Cardioprotective Effects of Pioglitazone in Type 2 Diabetes

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Antidiabetic medications that improve glycemic control as well as cardiovascular outcomes will be the mainstay of treatment for type 2 diabetes moving forward. This article reviews the beneficial effects of the thiazolidinedione pioglitazone of ameliorating hyperglycemia and improving cardiovascular risk factors. While the newer sodium–glucose cotransporter 2 inhibitor and glucagon-like peptide 1 receptor agonist drug classes have confirmed cardiovascular benefits, pioglitazone also has been shown to reduce major adverse cardiovascular events, in both people with type 2 diabetes and nondiabetic subjects with insulin resistance. Adverse effects associated with pioglitazone can be mitigated by its use at a lower dose and in combination with antidiabetic agents from other drug classes.

Despite advances in treatment strategies for diabetes, overall mortality is twofold higher in patients with type 2 diabetes (1), and cardiovascular mortality is approximately three- to fourfold higher compared with individuals without diabetes (2). Intensive glycemic control has been shown consistently to improve microvascular complications (3,4). However, the effect of glycemic control on macrovascular disease, particularly cardiovascular disease (CVD), is not clear (5,6).

The possible adverse cardiovascular outcomes associated with the thiazolidinedione rosiglitazone led to mandatory cardiovascular safety trials for approval of all new antidiabetic medications (7,8). Although initially intended to demonstrate noninferiority to placebo, these cardiovascular outcomes trials (CVOTs) of agents in two newer drug classes—sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists—in fact demonstrated superiority or improved cardiovascular outcomes compared with standard treatment. Because of the recent explosion of data from CVOTs of SGLT2 inhibitors (9–13) and GLP-1 receptor agonists (14,15) and relatively negative data associated with thiazolidinediones (16,17), pioglitazone has been relatively overlooked despite its beneficial effects on cardiovascular outcomes and durability of glycemic control. Given that it is now a generic medication available at a fraction of cost of the newer antidiabetic agents, there is renewed interest in this drug, particularly from a public health perspective (18).

Pioglitazone is the only true insulin sensitizer that is readily available. Although rosiglitazone is still available, it has fallen out of favor because of possible adverse cardiovascular outcomes and is rarely used. For pioglitazone, misinformation regarding its association with bladder cancer and worsening congestive heart failure (CHF) has contributed to reluctance to prescribe the drug on the part of both primary care providers and endocrinologists.

Because pioglitazone was approved by the U.S. Food and Drug Administration before its 2008 mandate of CVOTs, a true CVOT of pioglitazone has not been performed. Here, we review the currently available data on the effect of pioglitazone on cardiovascular outcomes.

Pioglitazone and Cardiovascular Outcomes

The effects of pioglitazone on cardiovascular outcomes are based on the results of multiple randomized clinical trials (RCTs), observational studies, analyses of real-world data, and meta-analyses of clinical trials. One of the earliest trials with pioglitazone was the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study (19), in which 5,238 subjects with type 2 diabetes and preexisting CVD were randomized to receive pioglitazone or placebo. After 2.9 years, although the effect of pioglitazone on the primary end point, which included leg revascularization, did not reach statistical significance, pioglitazone significantly reduced the composite three-point major adverse cardiovascular events (MACE) outcome, which included nonfatal myocardial infarction (MI), stroke, and death (hazard ratio [HR] 0.84, $P = 0.027$). Three-point MACE is the standard primary outcome in all recent CVOTs of newer antidiabetic medications. In patients with a history of stroke or MI, pioglitazone treatment led to a 28%

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and 24% lower risk of recurrent stroke (20) and MI (21), respectively. Although this study is reported as a negative study, it should be emphasized that the negative results primarily resulted from inclusion of leg revascularization in the primary end point; this outcome is usually resistant to interventions and is not included in the primary end points of most CVOTs.

Insulin resistance had been associated with an increased incidence of CVD (22–24), as well cerebrovascular accidents (25–27). In the PROactive study, pioglitazone treatment was associated with a decreased incidence of recurrent stroke (20). Because of potential benefits in cardiovascular outcomes with pioglitazone and the possible common link between the two conditions of insulin resistance, a large RCT, the IRIS (Insulin Resistance Intervention After Stroke) study, examined whether pioglitazone, an insulin sensitizer, improved cardiovascular outcomes in nondiabetic subjects who had had a prior stroke or transient ischemic attack (TIA) (28). In 3,876 insulin-resistant subjects with a history of stroke or TIA who were treated on average for 4.8 years, pioglitazone reduced the incidence of stroke or MI by 24% (HR 0.76, 95% CI 0.62–0.93, $P = 0007$). Furthermore, a planned secondary analysis from the same study demonstrated that pioglitazone versus placebo decreased the risk of acute coronary syndrome by 29% ($P = 0.02$) (29,30). The development of diabetes was also significantly reduced (HR 0.48, 95% CI 0.33–0.69).

