Primary Prevention of Cardiovascular Diseases in People With Diabetes Mellitus

A scientific statement from the American Heart Association and the American Diabetes Association

JOHN B. BUSE, MD, PHD, CO-CHAIR[1]
HENRY N. GINSBERG, MD, CO-CHAIR[2]
GEORGE L. BAKRIS, MD[3]
NATHANIEL G. CLARK, MD, MS, RD[4]
FERNANDO COSTA, MD[5]
ROBERT ECKEL, MD[6]
VIVIAN FONSECA, MD[7]
HERTZEL C. GERSTEIN, MD, MSC, FRCPC[8]
SCOTT GRUNDY, MD, PHD[9]
RICHARD W. NESTO, MD[10]
MICHAEL P. PIGNONE, MD, MPH[11]
JORGE PLUTZKY, MD[12]
DANIEL PORTE, MD[13]
RITA REDBERG, MD[14]
KIMBERLY F. STITZEL, MS, RD[5]
NEIL J. STONE, MD[15]

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.

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Diabetes is a disease defined by abnormalities of fasting or postprandial glucose and is frequently 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 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 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

From the [1]University of North Carolina School of Medicine, Chapel Hill, North Carolina; the [2]Department of Medicine, Columbia University, New York, New York; [3]Rush Presbyterian/St. Luke's Medical Center, Chicago, Illinois; the [4]American Diabetes Association, Alexandria, Virginia; the [5]American Heart Association, Dallas, Texas; the [6]University of Colorado Health Sciences Center, Denver, Colorado; [7]Tulane University Health Sciences Center, New Orleans, Louisiana; [8]McMaster University Medical Center, Hamilton, Ontario, Canada; the [9]Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, Texas; [10]Lahey Clinic Medical Center, Burlington, Massachusetts; the [11]Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; [12]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [13]VA San Diego Health Care, San Diego, California; the [14]Division of Cardiology, University of California, San Francisco, San Francisco, California; and [15]Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

Address correspondence to Henry N. Ginsberg, MD, College of Physicians and Surgeons, Irving Center for Clinical Research, 630 W. 168th St., P&F 9-510, New York, NY 10032. E-mail: hng1@columbia.edu.

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Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADA, American Diabetes Association; AHA, American Heart Association; ARB, angiotensin receptor blocker; CHD, coronary heart disease; CVD, cardiovascular disease; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; NHLBI, National Heart, Lung, and Blood Institute.

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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 designated diabetes as a "CVD risk equivalent" for setting treatment goals for LDL cholesterol (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 (e.g., 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. Three such risk calculators are the Framingham risk calculator (available at http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype = prof) (19), the U.K. Prospective Diabetes Study 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. 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 can coexist in one person (22). The ADA, in contrast, contends that once type 2 diabetes 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 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 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. Re-education of the patient about food selection and the importance of regular physical activity, combined with regular re-evaluation 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 and will improve hyperglycemia. Moderate weight loss (e.g., 7–10% 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. In the Look AHEAD (Action for Health in Diabetes) study, patients with type 2 diabetes with a BMI $\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 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 (e.g., those that restrict carbohydrate intake to <130 g/day) 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 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 strate-

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

Medical nutrition therapy
- To achieve reductions in LDL cholesterol:
  - Saturated fats should be <7% of energy intake.
  - Dietary cholesterol intake should be <200 mg/day.
  - 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 (25–35% of total calories) and should consist mainly of monounsaturated or polyunsaturated fat.
- Ample intake of dietary fiber (≥14 g per 1,000 calories consumed) may be of benefit.
- If individuals choose to drink alcohol, daily intake should be limited to one drink for adult women and two 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 1,200–2,300 mg/day (50–100 mmol/day), equivalent to 3,000–6,000 mg/day of sodium chloride.

