Approximately 1 of every 10 adults in the United States—amounting to about 25.8 million people—has diabetes mellitus, of which type 2 diabetes mellitus (T2DM) accounts for an estimated 90% to 95% of all diagnosed cases.¹ The prevalence of diabetes mellitus in the United States has increased substantially during the past 25 years,² with 1.9 million new cases diagnosed in adults aged 20 years or older in 2010 alone.¹ The prevalence of T2DM is expected to continue to increase, and by 2050, an estimated 1 in 3 US adults may have diabetes mellitus.³

During recent decades, the incidence of T2DM has increased in adolescents and young adults. Although diabetes mellitus is often thought of as a disease of middle age, increases in childhood obesity rates have led to the diagnosis of T2DM at much earlier ages than was previously the case. Depending on the study location, newly diagnosed T2DM has been reported at rates between 8% and 45% in adolescents.⁴ Among adolescents, girls were found to be 1.7 times more likely than boys to have T2DM, and cases in girls were commonly associated with polycystic ovary syndrome. Impaired glucose tolerance was seen in 25% of obese children between ages 4 and 10 years and in 21% of obese children between ages 11 and 18 years.⁴

The premature development of T2DM involves problems with multiple organs, including cardiovascular and renal impairment, leading to much earlier mortality and morbidity in affected individuals. In the coming decades, this early mortality and morbidity will likely lead to considerable direct and indirect costs to society.

The increasing prevalence of T2DM can be attributed to several factors, including the aging of the population, an increase in unhealthy dietary habits, sedentary lifestyles, and, most importantly, increasing prevalence of overweight and obesity.⁵ It has been estimated that approximately 90% of T2DM cases are attributable to excess body weight.⁶

The prevalence of overweight and obesity in the United States is exceptionally high. Based on 2007-2008 data from the National Health and Nutrition Examination Survey,⁷ the prevalence of overweight (ie, body mass index [BMI] ≥25) in men and women aged 20 years or more is 68.0%, and the prevalence of

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Mark D. Baldwin, DO, FACOI

Type 2 diabetes mellitus (T2DM), obesity, and cardiovascular disease (CVD) share a common pathogenic mechanism. The prevalence of each of these conditions is increasing at an alarming rate. Despite the availability of several treatment options for patients with T2DM and the use of intensive regimens combining several antidiabetic drugs, less than half of all patients reach a target glycosylated hemoglobin level of less than 7%. Given the rapid increase in the number of patients with T2DM and obesity, as well as the CVD morbidity and mortality associated with this burden, efforts must be made to change the course of disease. The author reviews clinical trial data on the effect of glucose control on CVD risk, the selection and timing of antihyperglycemic agents, the management of associated CVD risk factors, and strategies to improve patient adherence and acceptance—with the goal of assisting physicians in selecting appropriate management strategies for their patients with T2DM.

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obesity (ie, BMI ≥ 30) in this same group is 33.8%. In the past 10 years, the prevalence of obesity among adults in the United States has increased by 37%, while the prevalence of extreme obesity has increased at an even faster rate. Fortunately, the most recent estimates indicate that increases in obesity prevalence are currently occurring at a somewhat lower rate than that observed over the past 10 years, especially in women. Considering the link between T2DM and obesity, as well as the comorbidities and disabilities that frequently accompany both conditions, trends in obesity rates have serious implications for future healthcare costs.

In 2007, annual expenditures associated with diabetes mellitus in the United States were estimated at $174 billion in direct and indirect costs, including $116 billion in medical expenditures and $58 billion in lost productivity. The largest proportion (approximately $58 billion) of direct medical expenditures for diabetes mellitus can be attributed to diabetes-related chronic complications. Other direct medical costs attributed to diabetes mellitus include treatment for the primary condition ($27 billion) and general medical costs ($31 billion). After adjusting for gender-related and age-related differences, the average medical expenditures for individuals with T2DM are approximately 2.3 times higher than for individuals without T2DM.

The cumulative costs of diabetes-related macrovascular and microvascular complications increase substantially with disease duration. Target organ damage—frequently involving the eyes, heart, kidneys, peripheral nerves, and small, medium, and large blood vessels—is often well established by the time of the diagnosis of T2DM. Data from a Michigan health maintenance organization show that complications increase the annual costs associated with T2DM. Direct medical costs increased by 10% to 30% per plan member per year because of several factors, including a BMI increase of 10, treatment with oral antidiabetic or antihypertensive agents, kidney disease, cerebrovascular disease, or peripheral vascular disease. Independent cost increases of 60% to 90% were noted with insulin treatment, angina, and myocardial infarction. Dialysis was associated with an 11-fold increase in cost. The costs related to treatment of patients with T2DM are expected to rise as the prevalence of this disease continues to increase.

