

# A Review of Cardiovascular Comorbidities of Diabetes

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## Learning Objectives

After completing this continuing education article, the pharmacist or physician should be able to:

1. Review current data on the epidemiology of diabetes and cardiovascular disease (CVD).
2. Explain the risk factors and pathophysiology of diabetes and its cardiovascular comorbidities.
3. Discuss the importance of the diagnosis and treatment of diabetes and its comorbidities.
4. Recommend lifestyle changes for diabetes, hypertension, and dyslipidemia to reduce the risk of CVD.
5. Compare and contrast the risks and benefits of the various agents in the thiazolidinedione class.
6. Discuss the role of diabetes self-management education programs.
7. Implement pharmacologic-care strategies for the treatment of diabetes and cardiovascular complications, including combination therapy.

**D** iabetes is a heterogeneous group of diseases manifesting with elevated blood glucose levels. The disease can result from a deficiency in insulin production, increased insulin resistance, or a combination of these problems. Diabetes increases in prevalence with age and is more common in certain ethnic groups (eg, American Indians and Hispanic/Latino Americans). With an increasing elderly population and ethnic and racial diversity, diabetes is becoming more prevalent in the United States. In 2005, almost 21 million Americans of all ages were reported to have diabetes. More alarmingly, however, 6.2 million of these patients were unaware that they had the disease. With such a large number of Americans with diabetes, it is not surprising that this condition is very costly. The total annual cost of diabetes in

2002 was reported to be \$132 billion (11% of the US healthcare expenditure), and \$91.8 billion of this was direct costs. In fact, 1 of every 10 healthcare dollars is spent on diabetes and its complications in the United States. In addition, medical expenditures are approximately 2.4 times higher for patients with diabetes.<sup>1-3</sup>

The evidence clearly suggests that diabetes is linked to multiple complications, including microvascular and macrovascular disease. Microvascular complications, those that affect the smaller blood vessels, include neuropathy, retinopathy, and nephropathy. If these remain untreated, limb amputation, blindness, and/or kidney failure can result. Glycemic control has been demonstrated to reduce the development of microvascular complications and should be at the forefront of diabetes management. In fact, for every

drop of 1 percentage point in hemoglobin A1C levels, there is an estimated 40% reduction in microvascular complications.<sup>4,5</sup> Macrovascular sequelae, such as myocardial infarction (MI) and stroke, are the most life-threatening complications that arise from diabetes. In fact, 65% of patients with diabetes die from heart disease or stroke, and death rates are 2 to 4 times higher in patients with diabetes compared with those without the disease. To put it another way, adults with diabetes have the same risk for MI as a patient without diabetes who has had a previous MI.<sup>1</sup> Macrovascular complications are minimally to modestly impacted by glycemic control, however.<sup>4,5</sup> Thus, it is important to also control other risk factors for cardiovascular disease (CVD), such as blood pressure, dyslipidemia, and smoking. The National Diabetes Education Program (NDEP)<sup>6</sup> has devel-

## Case Study

Harvey is a 47-year-old obese Native American man who comes into your clinic with the following primary complaint: "I have been peeing a lot more throughout the day and at night and seem to be thirsty all the time. It feels just like when they diagnosed me with diabetes a year ago." As you look at his chart, you learn that he has a history significant for type 2 diabetes (1 year), hypertension (10 years), benign prostatic hyperplasia (1 year), and gout ("for as long as I can remember"). You also notice that he is taking metformin 1000 mg twice a day, rosiglitazone 4 mg daily, tamsulosin 0.4 mg daily, hydrochlorothiazide 25 mg daily, metoprolol 50 mg twice a day, and allopurinol 100 mg daily. He smokes 1 pack of cigarettes a day and has done so for the past 15 years. He also drinks 1 beer with dinner each night. His mother died at age 64 of breast cancer, and his father died at age 50 of an MI. He tells you that he measures his blood glucose once daily before breakfast, and for the past 3 to 4 months, they have been ranging from 150 to 200 mg/dL with an average of 180 mg/dL. His A1C from today was 9.1%, and his blood pressure was 138/78 mm Hg. His cholesterol was assessed last week, with the following values: total cholesterol, 201 mg/dL; HDL, 37 mg/dL; LDL, 131 mg/dL; and triglycerides, 130 mg/dL. All other labs are within normal limits. His waist circumference is measured today at 48 inches. Harvey tells you that he has stopped taking rosiglitazone about a month ago when his neighbor told him it was bad for him. What treatment options would you now recommend?