Physical activity
- To improve glycemic control, assist with weight loss or maintenance, and reduce risk of CVD, at least 150 min of moderate-intensity aerobic physical activity or at least 90 min 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 h 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 mmHg or diastolic blood pressure ≥80 mmHg should have blood pressure confirmed on a separate day.
- Patients with diabetes should be treated to a systolic blood pressure <130 mmHg and a diastolic blood pressure <80 mmHg.
- Patients with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg 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 mmHg or diastolic blood pressure ≥90 mmHg) 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, test for lipid disorders 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 cholesterol <100 mg/dl, HDL cholesterol >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.

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Table 1—*Continued*

Lifestyle management
In individuals with diabetes who are over the age of 40 years, without overt CVD, but with one or more major CVD risk factors, the primary goal is an LDL cholesterol level <100 mg/dl (2.6 mmol/l). If LDL-lowering drugs are used, a reduction of at least 30–40% in LDL cholesterol levels should be obtained. If baseline LDL cholesterol 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 mmHg 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 cholesterol 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.
The AHA suggests that in patients with triglyceride levels of 200–499 mg/dl, a non-HDL cholesterol (total cholesterol minus HDL cholesterol) 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 cholesterol to goal after triglyceride-lowering therapy. A non-HDL cholesterol 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 cholesterol 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 (e.g., statins) and fibrates or niacin may be necessary to achieve lipid targets, but this has not been evaluated in outcome 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 (75–162 mg/day) 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
At the present time, all of the recommendations listed above for patients with type 2 diabetes appear appropriate for those with type 1 diabetes as well.

gies to improve lipids (7). Overall, the AHA diet and lifestyle recommendations (30), the therapeutic lifestyle changes suggested by the National Cholesterol Education Program's Adult Treatment Panel 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 ω-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 ω-3 fatty acids in individuals with established CHD. For this reason, the AHA currently recommends 1 g/day eicosapentaenoic acid plus 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 β-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 min of moderate-intensity aerobic physical activity per week or at least 90 min of vigorous aerobic exercise per week is recommended. Thus, patients with diabetes should be encouraged to perform 30–60 min 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 (e.g., 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 h 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 (e.g., 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 electrocardiogram 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 5–7% of starting weight, with an improvement in blood pressure.
- For individuals with elevated plasma triglycerides and reduced HDL cholesterol, improved glycemic control, moderate weight loss (5–7% of starting weight), dietary saturated fat restriction, increased physical activity, and modest replacement of dietary carbohydrate (5–7%) by either monounsaturated or polyunsaturated fats may be beneficial.

Medical nutrition therapy

- To achieve reductions in LDL cholesterol, saturated fats should be <7% of energy intake, dietary cholesterol intake should be <200 mg/day, 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 (25–35% of total calories) and should consist mainly of monounsaturated or polyunsaturated fat.
- Ample intake of dietary fiber (≥14 g per 1,000 calories consumed) may be of benefit.
- If individuals choose to drink alcohol, daily intake should be limited to one drink for adult women and two 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 1,200–2,300 mg/day (50–100 mmol/day), equivalent to 3,000–6,000 mg/day of sodium chloride.

Physical activity

- To improve glycemic control, assist with weight loss or maintenance, and reduce risk of CVD, at least 150 min of moderate-intensity aerobic physical activity or at least 90 min 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 h 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 mmHg in the general population and doubles for every 20-mmHg systolic or 10-mmHg 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 100–115 mmHg to diastolic blood pressure targets of ≤90, ≤85, and ≤80 mmHg. 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 mmHg, the risk of major cardiovascular events was halved compared with the group with a target of ≤90 mmHg (42). For patients with diabetes, it generally is agreed that the appropriate diastolic blood pressure target is ≤80 mmHg.