Diabetes mellitus is the most common cause of end-stage renal disease in the United States. Annual Medicare costs for dialysis in 2007 were $8.6 billion, which averages $43,335 per patient per year. Cardiovascular disease (CVD) is the most common cause of death in patients with T2DM, and recent data analyses have demonstrated that T2DM decreases life expectancy. Using data from the Framingham Heart Study, Franco et al calculated the impact of T2DM after age 50 years on life expectancy and years lived with and without CVD. The researchers found that T2DM was associated with a markedly increased lifetime risk of CVD and with both CVD-related mortality and mortality from diabetes mellitus independent of CVD. Men aged 50 years or older with T2DM lived on average 7.5 years less than did men of the same age without T2DM. Women aged 50 years or older with T2DM lived on average 8.2 years less than did women of the same age without T2DM.

In another study using data from the Framingham Heart Study, Fox et al examined how the burden of CVD in the United States has been affected by changes in the prevalence of T2DM and other risk factors during the past several decades. The risk of CVD events in patients enrolled in the Framingham Heart Study during an “early” period (ie, 1952-1974) was compared with the risk of CVD events in patients enrolled in the study at a later period (ie, 1975-1998). The results showed that the number of CVD cases attributable to T2DM increased, and the number of cases attributable to smoking, hypertension, and elevated cholesterol, decreased or remained unchanged between these periods.

Most recently, a meta-analysis of data for 698,782 participants from 102 prospective studies (including 52,765 nonfatal or fatal vascular outcomes representing 8.49 million person-years) demonstrated that patients with T2DM have an approximate 2-fold increased risk for CVD—including myocardial infarction and stroke—irrespective of other conventional risk factors (eg, lipid, inflammatory, and renal markers). These findings emphasize the need for increased efforts to prevent T2DM and to aggressively control CVD risk factors in individuals with T2DM.

Given the rapid expansion in the number of patients with T2DM and obesity, and the high CVD morbidity and mortality rates associated with this burden, it is clear that efforts must be made to change the course of the disease process in patients.

Pathophysiologic Defects

In most patients, T2DM represents a “perfect storm” of heredity and environment acting in concert. For the predisposed patient, the excess body mass leads to alterations in multiple interconnected neuroendocrine hormones, including adipokine, catecholamine, corticosteroid, endocannabinoid, glucagon, insulin, and the renin-angiotensin-aldosterone (RAS) system.

Although the specifics of these physiologic interactions are beyond the scope of the present article, several points bear mention. Enhanced RAS activity leads to a number of deleterious effects on the cardiovascular system, including promotion of inflammation, vasoconstriction, vascular remodeling, thrombosis, and plaque rupture. Despite previous beliefs that adipose tissue has little metabolic function, adipocytes are actually a source of a number of mediators that promote inflammation and insulin resistance. In obese individuals, the adipose tissue outstrips the vascular supply, which leads to tissue hypoxia, inflammation, and angiogenesis. The net effect is accelerated atherosclerosis and increased cardiovascular risk.

Glycemic Control and Cardiovascular Disease

Cardiovascular disease constitutes the major cause of morbidity and mortality in patients with T2DM, accounting for at least 65% of deaths in these patients. In the United Kingdom Prospective Diabetes Study (UKPDS, consisting of...
patients with T2DM) and the Diabetes Control and Complications Trial (DCCT, consisting of patients with type 1 diabetes mellitus), evidence was found that intensive glycemic control prevents the development and progression of microvascular complications in patients with diabetes mellitus. However, whether intensive glucose lowering also prevents macrovascular disease and major cardiovascular events remains unclear.24

Three large-scale cardiovascular outcome trials evaluated the effects of intensive glucose control, rather than a specific therapeutic regimen, on macrovascular outcomes. These 3 trials were the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,25 the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,26 and the Veterans Affairs Diabetes Trial (VADT).27

The ACCORD Study Group25 compared the effect of an intensive glucose-lowering strategy (ie, target glycosylated hemoglobin [HbA1c] level, <6%) to that of a standard glucose-lowering strategy (ie, target HbA1c level, 7.0%-7.9%) on cardiovascular events in patients with T2DM who had either established CVD or additional CVD risk factors.25 A total of 10,251 patients (mean age, 62.2 y) with a median HbA1c level of 8.1% were enrolled in the study. Of these enrolled patients, 38% were women, and 35% had a previous cardiovascular event.

