

# Pioglitazone for the treatment of type 2 diabetes in patients inadequately controlled on insulin

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**Abstract:** Insulin resistance and impaired beta-cell function are primary defects that occur early in the course of development of type 2 diabetes. Insulin resistance leads to hyperinsulinemia in order to maintain normal glucose tolerance. In most cases of type 2 diabetes, beta-cell dysfunction develops subsequent to the development of insulin resistance, and it is not until such beta-cell dysfunction develops that any abnormality in glucose tolerance is seen. Insulin resistance is a primary defect in type 2 diabetes. The risk of coronary heart disease is significantly increased in patients with type 2 diabetes. Cardiovascular disease causes 80% of all diabetic mortality, and in 75% of those cases, it is a result of coronary atherosclerosis. These points provide a rationale for early and aggressive management of cardiovascular risk in patients with diabetes. Thiazolidinediones represent an effective tool for targeting some features of this increased risk as they decrease insulin resistance and can prevent and/or delay diabetes progression.

**Keywords:** pioglitazone, type 2 diabetes, insulin

## Pathophysiology of diabetic complications: implications for goals of therapy

### Background

Type 2 diabetes is a metabolic disorder in which the abnormal metabolic environment signaled by hyperglycemia (hemoglobin A<sub>1c</sub> [HbA<sub>1c</sub>]) is a continuous risk factor for associated complications. There is no A<sub>1c</sub> threshold, and the risk of complications (eg, retinal, renal, neural, cardiovascular [CV], and cutaneous) becomes worse with longer diabetes duration.<sup>1</sup> Many pathways are implicated in the causation of both microvascular and macrovascular complications. Brownlee's unified theory<sup>2</sup> suggests that a combination of factors is at work (eg, including elements of oxidative stress and endothelial dysfunction). Another aspect of disease development includes the individual's risk for complication susceptibility via his or her genetic and ethnic background and acquired factors.<sup>3</sup> Implications of this understanding are that a strategy of glucose control, early initiation of therapy, treatment of inflammation, endothelial dysfunction, and comorbidities is likely to decrease both microvascular and macrovascular complications.

In the pivotal Diabetes Control and Complications Trial (DCCT), investigators compared the use of intensive therapy with conventional treatment among 1,441 patients with type 1 diabetes.<sup>4</sup> The mean follow-up was 6.5 years between 1983 and 1993. In DCCT, intensive blood glucose control significantly reduced the risk of the development of microvascular disease (retinopathy 76%, nephropathy 50%, and neuropathy

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60%). When the DCCT ended, researchers continued to study more than 90% of the participants for a mean of 17 years. The follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC), revealed a 42% reduced risk in cardiovascular disease (CVD) events and a 57% reduced risk of nonfatal myocardial infarction (MI), stroke, or death from CV causes associated with intensive treatment.<sup>5</sup> The United Kingdom Prospective Diabetes Study (UKPDS)<sup>1</sup> 10 years after it ended and the Steno study<sup>6</sup> found a 50% reduction in CV outcomes at 8 years and a 30% reduction in mortality at 13 years associated with treating glucose, blood pressure, and lipids to goal levels.

Recent studies suggesting otherwise, including Veterans Affairs Diabetes Trial (VADT),<sup>7</sup> Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE),<sup>8</sup> and Action to Control Cardiovascular Risk in Diabetes (ACCORD),<sup>9</sup> actually confirm this in those patients with shorter duration of diabetes and with no significant preexisting microvascular or macrovascular complications. The negative results of these 3 studies as a whole can be explained by a poor choice of medications (eg, the use of sulfonylureas in ADVANCE), hypoglycemia, and weight gain with poor processes and methods of care (eg, ACCORD).<sup>10–12</sup> Additionally, patients included in these trials may have had tissues that were past the metabolic point of no return by virtue of longer diabetes duration and significant preexisting damage.<sup>13,14</sup>

## Insulin resistance

Insulin resistance is a primary defect in type 2 diabetes. As reported by Haffner et al,<sup>15</sup> 92% of patients with type 2 diabetes have insulin resistance. It can be defined as an impaired response to the physiological effects of insulin, including those on glucose, lipid, and protein metabolism, and the effects on vascular endothelial function.