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 mmHg are associated with improved outcomes compared with higher levels. In the ABCD (Appropriate Blood Pressure Control in Diabetes) trial, a mean systolic blood pressure of 132 mmHg 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 systolic blood pressure should be lowered below 140 mmHg, various groups have recommended systolic blood pressure targets of <135 mmHg (42) and <130 mmHg (8,44). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure study (45) will explicitly test the cardiovascular efficacy of lowering systolic blood pressure below 140 mmHg. It has randomized participants to two levels of systolic blood pressure con-

trol to determine whether a therapeutic strategy that targets a systolic blood pressure of <120 mmHg reduces the rate of CVD events more than a strategy that targets a systolic blood pressure of <140 mmHg (45).

Multiple studies that have used thiazide diuretics, 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 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 two 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 mmHg or diastolic blood pressure ≥80 mmHg should have blood pressure confirmed on a separate day.
- Patients with diabetes should be treated to a systolic blood pressure <130 mmHg and a diastolic blood pressure <80 mmHg.
- Patients with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 80–89 mmHg 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 mmHg or diastolic blood pressure ≥90 mmHg) 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, triglycerides are often elevated, HDL cholesterol is generally decreased, and LDL cholesterol may be elevated, borderline, or normal. LDL particles are small and dense, carrying less cholesterol per particle. Thus, the LDL cholesterol 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 cholesterol level generally is not recognized as the major lipid abnormality in patients with type 2 diabetes, clinical trials amply demonstrate that LDL cholesterol lowering with drugs will reduce risk for major coronary events regardless of diabetes status (52).

Elevated LDL cholesterol is identified as the primary target of lipid-lowering therapy by both the ADA and the AHA. The focus on LDL cholesterol is supported by results of controlled clinical trials that have shown that LDL cholesterol 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 over the age of 40 years and had no known vascular disease but had at least one 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/day in the Heart Protection Study and atorvastatin 10 mg/day in the Collaborative Atorvastatin Diabetes Study, which produced, respectively, a 33 and 40% reduction in LDL cholesterol 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 cholesterol values at baseline, the observed benefits (relative risk reduction) were independent of baseline LDL cholesterol and other lipid values. Indeed, these results supported the epidemiological observations that the relationship between CHD risk and blood LDL cholesterol is approximately linear when CHD is plotted on a logarithmic scale. This explains the uniform relative reduction in CHD risk seen with LDL cholesterol reductions of 30–40% over a wide range of LDL cholesterol values.

Triglyceride-rich lipoproteins, especially VLDLs, 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 cholesterol 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 cholesterol 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 600 mg gemfibrozil 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 Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial randomized 9,795 people with type 2 diabetes with average total cholesterol levels (116–251 mg/dl) and an elevated total-to-HDL cholesterol 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 an overall rise in creatinine of ~15% 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 cholesterol in high-risk patients when these levels are reduced, there is one difference in the organizations' recommendations. The ADA specifies therapeutic goals for HDL cholesterol (>40 mg/dl, with consideration of a higher target of >50 mg/dl in women) (8), whereas the AHA advocates efforts to raise HDL cholesterol without specifically designating goals of therapy (7). The most effective available drug for raising HDL cholesterol 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 cholesterol <100 mg/dl, HDL cholesterol >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 one or more major CVD risk factors, the primary goal is an LDL cholesterol level <100 mg/dl (2.6 mmol/l). If LDL-lowering drugs are used, a reduction of at least 30–40% in LDL cholesterol levels should be obtained. If baseline LDL cholesterol 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 mmHg 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 cholesterol 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 cholesterol and triglyceride-associated CVD risk. The AHA suggests that in patients with triglyceride levels of 200–499 mg/dl, a non-HDL cholesterol (total cholesterol minus HDL cholesterol) 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 cholesterol to goal after triglyceride-lowering therapy. A non-HDL cholesterol 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 cholesterol to >40 mg/dl (1.15 mmol/l); in women, an HDL cholesterol goal 10 mg/dl higher (>50 mg/dl) should be considered.
- Combination therapy of LDL-lowering drugs (e.g., statins) with fibrates or niacin may be necessary to achieve lipid targets, but this has not been evaluated in outcome 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 = 3,711), 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 75–162 mg/day.