Compared to the standard glucose-lowering group, the intensive glucose-lowering group in the ACCORD trial25 had a lower mean HbA1c level (6.4% intensive vs 7.5% standard) and a more rapid rate of HbA1c reduction in the first 4 months of treatment (>1.4% intensive vs -0.6% standard). Hypoglycemia requiring assistance and weight gain of more than 10 kg were also more frequent in the intensive glucose-lowering group (P < .001).25 The ACCORD trial was discontinued after a 3.5-year median follow-up because of a statistically significant increase in all-cause mortality in the intensive glucose-lowering study group (hazard ratio, 1.22; 95% confidence interval, 1.01-1.46; P = .04).

Similar to ACCORD, the ADVANCE trial26 evaluated the effect of glycemic control on vascular outcomes in patients with T2DM. A total of 11,140 patients with T2DM were randomly assigned to receive either standard glucose control (with target HbA1c defined on the basis of local guidelines) or intensive glucose control (target HbA1c level, ≤6.5%). After a median follow-up of 5 years, the mean HbA1c level was lower in the intensive glucose control group than in the standard glucose control group (6.5% intensive vs 7.3% standard, P < .001). The incidence of combined major macrovascular and microvascular events was reduced in patients receiving intensive glucose control compared to patients receiving standard treatment (18.1% intensive vs 20.0% standard, P = .01). This reduction was primarily the result of a statistically significant reduction in major microvascular events with intensive treatment (10.9% intensive vs 9.4% standard, P = .01).

The ADVANCE trial26 found no statistically significant differences from intensive vs standard glucose control on major macrovascular events, on death from CVD, or on death from any cause. Severe hypoglycemia, though uncommon in both groups, was more common in the intensive-control group than in the standard-control group (2.7% intensive vs 1.5% standard; P < .001).

The primary goal of the VADT27 was to compare the effects of intensive and standard glucose control on cardiovascular events in patients with long-standing T2DM. A total of 1719 military veterans (mean age, 60.4 y) whose diabetes mellitus was poorly controlled (mean baseline HbA1c level, 9.4%) on current treatment were enrolled in the study. The mean length of time since T2DM diagnosis was 11.5 years, and 40% of patients had previously had a cardiovascular event. Results showed that the mean HbA1c level was reduced to 6.9% in the intensive-treatment group compared to 8.4% in the standard-treatment group. Over a median follow-up of 5.6 years, there was no statistically significant effect of intensive glucose control on macrovascular or microvascular outcomes compared to standard glucose control.27

Interestingly, patients in ACCORD,25 ADVANCE,26 and VADT27 all had established T2DM (mean duration, 8-11 y) and either known CVD or multiple cardiovascular risk factors. Subset analysis of the 3 trials suggested benefits of intensive glycemic control on CVD in patients with shorter duration of T2DM, lower baseline HbA1c level, or absence of known CVD.28

Long-term epidemiologic follow-up of some landmark trials provides evidence that intensive glycemic control early in the course of T2DM may yield CVD benefits.29,30 Intensive glycemic control initiated in relatively young patients free of CVD risk factors was associated with a 57% reduction in major CVD outcomes in the DCCT-Epidemiology of Diabetes Interventions and Complications (EDIC) trial.29 However, the CVD benefit observed in DCCT-EDIC required 9 years of follow-up beyond the end of the trial to reach a level of statistical significance.29 In a 10-year follow-up of the UKPDS, statistically significant long-term reductions in myocardial infarction and all-cause mortality were observed in patients who had been randomly assigned to intensive glycemic control compared with patients assigned to conventional glycemic control.30

Skyler et al31 proposed, “as is the case with microvascular complications, it may be that glycemic control plays a greater role before macrovascular disease is well developed and a minimal or no role when it is advanced.”31 It is also apparent that it will take much longer to obtain macrovascular benefit from glucose control than it takes to obtain microvascular benefit from glucose control.

Results of these large, randomized trials suggest that intensive glycemic targets of 6% or less may be too aggressive. Current guidelines by the American Diabetes Association (ADA), the American Heart Association (AHA), and the American College of Cardiology (ACC)32—based on evidence obtained from ACCORD,25 ADVANCE,26 and VADT27 —reaffirm an HbA1c target goal of less than 7% for patients with T2DM. However, in the joint ADA/AHA/ACC position/scientific statement,28 the need for additional clarification regarding glycemic control was highlighted, and the following recommendations were provided:
Microvascular disease—Lowering HbA1c level to below or approximately 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. Therefore, the HbA1c goal for nonpregnant adults, in general, is <7%.

Macrovascular disease—In type 1 and type 2 diabetes, randomized controlled trials of intensive versus standard glycemic control have not shown a significant reduction in CVD outcomes during the randomized portion of the trials. However, long-term follow-up of the DCCT and UKPDS cohorts suggests that treatment to HbA1c targets below or near 7% in the years soon after the diagnosis of diabetes is associated with long-term reduction in risk of macrovascular disease. Until more evidence becomes available, the general goal of <7% appears reasonable.

