# PPARγ Agonists and Coronary Atherosclerosis

*Melanie S. Sulistio, MD, Adrienne Zion, PhD,*
*Nandish Thukral, MD, and Robert Chilton, DO*

**Corresponding author**
Melanie S. Sulistio, MD
University of Texas Health Science Center at San Antonio, Department
of Cardiology, 7300 Medical Drive, San Antonio, TX 78229, USA.
E-mail: sulistio@uthscsa.edu

The prevalence of type 2 diabetes mellitus (T2DM) is
growing at an alarming rate and reaching epidemic
proportions, and cardiovascular disease continues to be
one of the leading causes of death in the United States.
The key relationship between these two diseases (know-
ing that T2DM is a strong risk factor for cardiovascular
disease) is insulin resistance and the detrimental effect
it has on macrovasculature. Thiazolidinediones (TZDs)
are peroxisome proliferator–activated receptor γ agonists
that are beneficial in the treatment of T2DM and have
the added benefit of modifying lipid profiles. This review
discusses the basic science linking insulin resistance to
atherosclerosis and describes the major TZD trials in the
recent literature. It also addresses the clinical implica-
tions of these studies and media scrutiny surrounding the
recent controversial report that TZDs may be linked to an
increased risk of myocardial infarction.

## Introduction

As the prevalence of obesity continues to grow, more
people will develop type 2 diabetes mellitus (T2DM).
The underpinning of this obesity and T2DM pandemic
appears to be significantly related to overeating. Without
marked lifestyle change, the ravages of diabetes and the
subsequent consequences of cardiovascular disease (CVD)
will have a strong impact on future generations. The Dia-
betes Prevention Project [1] showed that weight loss was
largely achieved through modifications in diet and exer-
cise. Over 3.2 years, a weight loss of 4.98 kg accounted
for a 55% reduction in diabetes in a population at high
risk (age > 25 years, body mass index > 24, and impaired
glucose tolerance during an oral glucose tolerance test)
[1]. Unfortunately, Americans are an impatient people
who would rather take a pill than stick with long-term
behavioral interventions. Although public health propo-
nents constantly remind the population about the negative
consequences of obesity on morbidity and mortality, the
prevalence of T2DM continues to increase.

Current treatments that specifically target glucose
are beneficial for reducing microvascular disease but
fall short in the treatment of insulin resistance, which is
a core defect of macrovascular disease. As newer agents
for insulin resistance are developed, understanding of the
physiologic processes is essential. This article reviews the
basic science linking insulin resistance to coronary artery
disease, focusing on peroxisome proliferator–activated
receptors (PPARs), and also reviews clinical trials that
have demonstrated the efficacy of PPARγ agents to reduce
endovascular disease.

The nuclear receptors constitute one of the largest
groups of transcription factors [2•,3]. Members of this
protein family have structural and functional characteris-
tics across a wide range of metazoan species. PPAR family
members regulate the expression and repression of target
genes via binding to direct repeat response elements in the
promoter region of target genes with their obligate het-
erodimeric partner, the retinoid X receptor (RXR) [3,4].
The activity of the PPAR/RXR complex is modulated by
the availability of ligands for PPAR and RXR. Potentially,
the most relevant endogenous ligands for the PPARs are
long chain fatty acids and their metabolites. However,
the specific fatty acid metabolite that serves as an endog-
enous ligand for the PPARs has yet to be fully elucidated.
When engaged by ligands, PPARs recruit transcriptional
co-activators that are necessary to initiate target gene
transcription. These co-activators usually possess histone
acetylase activity or recruit other co-activators [4].

The PPAR nuclear receptor family was named for the
ability of the original member to induce hepatic peroxi-
some proliferation in mice in response to xenobiotic
stimuli. However, studies on the action and structure
of the three human PPAR isotypes (PPARα, PPARγ,
and PPARβ/δ) suggest that PPARs are ligand-activated
transcription factors belonging to the nuclear receptor
superfamily [3]. PPARs regulate transcription of target
genes by forming heterodimers with the RXR and bind-

ing to specific PPAR response elements in the promoter region of target genes [5,6]. In the absence of ligands, PPAR/RXR heterodimers can actively repress transcription through the recruitment of co-repressor complexes that contain a nuclear receptor co-repressor and/or silencing mediator for retinoid and thyroid receptors [7]. Conversely, in the presence of ligands, PPAR/RXR heterodimers activate transcription through the recruitment of co-activator proteins. Moreover, PPARs can also repress gene expression by antagonizing the activities of other signal-dependent transcription factors, such as the proinflammatory nuclear factor (NF)-κB [8].