Before the manifestation of the metabolic defects that lead to type 2 diabetes, fasting and postprandial insulin levels are similar and constant. As noted by Kendall and Bergenstal from the International Diabetes Center in Park Nicollet, Minneapolis, for the majority of patients who develop type 2 diabetes, insulin resistance leads to compensatory increases in circulating insulin, thereby preventing an increase in glucose levels.<sup>16</sup> As time progresses, the insulin resistance reaches a peak and stabilizes, while the compensatory increase in insulin continues to prevent fasting glucose levels from becoming abnormal. Their work and others have shown that, eventually, because of either early beta cell dysfunction or a

genetic limitation of beta cell capacity, beta cell compensation cannot keep up with the increased demand. Postprandial and ultimately fasting glucose levels become abnormal as a limitation in insulin response is reached.<sup>16</sup>

## Beta cell failure

Many patients who are insulin resistant do not manifest hyperglycemia because their ability to secrete insulin remains intact. However, functional defects in glucose-stimulated insulin secretion by beta cells, when combined with insulin resistance, can lead to impaired glucose tolerance, hyperglycemia, or type 2 diabetes. Beta cell function is progressively lost during the course of development of type 2 diabetes. Data suggest that the onset of beta cell dysfunction associated with diabetes occurs well before the development of hyperglycemia and may begin years before the diagnosis of the disease. By the time diabetes is diagnosed, up to 50% of beta cell function may already be lost. The extent of beta cell function remaining is critical because therapeutic approaches to the prevention or treatment of diabetes are more effective earlier in the disease, most likely because the beta cell response at this time is more robust.<sup>17</sup> Although glucose stimulates beta cells to secrete insulin, it may also modify beta cell function in a deleterious manner, ie, glucotoxicity or glucose desensitization may occur, which results in a decrease in insulin secretion. Animal models of diabetes have suggested that changes in lipid metabolism may contribute to the development of beta cell dysfunction. The role of lipotoxicity in humans with diabetes requires further research.<sup>18</sup>

A variety of theories for progressive beta cell failure have been proposed as explanations for the pathogenesis and progression of type 2 diabetes. A reduction in beta cell mass may help explain the impairment in maximal secretory capacity for insulin. This reduction may be caused by one or more factors: the rate of apoptosis (programmed cell death) may increase secondary to a deranged metabolic state, such as elevated levels of glucose or free fatty acids. In the normal pancreas, beta cell proliferation and neogenesis balance apoptosis. Under certain conditions such as hyperglycemia, the rate of apoptosis may outpace that of beta cell proliferation, resulting in a net loss of beta cells. Amyloid deposits have long been suspected as a potential cause of reduced beta cell mass. Although this relationship is difficult to study in humans, a variety of *in vivo* animal and *in vitro* experiments demonstrate that these deposits can be deleterious to beta cell function.<sup>19</sup>

## Emergence of thiazolidinediones

When thiazolidinediones (TZDs or glitazones) were introduced, they represented a new class of oral agents with a novel mechanism of action that reduced insulin resistance and improved glycemic control. Glitazones act as agonists of nuclear receptors called peroxisome proliferator-activated receptors-gamma (PPAR-gamma) to enhance the actions of insulin, leading to improvement in insulin-dependent glucose disposal and reductions in hepatic glucose output.<sup>20</sup>

Because of the natural history of diabetes progression,<sup>1</sup> it is imperative that physicians act aggressively and early to control/treat the disease (even prediabetes), which, by definition, will delay or even prevent complications. The presented, but unpublished, ACT-Now study by DeFronzo<sup>21</sup> seems to confirm smaller trials<sup>22</sup> that suggest delay in developing diabetes in patients with impaired glucose tolerance. TZD's durability of effect was shown in the 3-year stable A1C data from A Diabetes Outcome Progression Trial (ADOPT).<sup>23</sup>

Pioglitazone (Actos®; Takeda, Deerfield, IL, USA), alone and in combination, has been shown to be effective at improving glycemic control. Pioglitazone exerts additional beneficial effects on blood pressure, microalbumin, inflammation, endothelial dysfunction, and lipids. The GLAI<sup>24</sup> investigators found that pioglitazone and rosiglitazone have significantly different effects on plasma lipids independent of glycemic control or concomitant lipid-lowering or other antihyperglycemic therapy. Pioglitazone compared with rosiglitazone is associated with significant improvements in triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein (LDL) particle concentration, and LDL particle size.

