The Centers for Disease Control and Prevention (CDC) estimated that 18.8 million people in the United States had diagnosed diabetes mellitus in 2010, with an additional 7 million people having diabetes that was undiagnosed.1
Currently, the diagnosis of diabetes mellitus is made with repeat testing based on 1 of the following 3 findings:

1. Glycosylated hemoglobin (HbA1c) level is > 6.5%.
2. Fasting plasma glucose level is > 126 mg/dL.
3. 2-hour plasma glucose level is > 200 mg/dL during an oral glucose tolerance test. Adults with diabetes mellitus are 2 to 4 times more likely to die of cardiovascular disease (CVD) or stroke than are adults without diabetes.1

Although mortality from CVD has decreased among patients with type 2 diabetes mellitus (T2DM) in recent years, the rate of CVD-related death remains higher in the population with T2DM than in the population without this disease.1 In 2004, heart disease was listed as the cause of death on 68% of death certificates for people older than 65 years with diabetes mellitus.1 Therefore, it is especially important to decrease cardiovascular risk factors in this population. According to the CDC, control of low-density lipoprotein cholesterol (LDL-C levels), as well as blood pressure, can substantially reduce the risk of CVD in individuals with diabetes mellitus.1

Cardiovascular disease risk assessment
An important aspect of the management of diabetes mellitus is assessing CVD risk to determine the individual goals for each patient. Despite the known increased risk of CVD in individuals with diabetes, there remains a large population of such individuals who do not meet the goals outlined in the American Diabetes Association (ADA) standards of medical care in diabetes.2 By taking multiple factors into account, the physician can tailor the treatment goals of each patient to improve care and meet the ADA goals. This is especially important for high-risk patients, in whom the disease tends to be the least well controlled.1 The key factors in defining these goals appear to be the patient’s age, duration of disease, lipid panel results, degree of blood pressure control, HbA1c level, and tobacco use.

Three calculators used to determine global risks of patients with diabetes mellitus have been discussed in consensus statements published by the ADA and the American Heart Association (AHA): the Framingham Heart Study risk calculator (http://hp2010.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof), the United Kingdom Prospective Diabetes Study (UKPDS) risk engine (www.dtu.ox.ac.uk/riskengine/), and the ADA’s Diabetes Personal Health Decisions (PhD) risk assessment tool.5 However, the ADA retired the diabetes PhD risk assessment tool at the end of 2011, intending to have a new, improved online risk assessment tool available sometime in the first half of 2012.6 Furthermore, it is important to note that the ADA has recently questioned the validity of the Framingham risk calculator, noting that the Framingham Risk Score may overestimate risk by assuming that all patients with diabetes are at high risk of developing CVD.3,4

Lifestyle modification
Appropriate lifestyle modifications have been shown to stabilize glycemic control and to prevent and decrease CVD risk factors. In a 4-year study, the Look AHEAD (Action for Health in Diabetes) research group examined the effects of lifestyle modifications on CVD risk factors.7 In the study, participants were divided into a “diabetes support and education group” (DSE, the control group) and an “intensive lifestyle intervention group” (ILI).7 The ILI group was told to adhere to a 1200-1800-calorie diet and 175 minutes of physical activity each week. Risk factors evaluated at the end of the study were weight, fitness, HbA1c level, systolic blood pressure, diastolic blood pressure, LDL-C levels, high-density lipoprotein cholesterol (HDL-C) levels, and triglyceride levels.

With the exception of LDL-C levels, which were significantly greater in the ILI group than in the DSE group (P = .009), all of the CVD risk factors measured in the Look AHEAD study were decreased in members of the ILI group (P < .001 to P = .01).7 The study also found that when compared to the number of members in the DSE group, fewer members of the ILI group began to take diabetic medications over the 4-year period.

Specific ADA lifestyle recommendations and goals for decreasing the risk of CVD include moderate weight loss (ie, 7% - 10% of body weight per year) and dietary modification.2 Dietary guidelines include several recommendations for the limitation of fat. Patients should limit fat intake to 25% to 35% of total daily calories, and any fats consumed should consist of mainly monounsaturated and polyunsaturated fats. Saturated fats should be limited to less than 7% of energy intake, and dietary cholesterol intake should be less than 200 mg/day. Recommendations also include fiber intake of at least 14 grams per 1000 calories.

