Thiazolidinediones in the Treatment of Managed Care Patients With Type 2 Diabetes

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Abstract

Insulin resistance and progressive β-cell failure are fundamental defects in type 2 diabetes. Treatments that improve insulin sensitivity and β-cell function can improve these defects and improve glycemic control. The thiazolidinediones (TZDs) improve insulin sensitivity, fasting and postprandial plasma glucose levels, and glycosylated hemoglobin (HbA_{1c}) levels. These agents can be used as monotherapy, and they have been successfully combined with other antidiabetic therapies. The TZDs have also been associated with improvements in various cardiovascular risk factors, including hypertension, the dyslipidemic profile often observed in patients with diabetes or insulin resistance, aspects of endothelial dysfunction, abnormal hemostasis, and levels of several inflammatory markers. Studies are currently under way to evaluate the effects of TZDs on cardiovascular event rates. Accumulating evidence suggests that TZDs may enhance or preserve β-cell function and thus may have a more durable therapeutic effect than some of the other oral antidiabetic agents. Using TZDs as monotherapy or as a component of combination therapy will contribute to improved glycemic control and should reduce the risk of diabetic complications. A number of studies have shown that a strategy of aggressive use of pharmacologic agents to achieve glycemic control is associated with cost benefits.

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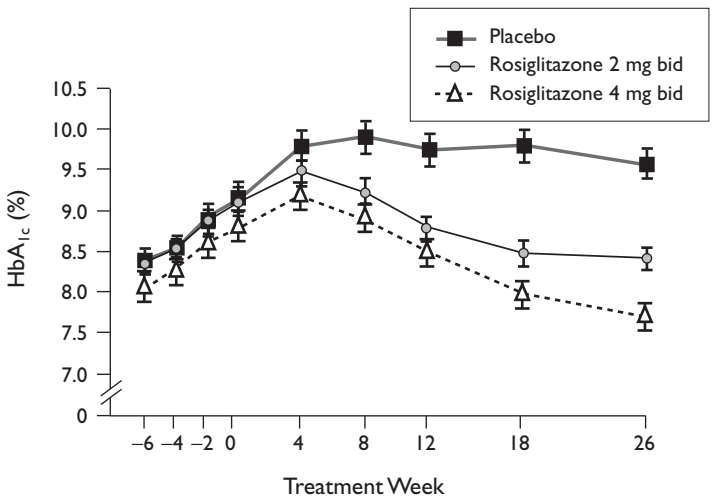
Insulin resistance is a central feature in a number of disease states, including type 2 diabetes, hypertension, dyslipidemia, atherosclerosis, and polycystic ovary syndrome. Insulin resistance frequently precedes the development of type 2 diabetes, although not all individuals who are insulin resistant develop clinical diabetes.[1,2] Subjects with impaired glucose tolerance and insulin resistance progress to type 2 diabetes at variable rates, depending on factors such as obesity, ethnicity, lack of physical activity, continued weight gain, and, especially, declining β-cell function. Various studies have evaluated the role of thiazolidinediones (TZDs) in the insulin-resistant state.[3-8] Improving insulin sensitivity with agents such as the TZDs can reduce insulin resistance associated with type 2 diabetes as well as significantly improve a number of important cardiovascular risk factors. This article will provide an overview of some of the data supporting these concepts.

···TZDs: MECHANISM OF ACTION AND GLYCEMIC EFFECTS···

TZDs bind to peroxisome proliferator-activated receptor-γ (PPARγ) sites, leading to transcription of genes involved in carbohydrate and lipid metabolism.[9] TZDs primarily augment insulin-stimulated glucose uptake in muscle and adipose tissue. Thus, insulin resistance is decreased in these tissues and, to a lesser extent, in hepatic tissue.[3] When used as monotherapy, TZDs decrease plasma glucose and glycosylated hemoglobin (HbA_{1c}) levels without causing hypoglycemia.[10,11]

During insulin and glucose infusions, TZD-treated patients had enhanced glucose disposal and improved insulin sensitivity.[3] Glycemic response and insulin sensitivity index after glucose administration and meals were also improved in

