Patients with diabetes have a greatly increased relative risk of developing cardiovascular disease when compared with patients without diabetes. Much of this risk is related to insulin resistance and is associated with both traditional and nontraditional cardiovascular risk factors. Therapy for diabetes must address these risk factors in an attempt to prevent and adequately treat cardiovascular disease. Pharmacologic therapy directed toward dyslipidemia and hypertension has a beneficial effect on risk factors and has been shown to decrease cardiovascular events. The effects of insulin and oral hypoglycemic agents on insulin resistance are variable, and their direct effect on cardiovascular disease is less clear. Metformin is the only oral hypoglycemic agent shown to decrease cardiovascular events independent of glycemia. The thiazolidinediones directly improve insulin resistance, decrease plasma insulin concentration, and have the potential to decrease the risk of cardiovascular disease in patients with diabetes. A number of studies have demonstrated that the thiazolidinediones produce changes in several cardiovascular risk factors associated with the insulin resistance syndrome, including lowering blood pressure, correcting diabetic dyslipidemia, improving fibrinolysis, and decreasing carotid artery intima-medial thickness. These agents bind a newly described class of receptors, peroxisome proliferator-activated receptors, which may have implications for atherosclerosis. Although these drugs increase low-density lipoprotein (LDL) cholesterol, they induce a favorable change in the LDL particle size and susceptibility to oxidation. Long-term clinical trials are being conducted to determine the effect that thiazolidinediones have on cardiovascular events in individuals with type 2 diabetes. ©2003 by Excerpta Medica, Inc.

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Insulin resistance and compensatory hyperinsulinemia not only contribute to hyperglycemia in type 2 diabetes but also play a pathophysiologic role in a variety of other metabolic abnormalities including (1) high levels of plasma triglycerides, (2) low levels of high-density lipoprotein (HDL) cholesterol, (3) hypertension, (4) abnormal fibrinolysis, and (5) CAD. Insulin resistance contributes to the development of atherosclerosis through multiple recognizable risk factors, such as hypertension, dyslipidemia, and hypercoagulability (Figure 1). Insulin resistance contributes to the development of atherosclerosis through multiple recognizable risk factors, such as hypertension, dyslipidemia, and hypercoagulability (Figure 1).7–10

Insulin resistance and compensatory hyperinsulinemia not only contribute to hyperglycemia in type 2 diabetes but also play a pathophysiologic role in a variety of other metabolic abnormalities including (1) high levels of plasma triglycerides, (2) low levels of high-density lipoprotein (HDL) cholesterol, (3) hypertension, (4) abnormal fibrinolysis, and (5) CAD.11,12

This cluster of abnormalities has been called the insulin resistance syndrome or the metabolic syndrome.13 The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) recently recognized the metabolic syndrome as a secondary therapeutic target for the prevention of cardiovascular diseases.7 Patients with the metabolic syndrome meet ≥3 of the following criteria: (1) triglycerides ≥150 mg/dL, (2) HDL <40 mg/dL in men and <50 mg/dL in women, (3) blood pressure ≥130/85 mm Hg, (4) fasting blood glucose ≥110 mg/dL, and (5) waist circumference >40 cm in men or >35 cm in women (Table 1).7

Because insulin resistance may play a pathophysiologic role in these abnormalities, it has been proposed that drugs that directly improve insulin sensitivity, such as the thiazolidinediones, may correct other abnormalities of the insulin resistance syndrome.
in addition to improving hyperglycemia. Thus, treatment of patients with type 2 diabetes with these agents may confer benefits beyond the lowering of glucose. Because of their beneficial effects on hyperinsulinemia and insulin resistance, the vascular effect of thiazolidinediones is a subject of considerable research interest (Table 2).

The purpose of this review is to assess the potential effect of current diabetes treatments on cardiovascular disease through risk factor reduction in patients with type 2 diabetes. The current recommended approach to each of the risk factors will be addressed and an attempt will be made to develop a strategy for reducing cardiovascular risk in patients with type 2 diabetes. The current recommended approach to each of the risk factors will be addressed and an attempt will be made to develop a strategy for reducing cardiovascular risk in patients with diabetes in general and for those with established cardiovascular disease in particular. Some of these principles also may apply to individuals with impaired glucose tolerance, many of whom have features of the insulin resistance syndrome.

