

Thiazolidinediones

The case for early use

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Editor's note: This commentary was originally solicited as part of a Point-Counterpoint feature, but the author of the Counterpoint failed to provide the promised manuscript.

Thiazolidinediones (TZDs), or “glitazones,” were first introduced for the treatment of type 2 diabetes in 1996, when troglitazone (Rezulin; Parke-Davis/Warner-Lambert) was approved by the Food and Drug Administration. Since the introduction of this unique class of compounds, many clinicians have embraced their use, whereas others have debated the role of insulin-sensitizing therapy for the management of type 2 diabetes. While troglitazone was withdrawn from the market in 2000 due to idiosyncratic hepatotoxicity, two other glitazones, pioglitazone (Actos; Takeda Chemical Industries) and rosiglitazone (Avandia; GlaxoSmith-Kline), continue to be widely used by clinicians.

Before the introduction of glitazones, conventional management of type 2 diabetes involved stepwise addition of medical nutrition therapy, sulfonylureas, and metformin. Despite broader use of early drug therapy, many patients do not achieve adequate blood glucose control (1). Even in those who do achieve treatment targets, a gradual deterioration in blood glucose control is often seen (2). These observations have prompted clinicians to use newer therapies, such as the glitazones, and have increased the use of early combination therapy to achieve glycemic targets

Glitazones uniquely target insulin resistance—a core physiologic defect in those with type 2 diabetes—and by so do-

ing significantly improve glucose control. Glitazones improve insulin action in muscle, adipose, and hepatic tissue by acting as agonists of peroxisome proliferator-activated receptor- γ (PPAR- γ) nuclear receptors. Activation of PPAR- γ results in a myriad of both metabolic and vascular effects by upregulating and downregulating expression of numerous genes, including genes known to regulate lipid and glucose metabolism, vascular function, thrombotic function, and the inflammatory response. Glitazones increase nonoxidative glucose disposal, increase triglyceride synthesis, and improve free fatty acid (FFA) metabolism (3). Glitazones also lower blood pressure, improve lipid metabolism (raising HDL cholesterol, reducing triglyceride levels, and increasing concentrations of large, buoyant LDL particles), and improve vascular reactivity and rheologic abnormalities common to type 2 diabetes and insulin resistance (4).

Glitazones' unique effects suggest that these compounds may have significant advantages over other commonly used glucose-lowering therapies. The potential of several of these advantages are outlined below and establish both the clinical benefit of glitazone therapy and the clinical potential of these and other insulin-sensitizing therapies:

- 1) The capacity of glitazones to improve and sustain intensive glucose control by increasing insulin sensitivity and β -cell secretory function
- 2) A role for glitazones in diabetes prevention
- 3) The use of glitazones to improve car-

diovascular disease (CVD) risk factors and reduce CVD events

Glitazones as glucose-lowering therapy: achieving and sustaining control

Intensive glucose control is the accepted standard for management of patients with type 2 diabetes. The landmark U.K. Prospective Diabetes Study (UKPDS) confirmed that intensive glycemic control can significantly reduce the risk of complications of diabetes (2). However, no single therapy (either oral hypoglycemic agents or insulin) proved superior with regard to achieving intensive treatment goals. However, UKPDS also confirmed that type 2 diabetes is a progressive disease, with deterioration in glycemic control observed in all treatment groups regardless of the initial therapy used. By 6 years of treatment, >50% of intensively treated subjects had HbA_{1c} (A1C) values that exceeded 8%. The deterioration in blood glucose control in type 2 diabetes is now felt to result from a decline in β -cell secretory function over time. Impaired insulin secretion, superimposed upon a background of continued insulin resistance, persists and can worsen with the use of sulfonylureas, metformin, or low-dose insulin therapy (3,5).

What added advantages does glitazone treatment offer when used either as monotherapy or in combination that might further benefit patients with type 2 diabetes? All commonly used oral agents, including the glitazones, have similar glucose-lowering effects (generally reducing A1C levels by ~1–2 percentage points). The glitazones uniquely target insulin resistance and thereby achieve stable blood glucose control over periods of ≥ 2 years (6,7). This sustained improvement in glucose control results in great part from an improvement in β -cell secretory function over time. The ability of glitazones to improve insulin secretion is unique among current diabetes therapies (8,9). The mechanism(s) by which glitazones improve insulin secretion is not fully understood, although improvement in FFA metabolism appears to play an important role in this unique beneficial effect. One theory is that glitazones reduce the “lip-

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Abbreviations: CVD, cardiovascular disease; DPP, Diabetes Prevention Program; FFA, free fatty acid; PPAR- γ , peroxisome proliferator-activated receptor- γ .