Figure. Mean Glycosylated Hemoglobin (HbA_{1c}) Over Time in Patients Treated With Rosiglitazone 4 mg and 8 mg Daily



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TZD-treated patients.[12,13] Low doses (100-400 mg/d) of troglitazone did not affect hepatic glucose production but, at doses of 600 mg daily, basal hepatic glucose production was suppressed.[12] Rosiglitazone has been shown to improve hepatic and muscle insulin sensitivity and to increase nonesterified fatty acid turnover in subjects with type 2 diabetes.[14]

In patients with type 2 diabetes, troglitazone, but not placebo, decreased fasting plasma glucose (FPG), HbA_{1c}, and insulin levels.[15-17] Combining troglitazone with other oral agents, such as sulfonylureas, α-glucosidase inhibitors, or nonsulfonylurea secretagogues, was more effective in decreasing glucose, HbA_{1c}, and basal plasma insulin levels than using these agents as monotherapy.[18-22] Six months of triple combination therapy with troglitazone added to maximal doses of sulfonylurea and metformin in patients with type 2 diabetes significantly decreased FPG, HbA_{1c}, and insulin levels without a significant increase in adverse events compared with placebo.[23] Addition of troglitazone significantly decreased insulin doses by up to 58% in patients with type 2 diabetes who were taking insulin.[24,25]

Rosiglitazone also has been demonstrated to be effective in lowering fasting and postprandial plasma glucose and HbA_{1c} levels in patients with type 2 diabetes. In one study, 493 patients with poorly controlled diabetes were randomized to treatment with rosiglitazone or placebo. After 6 months of treatment with rosiglitazone 4 mg and 8 mg, HbA_{1c} level was lowered by 1.21% and 1.54%, (**Figure**) and FPG was lowered by 3.2 mmol/L (58 mg/dL) and 4.2 mmol/L (76 mg/dL), respectively, compared with placebo.[11] Other studies have confirmed the ability of rosiglitazone to decrease FPG, free fatty acid, and HbA_{1c} levels in patients with type 2 diabetes.[26-29]

In a study conducted by Wolffenbuttel et al, addition of rosiglitazone (2 mg or 4 mg daily) to sulfonylurea treatment was evaluated in 574 patients with type 2 diabetes.[30] The HbA_{1c} level decreased by 0.6% and 1.0%, respectively, without any increase in hypoglycemia or hepatotoxicity. In another study, 348 obese patients inadequately controlled on the maximal dose of metformin were randomized to rosiglitazone 4 mg or 8 mg daily or placebo in addition to metformin 2.5 g daily.[31] Mean HbA_{1c} level decreased significantly by 0.97% and 1.18%, and FPG decreased by 2.2 mmol/L and 2.9 mmol/L, respectively, in the rosiglitazone-treated patients ($P<.001$ compared with placebo). In 319 poorly controlled insulin-treated patients, addition of rosiglitazone 2 mg or 4 mg twice daily significantly improved glycemic control and reduced insulin requirements. Overall, HbA_{1c} decreased by 0.6% and 1.2%, respectively, whereas it increased by 0.1% in the placebo group.[32] Research recently presented at the American Diabetes Association 62nd Scientific Sessions demonstrated significantly improved glycemic control when rosiglitazone was added to a fixed-dose combination of metformin and glyburide.[33]

Rosiglitazone also has been shown to significantly improve insulin sensitivity in subjects who showed a beneficial glycemic response.[3,11,34] In an analysis of 493 patients with type 2 diabetes, treatment with rosiglitazone 4 mg twice daily was

associated with a 24.6% reduction in insulin resistance compared with placebo.[11]

