Primary Prevention of Cardiovascular Diseases in People With Diabetes Mellitus: A Scientific Statement From the American Heart Association and the American Diabetes Association

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AHA/ADA Scientific Statement

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A Scientific Statement From the American Heart Association and the American Diabetes Association

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***Abstract*—**The American Heart Association (AHA) and the American Diabetes Association (ADA) have each published guidelines for cardiovascular disease prevention: The ADA has issued separate recommendations for each of the cardiovascular risk factors in patients with diabetes, and the AHA has shaped primary and secondary guidelines that extend to patients with diabetes. This statement will attempt to harmonize the recommendations of both organizations where possible but will recognize areas in which AHA and ADA recommendations differ. **(*Circulation.* 2007;115:114-126.)**

Key Words: AHA Scientific Statement ■ cardiovascular diseases ■ diabetes mellitus ■ primary prevention

Diabetes mellitus is a disease defined by abnormalities of fasting or postprandial glucose and frequently is associated with disorders of the eyes, kidneys, nerves, and circulatory system. Circulatory disorders associated with diabetes include coronary heart disease (CHD), stroke, peripheral arterial disease, cardiomyopathy, and congestive heart failure. Diabetes generally results in early death from cardiovascular diseases (CVDs). In 1999, the American Diabetes Association (ADA) and the American Heart Association (AHA) published a joint statement with the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Foundation International indicating the need for multiorganizational cooperation for prevention of CVD in patients with diabetes.[1] The present statement represents a joint response of the ADA and AHA to this challenge.

The ADA and AHA each have published guidelines for CVD prevention that overlap with the present statement: The ADA has issued separate recommendations for each of the cardiovascular risk factors in patients with diabetes, and the AHA has shaped primary and secondary guidelines that extend to patients with diabetes. The present document will attempt to harmonize the recommendations of both organizations where possible but will recognize areas in which ADA and AHA recommendations differ.

Clear clinical trial evidence published over the past decade suggests that broad-based treatment of dyslipidemia, hypertension, and hypercoagulability (as well as interventional cardiology and cardiovascular surgery during the acute coronary syndrome[2]) can improve the event-free survival rate in people with diabetes who already have clinical CVD. However, a much smaller body of clinical trial data addresses the issue of primary prevention of CVD in patients with diabetes and no known CVD. This is a critical issue because patients with diabetes have twice the risk of incident myocardial infarction and stroke as that of the general population. Furthermore, large numbers of people with diabetes do not survive their first event, and if they do survive, their mortality

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rate over the subsequent months to years is generally greater than that of the general population. As many as 80% of patients with type 2 diabetes mellitus will develop and possibly die of macrovascular disease. This represents a great societal cost, with major loss of life expectancy and quality of life.[3,4] Although the incidence of CVD events in patients with diabetes seems to have declined over the past decade,[5] implementation of preventive strategies is often inadequate.[6]

To facilitate clinical practice, the present statement is condensed into essential recommendations. No endeavor is made to recapitulate all of the clinical trial evidence that is thoroughly documented in the ADA and AHA reports on management of individual risk factors. For each of the risk factors, a sampling of relevant studies is discussed and referenced. Recommendations are made on the totality of evidence in the field, including studies of several types, such as controlled clinical trials (Table 1). When possible, studies under way that will further address these issues are also noted. With the exception of recommendations related to control of hyperglycemia, the recommendations provided in this document are appropriate for people both with and without diabetes; however, because of their higher risk for CVD, people with diabetes should derive even more benefit from these recommendations.

Comprehensive Risk Assessment

Recent guidelines for CVD management in diabetes are based on the premise that most patients with diabetes are at high risk for future CVD events. When diabetes exists in patients with established CVD, absolute risk for future events is very high. Even in the absence of CVD, both the ADA and the AHA identify diabetes as a high-risk condition for macrovascular CVD.[7,8] This conclusion was based on several factors, including a relatively high 10-year risk for CVD events, increased morbidity after the onset of CVD, and a high long-term risk for developing CVD.[9] For these reasons and to simplify the assessment of risk, the NHLBI Adult Treatment Panel III (ATP III) designated diabetes as a "CVD risk equivalent" for setting treatment goals for low-density lipoprotein cholesterol (LDL-C).[7,10] The same general strategy for LDL lowering is recommended by the ADA[8] and the British Hypertension Society guidelines.[11] This approach has also been applied to treatment of hypertension by both the ADA and the NHLBI.[12]