Recommendations for antiplatelet therapy

- Aspirin therapy (75–162 mg/day) 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 an 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, respectively (70). In support of these observational studies, both the U.K. Prospective Diabetes Study (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 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 two other ongoing clinical trials that directly test the hypothesis that more intensive glucose lowering in the setting of type 2 diabetes 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 —

The absolute CVD risk in patients with type 1 diabetes is lower than in patients with type 2 diabetes, 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 compared with that of nondiabetic individuals 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 than in type 2 diabetes. 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

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

SUMMARY —

People with either type 1 or type 2 diabetes 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.

APPENDIX —

G.L.B. has served on an advisory panel for and received honoraria from Novartis, Merck, Abbott, Biovail, and AstraZeneca and received grant/research support from AstraZeneca and Abbott. R.E. has served on an advisory panel for the Food and Drug Administration, Schering, Dowden Health Media, and Medical Decision Point; received honoraria from Pfizer, Merck, Abbott, and Kos; and received

grant/research support from Merck. V.F. has served on an advisory panel for and received honoraria from GlaxoSmithKline, Pfizer, Eli Lilly, and Novartis and received grant/research support from Pfizer, GlaxoSmithKline, Takeda, Aventis, Novartis, and AstraZeneca. H.C.G. has served on an advisory panel for sanofi-aventis, GlaxoSmithKline, Lilly, Novo Nordisk, and Bristol-Myers Squibb; received honoraria from sanofi-aventis, GlaxoSmithKline, Eli Lilly, and Novo Nordisk; and received grant/research support from sanofi-aventis, GlaxoSmithKline, King, and Wyeth-Ayerst. S.G. has served on an advisory panel for Pfizer, sanofi-aventis, Abbott, AstraZeneca, and Lilly; received honoraria from Merck, Schering-Plough, GlaxoSmithKline, Pfizer, Kos, and Bristol-Myers Squibb; and received grant/research support from Merck, Abbott, Kos, and GlaxoSmithKline. R.W.N. has received honoraria from GlaxoSmithKline, Merck, Pfizer, and Takeda. M.P.P. has served on an advisory panel for, received honoraria from, and received grant/research support from Bayer and Pfizer. J.G. has served on an advisory panel for and received honoraria from Merck, Takeda, Pfizer, and GlaxoSmithKline and received grant/research support from Takeda and GlaxoSmithKline. D.P. owns stock in AmCyte, Diamedica, Abbott, and Merck and has served on an advisory panel for Amylin, Bristol-Myers Squibb, Diamedica, Five-Prime Therapeutics, GlaxoSmithKline, Johnson & Johnson, Kowa Research Institute, Mannkind, Metacure, Sankyo, Takeda, Novartis, and sanofi-aventis. N.J.S. has served on an advisory panel for AstraZeneca, Merck, Pfizer, Reliant, sanofi-aventis, and SonoSite and received honoraria from AstraZeneca, Merck, Pfizer, Reliant, and sanofi-aventis.