(See page 8 for treatment options.)

oped a campaign to target the ABCs of diabetes management to improve clinical outcomes:

- A = Hemoglobin A1C
- B = Blood pressure
- C = Cholesterol

## Metabolic Syndrome

Insulin resistance is also a recognized component of a constellation of risk factors commonly referred to as *metabolic syndrome*.<sup>7</sup> **Table 1** lists an updated definition of the diagnostic criteria of the metabolic syndrome by the American Heart Association and the National Heart, Lung, and Blood Institute.<sup>8</sup> For a diagnosis of metabolic syndrome, 3 of the criteria listed in Table 1 are required. Identifying metabolic syndrome is important because of its link to cardiovascular morbidity and mortality<sup>9</sup> and the development of diabetes. In fact, metabolic syndrome is associated with a 5- to 9-fold increase in risk for the development of type 2 diabetes.<sup>10</sup>

## Diabetic Dyslipidemia

As a precursor to the onset of diabetes, lipid or cholesterol abnormalities begin occurring in what is known as an *asymptomatic diabetic prodrome*. During this time, very-low-density lipoprotein (VLDL) levels increase and the activity of insulin-dependent lipoprotein lipase, an enzyme that is normally responsible for removing triglycerides from food following consumption, slows. In a state of insulin deficiency, this enzyme is unable to work at maximum capacity, resulting in an increase in triglycerides in the bloodstream. Triglycerides enrich high-density lipoprotein (HDL) and low-density lipoprotein (LDL), resulting in the formation of small, dense LDL particles, which can be more easily oxidized. This leads to increased levels of potentially atherogenic particles and decreased HDL cholesterol levels. These triglyceride-enriched lipoproteins, in patients with insulin resistance and type 2 diabetes,

are able to enter vessel walls because of their smaller size, where they are oxidized. These particles bind to receptors on macrophages and are then phagocytized, subsequently leading to the formation of an atherosclerotic lesion.

This characteristic pattern—low HDL, elevated triglycerides, and small, dense LDL particles—is commonly referred to as *diabetic dyslipidemia*.<sup>11,12</sup> Currently, the National Cholesterol Education Program Adult Treatment Panel III (ATP III) and the American Diabetes Association (ADA) recommend the following goals: LDL <100 mg/dL, triglycerides <150 mg/dL, and HDL >40 mg/dL in men and >50 mg/dL in women (ADA only—ATP III classifies HDL levels). Currently, LDL remains the primary target of therapy because of its close association with CVD.<sup>13,14</sup> An optional LDL goal of <70 mg/dL has been proposed in patients with diabetes who also have evidence of CVD.<sup>15</sup> Statins are commonly used to achieve the LDL goal and improve other cholesterol parameters. Combination therapy with a fibric acid derivative, cholesterol absorption inhibitor, nicotinic acid derivative, or bile acid resin may also be warranted to achieve target cholesterol goals. Similar to hypertension, lifestyle modifications such as dietary changes, weight reduction, and increased physical activity should be encouraged. Dietary modifications should include reductions in saturated fat intake (<7% of total calories) and cholesterol (<200 mg/day) and increases in plant stanols and sterols (2 g/day) as well as soluble fiber (10-25 g/day).<sup>13</sup>

## Hypertension

Another component of the NDEP campaign to reduce CVD is blood pressure management. In addition to the direct association with CVD, hypertension is known to enhance albuminuria, a risk marker for heart disease.<sup>16</sup> Approximately 73% of patients with diabetes have hypertension, defined as blood pressure  $\geq$ 130/80 mm Hg or the use of antihypertensive therapy.<sup>1</sup> In addition, the higher the blood pressure

value, the higher the risk for MI, heart failure, stroke, and kidney disease.<sup>17</sup> The ADA recommends that blood pressure of patients with diabetes be assessed at every routine visit.<sup>14</sup>