**TABLE 1 Risk Determinants for the Diagnosis of the Metabolic Syndrome as Defined by the National Cholesterol Education Program Adult Treatment Panel III**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (waist circumference)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;40 in (&gt;102 cm)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;35 in (&gt;88 cm)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein. Reprinted with permission from JAMA.

**FIGURE 1.** Insulin resistance contributes to the development of atherosclerosis through multiple recognizable risk factors. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol. (Adapted from Diabetes Care, Am J Cardiol, and JAMA.)

**STRATEGIES THAT MAY REDUCE CARDIOVASCULAR EVENTS IN DIABETES**

Because of the multifaceted nature of the insulin resistance syndrome, most patients exhibit a spectrum of clinical abnormalities. Many of these abnormalities are amenable to intervention, and a multiple risk factor intervention approach is frequently required in these patients. Various strategies that may reduce cardiovascular events in patients with type 2 diabetes are shown in Table 3. Some of these strategies have been proved by intervention trials, whereas others are suggested by epidemiologic data.

Recent studies have demonstrated the importance of nontraditional risk factors for cardiovascular disease in diabetes. Traditional and nontraditional risk factors for cardiovascular disease that have been described in patients with diabetes are outlined in Table 4. Many of the nontraditional risk factors have been
Hypertension is frequently associated with type 2 diabetes and is a diagnostic criterion for the insulin resistance syndrome. The incidence of hypertension is approximately 2-fold higher in patients with diabetes than in individuals without diabetes. Potential mechanisms that may explain this association include (1) stimulation of the sympathetic nervous system, (2) increased responsiveness to angiotensin-converting enzyme inhibitors, and (3) impaired vasodilatory mechanisms.

Several studies have documented the value of treating hypertension in patients with diabetes. In particular, the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that a 12% reduction in cardiovascular events can be expected from a 10-mm Hg reduction in systolic blood pressure. Of note, the Hypertension Optimal Treatment (HOT) trial demonstrated a 67% risk reduction in cardiovascular mortality during a period of 4 years, only when the diastolic blood pressure was reduced to <80 mm Hg in patients with diabetes, in contrast to those without diabetes in whom a reduction to <90 mm Hg was sufficient to significantly reduce risk. It is also important to consider the results of the Heart Outcomes Prevention Evaluation (HOPE) Study, which demonstrated that despite almost equivalent levels of blood pressure, patients with diabetes treated with an angiotensin-converting enzyme inhibitor, ramipril, had a significant reduction in cardiovascular events and mortality. Thus, blood pressure targets have been set lower for patients with diabetes, and treatment with angiotensin-converting enzyme inhibitors is frequently recommended as first-line therapy in patients who have diabetes and hypertension.

Dyslipidemia: Lipid abnormalities occur in 30% to 50% of patients with type 2 diabetes. The characteristic pattern of dyslipidemia in patients with diabetes and insulin resistance is discussed in greater detail in another article in this supplement. These include low HDL cholesterol, elevated triglyceride levels, and an increase in small, dense low-density lipoprotein (LDL) particles, which are more atherogenic. Findings from the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) are therefore particularly relevant. In this study, which randomized men with a previous history of clinical cardiovascular events to either placebo or gemfibrozil, even a modest increase in plasma HDL cholesterol with gemfibrozil treatment led to a 24% reduction in vascular events in patients with diabetes. The importance of reduction of total cholesterol and LDL cholesterol has also been demonstrated in the diabetic subpopulations in several major clinical trials. Thus, the benefits of improving the dyslipidemic profile associated with insulin resistance are clear in patients with type 2 diabetes. The American Diabetes Association recommends the following target lipid levels in patients with diabetes: (1) LDL cholesterol <100 mg/dL, (2) HDL chole-
terol >45 mg/dL in men and >55 mg/dL in women, and (3) triglycerides <150 mg/dL.26

