Type 2 Diabetes and Cardiovascular Disease: Reducing the Risk

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At Bartels’s clinical practice at the University Primary Care Clinic at Belvidere, which is a primary care training site operated by the University of Illinois College of Medicine at Rockford, he is responsible for providing diabetic education to patients; teaching medical, pharmacy, and nurse practitioner students in the clinic setting; and conducting clinical research with investigational antidiabetic medications.

Bartels also provides didactic lectures on the pharmacology and therapeutics of cardiovascular and antidiabetic agents for medical and pharmacy students from the University of Illinois. He has given numerous invited presentations on diabetes management to pharmacists, physicians, and certified diabetes educators, and he has been involved in writing and publishing several key papers on diabetes and its management in pharmacy journals and other professional publications.

Michael H. Davidson, MD, FACC, FACP, is a board-certified cardiologist and founder, president, and chief executive officer of the Chicago Center for Clinical Research, presently part of Radiant Research. He is director of preventive cardiology and atherosclerosis research at Rush University Medical Center in Chicago, where he directs the multiple risk factor reduction lipid clinic, and a professor in the Department of Medicine and Pharmacology at Rush University School of Medicine. Davidson received his medical degree from Ohio State University School of Medicine in Columbus and completed a cardiology fellowship at Rush University Medical Center. He is a fellow of the American College of Cardiology and the American College of Chest Physicians.

An active researcher, Davidson’s clinical research background encompasses both pharmaceutical and nutritional clinical trials; his extensive research on statins, novel lipid-lowering drugs, and nonpharmacologic risk factor reduction has established him as a key opinion leader in this area. His research also includes extensive work with food additives, dietary supplements, and health claim petitions to the U.S. Food and Drug Administration.

Davidson is a prolific author and lecturer on lipid disorders, nutrition, and atherosclerosis, having coordinated more than 700 clinical trials in areas of preventive cardiology; published more than 130 articles in such medical journals as the Journal of the American Medical Association, the Journal of the American College of Cardiology, Circulation, and Atherosclerosis; and authored The Mobile Lipid Clinic: A Companion Manual.

William C. Gong, PharmD, FASHP, FCShP, is an associate professor of clinical pharmacy and director for residency and fellowship training at the University of Southern California School of Pharmacy. He received his PharmD from the University of Southern California and completed his residency in clinical pharmacy at the Los Angeles County+USC Medical Center. Gong practices at the Edward R. Roybal Comprehensive Health Care Center in the Diabetes Management Center and general medicine clinics as a clinical pharmacist. His specialty practice area includes diabetes care and the cardiovascular diseases, and he is currently a preceptor for the American Society of Health-System Pharmacists (ASHP) Diabetes Patient Care Traineeship.

As a faculty member, Gong is responsible for teaching in the primary care clerkships and providing lectures in the therapeutics series. He is actively involved with professional organizations, having served as vice chair and chair for the Primary Care Specialty Practice Group of ASHP, as an executive board member of the ASHP Section of Clinical Specialists, and on the ASHP Commission on Credentialing. He has published and given numerous presentations on ambulatory care pharmacy practice issues and diabetes care on the national and local levels. Gong is cited in the Congressional Record for pharmacy practice achievements, is a fellow of ASHP, and a fellow of the California Society of Health-System Pharmacists.
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S16 Continuing Education*:
   CE Submission Instructions and Posttest Worksheet

Target Audience
Pharmacists and physicians managing diabetic and prediabetic patient populations

Learning Objectives
Upon completion of this program, participants will be better able to
1. describe current, emerging and future drug therapies for type 2 diabetes mellitus (T2DM),
2. formulate treatment strategies and goals of therapy for T2DM,
3. analyze the results of cardiovascular outcome studies conducted in the T2DM patient population, and
4. evaluate the clinical and cost implications of reducing cardiovascular complications in T2DM.

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*A total of 0.20 CEUs (2.0 contact hours) for pharmacists (ACPE Program No. 221-000-07-003-H01) and a maximum of 2.0 AMA PRA Category 1 credits for physicians will be awarded for successful completion of this continuing education program. For faculty disclosures, please see page S13. For accreditation information, please see page S16.

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ABSTRACT

BACKGROUND: Type 2 diabetes (T2DM) is a major risk factor for developing cardiovascular disease (CVD). The growing epidemic of T2DM has contributed to CVD becoming the leading cause of morbidity and mortality in the United States.

OBJECTIVE: To review the pathophysiology of CVD; to demonstrate the interrelatedness of CVD, the metabolic syndrome, and T2DM; and to discuss treatment options that may reduce the risk of CVD in patients with T2DM.

SUMMARY: Recent data from the International Diabetes Federation show that the worldwide prevalence of T2DM is much higher than previously estimated. Managing patients with T2DM continues to severely burden the U.S. health care system. Furthermore, most costs associated with managing these patients are associated with treating CVD complications. Studies have shown that several agents can decrease the risk of CVD in patients with T2DM.

CONCLUSIONS: To combat the diabetes epidemic, clinicians should treat patients with T2DM and prediabetes early and aggressively to control their metabolic disturbances and reduce the risk of CVD. Diet, exercise, and several pharmacologic agents have been shown to reduce the risk of CVD.

KEYWORDS: Type 2 diabetes, Cardiovascular disease, Atherosclerosis, Thiazolidinediones

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Type 2 diabetes mellitus (T2DM) has reached the point of a global epidemic. According to newly released data from the International Diabetes Federation (IDF), 246 million people worldwide (5.9% of the world’s adult population) have diabetes and 46% of those affected are 40 to 59 years old.1 Previous figures from the World Health Organization (WHO) estimated that approximately 171 million people had diabetes.2 In 2005, estimates from the Centers for Disease Control and Prevention indicated that approximately 7% of the U.S. population, or 20.8 million people, had diabetes.3

T2DM accounts for 90% to 95% of all diagnosed cases and is usually associated with obesity, physical inactivity, older age, family history of diabetes, impaired glucose metabolism, and history of gestational diabetes. In addition, certain ethnic backgrounds have a higher prevalence of diabetes (African Americans, Hispanic/Latino Americans, American Indians, some Asian Americans, and native Hawaiians or other Pacific Islanders).3 Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States.4 T2DM diabetes is a major risk factor for developing macrovascular complications, including atherosclerosis, myocardial infarction (MI), stroke, and peripheral vascular disease. In adults with diabetes, the risk of death from heart disease and stroke is 2 to 4 times higher than in adults without diabetes.3 Furthermore, heart disease and stroke account for approximately 65% of deaths in people with diabetes.3 Because of the increasing prevalence of diabetes and the complexities of treating patients with multiple comorbidities, costs for T2DM are skyrocketing. Diabetes has become a major cause of morbidity and mortality and is a costly burden on the U.S. health care system. In 2002, the American Diabetes Association (ADA) estimated the total costs (medical expenditures and lost productivity) of diabetes at $132 billion ($92 billion in direct costs and $40 billion in indirect costs).3

Cardiovascular (CV) complications account for more than 50% of the total costs of managing diabetes complications. It is estimated that the costs for managing complications over a 30-year period are $47,240 per patient.5 Over this period, approximately $24,330 (52%) is spent on managing macrovascular complications.6 However, most of these costs occur very early in the progression of T2DM. During the first 5 years of treating patients with T2DM, 85% of the total costs of care are associated with managing macrovascular complications.6 Over the course of 10 years, management of macrovascular complications remains a significant contributor at 77% of the total cost of care.6 Consequently, minimizing CV complications with aggressive treatment in the early stages of T2DM may have a significant impact on decreasing health care system costs.