Several clinical trials have demonstrated reductions in CVD end points in patients with hypertension and diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS), tight blood pressure control (goal of <150/85 mm Hg) and less tight blood pressure control (goal of <180/105 mm Hg) were assessed in 1148 patients with type 2 diabetes and hypertension. After a median treatment period of 8.4 years with an angiotensin-converting enzyme (ACE) inhibitor or beta-blocker, the mean blood pressure in the tight control group was 144/82 mm Hg compared with 154/87 mm Hg in the less tight control group. Patients managed in the tight control group had a 24% reduction in any diabetes-related end point (95% confidence interval [CI], 8%-38%), a 32% reduction in diabetes-related mortality (95% CI, 6%-51%), and a 44% reduction in both fatal and nonfatal stroke (95% CI, 11%-65%). In addition, data from this trial suggest that for each 10-mm Hg reduction in mean systolic blood pressure, there is an estimated 12% reduction in diabetes complications, 15% reduction in diabetes-related deaths, and an 11% reduction in MI.<sup>18</sup>

In the diabetes subset of the Hypertension Optimal Treatment (HOT) study, 1501 patients with hypertension were randomized into target diastolic blood pressure (DBP) groups. The goal of the intensive group was <80 mm Hg; the goal in the conventional group was <90 mm Hg. Patients were treated with felodipine, a dihydropyridine calcium-channel blocker. At the conclusion of the study, the average blood pressure achieved in the intensive group was 140/81 mm Hg compared with 144/85 mm Hg for those in the conventional group. Patients in the intensive target group experienced a 51% reduction ( $P = .005$ ) in cardiovascular events compared with those in

**Table 1**

**Diagnostic Criteria of Metabolic Syndrome**

- Elevated waist circumference:**  
≥40 inches in men, ≥35 inches in women
- Elevated triglycerides:**  
>150 mg/dL *or* receiving therapy for hypertriglyceridemia
- Low high-density lipoprotein (HDL) levels:**  
<40 mg/dL in men, <50 mg/dL in women *or* receiving treatment for low HDL levels
- Elevated blood pressure:**  
≥130 mm Hg systolic blood pressure *or* ≥85 mm Hg diastolic blood pressure *or* receiving antihypertensive therapy
- Elevated fasting blood glucose:**  
>100 mg/dL *or* receiving medication for elevated fasting blood glucose

Adapted from Reference 8.

the conventional target group. In addition, the study found significant reductions in cardiovascular mortality even when the DBP differences between the 2 groups were ≤4 mm Hg.<sup>19</sup>

Based on the findings from these trials and other epidemiologic studies, both the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the ADA currently recommend a blood pressure goal of <130/80 mm Hg to reduce the risk for CVD morbidity and mortality.<sup>13,17,20</sup> Any class of antihypertensive agents can be used to achieve the target blood pressure goal, but ACE inhibitors and angiotensin receptor blockers are commonly used in patients with diabetes because of the added benefit of renal protection. Also, the Heart Outcomes Prevention Evaluation (HOPE) and Microalbuminuria Cardiovascular and Renal Outcomes–Heart Outcomes Prevention Evaluation (MICRO-HOPE) study results indicated that ACE inhibitor therapy using ramipril reduced the combined primary outcome of MI, stroke, or cardiovascular death by 25% (95% CI, 12%-36%;  $P = .0004$ ).<sup>21</sup> Regardless of the therapy chosen, patients should be adequately monitored and educated on the importance of medication adherence to achieve blood pressure goals to reduce the risk of CVD. In addition, JNC 7 recognizes *prehypertension*, a classification

that identifies patients at risk for developing hypertension. It is important to note that prehypertension is not classified as a disease but rather is a risk factor for CVD, especially in the diabetes population.<sup>22</sup>

**Reducing the Risk of CVD: Lifestyle Modifications**

Lifestyle recommendations are critical as an integral part of appropriate blood pressure management. Weight reduction of approximately 10 kg can result in a 5- to 20-mm Hg reduction in blood pressure. In addition, adopting the Dietary Approaches to Stop Hypertension (DASH) diet that focuses on fruit and vegetable intake with low-fat dairy products and reduced saturated and total fats should also be encouraged. Restricting dietary sodium intake to ≤2.4 g of sodium each day may lower blood pressure by 2 to 8 mm Hg. Performing ≥30 minutes of physical activity most days a week can help patients control blood pressure. Finally, restricting alcohol consumption to ≤2 drinks per day for men or 1 drink per day for women (where 1 drink is equivalent to 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof liquor) is also beneficial to achieve target blood pressure goals.<sup>17</sup>