Glycemic control: The importance of glycemic control in alleviating both microvascular and macrovascular outcomes is becoming more apparent based on clinical trial data.31-33 Control of diabetes, as measured by glycosylated hemoglobin levels, has been shown to predict cardiac events and mortality in patients with diabetes,34 and high levels of glycosylated hemoglobin are significantly associated with all causes of mortality in patients with diabetes.35 The relative risk of death from cardiovascular disease is increased, even in those without diabetes (many of whom may be insulin resistant) who have levels of glycosylated hemoglobin at the upper end of the normal range.36

Although numerous studies have demonstrated the beneficial effects of glycemic control on microvascular complications,31,37,38 fewer studies have shown a reduction in cardiovascular events with good glycemic control.32,39 Patients with type 2 diabetes have a higher mortality rate after a myocardial infarction (MI) than those without diabetes.40 The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study demonstrated a reduction in mortality in hospitalized patients with type 2 diabetes after an acute MI who were treated with an insulin infusion followed by intensive insulin therapy for 1 year; the benefits of this intervention lasted ≥5 years. Analysis of the UKPDS data by glycemic control also showed a significantly lower incidence of cardiovascular events in patients whose level of glycosylated hemoglobin was <7% of total hemoglobin. More importantly, the UKPDS demonstrated that patients who were obese and randomized to receive metformin had a significantly reduced rate of MI compared with those receiving conventional therapy when analyzed on an intention-to-treat basis.37 Although the reason for this difference is not clear, it may be related to moderate effects exerted by metformin on the insulin resistance syndrome. Thiazolidinediones were not included in the UKPDS. However, several long-term trials, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial, Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications (DREAM), and A Diabetes Outcome Progression Trial (ADOPT)41-43 are ongoing to evaluate their effect on prevention of cardiovascular events in patients with type 2 diabetes.

EFFECT OF THERAPY ON CARDIOVASCULAR RISK IN TYPE 2 DIABETES

Nonpharmacologic therapy: Medical nutrition therapy with a reduction in caloric intake should be designed to (1) decrease glucose, (2) improve the lipid profile, (3) lower blood pressure, and (4) induce weight loss.26 Nutrition therapy alone may reduce the risk of cardiovascular events, and moderate increases in physical activity will also affect mortality.44 Many of the risk factors associated with cardiovascular disease in diabetes may improve with lifestyle modifications.45,46 A study of patients without diabetes with elevated fasting and postload plasma glucose concentrations who were randomized to receive metformin, lifestyle modifications (7% weight loss and 150 minutes of exercise per week), or placebo demonstrated that either metformin treatment or lifestyle modifications were effective for reducing the incidence of diabetes (31% and 58%, respectively) after a mean follow-up duration of 2.8 years.45 Unfortunately, compliance with such treatment is generally poor, and pharmacologic therapy eventually becomes necessary in most patients.

Pharmacologic therapy: An ideal agent for the treatment of type 2 diabetes should (1) effectively lower blood glucose, (2) be safe and well tolerated, and (3) exert beneficial effects on components of the metabolic syndrome. Currently, several classes of oral pharmacologic agents with different mechanisms of action are available. All of the oral antidiabetic agents lower levels of glucose and glycosylated hemoglobin; however, the effects of these agents on cardiovascular risk factors differ. In particular, the oral antidiabetic agents have varying effects on insulin resistance and nontraditional cardiovascular risk factors (Table 5).

INSULIN SECRETAGOGUES: The insulin secretagogues include the sulfonylureas and meglitinides. These agents are effective in lowering plasma glucose levels.37 However, the effect of the insulin secretagogues on cardiovascular risk factors is limited to the indirect effects of lowering glucose. For example, improved glycemic control frequently leads to lower plasma triglyceride concentrations. The UKPDS clearly showed that sulfonylureas do not increase the risk of cardiovascular events.31 Thus, sulfonylureas provide some potential benefit on cardiovascular disease through improved glycemic control.