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1 —Effect of glitazone therapy on established and emerging CVD risk factors (18)

CVD risk factor	Impact of glitazone therapy
Hyperglycemia	Reduction in A1C
Hypertension	Reduction in blood pressure
Dyslipidemia	Reduction in triglycerides Increase in HDL cholesterol Increase in LDL particle size (less atherogenic particles)
Markers of endothelial inflammation	Decreased C-reactive protein Decreased white blood cell count Decreased fibrinogen Decreased matrix metalloproteinases-9 Decreased tumor necrosis factor- α
Markers of elevated thrombotic risk	Decreased plasminogen activator inhibitor-1 Decreased platelet aggregation

toxic” effect of elevated FFAs in the bloodstream, resulting in improved β -cell secretory function and β -cell mass. Large-scale clinical trials are currently underway to further define the role of glitazone therapy in maintaining glycemic control and sustaining β -cell secretory function (10). Current data support the use of glitazones in any patient with insulin resistance or in whom deterioration of blood glucose control is seen.

Glitazones and diabetes prevention

The prevalence of type 2 diabetes continues to increase, and recent estimates of the number of people in the U.S. with either diabetes or pre-diabetes may exceed 25 million (11). More effective therapies to prevent type 2 diabetes are being sought in hopes of limiting the impact of this epidemic. Both intensive lifestyle changes (12,13) and pharmacologic therapies (8,13,14) can reduce the risk of type 2 diabetes in high-risk individuals with pre-diabetes or a history of prior gestational diabetes. One common feature of the most effective preventive therapies is their ability to target insulin resistance. Intensive lifestyle changes, including moderate weight loss and increased physical activity (both of which improve insulin sensitivity), reduce the risk of progression to type 2 diabetes by >50% (12,13).

Pharmacologic therapies, including metformin (13) and the glitazones (8,14), can also significantly reduce the risk of progression to type 2 diabetes in those at high risk. Metformin therapy reduces risk by ~30%; however, this benefit is less than that seen with intensive lifestyle changes (13). Is metformin preventing diabetes or is it merely masking diabetes? It

has been suggested that at least a portion of the benefit derived from metformin therapy is in fact a result of early treatment rather than a true decrease in the risk of diabetes. This observation is supported by data from the Diabetes Prevention Program (DPP), where ~25% of metformin-treated subjects developed diabetes quickly after discontinuation of the drug (13). In contrast, in at least one study, glitazones have been shown to reduce the risk of diabetes by >50% (8), an effect similar in magnitude to that observed with intensive lifestyle changes. Furthermore, in those with a history of prior gestational diabetes, glitazones appear to both prevent and delay diabetes onset rather than simply mask hyperglycemia (8). In contrast, the development of diabetes following discontinuation of troglitazone in those with impaired glucose tolerance in the DPP resulted in an increase in diabetes onset that paralleled the rate seen in placebo-treated patients (14). These contrasting results suggest that while glitazone therapy may be an effective means of diabetes prevention, active treatment may be required to truly prevent diabetes. It must be noted that the populations in the TRIPOD (Troglitazone in Prevention of Diabetes) study (8) and the DPP (14) differ substantially, with those in TRIPOD receiving treatment before the onset of glucose intolerance, whereas subjects in the DPP were enrolled after glucose intolerance was present. Whether earlier treatment will in fact enhance the effectiveness of TZD therapy for diabetes prevention remains to be determined.

Why the difference between metformin and glitazones? Whether the greater benefit of glitazone therapy is a

consequence of specific improvements in insulin resistance, an improvement in β -cell secretory function, or other effects is not known. However, one plausible mechanism is explained by an “off-loading” of the β -cell due to reduced insulin requirements resulting from increased insulin sensitivity in peripheral tissue (8). Theoretically, off-loading preserves β -cell mass and improves secretory response, allowing secretion of insulin for a longer period (effectively preventing the development of diabetes).

Although no diabetes medication is presently approved for the treatment of pre-diabetes or for diabetes prevention, data from these clinical trials support the use of therapies that improve insulin sensitivity, including intensive lifestyle change and pharmacological insulin-sensitizing therapy to achieve maximal risk reduction. In years to come, the early identification of insulin resistance should allow for more directed use of glitazone therapy in diabetes prevention. Again, long-term clinical trials (15) that will further clarify the role of glitazone therapy for diabetes prevention are underway.

Glitazones and CVD risk reduction

Type 2 diabetes and insulin resistance are associated with a marked increase in the risk of CVD. Even in the absence of hyperglycemia, insulin resistance is associated with a two- to threefold increase in the risk of CVD (16). Insulin resistance contributes to the development of hyperglycemia as well as to a cluster of characteristic CVD risk factors, including an atherogenic lipid profile; hypertension; and a prothrombotic, proinflammatory vascular environment (17). Improving insulin sensitivity (at least by means of lifestyle change) can lower blood glucose, improve plasma lipids, lower blood pressure, and improve many of the characteristic vascular abnormalities common in those with type 2 diabetes (18).