## Side effects

### Edema

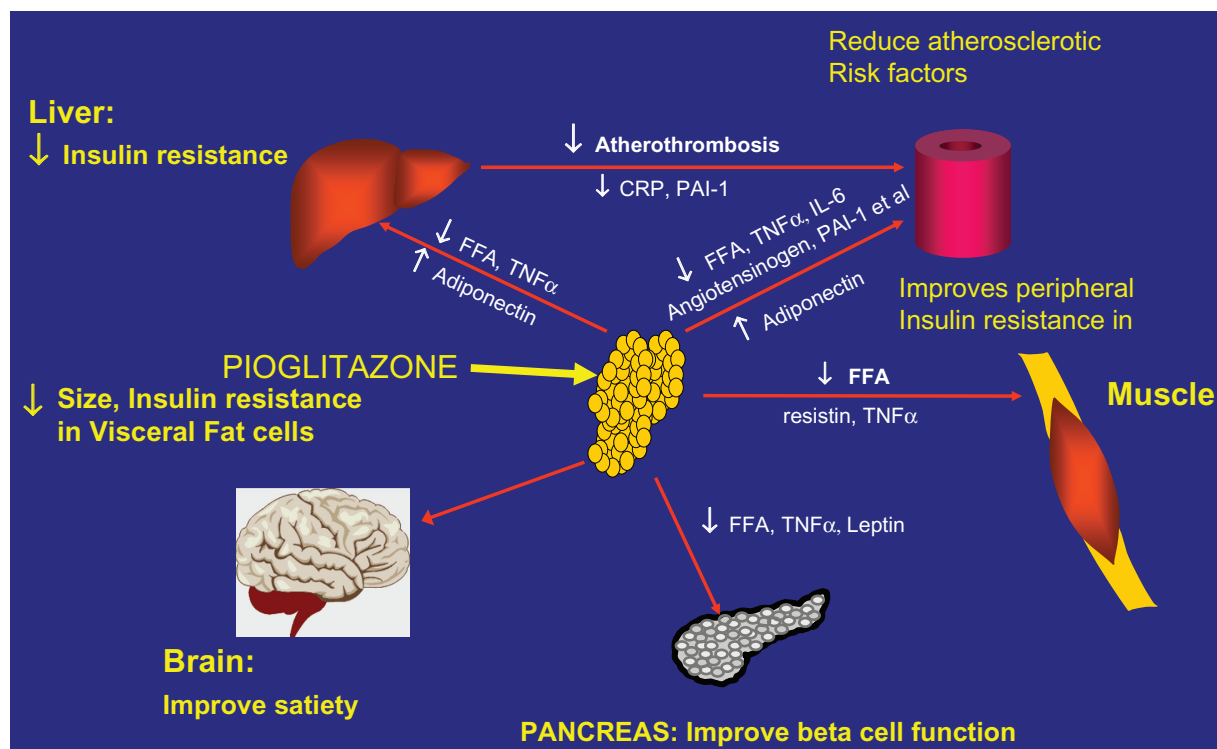
Safety concerns that have been raised with TZDs include the risk of fluid retention (mostly related to PPAR-gamma effect on salt and water retention by the kidney) and congestive heart failure (CHF), most likely to occur in those patients with diastolic dysfunction. The pioglitazone prescribing information warns that the agent, like other TZDs, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin.<sup>25</sup> Fluid retention may lead to or exacerbate CHF. It has been shown that the occurrence of CHF in patients taking TZDs may be a result of increased plasma volume unmasking previously asymptomatic and unrecognized diastolic dysfunction.<sup>26</sup> Only a minority of edema cases reported in glitazone-treated diabetic patients are associated with CHF.<sup>27</sup>

In a retrospective cohort study of 16,417 Medicare beneficiaries with diabetes discharged after hospitalization for heart failure, Masoudi et al<sup>28</sup> showed that TZDs were associated with reduced mortality. Mortality among those patients receiving TZD therapy (mean age 75.9 years,  $n = 2,226$ ) was significantly lower compared with patients receiving no insulin-sensitizing therapy (mean age 77 years,  $n = 12,069$ ). The adjusted hazard ratio (HR) was 0.87 (95% confidence interval [CI], 0.80–0.94). Thus, the issue of CHF is dissociated from the agent's general benefit in cardiac function.