Nonetheless, it is widely recognized that absolute risk for macrovascular CVD varies among individuals with diabetes, and an accurate assessment of risk clearly depends on the individuals' characteristics.[13–18] Indeed, it seems self-evident that some patients, such as children and young adults with recent-onset diabetes, are at relatively low risk of CVD over an intermediate time frame (eg, 10 years). For this reason, some investigators favor individualizing risk assessment on the basis of risk-prediction algorithms to provide more appropriate risk factor interventions than those recommended by general guidelines that are geared toward middle-aged and older individuals with type 2 diabetes mellitus. Three such risk calculators are the Framingham risk calculator (available at http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof),[19] the UK Prospective Diabetes Study (UKPDS) risk engine (available for download at http://www.dtu.ox.ac.uk/riskengine),[20] and the ADA's Diabetes PHD (Personal Health Decisions; available at http://diabetes.org/diabetesPHD), which has been extensively validated against clinical trials.[21] It is important to realize that unresolved issues still exist relating to the assessment of risk in many people with diabetes mellitus. For example, the AHA and the NHLBI have issued a statement on management of the metabolic syndrome and maintain that with regard to risk for CVD, the metabolic syndrome and type 2 diabetes mellitus can coexist in one person.[22] The ADA, in contrast, contends that once type 2 diabetes mellitus is present, the metabolic syndrome no longer pertains because CVD risk factors characteristic of the metabolic syndrome are largely subsumed in the type 2 diabetes mellitus syndrome.[23]

Lifestyle Management

Lifestyle measures such as medical nutrition therapy and aerobic exercise have been demonstrated to modify lipids and reduce blood pressure and are integral to the management of glycemia and weight control.[24,25] Numerous epidemiological analyses suggest that nutrition and physical activity are predictors of age-specific mortality and cardiovascular event rates. Although lifestyle intervention in patients with type 2 diabetes mellitus has traditionally focused almost exclusively on weight loss, most experts in the field today believe the major focus of lifestyle intervention should be on improving glycemic control and controlling other major CVD risk factors. Weight control remains an important component of lifestyle management. Reeducation of the patient about food selection and the importance of regular physical activity, combined with regular reevaluation and behavioral interventions to maintain adherence, may be the most successful approach to improve long-term outcomes.[22,24] To date, short-term studies of medical nutrition therapy,[7,24] physical activity, and comprehensive lifestyle approaches have been shown to improve the control of risk factors and intermediate markers of CVD risk.

Weight

Weight reduction in obese persons will reduce all of the CVD risk factors associated with type 2 diabetes mellitus and will improve hyperglycemia. Moderate weight loss (eg, 7% to 10% of body weight in 1 year) is often attainable, whereas efforts to achieve ideal body weight in short periods of time usually fail. Even if no weight reduction can be achieved, weight maintenance is certainly preferable to weight gain. Diets low in carbohydrate (and therefore high in fat) may be associated with greater weight loss in the short term but have not been demonstrated to result in greater weight loss after 1 year than diets with more balanced proportions of fats and carbohydrates.[26,27]

No long-term, large-scale study of lifestyle intervention or intentional weight loss has been adequately powered to examine CVD end points in individuals with diabetes mellitus. In the Look AHEAD (Action for Health in Diabetes) study, patients with type 2 diabetes mellitus with a body mass index $\geq$25 kg/m^2 have been randomized to an intensive weight loss program (calorie restriction and physical activity) or to diabetes support and education and are being followed

TABLE 1. Recommendations for Primary Prevention of CVD in People With Diabetes

Lifestyle management

Weight

Structured programs that emphasize lifestyle changes such as reduced fat (<30% of daily energy) and total energy intake and increased regular physical activity, along with regular participant contact, can produce long-term weight loss on the order of 5% to 7% of starting weight, with improvement in blood pressure.

For individuals with elevated plasma triglycerides and reduced HDL-C, improved glycemic control, moderate weight loss (5% to 7% of starting weight), dietary saturated fat restriction, increased physical activity, and modest replacement of dietary carbohydrate (5% to 7%) by either monounsaturated or polyunsaturated fats may be beneficial.

Medical nutrition therapy

To achieve reductions in LDL-C:

Saturated fats should be <7% of energy intake

Dietary cholesterol intake should be <200 mg/d.

Intake of *trans*-unsaturated fatty acids should be <1% of energy intake.

Total energy intake should be adjusted to achieve body-weight goals.

Total dietary fat intake should be moderated (25% to 35% of total calories) and should consist mainly of monounsaturated or polyunsaturated fat.

Ample intake of dietary fiber (≥14 g per 1000 calories consumed) may be of benefit.

If individuals choose to drink alcohol, daily intake should be limited to 1 drink for adult women and 2 drinks for adult men. One drink is defined as a 12-oz beer, a 4-oz glass of wine, or a 1.5-oz glass of distilled spirits. Alcohol ingestion increases caloric intake and should be minimized when weight loss is the goal. Individuals with elevated plasma triglyceride levels should limit alcohol intake, because intake may exacerbate hypertriglyceridemia.

In both normotensive and hypertensive individuals, a reduction in sodium intake may lower blood pressure. The goal should be to reduce sodium intake to 1200 to 2300 mg/d (50 to 100 mmol/d), equivalent to 3000 to 6000 mg/d of sodium chloride.

Physical activity

To improve glycemic control, assist with weight loss or maintenance, and reduce risk of CVD, at least 150 minutes of moderate-intensity aerobic physical activity or at least 90 minutes of vigorous aerobic exercise per week is recommended. The physical activity should be distributed over at least 3 days per week, with no more than 2 consecutive days without physical activity.

