

## Treating Diabetes: Cardiovascular Benefits of Antidiabetes Drugs

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### **Abstract**

Type 2 diabetes is a metabolic disorder that, if untreated, can result in macrovascular and microvascular complications. Lowering blood glucose levels primarily reduces microvascular risk; other treatment strategies are necessary to lower the risk for macrovascular disease. Because most patients with diabetes die of macrovascular disease, it is vitally important that patients with diabetes receive aggressive therapies to lessen this risk. It has been found that the risk for macrovascular complications begins even earlier than the risk for microvascular complications. Therefore, patients with insulin resistance (now called prediabetes) should be identified and treated to lower their risk of cardiovascular disease and reduce their risk for progression to diabetes. Two cases are reviewed—a patient with prediabetes and the metabolic syndrome, and a second patient with type 2 diabetes and advanced cardiovascular disease. A review of potential cardiovascular therapies is included.

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### **Case 1: The Metabolic Syndrome**

J.L. was a 64-year-old white man who had been treated for the metabolic syndrome. He was brought to the clinic by his wife. The patient disliked seeing physicians, but his wife told him he had multiple risk factors of the syndrome. He complained of weight gain, particularly around his waist, and subjective feelings of hypoglycemia after eating a meal or snack with a high carbohydrate content. He had a history of hypertension; low high-density lipoprotein (HDL) cholesterol and high triglyceride levels; and a family history of heart disease.

He had no other medical problems and no history of surgery. His mother died at age 60 of heart disease and his father died at age 52 of a heart attack. He had 1 brother who had had coronary artery bypass surgery. There was no family history of diabetes. His ancestors were from eastern Europe. The patient was employed as an attorney. He worked long hours and did not exercise. His only medications were metoprolol and losartan.

**Findings.** On examination he was 5'11" tall and weighed 86.4 kg (192 lb; body mass index = 26.8 kg/m<sup>2</sup>) with a marked central distribution of his body fat. His blood pressure was 135/86 mm Hg and pulse was 60 bpm. His examination was unremarkable, with no evidence of diabetic complications.

His initial laboratory results were fasting plasma glucose = 118 mg/dL, fasting insulin level = 31.1 µU/mL, C-peptide level = 2.5 ng/dL, total cholesterol level = 164 mg/dL, triglyceride level = 222 mg/dL, HDL cholesterol level = 33 mg/dL, low-density lipoprotein (LDL) cholesterol level = 87 mg/dL. His renal and liver function tests were completely normal, as was his urine microalbumin ratio (<20). His glycosylated hemoglobin (HbA<sub>1c</sub>) level was 5.7% (normal 4% to 6%).

**Treatment.** These laboratory results were discussed with the patient. He was told that he had impaired fasting glucose (IFG) with insulin resistance (elevated fasting insulin level). The metabolic syndrome was explained to him, with a spe-

cific explanation of his dyslipidemia and the prognostic implication of a low HDL cholesterol level and a high triglyceride level. He was counseled to see a dietitian to learn about medical nutrition therapy. He was also advised to start walking, gradually working up to 45 minutes 5 days per week. His losartan was increased to lower his blood pressure to less than the target of 130/80 mm Hg. He was started on aspirin 81 mg/day. He was advised to obtain a treadmill test to assess cardiac status before beginning his exercise program.

He adamantly refused to see the dietitian or change his diet. He did gradually increase his exercise (he started walking the dog when he got home from work). His treadmill test was negative.

After 3 months his weight and laboratory values were unchanged. He had read about the metabolic syndrome and wanted to start an oral medication, because he thought he would be unlikely to change his habits. Pioglitazone 30 mg/day was chosen to treat his insulin resistance and improve his dyslipidemia.\* Gemfibrozil could have been chosen to treat the elevated triglyceride levels, but would not have lowered his insulin resistance. The patient was asked to come in every other month for liver function tests for the first year on pioglitazone.

After 4 months on therapy with pioglitazone his triglyceride levels fell from 222 to 156 mg/dL and his HDL cholesterol level increased from 33 to 41 mg/dL. His fasting insulin level decreased from 31 to 18  $\mu$ U/mL and his fasting plasma glucose level fell from 118 to 96 mg/dL. His blood pressure decreased to 128/76 mm Hg.