In the United States, smoking is the most preventable cause of mortality and is responsible for 1 of every 5 deaths. Smoking is associated with

reduced fasting insulin levels and increased blood glucose levels.<sup>23</sup> In the Nurses' Health Study, 114 247 women without diabetes, heart disease, or cancer were followed for 12 years. During this time, 2333 incident cases of type 2 diabetes were confirmed. After controlling for other risk factors, the relative risk of developing type 2 diabetes among women who smoked 25 or more cigarettes per day was 1.42 (95% CI, 1.18-1.72) compared with women who had never smoked.<sup>24</sup> Not only has smoking been implicated in the development of diabetes, it also increases the risk for microvascular complications. Thus, smoking cessation should be encouraged for all patients who smoke at every patient encounter.

### 5 Keys to Approaching Smoking Cessation

- Ask—about the patient's current tobacco use
- Assess—interest in smoking cessation for current smokers
- Advise—as to the importance of smoking cessation
- Assist—in establishing a quit date, providing patient education, and helping in medication selection, if warranted
- Arrange—follow-up telephone calls or visits after the quit date

Behavioral strategies and patient/group counseling may also be a part of smoking cessation management. Pharmacologic options such as nicotine replacement therapy, bupropion, tricyclic antidepressants, and varenicline are effective in helping patients stop smoking. These therapies should be tailored to meet the needs of the individual patient.<sup>23,25</sup>

### Reducing the Risk of CVD: Controlling Blood Glucose

Adequate glycemic control should

also be implemented as an essential component for the management of diabetes to reduce microvascular and macrovascular complications. Early diagnosis and treatment of diabetes is encouraged to reduce the complications associated with the disease. In fact, the classification of *prediabetes* (fasting blood glucose 100-125 mg/dL) by the ADA is used to target patients who are at risk for the development of diabetes and its complications. For patients with diabetes, a fasting preprandial blood glucose goal of 90 to 130 mg/dL and a postprandial blood glucose goal of <180 mg/dL are currently advised by the ADA. Also, hemoglobin A1C levels are targeted to <7% in the general population but may be targeted to <6% in individual patients.<sup>14</sup>

Metformin, a biguanide, is considered to be the gold standard of therapy for the treatment of type 2 diabetes.<sup>14</sup> In addition to its ability to reduce fasting blood glucose and hemoglobin A1C levels via reducing hepatic gluconeogenesis, metformin has been shown to reduce cardiovascular events and deaths compared with other therapies.<sup>26,27</sup> Because many patients will require more than one medication to achieve glycemic control, the benefit of combination therapy for cardiometabolic risk reduction has been evaluated. Thiazolidinediones (TZDs), which include pioglitazone and rosiglitazone, are peroxisome proliferator-activated receptor (PPAR)-gamma agonists that mediate glucose and lipid metabolism via activation of the nuclear transcription factor. PPAR-gamma activation results in triglyceride reduction and improvements in insulin sensitivity.<sup>10</sup>

In a 12-month, randomized, double-blind, multicenter, parallel-group trial, glucose, coagulation, and fibrinolysis parameters in patients with a ≥6-month history of type 2 diabetes and metabolic syndrome who were experiencing either poor glycemic control or adverse effects on the maximum dose of metformin were assessed. A group of

96 patients continued to receive metformin but were randomized to receive either pioglitazone 15 mg once daily or rosiglitazone 4 mg once daily for 12 months. No changes in either group were noticed after 3 and 6 months of treatment. After 9 and 12 months of therapy, however, hemoglobin A1C levels, fasting plasma glucose, and postprandial blood glucose levels were significantly reduced in both groups. Total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels improved after 1 year of treatment in the pioglitazone group ( $P < .05$  for comparison to baseline and to the rosiglitazone group). No significant improvements in total cholesterol, LDL cholesterol, or triglycerides were noted in the rosiglitazone group, however. Lipoprotein(a) levels, a risk marker for atherosclerosis, were significantly improved in the pioglitazone group compared with baseline ( $P < .05$ ) and to the rosiglitazone group ( $P < .05$ ). Both groups had significantly reduced homocysteine levels, another marker of atherosclerosis ( $P < .05$  for both groups).<sup>28</sup>