For long-term maintenance of major weight loss, a larger amount of exercise (7 hours of moderate or vigorous aerobic physical activity per week) may be helpful.

Blood pressure

Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg should have blood pressure confirmed on a separate day.

Patients with diabetes should be treated to a systolic blood pressure <130 mm Hg and a diastolic blood pressure <80 mm Hg.

Patients with a systolic blood pressure of 130 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg should initiate lifestyle modification alone (weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products) for a maximum of 3 months. If, after these efforts, targets are not achieved, treatment with pharmacological agents should be initiated.

Patients with hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) should receive drug therapy in addition to lifestyle and behavioral therapy.

All patients with diabetes and hypertension should be treated with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. Other drug classes demonstrated to reduce CVD events in patients with diabetes (β-blockers, thiazide diuretics, and calcium channel blockers) should be added as needed to achieve blood pressure targets.

If ACE inhibitors, ARBs, or diuretics are used, renal function and serum potassium levels should be monitored within the first 3 months. If stable, follow-up could occur every 6 months thereafter.

Multiple-drug therapy is generally required to achieve blood pressure targets.

In elderly hypertensive patients, blood pressure should be lowered gradually to avoid complications.

Orthostatic measurement of blood pressure should be performed in people with diabetes and hypertension when clinically indicated.

Patients not achieving target blood pressure despite multiple-drug therapy should be referred to a physician specializing in the care of patients with hypertension.

Lipids

In adult patients, lipid levels should be measured at least annually and more often if needed to achieve goals. In adults under the age of 40 years with low-risk lipid values (LDL-C <100 mg/dL, HDL-C >50 mg/dL, and triglycerides <150 mg/dL), lipid assessments may be repeated every 2 years.

Lifestyle modification deserves primary emphasis in all diabetic individuals. Patients should focus on the reduction of saturated fat and cholesterol intake, weight loss (if indicated), and increases in dietary fiber and physical activity. These lifestyle changes have been shown to improve the lipid profile in patients with diabetes.

In individuals with diabetes who are over the age of 40 years, without overt CVD, but with 1 or more major CVD risk factors, the primary goal is an LDL-C level <100 mg/dL (2.6 mmol/L). If LDL-lowering drugs are used, a reduction of at least 30% to 40% in LDL-C levels should be obtained. If baseline LDL-C is <100 mg/dL, statin therapy should be initiated based on risk factor assessment and clinical judgment. Major risk factors in this category include cigarette smoking, hypertension (blood pressure >140/90 mm Hg or use of antihypertensive medication), low HDL cholesterol (<40 mg/dL), and family history of premature CHD (CHD in male first-degree relative ≤55 years of age; CHD in female first-degree relative ≤65 years of age).

In individuals with diabetes who are under the age of 40 years, without overt CVD, but who are estimated to be at increased risk of CVD either by clinical judgment or by risk calculator, the LDL-C goal is <100 mg/dL, and LDL-lowering drugs should be considered if lifestyle changes do not achieve the goal.

The ADA and AHA suggest different approaches to the management of HDL- and triglyceride-associated CVD risk.

TABLE 1. Continued

The AHA suggests that in patients with triglyceride levels of 200 to 499 mg/dL, a non–HDL-C (total cholesterol minus HDL-C) goal of ≤130 mg/dL is a secondary target. If triglycerides are ≥500 mg/dL, therapeutic options include fibrate or niacin before LDL-lowering therapy and treatment of LDL-C to goal after triglyceride-lowering therapy. A non–HDL-C level ≤130 mg/dL should be achieved if possible.
The ADA suggests lowering triglycerides to <150 mg/dL (1.7 mmol/L) and raising HDL-C to >40 mg/dL (1.15 mmol/L). In women, an HDL goal 10 mg/dL higher (>50 mg/dL) should be considered.
Combination therapy of LDL-lowering drugs (eg, statins) and fibrates or niacin may be necessary to achieve lipid targets, but this has not been evaluated in outcomes studies for either CVD event reduction or safety.
Tobacco
All patients with diabetes should be asked about tobacco use status at every visit.
Every tobacco user should be advised to quit.
The tobacco user's willingness to quit should be assessed.
The patient can be assisted by counseling and by developing a plan to quit.
Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion) should be incorporated as needed.
Antiplatelet agents
Aspirin therapy (75 to 162 mg/d) should be recommended as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those who are >40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).
People with aspirin allergy, bleeding tendency, existing anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease are not candidates for aspirin therapy. Other antiplatelet agents may be a reasonable alternative for patients with high risk.
Aspirin therapy should not be recommended for patients under the age of 21 years because of the increased risk of Reye's syndrome associated with aspirin use in this population. People under the age of 30 years have not been studied.
Glycemic control
The A1c goal for patients in general is <7%.
The A1c goal for the individual patient is an A1c as close to normal (<6%) as possible, without causing significant hypoglycemia.
Type 1 diabetes mellitus
At the present time, all of the recommendations listed above for patients with type 2 diabetes mellitus appear appropriate for those with type 1 diabetes as well.