**Commentary.** This patient was evaluated for his risk of developing type 2 diabetes and macrovascular disease. Based on his clinical presentation and family history, the diagnosis of the metabolic syndrome was fairly straightforward. Simply looking at the patient revealed his central obesity. In addition, his hypertension, dys-

lipidemia, and family history of early heart disease made the case for risk-factor modification to aggressively lower his risk for a cardiovascular event. His elevated fasting glucose level indicated he had IFG. It was not necessary to measure a fasting insulin or C-peptide level to make the diagnosis of the metabolic syndrome in this man. Based on his elevated fasting glucose level and dyslipidemia, it can be assumed that he has insulin resistance. However, insulin and C-peptide levels were obtained and were provided to further illustrate the pathophysiology of this condition and the response to treatment.

#### **Case 2: Treatment of Diabetes in a Patient with Severe Pre-existing Macrovascular Disease**

M.T. was a 76-year-old Cuban nun who was referred for treatment of diabetes. She had had type 2 diabetes for at least 20 years. At the time of referral she was on glipizide plus 70/30 mixture insulin, which she was supposed to be taking twice per day (but generally took only once per day). Her fasting blood glucose levels were in the 40s and her pre-supper blood glucose levels were in the 400s.

She had advanced coronary artery disease. Eight years previously she had had a cardiac angiogram with attempted angioplasty. During the procedure she had had a cardiac arrest, then underwent emergency coronary artery bypass surgery and was in the cardiac intensive care unit for more than 1 month.

After a prolonged period of cardiac rehabilitation she did reasonably well, but 6 years later developed angina, first with exercise and then at rest. She again had a coronary angiogram with attempted stent placement, and once again had a cardiac arrest from which she took several months to recover. Because of the severity of her coronary artery disease she was left with intractable angina. The exertion associated with getting out of bed and dressing herself would precipitate significant anginal symptoms.

M.T. decided against ever seeing a physician again, but her parishioners and fellow nuns were so worried about her fre-

\*Off-label use.

quent episodes of hypoglycemia that she agreed to see a physician for diabetes management.

**Findings.** On physical examination she was 5'1" tall and weighed 88 kg (195 lb). Her blood pressure was 145/92 mm Hg and her pulse was 80 bpm. She had mild-to-moderate background retinopathy and a decrease in sensation to monofilament testing in her lower extremities. Her cardiac examination revealed a normal rhythm, S1 and S2, with an S4 but no S3. She had a 2/6 systolic murmur at the left sternal border without radiation. Her peripheral pulses were decreased throughout, but she had no bruits. Her lungs were essentially clear, without rales. Her feet were slightly cool, but had no ulcers or other lesions. She did have 1 to 2+ bilateral pitting pedal edema.

At the time of referral, her glucose levels fluctuated as noted above. Her laboratory results showed a serum creatinine level of 1.6 mg/dL with 1+ protein on urine dipstick. Her liver function was normal. A fasting C-peptide level was 2.6 mg/dL with a corresponding glucose level of 121 mg/dL (suggesting that she had a fair amount of endogenous insulin secretion). Her LDL cholesterol level was 126 mg/dL, her HDL cholesterol level was 29 mg/dL, and her triglyceride level was 260 mg/dL.

She was unable to tolerate statins because they caused diffuse muscle aches. She was taking furosemide and sublingual and long-acting nitroglycerin as needed.

**Treatment.** To prevent hypoglycemia, her 70/30 insulin was switched to NPH insulin given twice per day before breakfast and before supper. It was hoped that her endogenous insulin secretion (enhanced by the glipizide) would work in concert with the NPH insulin. She was also referred to an ophthalmologist.

Her macrovascular risk factors needed to be addressed, as well. A low-dose statin was restarted, but she developed the same side effects as she had had previously. She said she was "allergic" to beta-blockers and would not take them. However, we were able to add a daily aspirin and an

angiotensin-converting enzyme inhibitor. She was encouraged to adhere to use of the long-acting nitrates, which helped lessen her symptoms somewhat.