In addition to diet, physical activity is an important lifestyle intervention for decreasing CVD risk. Patients should be chal-
Lipid control

The ADA recommends that patients with diabetes mellitus maintain an LDL-C level of less than 100 mg/dL as a primary goal. Patients with diabetes mellitus and known CVD should strive for an even lower LDL-C goal, of less than 70 mg/dL. Research suggests that HDL-C and triglycerides have less influence than LDL-C on cardiovascular events in people with diabetes. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, the addition of fenofibrate to statin therapy led to an increase in HDL-C levels and a decrease in triglyceride levels in a group of individuals with T2DM. However, these changes did not result in a decreased incidence of cardiovascular events compared to the group receiving statin therapy alone.

It appears, however, that the raw numbers do not provide a complete picture. The 2001 National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), as well as the 2004 updated guidelines, maintain that, although LDL-C should be the primary treatment target in diabetes mellitus, there is considerable benefit in risk stratification of patients based on secondary treatment goals. An important point that should be kept in mind is that the lipid profile in patients with diabetes is more atherogenic than in those without diabetes, making the full lipid profile crucial to treatment decisions. Another reason to consider treatment targets in addition to LDL-C is the complicated cascade of events in the lipid metabolism of people with diabetes.

In patients with diabetes mellitus, major consequences of insulin resistance occur in lipid metabolism—the unrestricted release of hormone-sensitive lipase and the functional loss of lipoprotein lipase, both of which result in increases in free fatty acids, triglycerides, and very-low-density lipoprotein cholesterol (VLDL-C). With an increase in triglycerides, there is also an increase in cholesterol ester transfer proteins, resulting in structural changes in the LDL-C and HDL-C particles. These changes make the cholesterol particles easier targets for lipolysis by hepatic lipase. When acted on by hepatic lipase, LDL-C is converted from large, buoyant (ie, “fluffy, puffy”) particles into smaller, denser, and more numerous particles known to be more atherogenic. The increase in triglycerides causes HDL-C to be catabolized by the kidneys, thus directly lowering the HDL-C level.

The burden of lipoproteins other than LDL-C that contribute to atherogenesis can be determined by calculating either the apolipoprotein B (ApoB) or non-HDL-C level. Apolipoprotein B is present in each particle of chylomicron, LDL-C, VLDL-C, intermediate-density lipoprotein, and lipoprotein-a, all of which are considered atherogenic. Non-HDL-C reflects the sum of LDL, VLDL-C, intermediate-density lipoprotein, and lipoprotein-a. Both ApoB and non-HDL-C have been shown to be better predictors of cardiovascular events than LDL-C. The level of ApoB can be obtained only by direct laboratory measurement. The level of non-HDL-C can be determined with a basic lipid profile (by subtracting HDL-C from total cholesterol) in a nonfasting state.

In the consensus conference report from the ADA and the American College of Cardiology Foundation (ACCF), the goals for ApoB, LDL-C, and non-HDL-C in patients at cardiometabolic risk are as follows:

- **High risk**: ApoB is < 90 mg/dL, LDL-C < 100 mg/dL, non-HDL-C < 130 mg/dL.
- **Very high risk**: ApoB is < 80 mg/dL, LDL-C < 70 mg/dL, non-HDL-C < 100 mg/dL.

Consideration of these additional factors will allow clinicians to increase the accuracy of CVD risk prediction for patients with diabetes mellitus.

Blood pressure control

Current ADA recommendations for blood pressure control in patients with diabetes mellitus include the initiation of drug therapy if systolic blood pressure (SBP) is more than 140 mm Hg and if diastolic blood pressure (DBP) is more than 90 mm Hg based on 2 measurements on...
Glycemic control

Patients with diabetes mellitus.9,15 The blood pressure control (target SBP is 140 mm Hg) with intensive blood pressure ranging between 130 and 139 mm Hg, lifestyle modification alone should be tried for 3 months. If after these lifestyle modification efforts, SBP of less than 130 mm Hg or DBP of less than 80 mm Hg is not achieved, treatment with pharmaceutical agents should be started.2