This statement supports the view that treatment should be individualized for patients with T2DM—with more aggressive, earlier HbA1c targets potentially appropriate for younger patients with diabetes mellitus, and standard HbA1c goals appropriate for patients with established T2DM in whom CVD is known or likely to be present.

Selection and Timing of Antidiabetic Agents for Glycemic Control
Early diagnosis of T2DM—even in patients with impaired glucose tolerance—is important because early, aggressive intervention can alter the course of the disease, presumably by preserving β-cell function and reducing the development of microvascular and macrovascular complications. A growing body of evidence supports early and aggressive treatment initiation with a combination of antidiabetic agents that have the potential to alter the long-term course of T2DM. Antidiabetic medications that reduce peripheral insulin resistance have the potential to spare pancreatic β cells from premature exhaustion early in the disease process.

Metformin and thiazolidinediones (TZDs) are insulin sensitizers available for the initial treatment of patients with T2DM. Although these classes of agents are effective in improving insulin resistance, each class is associated with unique treatment-related adverse events, including reductions in bone density and increased fracture rates in postmenopausal women and retention of salt and water (with TZD use) and gastrointestinal intolerance (with metformin use).

Incretin-based medications—including glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors—address some of the challenges associated with traditionally available oral antidiabetic agents, such as metformin and TZDs. In addition to improving β-cell function, these incretin-based agents stimulate insulin secretion and inhibit glucagon secretion. Because these agents are still relatively new, their long-term risks of exposure have not been determined.

Because excess weight and obesity are prominent features of T2DM, it is important to use antidiabetic agents that do not induce unnecessary weight gain, particularly central weight gain, which is thought to be most atherogenic. Metformin is generally weight-neutral, with a low risk of hypoglycemia. Thiazolidinediones, sulfonylureas, and insulin are all associated with weight gain, though newer analog insulins may cause less weight gain than older human insulin. Despite their link to weight gain, TZDs are associated with improvements in long-term β-cell function and CVD risk factors. Incretin-based agents have been shown to be either weight-neutral (DPP-4 inhibitors) or to cause weight loss (GLP-1 receptor agonists).

Treatment guidelines for T2DM recommend selecting medications based on their overall safety and ability to achieve the HbA1c goal. The ADA algorithm for the treatment of patients with T2DM (Figure 1) takes into account the characteristics of individual interventions, including their synergies and expense, with the goal of achieving and maintaining an HbA1c level of less than 7%. However, because T2DM is a progressive disease characterized by worsening glycemia, the use of more than 1 medication will be necessary for the majority of patients. Selection of agents should be made on the basis of their glucose-lowering effectiveness and the synergy of medication combinations. Antihyperglycemic drugs with different mechanisms of action will generally have the greatest synergy.

Considerations of Cardiovascular Disease Risk
Selection of a treatment regimen for patients with T2DM includes evaluation of the effects of medications on overall CVD risk. Older oral antidiabetic agents may reduce hyperglycemia, but they may also be associated with increases in CVD risk. For example, sulfonylureas and insulin, especially in the setting of ineffective lifestyle modification, frequently cause weight gain, leading to increased difficulty with glycemic control. Sulfonylureas may also be linked to increased CVD risk, though it is unclear whether this is a direct effect of the drugs, a marker of increased event rate caused by hypoglycemia, or a waning legacy effect reflective of declining control of diabetes mellitus.

Thiazolidinediones may cause weight gain, but this effect is often associated with volume expansion rather than reductions in glycemic control. In addition, TZDs have been associated with an increased risk of congestive heart failure and, in the case of rosiglitazone maleate, an increased risk of CVD. By contrast, a meta-analysis of trials of the TZD pioglitazone hydrochloride indicates the possibility of an ischemic cardiovascular benefit.

Markers of CVD risk have been assessed in several trials of incretin-based agents. In general, GLP-1 receptor agonists produced small but statistically significant reductions in systolic blood pressure (of 1-7 mm Hg) and no statistically significant reductions in diastolic blood pressure. Insufficient data exist for the effects of DPP-4 inhibitors on CVD risk. Clinical studies have demonstrated that low-density lipoprotein cholesterol (LDL-C) levels are reduced by 1 to 17 mg/dL with GLP-1 receptor agonists and increased by 3 to 9 mg/dL with DPP-4 inhibitors. Changes in high-density lipoprotein cholesterol (HDL-C) levels are generally minimal with the use of...
either GLP-1 receptor agonists or DPP-4 inhibitors. 