Unfortunately, her diabetes remained very poorly controlled and she took her insulin only once per day, usually in the morning. She was not a candidate for metformin (her creatinine was 1.6 mg/dL), but pioglitazone 15 mg every other day was added. Her chronic pedal edema worsened slightly initially, but stabilized with an increase in her furosemide dose. Over 16 weeks her pioglitazone was very gradually increased to a maximal tolerated dose of 30 mg/day. As her pioglitazone dose increased and her insulin resistance lessened, her insulin requirement decreased and her glucose levels stabilized. Eventually she was taking pioglitazone 30 mg/day, glipizide 20 mg twice per day, and 10 units of NPH insulin in the morning. Her blood glucose levels were generally in the range of 100 to 200 mg/dL before meals and she no longer had episodes of hypoglycemia or severe hyperglycemia. Additionally, her exercise tolerance gradually improved and she became able to accomplish her normal activities of daily living without limiting angina.

**Commentary.** This patient could have benefited from preventive care years before she was seen in our clinic. At the time she was initially evaluated she had very advanced macrovascular complications and suffered from acute complications of her diabetes (frequent episodes of hypo- and hyperglycemia). She had had negative experiences with the healthcare profession and was unwilling to undergo further diagnostic testing; moreover, she adhered only partially to the recommended treatment plan. Nevertheless, the overall goal with this individual was to bring her blood glucose levels into a safe range (prevention of long-term complications was less of a goal given her severe cardiovascular disease) and to do whatever was possible to reduce the risk of further progression of her macrovascular disease. Regarding macrovascular disease, simple

**Table 1.** Clinical Identification of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity* (waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglyceride level	>150 mg/dL
HDL cholesterol level	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	>130/>80 mm Hg
Fasting glucose level	>110 mg/dL

Three or more features are required to diagnose the metabolic syndrome.

\*Some men with a marginal increase in waist circumference but a strong genetic history for the metabolic syndrome should benefit from lifestyle changes similarly to men with full features of the syndrome.

HDL = high-density lipoprotein.

Source: Reference 1.

measures, such as the addition of a daily aspirin, can be very helpful.

Treatment of this patient's hyperglycemia required careful titration of medication. Her cardiac status limited use of medication, although on examination she did not seem to have significant congestive heart failure (she refused a cardiac echocardiogram or other measures of her ejection fraction). She did have pedal edema. On insulin plus a sulfonylurea agent her blood glucose levels were unsafe, particularly because she self-administered her insulin fairly randomly (although a longer-acting insulin such as insulin glargine might have produced fewer episodes of hypoglycemia than did regular and NPH insulin). Metformin was contraindicated based on her serum creatinine level and possible underlying congestive heart failure. Similarly, use of a thiazolidinedione, which can cause an

increase in fluid retention (particularly in patients taking insulin), could have been problematic. However, because of her frequent episodes of hypoglycemia and lack of a history of frank congestive heart failure, it was decided to start very cautiously with a low dose of pioglitazone. This drug was added with several goals in mind. First it was hoped that pioglitazone would decrease her insulin resistance and help reduce her need for exogenous insulin. Second, the patient did not tolerate statins and it was hoped that the potential cardiovascular benefits of pioglitazone (increased HDL cholesterol level, increased LDL cholesterol particle size, decreased vascular reactivity, and decreased progression of intimal medial thickness) would have benefit.

**Addendum to Case 2.** Eighteen months later, the patient continued to be fairly stable. She was able to perform her responsibilities in the convent where she lives (providing free meals to the poor in downtown Los Angeles). As her health improved her adherence with her medical management became much better and management of her condition was easier. Her HbA<sub>1c</sub> level ranged from 7.5% to 8.0% (above 7%, but a higher target given her cardiovascular disease). Her HDL cholesterol increased from 29 to 38 mg/dL on the pioglitazone, with a decrease in her triglycerides from 260 to 145 mg/dL. Her LDL cholesterol level was essentially unchanged.

