part of routine evaluation Encourage 30 minutes of moderate-intensity exercise 3 to 4 times per week as well as increased physical activity in daily life habits for persons who are inactive Encourage regular exercise to improve conditioning and optimize fitness level Advise medically supervised programs for those with low functional capacity and/or comorbidities Promote environmental factors conducive to health (ie, golf courses that permit walking)			
Weight management  Goal: Achieve and maintain desirable BMI and waist circumference	Measure patient's weight and height, BMI, and waist circumference at each visit as part of routine evaluation Desirable BMI range: 21 to 25 kg/m². Desirable waist circumference for men <102 cm and women <88 cm. Start weight management and physical activity as appropriate.			
Estrogens	Consider estrogen replacement therapy in postmenopausal women, especially those with multiple CHD risk factors, such as elevated LDL; efficacy for CVD risk reduction in diabetic women not proved  Individualize estrogen replacement therapy recommendation consistent with other health risks			

TG indicates triglycerides; BMI, body mass index.

## Management of Diabetic Nephropathy

More than one strategy has been shown to slow the progression of nephropathy in patients with diabetes. A general approach is outlined in Table 6. Specific interventions include control of hyperglycemia, treatment of hypertension (particularly by use of ACE inhibitors), sodium restriction, and dietary protein restriction. Treatment of hypertension with ACE inhibitors can retard the progression of diabetic nephropathy. ACE inhibitors in fact may have favorable effects on nephropathy even in the absence of hypertension, although it is uncertain whether normotensive patients should use them clinically for this purpose.

## Invasive Management of Coronary Artery Disease

Recent studies<sup>113–116</sup> indicate that coronary angioplasty is less efficacious for patients with diabetes than for those without; these reports further reveal that coronary artery bypass surgery is the preferred therapy in patients with diabetes when invasive management is required. Most of the benefit from coronary bypass grafting seems to result from use of the internal mammary artery. Thus, at present, the preferred invasive approach for coronary revascularization in patients with diabetes is use of internal mammary arteries with bypass grafting. Extensive data are not yet available with use of coronary stents in patients with diabetes, but regardless, bypass grafting seems to be preferred.

## Primary Prevention

Type 2 diabetes can be viewed as the end product of years of metabolic stress accompanying a state of insulin resistance. It seems that in patients with insulin resistance, the “clock starts ticking” for acceleration of atherogenesis long before the onset of hyperglycemia.<sup>11</sup> Thus, early detection of the risk factors associated with the metabolic syndrome is needed for institution of appropriate primary prevention measures in patients at risk for diabetes. Clinical evidence of insulin resistance includes abdominal obesity (or borderline abdominal obesity), high-normal blood pressure (or mild hypertension), high-normal triglycerides (150 to 250 mg/dL), reduced HDL cholesterol (<40 mg/dL in men; <50 mg/dL in women), borderline high-risk LDL cholesterol (130 to 159 mg/dL), and in some patients, IFG (110 to 126 mg/dL). The detection of IFG seems particularly significant; it usually signifies long-standing insulin resistance and is a strong risk factor for type 2 diabetes. The AHA has recently published a guide to primary prevention of CVD.<sup>117</sup> This guide integrates well with efforts for early detection of the metabolic syndrome, and it recommends interventions to reduce the risk for CVD for patients without established CVD. If these guidelines are followed, they probably would delay the onset of type 2 diabetes as well as reducing risk for CVD. The American Diabetes Association likewise has recently updated its recommendations for management and risk reduction in patients with diabetes.<sup>118</sup>

## Primary Prevention of CVD in Diabetic Patients

The guide outlined for primary prevention of CVD is expanded to include diabetic patients in Table 7. Goals for smoking cessation, blood pressure control, physical activity, and weight management are the same as for nondiabetic

patients. However, more aggressive management of cholesterol and other lipids is indicated for diabetic patients, as discussed by the recent American Diabetes Association reports.<sup>118–120</sup> Treatment of hyperglycemia should follow the same regimen as discussed under secondary prevention.

## Implications for Treatment of Patients With Type I Diabetes

The predominant risk factor for CHD in patients with type 1 diabetes is duration of disease. Nonetheless, smoking, hypertension, renal disease (macroalbuminuria and renal insufficiency), and dyslipidemia remain important. Effective treatment of hyperglycemia reduces microvascular complications of type 1 diabetes.<sup>106</sup> It also may reduce risk for macrovascular disease.<sup>106</sup> Modification of other CVD risk factors almost certainly will reduce risk. This would include not only tobacco avoidance but also maintenance of blood pressures <130/85 mm Hg, screening for microalbuminuria, and reducing triglycerides to at least <200 mg/dL and perhaps lower. The optimal LDL-cholesterol level in patients with diabetes is ≤100 mg/dL; however, use of cholesterol-lowering drugs to achieve this goal in younger patients with type 1 diabetes may not be appropriate. Aspirin also can be administered in patients who have long-standing type 1 diabetes and in whom goals for glycohemoglobin are not achieved.

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KEY WORDS: AHA Scientific Statements ■ diabetes mellitus ■ risk factors ■ cardiovascular diseases

## Diabetes and Cardiovascular Disease: A Statement for Healthcare Professionals From the American Heart Association

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