A similarly designed study using glimepiride, a second-generation sulfonylurea, was conducted. In this 12-month, double-blind, randomized, controlled, multicenter trial, 91 patients with a ≥6-month history of type 2 diabetes and metabolic syndrome with poor glycemic control or who were intolerant of diet, oral hypoglycemic agents, or metformin were included to assess various glycemic, coagulation, and fibrinolysis end points. All patients received glimepiride 4 mg/day divided into 2 doses. Patients were then randomized to receive pioglitazone 15 mg once daily or rosiglitazone 4 mg once daily. After 9 and 12 months of treatment, patients in both groups experienced significant improvements in glycemic control as determined by hemoglobin A1C, fasting plasma glucose, and postprandial blood glucose levels, compared with baseline. Comparisons to each treatment group were not sig-

nificant. Patients in the pioglitazone group experienced improvements in all cholesterol parameters after 12 months of treatment when compared with baseline. Patients treated with rosiglitazone experienced improvements in cholesterol parameters, except for HDL when compared with baseline. These values were significantly different between the 2 treatment groups, however (Table 2).<sup>29</sup> The findings on lipid profiles are consistent with data from a meta-analysis that found that total cholesterol, LDL, and triglyceride levels were higher in patients treated with rosiglitazone compared with pioglitazone.<sup>30</sup>

Although TZDs have demonstrated positive results in the previous studies, the same findings were not elucidated in a secondary prevention trial. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial was a randomized, prospective study of 5238 patients with type 2 diabetes and a history of macrovascular disease defined as an MI or stroke  $\geq 6$  months prior to study entry, acute coronary syndrome or coronary artery bypass surgery  $\geq 3$  months prior to study entry, or objective evidence of coronary artery disease or obstructive arterial disease in the leg. Patients were randomized to receive either pioglitazone 15 mg once daily titrated to 45 mg once daily or placebo, in addition to current diabetes medications. After an average of 34.5 months of therapy, 19.7% of patients in the pioglitazone group compared with 21.7% of patients in the placebo group experienced  $\geq 1$  event of the primary composite end point: all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle (hazard ratio [HR], 0.90; 95% CI, 0.80-1.02;  $P = .095$ ). In addition, patients treated with pioglitazone experienced improvements in most cholesterol parameters, although LDL levels slightly increased.<sup>31,32</sup>

**Table 2**

<b>Treatment Group Differences: Pioglitazone Versus Rosiglitazone, <math>P &lt; .05</math> for All</b>		
	<b>Pioglitazone (mg/dL)</b>	<b>Rosiglitazone (mg/dL)</b>
Total cholesterol	179	224
Low-density lipoprotein	110	141
High-density lipoprotein	46	43
Triglycerides	121	191

Adapted from Reference 29.

**Late-breaking Safety Issues**

Recent attention has been placed on the safe use of rosiglitazone in patients with diabetes.<sup>33</sup> A meta-analysis of 42 trials comparing rosiglitazone with placebo and other comparators found an increased risk for MI (summary odds ratio for MI, 1.43 [95% CI, 1.03-1.98;  $P = .03$ ]) and death from cardiovascular causes (summary odds ratio for death from cardiovascular causes, 1.64 [95% CI, 0.98-2.74;  $P = .06$ ]). Similar findings were noted when rosiglitazone was compared with other drugs as well as placebo, suggesting that other drugs were not necessarily

protective of harmful effects. The authors discovered similar findings when looking at shorter-term trials (ie, 24-52 weeks), which may suggest that the risk for MI is a concern even following short-term treatment with the medication.

Debate over the question of how rosiglitazone increases the risk for MI is ongoing. Several theories have been posited, including the medication's adverse effect on the lipid profile; its ability to cause heart failure, which ultimately increases myocardial oxygen demand to cause ischemia; and its ability to induce a state of physiologic

**Table 3**

<b>American Diabetes Association Recommendations for the Use of Aspirin in Patients With Diabetes</b>	
<b>Primary Prevention</b>	
<b>Type 1 Diabetes</b>	
Men and women >40 years of age or those with additional risk factors such as a family history of CVD, hypertension, smoking, dyslipidemia, albuminuria	
<b>Type 2 Diabetes</b>	
Men and women >40 years of age or those with additional risk factors such as a family history of CVD, hypertension, smoking, dyslipidemia, albuminuria	
<b>Secondary Prevention</b>	
Use in men and women with diabetes who have a history of MI, vascular bypass procedure, stroke, peripheral vascular disease, angina, and/or claudication	
<b>Comments</b>	
Aspirin use not recommended in patients with aspirin allergy, recent gastrointestinal bleeding, anticoagulant therapy, active hepatic disease	
Aspirin should not be used in patients <21 years of age due to the risk for Reye's syndrome	

Adapted from Reference 37.