Clinical experience has taught us that a no-added-salt diet markedly reduces the risk of edema in this population. Hydrochlorothiazide, amiloride, and spironolactone are preferred over furosemide for the treatment of mild edema.<sup>29</sup> Clinically, we have also seen prevention and treatment of edema with ranolazine, a drug that improves diastolic dysfunction. This disconnect between edema, CHF, and beneficial effects on the heart seems confirmed mechanistically by reduced steatosis of the heart<sup>30</sup> and improved myocardial blood flow.<sup>31</sup>

Pioglitazone reduced the composite endpoint of all-cause mortality, nonfatal MI, and stroke in patients with type 2 diabetes who had a high risk of macrovascular events, according to Dormandy et al<sup>32</sup> in the Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE Study). PROACTIVE was a prospective, randomized controlled trial that included 5,238 patients with type 2 diabetes who had evidence of macrovascular disease. Meta-analysis by Lincoff et al<sup>33</sup> confirmed these results, concluding that pioglitazone is associated with a significantly lower risk of death, MI, or stroke among a diverse population of patients with diabetes. Serious CHF was increased by pioglitazone, although without an associated increase in mortality. A total of 19 trials enrolling 16,390 patients were analyzed. Death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,836 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72–0.94;  $P = 0.005$ ).

There has been a debate about a possible increase in adverse CV events with rosiglitazone since Nissen and Wolski<sup>34</sup> published their meta-analysis, and a Cochrane review<sup>35</sup> appears to confirm this. The Food and Drug Administration, the European Medicines Agency, and the Health Canada have all weighed in and assigned a black box warning for an increased risk of ischemic CV events for rosiglitazone. No such warning was issued for pioglitazone. Moreover, a population cohort study of 40,000 patients<sup>36</sup> and another study of real-world use by 90,000 patients<sup>37</sup> would



**Figure 1** Pleiotropic effects of pioglitazone. Modifying the adipocytokine syndrome: a model relating obesity, insulin resistance, and beta cell dysfunction and atherosclerotic cardiovascular disease.

seem to confirm this difference. The 2 agents appear to differ in the way they “turn on” genes, even though both agents are PPAR-gamma agonists.<sup>38,39</sup> Clinically, the 2 agents have different effects on lipid patterns, as discussed earlier, thus emphasizing pioglitazone’s benefits in practice.

### Weight gain

In intensively insulin-treated, obese type 2 diabetic patients, at equivalent glycemic control, the addition of pioglitazone causes greater weight gain, but causes a similar increase in body water that is mainly extracellular and interstitial compared with intracellular increase with insulin therapy alone.<sup>40</sup> Pioglitazone also increases the filtered load of sodium reabsorbed at the distal nephron, with no net change in fractional excretion rate of sodium. From our experience, attention to issues and therapies discussed above can keep these risks to a minimum.

As has been suggested, there is also some nonedematous weight gain associated with TZDs. The agents have been shown to increase weight from 2 to 8 lbs in patients; however, 50% do not experience increased weight and have had weight loss if a eucaloric or hypocaloric diet is maintained.<sup>41</sup> With proper dietary reinforcement, TZD-associated weight changes may be reduced or even absent.<sup>42</sup>

The combination of TZDs with antidiabetic agents that are weight neutral or that promote weight loss may represent an important future direction for therapy.

Weight gain can be obviated with combination exenatide administration. Combination of pioglitazone and exenatide (Byetta®; Eli Lilly and Amylin, Indianapolis, IN, USA) causes nearly as much weight loss (~4 lb) as with exenatide alone (~5 lbs/30 weeks).<sup>14</sup> Weight gain is more pronounced when TZDs are combined with sulfonylureas or insulin<sup>43</sup> versus in combination with metformin<sup>44,45</sup> or exenatide.<sup>46</sup>

### Bone effects

It appears that pioglitazone is associated with a modest increased risk of distal bone fractures in women.<sup>47</sup> A letter to physicians issued by Takeda Pharmaceuticals in 2007 reported an analysis of its pioglitazone clinical trials database.<sup>48</sup> They compared the incidence of fractures in more than 8,100 patients treated with pioglitazone with more than 7,400 patients treated with a comparator. The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this data set on pioglitazone is, therefore, 0.8 fractures per 100

patient years of use. There was no increased risk of fractures identified in men. A recent large database study (~18,000 patients) confirmed a clear but low risk of TZD-associated fractures.<sup>49</sup>

The mechanism is in part related specifically to a TZD effect on shifting precursor cell production from osteoblasts to fat cells in the bone marrow, resulting in decreased bone formation. However, part of the effect seems to be related to decreasing insulin resistance by any means, in that in doing so, one decreases insulin and amylin (which stimulate osteoblast and decrease osteoclast formation), thus decreasing bone formation and increasing resorption. Moreover, Americans have a high incidence of vitamin D deficiency.