The ACCORD trial compared standard blood pressure control (target SBP is < 140 mm Hg) with intensive blood pressure control (target SBP is < 120 mm Hg) in patients with diabetes mellitus.9,15 The researchers used the rate of cardiovascular events as an indicator of optimal blood pressure control. The investigators found no statistically significant difference in the total number of cardiovascular events in the intensive vs the standard blood pressure control group. They did note, however, that patients in the intensive control group had a higher incidence of adverse effects from medications and used a larger number of antihypertensive medications compared with patients in the standard control group.9,15

Glycemic control

The ADA recommends an HbA1c level of less than 7% as a goal for glycemic control in patients with diabetes mellitus. This laboratory value should be monitored every 6 months in patients with stable glycemic control.2

In an investigation of the benefits of tight glycemic control in patients with diabetes, the ACCORD researchers divided participants into an intensive therapy group and a standard therapy group.9,16 The intensive therapy group was given the goal of keeping their HbA1c level below 6.0%, and the standard therapy group was given the goal of keeping their HbA1c level between 7.0% and 7.9%. Participants in the intensive therapy group were forced to quit treatment before the study was completed because they had a higher risk of mortality than the standard care group. The investigators concluded that standard glycemic control, such as that recommended by the ADA, along with control of other cardiovascular risk factors, is the best overall approach to treatment of patients with T2DM.2,9,16

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study and the UKPDS have demonstrated that HbA1c levels less than 7% will decrease the incidence of CVD.17,18 In the DCCT/EDIC study, in which patients with type 1 diabetes mellitus were followed up for 17 years, a 42% reduction in CVD risk was found in those patients undergoing intensive glycemic control.17 In the UKPDS, which followed up patients with T2DM for 10 years, the risk of myocardial infarction was decreased by 15% to 33% in individuals using intensive glycemic treatment.18

Authors of the ACCORD trial concluded that other comorbidities were the cause of the higher mortality observed in the intensive treatment group.18 Because of the discrepancy in outcomes between standard glycemic control and intensive glycemic control, some authors have suggested that patients with longstanding diabetes mellitus or other comorbidities be given more time to achieve their glycemic goals (eg, 6 months to 1 year). In addition, if a patient has a longstanding diagnosis of diabetes (eg, 10-15 years), HbA1c goals should remain at 7.0%. By contrast, a more recent diagnosis of diabetes may prompt an HbA1c goal of 6.0.20

Aspirin in primary prevention

In 2007, the ADA and AHA jointly recommended that low-dose aspirin (acetylsalicylic acid, 75-162 mg/day) be used as a primary prevention strategy in patients with diabetes mellitus who are at increased cardiovascular risk.21 After publication of this recommendation, the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes22 and the Prevention of Progression of Arterial Disease and Diabetes23 trials raised doubts about the efficacy of low-dose aspirin in patients with diabetes mellitus. As a result of these results, the ADA, AHA, and ACCF convened in 2009 to review and synthesize available evidence and update recommendations.21 During the evaluation to determine the updated recommendations, the joint committee considered not only the benefits of aspirin for preventing coronary artery disease, but also the known problem of gastrointestinal bleeding with daily use of aspirin.

The joint committee concluded that low-dose aspirin (75-162 mg/day) for CVD prevention is “reasonable” for adults with diabetes mellitus who have no history of vascular disease but who are at increased risk of CVD (10-year risk is > 10%) and are not at increased risk of bleeding.12 The committee added that aspirin should not be recommended for CVD prevention if patients are at low risk of CVD (10-year risk...
is < 5%), noting that the potential adverse effects from bleeding offset the potential benefits. Low-dose aspirin “might be considered” for CVD prevention in patients with diabetes who are at intermediate risk of CVD (10-year risk = 5%-10%).

The joint committee also stressed that all modifiable CVD risk factors should be addressed and optimally managed for patients using aspirin. Helping patients reach their individual cardiovascular goals through such management will decrease their 10-year CVD risk, meaning that fewer patients with diabetes mellitus will need to continue taking aspirin and be at risk for the adverse effects of this medication.

Final notes
It is evident that prevention of CVD in patients with T2DM requires a multifactorial approach. This approach includes management of CVD risk factors with both pharmaceutical interventions and lifestyle modifications. Many patients with diabetes mellitus are currently not achieving recommended treatment goals and targets. By improving the quality of care for these patients, we can decrease the occurrence of CVD and promote a happier and healthier life for individuals with diabetes mellitus.

References
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