Metabolic Syndrome

The growing epidemic of obesity in the United States is a major
Approximately 90% of patients with T2DM are overweight (body mass index [BMI] 25-29 kg/m²), 60 million are obese (BMI 30-39 kg/m²), and 9 million are morbidly obese (BMI >40 kg/m²). 7 Approximately 90% of patients with T2DM are classified as obese. 7 Obese patients are prone to develop CVD, including chronic venous insufficiency, hypertension, hyperlipidemia, atherosclerosis, stroke, deep vein thrombosis, and peripheral vascular disease. 7 Furthermore, abdominal obesity has been clearly implicated in the development of insulin resistance and the pathogenesis of T2DM and is considered a significant component of the metabolic syndrome. 8-12

The metabolic syndrome has been described by several medical organizations as a cluster of metabolic abnormalities, including insulin resistance, hyperglycemia, hypertension, reduced high-density lipoprotein cholesterol (HDL-C) levels, and increased triglyceride (TG) levels. 8 Table 1 lists specific definitions of the metabolic syndrome from major medical organizations. 9-13-17 However, in the United States, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition is generally applied. It is hypothesized that genetic factors predispose the patient to developing the metabolic syndrome, along with acquired factors such as obesity, physical inactivity, and high-carbohydrate diets. 9 Approximately 86% of patients with T2DM have the metabolic syndrome. 18 More important, the prevalence of CVD markedly increases in patients who have this syndrome. 18 Furthermore, the IDF strongly suggests that the metabolic syndrome is the driving force behind the global epidemics of T2DM and CVD. 17

Pathogenesis of Cardiovascular Disease

Clustered metabolic disorders (hyperglycemia, dyslipidemia, and hypertension), that is, the metabolic syndrome, contribute to the development and progression of CVD. Genetic susceptibility and environmental factors, including poor nutrition, obesity, and lack of physical activity, also play a significant role in developing CVD. 18-22 Mature adipocytes produce several adipokines (proinflammatory mediators), including C-reactive protein (CRP), interleukin-6, tumor necrosis factor-alpha (α), visfatin, leptin, resistin, angiotensinogen, and plasminogen activator inhibitor-1 (PAI-1), that are associated with developing CVD. 22 Research has shown that circulating levels of several adipokines are elevated in obese and insulin-resistant states. Additionally, visceral fat appears to secrete higher levels of adipokines than subcutaneous fat. Figure 1 shows how visceral fat accumulation contributes to the metabolic syndrome and leads to the dysregulation of certain adipokines. 22 Loss of visceral fat is associated with decreased circulating levels of most adipokines, but increased levels of adiponectin. 22 Researchers have found that adiponectin has antiatherogenic properties, whereas other adipokines have atherogenic properties. Furthermore, emerging evidence suggests that certain adipokines may directly affect the endothelium and the progression of atherosclerosis through proinflammatory properties. 23

Endothelial dysfunction is one of the earliest events in the pathogenesis of CVD. 24 The endothelium, the innermost layer of blood vessels, is an active organ that regulates multiple vascular functions. It not only acts as a barrier but also regulates vascular growth, platelet function, and coagulation. When the endothelium is healthy, it releases nitric oxide (NO) and maintains a balance between various functions such as dilatation/constriction, growth inhibition/promotion, antithrombosis/prothrombosis, and anti-inflammation/proinflammation. Under certain conditions (e.g., elevated or oxidized low-density lipoprotein cholesterol [LDL-C], diabetes, hypertension) NO is reduced, leading to imbalance of 1 or more of these functions and a proatherogenic state. 26 The compensatory responses that alter the normal homeostatic properties of the endothelium are key in the development of atherosclerosis.

The proinflammatory state has been directly linked to insulin resistance and atherogenesis. 9 Studies have shown that CRP is a strong predictor of cardiovascular events. 21 Elevated CRP levels are found in obese patients and in those with the metabolic syndrome and are directly correlated with the amount of body fat assessed by BMI and high waist circumference. CRP decreases NO production and directly influences atherogenesis by inducing the expression of adhesion molecules and leukocyte mediators, which promote adherence to the endothelium. 23

Insulin resistance and several other factors related to central adiposity have been implicated in endothelial dysfunction. Hyperglycemia induces free radical production and increases superoxide production and oxidative stress, which contributes to atherogenesis. Hyperglycemia also augments the expression of adipokines, further inducing adipokine-related endothelial dysfunction. 21 Additionally, impaired insulin action in adipose tissue results in elevated rates of lipolysis and free fatty acid (FFA) release. 21 The increased availability of FFAs leads to several detrimental metabolic effects, including impaired insulin secretion; insulin resistance; impaired vasodilation; reduced NO production; increased levels of small, dense, highly atherogenic LDL-C; and decreased HDL-C levels.