References

1. American Diabetes Association, National Heart, Lung, and Blood Institute, Juvenile Diabetes Foundation International, National Institute of Diabetes and Digestive and Kidney Diseases, American Heart Association: Diabetes mellitus: a major risk factor for cardiovascular disease: a joint editorial statement by the American Diabetes Association; the National Heart, Lung, and Blood Institute; the Juvenile Diabetes Foundation International; the National Institute of Diabetes and Digestive and Kidney Diseases; and the American Heart Association. *Circulation* 100: 1132–1133, 1999
2. Safley DM, Marso SP: Diabetes and percutaneous coronary intervention in the setting of an acute coronary syndrome. *Diab Vasc Dis Res* 2:128–135, 2005
3. Hogan P, Dall T, Nikolov P, American Diabetes Association: Economic costs of diabetes in the US in 2002. *Diabetes Care* 26:917–932, 2003
4. Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF: Lifetime risk for diabetes mellitus in the United States. *JAMA* 290:1884–1890, 2003
5. Fox CS, Coady S, Sorlie PD, Levy D, Meigs JB, D'Agostino RB Sr, Wilson PW, Savage PJ: Trends in cardiovascular complications of diabetes. *JAMA* 292:2495–2499, 2004
6. Saydah SH, Fradkin J, Cowie CC: Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 291:335–342, 2004
7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
8. American Diabetes Association: Standards of medical care in diabetes–2006. *Diabetes Care* 29 (Suppl. 1):S4–S42, 2006
9. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
10. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ, National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, American Heart Association: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 110:227–239, 2004 [erratum in *Circulation* 110:763, 2004]
11. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM, BHS Guidelines Working Party, British Hypertension Society: British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 328:634–640, 2004 [erratum in *BMJ* 328:926, 2004]
12. Lee CD, Folsom AR, Pankow JS, Brancati FL, Atherosclerosis Risk in Communities (ARIC) Study Investigators: Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. *Circulation* 109:855–860, 2004
13. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National High Blood Pressure Education Program Coordinating Committee: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 289: 2560–2572, 2003 [erratum in *JAMA* 290: 197, 2003]
14. Evans JM, Wang J, Morris AD: Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *BMJ* 324:939–942, 2002 [erratum in *BMJ* 324: 1357, 2002]
15. Simons LA, Simons J: Diabetes and coronary heart disease. *N Engl J Med* 339: 1714–1715, 1998
16. Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, Nathan DM, Manson JE: The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch Intern Med* 161:1717–1723, 2001
17. Lotufo PA, Gaziano JM, Chae CU, Ajani UA, Moreno-John G, Buring JE, Manson JE: Diabetes and all-cause and coronary heart disease mortality among US male physicians. *Arch Intern Med* 161:242–247, 2001
18. Cho E, Rimm EB, Stampfer MJ, Willett WC, Hu FB: The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. *J Am Coll Cardiol* 40:954–960, 2002
19. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using risk factor categories. *Circulation* 97:1837–1847, 1998
20. Stevens RJ, Kothari V, Adler AI, Stratton IM, United Kingdom Prospective Diabetes Study (UKPDS) Group: The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin Sci (Lond)* 101:671–679, 2001 [erratum in *Clin Sci (Lond)* 102: 679, 2002]
21. Eddy DM, Schlessinger L: Archimedes: a trial-validated model of diabetes. *Diabetes Care* 26:3093–3101, 2003
22. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F, American Heart Association, National Heart, Lung, and Blood Institute: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: executive summary. *Circulation* 112:2735–2752, 2005 [errata in *Circulation* 112:e297, e298, 2005]
23. Kahn R, Buse J, Ferrannini E, Stern M, American Diabetes Association, European