The greatest effect from antihyperglycemic agents on lipid profile has been observed with triglyceride level. Reductions in triglyceride level of 12 to 40 mg/dL have been reported with GLP-1 receptor agonists. Triglyceride changes observed with DPP-4 inhibitors range from a reduction of 35 mg/dL to an increase of 16 mg/dL.

In the Liraglutide Effect and Action in Diabetes (LEAD)-6 study, the safety and efficacy of the GLP-1 receptor agonist liraglutide (1.8 mg once daily) were compared with those of the GLP-1 receptor agonist exenatide (10 μg twice daily) in individuals with inadequately controlled T2DM who were taking maximally tolerated doses of metformin, sulfonylurea, or both. Liraglutide and exenatide were found to produce similar reductions in LDL-C levels (8 mg/dL vs 7 mg/dL, respectively), but liraglutide demonstrated a statistically significant greater reduction in triglyceride level compared to exenatide (36 mg/dL vs 20 mg/dL, respectively; P = .0485).

Although the evidence is limited, DPP-4 inhibitors have also been shown to produce beneficial effects on blood pressure and lipid level. In patients with moderate hypertension and no diabetes mellitus, the DPP-4 inhibitor sitagliptin phosphate (50-100 mg daily) reduced systolic and diastolic blood pressure by more than 2 mm Hg compared to placebo. Sitagliptin also reduced plasma triglyceride level by 10% to 15% and increased HDL-C level by more than 5% in doses of 25 to 100 mg daily as monotherapy over 12 weeks in patients with T2DM.

Analysis of data from 8 randomized phase II and phase III clinical trials suggests a potential reduction in cardiovascular events with the use of saxagliptin in patients with T2DM. However, results from large, prospective clinical outcome trials are needed before any conclusive statements can be made regarding the effects of saxagliptin on CVD risk.

Incretin-based agents should not be primarily prescribed based on their effects on CVD risk. However, the effects of GLP-1 receptor agonists on blood pressure and the effects of GLP-1 receptor agonists and DPP-4 inhibitors on lipid profile could be considered added benefits for all patients with T2DM.

Control of Nonglycemic Risk Factors

Although glycemic control is an important predictor of complications and costs associated with T2DM, nonglycemic risk factors are far more important in determining global CVD risk and outcomes. The ADA standards of medical care, a scientific statement from the ADA and AHA on prevention of CVD in patients with diabetes mellitus, and the American Association of Clinical Endocrinologists (AACE) medical guidelines for clinical practice all recommend a comprehensive approach for treatment of patients with T2DM that includes effective glycemic control and management of body weight, blood pressure, lipids, and other CVD risk factors. Unfortunately, simultaneous control of hyperglycemia and cardiovascular risk factors is difficult to achieve.

Only 7% of patients with T2DM in the US primary care setting have been shown to simultaneously achieve all 3 of the ADA goals (ie, HbA₁c < 7%, blood pressure < 130/80 mm Hg, LDL-C < 100 mg/dL). In Norway, data from a nationwide study demonstrated that 13% of patients with T2DM achieved the combined study targets of HbA₁c less than 7.5%, blood pressure less than 140/85 mm Hg, and total cholesterol/HDL-C ratio less than 4.0. In addition, an analysis of published literature revealed that among patients with diabetes mellitus, treatment outcomes were not superior with physicians who were specialists or subspecialists than with physicians who were primary care generalists.

Numerous studies have demonstrated the efficacy of controlling individual cardiovascular risk factors for preventing or slowing CVD in individuals with diabetes mellitus. Substantial bene-
Body Weight

Even small reductions in body weight have been shown to have beneficial effects on cardiovascular risk factors in patients with T2DM. Anderson et al. performed a meta-analysis of the effects of weight loss on patients with obesity and T2DM, including data on cardiovascular risk factors at 12-week follow-up. In this meta-analysis, weight reduction (9.6% from baseline) was associated with improvements in other CVD risk factors, including fasting plasma glucose level (-25.7% from baseline), total serum cholesterol level (-9.2% from baseline), LDL-C level (-11.0% from baseline), triglyceride level (-26.7% from baseline), systolic blood pressure (-8.1% from baseline), and diastolic blood pressure (-8.6% from baseline). The authors concluded that weight reduction may be the most important component in the treatment of obese patients with T2DM.

The Action for Health in Diabetes (Look AHEAD) trial, an ongoing investigation sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, is evaluating whether modest weight loss (≥7%) and increased physical activity (≥175 min per week) can reduce the incidence of fatal and nonfatal heart attack and stroke in overweight individuals with T2DM. The primary hypothesis of Look AHEAD is that the incidence of the first postrandomization occurrence of a composite outcome (ie, cardiovascular death, hospitalized angina, nonfatal myocardial infarction, nonfatal stroke) over a planned 13.5-year follow-up will be reduced among participants assigned to lifestyle intervention. The most recent ADA nutrition and intervention recommendations also underscore the importance of weight management and physical activity.