Emerging data continue to support the proposal that abdominal obesity increases CVD risk via production of adipokines, which appear to play a central role and may serve as the cellular link mediating both the metabolic syndrome of insulin resistance and the endothelial dysfunction present in the obese state. 26 Treatment that is focused on reducing total body and visceral fat may help reverse the metabolic and vascular abnormalities. Studies have shown that lifestyle interventions resulting in weight loss and increased physical activity lead to decreased inflammatory proteins and reduced insulin resistance. Several drugs also can reduce inflammatory adipokines. These agents include thiazolidinediones (TZDs), statins, fibrates, niacin, aspirin, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs). 21
Type 2 Diabetes Treatment Options and Goals of Therapy

A wide range of treatment options exist for patients with T2DM. Treatment should be considered in all patients who meet the diagnostic criteria for diabetes mellitus:

- Symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) plus casual (any time of day without regard to meals) plasma glucose concentration ≥200 mg/dL.
- Fasting (no caloric intake for at least 8 hours) plasma glucose

### TABLE 1: Definitions of Metabolic Syndrome From Major Organizations

<table>
<thead>
<tr>
<th>Organization</th>
<th>WHO(^{13,14})</th>
<th>NCEP ATP III(^{15})</th>
<th>AHA/NHLBI(^{16})</th>
<th>AACE(^{18})</th>
<th>IDF(^{17})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic criteria</strong></td>
<td>Insulin resistance (refer to glucose intolerance section) + any 2 components</td>
<td>Three or more components</td>
<td>Any 3 of the 5 components</td>
<td>Diagnosis based on clinical judgment of risk factors</td>
<td>Central obesity + any 2 components</td>
</tr>
<tr>
<td><strong>Abdominal obesity</strong></td>
<td>BMI &gt;30 kg/m² and/or waist:hip ratio Men &gt;0.9 Women &gt;0.85</td>
<td>Waist circumference Men &gt;40 inches (102 cm) Women &gt;35 inches (88 cm)</td>
<td>Waist circumference Men ≥40 inches Women ≥35 inches</td>
<td>BMI &gt;25 kg/m² or waist circumference Men &gt;40 inches Women &gt;35 inches</td>
<td>Waist circumference Europids Male ≥94 cm Female ≥80 cm South Asians and Chinese Male ≥90 cm Female ≥80 cm Japanese Male ≥85 cm Female ≥80 cm Specific data is not yet available for other ethnic groups</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>Elevated TGs</td>
<td>TGs ≥150 mg/dL.</td>
<td>TGs ≥150 mg/dL or drug therapy for elevated TGs</td>
<td>TGs &gt;150 mg/dL.</td>
<td>TGs ≥150 mg/dL or specific treatment for elevated TGs</td>
</tr>
<tr>
<td>Reduced HDL-C</td>
<td>HDL-C Men &lt;35 mg/dL Women &lt;39 mg/dL</td>
<td>HDL-C Men &lt;40 mg/dL Women &lt;50 mg/dL</td>
<td>HDL-C Men &lt;40 mg/dL Women &lt;50 mg/dL or drug therapy for low HDL-C</td>
<td>HDL-C Men &lt;40 mg/dL Women &lt;50 mg/dL or specific treatment for low HDL-C</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>SBP ≥140 mm Hg or DBP ≥90 mm Hg or drug therapy for hypertension</td>
<td>BP ≥130/85 mm Hg</td>
<td>BP ≥130 mm Hg or DBP ≥85 mm Hg or drug therapy for hypertension</td>
<td>BP &gt;130/85 mm Hg</td>
<td>SBP ≥130 mm Hg or DBP ≥85 mm Hg or treatment of previously diagnosed hypertension</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>Any of the following: T2DM Impaired FPG Impaired glucose tolerance If normal FPG (&lt;110 mg/dL) glucose uptake below the lowest quartile</td>
<td>FPG ≥110 mg/dL.</td>
<td>FPG ≥100 mg/dL or drug therapy for elevated glucose</td>
<td>FPG 110-126 mg/dL 2-hour postglucose challenge 140-200 mg/dL</td>
<td>FPG ≥110 mg/dL or previously diagnosed T2DM If FPG &gt;100 mg/dL, oral glucose tolerance test strongly recommended but not required for diagnosis of syndrome</td>
</tr>
</tbody>
</table>

AACE=American Association of Clinical Endocrinologists; AHA/NHLBI=American Heart Association/National Heart, Blood, and Lung Institute; BMI=body mass index; BP=blood pressure; CVD=cardiovascular disease; DBP=diastolic blood pressure; FPG=fasting plasma glucose; HDL-C=high-density lipoprotein cholesterol; IDF=International Diabetes Federation; NCEP ATP=National Cholesterol Education Program Adult Treatment Panel; SBP=systolic blood pressure; T2DM=type 2 diabetes mellitus; TGs=triglycerides; WHO=World Health Organization.
recommendations state that reductions, when treating T2DM, Thiazolidinediones have also shown beneficial effects. In this study, a reduction in risk of CVD. However, lifestyle changes are often inadequate. Accordingly, the recent consensus statement from the ADA and the European Association for the Study of Diabetes (EASD) recommends initiating drug therapy immediately and in a step-wise approach when treating patients with T2DM. The following interventions are recommended:

- Step 1: Initiate metformin (if no contraindications) and lifestyle changes to decrease weight and increase physical activity.
- Step 2: Add other therapy, including TZDs, sulfonylureas, and/or basal insulin, to meet glycemic goals.

Additional agents that may be used include α-glucosidase inhibitors, meglitinides, pramlintide (amylin analog), exenatide (glucagon-like peptide [GLP-1] receptor agonist), and sitagliptin (dipeptidyl peptidase-IV [DPP-IV] inhibitor). The ADAs and the EASDs T2DM treatment algorithm (Figure 2), based on clinical trials and experience, considers individual therapies, synergistic effects of therapies, and cost of treatments. When treating T2DM, patients may initially be controlled with monotherapy but because of the progressive nature of the disease will eventually require a combination of agents to meet glycemic goals. Table 2 provides a comparison of currently available T2DM oral treatment options. To minimize complications, management of diabetes has increasingly become more aggressive. The recent consensus statement from the ADA and EASD recommends initiating or changing therapy when the glycosylated hemoglobin (AIC) is 7% or greater. Since research has shown the interrelationships among the components associated with T2DM (hypertension, dyslipidemia, hyperglycemia/insulin resistance, and obesity), a multifactorial treatment approach is key to facilitate addressing all metabolic disturbances concomitantly.

Because of the increasing number of patients developing T2DM and the impact on CV complications and health care costs, the ADA has undertaken a more proactive approach to help control this epidemic. The ADAs recent position statement discusses specific nutrition recommendations and other interventions to prevent the onset of T2DM. This statement recommends moderate weight loss (5%-7%), decreased caloric and fat intake (by approximately 30%), and regular physical activity for primary prevention in patients at high risk for developing diabetes. Several studies have shown the benefits of lifestyle changes, such as diet and exercise, in patients with impaired glucose tolerance. Diet, exercise, and diet plus exercise interventions were associated with 31% (P < 0.030), 46% (P < 0.0005), and 42% (P < 0.005) reductions, respectively, in the risk of developing T2DM, whereas a second study with more intensive individualized diet and exercise counseling reduced the risk of T2DM by 58% (P < 0.001). Another study using diet and exercise showed reduced incidence of metabolic syndrome by 41% (P < 0.001).