Pioglitazone 45 mg daily significantly reduced HbA_{1c} level by 2.5% compared with an increase of 0.8% in the placebo-treated group during a 26-week period.[35] In a double-blind, placebo-controlled study, patients with type 2 diabetes were randomly assigned to receive pioglitazone 15 mg daily (n=184), 30 mg daily (n=189), or placebo (n=187) in addition to a sulfonylurea.[36] The addition of pioglitazone to a sulfonylurea in patients with poorly controlled diabetes (HbA_{1c} >8%) significantly improved glycemic control. Compared with placebo, HbA_{1c} level decreased by 0.9% in the group receiving pioglitazone 15 mg and 1.3% in the 30-mg group ($P<.05$). The combination of pioglitazone 30 mg and metformin decreased HbA_{1c} level by 0.83%, and in the group taking placebo and metformin, HbA_{1c} level was decreased by 0.05%.[37] In another study, 566 patients with diabetes who were poorly controlled on insulin showed a decrease in HbA_{1c} of 0.7% and 1.0%, respectively, when pioglitazone 15 mg or 30 mg was added for 16 weeks.[38] These studies indicate that the TZDs are effective in reducing insulin resistance and improving glycemic control in patients with type 2 diabetes.

···TZDs AND β-CELL FUNCTION···

TZDs may have a positive effect on β-cell function. In a study in db/db mice, rosiglitazone, but not glyburide or metformin, was associated with an increase in β-cell insulin content.[39] Several intriguing studies suggest that TZDs may preserve or enhance β-cell function, leading to a more durable improvement in glycemic control.[11,40-43] In an analysis of nearly 500 patients with type 2 diabetes, treatment with rosiglitazone 4 mg twice daily was associated with a 60% improvement in β-cell function, as measured by the homeostasis model assessment (HOMA), compared with placebo.[11] In a study conducted by Fonseca et al, β-cell function as measured by the HOMA technique improved in patients with diabetes when rosiglitazone was added to metformin.[31] The authors postulated that there may be a beneficial rosiglitazone-related effect on lipotoxicity and/or glucose toxicity.

The Diabetes Outcomes Progression Trial (ADOPT) will evaluate the loss of glycemic control during monotherapy, β-cell function, insulin sensitivity, and cardiovascular risk markers in patients with recently diagnosed type 2 diabetes randomized to treatment with rosiglitazone, metformin, or glyburide.[44] The potential for improving β-cell function is important because declining β-cell function has been associated with progressive loss of glycemic control in subjects with type 2 diabetes.[45]

···PREVENTING OR DELAYING TYPE 2 DIABETES···

Recently published studies indicate that reducing insulin resistance may delay or prevent the onset of diabetes in individuals who are at high risk for developing type 2 diabetes. In the Diabetes Prevention Program (DPP), 3234 persons with impaired glucose tolerance but who did not have diabetes were randomly assigned to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of at least a 7% weight loss and at least 150 minutes of physical activity per week.[46] After an average follow-up period of 2.8 years, the subjects in the lifestyle-modification group had a 58% reduction in the incidence of type 2 diabetes, while those treated with metformin showed a 32% reduced incidence of diabetes. Thus, both lifestyle modification and metformin, both of which can improve insulin sensitivity, were useful in reducing the progression from impaired glucose tolerance to type 2 diabetes.

Troglitazone was shown to significantly decrease insulin resistance and improve glucose tolerance in 18 obese subjects with normal or impaired glucose tolerance.[4] In another study, 16 obese subjects with impaired glucose tolerance reverted to normal glucose tolerance after 12 weeks of troglitazone therapy.[8] The Troglitazone in the Prevention of Diabetes (TRIPOD)

study randomized more than 200 women with a history of gestational diabetes and impaired glucose tolerance to either troglitazone or placebo.[47] Insulin sensitivity was improved after 3 months of treatment with troglitazone. Moreover, after a mean follow-up period of 30 months, the troglitazone-treated subjects had a 56% reduction in development of type 2 diabetes compared with placebo-treated subjects. Treatment with rosiglitazone also improved insulin sensitivity in patients with impaired glucose tolerance.[48,49] In a study of 18 individuals with impaired glucose tolerance, treatment with rosiglitazone 4 mg twice daily (N=8) for 12 weeks was associated with improved insulin sensitivity compared with baseline (mean 36% increase; P=.025) and placebo (P=.0003).[48] Ongoing trials, such as the Diabetes REduction Assessment with Ramipril and Rosiglitazone Medication (DREAM), are seeking to confirm and extend these results.

