New Drugs and Technologies

New Drugs for the Treatment of Diabetes Mellitus
Part I: Thiazolidinediones and Their Evolving Cardiovascular Implications

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The cardiovascular disease (CVD) risk associated with diabetes mellitus (DM) has become increasingly evident, accounting for ≈80% of deaths among patients with this disease1 and making CVD risk modification a key therapeutic objective in diabetic patients. Indeed, in some clinical contexts, DM has been elevated to a coronary heart disease risk equivalent for risk reduction strategies.1–4 The rapidly increasing global burden of DM,5 coupled with the associated CVD risk, underscores the imperative for continued generation and application of evidence-based therapies to reduce CVD risk in this high-risk cohort.

In this 2-part series, we first review the CVD effects of the thiazolidinedione medications, the most broadly investigated class of antihyperglycemic drugs evaluated in the context of CVD risk. In the second part, we review the modulators of the incretin axis that have most recently achieved US Food and Drug Administration approval, with a focus on CVD considerations; introduce selected drugs in advanced development; summarize glucose control strategies for cardiovascular patients; and discuss the regulatory review of glucose-lowering medications.

Thiazolidinediones: Peroxisome Proliferator–Activated-γ Agonists

Ciglitazone, the first thiazolidinedione, was discovered in a compound-screening program for lipid-lowering agents and serendipitously observed to lower glucose in experimental animals, but it failed in clinical testing as a result of toxicities.6 Troglitazone became the first thiazolidinedione approved to treat type 2 DM (T2DM) in 1997, with little understanding of its mechanism of action. Subsequently, the peroxisome proliferator–activated (PPAR-γ) receptor, a nuclear receptor that regulates gene transcription, was identified as the thiazolidinedione target of action.7 PPAR-γ is a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors8 that, when activated, dimerizes with the retinoid X receptor and binds to DNA (PPAR-response element) to regulate gene transcription through coordinate transactivation and transrepression.9 PPAR-γ is expressed most prominently in adipocytes, regulating adipogenesis10 and glucose and lipid metabolism; it also is expressed in hepatocytes, skeletal muscle, cardiac muscle, colonic epithelium, vascular endothelial cells, renal collecting duct epithelium, and macrophages. The presence of the receptor in cell lines involved in atherogenesis has prompted much interest in its potential as a therapeutic target for CVD.

In 1999, 2 additional thiazolidinedione medications were approved, rosiglitazone (Avandia) and pioglitazone (Actos). Troglitazone was withdrawn in 2000 because of rare, idiosyncratic hepatotoxicity, an adverse effect not observed with other thiazolidinediones. Because of their effects on improving insulin resistance, a fundamental element of T2DM, and low risk of hypoglycemia, the thiazolidinediones have been incorporated very rapidly into clinical practice, currently representing close to 25% of all oral antihyperglycemic prescriptions.

Metabolic Effects

Adipogenesis

The thiazolidinediones increase body weight, in part because of differentiation of adipocytes and expansion of adipocyte mass.11 Given the association between increased adiposity and CVD risk, the long-term CVD implications of this phenomenon require continued investigation. However, some unique features of adiposity associated with thiazolidinediones warrant consideration and may abrogate some (or all) of the potential increment in CVD risk typically associated with increased weight. Activation of PPAR-γ stimulates differentiation to insulin-sensitive smaller adipocytes11 and redistributes fat from visceral to subcutaneous depots, a pattern that has been associated with lower CVD risk,12 supported by improved adipokine profiles following treatment with thiazolidinediones such as increased adiponectin and decreased tissue necrosis factor-α.13 In addition, thiazolidinediones reduce circulating free fatty acids, likely via potentiation of antilipolytic effects of insulin and upregulation of adipocyte free fatty acid transporters,14 with potential favorable effects on liver and skeletal muscle metabolism,7 β-cell function,15 vascular inflammation and endothelial function,16 and myocardial viability.17 Thus, the net effect of thiazolidinedione treatment is an increased mass of small,
insulin-sensitive subcutaneous adipocytes with decreased lipolytic activity, resulting in decreased circulating free fatty acids and improved adipocytokine profiles.