#### Definition of the Metabolic Syndrome

The metabolic syndrome has been defined in the guidelines from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]).<sup>1</sup> Table 1 lists the criteria for the diagnosis—3 or more criteria must be met to diagnose the syndrome. The major component of the syndrome is insulin resistance, which is promoted by excess body fat (primarily abdominal obesity), physical inactivity, and a genetic predisposition to insulin resistance.<sup>1</sup> These risk factors enhance the risk for coronary heart dis-

ease (CHD) at any given LDL cholesterol level. Management of the syndrome (which will be discussed below) has 2 major objectives: to reduce the underlying causes (such as obesity and physical inactivity) and to treat the associated nonlipid and lipid risk factors.

The ATP III guidelines also introduced the concept of calculating non-HDL cholesterol levels in patients with the metabolic syndrome. This concept was based on evidence that elevated triglyceride levels are an independent risk for CHD.<sup>1</sup> Elevated triglyceride levels tend to be observed in patients with the metabolic syndrome, and some triglyceride-rich particles such as partially degraded very-low-density lipoprotein (VLDL) particles (remnant lipoproteins) are atherogenic. These particles are not necessarily measured in routine lipid panels, but can be identified by a calculation of non-HDL cholesterol (the sum of LDL + VLDL cholesterol, calculated as the total cholesterol – HDL cholesterol). **Table 2** lists the target levels for triglycerides, non-HDL cholesterol, and LDL cholesterol.

In the Third National Health and Nutrition Examination Survey (NHANES III) a study using the ATP III guidelines (Table 1) for diagnosing the metabolic syndrome was performed to determine the prevalence of the syndrome in the US population.<sup>2</sup> Based on these criteria, the unadjusted prevalence of the metabolic syndrome among adults in the United States was found to be 21.8% and the age-adjusted prevalence to be 23.7%.<sup>2</sup> Overall, Mexican-Americans had the highest age-adjusted prevalence of the metabolic syndrome (31.9%). Rates were similar between men and women and increased with age (Figure). Based on census data, approximately 47 million people living in the United States have the metabolic syndrome.<sup>2</sup>

**Prediabetes: Impaired Glucose Tolerance Plus Impaired Fasting Glucose**

Prediabetes is a term that was recently adopted to describe the 2 conditions known as impaired glucose tolerance (IGT) and IFG.<sup>3</sup> IGT is defined as a 2-hour

**Table 2.** Classification of Various Lipid Levels

Triglycerides	Level (mg/dL)	Comments
Normal	<150	—
Borderline high	150 to 199	Treat with weight reduction + physical activity
High	200 to 499	Use treatment targets for non-HDL cholesterol; treat also with weight reduction + physical activity
Very high	>500	Lower triglycerides to prevent acute pancreatitis first; then consider non-HDL/LDL cholesterol lowering
Risk Category	LDL Goal (mg/dL)	Non-HDL Cholesterol Goal (mg/dL)
CHD and CHD risk equivalent* (10-year risk for CHD >20%)	<100	<130
Multiple (2+) risk factors† and 10-year risk <20%	<130	<160
0 to 1 risk factor	<160	<190

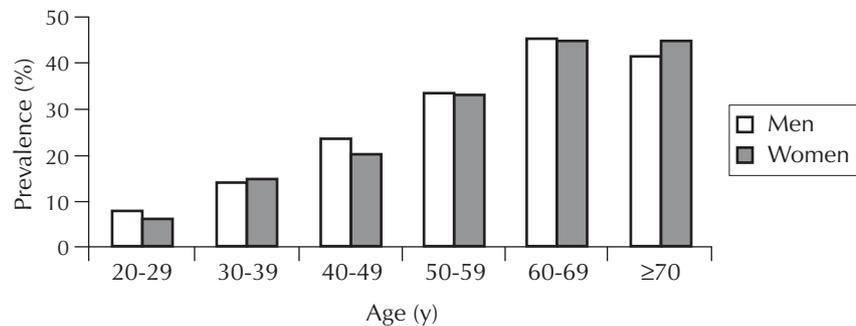
\*CHD risk equivalents are diabetes, symptomatic carotid artery disease, peripheral arterial disease, and abdominal aortic aneurysm.

†Major risk factors: cigarette smoking; hypertension (BP >140/90 mm Hg or on antihypertensive medication); HDL cholesterol level < 40 mg/dL (HDL >60 mg/dL removes 1 risk factor); family history of premature CHD (CHD in male first-degree relative < 55 y; CHD in female first-degree relatives < 65 y); age (men > 45 y; women > 55 y).