Association for the Study of Diabetes: The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 28:2289–2304, 2005
24. Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson JL, Garg A, Holzmeister LA, Hoogwerf B, Mayer-Davis E, Mooradian AD, Purnell JQ, Wheeler M, American Diabetes Association: Nutrition principles and recommendations in diabetes. *Diabetes Care* 27 (Suppl. 1):S36–S46, 2004
25. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C: Physical activity/exercise and type 2 diabetes. *Diabetes Care* 27: 2518–2539, 2004
26. Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, Szapary PO, Rader DJ, Edman JS, Klein S: A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 348:2082–2090, 2003
27. Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams M, Gracely EJ, Samaha FF: The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med* 140:778–785, 2004
28. Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard VS, Johnson KC, Kahn SE, Knowler WC, Yanovski SZ, Look AHEAD Research Group: Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials* 24:610–628, 2003
29. Vollmer WM, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Morton DG, Conlin PR, Svetkey LP, Erlinger TP, Moore TJ, Karanja N, DASH-Sodium Trial Collaborative Research Group: Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. *Ann Intern Med* 135:1019–1028, 2001
30. Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Van Horn L, Winston M, Wylie-Rosett J, American Heart Association Nutrition Committee: Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation* 114:82–96, 2006
31. Montori VM, Farmer A, Wollan PC, Dinneen SF: Fish oil supplementation in type 2 diabetes: a quantitative systematic review. *Diabetes Care* 23:1407–1415, 2000
32. Stanger O, Herrmann W, Pietrzik K, Fowler B, Geisel J, Dierkes J, Weger M: Clinical use and rational management of homocysteine, folic acid, and B vitamins in cardiovascular and thrombotic diseases. *Z Kardiol* 93:439–453, 2004
33. Jha P, Flather M, Lonn E, Farkouh M, Yusuf S: The antioxidant vitamins and cardiovascular disease: a critical review of epidemiologic and clinical trial data. *Ann Intern Med* 123:860–872, 1995
34. Wang C, Chung M, Lichtenstein A, Balk E, Kupelnick B, DeVine D, Lawrence A, Lau J: Effects of omega-3 fatty acids on cardiovascular disease. *Evid Rep Technol Assess (Summ)* 94:1–8, 2004
35. Kris-Etherton PM, Harris WS, Appel LJ, American Heart Association Nutrition Committee: Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 107:2747–2757, 2003
36. Lonn E, Yusuf S, Hoogwerf B, Pogue J, Yi Q, Zinman B, Bosch J, Dagenais G, Mann JF, Gerstein HC: Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes: results of the HOPE study and MICRO-HOPE substudy. *Diabetes Care* 25:1919–1927, 2002
37. Lichtenstein AH: Nutrients and cardiovascular disease: no easy answers. *Curr Opin Lipidol* 16:1–3, 2005
38. Kamalesh M, Feigenbaum H, Sawada S: Challenge of identifying patients with diabetes mellitus who are at low risk for coronary events by use of cardiac stress imaging. *Am Heart J* 147:561–563, 2004
39. Cheng YJ, Lauer MS, Earnest CP, Church TS, Kampert JB, Gibbons LW, Blair SN: Heart rate recovery following maximal exercise testing as a predictor of cardiovascular disease and all-cause mortality in men with diabetes. *Diabetes Care* 26:2052–2057, 2003
40. Mora S, Redberg RF, Sharrett AR, Blumenthal RS: Enhanced risk assessment in asymptomatic individuals with exercise testing and Framingham risk scores. *Circulation* 112:1566–1572, 2005
41. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360:1903–1913, 2002 [erratum in *Lancet* 361:1060, 2003]
42. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S, HOT Study Group: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 351:1755–1762, 1998
43. Estacio RO, Jeffers BW, Gifford N, Schrier RW: Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 23 (Suppl. 2):B54–B64, 2000
44. Lenfant C, Chobanian AV, Jones DW, Roccella EJ, Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension* 41:1178–1179, 2003
45. ACCORD Study Group: The ACCORD trial: a multidisciplinary approach to control cardiovascular risk in type 2 diabetes mellitus. *Pract Diabetol* 23:6–11, 2004
46. Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, Woodward M, MacMahon S, Blood Pressure Lowering Trialists' Collaboration: Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 165: 1410–1419, 2005
47. Varughese GI, Lip GY: Antihypertensive therapy in diabetes mellitus: insights from ALLHAT and the Blood Pressure-Lowering Treatment Trialists' Collaboration meta-analysis. *J Hum Hypertens* 19:851–853, 2005
48. Heart Outcomes Prevention Evaluation Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355:253–259, 2000 [erraum in *Lancet* 356:860, 2000]
49. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288:2981–2997, 2002 [errata in *JAMA* 289:178, 2003 and 291: 2196, 2004]
50. Bakris GL, Gaxiola E, Messerli FH, Mancia G, Erdine S, Cooper-DeHoff R, Pepine CJ, INVEST Investigators: Clinical outcomes in the diabetes cohort of the INternational VErapamil SR-Trandolapril study. *Hypertension* 44:637–642, 2004
51. Haffner SM, American Diabetes Association: Dyslipidemia management in adults with diabetes. *Diabetes Care* 27 (Suppl. 1):S68–S71, 2004
52. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, Cholesterol Treatment Trialists' (CTT) Collaborators: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 366:1267–1278, 2005 [erratum in *Lancet* 366:1358, 2005]