Can a diabetes therapy truly reduce CVD risk in patients with insulin resistance or type 2 diabetes? Both metformin and insulin have beneficial effects on some CVD risk factors. However, neither has demonstrated the broad array of vascular effects reported with glitazone therapy. Metformin may reduce cardiovascular risk in obese patients with diabetes (19), and insulin has been shown to reduce mortality after myocardial infarction (20). Glitazones have been shown to improve many of the traditional, as well as the emerging, risk factors associated with

CVD (4,21). The effects of glitazone therapy on these risk factors are summarized in Table 1. Recent clinical studies have demonstrated a reduction in clinical measures of atherosclerosis with glitazone treatment (8,22), including a reduction in the rate of restenosis following stent implantation (22,23).

While outcome trials demonstrating a reduction in cardiovascular events with glitazones are not yet complete, the preponderance of evidence supports that these agents can significantly alter CVD risk. Clinical trials such as Bypass Angioplasty Revascularization Investigation Diabetes (BARI 2D) (24) will provide data on the potential effectiveness of glitazones, as compared with other approaches to glucose-lowering therapies. In years to come, glitazone therapy will likely be included with other standard therapies for CVD risk reduction in diabetes, such as aspirin, ACE inhibitors/angiotensin 2 receptor blockers, and statins.

Glitazones: other considerations

Despite the many advantages of glitazones noted above, some clinicians remain skeptical about these benefits, arguing that therapy remains unproven and experience with this class of drugs is limited. In addition, some have argued that the higher cost of glitazone therapy cannot be justified given that there are less expensive alternatives with similar effects on glucose control. Still others have persistent concerns about the long-term safety of glitazones, noting the potential for these agents to promote fluid retention and weight gain and to increase the risk for heart failure.

Clinicians in the U.S. have prescribed glitazones for much of the past 7 years, and there are >10 million patient-years of experience with glitazones. The glitazones are well tolerated, with adherence rates comparable to both metformin and the sulfonylureas. Although fluid retention can occur, it generally develops in only a small fraction of patients (3–15%), with the greatest risk in patients treated with insulin. Weight gain with glitazone therapy averages 3–6 kg over the 1st year of therapy, a rate comparable to that seen with initiation of insulin.

An additional concern is the widely reported association of glitazone therapy with heart failure. A higher risk of heart failure has been reported in some studies (25), whereas others have actually suggested a reduced risk of heart failure in

glitazone-treated patients (26). A recent analysis demonstrated reduced mortality in patients with a prior history of heart failure who were treated with glitazones (27). Hospital admission rate was also similar with all therapies, although those treated with glitazones did have a modestly higher readmission rate for heart failure (hazard ratio 1.06) (27). Given the myriad beneficial effects of glitazones on CVD risk factors (Table 1), the equivocal safety concerns from fluid retention in weight gain do not appear to outweigh the potential benefit of glitazone treatment in individuals who are at highest risk for heart disease, including those with a history of heart failure.

Finally, the argument that the higher costs of glitazones limit their utility is both shortsighted and misleading. Newer drugs are more costly when compared with generic formulations of older compounds. However, drug acquisition cost alone does not account for the potential of newer, more effective therapies to limit costs associated with diabetes complications. Currently, nearly 50% of spending for diabetes care is for inpatient care, and much of this cost is attributable to treatment of secondary complications, including CVD (28). Drug therapy currently accounts for only 20% of costs associated with diabetes management. Careful assessment of both the clinical and financial benefit of long-term use of glitazones must be completed to accurately determine the true cost of therapy. Until such studies are complete, we must not discount any therapy simply because of its higher initial expense. Providers and patients must identify the most effective treatments for individual patients, targeting optimal glucose control and maximal reduction in the risk of complications.

Conclusions

The advantages of glitazone therapy are clear. The time has come to accept insulin-sensitizing therapy as a standard of treatment for patients with type 2 diabetes. Glitazones are safe and effective and the most effective pharmacologic treatment for insulin resistance. By treating this core defect, glitazone therapy can achieve sustained improvements in glycemic control. In years to come, glitazones will likely emerge as exceptional therapy for those with pre-diabetes. In addition, glitazones possess the potential to significantly reduce the risk of CVD in diabetes. Ongoing clinical trials, including the PROspective Pioglit-

Azone Clinical Trial In MacroVascular Events (PROactive) study, will help clarify how glitazone therapy will best be used in our diabetes patients. At present, glitazones must be considered early in the course of management for type 2 diabetes, particularly in those at significant risk for cardiovascular complications.

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