up to determine the effect of these interventions on CVD events.[28]

Medical Nutrition Therapy

Although numerous studies have attempted to identify the optimal combination of macronutrients to prevent CVD, it is unlikely that any one such combination of macronutrients exists. The best mix of carbohydrate, protein, and fat seems to vary according to individual circumstances. The cardiovascular efficacy and safety of low- or moderately low-carbohydrate diets in diabetes have not been well studied. Very-low-carbohydrate diets (eg, those that restrict carbohydrate intake to <130 g/d) are not recommended for patients with diabetes because ample intake of fruits, vegetables, grains, legumes, and low-fat dairy products provides vitamins, minerals, fiber, and protein. In the general population, studies of a variety of medical nutrition therapy techniques to reduce blood pressure have focused on weight loss, sodium restriction, reduction of alcohol intake, and an increase in the intake of potassium and calcium. For example, the Dietary Approaches to Stop Hypertension (DASH) diet, which encourages the intake of fruits, vegetables, and low-fat dairy products, particularly when those foods are combined with sodium restriction, was associated with substantial improvements in blood pressure.[29] The restriction of saturated fats, dietary cholesterol, and *trans*-unsaturated fats and the incorporation of increased dietary fiber and monounsaturated and polyunsaturated fats into the diet are recommended dietary strategies to improve lipids.[7] Overall, the AHA diet and lifestyle recommendations,[30] the therapeutic lifestyle changes suggested by the National Cholesterol Education Program's ATP III,[7] and the ADA nutrition guidelines[8] address all of these issues.

Supplementation of a healthy diet with antioxidant vitamins, B vitamins to lower homocysteine, or specific fatty acids (such as omega-3 fatty acids) is not recommended by either the AHA[30] or the ADA at this time for healthy persons.[8] Although each of these has been demonstrated to be associated with lower CVD risk in published epidemiological analyses, no consistent findings have emerged from large-scale, randomized trials in people with diabetes.[30–33] Of all the supplements, the strongest data for benefit are with omega-3 fatty acids in individuals with established CHD. For this reason, the AHA currently recommends 1 g/d eicosapentaenoic acid + docosahexaenoic acid for individuals with established disease.[34,35] On the other hand, randomized trials of vitamin E, folate, and B vitamins, as well as other antioxidants such as beta-carotene or antioxidant cocktails, have not shown benefit.[36,37]

Physical Activity

To improve glycemic control, assist with weight maintenance, and reduce the risk of CVD (on the basis of epidemiological studies), at least 150 minutes of moderate-intensity aerobic physical activity per week or at least 90 minutes of vigorous aerobic exercise per week is recommended. Thus, patients with diabetes should be encouraged to perform 30 to 60 minutes of moderate-intensity aerobic activity such as brisk walking on most (preferably all) days of the week, supplemented by an increase in daily lifestyle activities (eg,

walking breaks during the workday, gardening, and household work). For long-term maintenance of major weight loss, a larger amount of exercise (a minimum of 7 hours of moderate or vigorous aerobic physical activity per week) is helpful.

Before beginning a program of physical activity that is more vigorous than brisk walking, people with diabetes should be assessed for conditions that might contraindicate certain types of exercise or predispose to injury (eg, severe autonomic neuropathy, severe peripheral neuropathy, preproliferative or proliferative retinopathy). One potential area of controversy is the circumstance under which a graded exercise electrocardiogram stress test is indicated. Unfortunately, no randomized trials or large cohort studies have evaluated the utility of exercise stress testing specifically in people with diabetes. Moreover, if cardiac stress imaging is performed, it is difficult to identify which individuals with diabetes are at low risk.[38] The low predictive value of a negative stress test in those with diabetes confirms the need to treat risk factors for atherosclerosis intensively regardless of the results of exercise testing and indicates that patients with diabetes require close follow-up, with a lower threshold for proceeding to angiography than patients without diabetes. Indeed, those patients with diabetes who are unable to exercise are at the greatest risk of CHD events, and in some analyses, the most important prognostic variables for CVD and all-cause death were not exercise ECG changes but fitness-related variables such as exercise duration and heart rate recovery.[39,40] Because of these uncertainties, the decision to perform stress testing for patients beginning a vigorous exercise program must be made on an individual basis.

Recommendations for Lifestyle Intervention for Primary Prevention of CVD

Weight Management

- Structured programs that emphasize lifestyle changes such as reduced fat (<30% of daily energy) and total energy intake and increased regular physical activity, along with regular participant contact, can produce long-term weight loss on the order of 5% to 7% of starting weight, with an improvement in blood pressure.
- For individuals with elevated plasma triglycerides and reduced high-density lipoprotein cholesterol (HDL-C), improved glycemic control, moderate weight loss (5% to 7% of starting weight), dietary saturated fat restriction, increased physical activity, and modest replacement of dietary carbohydrate (5% to 7%) by either monounsaturated or polyunsaturated fats may be beneficial.