PPAR is expressed in human endothelial cells, monocytes, and fully differentiated macrophages. Vascular smooth muscle cells (VSMCs) may also be an important target of PPAR activators [9]. As such, PPAR activators inhibit migration of VSMCs, release of matrix-degrading enzymes [10], and expression of the angiotensin II type 1 receptor [11,12]. These effects appear to modulate fatty streak formation and potentially attenuate the arterial response to injury that occurs after coronary intervention.

## Insulin Resistance and the Role of Thiazolidinediones

Insulin resistance is widely recognized as a core physiologic defect in T2DM, the cellular etiology of which has been linked to accelerated atherosclerosis [13,14]. Thiazolidinediones (TZDs) are among the most studied agents with insulin-sensitizing effects [15], although metformin has also been shown to improve insulin sensitivity [15–17].

The effect of PPARγ activators in vascular disease has been examined in various animal models. Arslanian et al. [16] were the first to report a reduction in intimal hyperplasia following troglitazone treatment in a rat vascular injury model. The location of PPARs in human tissue was first described by Auboeuf et al. [3] in 1997 and quantified by real-time competitive polymerase chain reaction. In lean control patients, the largest tissue distribution of PPARγ was found to be in adipose tissue and the large intestine, with low levels detected in skeletal muscle. These important findings generated interest in the biologic role of PPARγ in human tissue, suggesting that PPARγ may not be a major contributor in the regulation of gene transcription in human skeletal muscle.

To date, the definitive role of PPARγ in human tissue remains unclear. One theory suggests that the beneficial effect of PPARγ agonists on peripheral insulin resistance may not be related to a direct action in muscle cells, whereas in very high adipose tissue distribution, it could exert an action directly on adipocytes, leading to improvement in muscle glucose uptake and insulin resistance [5]. However, in a mouse model deficient in adipose tissue, PPARγ ligands improved insulin sensitivity, suggesting a beneficial effect of TZDs outside adipose tissue (ie, muscle) [18]. In relation to the role of PPARγ in insulin resistance, two other important

observations should be considered. Norris et al. [19] found that insulin sensitivity in skeletal muscle was normal but impaired in the liver of mice with muscle-specific deletion of PPARγ. Hevener et al. [20] suggested that selective deletion of PPARγ in skeletal muscle caused insulin resistance in muscle. However, Auboeuf et al. [3] proposed that these apparent conflicts might have been due to different animal strains. Lastly, an independent mechanism not yet defined is plausible. It is obvious that major gaps in our understanding of the mechanistic benefits of TZDs regarding insulin resistance continue. Future research may elucidate these important pathways.

## Free Fatty Acids Modulate PPAR Activity

In addition to the properties previously discussed, free fatty acids (FFAs) have PPAR nuclear receptor ligands with associated binding properties [21]. The discovery that some FFAs can act as hormones that control transcription factor activity supports the concept that FFAs are not merely molecules providing passive energy, but metabolic regulators as well [22–24].

Circulating high plasma FFAs are known to activate PPAR nuclear receptors. High plasma circulating FFAs (frequently seen in individuals with diabetes) can increase mitochondrial uncoupling of protein levels in animals, primarily through PPARα activation. This has been correlated with low cardiac phosphocreatine to adenosine triphosphate ratios in those with diabetes and dilated cardiomyopathy, a population with a significantly higher rate of cardiovascular mortality [25].

Belfort et al. [26•] illustrated organ toxicity reversal in patients with nonalcoholic steatohepatitis, a chronic liver condition characterized by insulin resistance and hepatic fat accumulation. In that study, 55 patients with impaired glucose tolerance and T2DM were randomized to receive either 45 mg/d of pioglitazone or placebo for 28 weeks. Complex metabolic testing with liver biopsies was performed at baseline. At the conclusion of the study there was a significant improvement in liver fibrosis, with concomitant reductions in both FFA and triglyceride levels. In other clinical studies, triglyceride levels correlated with FFA levels [27]. In a small study of 15 patients with high myocardial triglyceride content, Szczepaniak et al. [28] found high triglyceride levels were correlated with elevated left ventricular mass as measured by cardiac imaging.