## Case Study Treatment Options

Patients like Harvey, who have diabetes, are at increased risk for microvascular and macrovascular complications. Thus, achieving glycemic, blood pressure, and cholesterol goals are vital to reduce the risk for these complications, especially CVD. Harvey also meets the criteria for the metabolic syndrome (ie, low HDL levels, hypertension, elevated fasting blood glucose, and elevated waist circumference), another strong CVD predictor. The importance of medication adherence should be emphasized to help Harvey achieve these goals. The recent controversy surrounding rosiglitazone has spurred patients to present with concerns about its safety. The FDA has voted to keep the product on the market unless further studies demonstrate the need to remove it. The highest risk for MI appears to be in older patients, those with existing coronary disease, and in patients taking insulin, none of which describe Harvey. His lipid panel is somewhat concerning, however. He is not at his LDL, HDL, or total cholesterol goals. Rosiglitazone has been noted to have an adverse effect on the lipid profile and thus may potentially push his cholesterol values further from goal. Therefore, if TZD therapy is to be continued, the patient should be educated about the risks versus the benefits of pioglitazone, which may have a more favorable effect on the lipid profile. TZD therapy has also been shown to improve lipoprotein(a) and homocysteine levels, both of which are markers of atherosclerosis. Combination therapy consisting of metformin and a TZD has shown efficacy in lowering the risk for heart disease. Educating Harvey on the signs and symptoms of an MI is also warranted. If noncompliance with TZD therapy is a concern because of his fear of adverse effects, suggesting a therapy switch to a sulfonyleurea may be warranted. It is important that he take his medication daily to achieve his fasting blood glucose (90-130 mg/dL) and hemoglobin A1C (<7%, possibly <6%) target values. Harvey will also need therapy to attain his cholesterol goals: LDL goal, <100 mg/dL and HDL goal, >40 mg/dL. Statins are considered first-line agents to achieve the primary cholesterol target, LDL. Once the LDL goal has been achieved,

secondary targets such as HDL and/or the metabolic syndrome may be considered. Although his blood pressure is currently managed with hydrochlorothiazide and metoprolol, he is not at the blood pressure goal for patients with diabetes: <130/80 mm Hg. Increasing the dose of hydrochlorothiazide most likely will not offer any additional blood pressure-lowering benefits, and increasing the beta-blocker may mask signs of hypoglycemia. Initiation with an ACE inhibitor would be a good choice to reduce blood pressure, lower his risk of CVD, and provide protection against the development of nephropathy. Ensuring that Harvey's potassium level and serum creatinine are within range is important for the safe use of ACE inhibitor therapy. With the exception of his cholesterol parameters, all other labs were within normal levels.

Smoking cessation should be encouraged in this patient. It is important to assess Harvey's stage in the cessation process and to assure him that help is available whenever he is ready to quit. Smoking cessation can help lower his blood pressure, reduce the risk for lung and heart disease, and improve his overall quality of life. If he is not ready to quit smoking today, smoking cessation should be assessed and encouraged at every patient encounter.

Because Harvey has type 2 diabetes and his age is >40 years, he is also a candidate for aspirin therapy for the primary prevention of CVD. He also has a family history of heart disease (father died from an MI at age 50) and currently smokes. Thus, initiation of aspirin 75-162 mg/day can help reduce thromboxane synthesis to prevent platelet aggregation. Encouraging physical activity, weight loss, and dietary modifications such as reductions in saturated fats, cholesterol, and sodium; increasing soluble fiber and plant stanols/sterols; and monitoring carbohydrate intake are also important lifestyle modifications to help achieve blood pressure, cholesterol, and glycemic goals. Finally, enrolling Harvey in a DSME program where he is at the center of the decision-making process are important steps to consider for the successful management of his health.