Medical Nutrition Therapy

- To achieve reductions in LDL-C, saturated fats should be <7% of energy intake, dietary cholesterol intake should be <200 mg/d, and intake of *trans*-unsaturated fatty acids should be <1% of energy intake.
- Total energy intake should be adjusted to achieve body-weight goals.
- Total dietary fat intake should be moderated (25% to 35% of total calories) and should consist mainly of monounsaturated or polyunsaturated fat.
- Ample intake of dietary fiber (≥14 g per 1000 calories consumed) may be of benefit.
- If individuals choose to drink alcohol, daily intake should be limited to 1 drink for adult women and 2 drinks for adult men. One drink is defined as a 12-oz beer, a 4-oz glass of wine, or a 1.5-oz glass of distilled spirits. Alcohol ingestion increases caloric intake and should be minimized when weight loss is the goal. Individuals with elevated plasma triglyceride levels should limit alcohol intake because intake may exacerbate hypertriglyceridemia. Alcohol ingestion can also increase blood pressure.
- In both normotensive and hypertensive individuals, a reduction in sodium intake may lower blood pressure. The goal should be to reduce sodium intake to 1200 to 2300 mg/d (50 to 100 mmol/d), equivalent to 3000 to 6000 mg/d of sodium chloride.

Physical Activity

- To improve glycemic control, assist with weight loss or maintenance, and reduce risk of CVD, at least 150 minutes of moderate-intensity aerobic physical activity or at least 90 minutes of vigorous aerobic exercise per week is recommended. The physical activity should be distributed over at least 3 days per week, with no more than 2 consecutive days without physical activity.
- For long-term maintenance of major weight loss, a larger amount of exercise (7 hours of moderate or vigorous aerobic physical activity per week) may be helpful.

Blood Pressure

Epidemiological analyses and randomized clinical trials have demonstrated the impact of elevated blood pressure as a risk factor for both microvascular and macrovascular disease in diabetes. As a result, many have argued that blood pressure management is the most critical aspect of the care of the patient with diabetes. Epidemiological analyses show that higher risk for cardiovascular events and mortality starts at a blood pressure >115/75 mm Hg in the general population and doubles for every 20-mm Hg systolic or 10-mm Hg diastolic increase.[41] However, the question of what systolic and diastolic blood pressure goals should be targeted is not completely answered by currently available outcome trials.

The Hypertension Optimal Treatment trial[42] randomized patients with diastolic blood pressure of 100 to 115 mm Hg to diastolic blood pressure targets of ≤90, ≤85, and ≤80 mm Hg. Although the overall study did not demonstrate a benefit from lower diastolic blood pressure targets, a post hoc analysis of subjects with diabetes did demonstrate a significant decline in the rate of major cardiovascular events with lower diastolic blood pressure targets. In the group randomized to a diastolic target of ≤80 mm Hg, the risk of major cardiovascular events was halved compared with the group with a target of ≤90 mm Hg.[42] For patients with diabetes, it generally is agreed that the appropriate diastolic blood pressure target is ≤80 mm Hg.

Although studies similar to the Hypertension Optimal Treatment trial have not been conducted to examine specific systolic blood pressure targets, placebo-controlled studies demonstrate robustly that systolic blood pressure levels <140 mm Hg are associated with improved outcomes compared with higher levels. In the ABCD trial (Appropriate

Blood Pressure Control in Diabetes), a mean systolic blood pressure of 132 mm Hg was achieved in the more intensively treated group; however, no significant reduction in CVD end points occurred, although total mortality rate was reduced.[43] Thus, although it is unclear exactly how much the systolic blood pressure should be lowered below 140 mm Hg, various groups have recommended systolic blood pressure targets of <135 mm Hg[42] and <130 mm Hg.[8,44] The ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure study[45] will explicitly test the cardiovascular efficacy of lowering the systolic blood pressure below 140 mm Hg. It has randomized participants to 2 levels of systolic blood pressure control to determine whether a therapeutic strategy that targets a systolic blood pressure of <120 mm Hg reduces the rate of CVD events more than a strategy that targets a systolic blood pressure of <140 mm Hg.[45]

Multiple studies that have used thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), β-blockers, and calcium channel blockers have demonstrated benefits on microvascular end points and combined cardiovascular end points.[46] In general, more consistent clinical trial evidence supports the hypothesis that blood pressure should be lowered to the safest minimal level to reduce adverse CVD outcomes than the notion that there is a clear rank ordering in the effectiveness of various antihypertensive agents. However, several relatively small trials suggest that ACE inhibitors may be associated with better CVD outcomes than are dihydropyridine calcium channel blockers. Furthermore, many[46–48] but not all[49] recent studies with ACE inhibitors and ARBs suggest benefits that cannot be fully attributed to blood pressure lowering in preventing and delaying the progression of advanced diabetic kidney disease.[46,47] For these reasons, current guidelines[8] suggest that ACE inhibitors are the drugs of choice in the initial management of hypertension in people with diabetes or kidney disease.