α-GLUCOSIDASE INHIBITORS: There are 2 drugs in this class that are approved for clinical use: acarbose and miglitol. The α-glucosidase inhibitors inhibit enzymes that digest carbohydrates and thus decrease postprandial glycemic fluctuations.47 The effect of this decrease in postprandial glucose on cardiovascular events has not been studied. A few studies suggest that this effect is associated with decreased postprandial oxidative stress and activation of coagulation.48 Over-

<table>
<thead>
<tr>
<th>TABLE 5</th>
<th>Effects of Various Therapeutic Interventions on Components of Insulin Resistance15,47</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Weight control</td>
<td>+</td>
</tr>
<tr>
<td>Increased activity</td>
<td>±</td>
</tr>
<tr>
<td>Biguanides</td>
<td>+</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>+</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>+</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>+</td>
</tr>
<tr>
<td>+ = positive; − = negative; ± = may be positive or negative; ? = unknown.</td>
<td></td>
</tr>
</tbody>
</table>
all, the effect of the α-glucosidase inhibitors on other cardiovascular risk factors is minimal.

BIGUANIDES: Metformin is the only biguanide available for clinical use. Its efficacy as monotherapy and in combination with other agents is well established. To date, metformin is the only drug that has been shown to decrease cardiovascular events in patients with type 2 diabetes, independently of glycemic control. Although metformin has a small effect as a peripheral insulin sensitizer, its main mechanism is inhibiting hepatic gluconeogenesis. Nevertheless, metformin treatment lowers plasma insulin levels and corrects many of the nontraditional risk factors associated with the insulin resistance syndrome.

THIAZOLIDINEDIONES: The thiazolidinediones have emerged as an important therapeutic drug class in the management of type 2 diabetes, and their efficacy in lowering plasma glucose is well established. The glucose-lowering effects of the thiazolidinediones are mediated primarily by decreasing insulin resistance at the level of the muscle and thereby increasing glucose uptake. Thiazolidinediones also increase glucose disposal in muscle and fat and reduce hepatic glucose production. The actions of the thiazolidinediones are mediated through binding and activation of the peroxisome proliferator-activated receptor (PPAR)-γ receptor, a nuclear receptor that has a regulatory role in differentiation of cells, particularly adipocytes. This receptor is also expressed in several other tissues, including vascular tissue. In addition, thiazolidinediones lower plasma free fatty acid concentrations and indeed may indirectly improve insulin sensitivity by this decrease in free fatty acids. Because free fatty acids are involved in lipid metabolism and also have deleterious effects on the vasculature, this reduction in plasma free fatty acids may have a beneficial effect on cardiovascular disease.

The thiazolidinediones have the potential to alter metabolic conditions beyond the management of glycemia. Because the thiazolidinediones target insulin resistance, these agents may improve many of the risk factors associated with the insulin resistance syndrome. Although data on the effect of the thiazolidinediones on cardiovascular outcomes are currently lacking, results of ongoing clinical trials are eagerly awaited and are likely to support the use of these agents in minimizing adverse cardiovascular events. At this time, it appears that the thiazolidinediones exert numerous nonglycemic effects that may improve cardiovascular outcomes.

**BENEFICIAL EFFECTS OF INSULIN-SENSITIZING AGENTS ON CARDIOVASCULAR RISK FACTORS**

Several epidemiologic studies have shown that hyperinsulinemia is an independent risk factor for cardiovascular disease. Correction of insulin resistance is clearly important in the management of type 2 diabetes and may decrease the risk of cardiovascular disease. In the UKPDS, patients with type 2 diabetes treated with metformin, which decreases hyperinsulinemia and insulin resistance, had a 30% reduction in cardiovascular disease events and mortality compared with those given conventional treatment. As noted earlier, the thiazolidinediones also improve insulin sensitivity and may exert numerous nonglycemic effects in patients with type 2 diabetes. Additional clinical trials are currently being conducted to evaluate whether treatment of diabetes with agents that reduce insulin resistance, such as the thiazolidinediones, is superior to treatment with agents that stimulate insulin secretion, such as the sulfonylureas.