Numerous options exist for the prevention and management of obesity. Treatment for patients with obesity should be individually tailored to match the patient’s age, sex, degree of obesity, health risks, metabolic and psychosocial characteristics, and outcomes of previous weight loss attempts. Among the most important goals of obesity management are preferential reduction of abdominal fat, amelioration of obesity-related health risks, improvements in comorbidities and quality of life, and reductions in mortality rate.

Establishing realistic goals before initiating a weight-reduction strategy is important. Even moderate weight loss (ie, 5% of body weight) is associated with decreased insulin resistance and improvements in glucose control, lipid profile, and blood pressure in patients with T2DM. However, challenges related to patient adherence and motivation exist. For example, weight gain associated with antidiabetic medications may increase cardiovascular risk and reduce adherence to treatment. Intensive, long-term intervention with lifestyle modification and behavioral and pharmacologic treatment is needed to achieve and maintain weight loss.

Blood Pressure

Even small elevations of blood pressure can have deleterious effects on patients with or without diabetes mellitus. In patients with a baseline blood pressure of 115/75 mm Hg, an increase of 20 mm Hg to the systolic blood pressure or an increase of 10 mm Hg to the diastolic blood pressure doubles the risk of cardiovascular mortality. Each subsequent increase of 20 mm Hg to the systolic blood pressure or 10 mm Hg to the diastolic blood pressure again doubles the risk of cardiovascular-related death.

Overall blood pressure reduction provides beneficial outcomes in patients with T2DM. The UKPDS 38 trial showed that tight control of blood pressure (ie, target <150/85 mm Hg) compared to less aggressive blood pressure control produced an overall 24% risk reduction in fatal and nonfatal diabetes mellitus endpoints, a 37% risk reduction in microvascular complications, and a 32% risk reduction in diabetes mellitus-related deaths.

Current guidelines from the ADA, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), and the National Kidney Foundation recommend a systolic blood pressure less than 130 mm Hg and a diastolic blood pressure less than 80 mm Hg for patients with T2DM.

In clinical practice, multiple agents are needed for adequate blood pressure control. Many currently available agents—both generic and proprietary—are pleotropic, blunting the effects of the altered neuroendocrine system. Blood pressure reductions achieved with an inhibitor of the RAS system may have unique advantages for initial or early treatment of patients with hypertension. The clinical effects of angiotensin II include progression of vascular disease from hypertension to atherosclerosis to myocardial infarction, as well as vascular and myocardial remodeling and heart failure—culminating in end-stage organ failure and death. Angiotensin II plays the central role in driving this progression and has direct pathobiologic effects on a variety of tissues at each stage in the development of CVD.