Several drugs have demonstrated favorable outcomes in preventing or delaying the onset of diabetes. Metformin, acarbose, and orlistat have shown positive trends in reducing the progression to T2DM (relative risk reduction, 31%, 25%, and 37%, respectively). Thiazolidinediones have also shown beneficial effects on T2DM risk reduction. The Troglitazone in the Prevention of Diabetes (TRIPOD) trial showed reduced progression to diabetes (overall relative risk reduction, 56%, P = 0.02). In this study, a small group of Hispanic women (n = 133) with a past history of gestational diabetes were randomized to treatment with troglitazone or placebo with a median follow-up of 30 months. As a follow-up study to TRIPOD, the Pioglitazone in the Prevention of Diabetes (PIPOD) trial also showed positive results. PIPOD was conducted as an open-label, 3-year observational trial in 89 patients from the TRIPOD study. Pioglitazone halted the decline in beta (β)-cell function in patients previously treated with placebo and main-
Management of Hyperglycemia in Type 2 Diabetes

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Emerging studies are beginning to show that peroxisome proliferator-activated receptor (PPAR) agonists, including the TZD subclass for treating diabetes, have unique properties that may reverse the progression of atherosclerosis. PPARs regulate the expression of genes that control lipid metabolism and inhibit expression of proinflammatory genes. The PPAR family comprises 3 types of receptors—alpha (α), gamma (γ), and delta (δ). These receptors are found in the major cell types (e.g., macrophages, smooth muscle cells, lymphocytes, and endothelial cells) that are located in atherosclerotic lesions.

Activation of PPAR-α increases HDL-C synthesis, stimulates reverse cholesterol transport, decreases TG levels, and stimulates fatty acid oxidation. When PPAR-γ is activated, insulin sensitization, glucose homeostasis, lipid metabolism, and adipocyte differentiation occur. Researchers are studying the effects of PPAR-δ activation on fatty acid metabolism and obesity. Available drug therapy targeting PPARs include TZDs (PPAR-γ agonists) and fibrates (PPAR-α agonists).

Natural ligands for PPAR receptors include fatty acids and oxidized fatty acids. When the PPAR receptor is activated, there is a direct effect on vascular and inflammatory cells resulting in decreased cytokines, chemokines, and adhesion molecules and increased cholesterol efflux. Upon PPAR activation, there is also an indirect effect on adipose tissue, liver, and skeletal muscle that results in decreased FFA, glucose, and TG levels and increased insulin sensitivity and HDL-C levels. Both the direct and indirect effects reduce inflammation and diminish the progression of atherosclerosis.

Specific to TZDs, activation of the PPAR-γ receptor reduces insulin resistance, preserves pancreatic β-cell function, and may improve the CV risk profile by exerting positive effects on the dyslipidemia associated with T2DM. In addition, there is a decrease in renal microalbumin excretion, blood pressure, and arterial wall adhesion molecules proliferation/migration, as well as a reduction in PAI-1, CRP, and FFA levels. Circulating adiponectin, an antiatherogenic adipokine, is increased. Studies have shown that increased levels of adiponectin lead to improved insulin sensitivity and reduced risk of MI. Additionally, studies have shown that metformin reduces PAI-1 levels in patients with T2DM. Therefore, combined therapy with a TZD and metformin may have synergistic effects on reducing CV complications.

Cardiovascular Disease Risk Reduction

Patients with T2DM typically have several CV risk factors, which are listed in Table 3. The main treatment goal is to decrease the incidence of CV morbidity and mortality by reducing or eliminating...
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<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Expected Decrease in A1C (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Role in Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides $^{29}$</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Metformin hydrochloride (Glucophage, Glucophage XR)</td>
<td>Decreases hepatic glucose production</td>
<td>1-2</td>
<td>Inexpensive, weight loss, does not induce hypoglycemia, potential beneficial effect on CV outcomes</td>
<td>Contraindicated in renal disease or dysfunction and in heart failure patients requiring pharmacologic treatment, GI AEs, lactic acidosis (rare)</td>
<td>First-line therapy when contraindications do not exist</td>
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<tr>
<th>Thiazolidinediones (TZDs)</th>
<th>PPAR-$\gamma$ agonists $^{29}$</th>
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<tbody>
<tr>
<td>Pioglitazone hydrochloride (Actos)</td>
<td>Increases sensitivity of muscle, fat, and liver to exogenous insulin, activation of PPAR-$\gamma$ receptor plays a role in glucose and lipid metabolism</td>
<td>1-1.5</td>
<td>Pioglitazone: may improve lipid profile and provide CV benefits</td>
<td>Weight gain, fluid retention, may exacerbate heart failure, expensive</td>
<td>Treating insulin resistance and for CV benefits, including improved lipid profile with use of pioglitazone</td>
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<tr>
<td>Rosiglitazone maleate (Avandia)</td>
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<tr>
<th>Sulfonylureas $^{29}$</th>
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</thead>
<tbody>
<tr>
<td>Glipizide (Glucotrol), Glyburide (DiaBeta, Glynase Micronase) Glimepiride (Amaryl)</td>
<td>Enhances insulin secretion</td>
<td>1.5</td>
<td>Inexpensive</td>
<td>Initial weight gain, hypoglycemia, long-term therapeutic failure due to loss of $\beta$-cell function</td>
<td>When metformin and TZDs are contraindicated and/or cost is a consideration; may be useful for patients with noninsulin-resistant T2DM</td>
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<tr>
<th>Meglitinides $^{29}$</th>
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</thead>
<tbody>
<tr>
<td>Repaglinide (Prandin) Nateglinide (Starlix)</td>
<td>Stimulates insulin secretion (binds to different receptor than sulfonylurea)</td>
<td>1-1.5</td>
<td>Reduces blood glucose quickly, short-acting, less likely than sulfonylureas to cause hypoglycemia</td>
<td>Initial weight gain, short-acting, frequent dosing, expensive</td>
<td>Alternative agent if hypoglycemia is an issue with sulfonylurea; may help control postprandial hyperglycemia</td>
</tr>
</tbody>
</table>

$^{1}$A1C=hemoglobin A1C (glycosylated hemoglobin); AEs=adverse events; CV=cardiovascular; $\gamma$=gamma; GI=gastrointestinal; GIP=gastric inhibitory polypeptide; GLP-1=glucagon-like peptide-1; PPAR=peroxisome proliferator-activated receptor; T2DM=type 2 diabetes mellitus.

modifiable CV risk factors. Studies have shown a direct relationship between the A1C level and the number of coronary heart disease (CHD) events. Figure 3 demonstrates this relationship and shows that as the A1C approaches and exceeds 7%, the number of CHD events per 100 persons increases substantially. $^{27}$