BP = blood pressure; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Source: Reference 1.

plasma glucose level (after a 75-g glucose challenge) of 140 to 199 mg/dL. IFG is defined as a fasting plasma glucose level of 110 to 125 mg/dL (verified on a subsequent occasion).<sup>4</sup> IGT is a relatively new term. These abnormalities are associated with risks for developing diabetes and macrovascular disease, although the risks are not identical. The Diabetes Epidemiology: Collaborative Analysis of

**Figure.** Age-Specific Prevalence of the Metabolic Syndrome Among 8814 Adults

Source: Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults. Findings from the Third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356-359. Reprinted with permission.

Diagnostic Criteria in Europe study<sup>5</sup> was carried out to evaluate the clinical significance of the new diagnostic criteria. Fourteen centers were involved in the study; a total of 25,364 individuals underwent oral glucose tolerance testing and were followed up for a median of 7.3 years. Some interesting data were obtained. First, the fasting plasma glucose level did not vary with age, although diabetes rates and 2-hour glucose values increased over time. Similarly, rates of IGT increased with age but IFG decreased with advancing age. No specific cutpoints were found in the dataset for defining IGT or fasting plasma glucose levels (as has been found in other studies); however, the 2-hour glucose level predicted mortality, from cardiovascular disease and all other causes. The greatest risk was observed in patients with isolated elevations in their 2-hour glucose levels (with normal fasting glucose levels). The risk for death was continuous with increasing 2-hour glucose levels, but was not predicted by HbA<sub>1c</sub> levels.

It is well known that IGT is related to cardiovascular disease.<sup>6,7</sup> With few exceptions,<sup>8</sup> data on this subject have shown that IGT is a significant risk factor for the development of cardiovascular disease. According to the American Diabetes Association (ADA),<sup>3</sup> the risk of developing cardiovascular disease is increased by 1.5-fold in patients with prediabetes (and

increased 2- to 4-fold in patients with diabetes). In a population-based study using 2583 patients from the Framingham cohort, metabolic risk factors for CHD—including obesity, hypertension, decreased HDL levels, elevated triglyceride levels, and hyperinsulinemia—showed a continuous increase across the spectrum of nondiabetic glucose tolerance.<sup>9</sup> This increase began at the lowest quintiles of normal fasting glucose.<sup>9</sup> A Japanese study of 2651 patients showed a significant increased risk of death from cardiovascular disease in patients with IGT compared with those with normal glucose tolerance.<sup>10</sup> When reanalyzed, these results did not hold true for the IFG group. The authors concluded that postchallenge hyperglycemia is an important predictor for the development of atherosclerosis. These results were echoed in the Chicago Heart study in men<sup>11</sup> and the Rancho Bernardo study in older women.<sup>12</sup> More recently, in the United States, a gradient of mortality associated with abnormal glucose tolerance was found that ranged from 40% in those with IGT to 110% in those with overt diabetes.<sup>13</sup> These associations were independent of other established cardiovascular risk factors. The European Prospective Investigation of Cancer and Nutrition study showed a 270% increase in cardiovascular events and death in men 40 to 74 years of age whose HbA<sub>1c</sub> levels were 5.0%

to 5.4% compared with those whose levels were <5.0% over 4 years.<sup>14</sup> No evidence has suggested, however, that lowering glycemia in patients with IGT improves outcomes of macrovascular disease.

As noted above, the ADA, Centers for Disease Control and Prevention, and the National Institutes of Health defined IGT and IFG under the new label of *prediabetes*.<sup>3</sup> The idea of this term is to make the public and health professionals aware of the risks associated with this state and the need to address the macrovascular risk as well as the risk for progression to diabetes. Based on data from the Diabetes Prevention Program (DPP), it is estimated that most people with prediabetes will develop diabetes within 10 years if lifestyle modification is not undertaken.<sup>3</sup> One important point to consider is that although mild elevations in glucose levels lead to an increased risk for cardiovascular disease, there is no evidence that lowering the glucose levels will lower the risk for cardiovascular disease. Many of these patients have multiple metabolic abnormalities (such as diabetic dyslipidemia and hypertension) that also must be addressed.