Lipid metabolism and oxidation: Metformin has a favorable, albeit modest, effect on plasma lipids, particularly lowering levels of triglycerides and LDL cholesterol; however, it has little if any effect on HDL cholesterol levels. In contrast, several studies have observed beneficial effects of the thiazolidinediones on lipid metabolism. Published data indicate that all the thiazolidinediones increase HDL cholesterol, although only troglitazone and pioglitazone have been shown to consistently lower triglycerides. PiroglibZONE and rosiglitazone both increase HDL and LDL cholesterol levels. Differences between the thiazolidinediones with respect to their lipid effects may reflect the fact that populations with different baseline values have been studied, and a randomized comparative trial is needed to determine whether a true difference exists.

The effects of the thiazolidinediones on LDL cholesterol are complex and discussed in detail in another article in this supplement. Patients with type 2 diabetes (or individuals who are insulin resistant) are more likely than those without diabetes or insulin resistance to have small dense, triglyceride-rich LDL cholesterol particles, which are highly susceptible to oxidation. Oxidative modification confers atherogenic properties on these small, dense LDL cholesterol particles. This characteristic is a key initial event in the progression of atherosclerosis, and the presence of small, dense LDL is an independent risk factor for cardiovascular disease. The thiazolidinediones have been shown in some studies to increase levels of total cholesterol and/or LDL cholesterol. Although there is an increase in LDL cholesterol, this increase is predominantly in the larger, buoyant particles of LDL cholesterol, which may be less atherogenic. Concomitantly, the small, dense LDL cholesterol particles have been shown to decrease with thiazolidinedione therapy.

**Blood pressure:** Improving insulin sensitivity has the potential to lower blood pressure in patients with insulin resistance and/or diabetes. The effects of thiazolidinediones on blood pressure have been examined in several different experimental and clinical settings. A study of 24 hypertensive patients without diabetes treated with rosiglitazone demonstrated that rosiglitazone treatment that was added onto the patient’s usual antihypertensive medication resulted in a decrease in both systolic and diastolic blood pressure and improved insulin resistance. Oghihara et al demonstrated significant reduction in blood pressure in hypertensive subjects with type 2 diabetes who were treated with troglitazone. In another study of 203
patients with type 2 diabetes, treatment with rosiglitazone significantly reduced ambulatory blood pressure. Scherbaum et al also reported decreases in systolic blood pressure by pioglitazone in normotensive and hypertensive patients with diabetes. Similar results were also seen in patients who were not hypertensive but had type 2 diabetes and in those without diabetes who were obese.

A potential mechanism for thiazolidinedione-mediated decreases in blood pressure may be improved insulin sensitivity, which promotes insulin-mediated vasodilation. Alternative hypotheses for the decrease in blood pressure may include inhibition of intracellular calcium and myocyte contractility and endothelin-1 expression and secretion. Pioglitazone has been shown to inhibit renal artery proliferation in animal models, which generated reductions in blood pressure.

**Endothelial dysfunction:** Vascular endothelium is involved in the regulation of vascular tone, vessel permeability, and angiogenesis. Various paracrine vaso-dilatory and vasoconstrictor factors, most notably nitric oxide and endothelin-1, determine vascular tone. The endothelium plays a vital role in the maintenance of blood fluidity, tone of the vascular wall, and permeability. Endothelial dysfunction is central to many vascular diseases, including atherosclerosis and diabetic microangiopathy. Endothelial function is disturbed by many of the individual features of the insulin resistance syndrome, including hypertension, dyslipidemia, and hyperglycemia. The regulation of endothelial function and its abnormalities in the metabolic syndrome are discussed in greater detail in another article in this supplement.

Avena et al demonstrated normalization of impaired brachial artery flow-mediated dilatation in troglitazone-treated human subjects with peripheral vascular disease. Although this observation was disputed in a study by Tack et al, the results have been reproduced in other studies. Improvement of vascular reactivity in patients with obesity without diabetes after treatment with rosiglitazone has also been reported. This improvement was associated with beneficial changes in several markers of inflammation and endothelial activation.