There are several classes of agents that are used to decrease the risk of CV complications such as MI and stroke. Through blood pressure lowering and other positive effects, antihypertensive agents reduce CV complications. Studies have shown that antihypertensive therapy is associated with a 35% to 40% reduction in stroke incidence and a 20% to 25% reduction in MIs. $^{31}$ Because of renoprotective effects, ACE inhibitors and ARBs are often used as initial therapy in patients with diabetes. $^{31}$ The ADA blood pressure goal for patients with diabetes is $<130/80$ mm Hg. $^{31}$ Typically, patients with T2DM will require multiple agents to reach this goal. In addition, low-dose aspirin therapy, smoking cessation, and other lifestyle changes have proved beneficial. $^{27}$

Numerous studies with statins, fibrates, and other antihyperlipidemic agents have demonstrated the ability of these agents to reduce CV complications. $^{52-56}$ Patients with T2DM typically have mild to moderately increased LDL-C, elevated TG, and low HDL-C levels. The NCEP ATP III LDL-C goal for patients with diabetes is $<100$ mg/dL. If the TG level is $>500$ mg/dL, the TG level should be addressed before the LDL-C level is treated to avoid pancreatitis. $^{15}$ In addition, identification and treatment of the metabolic syndrome risk factors is recommended. Previously, low HDL-C was not considered a primary goal of treatment, but was treated by diet, exercise, and select lipid-lowering agents once the LDL-C.
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A CHD working group (25 investigators with expertise in epidemiology, endocrinology, molecular biology, public health, lipid metabolism, cardiovascular medicine, and preventive cardiology) addressed the impact of low HDL-C levels as a risk factor for CVD. This group concluded that by increasing HDL-C levels, the frequency of coronary artery disease (CAD) was reduced. More specifically, studies have shown that for every 1 mg/dL increase in HDL-C level, the incidence of CAD was decreased 2% to 3%. Recent evidence from a large matched retrospective cohort study (matched on HDL-C and TG levels, age, sex, and year of HDL-C and TG measurement) of patients who were treated with fibrates compared with patients who were not

### Table 2: Selected Drug Therapy Options for Type 2 Diabetes (continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Expected Decrease in A1C (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Role in Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-glucosidase inhibitors&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Serves the rate of polysaccharide digestion in the small intestine</td>
<td>0.5-0.8</td>
<td>Decreases postprandial hyperglycemia without causing hypoglycemia</td>
<td>Frequent GI AEs, including flatulence; frequent dosing, expensive</td>
<td>Useful for targeting postprandial hyperglycemia</td>
</tr>
<tr>
<td>Amylin agonists&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Synthetic analog of amylin, a ß-cell hormone inhibitor glucagon in a glucose-dependent manner</td>
<td>0.5-1</td>
<td>Weight loss, helps prevent postprandial hyperglycemia</td>
<td>Injections, frequent dosing, GI AEs, may worsen insulin-induced hypoglycemia, expensive</td>
<td>Use as adjunctive therapy in inadequately controlled patients using mealtime insulin (may be used with concurrent sulfonylurea agent and/or metformin)</td>
</tr>
<tr>
<td>Incretin mimetics/enhancers</td>
<td></td>
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<tr>
<td>Dipeptidyl peptidase-4 (DPP-4) inhibitors</td>
<td></td>
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<tr>
<td>Sitagliptin phosphate (Januvia)&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Slows the inactivation of incretin hormones (GLP-1 and GIP), which are involved in glucose homeostasis resulting in increased insulin release and decreased glucagon levels</td>
<td>0.6-0.8</td>
<td>Weight neutral, does not induce hypoglycemia, may improve ß-cell function</td>
<td>Expensive, very little clinical experience</td>
<td>Use as monotherapy or as adjunct therapy for inadequately controlled patient using metformin or TZD</td>
</tr>
<tr>
<td>Incretin mimetics/enhancers</td>
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<tr>
<td>Glucagon-like peptide-1 agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Exenatide (Byetta)&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Binds to GLP-1 receptors on the pancreatic ß-cells and potentiates glucose-mediated insulin secretion</td>
<td>0.5-1</td>
<td>Weight loss, potential ß-cell preservation</td>
<td>Injections, frequent dosing, GI AEs, expensive, modest clinical experience</td>
<td>Use as adjunct therapy for patient inadequately controlled with sulfonylurea or metformin</td>
</tr>
</tbody>
</table>

A1C=hemoglobin A1C (glycosylated hemoglobin); AEs=adverse events; CV=cardiovascular; ß=gamma; GI=gastrointestinal; GIP=gastric inhibitory polypeptide; GLP-1=glucagon-like peptide-1; PPAR=peroxisome proliferator-activated receptor; T2DM=type 2 diabetes mellitus.
using fibrates showed beneficial outcomes with increased HDL-C levels for fibrate-treated patients. The study showed that for every 5 mg/dL increase in HDL-C level, there was a 26% reduction in CVD risk. Emerging evidence continues to show the antiatherosclerotic properties of HDL-C. In addition to its pivotal role in reverse cholesterol transport, HDL-C enhances NO bioavailability and has potential anti-inflammatory, antithrombotic, antioxidant, and antiapoptotic properties. As a result of researchers improving their knowledge of factors that promote HDL-C levels and its function, new drug therapies (e.g., more potent PPAR agonists) are in development.

Since patients with T2DM often exhibit mixed dyslipidemia, multiple agents may be required to reach treatment goals. However, there is an increased risk of adverse drug events (ADEs) when higher doses are used and/or certain antihyperlipidemic agents are combined (e.g., rhabdomyolysis when combining statins and fibrates) are combined. TZDs may have beneficial effects on the T2DM lipid profile without increasing the risk of rhabdomyolysis. A few studies have evaluated the lipid-lowering effects of pioglitazone and rosiglitazone. Compared with rosiglitazone, pioglitazone has shown a more favorable effect on lipid profiles. In a study that was specifically designed to compare lipid effects of the TZDs, pioglitazone demonstrated beneficial effects on TG, HDL-C, and LDL-C levels (Table 4). However, both pioglitazone and rosiglitazone produce larger, more buoyant LDL-C particles, which are less atherogenic than the small, dense LDL-C particles normally found in patients with diabetes.

As depicted in the drug therapy chart (Table 2), CV benefits have been achieved when certain T2DM agents have been used. In the United Kingdom Prospective Diabetes Study (UKPDS), overweight, metformin-treated patients (n = 342) showed improved CV outcomes (39% reduction in MI; P = 0.01 and 30% reduction in all macrovascular diseases; P = 0.02). In patients with type 1 diabetes, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group showed that intensive diabetes treatment with insulin had beneficial effects on CVD. The primary outcome was defined as a CV event that required revascularization. Compared with conventional treatment, intensive treatment reduced the risk of any CVD by 42% (95% confidence interval [CI], 9%-63%; P = 0.02) and the risk of nonfatal MI, stroke, or death from CVD by 57% (95% CI, 12%-79%; P = 0.02).