The role of RAS inhibition, using the angiotensin-converting enzyme inhibitor (ACEI) captopril, in slowing the progression of renal disease in patients with type 1 diabetes mellitus was established by Lewis et al. In 2001, 2 studies established the efficacy of the angiotensin receptor blockers (ARBs) losartan potassium and irbesartan in slowing the progression of renal disease in patients with T2DM. In the large, well-designed Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study, involving patients with hypertension and left ventricular hypertrophy, use of losartan was more effective than atenolol in reducing the composite primary endpoints of cardiovascular mortality, stroke, and myocardial infarction.
<table>
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<th>CVD Risk Factor</th>
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<tr>
<td>Hypertension(^{46,48})</td>
<td>□ Measure BP at all routine visits □ BP ≥130/80 mm Hg on 2 separate visits confirms HTN diagnosis</td>
<td>BP &lt;130/80 mm Hg*</td>
<td>□ Lifestyle therapy for maximum 3 mo with BP 130-139/80-89 mm Hg¹ □ Initial pharmacotherapy should include ACEI or ARB □ If goals not achieved, add thiazide diuretic for patients with eGFR ≥30 ml/min/1.73 m²; add loop diuretic for patients with eGFR &lt;30 ml/min/1.73 m² □ ≥2 agents at maximum doses generally required to achieve targets</td>
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<td>Hyperlipidemia(^{46,48})</td>
<td>□ Measure fasting lipid profile annually in most patients □ Repeat lipid assessment every 2 y in patients with low-risk lipid values (LDL-C &lt;100 mg/dL, HDL-C &gt;50 mg/dL, TG &lt;150 mg/dL) □ LDL-C &lt;100 mg/dL³ □ LDL-C reduction of -30%-40% from baseline is alternative goal □ TG &lt;150 mg/dL; HDL-C &gt;40 mg/dL (men) and &gt;50 mg/dL (women) desirable</td>
<td>□ Lifestyle therapy for all patients with T2DM and hyperlipidemia⁷ □ Statins are drugs of choice for lowering LDL-C □ Add statins to lifestyle therapy for patients with overt CVD; without CVD but age &gt;40 y and ≥1 CVD risk factor (regardless of baseline LDL-C); with LDL-C =100 mg/dL; or with multiple CVD risk factors</td>
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<td>Antiplatelet therapy(^{46,48})</td>
<td>Assess CVD risk every 5 y in most patients unless risk factors change³</td>
<td>Prevention of CVD event</td>
<td>□ Consider aspirin (75-162 mg/d) as primary prevention strategy in patients at increased CVD risk (10-y risk &gt;10%); this includes most men age &gt;50 y and most women age &gt;60 y who have at least 1 additional major risk factor (eg, family history of CVD, HTN, smoking, dyslipidemia, albuminuria) □ Aspirin should not be recommended for primary CVD prevention in adults at low CVD risk (10-y CVD risk &lt;5%), such as men age &lt;50 y and women age &gt;60 y with no major additional CVD risk factors □ Clinical judgment is required to determine if aspirin is needed for primary CVD prevention in adults at moderate CVD risk (10-y CVD risk 5%-10%) □ Use aspirin (75-162 mg/d) as secondary CVD prevention in patients with history of CVD □ Combination therapy with aspirin (75-162 mg/d) and clopidogrel (75 mg/d) is reasonable for up to 1 y after acute coronary syndrome</td>
</tr>
<tr>
<td>Smoking cessation(^{46,48})</td>
<td>□ Ask about tobacco use at all patient visits □ Assess user’s willingness to quit</td>
<td>Smoking cessation</td>
<td>□ Advise all patients not to smoke or to quit smoking □ Patient can be assisted by counseling and by developing plan to quit □ Incorporate follow-up, referral to special programs, or pharmacotherapy (eg, nicotine replacement, bupropion) as needed</td>
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Figure 2. Summary of select recommendations for the prevention and management of cardiovascular disease (CVD) complications in patients with type 2 diabetes mellitus (T2DM).\(^{46-48}\) **Abbreviations:** ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride. *Based on patient characteristics and response to treatment, higher or lower systolic BP targets may be appropriate. †Lifestyle therapy consists of reducing sodium intake (<1,500 mg/d) and excess body weight; increasing consumption of fruits, vegetables (8-10 servings/d), and low-fat dairy products (2-3 servings/d); avoiding excessive alcohol consumption (≤2 servings/d in men, ≤1 serving/d in women); and increasing physical activity levels. In individuals with overt CVD, an LDL-C goal <70 mg/dL, using a high dose of statin, is an option. §A sample risk assessment calculator can be found at http://hp2010.nhlbi.nih.gov/calculator.asp. //For patients with CVD and documented aspirin hypersensitivity, clopidogrel (75 mg/d) should be used.

This finding was mainly the result of reduction in the risk of stroke in the losartan group.\(^{70,71}\)

Inhibition of RAS has also provided beneficial effects on cardiovascular outcomes in high-risk patients with T2DM,\(^{72}\) in patients with T2DM and heart failure,\(^{73-76}\) and in patients with T2DM and nephropathy.\(^{77}\) In a meta-analysis of 12 randomized controlled trials evaluating the efficacy of RAS inhibition in prevention of diabetes mellitus, the use of...
an ACEI or ARB was associated with reductions in the incidence of newly diagnosed T2DM by 27% and 23%, respectively—and by 25% in the pooled analysis. Most recently, the blood pressure arm of the ADVANCE trial demonstrated that routine administration of a fixed combination of the ACEI perindopril erbumine and the diuretic indapamide reduced combined microvascular and macrovascular outcomes, as well as CVD risk and total mortality.  

Dyslipidemia  
Multiple clinical trials have demonstrated beneficial effects from pharmacologic treatments (primarily statins) on CVD outcomes in patients with T2DM and elevated levels of LDL-C—including primary and secondary prevention of CVD events and cardiovascular deaths. However, most patients with T2DM have a pattern of dyslipidemia that includes low levels of HDL-C and elevated levels of triglycerides. The clinical trial data related to the treatment of such patients are not as robust. Canner et al. reported that nicotinic acid can reduce CVD outcomes, though this study consisted of individuals without T2DM. Gemfibrozil has been shown to decrease rates of CVD events in a nondiabetic cohort and in a diabetic subgroup in one of the larger trials. However, in a large trial specific to patients with diabetes mellitus, fenofibrate failed to reduce overall cardiovascular events.  