**Glycemia**
The thiazolidinediones typically reduce hemoglobin A1c by 1% to 2% compared with placebo, similar to effects observed with metformin and sulfonylureas in head-to-head comparisons. The thiazolidinediones increase skeletal muscle glucose uptake via modulation of humoral adipocytokines that directly affect skeletal muscle insulin sensitivity (eg, leptin, adiponectin, tumor necrosis factor-α, interleukin-6) and, to a lesser degree, reduce hepatic glucose production. The thiazolidinediones also preserve β-cell function in animal models of DM, an effect suggested in humans by the superior durability of glucose control with thiazolidinediones compared with metformin or sulfonylureas and the prevention of incident DM in patients with impaired glucose metabolism.

**Lipid Metabolism**
Both rosiglitazone and pioglitazone increase high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c), shifting the LDL particle profile toward larger, more buoyant particles with little change in LDL particle concentration; pioglitazone (but not rosiglitazone) decreases triglycerides. One randomized, controlled clinical trial compared the lipid effects of rosiglitazone and pioglitazone in 802 patients with T2DM (Figure 1). Both drugs increased HDL-c (pioglitazone more than rosiglitazone).
zone); both drugs increased LDL-c mass (rosiglitazone more than pioglitazone); and pioglitazone decreased and rosiglitazone increased triglycerides. LDL particle concentration decreased with pioglitazone and increased with rosiglitazone, associated with a significantly greater increase in particle size with pioglitazone compared with rosiglitazone.23 One potential mechanism that may contribute to the observed disparate effects on lipid profiles is the activation by pioglitazone of hepatic PPAR-\(\gamma\),25 the target of action of fibric acid derivatives, an effect that has not been observed with rosiglitazone. The lipid effects were independent of glycemia, with similar glucose control between the 2 groups. The clinical relevance of these observations remains uncertain, especially in the context of widespread statin use in the population with DM. The effects of pioglitazone on HDL and triglycerides, however, are additive to the statin effects.26 These observations may aid in the interpretation of CVD clinical outcomes observations discussed below.

**Cardiovascular Effects**

**Inflammation**

Systemic inflammation is associated with atherosclerosis and CVD risk,27–29 as well as the development of T2DM.30 In cell preparations31–34 and in human studies,35,36 thiazolidinediones inhibit inflammation independently of glucose effects. Like the lipid effects, the impact of the thiazolidinediones on inflammation is additive to that observed with statins.26 The net influence of inflammatory modulation of the thiazolidinediones on the risk for CVD and development of T2DM remains to be defined.

**Endothelial Function and Hypertension**

The thiazolidinediones favorably affect peripheral and coronary endothelial dysfunction37–39 and modestly improve blood pressure.40 Proposed mechanisms for these effects include improved endothelium-dependent vasodilation41 and improved vasomotor tone via increased expression of vascular endothelial growth factor and reduced leakage41 and improved vasomotor tone via increased expression of endothelin-1.42 The thiazolidinediones also partially inhibit voltage-gated (L-type) calcium channels, the target of action of dihydropyridine calcium channel blockers.43 Although the blood pressure effects are small (2 to 3 mm Hg), epidemiological estimates suggest that such changes may yield relative reductions of 15% to 20% for stroke and 10% to 15% for myocardial infarction (MI)44 and therefore may be important on a population basis.

**Edema and Heart Failure**

New or worsening peripheral edema is common with thiazolidinedione use, ranging from 2.5% to 16.2% incidence, with risk increasing with age, increasing drug dose, female sex, declining renal function, and concomitant insulin use.45–51 Whether the peripheral edema associated with thiazolidinediones reflects adverse myocardial effects, an effect on renal sodium reclamation with plasma volume expansion, capillary leak, or some combination of these effects remains unclear.

One of the most likely mechanisms underpinning peripheral edema with thiazolidinediones is increased renal sodium reclamation and plasma volume expansion.52–54 The PPAR-\(\gamma\) expressed in the renal collecting duct epithelium, where its activation increases expression of the epithelial sodium channel-\(\gamma\) and increases distal sodium reclamation.52–54 A collecting duct–specific PPAR-\(\gamma\) knockout mouse was resistant to increases in plasma volume associated with both rosiglitazone55 and pioglitazone.56 In wild-type mice treated with pioglitazone, concomitant treatment with amiloride (an antagonist of epithelial sodium channel-\(\gamma\); 50 mg/d) added; or to discontinue rosiglitazone. Hematocrit was reassessed after 7 days.57 Subjects who continued on rosiglitazone alone or were treated with furosemide experienced a continued decline in hematocrit (−0.89% and −0.70%, respectively); hydrochlorothiazide halted but did not reverse the trend (−0.02%); spironolactone was associated with an increased hematocrit (0.24%). Compared with those continued on rosiglitazone, only the hematocrit changes with hydrochlorothiazide and spironolactone were statistically significant (P<0.05). This study is limited by its small size, short duration of assessment, and use of hematocrit as the primary indicator of plasma volume. These provocative findings demonstrate a plausible mechanism of PPAR-\(\gamma\)-dependent sodium retention and suggest amiloride or spironolactone (Aldactone) as potential targeted therapies for the treatment or prevention of edema in humans, a hypothesis that requires confirmation.