Thus, a clinician's decision to use TZDs in perimenopausal women will depend on weighing the benefits of their use in glycemic control, lipid benefit, decreasing insulin resistance, and likely reduction in CV outcomes compared with a low risk of distal fractures that may be mitigated by administration of vitamin D, calcium, and bisphosphonates in women at higher risk.

## TZDs in combination therapy

Given type 2 diabetes results from a combination of insulin resistance and beta cell dysfunction, the combination of a TZD and an incretin mimetic offers a combination of characteristics (eg, glycemic control, reduced insulin resistance, decreased weight, potential cardiovascular benefits, and beta cell preservation) that addresses many of the pathophysiologic underpinnings of type 2 diabetes. A recent small placebo-controlled study assessed the effects of exenatide used with a TZD with or without metformin. Exenatide demonstrated a greater incidence of  $HbA_{1c} < 7\%$ ; greater reductions in fasting blood glucose levels, postprandial glucose levels, and body weight; and improved beta cell function versus the TZD/placebo group. Dual effects on insulin sensitivity (TZD) and insulin secretion (exenatide) make the TZD/exenatide combination a rational treatment option for patients who do not attain glycemic control with a single agent. Studies undertaken to evaluate the effects on CV outcomes and the potential for prevention of type 2 diabetes with impaired glucose tolerance may reveal additional advantages of this combination approach.<sup>46</sup>

If a patient has an  $HbA_{1c}$  value of 7.5% or lower, it may be possible to achieve a goal  $HbA_{1c}$  value of 6.5% with the use of monotherapy, according to a recent treatment algorithm from the American Association of Clinical Endocrinologists (AACE).<sup>50</sup> If monotherapy fails to achieve that goal, one

usually progresses to dual and then to triple therapy, which includes the addition of a TZD. If the use of dual therapy fails, one might add TZD or glargine – here we suggest the advantages of TZD before starting glargine. Earlier combination therapy, initially, is also a major new recommendation of the new AACE guidelines. However, if not at glycemic goals with 3 noninsulin agents, insulin therapy should be initiated, with or without additional agents.<sup>50</sup>

We emphasize, however, in our large clinical experience that considering a patient a “noninsulin-therapy failure” should be reserved for those who avoid intake of concentrated sweets. We have observed that too often the insulin is started in patients eating sweets, resulting in increased weight. These patients also commonly experience recurrent hypoglycemia, especially if they avoid sweets for a few days, increasing appetite (causing more weight gain), and “rebound” hyperglycemia. These patients may then be prescribed inappropriate increases in insulin doses for the rebound hyperglycemia, leading to a vicious cycle. Thus, only when triple therapy fails to achieve glycemic control in the patient on the right diet, can one say that it is likely that the insulin-secretory capacity of the beta cells has exceeded; thus, insulin therapy is needed. One can then institute therapy as basal with or without prandial (eg, basal-bolus insulin).<sup>50</sup>

## Insulin: a brief review

As Nathan et al recently discussed, we have the most clinical experience with insulin as it is our oldest medication.<sup>51</sup> It is the most effective therapy for lowering glycemia, and when used in adequate doses, it can decrease elevated  $HbA_{1c}$  to, or close to, therapeutic goal. Although initial therapy is aimed at increasing basal insulin supply with long-acting insulins,<sup>50</sup> patients may also require prandial therapy with short- or rapid-acting insulins.<sup>50</sup> Insulin analog with longer, nonpeaking profiles decrease the risk of hypoglycemia modestly compared with isophane or NPH insulin, and analog with very short durations of action reduce the risk of hypoglycemia compared with regular insulin, as per discussion of Nathan et al.<sup>51</sup> Very-rapid-acting and long-acting insulin analogs have not been shown to lower  $HbA_{1c}$  levels more effectively than the older, rapid-acting or intermediate-acting formulations. Although insulin has beneficial effects on lipids, it is associated with weight gain of about 2–4 kg. Weight gain can be excessive in patients whose insulin is adjusted to compensate for eating more calories than they use. Furthermore, insulin therapy is associated with hypoglycemia. The incidence of severe hypoglycemia in the intensive treatment group

in the DCCT ranged from 2 to 6 times that observed with conventional treatment.<sup>4</sup>

EDIC, the DCCT follow-up, revealed that intensive treatment reduced the risk of any CVD event by 42% (95% CI, 9%–63%;  $P=0.02$ ) and the risk of nonfatal MI, stroke, or death from CVD by 57% (95% CI, 12%–79%;  $P=0.02$ ).<sup>5</sup> The decrease in A1C values during the DCCT was significantly associated with most of the positive effects of intensive treatment on the risk of CVD.