Recently, interest in natural ligands and PPAR modulation has increased due to greater emphasis on lifestyle behaviors as a means to reduce adiposity. Olive oil is a complex compound found in Mediterranean-type diets and is composed chiefly of fatty acids, vitamins, volatile components, water-soluble components, and microscopic bits of olive. Primary fatty acids are composed of oleic and linoleic acid, with the greater proportion given to oleic acid. The concept of PPAR activation through

fatty acids is in agreement with the idea that fatty acids provoke similar physiologic actions as peroxisomal proliferators (ie, they lower serum triglycerides) [29]. Resting metabolic rate, assessed via total-body oxygen consumption, was significantly higher in rats fed olive oil compared with those fed oil not containing olive [30].

## Influence of PPARs in Atherosclerosis

The mechanisms responsible for coronary artery disease in obesity are complex. Excessive lipid accumulation within the myocardium has been found to be cardiotoxic in animal models. For example, in a study with obese rats, intracellular accumulation of triglycerides caused myocardial dysfunction [16,31]. Efforts are underway to evaluate whether cardiac lipotoxicity in human obesity and T2DM is of clinical importance, and whether it could be reversed with the use of a TZD (ie, PPARγ agonist).

The PPAR receptor family of transcription factors controls the expression of key genes involved in the regulation of metabolism, inflammation, and thrombosis, which are integral components in the development of atherosclerosis. At the core of atherosclerosis is inflammation that begins early and is amplified by classical risk factors. The role of PPAR agonists in atherosclerosis was first studied in detail by Collins et al. [32] using the TZD troglitazone in low-density lipoprotein receptor-deficient mice, both with and without diabetes. In mice receiving TZD, aortic atherosclerosis was significantly reduced compared with those receiving placebo.

Originally derived from bench research in macrophages, the role of PPARs in vascular biology is central to understanding the relationship between plaque rupture and atherosclerosis in humans. PPARγ has important clinical effects related to lipid and glucose metabolism [33]. PPARγ can manage metabolism from the cell nucleus; it is a ligand-activated transcription factor and belongs to the nuclear receptor superfamily. PPARs regulate transcription of target genes responsible for producing active proteins with important metabolic effects throughout the body. In T2DM, PPARγ reduces glucose due to its insulin-sensitizing effects through increased cellular glucose uptake, reduced hepatic glucose, and modified lipid metabolism [15,16]. Once the PPAR ligand is activated, it can repress gene expression by antagonizing proinflammatory transcription factors, such as NF-κB [34–36]. PPARγ has other important effects, including the reductions of inducible nitric oxide (NO) synthase expression, matrix metalloproteinase, and multiple interleukin expression (released by macrophages). It increases endothelial NO production without changing endothelial NO synthase expression by modulating endothelial NO synthase phosphorylation [37–39].

Atherosclerotic coronary vascular disease is a complication of insulin resistance syndrome. This syndrome is found not only in individuals with T2DM, but in patients with other conditions without diabetes. Insulin-sensitizing drugs (ie, TZDs) can significantly improve insulin resistance by improving metabolic and cellular changes in vascular tissue that expresses PPARs. PPARγ nuclear receptors are expressed in endothelial cells, macrophages, and vascular smooth muscle cells [40]. The PPARγ agonist inhibits inflammatory processes, including cytokine production and expression of NO synthase in vascular beds [37,41]. Chen et al. [42] studied how apolipoprotein E (apoE)–knockout mice fed a Western-type diet with troglitazone for 2 months compared with mice given a placebo. Troglitazone significantly increased scavenger receptor expression for oxidized low-density lipoprotein in macrophage foam cells. It further reduced fatty streak lesion formation by modulating metabolic extracellular environments and arterial wall cell functions. As the authors suggest, other factors may explain the antiatherogenic effects of troglitazone, such as the anti-inflammatory effects of PPARs in tandem with cell adhesion inhibition, increasing high-density lipoprotein cholesterol, and antioxidation [17].