Additional effects of the thiazolidinediones may contribute to the observed peripheral edema, including their effects on the L-type calcium channel that may result in dihydropyridine-like effects53 and the increased expression of vascular endothelial growth factor, which increases microvascular permeability.54 Therefore, it remains possible that some component of thiazolidinedione-associated peripheral edema is due to a peripheral capillary leak phenomenon.

Beyond peripheral edema with the thiazolidinediones, in which the clinical relevance remains unclear,56 a greater concern exists for the much less common but more serious incident or worsening heart failure (HF) with these drugs.48–51,56,57 The annualized placebo-subtracted increment in incident HF, even in high-risk cohorts, is 0.25% to 0.45% per year.48,49,58 Although relatively uncommon, the morbidity and mortality implications of these observations have prompted explicit product label warnings against the use of rosiglitazone or pioglitazone in patients with New York Heart Association class III or IV HF and a caution for use in patients with class II HF.50,51 These cautions are supported by a position statement from a joint panel of the American Diabetes Association and the American Heart Association.57 In May 2007, the Food and Drug Administration recommended amplifying the
HF warning in the product label of both rosiglitazone and pioglitazone to caution against any use in patients with any degree of HF, with an update of the product label for both drugs forthcoming.

No studies to date have demonstrated a pernicious effect of thiazolidinediones on myocardial structure or function. On the contrary, data from ex vivo experiments and animal models suggest favorable myocardial effects of the thiazolidinediones such as reduced myocyte and cardiac hypertrophy and improved systolic and diastolic performance.59–61 Likewise, in randomized clinical trials evaluating the effects of thiazolidinediones on echocardiographic parameters in patients with T2DM without HF, no untoward effects on cardiac structure or function were observed with either troglitazone or rosiglitazone.62,63 In a randomized trial of troglitazone versus glyburide, echocardiograms were assessed at baseline and after 48 weeks of treatment in 114 subjects. Compared with baseline measures, troglitazone was associated with significantly improved stroke volume index (32.4 versus 34.9 mL/m²; P<0.1) and cardiac index (2.4 versus 2.6 mL·min⁻¹·m⁻²; P<0.1); glyburide had no effect on these parameters.62 In a similar study, the effect of 52 weeks of treatment with rosiglitazone compared with glyburide on echocardiographic parameters was assessed in an open-label, randomized, multicenter trial that enrolled 203 patients with T2DM without HF. Only 118 participants (58%) were assessed at 52 weeks, with no significant differences observed between the rosiglitazone and glyburide groups in left ventricular ejection fraction (65.9% versus 66.6%, respectively), left ventricular mass index (79.5 versus 78.0 g/m²), or left ventricular end-diastolic volumes (99.7 versus 90.8 mL).63 The validity of the observations from both of these studies is notably uncertain as a result of the small sample sizes, high attrition rates, open-label study designs, and inclusion of subjects at low HF risk.

In the setting of prevalent HF, 2 randomized trials have assessed the effects of thiazolidinediones. The effect of 52 weeks of treatment with rosiglitazone versus placebo added to background DM therapy was assessed in a randomized, blinded study of 224 patients with T2DM, New York Heart Association class I and II HF, and left ventricular ejection fraction ≤45%.64 New or worsening peripheral edema was increased in the rosiglitazone- compared with the placebo-treated patients (25.5% versus 8.8% respectively; P=0.037), with increased use of HF medications in the rosiglitazone group. However, no significant difference was observed in ejection fraction between groups (36.3% versus 37.1%; P=0.09), and the E:A ratio as an estimate of diastolic performance was significantly improved with rosiglitazone versus placebo (1.37 versus 1.12; P=0.003). Like the prior studies in non-HF patients, however, the study validity is challenged by a high rate of attrition, with only 80% of the cohort completing the study.