stress through hemoglobin A1C reduction to cause ischemia. Consideration has been given to differences in the pattern of gene activation and suppression via PPAR-gamma agonism.<sup>33</sup> At the time of publication, the US Food and Drug Administration (FDA) convened with an expert panel to discuss the increased cardiovascular risks asso-

ciated with rosiglitazone based on the meta-analysis findings. The majority voted to keep rosiglitazone available on the market,<sup>34</sup> although the committee advised the immediate institution of warning labels and educational efforts. Questions about the data were raised, such as the consistency of the findings, especially in the trials that

had comparator arms instead of placebo; in addition, the risk for ischemia appeared to be highest in patients receiving long-term nitrates and in those taking insulin. The chair of the FDA advisory committee published a report suggesting that future clinical trials involving medications for the treatment of type 2 diabetes should

attempt to use clinical outcomes for end points, such as reductions in CVD, rather than surrogate markers alone such as hemoglobin A1C reduction.<sup>35</sup>

### Does This Hold True for Pioglitazone?

A recent meta-analysis of pioglitazone was published in light of these findings with rosiglitazone. A total of 19 trials enrolling 16 390 patients that were randomized, double-blind, and controlled with either placebo or an active comparator were included. Overall, patients in the studies were adults with type 2 diabetes who were experiencing inadequate glycemic control. The primary objective of most studies was the efficacy of pioglitazone in improving glycemic control compared with either placebo, insulin, metformin, sulfonylureas, rosiglitazone, or in combination with other therapies. Treatment durations ranged from 4 months to 3.5 years.

The primary composite end point was death from any cause, nonfatal MI, or nonfatal stroke. This end point occurred in 375 of 8554 patients (4.4%) receiving pioglitazone compared with 450 of 7836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72-0.94;  $P = .005$ ). The effects were similar across different trial durations, across studies with different comparator groups, and among patients with or without established vascular disease. Although not a large prospective trial, this meta-analysis suggests that pioglitazone therapy may actually lower the risk for cardiovascular events.<sup>36</sup>

### Additional Approaches to Managing Glucose Levels

As with blood pressure and cholesterol, lifestyle modifications should be considered in patients with diabetes to lower blood glucose levels. Carbohydrate monitoring either by counting or exchanges should be encouraged to help patients achieve glycemic goals. Low-carbohydrate diets (<130 g/day) are not recommended, however,

because the long-term effects of these diets are unknown. The ADA also advises  $\geq 150$  minutes each week of moderate-intensity physical activity or 90 minutes each week of vigorous aerobic exercise to reduce the risk of CVD.<sup>14</sup>

The ADA has developed recommendations for the use of aspirin in patients with diabetes. Aspirin reduces the risk for CVD by acting as an inhibitor of thromboxane synthesis to reduce vasoconstriction and platelet aggregation.<sup>37</sup> A great deal of evidence has demonstrated the benefit of aspirin in the primary and secondary prevention of heart disease in men and women with diabetes.<sup>19,38-40</sup> **Table 3** lists specific recommendations on the use of aspirin in patients with diabetes. Doses of 75 to 162 mg/day are typically recommended and have been shown to be as effective as higher doses of aspirin. It is important to note that enteric-coated formulations do not appear to reduce the risk for gastrointestinal bleeding.<sup>37</sup>

### The Importance of the Patient's Own Effort

Achieving glycemic, lipid, and blood pressure goals is essential to reducing the risk of diabetic complications. A critical component in the successful management of this condition involves properly educating patients in self-management techniques and lifestyle changes, such as increasing physical activity, making dietary modifications, and losing weight. The ADA has developed national standards for diabetes self-management designed to define high-quality diabetes self-management education (DSME) programs that can be implemented in diverse settings. No program is preferred over another; however, programs that are culturally and age appropriate, incorporate psychosocial and behavioral strategies, and group settings have been found to be effective. One of the standards set forth for a DSME entity is the provision of education by  $\geq 1$  instructor who has recently received

education and experiential preparation in diabetes education or is a certified diabetes educator. The standard also states that  $\geq 1$  of the instructors should be a registered nurse, dietitian, or pharmacist. A multidisciplinary team approach is encouraged to achieve patient goals and improve outcomes. Finally, patient input should be at the center of decision making, because a patient's buy-in is critical to the success of therapy.<sup>41</sup>

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