### **Prevention of Progression of Prediabetes to Diabetes**

Treatment of prediabetes and metabolic syndrome involves lowering macrovascular risk (lipid lowering, aggressive control of hypertension, use of aspirin, etc). Treatment also comprises strategies to prevent the development of type 2 diabetes. Data from a number of clinical trials designed to prevent the progression to type 2 diabetes in patients with IGT are available.<sup>15</sup> The Da Qing study,<sup>16</sup> The Finnish Diabetes Prevention Study,<sup>17</sup> and the DPP<sup>18</sup> performed in the United States all showed a significant reduction (42% to 58%) in the relative risk for developing diabetes in patients with IGT who followed a lifestyle program of weight reduction and exercise.

In the DPP, 3234 patients were observed for an average of 2.8 years.<sup>18</sup> Patients were assigned to placebo, lifestyle changes, or metformin (or troglitazone,

which was discontinued after 10 months). In the lifestyle group, patients achieved a 5% to 10% reduction in body weight (approximately 4 to 7 kg) by performing moderate exercise at least 150 minutes per week (74% adherence at 24 months with 58% adherence at the last visit). The lifestyle arm of the study reduced the incidence of diabetes by 58% compared with placebo.<sup>18</sup> These data, and those from the other studies mentioned above, indicate clearly that lifestyle modification, with relatively modest changes in weight and exercise, is the best approach for the prevention of type 2 diabetes in patients with prediabetes.

Drug therapy has also been helpful in preventing the progression to diabetes, although it has not yet been proven to be as effective as lifestyle changes. In the DPP, metformin was associated with a 31% reduction in the risk of developing diabetes.<sup>18</sup> This reduction in risk was most pronounced in younger, more overweight patients and was associated with a 3% reduction in body weight. In the DPP, patients who had been treated for only 10 months with troglitazone (which was withdrawn from the study as a result of an episode of fatal hepatotoxicity that occurred in 1 patient) still had a 23% reduction in the risk for developing diabetes 2 years later.<sup>18</sup> Finally, in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus, acarbose was associated with a 24% reduction in the risk of developing diabetes.<sup>19</sup>

In a smaller study, the Troglitazone in the Prevention of Diabetes trial,<sup>20</sup> 200 nonpregnant women with a recent history of gestational diabetes and current IGT were randomized to receive 400 mg troglitazone or placebo and observed for approximately 28 months. The troglitazone group had a 56% reduction in the risk of developing diabetes. This difference was paralleled by an improvement in insulin sensitivity and beta-cell function. Additionally, a reduction in the progression of carotid intimal medial thickness was observed. This study, although relatively small, showed the profound impact of decreasing insulin resistance in patients at

high risk for developing type 2 diabetes and suggested that the thiazolidinedione class of drugs may be helpful in diabetes prevention.

#### **Treatment of Type 2 Diabetes: Cardiovascular Effects of Antidiabetes Agents**

The major classes of oral antidiabetes medications all reduce hyperglycemia to a similar degree, although through different mechanisms with different onsets of action.<sup>21</sup> Reduction of hyperglycemia reduces the risk for microvascular complications (retinopathy, nephropathy, neuropathy) in patients with type 2 diabetes.<sup>22</sup> However, as noted above, most patients with diabetes die of macrovascular disease. Therefore, an understanding of the cardiovascular effects of various oral antidiabetes medications is necessary.

The insulin secretagogues (sulfonylurea agents, repaglinide, and nateglinide), in addition to exogenous insulin, do not have consistent effects on lipid levels, beyond those associated with improved diabetic control. They are also not associated with a reduction in macrovascular complications, although they reduce the risk for microvascular complications.<sup>22</sup> Metformin tends to lower total and LDL cholesterol levels by 5% to 10%<sup>23</sup> and may slightly decrease triglyceride levels; HDL cholesterol levels are unchanged. Other atherogenic risk factors may be improved by metformin, as well.<sup>24</sup> In the United Kingdom Prospective Diabetes Study, use of metformin was associated with a reduction in myocardial infarction.<sup>25</sup>