The thiazolidinediones act on the endothelium via various mechanisms, namely their action on nitric oxide synthesis, modulation of the nuclear receptor, PPAR-γ, and effects on various cytokines, including adhesion molecules involved in the atherosclerotic process. Recently, metformin also has been shown to improve endothelial function. Because the biguanides do not stimulate PPARs, other mechanisms are likely to be involved in the pathogenesis of endothelial dysfunction in insulin resistance.

The thiazolidinediones may also prevent the progression of atherosclerosis by inhibiting the expression of monocyte chemoattractant protein-1 in endothelial cells. In addition to an attenuated response to tumor necrosis factor-α, other mediators of inflammation are also suppressed. Profound anti-inflammatory properties and antioxidant effects have been observed in patients with type 2 diabetes treated with thiazolidinediones; hence, these agents may be of benefit at the vascular level. A study evaluating troglitazone showed a profound reduction in the levels of nuclear factor-κB, a molecule that induces inflammatory cytokines, such as tumor necrosis factor-α, monocyte chemoattractant protein-1, adhesion molecules (soluble intercellular adhesion molecule-1), and reactive oxygen species. Thus, the thiazolidinediones exert anti-inflammatory actions that may contribute to their putative antiatherosclerotic effects.

**Vascular wall abnormalities:** B-mode ultrasound is a noninvasive method for evaluating carotid intima-media complex thickness, which is an indicator for early atherosclerosis and is associated with insulin resistance. This measurement may serve as a surrogate marker for atherosclerotic events because patients with increased intima-media complex thickness have a higher rate of cardiovascular events over time. Treatment with troglitazone was shown to significantly decrease intima-media thickness in patients with type 2 diabetes. Koshiyama et al recently reported a significant decrease in the intima-media thickness in patients with type 2 diabetes who are treated with pioglitazone. It is possible that these effects of the thiazolidinediones are direct cellular effects on the atherosclerotic process that are not linked to their effects on insulin resistance.

In acute coronary events, plaque rupture is a core event. Exposure of the highly thrombogenic lipid core to circulating coagulation factors can lead to a progressive cascade that results in occlusion of the vessel. Matrix metalloproteinases, produced by monocyte-derived macrophages and vascular smooth muscle cells, contribute to this process. Troglitazone and rosiglitazone have been shown to inhibit the expression and functional activity of matrix metalloproteinase-9 in human monocyte-derived macrophages and human vascular smooth muscle cell.

**Fibrinolysis, coagulation, and inflammation:** Decreased fibrinolytic activity in association with elevated plasma plasminogen activator inhibitor type-1 (PAI-1) is associated with increased risk of atherosclerosis and cardiovascular disease. PAI-1 is the primary inhibitor of endogenous tissue plasminogen activator and is elevated both in patients with diabetes and in those who are insulin resistant without diabetes. Increased PAI-1 levels are now recognized as an integral part of the insulin resistance syndrome and correlate significantly with plasma insulin. Insulin infusion during infarction and postinfarction periods (which is known to improve outcomes) has been shown to decrease plasma PAI-1 levels. Immuno-histochemical analysis of the coronary lesions from patients with CAD has demonstrated an imbalance of the local fibrinolytic system with increased coronary artery tissue PAI-1 levels in patients with type 2 diabetes. Impaired fibrinolysis is also noted in other insulin-resistant states, such as the polycystic ovary syndrome. Fonseca et al demonstrated a decrease in plasma PAI-1 levels in patients with diabetes.
treated with a thiazolidinedione. This observation has been confirmed in several studies. The postulated mechanism for the effect of the thiazolidinediones is via the activation of PPAR-\(\gamma\) and subsequent suppression of PAI-1.