Regardless of the initial therapy, most patients will require multiple-drug therapy for hypertension in the setting of diabetes. Thiazide diuretics, β-blockers, ACE inhibitors, ARBs, and calcium channel blockers are beneficial in reducing CVD incidence in patients with diabetes. Although ACE inhibitors and ARBs may be the preferred agents for the initial therapy of hypertension in diabetes, a low-dose thiazide diuretic generally should be one of the first 2 drugs used for management of hypertension in these patients. Calcium channel blockers and β-blockers are effective blood pressure–lowering agents and certainly should be considered as additional therapy in patients treated with ACE inhibitors or ARBs.[50]

Recommendations for Blood Pressure Control

- Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg should have blood pressure confirmed on a separate day.
- Patients with diabetes should be treated to a systolic blood pressure <130 mm Hg and a diastolic blood pressure <80 mm Hg.
- Patients with a systolic blood pressure of 130 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg should initiate lifestyle modification alone (weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products) for a maximum of 3 months. If, after these efforts, targets are not achieved, treatment with pharmacological agents should be initiated.
- Patients with hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) should receive drug therapy in addition to lifestyle and behavioral therapy.
- All patients with diabetes and hypertension should be treated with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. Other drug classes demonstrated to reduce CVD events in patients with diabetes (β-blockers, thiazide diuretics, and calcium channel blockers) should be added as needed to achieve blood pressure targets.
- If ACE inhibitors, ARBs, or diuretics are used, renal function and serum potassium levels should be monitored within the first 3 months. If levels are stable, follow-up could occur every 6 months thereafter.
- Multiple-drug therapy generally is required to achieve blood pressure targets.
- In elderly hypertensive patients, blood pressure should be lowered gradually to avoid complications.
- Orthostatic measurement of blood pressure should be performed in people with diabetes and hypertension when clinically indicated.
- Patients who do not achieve target blood pressure despite multiple-drug therapy should be referred to a physician specializing in the care of patients with hypertension.

Lipids

In patients with type 2 diabetes mellitus, triglycerides are often elevated, HDL-C is generally decreased, and LDL-C may be elevated, borderline, or normal. LDL particles are small and dense, carrying less cholesterol per particle. Thus, the LDL-C concentration may be misleading: There will be more LDL particles for any cholesterol concentration if the LDL particles are small and dense. Additionally, these small, dense LDL particles may be more atherogenic than would be suspected by their concentration alone, because in vitro and cell culture studies suggest they may be more readily oxidized and glycated.[10,51] Although an elevated LDL-C level generally is not recognized as the major lipid abnormality in patients with type 2 diabetes mellitus, clinical trials amply demonstrate that LDL-C lowering with drugs will reduce risk for major coronary events regardless of diabetes status.[52]

Elevated LDL-C is identified as the primary target of lipid-lowering therapy by both the ADA and the AHA. The focus on LDL-C is supported by results of controlled clinical trials that have shown that LDL-C lowering with statins will reduce the risk of major CVD events in patients with diabetes. For example, the Heart Protection Study and the Collaborative Atorvastatin Diabetes Study both included large numbers of patients with diabetes who were >40 years of age and had

no known vascular disease but had at least 1 major cardiovascular risk factor or evidence of retinopathy or microalbuminuria.[53,54] Subjects were randomized in a double-masked, placebo-controlled fashion to simvastatin 40 mg/d in the Heart Protection Study and atorvastatin 10 mg/d in the Collaborative Atorvastatin Diabetes Study, which produced, respectively, a 33% and 40% reduction in LDL-C associated with a 31% and 37% reduction in combined cardiovascular end points. Although these trials showed an increased absolute CHD risk associated with higher LDL-C values at baseline, the observed benefits (relative risk reduction) were independent of baseline LDL-C and other lipid values. Indeed, these results supported the epidemiological observations that the relationship between CHD risk and blood LDL-C is approximately linear when CHD is plotted on a logarithmic scale. This explains the uniform relative reduction in CHD risk seen with LDL-C reductions of 30% to 40% over a wide range of LDL-C values.

Triglyceride-rich lipoproteins, especially very-low-density lipoproteins, are often elevated in patients with diabetes, appear to be atherogenic, and represent a secondary target of lipid-lowering therapy (after the goal for LDL-C is attained). The ADA recognizes serum triglycerides as a surrogate for atherogenic triglyceride-rich lipoproteins and suggests a target of <150 mg/dL.[8] The AHA suggests an alternative approach—namely, for patients with diabetes and no clinical CVD whose triglyceride level is >200 mg/dL, the AHA recommends a non-HDL target of <130 mg/dL.[7]