## Effect of PPARs on Glucose Metabolism, Lipids, and Insulin Resistance

PPAR agonists are a relatively new class of therapeutic agents for the treatment of dysglycemia associated with T2DM. Evidence has shown they improve insulin sensitivity in muscle, liver, and fat at the cellular level, resulting in lowered hyperglycemia in individuals with diabetes [19,32]. On average, TZDs lower glycosylated hemoglobin approximately 0.8% to 1.2%. Effects on lipids have been more difficult to analyze, in part because TZDs do not share all metabolic characteristics but do share some glucose-lowering effects. This may be explained to some extent by the different effects of each compound on nuclear transcriptional factors (selective PPARγ modulators) that regulate gene expression relevant to metabolism. Nagashima et al. [43] evaluated changes in lipoprotein metabolism in T2DM patients receiving pioglitazone and proposed two major reasons for the lower triglyceride levels observed in the group receiving pioglitazone. First, an increase in the fractional clearance rate of very low-density lipoprotein (VLDL) triglycerides from the circulation without changing direct removal of VLDL particles was observed. Secondly, there was a concomitant increased inhibition of apoC-III production rates. The reduction in triglyceride levels attributed to pioglitazone was most likely due to an increase in fractional clearance rate of VLDL triglycerides caused by lipoprotein lipase–mediated lipolysis. This important clinical research elucidated some of the metabolic-lowering effects of TZDs on triglycerides seen in the large trial completed by Goldberg et al. [44]. The trial found that pioglitazone reduced triglycerides by 51.9 mg/dL and rosiglitazone increased them by 13 mg/dL ($P < 0.001$ between treatments), thus having significantly

different effects on plasma lipids independent of glycemic control or concomitant lipid lowering. Triglyceride elevations are clinically important for at least two reasons. First, there is increased atherogenic risk in patients with small, dense low-density lipoprotein particles frequently manifested by high triglycerides and low high-density lipoprotein. Secondly, Ting et al. [45•] demonstrated that high triglycerides activate inflammatory vascular cell processes. Triglyceride-rich lipoproteins alone did not elicit inflammation in human aortic endothelial cells; however, significant benefits in the inflammatory response through a 10-fold increase in cytokine stimulation occurred with the addition of triglyceride-rich lipoproteins. In another study, Dichtl et al. [8] found triglyceride-rich VLDL activated a key transcriptional regulator of NF-κB and activator protein. Lastly, Nordestgaard et al. [46] completed follow-up on a prospective cohort study involving 13,981 men and women in Copenhagen, Denmark who were followed for 26 years (1978–2004). They found that increased nonfasting triglyceride levels were significantly (age and multifactorally adjusted hazard ratios) associated with increased risk of myocardial infarction (MI), ischemic heart disease, and death [46].

## Recent Large Trials of T2DM and Impaired Fasting Glucose

Four large TZD trials account for the largest databases for treatment of T2DM and impaired fasting glucose: one studied the effects of pioglitazone and the other three studied the effects of rosiglitazone.

### PROactive

The landmark Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive) study [47•] was one of the most controversial trials in recent years. It was designed to assess secondary prevention in patients with T2DM using the TZD pioglitazone (highest tolerated dose up to 45 mg) in comparison with other hypoglycemic agents. The primary end point was complex and included procedurally related end points. The trial enrolled 5238 patients with T2DM with a 34-month follow-up. The primary end point was not significant (hazard ratio [HR] of 0.90; 95% CI, 0.80–1.02; $P = 0.095$ with a trend toward the TZD treatment). It included first occurrence of any of the events in the following composite: all-cause mortality; nonfatal MI; acute coronary syndromes; cardiac intervention, including coronary artery bypass graft, or percutaneous coronary intervention; stroke; major leg amputation (above the ankle); bypass surgery; or revascularization in the leg. Examining the actual number of patients in the primary end point groups, atherosclerosis was most advanced in the group receiving pioglitazone. With regard to the secondary end point, 301 patients reached the secondary end point (composite of all-cause mortality, nonfatal MI, and stroke) compared with 358

in the placebo group (HR of 0.84; 95% CI, 0.72–0.98; $P = 0.027$). It should be noted that the patients enrolled in the study continued a regimen of standard drug treatments for CVD (more than half of the patients had already experienced an MI or stroke) in this high-risk group of T2DM patients.

One of the most interesting findings of the PROactive substudy analysis was the inclusion of patients with previous stroke; 486 patients were enrolled in the pioglitazone group and 498 in the placebo group. In secondary prevention of fatal or nonfatal stroke, incidence was significantly reduced with pioglitazone (HR of 0.53; event rate of 5.6% for pioglitazone compared with 10.2% for placebo; 95% CI, 0.34–0.85; $P < 0.0085$), and cardiovascular death, nonfatal MI, or nonfatal stroke was reduced as well (HR of 0.72; event rate of 13.0% for pioglitazone vs 17.7% for placebo; 95% CI, 0.52–1.00; $P < 0.0467$). Secondary prevention of stroke carried a relative risk reduction of 47%. Thus, no benefits were observed in the primary prevention of stroke in this trial [19]. On closer examination of the number of patients with T2DM treated with pioglitazone, fewer cardiovascular events are revealed. Although the statistics related to the primary end point make this a negative trial, one must consider the importance of the role that standard-of-care treatments, including statins, acetylsalicylic acid, and angiotensin receptor inhibitors, on top of pioglitazone may have in reducing cardiovascular events in this high-risk patient population.