We have also learned that if control is poor with insulin, then the risk of death is increased.<sup>52</sup> Mechanisms of these increased risks, we believe, are associated with insulin in patients not well controlled include increased endothelial dysfunction, and inflammation, as well as the adverse effects of weight gain and hypoglycemia.

## **TZD vs insulin therapy**

### **Adding insulin or pioglitazone when other therapies fail**

Aljabri et al compared the efficacy of adding pioglitazone or bedtime NPH insulin to maximal doses of metformin/sulfonylurea in type 2 diabetes patients with poor glucose control. In their 62-patient, open-label, randomized, controlled trial, they studied type 2 diabetes patients with  $HbA_{1c} > 8.0\%$ . Patients received either pioglitazone or bedtime NPH insulin in addition to their usual diabetes medication for 16 weeks.<sup>53</sup>  $HbA_{1c}$  levels were lowered to a similar degree in each treatment arm (pioglitazone:  $-1.9\% \pm 1.5\%$ ; insulin:  $-2.3\% \pm 1.5\%$ ;  $P=0.32$ ), but hypoglycemia was less common among patients who received pioglitazone than among those who received insulin (37% vs 68%;  $P=0.02$ ). Pioglitazone, but not insulin, resulted in an increase in HDL-C levels. Both treatments had similar effects on weight, other lipid values, blood pressure, and urine microalbumin levels.

Pioglitazone has also shown efficacy among patients who failed sulfonylurea. In an open-label, randomized, controlled trial of 281 patients with at least 3 months of inadequate glycemic control ( $HbA_{1c} = 7.4\%–14.7\%$ ) on a sulfonylurea. Combination therapy using insulin and pioglitazone reduced  $HbA_{1c}$  more than either insulin alone or adding pioglitazone to sulfonylurea, but resulted in more weight gain.<sup>54</sup> These findings were similar to those of an open-label trial of 217 patients inadequately controlled on metformin and sulfonylurea, with each drug dosed at  $\geq 50\%$  of the recommended maximum. Patients were randomized to add either insulin glargine or rosiglitazone. Both groups had equivalently reduced A1C after 24 weeks ( $-1.7\%$  for glargine vs  $-1.5\%$  for rosiglitazone).<sup>55</sup>

Thirty-six patients inadequately controlled on metformin and sulfonylurea/meglitinide were randomized to add-on therapy with insulin glargine or pioglitazone for 26 weeks. The effect on beta cell function was more favorable with insulin glargine measured by proinsulin ( $P=0.04$ ), while the improvement in insulin sensitivity measured by adiponectin ( $P=0.04$ ) and HDL-C ( $P < 0.01$  vs NS) (all  $P$  between groups  $< 0.01$ ) was more favorable in the pioglitazone group. The results demonstrate the characteristic differences in the effects of insulin glargine and pioglitazone on measures of beta cell function, insulin sensitivity, and cardiac load. Insulin glargine resulted in better relief of beta cell stress, and pioglitazone increased adiponectin and HDL-C and also BNP and NT-pro-BNP concentrations.<sup>56</sup>

An interpretation of the above data might auger for avoiding insulin until the patient fails all 3 agents (TZD, metformin, and sulfonylurea), as long as one pays attention to avoidance of potential side effects of sulfonylurea and TZD, and might auger for use of an incretin instead of an oral hypoglycemic agent to avoid hypoglycemia and undue weight gain.

## **TZD plus insulin**

However, if a patient is not at goal with 3 noninsulin therapies, there is great logic and clinical value to keeping a TZD on board as insulin therapy is initiated, as long as attention is paid to potential downsides.