The effect of pioglitazone versus glyburide was assessed in a 24-week trial of patients with T2DM, impaired systolic function (ejection fraction <40%), and New York Heart Association class II or III HF. This study was stopped before completion for reasons that have not been made public, and although not yet published, summary results are in the product label.50 Hospitalization for HF was numerically higher in the pioglitazone versus glyburide group (9.9% versus 4.7%; no probability value provided), most notably in insulin-treated patients and those >64 years of age. It is unclear whether effects on cardiac structure and function were assessed.

Incident HF associated with thiazolidinediones also has been observed in randomized trials of patients without HF but at increased CVD risk. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study (described below), >5000 patients with T2DM and prevalent CVD were randomized to receive pioglitazone versus placebo added to background diabetes therapy, with a median duration of 2.9 years.48 Nonadjudicated HF hospitalization occurred in 149 patients treated with pioglitazone versus 108 treated with placebo (5.7% versus 4.1%; P=0.007), with no evident increase in HF-associated mortality (25 [0.96%] versus 22 [0.84%] cases). Subsequently, the HF events underwent blinded central adjudication, with a slight attenuation of the absolute difference in incident HF hospitalization (5.5% versus 4.2%; probability value not reported).58

In the Rosiglitazone Evaluated for Cardiovascular Outcomes (RECORD) study,49 4447 overweight and obese patients with T2DM and inadequate glycemic control on maximum-dose metformin or sulfonylurea were recruited. In this open-label study using a noninferiority design, patients on metformin were randomized to have rosiglitazone or sulfonylurea added; those on sulfonylurea were randomly assigned to the addition of either rosiglitazone or metformin. In a publication of the interim results, after a mean treatment duration of 3.8 years, 38 adjudicated HF hospitalization events had occurred in rosiglitazone-treated patients compared with 17 in the control group (1.7% versus 0.8%; P=0.006).

These study results consistently reflect the low absolute incidence of HF requiring hospitalization, with quantitatively similar placebo-subtracted increased risk (∼1%) associated with both available thiazolidinediones, each over ∼4 years of trial surveillance. These observations underscore the importance of continued investigations into the mechanistic underpinnings of HF with thiazolidinediones and support the present cautions on the use of these drugs in HF patients and the importance of regular clinical evaluation for signs and symptoms of HF in thiazolidinedione-treated patients.

In an observational study analyzing data from >16 000 older diabetic patients discharged from US hospitals with a diagnosis of HF, despite the HF contraindications, >15% were treated at discharge with a thiazolidinedione.65 Compared with patients treated with neither metformin nor a thiazolidinedione (n=12 069), the hazard ratio (HR) for 1-year mortality was significantly lower in patients prescribed a thiazolidinedione (n=2226; adjusted HR, 0.87; 95% confidence interval [CI], 0.80 to 0.94) or both metformin and thiazolidinedione (n=261; adjusted HR, 0.76; 95% CI, 0.58 to 1.00). These observational data are only hypothesis generating, with randomized clinical trials needed before thiazolidinedione therapy is considered in this high-risk group of patients.
Atherosclerosis Development and Progression

The thiazolidinediones inhibit vascular smooth muscle and endothelial cell migration and proliferation of both animal and human cell lines\(^66,67\) and reduce atherosclerosis in the LDL-receptor–null mouse model.\(^68\) Likewise, controlled clinical trials with treatment durations ranging from 6 to 18 months have reported favorable effects on carotid intima-media thickness\(^69–73\) (Figure 2) and restenosis after percutaneous coronary intervention\(^74–78\) (Figure 3). These effects on imaging intermediates of atherosclerosis are independent of glucose control and consistent across the thiazolidinedione class. These observations support the potential efficacy of thiazolidinediones on atherosclerosis and further investigation into their effects on CVD risk.