···NONGLYCEMIC EFFECTS OF TZDs···

In addition to decreasing blood glucose levels, the TZDs have shown promise in reducing some of the other components of insulin-resistant states, including hypertension and several other cardiovascular risk factors. The utility of TZDs is being investigated in numerous metabolic disorders.[50]

Vascular Effects

Agents that increase insulin sensitivity also improve endothelial-dependent vascular response to insulin.[51-55] Rosiglitazone 4 mg twice daily significantly reduced diastolic blood pressure in 104 patients treated for 1 year.[56] Troglitazone 400 mg daily significantly reduced blood pressure at rest and systolic blood pressure response to mental stress in patients with type 2 diabetes.[57] Studies have also shown that the TZDs improve brachial artery vasoactivity.[51,58] In one analysis, 11 obese patients who did not have diabetes were treated with rosiglitazone 4 mg daily. Brachial artery vasoactivity increased from 4% to 10% in these patients after 6 weeks of treatment (P<.05).[58]

In another study conducted by Natali et al, 93 patients with type 2 diabetes were allocated to treatment with rosiglitazone 4 mg twice daily, metformin 500 mg 3 times daily, or placebo.[59] Forearm blood flow response, measured by plethysmography, to graded intra-arterial infusions of acetylcholine was used to measure endothelial function. The slope of the acetylcholine dose-response curve (units = δ blood flow percent per log of mg/min/dL of acetylcholine) improved with rosiglitazone (from 276 ± 36 to 385 ± 48, P<.05), but did not change in the metformin-treated or placebo-treated groups. Because treatment-induced changes in endothelium acetylcholine-dependent vasodilatation were unrelated to changes in either glycemic control or insulin sensitivity, treatment with rosiglitazone appeared to have a direct and positive effect on endothelial function.

Insulin resistance and elevated fasting insulin levels are associated with increases in plasminogen activator inhibitor-1 (PAI-1), which can result in impaired ability to lyse clots, thus increasing the risk of thrombosis.[60] Elevated PAI-1 levels are associated with an increased risk of cardiovascular events. The TZDs are able to reduce PAI-1 activity.[61,62] Additionally, platelet aggregation may be increased in patients with diabetes compared with healthy controls.[63] In one analysis, troglitazone inhibited in vitro platelet aggregation, but pioglitazone failed to do so.[64]

Dyslipidemia

Individuals who have insulin resistance typically exhibit a characteristic dyslipidemia that includes increased small, dense low-density lipoprotein cholesterol (LDL-C) particles, increased triglyceride levels, and decreased high-density lipoprotein cholesterol (HDL-C) levels.[65,66] This lipid profile has been associated with worsened cardiovascular outcomes.[65,67,68] Data from studies such as the Veterans Affairs HDL-Cholesterol Intervention Trial (VA-HIT) and the

HDL-Atherosclerosis Treatment Study (HATS) indicate that improving the dyslipidemic profile characteristic of insulin resistance may lead to improved cardiovascular outcomes.[69,70]

TZDs have been shown to increase LDL-C particle size, increase HDL-C, and decrease free fatty acid and triglyceride levels. Improvement in lipid profiles occurred with troglitazone in nondiabetic, hyperinsulinemic cardiac patients.[71] In an analysis conducted by Mathisen et al, 30 mg of pioglitazone for 6 weeks increased HDL-C by 12% and decreased triglycerides by 21% compared with placebo.[72]

Although rosiglitazone was found to increase LDL and total cholesterol levels in some studies, this was associated with increased LDL particle size, resulting in a reduced proportion of small, dense LDL-C particles and a greater proportion of larger, more buoyant LDL-C particles, which are believed to be less atherogenic.[73-75] Freed et al found that treatment with rosiglitazone 4 mg twice daily increased LDL-C particle size in 52% of patients with type 2 diabetes; the presumably more atheroprotective HDL_2 subfraction increased by 13%.[73] These studies suggest that TZDs can improve the dyslipidemia associated with insulin resistance and therefore might potentially decrease the risk of adverse cardiovascular consequences.