Scheen wrote that from theoretical point of view, the combination of an insulin sensitizer (a glitazone) with exogenous insulin is appealing.<sup>20</sup> This is for several reasons including a lower insulin dose is likely, improvement of the patient's metabolic control, improvements in lipid profile, and even the possibility of eliminating the need for insulin in those not given insulin sensitizers prior to starting insulin. In addition, Scheen reported that glitazones may exert some beneficial effects beyond improvement of glycemic control, especially by improving cardiovascular outcomes, possibly by obtaining the beneficial effects that it has on inflammation, endothelial dysfunction, and lipids.<sup>20</sup> Similarly, Yamanouchi<sup>57</sup> also discusses benefits, safety issues (and mitigation of such), and a significant potential atherosclerotic benefit to using pioglitazone with insulin.

A study revealed that pioglitazone significantly reduced ( $P < 0.05$ ) insulin dose requirements 2 weeks after initiation of treatment. At the end of the study, relative to baseline, pioglitazone reduced daily insulin dosages by 12.0 U ( $P < 0.001$ ), a 21.5% (12.0/55.8 U at baseline) group mean average reduction. Pioglitazone also significantly increased

HDL-C levels, decreased triglyceride levels, shifted LDL particle concentrations from small to large, and increased mean LDL particle size.<sup>58</sup> In the PROACTIVE trial, a third of the patients were on insulin at baseline, about a half received pioglitazone. Those patients on insulin and pioglitazone needed ~20% less insulin, had a simplified regimen, had a greater drop in HbA<sub>1c</sub> (0.93 vs 0.45) and 9% were able to stop insulin.<sup>59</sup>

Hypoglycemia, edema, and weight gain often accompany the use of insulin and TZDs<sup>60,62</sup> and must assiduously be addressed when maintaining TZDs with insulin. Scheen reported that hypoglycemia usually occurs in the first few days or weeks of combined therapy and could be quite easily avoided by an appropriate reduction in daily insulin dosages.<sup>20</sup>

In the randomized, controlled trial comparing 15 and 30 mg of pioglitazone and placebo, in combination with insulin, patients in the placebo treatment group in general experienced no alterations in body weight (−0.04 kg mean change from baseline).<sup>63</sup>

Weight gain associated with glitazones in insulin-treated patients with type 2 diabetes appears to be similar to or even slightly higher than the weight gain reported in monotherapy or when glitazones are given in combination with metformin or sulphonylureas. In the randomized, controlled trial comparing 15 and 30 mg pioglitazone and placebo, in combination with insulin, edema was reported in 7.0% of patients in the placebo plus insulin arm versus 12.6% in the 15 mg pioglitazone plus insulin arm and 17.6% in the 30 mg pioglitazone plus insulin group.<sup>64</sup>

If one pays attention to potential risks for each agent independently, one should be able to avoid, in the majority of clinical situations, the potential additive risks. Thus, for TZDs, advise a low-salt diet, do not use the drug in patients with class 3/4 CHF, avoid the drug in patients with significant preexisting edema from other causes (eg, venous insufficiency), and advise a eucaloric diet. For insulin, similar strategy regarding a low-salt diet to avoid insulin-induced edema, a eucaloric no-concentrated sweets diet, and an appropriate dose adjusting to avoid hypoglycemia will obviate undue side effects of combining the 2 agents.

## Adding TZD to existing insulin

In some situations, patients are on insulin and the question arises regarding the value of adding a TZD. This was evaluated in 566 patients receiving stable insulin regimens for >30 days who had HbA<sub>1c</sub> levels > 8.0% and plasma C-peptide levels > 0.7 µg/L. They were randomized to receive once-daily 15 or 30 mg pioglitazone, or placebo in a

16-week multicenter, double-blind, placebo-controlled trial. Patients receiving 15 or 30 mg pioglitazone had statistically significant decreases in HbA<sub>1c</sub> levels compared with baseline (−1.0% and −1.3%, respectively;  $P < 0.0001$ ).<sup>20</sup>