A number of large-scale, randomized, controlled clinical trials assessing the CVD effects of the thiazolidinediones have been completed or are underway\(^79–82\) (the Table). Although most studies are 2 to 4 years from completion, the PROactive study results and an interim report from the RECORD trial have been published,\(^48,49\) as have results of meta-analyses of the accumulated rosiglitazone trial database examining CVD effects.\(^83–86\)

The PROactive trial was a double-blind, placebo-controlled study that enrolled 5238 patients with T2DM and prevalent CVD with a primary composite end point that included all-cause mortality, MI, stroke, acute coronary syndrome, coronary or leg revascularization, or leg amputation.\(^48\) Participants were randomized to receive pioglitazone titrated to 45 mg/d versus placebo added to existing DM therapy for an average of 2.9 years.\(^48\) Despite accumulating >1000 primary end point events (514 in the pioglitazone arm versus 572 in the placebo arm) (Figure 4A), the trend toward a 10% relative reduction favoring pioglitazone failed to achieve statistical significance (HR, 0.9; 95% CI, 0.8 to 1.02; \(P=0.095\)). Treatment with pioglitazone, however, did significantly reduce the prospectively identified principal secondary composite end point of all-cause mortality/MI/stroke (HR, 0.84; 95% CI, 0.72 to 0.98; \(P=0.027\)) (Figure 4B); of note, this end point excluded silent MI, which was included in the primary composite end point.\(^48\) In prespecified subgroup analyses, pioglitazone compared with placebo decreased stroke risk among those with a history of stroke at study entry (5.6% versus 10.2%, respectively; HR, 0.53; 95% CI, 0.34 to 0.85)\(^79\) and MI risk among patients with a history of MI at study entry (5.3% versus 7.2%, respectively; HR, 0.74; 95% CI, 0.58 to 0.99).\(^80\) Pioglitazone compared with placebo was associated with an absolute 0.6% lower hemoglobin A1c, 21 mg/dL lower triglycerides, 3.9 mg/dL higher HDL-c, and 3 mm Hg greater reduction in systolic blood pressure.\(^48\) The relative contributions of these effects to the observed results remain unclear. These data suggest that the use of pioglitazone in patients with T2DM and CVD may improve CVD

Figure 2. Summary of effects of thiazolidinediones (TZD) on carotid intima-media thickness (IMT) in randomized controlled trials. For each study, the difference in IMT between groups was statistically significant, with \(P<0.05\) for all comparisons. Tro indicates troglitazone; Usual, usual care; Pio, pioglitazone; Rosi, rosiglitazone; Plac, placebo; Glim, glimeperide; and CAD, coronary artery disease.\(^69–73\)

Figure 3. Summary of effects of thiazolidinediones (TZD) on coronary estimates of restenosis using coronary intravascular ultrasound after percutaneous coronary intervention with bare-metal stenting in randomized controlled trials. For each study, the difference in neointimal measure between groups was statistically significant, with \(P<0.05\) for all comparisons. Abbreviations as in Figure 1.\(^74–78\)
risk. However, the lack of statistical significance in the primary end point comparison and the statistically significant increase in HF hospitalization (described above) raise important challenges to the validity, generalizability, and risk-benefit assessment of the study results. These observations with regard to atherosclerotic event risk reduction have been supported by a subsequent meta-analysis of patient-level data from 19 controlled trials of pioglitazone comprising 16 390 patients in which pioglitazone was associated with statistically reduced risk for a composite of death/MI/stroke (HR, 0.82; 95% CI, 0.72 to 0.94; \( P = 0.005 \)).

No clinical trial has yet rigorously assessed the CVD effects of rosiglitazone, but a series of recently published analyses have yielded a concerning safety signal in this regard. In a meta-analysis of summary-level data evaluating the CVD effects of rosiglitazone versus placebo or active controls from 42 trials, none of which were designed to assess CVD effects, rosiglitazone was associated with a significant 43% relative increased odds for MI (odds ratio, 1.43; 95% CI, 1.03 to 1.98) and a trend toward a 64% increased odds for cardiovascular death (odds ratio, 1.64; 95% CI, 0.98 to 2.74). A number of important limitations of this analysis and its interpretation beyond those discussed in the primary report should be noted. The trials had extremely low CVD event rates, including many with 0 or only 1 event, prompting the investigators to use the Peto fixed-effects statistical method to account for the low number of events and to exclude from the analyses those trials with no events reported.