Several meta-analyses and real-world studies have confirmed the observations summarized above (31). A meta-analysis of nine RCTs of pioglitazone with 12,026 participants demonstrated that pioglitazone treatment was associated with a decreased risk of MACE in individuals with prediabetes or insulin resistance (relative risk [RR] 0.77, 95% CI 0.64–0.93) and in those with type 2 diabetes (RR 0.83, 95% CI 0.72–0.97) (32). Another, similar meta-analysis of 10 RCTs, which included patients with CVD who were on pioglitazone treatment, also reported a reduced risk of MACE (33). A recent meta-analysis, which included 19,645 patients from 26 RCTs, examined the effect of pioglitazone on primary and secondary prevention of cardiovascular events in patients at risk for developing type 2 diabetes. Pioglitazone was found to reduce three-point MACE in subjects with preexisting coronary artery disease by 32% (RR 0.6, 95% CI 0.7–0.9), which was mainly the result of a reduction in nonfatal MI and stroke (34). However, the cardioprotective effects of pioglitazone were not observed in patients without a history of CVD. Pioglitazone also reduced albuminuria by 18.5%.

In a retrospective analysis of 91,511 U.K. patients with type 2 diabetes who were followed for 7.1 years, pioglitazone, compared with metformin, reduced all-cause mortality by 31–39% (35). Similar results were reported in another European study of a large cohort of 56,536 patients with type 2 diabetes who were first-time users of pioglitazone or insulin. Mortality was 67% lower in patients treated with pioglitazone (36).

Although pioglitazone reduced cardiovascular events in patients with prior cardiovascular events, with or without type 2 diabetes, its effect in patients with recently diagnosed type 2 diabetes inadequately controlled on metformin is not clear. In a recent Italian pragmatic study, TOSCA-IT (Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Intervention Trial) (37), patients with type 2 diabetes inadequately controlled on metformin were randomized to receive pioglitazone or a sulfonylurea as add-on therapy. After a median follow-up of 4.8 years, there was no difference in cardiovascular events between the two groups. However, the lack of cardioprotection from pioglitazone in this study could have been the result of the following reasons: *1*) only 11% of participants had had a prior cardiovascular events, and thus it was mainly a primary prevention trial; *2*) there were methodological problems: the study was unblinded and the discontinuation rate was higher in patients on pioglitazone; and *3*) the event rate in this study was extremely low, and the study likely was underpowered to detect any significant difference between the two groups. Regardless, it appears that, as with SGLT2 inhibitors and GLP-1 receptor agonists, the beneficial cardiovascular effects of pioglitazone are observed mainly in patients with preexisting CVD (10,14).

Potential Mechanisms of the Cardiovascular Benefits of Pioglitazone

It is well known that targeting hyperglycemia alone has only minimal effects on cardiovascular outcomes. The question arises as to how the antihyperglycemic agent pioglitazone is effective in atherosclerotic cardiovascular disease (ASCVD). Pioglitazone is the only true insulin sensitizer currently available. It ameliorates insulin resistance, which is one of the core metabolic defects in the pathogenesis of type 2 diabetes and possibly of ASCVD. In smaller mechanistic studies, pioglitazone compared with the sulfonylurea glimepiride reduced the progression of atherosclerosis measured by intravascular ultrasound (38). In the CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) study, pioglitazone also reduced the rate of increase of carotid intima-media thickness (CIMT) (39). In the ACT NOW (Actos Now for Prevention of Diabetes) study, pioglitazone similarly reduced the rate of progression of CIMT in patients with prediabetes (40).