Mattoo et al sought to determine the effect of 30 mg pioglitazone plus insulin versus placebo plus insulin on glycemic control, serum lipid profile, and selected cardiovascular risk factors in patients with type 2 diabetes whose disease was inadequately controlled with insulin therapy alone despite efforts to intensify such treatment.<sup>65</sup> They randomized 289 patients in the 6-month, double-blind, prospective, multicenter, placebo-controlled, parallel-group study. After an insulin intensification period, the patients with HbA<sub>1c</sub> ≥ 7.0% were randomized to pioglitazone plus insulin or placebo plus insulin. Placebo plus insulin produced no significant changes in HbA<sub>1c</sub> or fasting plasma glucose. The between-treatment differences for A1C (−0.55%;  $P < 0.002$ ) and fasting plasma glucose (−1.80 mmol/L;  $P < 0.002$ ) occurred despite a reduction of insulin dose in the pioglitazone plus insulin group from baseline (−0.16 U/d kg;  $P < 0.002$ ). Significant between-group differences were observed for HDL-C and high-sensitivity C-reactive protein. Adding pioglitazone to insulin in these study patients with type 2 diabetes whose disease was inadequately controlled with insulin monotherapy further improved their glycemic control.<sup>65</sup>

The Pioglitazone 343 Study Group<sup>66</sup> sought to determine the effects of pioglitazone treatment combined with insulin on glucose and lipid metabolism in patients with type 2 diabetes. In a multicenter, double-blind study, 690 patients with diabetes poorly controlled with a stable insulin dose were randomized to 30 or 45 mg pioglitazone once-daily for 24 weeks. Statistically significant, dose-dependent mean decreases from baseline were seen in the 30- and 45-mg pioglitazone groups for HbA<sub>1c</sub> and fasting plasma glucose. Insulin dosage also decreased significantly from baseline. Decreases in triglycerides, very LDL-cholesterol, and free fatty acids and increases in HDL-C were also observed from baseline.<sup>66</sup>

Another 30-mg pioglitazone regimen with insulin was previously shown in a 16-week study to be generally well tolerated and resulted in clinically relevant improvements in both glucose and lipid metabolism. Successful termination of insulin therapy with the addition of pioglitazone has been seen.<sup>67</sup>

TZD-based oral combination therapy has been shown to efficiently and safely substitute for relatively high-dose insulin injection therapy in some patients with type 2 diabetes. The high success rate of switching from insulin treatment to oral agent therapy is mainly due to the pioglitazone-mediated

improvement of insulin resistance, improving beta-cell function. This study looked at 36 subjects, with an average insulin dose of  $0.46 \pm 0.17$  U/kg body weight, a duration of insulin therapy of  $6.1 \pm 8.2$  years, and an average HbA<sub>1c</sub> of  $6.8 \pm 1.3\%$ , who were switched from insulin injection therapy to pioglitazone, glimepiride, and voglibose combination therapy. The success rate of switch therapy was 83% (30/36).<sup>68</sup>

### Value of getting off insulin

Pioglitazone may induce a beneficial effect on atherosclerosis<sup>69,70</sup> compared with insulin because treatment that improved insulin resistance reduced the recurrence of acute coronary syndrome more effectively than insulin upregulation therapy.<sup>71</sup> Moreover, hyperinsulinemia has been reported to be an independent risk factor for macrovascular disease.<sup>72</sup> Although intensive glucose-lowering therapy comprising insulin injection did not show any preventive effect on stroke, pioglitazone significantly reduced the recurrence of stroke by 47%.<sup>73</sup>

### Conclusions

Insulin resistance and obesity, the key components of type 2 diabetes, increase the incidence of CVD in the type 2 diabetes patients. Insulin resistance is a major etiological factor in type 2 diabetes, and of course diabetes accentuates the CV risk factors of the insulin resistance syndrome.

TZDs represent an effective tool for targeting some features of this increased risk as they decrease insulin resistance and therefore can prevent and/or delay diabetes progression. If we can alter the natural history of diabetes, we may be able to lessen microvascular and macrovascular complications. To achieve this, we must improve CV risk factors in type 2 diabetes patients. In this regard, pioglitazone has been shown to have beneficial effects on the lipid profile, as well as likely other associated CV benefits.

Clinical value accrues from adding TZDs to noninsulin therapy and keeping TZDs on board among those who start insulin therapy, and adding TZDs to existing insulin therapy. It is important for the clinician to recognize potential side effects and avoid use among inappropriate patients. When using pioglitazone, the patient should be seen regularly to quickly mitigate any side effects.

Patients taking insulin may benefit from the addition of a TZD by achieving weight loss, less hypoglycemia, an improvement in endothelial function, and a reduction in inflammation. Some patients may even come off insulin with pioglitazone treatment.

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### Disclosure

Dr Schwartz has served on the speakers' bureau and advisory board for Takeda Pharmaceuticals.

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