The thiazolidinediones have not yet been studied in long-term clinical trials to evaluate their effectiveness at lowering cardiovascular events. However, a number of surrogate endpoints have been improved through the use of this class of medication. As previously reviewed,<sup>26</sup> pioglitazone and rosiglitazone have different effects on lipid profiles. Both raise HDL cholesterol levels and increase LDL cholesterol particle size. Rosiglitazone increases total and LDL cholesterol levels and in some cases raises triglyceride levels.<sup>27</sup> Pioglitazone has a fairly neutral

effect on total and LDL cholesterol levels (compared with placebo) and decreases triglyceride levels.<sup>28-30</sup> Both drugs seem to lower blood pressure levels.<sup>31,32</sup> The thiazolidinedione class of drugs appears to decrease carotid intimal medial thickness (a marker for atherosclerotic progression) in patients with type 2 diabetes.<sup>33,34</sup> Vascular reactivity measured as response to stenting and other procedures is reduced by these agents.<sup>35,36</sup> Ultimately, 1 or both of the thiazolidinediones will likely be shown to reduce cardiovascular events in patients with diabetes, but outcomes data are not yet available.

#### **Treatment of Dyslipidemia**

Treatment targets for patients with diabetes generally recommend achieving an LDL cholesterol level of less than 100 mg/dL as a primary target.<sup>2,37</sup> In ATP III,<sup>2</sup> diabetes is considered a CHD equivalent. It seems reasonable to consider patients with prediabetes to be at high risk and to treat them aggressively. The first therapy, as with any dyslipidemic patient, is therapeutic lifestyle changes. It is recommended that patients restrict saturated fat to less than 7% of total calories and cholesterol level intake to less than 200 mg/day. Patients should consider an increase in viscous (soluble) fiber (10 to 25 g/day) and plant stanols/sterols (2 g/day) as options to enhance lipid lowering. If patients do not reach the target range after 3 months of therapeutic lifestyle changes, pharmaceutical treatment should be added. Generally drug therapy involves adding a statin and titrating up until the LDL cholesterol level is less than 100 mg/dL. Bile acid sequestrants (such as cholestyramine, colestipol, and colesevelam) can be added, but are relatively contraindicated in patients with triglyceride levels much above 200 mg/dL. Nicotinic acid (niacin) effectively raises HDL cholesterol levels and can lower both LDL and triglyceride levels, but can increase insulin resistance and therefore is relatively contraindicated in patients with diabetes. If nicotinic acid is used, blood glucose levels should be observed carefully and antidiabetic thera-

pies changed to maintain an HbA<sub>1c</sub> level of less than 7%.<sup>38</sup> Fibric acid derivatives (gemfibrozil and fenofibrate), effective at lowering triglycerides and raising HDL cholesterol levels, have been proven to reduce the risk of cardiovascular events.<sup>39</sup> They should be used only with caution in combination with statin therapy because the risk for rhabdomyolysis is increased.<sup>40</sup>

### Treatment of Hypertension

Many studies have been performed to evaluate the effect of blood pressure lowering in patients with diabetes. Not only can blood pressure reduction lower the risks of cardiovascular complications and stroke,<sup>41</sup> but lowering levels even a relatively small amount (lowering of systolic blood pressure by 10 mm Hg and diastolic blood pressure by 5 mm Hg) can also decrease the risk for microvascular complications.<sup>42</sup> Because a large benefit can be obtained from even small improvements in blood pressure lowering, attempting to reach the ADA target of less than 130/80 mm Hg is an appropriate goal when treating hypertension in patients with diabetes.<sup>43</sup> These targets should also be considered when treating patients with prediabetes who are at increased risk for cardiovascular events.

### Conclusion

Patients with prediabetes and diabetes are at high risk for macrovascular disease. Weight loss and exercise can prevent the progression of prediabetes to diabetes, but modifiable risk factors for cardiovascular events must be aggressively treated in these patients. It is important to lower blood glucose levels into the near-normal range to prevent the development of diabetic microvascular complications. Antidiabetes drugs, which can lower blood glucose levels as well as lower the risk for cardiovascular events, are ideal because they treat both disorders. However, if lipid levels or blood pressure remain elevated, treatment should be initiated early and ADA targets should be achieved and maintained. In this manner, both the morbidity

and mortality associated with prediabetes and diabetes can be reduced.

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