More recently, studies with pioglitazone and rosiglitazone have shown improved CV outcomes. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study, T2DM patients at high risk for fatal MI and stroke treated with pioglitazone experienced a reduction in the secondary endpoint (composite of all-cause mortality, MI, or stroke). Study results suggested that compared with placebo-treated patients, pioglitazone-treated patients experienced a 16% reduction (P = 0.027) in the composite event rate of all-cause mortality, nonfatal MI
(excluding silent MI), and stroke. Although the secondary endpoint was met, the composite primary endpoint, which included death from any cause, nonfatal MI, stroke, acute coronary syndrome, leg amputations, coronary revascularization, or leg revascularization, was not met. A recent abstract from the EASD annual meeting showed positive lipid trends in a subanalysis of the PROactive trial, which evaluated the effects of pioglitazone on lipid profiles. Pioglitazone-treatment groups showed favorable effects on TG and HDL-C levels and the LDL-C/HDL-C ratio.

An additional subanalysis of the PROactive trial showed that pioglitazone reduced the risk of secondary stroke in high-risk T2DM patients by 28% ($P < 0.05$) compared with placebo. In this subanalysis, 984 patients with a prior history of stroke were treated with pioglitazone or placebo. There was a 10.2% versus 5.6% reduction in stroke (hazard ratio, 0.53; 95% CI, 0.34-0.94; $P=0.008$) for pioglitazone versus placebo-treated patients, respectively. In a similar fashion, the Study of Atherosclerosis with Ramipril and Rosiglitazone (STARR), an ongoing substudy of the DREAM trial, is evaluating whether the combination of rosiglitazone and ramipril can induce regression of atherosclerosis. Carotid ultrasound will be used to evaluate the change in the mean carotid artery intima-media thickness (CIMT) and analyze the progression of atherosclerosis. This study is scheduled for completion in the second quarter of 2007.

Recently published, the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO study), is a randomized controlled multicenter trial in patients with T2DM. Patients ($n=462$) were newly diagnosed and currently treated with diet and exercise, sulfonylurea, metformin, insulin, or any combination of these. In addition to current therapy, patients received

### Table 5

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Trial Name</th>
<th>Expected Completion</th>
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</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>The Effect of Pioglitazone and Rosiglitazone on Atherosclerotic and Inflammatory Markers in Patients With Metabolic Syndrome: A Prospective, Randomized, Open-Label, Crossover Trial</td>
<td>Mid 2007</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Actos Now for Prevention of Diabetes (ACT NOW)</td>
<td>Mid 2007</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>A Double-Blind, Randomized, Comparator-Controlled Study In Subjects With Type 2 Diabetes Mellitus Comparing the Effects of Pioglitazone HCl Versus Glimepiride on the Rate of Progression of Coronary Atherosclerotic Disease as Measured by Intravascular Ultrasound (PERISCOPE)</td>
<td>Mid 2008</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Treatment of Coronary Atherosclerosis and Calcification by Insulin Sensitizers in Insulin-Resistant Patients: Evaluated by EBCT, 16-Slice MDCT Coronary Angiography/Scanning, and Intravascular Ultrasound</td>
<td>Mid 2008</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>A Diabetes Outcome Progression Trial (ADOPT)</td>
<td>Mid 2007</td>
</tr>
<tr>
<td>Glyburide</td>
<td>The Study of Atherosclerosis With Ramipril and Rosiglitazone (STARR)</td>
<td>Mid 2007</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>A Multicenter Randomized Double-Blind Trial Comparing Rosiglitazone to Placebo for the Prevention of Atherosclerosis Progression After Coronary Bypass Surgery in Diabetic Patients</td>
<td>End 2007</td>
</tr>
<tr>
<td>Insulin</td>
<td>Non-Traditional Cardiovascular Risk Factors and Atherosclerosis in Type 2 Diabetes</td>
<td>End 2007</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Markers and Mechanisms of Vascular Disease in Type 2 Diabetes</td>
<td>End 2007</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>A Trial of the Effect of Rosiglitazone as Add-on to Metformin Therapy on Endothelial Function in Subjects With Type 2 DM (GATE)</td>
<td>End 2007</td>
</tr>
<tr>
<td>Insulin</td>
<td>Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D)</td>
<td>Mid 2007</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Glycemic Control and Complications in Diabetes Mellitus Type 2-Veterans Affairs Diabetes Trial (VADT)</td>
<td>End 2007</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Glycemic Control and Complications in Diabetes Mellitus Type 2-Veterans Affairs Diabetes Trial (VADT)</td>
<td>End 2007</td>
</tr>
</tbody>
</table>
either pioglitazone or glimepiride. Measurement of CIMT was chosen as the primary outcome because CIMT is a marker of atherosclerosis and independently predicts CV events. At the end of the study period (week 72), progression of mean CIMT was less with pioglitazone compared with glimepiride (-0.001 mm vs. +0.012 mm; 95% CI, -0.024 to -0.002; P = 0.02). Other benefits of pioglitazone included increased HDL-C levels and reduced TG levels. ADEs leading to study discontinuation occurred 11.3% for pioglitazone-treated patients versus 8.3% for glimepiride-treated patients. Hypoglycemia was slightly more common with glimepiride-treated patients, while pioglitazone-treated patients more commonly experienced peripheral edema and weight gain. There was 1 case of new congestive heart failure in the pioglitazone treatment group. The results of the CHICAGO study combined with the results of the PROActive trial and its substudies indicate that certain subsets of patients may experience CV benefits when treated with pioglitazone. Several ongoing and new trials are evaluating TZD and CV risk reduction (Table 5). On the basis of the results of these trials, changes in the treatment of patients with T2DM or prediabetes may occur.

### Emerging and Future Drug Therapy

In addition to the current treatments available for patients with T2DM and the potential new therapeutic effects of existing therapy (e.g., reducing CV risk), there are several emerging and future therapy options. Incretin mimetics/enhancers include GLP-1 receptor agonists, GLP-1 analogs, and DPP-IV inhibitors. Incretin hormones, secreted from the gastrointestinal tract in response to nutrient ingestion, aid in the overall maintenance of glucose homeostasis. More specifically, release of GLP-1 stimulates glucose-dependent insulin secretion, inhibits release of glucagon, slows gastric emptying, and reduces food intake (due to promotion of satiety). Since GLP-1 is reduced in patients with impaired glucose tolerance and T2DM, agents that mimic the actions of incretin hormones may be beneficial therapeutic options.