In vitro studies with troglitazone have demonstrated not only direct effect on the vessel wall leading to a decreased synthesis of PAI-1 but also indirect effects on hepatic synthesis as a result of the attenuation of hyperinsulinemia. Pioglitazone was found to have a similar effect. Treatment with rosiglitazone also has been shown to decrease PAI-1 levels. Therefore, PAI-1 reduction may well be a class effect of the insulin sensitizers. Although increases in PAI-1 levels are associated with an increased risk of myocardial infarction, no study has demonstrated a diminution of this risk with reduction in plasma PAI-1 levels. Consequently, clinical trials are necessary to demonstrate such a benefit.

As with elevated levels of PAI-1, increases in plasma concentrations of markers of inflammation, such as C-reactive protein, are associated with both the insulin resistance syndrome and cardiovascular disease. Fuell et al. reported reductions in the proinflammatory markers interleukin-6, C-reactive protein, and white blood cells in patients with type 2 diabetes treated with rosiglitazone, whereas Haffner et al. reported a reduction in levels of matrix metalloproteinase-9 and C-reactive protein in patients with type 2 diabetes treated with rosiglitazone. These effects may be related to the decrease in insulin resistance and may have beneficial consequences for long-term cardiovascular risk.

**Albuminuria:** Urinary microalbuminuria is routinely monitored in clinical practice and is recognized as a marker of cardiovascular disease and diabetic nephropathy. Current methods of reducing microalbuminuria include strict glycemic control and use of angiotensin-converting enzyme inhibitors. Imano et al. showed reductions in the urinary microalbumin-to-creatinine ratio during a 12-week clinical trial when troglitazone was compared with metformin. Similar effects have been noted with rosiglitazone. In fact, in a 52-week open trial of patients with type 2 diabetes given either rosiglitazone or glyburide, patients treated with rosiglitazone had a significant reduction in the urinary albumin-to-creatinine ratio compared with baseline (Figure 2). Laboratory work revealed that PPAR-\(\gamma\) receptors are not only expressed in mesangial cells of animal models but also inhibit both mesangial cell proliferation and angiotensin II–induced PAI-1 expression. Consequently, thiazolidinedione therapy may represent an alternative method for reducing proteinuria and subsequent nephropathy.

**Body weight:** Clinical trials suggest that the thiazolidinediones may increase body weight. However, the weight gain is accompanied by improvement in glycemic control and may also be secondary to fluid retention. Stimulation of adipogenesis through PPAR-\(\gamma\) is another potential mechanism for weight gain. This is a site-specific effect, with weight gain

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**FIGURE 2.** Mean percent change from baseline and 95% confidence interval in urinary albumin/creatinine ratio (ACR) in patients with type 2 diabetes after 52 weeks of treatment with rosiglitazone (squares) or glyburide (circles). Open symbols indicate values for all patients in each group. Closed symbols indicate patients with baseline microalbuminuria in each group. (Reprinted with permission from J Hum Hypertens.)
occurring from an increase in subcutaneous fat while a decrease in visceral fat content occurs (ie, fat redistribution). The clinical significance of increased body weight with the thiazolidinediones is unclear. Weight gain usually increases insulin resistance, which in turn increases glucose. However, the thiazolidinediones clearly decrease insulin resistance and glucose despite mild weight gain.

Thus, other mechanisms must be involved in the relation of weight to insulin resistance. For instance, increased intra-abdominal fat is associated with increased insulin resistance. The redistribution of body fat mediated by the thiazolidinediones may therefore be important. In fact, studies do support this hypothesis. Kelley et al demonstrated that treatment with troglitazone in human subjects with type 2 diabetes decreases intra-abdominal fat mass but does not affect total body fat or weight. Similar effects have been observed in patients with type 2 diabetes who were treated with rosiglitazone or pioglitazone. Thus, the thiazolidinediones may reduce fat accumulation in the visceral abdominal cavity by improving insulin sensitivity.

CONGESTIVE HEART FAILURE AND TYPE 2 DIABETES

Nichols et al have recently reported that congestive heart failure was prevalent in 11.8% of subjects with diabetes and 4.5% of control subjects. Furthermore, in subjects free of congestive heart failure at baseline, they observed incident cases of congestive heart failure in 7.7% of subjects with diabetes and in only 3.4% of control subjects. Thus, patients with diabetes are at high risk for congestive heart failure, which should be considered when evaluating data relating to the use of medications for treating diabetes.