The "fibrate" class of lipid-lowering drugs is useful for lowering elevated triglyceride or non–HDL-C levels; however, clinical trials of these drugs have reported mixed results. In the Helsinki Heart Study, 135 patients with diabetes and no known vascular disease were randomized to gemfibrozil 600 mg twice daily or placebo.[55] In association with a 10% reduction of LDL, a 6% increase in HDL, and a 26% reduction in triglycerides, there was a 68% relative risk reduction in coronary death and nonfatal myocardial infarction; this result did not reach statistical significance, however, because of the small number of patients.[55,56] The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial randomized 9795 people with type 2 diabetes mellitus with average total cholesterol levels (116 to 251 mg/dL) and an elevated total cholesterol–to–HDL-C ratio (>4) or triglycerides >89 mg/dL to fenofibrate or placebo.[57] In the overall population, fenofibrate treatment did not reduce the primary end point of first myocardial infarction or CHD death. Almost 80% of the FIELD population was free of clinical CVD at the start of the study, and in this prespecified subgroup, there was a 19% reduction in total cardiovascular events (CVD death, nonfatal myocardial infarction, stroke, and carotid and coronary revascularization; $P=0.004$) in the fenofibrate-treated group.[58] The effect of fenofibrate on the primary end point in subjects without prior CVD was not provided. A concern in the FIELD trial was a rise in creatinine of ≈15% overall in the group treated with fenofibrate; this was completely reversible at 6 weeks after the end of the study and the cessation of fenofibrate therapy. It is not known whether the temporary rise in creatinine over the course of the study had any adverse consequences. Additionally, when fibrates are used in combination with statins, attention must be paid to the risk for myositis and rhabdomyolysis. The ACCORD study will examine whether a fibrate combined with a statin is safe and whether together they provide CVD benefits beyond those of statin therapy alone.[45]

Although both the ADA and the AHA support efforts to raise HDL-C in high-risk patients when these levels are reduced, there is one difference in the organizations' recommendations. The ADA specifies therapeutic goals for HDL-C (>40 mg/dL, with consideration of a higher target of >50 mg/dL in women),[8] whereas the AHA advocates efforts to raise HDL-C without specifically designating goals of therapy.[7] The most effective available drug for raising HDL-C levels is nicotinic acid. Clinical trials suggest CVD risk reduction with nicotinic acid, although no trials of this drug that specifically target patients with diabetes have been performed. Furthermore, at higher doses, nicotinic acid can worsen hyperglycemia.

Recommendations for Lipid Management

- In adult patients, lipid levels should be measured at least annually and more often if needed to achieve goals. In adults under the age of 40 years with low-risk lipid values (LDL-C <100 mg/dL, HDL-C >50 mg/dL, and triglycerides <150 mg/dL), lipid assessments may be repeated every 2 years.
- Lifestyle modification deserves primary emphasis in all diabetic individuals. Patients should focus on the reduction of saturated fat and cholesterol intake, weight loss (if indicated), and increases in dietary fiber and physical activity. These lifestyle changes have been shown to improve the lipid profile in patients with diabetes.
- In individuals with diabetes who are over the age of 40 years, without overt CVD, but with 1 or more major CVD risk factors, the primary goal is an LDL-C level <100 mg/dL (2.6 mmol/L). If LDL-lowering drugs are used, a reduction of at least 30% to 40% in LDL-C levels should be obtained. If baseline LDL-C is <100 mg/dL, statin therapy should be initiated on the basis of risk factor assessment and clinical judgment. Major risk factors in this category include cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or use of antihypertensive medication), low HDL-C (<40 mg/dL), and family history of premature CHD (CHD in male first-degree relative ≤55 years of age; CHD in female first-degree relative ≤65 years of age).
- In individuals with diabetes who are under the age of 40 years, without overt CVD, but who are estimated to be at increased risk of CVD either by clinical judgment or by risk calculator, the LDL-C goal is <100 mg/dL, and LDL-lowering drugs should be considered if lifestyle changes do not achieve the goal.
- The ADA and AHA suggest different approaches to the management of HDL-C and triglyceride-associated CVD risk. The AHA suggests that in patients with triglyceride levels of 200 to 499 mg/dL, a non–HDL-C (total cholesterol minus HDL-C) goal of ≤130 mg/dL is a secondary target. If triglycerides are ≥500 mg/dL, therapeutic options include fibrate or niacin before

LDL-lowering therapy and treatment of LDL-C to goal after triglyceride-lowering therapy. A non–HDL-C level ≤130 mg/dL should be achieved if possible. The ADA suggests lowering triglycerides to <150 mg/dL (1.7 mmol/L) and raising HDL-C to >40 mg/dL (1.15 mmol/L); in women, an HDL-C goal 10 mg/dL higher (>50 mg/dL) should be considered.
- Combination therapy of LDL-lowering drugs (eg, statins) with fibrates or niacin may be necessary to achieve lipid targets, but this has not been evaluated in outcomes studies for either CVD event reduction or safety.

Tobacco

Cigarette smoking is a strong and modifiable risk factor for macrovascular disease both in the general population and for patients with diabetes.[59,60] Recently, a randomized, prospective trial of smoking cessation with long-term follow-up to assess effects on cardiovascular outcomes demonstrated a reduction in mortality rate with a trend toward reduction of CVD deaths.[61] These data have not been reported for individuals with diabetes, nor have rates for nonfatal CVD events been reported.

Smoking history must be ascertained and reviewed regularly. All patients with diabetes should be counseled not to start smoking or to quit if they are smoking. In patients willing to consider stopping smoking, it is appropriate to refer them to a formal smoking cessation program and to consider prescribing nicotine substitutes and/or bupropion hydrochloride.