Exenatide, a GLP-1 receptor agonist (exendin analog), mimics the action of the incretin GLP-1, resulting in enhanced glucose-dependent insulin secretion by pancreatic β-cells. Additionally, exenatide suppresses inappropriately elevated glucagon secretion and slows gastric emptying. Exenatide, an injectable agent for patients with T2DM, is indicated as adjunctive therapy for T2DM patients who have not achieved glycemic control and are taking metformin, a sulfonylurea, or metformin in combination with a sulfonylurea.

The U.S. Food and Drug Administration (FDA) recently approved sitagliptin, a DPP-IV inhibitor. DPP-IV is present in many tissues and affects numerous body proteins. Of importance in T2DM, DPP-IV rapidly breaks down the incretin hormones GLP-1 and gastric inhibitory polypeptide. DPP-IV inhibitors affect the overall maintenance of glucose metabolism by inhibiting the degradation of GLP-1. Sitagliptin, an oral agent for patients with T2DM, is indicated for use as monotherapy or in combination with metformin or a TZD when adequate glycemic control has not been achieved.

Clinical data for vildagliptin, a second DPP-IV inhibitor, has been submitted to the FDA for approval. Recently, new clinical data supporting the efficacy of vildagliptin was presented at the World Diabetes Congress of the IDF. This agent may be available to the market during the second quarter of 2007. Additionally, several other DPP-IV inhibitors are in various stages of development. After clinical experience with DPP-IV inhibitors is gained, their role in treating patients with T2DM will be better established.

Several GLP-1 analogs are currently in development. Liraglutide, an injectable, long-acting DPP-IV-resistant GLP-1 analog, is in phase III clinical trials. Initial studies of liraglutide monotherapy and in combination with metformin have shown improved glycemic control and weight loss.

Dual α/γ PPAR agonists (e.g., muraglitazar, tesiglitazar) looked promising for the treatment of T2DM because they improved insulin resistance and alleviated atherogenic lipidemia. However, clinical trials with muraglitazar, tesiglitazar, and other dual agonists have been discontinued due to increased risk of cardiotoxicity. The discovery of a third type of PPAR receptor, PPAR-δ, may become a better target for drug therapy. PPAR-δ appears to play a central role in energy metabolism and may counterbalance the negative effects of dual alpha/gamma PPAR agonists. Compounds targeting individual PPARs and all 3 PPARs (pan-PPAR agonists) are in various stages of development for T2DM, obesity, the metabolic syndrome, and dyslipidemia.

Rimonabant, a selective cannabinoid type 1 receptor blocker that suppresses the endocannabinoid system centrally and peripherally, has received an approvable letter from the FDA for treatment of obesity. The endocannabinoid system is a neuromodulatory system that plays a role in the regulation of food intake and energy homeostasis. Rimonabant has positive effects on reducing caloric intake, hyperglycemia, and HDL-C and TG levels. Furthermore, some of these effects occur independent of weight loss. It is postulated that rimonabant enhances mRNA expression of adiponectin, which has antiatherogenic properties.

Clinical studies have shown that rimonabant is effective in the treatment of overweight or obese patients with T2DM. Rimonabant-treated patients experienced weight loss (2.3 kg–5.3 kg) and improved glycemic and blood pressure control. Additionally, rimonabant-treated patients experienced improvements in atherogenic dyslipidemia and reduced prevalence of the metabolic syndrome. In a large randomized trial that evaluated rimonabant plus diet and exercise compared with placebo, rimonabant-treated patients experienced more weight loss; decreased waist circumference, lower TG levels, and higher HDL-C levels.

### Use and Cost Considerations

Cardiovascular complications are a major component of T2DM
that contribute significantly to the costs of managing diabetes. Therefore, it is important to not only treat hyperglycemia but also to identify treatment plans and antidiabetic agents that may improve CVD outcomes. Global risk reduction via multifactorial management and treatment of underlying risk factors is recommended. Lifestyle changes should be an ongoing intervention for all patients with T2DM. Weight loss will help reduce insulin resistance, LDL-C levels, and blood pressure. In addition, increased physical activity will facilitate weight loss; decrease blood pressure, VLDL-C (very low-density lipoprotein cholesterol), and LDL-C levels; and increase HDL-C levels. Patients should be provided with specific diet and exercise recommendations and referred to a dietician when necessary.

For successful treatment, it is vitally important for the patient to actively participate in the treatment plan. There are several choices for drug therapy. If there are no contraindications, including renal disease (SCr >1.5 mg/dL for males and >1.4 mg/dL for females), heart failure requiring pharmacologic treatment, or acute or chronic metabolic acidosis, then metformin should be initiated first. Metformin is one of the most cost-effective treatments for T2DM, and on the basis of the UKPDS, patients may experience beneficial CV outcomes and weight loss when treated with this agent. If the patient does not reach his or her glycemic goal with monotherapy, concomitantly with metformin or sulfonylurea, and improved tolerability. A study evaluating the long-term safety of pioglitazone versus glyburide suggested that patients who were treated with pioglitazone were less likely to discontinue treatment because of lack of efficacy or ADEs (12.8% vs. 20.8%; P = 0.032).

There is not an abundance of literature that specifically evaluates the cost-effectiveness of treating patients with antidiabetic agents to reduce CVD complications. Factors to consider include the costs associated with standard office visits, drug therapy, and monitoring compared with the costs of treating complications, which are often due to CVD and require emergency room visits, hospitalizations, and more intensive treatment. A utilization study found that adding rosiglitazone in combination with sulfonylurea therapy decreased the use of medical resources such as hospitalizations and emergency room visits. Cost estimates from 2002 associated with diabetes were $132 billion per year. On the basis of the current prevalence of T2DM and projected population growth from the U.S. Census Bureau, this number is expected to increase to $156 billion by 2010 and to $196 billion by 2020.

If the incidence of T2DM continues to rise exponentially due to the increasing number of obese persons, these costs could become substantially higher. Furthermore, when evaluating costs for inpatient care days, nursing home care days, and outpatient care (including physician office, emergency, hospital outpatient, home health, and hospice care visits), researchers find that treatment of patients with CVD is associated with the highest costs compared with all other T2DM complications. To decrease CVD morbidity and mortality, all treatments options (e.g., lifestyle
changes, metformin, TZDs, statins, fibrates, ACE inhibitors, ARBs, low-dose aspirin therapy) that have been shown to reduce CV risk factors and improve CVD outcomes should be considered and used when appropriate.