### Table. Summary of Completed and Ongoing Randomized, Controlled, Clinical Trials Evaluating the Effect of Thiazolidinedione Medications

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Treatments</th>
<th>Sample Size, n</th>
<th>Duration, y</th>
<th>End Point</th>
<th>Anticipated Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROactive</td>
<td>Prevent CV events</td>
<td>pio vs plac</td>
<td>5238</td>
<td>4</td>
<td>MI, CVA, amputation, revascularization, CV death</td>
<td>Published ( ^{46,79,80} )</td>
</tr>
<tr>
<td>DREAM</td>
<td>Prevent IGT—diabetes and death</td>
<td>rsg vs plac</td>
<td>5269</td>
<td>3</td>
<td>New diabetes or death</td>
<td>Published ( ^{22} )</td>
</tr>
<tr>
<td>ADOPT</td>
<td>Maintain glucose control</td>
<td>rosi vs glyb vs met</td>
<td>4360</td>
<td>5</td>
<td>Time to monotherapy failure</td>
<td>Published ( ^{11} )</td>
</tr>
<tr>
<td>ACT NOW</td>
<td>Prevent IGT—diabetes</td>
<td>pio vs plac</td>
<td>600</td>
<td>3</td>
<td>New diabetes</td>
<td>2008</td>
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<tr>
<td>RECORD</td>
<td>Prevent CV events</td>
<td>met+rsg; rsg+su; met+su</td>
<td>4447</td>
<td>6</td>
<td>Time to CV event composite</td>
<td>2009</td>
</tr>
<tr>
<td>BARI-2D ( ^{11} )</td>
<td>Prevent death and CV events</td>
<td>IP (ins−su) vs IS (TZD−met)</td>
<td>3000</td>
<td>5</td>
<td>All-cause mortality</td>
<td>2010</td>
</tr>
<tr>
<td>IRIS ( ^{22} )</td>
<td>Prevent CV events</td>
<td>pio vs plac</td>
<td>3136</td>
<td>3</td>
<td>CVA or MI</td>
<td>2012</td>
</tr>
</tbody>
</table>

DREAM indicates Diabetes Reduction Assessment With Rosiglitazone and Ramipril Medication; ADOPT, Diabetes Outcome Progression Trial; ACT NOW, Actos Now for Prevention of Diabetes; BARI-2D, Bypass Angioplasty Revascularization Intervention in Type 2 Diabetes; IRIS, Insulin Resistance After Stroke Trial; CV, cardiovascular; pio, pioglitazone; plac, placebo; CVA, cerebrovascular accident; IGT, impaired glucose tolerance; rsg, rosiglitazone; glyb, glyburide; met, metformin; su, sulfonylurea; IP, insulin-providing therapy; ins, insulin; and IS, insulin-sensitizing therapy.
death. However, all methods yielded a point estimate of increased CVD odds with rosiglitazone (MI, ranging from 1.26 to 1.43; cardiovascular death, ranging from 1.17 to 1.64).\(^8\) Further support for a risk signal for increased MI associated with rosiglitazone derives from a subsequent meta-analysis of 4 controlled trials of >12 months’ duration with cardiovascular event monitoring, revealing a 42% increased risk for MI (95% CI, 6 to 91; \(P=0.02\)) with no increased risk for CV mortality observed (relative risk, 0.90; 95% CI, 0.63 to 1.26; \(P=0.53\)).\(^6\) In addition, results from meta-analyses of patient-level data have been made public by GlaxoSmithKline, the manufacturer of rosiglitazone, with results that are quantitatively similar to the observations of Nissen and Wolski,\(^3\) with an estimated 31% increased hazard for MI (HR, 1.31; 95% CI, 1.01 to 1.70). Further reflecting the statistical challenges of these analyses, one can consider the actual sum of all MI events reported by Nissen and Wolski: 86 of 14,371 patients assigned to rosiglitazone (0.60%) versus 72 of 11,634 control patients (0.62%). Although not respecting the original trial randomizations, these data indicate that participants had an \(\approx 6\) in 1000 risk for MI regardless of treatment group; and although the odds ratio point estimates are large in magnitude, the extremely small number of events yields very small absolute risk increments, ranging 0.07% to 0.4% (ie, number needed to treat to harm ranging from 250 to >1400).

These observations prompted publication of interim results from the RECORD trial (described above), which was designed to assess the CVD effects of rosiglitazone versus metformin or sulfonylurea.\(^4\) With only 80 adjudicated MI events evaluable, the MI hazard was not statistically different between rosiglitazone and controls (43 of 2220 versus 37 of 2227; HR, 1.16; 95% CI, 0.75 to 1.8; \(P=0.5\)). Although underpowered and imprecise given the very low number of events, these results are qualitatively similar to the meta-analysis results and are not countered by any available trial data.