Inflammation

Increasing evidence suggests that inflammation has an important role in the development and progression of atherosclerotic coronary heart disease and stroke. A number of inflammatory markers have been shown to be elevated in subjects with and at risk for cardiovascular disease. Recent studies suggest that highly sensitive C-reactive protein (hsCRP) measurements may be a better predictor of coronary heart disease than LDL-C levels.[76] In addition, hsCRP may also be a clinical marker for insulin resistance or the metabolic syndrome. A recent study demonstrated that rosiglitazone treatment was associated with an approximately 25% reduction in hsCRP.[77]

···POTENTIAL ADVERSE EFFECTS OF TZD THERAPY···

Because serious hepatotoxicity with troglitazone led to its withdrawal from the market, patients on TZD therapy are recommended to have liver enzyme activity monitored before initiating TZD therapy every 2 months for the first 12 months of therapy and periodically thereafter.[78,79] However, recent studies suggest that hepatotoxicity is not a class effect.[80,81] Clinical trials with rosiglitazone conducted in nearly 4600 patients have shown that the incidence of liver abnormalities was minimal; 0.25% in both rosiglitazone-treated and placebo-treated patients.[82] Similar findings have been observed with pioglitazone.[83]

Increased abdominal or visceral fat is associated with insulin resistance, possibly because of the increased release of free fatty acids. Improved insulin sensitivity is associated with decreased abdominal fat.[84-85] Treatment with TZDs may be associated with an increase in body mass index in some patients. However, some studies of TZD treatment have shown a redistribution of body fat, with a significant decrease in visceral-to-subcutaneous fat ratio.[86-89] This redistribution of body fat may contribute to reducing insulin resistance in patients with type 2 diabetes. Rosiglitazone therapy in patients with diabetes also may improve hepatic enzyme levels, possibly as a result of fat mobilization out of the liver.[90]

Weight gain is a side effect that may be associated with TZD treatment, particularly when using higher doses.[10] Weight gain may result from increased adipose tissue and/or fluid retention. However, initial studies suggest that the weight increase is not predominantly associated with an increase in visceral fat and hence may be of lesser metabolic consequence.[85] Recent studies suggest that weight gain is not inevitable with TZD use and may be dependent on the dose of the TZD.[91,92] In one study, 8 patients treated with TZDs lost weight during 12 weeks of therapy on

a very low-calorie diet.[92] Weight loss was similar to that achieved by patients who were not treated with thiazolidinediones.

TZDs should be used with caution in patients with edema because these agents can cause fluid retention, which could exacerbate or lead to heart failure.[78,79] Patients with New York Heart Association class 3 and 4 cardiac status were not studied during the clinical trials with either rosiglitazone or pioglitazone, and TZDs are not recommended in these patients.[78,79] The combination of insulin and TZDs may be problematic among those with milder degress of CHF.[93] Metformin is contraindicated in patients with congestive heart failure who require pharmacologic therapy.[94]

In clinical trials, the frequency of anemia was greater with the combination of rosiglitazone plus metformin compared with metformin alone. Lower pretreatment hemoglobin/hematocrit levels may have contributed to this higher reporting rate. Mild anemia is sometimes associated with these agents but is rarely severe enough to be clinically significant.

···EVOLVING ROLE OF TZDs IN CLINICAL PRACTICE···

Type 2 diabetes is increasing at epidemic proportions in the United States and many other countries around the world.[95] Despite the availability of several new classes of oral antidiabetic agents and insulin analogues, many patients with type 2 diabetes do not achieve optimal glycemic control.[96,97] One analysis of more than 270 000 patient records audited in community practices revealed that less than 45% of patients attained the American Diabetes Association goal of an HbA_{1c} less than 7%.[98]