### Conclusions

T2DM has reached epidemic proportions, resulting in increased morbidity and mortality due to CVD. In fact, on the basis of the 2006 data from the IDF, the global prevalence of T2DM has continued to increase at a rapid pace. Studies have shown the impact of obesity and T2DM on the progression of atherosclerosis and CVD. T2DM has become a major burden on the U.S. health care system. Because of the rising population of obese persons resulting in increased prevalence of T2DM, the costs associated with T2DM will continue to rise at exorbitant rates if drastic changes do not occur. The majority of costs associated with T2DM are due to CV complications, with most of these costs occurring within the first 10 years after the patient is diagnosed with T2DM. Therefore, with early and aggressive treatment plans for controlling T2DM, health care costs associated with managing CVD events can be minimized. Patients with prediabetes, i.e., those with impaired fasting glucose or impaired glucose tolerance, should be educated about the importance of lifestyle interventions. All patients should be routinely educated about their disease and instructed about lifestyle changes such as diet, exercise, and smoking cessation. Pharmacists have the opportunity to play a vital role on the health care team by educating patients about the benefits of their treatment plans, monitoring for adherence to therapy and for ADEs, and recommending additional therapy when appropriate.

There are many treatment options for patients with T2DM. Drug therapy that is safe and effective, tolerable, and acceptable to the patient should be selected. Other important goals include selecting agents that can provide maximum benefit to the patient by affecting more than one metabolic disturbance, decreasing overall treatment costs, and improving the patient’s quality of life by reducing morbidity associated with CVD. Agents, including TZDs, statins, fibrates, aspirin, ACE inhibitors, and ARBs that have been shown to demonstrate beneficial CV outcomes in patients with T2DM, should be considered standard treatment options. In summary, initiating early and aggressive treatment that includes lifestyle changes and multiple agents with proven abilities to reduce the risk of CVD will provide the greatest benefit when managing patients with T2DM.

### Acknowledgment

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### DISCLOSURES

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Bartels served as principal author of the study. Study concept and design were contributed by all authors.

### REFERENCES


differentiation, and apoptosis.


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Posttest Worksheet: Type 2 Diabetes and Cardiovascular Disease: Reducing the Risk

1. According to the new worldwide data from the International Diabetes Federation, what is the estimated number of individuals with diabetes mellitus?
   a. 177 million
   b. 246 million
   c. 510 million
   d. 95 million

2. The leading cause of morbidity and mortality in the United States is
   a. lung cancer.
   b. chronic obstructive pulmonary disease.
   c. cardiovascular disease.
   d. type 1 diabetes mellitus.

3. The metabolic syndrome is most often described as a cluster of metabolic abnormalities including
   a. hyperglycemia, hypothyroidism, and hypertension.
   b. hyperglycemia, dyslipidemia, and orthostatic hypotension.
   c. hypogonadism, hypertension, and anorexia.
   d. hyperglycemia, insulin resistance, hypertension, and dyslipidemia.

4. Which lipid abnormalities are typically found in patients with the metabolic syndrome and/or type 2 diabetes mellitus?
   a. Elevated LDL-C levels
   b. Low HDL-C levels
   c. Elevated triglyceride levels
   d. All of the above
5. Elevated levels of all of the following adipokines are associated with developing cardiovascular disease except
   a. adiponectin.
   b. leptin.
   c. C-reactive protein (CRP).
   d. plasminogen activator inhibitor-1 (PAI-1).

6. Visceral fat secretes higher levels of adipokines than subcutaneous fat.
   a. True
   b. False

7. Atherosclerosis is best defined as
   a. a metabolic disorder of the arterioles.
   b. a chronic inflammatory disease of the large and medium-sized arteries.
   c. hardening of the coronary arteries.
   d. impaired insulin action in the adipose tissue.

8. All of the following are key factors in the pathogenesis of cardiovascular disease except
   a. altered homeostatic properties of the endothelium.
   b. insulin resistance and hyperglycemia.
   c. decreased levels of C-reactive protein (CRP).
   d. elevated LDL-C and oxidized LDL-C.

9. All of the following agents reduce inflammatory adipokines except
   a. thiazolidinediones (TZDs).
   b. fibrates, statins and niacin.
   c. angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers.
   d. sulfonylureas.

10. According to the consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes (August 2006), step 1 for treating patients with type 2 diabetes mellitus includes
   a. lifestyle changes, including diet and exercise.
   b. starting glimepiride (if no contraindications).
   c. starting metformin (if no contraindications).
   d. Both a and c

11. The American Diabetes Association recommends the following A1C treatment goal:
   a. Equal to 7%
   b. Less than 7%
   c. Greater than 7.5%
   d. Less than 6%

12. Which interventions have shown the most benefit for preventing the onset of type 2 diabetes mellitus?
   a. ACE inhibitors
   b. Lifestyle changes, including diet and exercise
   c. Thiazolidinediones (TZDs)
   d. Both b and c

13. Peroxisome proliferator-activated receptor (PPAR) agonists include
   a. thiazolidinediones (TZDs) and fibrates.
   b. statins and niacin.
   c. aspirin.
   d. None of the above

14. In TZDs, activation of the PPAR-γ receptor reduces insulin resistance, preserves pancreatic β-cell function, and exerts positive effects on dyslipidemia.
   a. True
   b. False

15. All of the following are cardiovascular risk factors except
   a. hypertension.
   b. diabetes.
   c. dyslipidemia.
   d. physical activity.

16. According to JNC 7, the blood pressure goal for patients with diabetes (without renal disease) is
   a. less than 140/90 mm Hg.
   b. less than 135/85 mm Hg.
   c. less than 130/80 mm Hg.
   d. less than 130/85 mm Hg.

17. According to the NCEP ATP III guidelines, the LDL-C goal for patients with diabetes is
   a. less than 100 mg/dL or less than 70 mg/dL if evidence of cardiovascular disease.
   b. less than 130 mg/dL.
   c. greater than 40 mg/dL.
   d. less than 160 mg/dL.

18. Which antidiabetic agent has the most beneficial effect on atherosclerosis and the dyslipidemia associated with type 2 diabetes mellitus?
   a. Metformin
   b. Glipizide
   c. Acarbose
   d. Pioglitazone

19. Cardiovascular complications are more prevalent than other type 2 diabetes complications and contribute significantly to the costs of managing this disease.
   a. True
   b. False

20. How can pharmacists help improve the care of patients with type 2 diabetes?
   a. Monitor for efficacy, adverse event, and adherence to the treatment plan
   b. Recommend agents with beneficial cardiovascular outcomes
   c. Educate and involve patients in their care plan
   d. All of the above