Apart from its beneficial effects on skeletal muscle insulin sensitivity and β-cell function, pioglitazone improves several

cardiovascular risk factors, including lowering plasma free fatty acid concentrations, which play a major role in skeletal muscle, hepatic, and adipocyte insulin resistance and endothelial dysfunction (41). In addition to metabolic effects, pioglitazone also has potent anti-inflammatory properties. It increases the anti-inflammatory cytokine adiponectin, while reducing proinflammatory cytokines tumor necrosis factor-α and the procoagulant factor plasminogen activator inhibitor-1 (42,43). In a meta-analysis of 15 RCTs, pioglitazone also improved conventional cardiovascular risk factors; it was found to lower triglycerides by 0.2 mmol/L, reduce LDL cholesterol by 0.13 mmol/L, and increase HDL cholesterol by 0.068 mmol/L (44). Similar observations were noted in another recent meta-analysis, which only analyzed the effect of pioglitazone monotherapy and showed that, compared with other antihyperglycemic drugs, pioglitazone had a favorable effect on lipid metabolism and systolic and diastolic blood pressure (45). In addition, small trials have shown that pioglitazone improves left ventricular function (46) and have suggested that it has direct anti-atherosclerotic effects in the arterial wall. Thus, the combination of effects of pioglitazone on insulin sensitivity, lipid profile, blood pressure, systemic inflammation, and possibly directly on the vascular endothelium likely contribute to the beneficial effects of pioglitazone on cardiovascular outcomes in type 2 diabetes.

Adverse Effects of Pioglitazone

One of the factors limiting widespread use of pioglitazone is concern about potential adverse effects. Here, we address the important common adverse effects, including weight gain, fluid retention and worsening of CHF, fractures, and the risk of bladder cancer, as well as ways to mitigate them.

Pioglitazone therapy is associated with a weight gain of ∼2–3 kg over 1 year (47). However, the weight gain associated with pioglitazone is dose related; if the higher 45-mg dose is avoided, weight gain will be relatively modest. Again, the weight gain is primarily the result of redistribution of fat. Visceral fat is reduced, and fat in subcutaneous adipose tissue is increased, which is metabolically healthier (41,48). Thus, despite an increase in fat mass, the amount of anti-inflammatory adipokine adiponectin is increased, while proinflammatory adipokines are decreased (42).

The issue with fluid retention and CHF is a concern, although not all studies have shown increased incidence of CHF. Pioglitazone should not be used in patients with symptomatic heart failure. If edema is the main concern, combination therapy with a low-dose diuretic or SGLT2 inhibitor might lessen this problem. In fact, when empagliflozin was added to pioglitazone, there was net weight loss (49,50).

With regard to fractures, this concern is mostly limited to post-menopausal women and primarily involves distal fractures (51). Pioglitazone should be used cautiously in patients with a risk of fractures.

The concern about bladder cancer with pioglitazone was initially raised during the PROactive study, in which a nonsignificant increase in bladder cancer was noted. However, during the subsequent long-term observational study, in which PROactive participants were followed for 8.7 years, there was no increase in risk of bladder cancer (52). A meta-analysis in the *British Journal of Medicine* was the first study to link bladder cancer to pioglitazone (16,17); however, there was no association when bladder cancer cases during the first year were subsequently excluded (52). Two large, observational studies that analyzed 10-year follow-up data on patients treated with pioglitazone did not find any association with bladder cancer (53). Similarly, in a multinational cohort with >1 million patients with type 2 diabetes, the HR for bladder cancer with pioglitazone was 1.01 (P = NS) (53). Another meta-analysis involving a large number of patients did not find evidence to link pioglitazone and bladder cancer (54). Thus, although at present there is no causal relationship between pioglitazone treatment and bladder cancer, this drug should be avoided in patients with active bladder cancer and those with a history of prior bladder cancer.

When to Use Pioglitazone

Along with comprehensive lifestyle modification, metformin is recommended as the first-line therapy for all patients with type 2 diabetes, and other medications may be added subsequently (55). A recent study demonstrated that early intensive treatment with a combination of metformin, pioglitazone, and exenatide provides more durable glycemic control than standard stepwise intensification of antihyperglycemic therapy (56).

Pioglitazone may be started as monotherapy or in combination with metformin and an SGLT2 inhibitor or GLP-1 receptor agonist, particularly in patients with preexisting CVD and those at a high risk of CVD. Because most patients with type 2 diabetes are obese, weight gain and edema are concerns that discourage many primary care providers from prescribing this medication. This issue can be addressed by using a lower dose of pioglitazone (15 or 30 mg/day) and using it in combination with an SGLT2

inhibitor or GLP-1 receptor agonist. We have shown earlier that even low-dose pioglitazone (15 mg/day) improved glycemic control, β-cell function, and inflammation with minimal weight gain (57). In fact, a combination of pioglitazone with one of the newer antidiabetic agents may have synergistic cardioprotective effects.

DUALITY OF INTEREST

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AUTHOR CONTRIBUTIONS

D.T. and C.S.-H. researched data, wrote/edited the manuscript, and contributed to the discussion. R.E.J.R. edited the manuscript and contributed to the discussion. D.T. is the guarantor of this work and, as such, takes responsibility for the integrity of this review.

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