For most patients with T2DM, the first priority of dyslipidemia management is to lower LDL-C levels to a target goal of less than 100 mg/dL for primary prevention and less than 70 mg/dL for secondary prevention. In both cases, the use of statins are considered the recommended first pharmacologic step. However, as previously stated, patients with T2DM often have multiple derangements in their lipid profile and require multiple-drug therapy. If HDL-C level is less than 40 mg/dL and LDL-C level is between 100 and 129 mg/dL, gemfibrozil or niacin might be used if a patient is intolerant to statins.  

Niacin is the most effective agent for raising HDL-C level. At high doses, niacin can substantially increase blood glucose level. However, recent studies demonstrate that at modest doses (750-2000 mg/d) of niacin, substantial improvements in LDL-C, HDL-C, and triglyceride levels are accompanied by only modest changes in glucose level, which are generally amenable to adjustment of the patient’s antihyperglycemic medications. Combination therapy (e.g., statin plus fibrate, statin plus niacin) should be used with caution in patients with T2DM because the rate of adverse events is increased with use of combination therapy, and the effects of combination therapy on CVD outcomes are unknown.  

Antiplatelet Therapy  
Atherothrombosis is a leading cause of death in patients with T2DM. Platelets play a pivotal role in atherothrombosis, and platelets of patients with T2DM are hyperreactive. Numerous studies have investigated the usefulness of antiplatelet therapy for primary and secondary prevention of atherothrombotic events in patients with diabetes mellitus. Although aspirin has been shown to be effective in the secondary prevention of CVD morbidity and mortality, its net benefit in primary prevention among patients with no previous cardiovascular events is more controversial, and individualization of treatment may be necessary.  

Current guidelines recommend primary prevention of atherothrombosis in patients with T2DM who are at increased CVD risk (10-year risk >10%). These patients include most men older than 50 years and most women older than 60 years who have at least 1 additional major risk factor for CVD (eg, family history of CVD, hypertension, smoking, dyslipidemia, albuminuria).  

Smoking Cessation  
A large body of evidence links cigarette smoking to health risks in individuals with and without T2DM. Individuals with T2DM have a heightened risk of CVD and premature death and an increased rate of microvascular complications of diabetes mellitus. In addition, smoking may play a role in the development of T2DM. Addressing this modifiable risk factor is crucial in cardiovascular risk reduction. Assessing the patient’s stage of change can be helpful in determining the preferred type of intervention.  

Patient Adherence and Acceptance  
It is often challenging for patients with T2DM to adhere to their treatment regimens. Figure 3 provides a list of patient-related and medication-related barriers to treatment adherence in patients with T2DM. Treatment adherence is fundamental to achieving good glycemic control in patients, with multiple studies showing a clear relationship between adherence with treatment regimens and HbA1c goal attainment. Therefore, it is important to proactively address potential barriers to treatment that patients perceive and encounter.

It is also important that patients be aware of the health care professional's perspectives in type 2 diabetes, cardiovascular risk, and treatment goals, pp 52-60, © 2010, with permission from JTE Multimedia.
involved in selecting their antidiabetic medication regimens, and treatment goals must be agreed upon between patient and physician. Better communication by providers and improved patient education regarding the risks and benefits of various medications can help patients and physicians agree on specific strategies needed to meet treatment goals. Patients who share in the treatment decision-making process and who believe in the self-efficacy and self-management of their care are more likely to be in agreement with achieving treatment goals.54

Conclusion
Cardiovascular disease is the most common cause of morbidity and mortality in patients with T2DM. Intensive glycemic control has been shown to prevent the development and progression of microvascular complications in patients with T2DM. However, the effect of intensive glucose control on the prevention of macrovascular disease and major cardiovascular events remains unclear. Although adequate glycemic control is an important part of the prevention of complications in patients with T2DM, the control of nonglycemic risk factors, including body weight, blood pressure, and lipid levels, is far more important in determining global CVD risk and outcomes.

References


Partnership to Fight Chronic Disease

The American Osteopathic Association has been an active member of the Partnership to Fight Chronic Disease (PFCD) since 2007. This supplement promotes the ideals of this partnership.

The PFCD is a national and state-based coalition of hundreds of provider, patient, community, business, and labor groups committed to raising awareness of the leading causes of death, disability, and rising healthcare costs in the United States—chronic diseases such as diabetes, asthma, cancer, and heart disease. In addition, the PFCD has worked to ensure that prevention and wellness measures were incorporated into healthcare reform legislation passed by Congress in 2010.

For additional information, visit www.fightchronicdisease.org.