53. Collins R, Armitage J, Parish S, Sleigh P, Peto R, Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361:2005–2016, 2003
54. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH, CARDS Investigators: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 364:685–696, 2004
55. Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, Frick MH: Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 15:820–825, 1992
56. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V: Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 317: 1237–1245, 1987
57. FIELD Study Investigators: The need for a large-scale trial of fibrate therapy in diabetes: the rationale and design of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [ISRCTN64783481]. *Cardiovasc Diabetol* 3:9, 2004
58. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M, FIELD Study Investigators: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 366: 1849–1861, 2005
59. Haire-Joshu D, Glasgow RE, Tibbs TL: Smoking and diabetes. *Diabetes Care* 22: 1887–1898, 1999
60. Haire-Joshu D, Glasgow RE, Tibbs TL: Smoking and diabetes. *Diabetes Care* 27 (Suppl. 1):S74–S75, 2004
61. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, Lung Health Study Research Group: The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 142:233–239, 2005
62. Hayden M, Pignone M, Phillips C, Mulrow C: Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the Preventive Services Task Force. *Ann Intern Med* 136:161–172, 2002
63. Antithrombotic Trialists' Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 324: 71–86, 2002 [erratum in *BMJ* 324:141, 2002]
64. ETDRS Investigators: Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study report 14. *JAMA* 268:1292–1300, 1992
65. Steering Committee of the Physicians' Health Study Research Group: Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 321:129–135, 1989
66. Sacco M, Pellegrini F, Roncaglioni MC, Avanzini F, Tognoni G, Nicolucci A, PPP Collaborative Group: Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care* 26:3264–3272, 2003
67. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE: A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 352:1293–1304, 2005
68. American College of Endocrinology: Consensus statement on guidelines for glycemic control. *Endocr Pract* 8 (Suppl. 1):5–11, 2002
69. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Cats VM, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D, European Society of Cardiology Committee for Practice Guidelines: European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 10:S1–S10, 2003
70. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH: Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 141:421–431, 2004
71. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998 [erratum in *Lancet* 354:602, 1999]
72. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *Am J Cardiol* 75:894–903, 1995
73. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353:2643–2653, 2005
74. Snow V, Weiss KB, Mottur-Pilson C, Clinical Efficacy Assessment Subcommittee of the American College of Physicians: The evidence base for tight blood pressure control in the management of type 2 diabetes mellitus. *Ann Intern Med* 138:587–592, 2003
75. Abraira C, Duckworth W, McCarren M, Emanuele N, Arca D, Reda D, Henderson W, VA Cooperative Study of Glycemic Control and Complications in Diabetes Mellitus Type 2: Design of the cooperative study on glycemic control and complications in diabetes mellitus type 2: Veterans Affairs Diabetes Trial. *J Diabetes Complications* 17:314–322, 2003
76. Study rationale and design of ADVANCE: Action in Diabetes and Vascular Disease–Preterax and Diamicron MR Controlled Evaluation. *Diabetologia* 44:1118–1120, 2001
77. Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, O'Leary DH, Genuth S, Diabetes Control and Complications Trial, Epidemiology of Diabetes Interventions and Complications Research Group: Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 348: 2294–2303, 2003
78. Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KY, Smithline Kinder L, Ellis D, Becker DJ: Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 26:1374–1379, 2003
79. Lewis S, MacLeod M, McKnight J, Morris A, Peden N, Prescott R, Walker J, Royal College of Physicians of Edinburgh Diabetes Register Group: Predicting vascular risk in type 1 diabetes: stratification in a hospital based population in Scotland. *Diabet Med* 22:164–171, 2005
80. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC: Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia* 46:760–765, 2003