In an observational analysis of administrative data, the comparative risk for MI and coronary revascularization associated with rosiglitazone, metformin, or sulfonylurea was assessed.\(^5\) This study used propensity matching to account for differences in patient mix and included 26,391 patients matched on dual oral therapy, and 23,461 patients on combination therapy with insulin, with an average follow-up of just >1 year. The data set comprised a total of 323 MIs and 582 coronary revascularizations, and in overall analyses combining all 3 strata, a nonsignificant 7% reduced risk existed for the combined MI/coronary revascularization end point associated with rosiglitazone versus all other therapies (adjusted HR, 0.93; 95% CI, 0.8 to 1.1).

Another observational analysis of administrative data provides further support for qualitatively different effects of pioglitazone and rosiglitazone on CVD risk, comparing the rates of MI and coronary revascularization between T2DM patients treated with pioglitazone versus rosiglitazone.\(^6\) This study included 14,807 patients treated with pioglitazone and 15,104 treated with rosiglitazone, with 1.2 years of mean follow-up. After statistical adjustment, pioglitazone versus rosiglitazone was associated with a 22% lower rate of MI (adjusted HR, 0.78; 95% CI, 0.63 to 0.96) and 15% decrease in the composite of MI and coronary revascularization (adjusted HR, 0.85; 95% CI, 0.75 to 0.98).

Although most thiazolidinedione effects on CVD intermediates and disease are qualitatively similar across the class, the disparate observations between pioglitazone and rosiglitazone related to CVD risk suggest key differences between these drugs. One potential difference may relate to the effects on lipoproteins favoring pioglitazone, as discussed above.\(^23\)\(^24\) However, the CVD risk signal in the rosiglitazone meta-analyses derives primarily from studies of only 6-month duration, a time course during which it is unlikely that lipid modulation would markedly alter event rates by modulation of disease development or progression. Instead, mechanisms associated with atherosclerotic plaque instability and rupture and/or some prothrombotic effects might be implicated, although no specific mechanisms in this regard are yet readily apparent. Therefore, although the lipid effects may contribute, it is likely that other features discerning these drugs account for the observed differences. In this context, the differential lipid effects may serve simply to signal fundamental metabolic differences between the 2 compounds.

This hypothesis is supported by microarray analyses of RNA expression from adipocytes exposed ex vivo to rosiglitazone, pioglitazone, and troglitazone.\(^9\) Although significant overlap in gene regulation was observed between the 3 drugs, discordance between them was substantial. For example, only 23 of 57 genes (40%) were concordantly affected by rosiglitazone and pioglitazone, with an additional 25 genes affected only by troglitazone. These differential effects on gene regulation may underpin the disparate observations on CVD effects of the thiazolidinediones, requiring continued investigation.

**Conclusions**

In summary, thiazolidinedione effects on the cardiovascular system extend beyond their impact on glucose metabolism, yielding much interest in their effect on CVD risk, with numerous trials underway. Both rosiglitazone and pioglitazone are similarly associated with peripheral edema and, much less commonly, HF, warranting continued caution for their use in HF patients according to their product labels, Food and Drug Administration guidance, and AHA/American Diabetes Association recommendations.\(^5\) Pioglitazone has demonstrated favorable trends for CVD risk reduction in the PROactive study, the largest CVD outcomes trial of glucose-modifying therapy completed to date. The safety signal associated with potential increased CVD risk associated with rosiglitazone warrants caution for its use, but the paucity of evaluable data in this context justifies continued clinical trial assessment with judicious safety monitoring of ongoing clinical trials. Until such additional safety and efficacy data are available, in the context of what may now appear to be safer alternatives to rosiglitazone available, including but not limited to pioglitazone, its routine use in the treatment of hyperglycemia in patients with T2DM at increased CVD risk cannot be recommended.
Scholarly Paper

Disclosures

Dr Inzucchi reports having received grant/research support and/or honoraria from or having been a consultant for Eli Lilly, Takeda Pharmaceuticals North America, Merck and Company, Novartis, Novo Nordisk, and Pfizer. Dr McGuire reports having received grant/research support and/or honoraria from or having been a consultant for GlaxoSmithKline, Takeda Pharmaceuticals North America, Pfizer, and Johnson & Johnson.

References


Key Words: cardiovascular diseases ▪ diabetes mellitus ▪ drugs ▪ glucose ▪ thiazolidinediones
New Drugs for the Treatment of Diabetes Mellitus: Part I: Thiazolidinediones and Their Evolving Cardiovascular Implications
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Circulation. 2008;117:440-449
doi: 10.1161/CIRCULATIONAHA.107.704080
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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