Ghazzi et al investigated whether patients with type 2 diabetes treated with troglitazone 800 mg daily (a dose higher than that used in clinical practice) or glyburide developed any cardiac mass increase or functional impairment. Findings from 2-dimensional echocardiography and pulsed Doppler demonstrated that both troglitazone and glyburide did not change left ventricular mass index significantly over 48 weeks. These findings are reassuring and are in contrast to the animal studies. Similar studies have been conducted with rosiglitazone and pioglitazone and have also demonstrated no adverse effect on cardiac mass or function. In a study of 203 patients with type 2 diabetes randomized to receive either rosiglitazone or pioglitazone and glyburide developed any cardiac mass increase or functional impairment. Findings from 2-dimensional echocardiography and pulsed Doppler demonstrated that both troglitazone and glyburide did not change left ventricular mass index significantly over 48 weeks. These findings are reassuring and are in contrast to the animal studies. Similar studies have been conducted with rosiglitazone and pioglitazone and have also demonstrated no adverse effect on cardiac mass or function. In a study of 203 patients with type 2 diabetes randomized to receive either rosiglitazone or pioglitazone and glyburide developed any cardiac mass increase or functional impairment. Findings from 2-dimensional echocardiography and pulsed Doppler demonstrated that both troglitazone and glyburide did not change left ventricular mass index significantly over 48 weeks. These findings are reassuring and are in contrast to the animal studies. Similar studies have been conducted with rosiglitazone and pioglitazone and have also demonstrated no adverse effect on cardiac mass or function. In a study of 203 patients with type 2 diabetes randomized to receive either rosiglitazone or pioglitazone and glyburide developed any cardiac mass increase or functional impairment. Findings from 2-dimensional echocardiography and pulsed Doppler demonstrated that both troglitazone and glyburide did not change left ventricular mass index significantly over 48 weeks. These findings are reassuring and are in contrast to the animal studies. Similar studies have been conducted with rosiglitazone and pioglitazone and have also demonstrated no adverse effect on cardiac mass or function. In a study of 203 patients with type 2 diabetes randomized to receive either rosiglitazone or pioglitazone and glyburide developed any cardiac mass increase or functional impairment. Findings from 2-dimensional echocardiography and pulsed Doppler demonstrated that both troglitazone and glyburide did not change left ventricular mass index significantly over 48 weeks. These findings are reassuring and are in contrast to the animal studies. Similar studies have been conducted with rosiglitazone and pioglitazone and have also demonstrated no adverse effect on cardiac mass or function. In a study of 203 patients with type 2 diabetes randomized to receive either rosiglitazone or pioglitazone and glyburide developed any cardiac mass increase or functional impairment. Findings from 2-dimensional echocardiography and pulsed Doppler demonstrated that both troglitazone and glyburide did not change left ventricular mass index significantly over 48 weeks. These findings are reassuring and are in contrast to the animal studies. Similar studies have been conducted with rosiglitazone and pioglitazone and have also demonstrated no adverse effect on cardiac mass or function. In a study of 203 patients with type 2 diabetes randomized to receive either rosiglitazone or pioglitazone and glyburide developed any cardiac mass increase or functional impairment.

CONCLUSIONS

A multiple risk factor approach is needed in patients with type 2 diabetes. Because many risk factors are linked with insulin resistance, treatment with insulin sensitizers has the potential to modulate these risk factors favorably. Although the effect of metformin on cardiovascular risk factors is modest, a significant effect on cardiovascular events has been demonstrated independent of hypoglycemic effects. The thiazolidinediones have many important effects beyond lowering blood glucose. By targeting insulin resistance, they improve many cardiovascular risk factors associated with the insulin resistance syndrome. In particular, they (1) increase levels of HDL cholesterol, (2) improve endothelial function and fibrinolysis, and (3) decrease carotid intimal thickness. Several
clinical trials designed to investigate the effect these agents have on reducing cardiovascular events are under way.