Earlier diagnosis and prompt initiation of nonpharmacologic lifestyle intervention are important. When patients fail to attain adequate glycemic control after 3 months of medical nutrition therapy and appropriately prescribed increased physical activity, pharmacologic therapy should be initiated.[99] Many clinicians initiate therapy with a single oral antidiabetic agent. If monotherapy is not effective in controlling hyperglycemia at maximally effective doses, a second oral agent with a mechanism of action complementary to the first agent is often added within a few months. When a combination of 2 oral agents does not achieve glycemic goals, a third oral agent or insulin may be added. In clinical practice, this progression often takes much longer than is optimal and many patients never achieve glycemic goals. Appropriate dosing and timely titration of medication that may include the use of combination antidiabetic therapies should result in better glycemic control and may be associated with a reduction in both short- and long-term complications.

Melikian et al conducted a retrospective database analysis of average annual pharmacy and medical costs for patients with diabetes within a managed care organization (study period from June 1999 to April 2001).[100] The average cost per patient with diabetes was $11 077 annually. Notably, annual costs for diabetes medications per patient were only 5% of total cost per patient ($561) compared with $1267 for prescription medications treating comorbid conditions. Although oral antidiabetic medications improve glycemic control, which has been shown to prevent diabetic complications, prescriptions for these medications represented only a very small percentage of total diabetes healthcare expense. That optimal provision of antidiabetic medications is associated with significant cost benefits is a concept that is receiving increasing support.

Presently, TZDs are often added as second- or third-line agents to patients not at goal on monotherapy with a biguanide or a sulfonylurea. Addition of TZDs may not take place until after a prolonged period of inadequate control on prior therapy. Many patients would likely benefit from more timely and aggressive implementation of antidiabetic therapy with TZDs.

Early in the course of diagnosed type 2 diabetes, the insulin-resistance component may be more pronounced than the insulin-secretory deficit, and an insulin

sensitizer may therefore be an appropriate treatment strategy for earlier diabetes management. The TZDs are effective in treating insulin resistance. Biguanides also improve peripheral insulin sensitivity, although to a lesser extent when compared with TZDs.[101,102] Currently, many physicians initially use metformin therapy in patients with type 2 diabetes who have not been adequately controlled with lifestyle modifications. Alternatively, a TZD might be considered for first-line therapy, particularly in individuals who have renal insufficiency, those who have difficulty tolerating the gastrointestinal side effects of metformin, or in patients for whom metformin is contraindicated. Because of the beneficial lipid effects already noted, considering TZD therapy may also be appropriate early in the management of patients with type 2 diabetes who have low HDL-C levels with or without accompanying hypertriglyceridemia.

When patients treated with metformin monotherapy do not achieve glycemic goals, many physicians add a sulfonylurea or another insulin secretagogue. However, a TZD might be considered, especially in patients at increased risk for the occurrence or consequences of hypoglycemia. The efficacy of combining a TZD with a biguanide has been clearly demonstrated, offers the benefit of complementary mechanisms of action, and improves insulin sensitivity.[3,31,101] In a study conducted by Fonseca et al, 348 patients inadequately controlled on metformin alone were randomly assigned to additional therapy with placebo, rosiglitazone 4 mg daily, or rosiglitazone 8 mg daily.[31] Mean HbA_{1c} level decreased by 1.0% in the rosiglitazone 4-mg group and by 1.2% in the 8-mg group ($P<.001$). Both insulin sensitivity and β-cell function improved with the addition of rosiglitazone. Thus, the combination of a TZD with a biguanide may provide an appealing treatment strategy, especially if ongoing investigations confirm that TZDs help to enhance and preserve β-cell function.[40,103]

Beale et al evaluated the cost effectiveness of rosiglitazone monotherapy using long-term modeling of disease progression and complications.[104] Recent data from the open-label extension of a double-blind, controlled study showed that rosiglitazone sustained glycemic control for 2.5 years in patients who remained on this agent. A comparison of rosiglitazone data with United Kingdom Prospective Diabetes Study (UKPDS) 10-year trends in HbA_{1c} for other antidiabetic agents suggested that rosiglitazone reduces the rate of long-term glycemic increase by more than 50%, indicating that early use of rosiglitazone may provide durable glycemic control, thereby providing an effect that helps to limit the occurrence or the progression of diabetic complications. An economic model of healthcare for type 2 diabetes was used to project the long-term impact of rosiglitazone monotherapy compared with glyburide monotherapy.[105] In all tested scenarios, treatment with rosiglitazone was associated with better survival, reductions in visual loss and clinical nephropathy, and improved quality of life. The authors therefore suggested that rosiglitazone may be a cost-effective alternative to sulfonylureas for first-line therapy in patients with type 2 diabetes.