Recommendations for Tobacco Use Cessation

- All patients with diabetes should be asked about tobacco use status at every visit.
- Every tobacco user should be advised to quit.
- The tobacco user's willingness to quit should be assessed.
- The patient can be assisted by counseling and by developing a cessation plan.
- Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion) should be incorporated as needed.

Antiplatelet Agents

Aspirin is widely regarded as the most cost-effective intervention to reduce CVD in the general population and in patients with diabetes.[62,63] The Early Treatment of Diabetic Retinopathy Study is the only large randomized, controlled trial of aspirin in people with diabetes (n=3711), but it included people with and without CVD; for the overall population in this study, the relative risk among aspirin-treated patients was 0.91 for death and 0.83 for fatal and nonfatal myocardial infarction.[64] Numerous epidemiological studies support these findings.[65–67] It is commonly recognized that aspirin is associated with an increased risk of gastrointestinal bleeding; to minimize the potential that the risk might exceed the benefits, it is generally recommended that aspirin therapy not be used for CVD prevention in populations with annual CVD risks substantially <1% and that aspirin be limited to doses of 75 to 162 mg/d.

Recommendations for Antiplatelet Therapy

- Aspirin therapy (75 to 162 mg/d) should be recommended as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those who are >40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).
- People with aspirin allergy, bleeding tendency, existing anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease are not candidates for aspirin therapy. Other antiplatelet agents may be a reasonable alternative for patients at high risk.
- Aspirin therapy should not be recommended for patients under the age of 21 years because of the increased risk of Reye's syndrome associated with aspirin use in this population. People under the age of 30 years have not been studied.

Glucose Management

Glycemic control clearly reduces microvascular complications in patients with diabetes; however, one of the most hotly debated clinical questions in diabetes is whether better glycemic control is associated with a reduction in CVD outcomes and how low we should go in pursuing glycemic targets. The ADA recommends a glycosylated hemoglobin A_{1c} (A1c) target of <7.0% in general but suggests targeting an A1c as close to normal (<6%) as possible without causing significant hypoglycemia in individual patients.[8] Other guidelines are generally consistent with this recommendation, although the specific numbers recommended are different.[68,69] These recommendations are largely based on epidemiological studies that suggest that each 1% increase in A1c is associated with a 15% and 18% increase in the relative risk of CVD for patients with type 1 and type 2 diabetes mellitus, respectively.[70] In support of these observational studies, both the UKPDS[71] and the Diabetes Control and Complications Trial[72] reported a nonsignificant trend toward a lower risk of CVD with lower A1c levels. A recent long-term follow-up of the Diabetes Control and Complications Trial suggested that 6 years of intensified insulin therapy has long-term CVD benefits.[73] Nevertheless, no clinical trials of a glycemic intervention have provided clear-cut evidence that glucose lowering reduces the risk of CVD. Moreover, as lower targets are achieved, the risk of severe hypoglycemia increases. Thus, there is certainly a floor below which benefits will be counterbalanced by risk. In the ACCORD trial, 10 000 subjects with type 2 diabetes mellitus have been randomized to either a standard treatment group, with an A1c goal of ≈7.5%, or an intensive treatment group, with an A1c goal of <6.0%.[74] There are also 2 other ongoing clinical trials that directly test the hypothesis that more intensive glucose lowering in the setting of type 2 diabetes mellitus will be associated with a reduction in CVD events.[75,76] Among patients with diabetes, glycemic control to reduce microvascular complications is clearly of benefit.

Recommendations for Glycemic Control

- The A1c goal for patients in general is <7%.
- The A1c goal for the individual patient is as close to normal (<6%) as possible without causing significant hypoglycemia.

Type 1 Diabetes Mellitus

The absolute CVD risk in patients with type 1 diabetes mellitus is lower than in patients with type 2 diabetes mellitus, in part because of their younger age and the lower prevalence of CVD risk factors. However, the relative risk of CVD in people with type 1 diabetes mellitus compared with that of nondiabetics of similar age is dramatically increased in men and women and is associated with classic cardiovascular risk factors and nephropathy but not glycemic control.[77–80] No data suggest that the interventions documented to be of benefit in reducing CVD are less effective in patients with type 1 diabetes mellitus than in type 2 diabetes mellitus. This is particularly true of lipid lowering with a statin,[53] aspirin therapy,[64] and glucose management.[72]

Recommendations for Patients With Type 1 Diabetes Mellitus

At the present time, all of the recommendations listed above for patients with type 2 diabetes mellitus appear appropriate for those with type 1 diabetes mellitus as well.

Summary

People with either type 1 or type 2 diabetes mellitus are at increased risk for CVD and have worse outcomes after surviving a CVD event. In this joint statement, we have attempted to summarize the evidence supporting lifestyle and medical interventions that will prevent the development of CVD in people with diabetes. The aggressive use of lifestyle modifications can reduce or delay the need for medical intervention. Appropriate lifestyle and medical interventions will reduce the occurrence of CVD and allow people with diabetes to live healthier and longer lives.

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