···OUTCOMES RESEARCH···

The value of earlier and more consistent use of TZDs will be emphasized if ongoing outcomes research investigations demonstrate that treatment with these agents improves cardiovascular outcomes in patients with type 2 diabetes. Outcomes studies of particular note include the DREAM trial and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, which are studying the effect of TZDs on primary prevention of diabetes, maintenance of glycemic control, and effect on cardiovascular end points. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2) trial are focused on assessing the ability of TZDs to reduce cardiovascular events.

In type 2 diabetes, insulin resistance is evident many years before the onset of hyperglycemia and often before diabetes is diagnosed. Strategies that decrease insulin resistance, such as lifestyle changes and metformin in the DPP and a TZD in the TRIPOD study, are demonstrating the potential to delay or prevent the onset of type 2 diabetes.

Delaying or preventing the development of type 2 diabetes would likely lead to significant reductions in morbidity and mortality and substantial savings in healthcare costs associated with management of this disease. The DPP investigators presented a cost-effectiveness analysis of their study at the American Diabetes Association 62nd Scientific Sessions and concluded that, "over 3 years, the intensive lifestyle and the metformin/standard lifestyle interventions were effective and cost-effective from the perspective of a health system and society."[106]

Studies are presently under way to assess the efficacy of TZDs in obese and overweight patients with impaired glucose tolerance and a strong family history of diabetes. The National Institutes of Health have used the term prediabetic to refer to some of these patients. Many of these patients also have the metabolic syndrome and might benefit from the potential cardiovascular benefits of early use of TZDs. If, in these ongoing studies, the insulin sensitivity, enhanced β-cell function, and vascular effects of TZDs are shown to delay or prevent the onset of diabetes and/or reduce cardiovascular events, they will likely have a prominent role in the treatment of patients with prediabetes and/or the metabolic syndrome.

···CONCLUSION···

The TZDs are a newer class of antidiabetic agents with a unique mechanism of action mediated through the PPARγ nuclear receptor system. These agents have been shown to exert multiple effects on various systems. They reduce insulin resistance and are effective and useful both as monotherapy and in combination with biguanides, sulfonylureas, and insulin. The TZDs have a relatively slow onset of action and therefore may not be ideal as monotherapy in situations for which rapid control of hyperglycemia is essential. Long-term prospective trials are needed to further address the potential for prevention of diabetes, delay in the development of atherosclerosis, and reduction in cardiovascular consequences. Until the results of prospective clinical trials are available, treatment with TZDs should remain focused on monotherapy in patients who are unresponsive to lifestyle (eg, nonpharmacologic) therapy and combination therapy with other antidiabetic agents. The effect of TZDs on HDL-C levels, LDL-C particle size and buoyancy, and triglyceride levels should be especially valuable in patients who have dyslipidemia with low HDL-C or elevated triglyceride levels. If ongoing outcomes studies show that the effects on insulin sensitivity, enhanced β-cell function, and vascular benefits of TZDs delay or prevent the onset of diabetes and reduce cardiovascular events, these agents may acquire a prominent role in the treatment of patients with prediabetes or the metabolic syndrome. In addition to their antihyperglycemic effects, the TZDs also exert beneficial effects on insulin sensitivity, dyslipidemia, and other cardiovascular risk factors in patients with type 2 diabetes. The indications and clinical role of the TZDs are likely to expand in the future. Until that time, because many patients with type 2 diabetes fail to achieve therapeutic goals, earlier and more aggressive therapy using appropriate choices from all of the antidiabetic agents, including the TZDs, will be beneficial.

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