### DREAM

The next large trial was Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications (DREAM) [48]. Patients aged 30 years or older with impaired fasting glucose, impaired glucose tolerance, or both and no previous CVD were enrolled ($n = 5269$). Patients were randomly assigned to receive 4 mg/d of rosiglitazone for the first 4 months, which was then titrated to 8 mg/d thereafter in this 2 x 2 factorial design. Patients were concurrently assigned to treatment with 15 mg/d of ramipril or placebo. The primary end point was incident diabetes or death from any cause during the active-treatment period. The mean age of participants was 54 years, and all were followed for 3 years. There were 306 patients (11.6%) in the rosiglitazone group and 686 patients (26.0%) in the placebo group who developed the composite primary end point (HR of 0.40; 95% CI, 0.35–0.46; $P < 0.0001$). Of the patients who became normoglycemic, 1330 (50.5%) were in the rosiglitazone group compared with 798 (30.3%) in the placebo group (HR of 1.71; 95% CI, 1.57–1.87; $P < 0.0001$).

*Applying these results to clinical practice*

For most cardiologists, one of the biggest questions is whether glucose-lowering agents such as the TZDs prevent hard cardiovascular end points. Certainly, the Heart Outcomes Prevention Evaluation (HOPE) study [49•] dem-

**Table 1. Results of the DREAM study**

| Drug regimen | Patients, n | MI, n (%) | CV death, n (%) |
|---|---|---|---|
| Placebo + placebo | 1321 | 6 (0.5) | 5 (0.4) |
| Rosiglitazone + placebo | 1325 | 5 (0.4) | 5 (0.4) |
| Ramipril + placebo | 1313 | 3 (0.2) | 5 (0.4) |
| Rosiglitazone + ramipril | 1310 | 11 (0.8) | 7 (0.5) |

CV—cardiovascular; DREAM—Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; MI—myocardial infarction.

onstrated that ramipril clearly reduces cardiovascular events. However, the high dose of 15 mg/d of ramipril has provoked questions. Data regarding the relationship of cardiovascular end points to the specific arms representing either ramipril or rosiglitazone alone have until recently only been available from Krall [49•]. In Krall's analysis, the number of patients developing MI is reported as follows: placebo/placebo arm, six patients; rosiglitazone/placebo arm, five patients; ramipril/placebo arm, three patients. The surprise was the increase in MIs when rosiglitazone was added to ramipril ($n = 11$) (Table 1). The causes remain unexplained, but several possibilities should be examined. These results may have occurred simply by chance or possibly by synergistic activity between rosiglitazone and ramipril, which magnified MI rates. Each of the different composite cardiovascular end points produced the most events, with the combination of rosiglitazone/ramipril topping the list. Clearly, more information is required to answer these questions.

**ADOPT**
A Diabetes Outcome Progression Trial (ADOPT) [50] was a 4- to 6-year study of glycemic durability in 4360 people recently diagnosed with T2DM. Patients were randomly assigned to monotherapy with rosiglitazone, metformin, or glibenclamide for a median of 4 years. The primary end point of the study was the time from randomization to treatment failure, which was defined as confirmed hyperglycemia (fasting plasma glucose levels > 180 mg/dL). The cumulative incidence of treatment failure at 5 years was 15% with rosiglitazone, 21% with metformin, and 34% with glibenclamide. However, if fasting plasma glucose levels greater than 140 mg/dL were used as a cut-off, it could be assumed that the results would be similar. Focusing on cardiovascular events during this trial, new data have shown that during the 4- to 6-year follow-up there were 24 (1.6%) serious adverse events in the rosiglitazone arm, 20 (1.4%) in the metformin arm, and 14 (0.009%) in the glibenclamide arm.

**RECORD**
The latest trial assessing cardiovascular end points is Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) [51]. RECORD is still not completed but has enrolled 4447 patients with T2DM in an open-label, 6-year cardiovascular outcomes trial (with prospectively defined cardiovascular end points) that started in 2000. Interim analysis of unblinded cardiovascular end points with a mean follow-up of 3.75 years did not reveal significant differences between rosiglitazone and the control group regarding MI and death. There were 43 acute MIs in the rosiglitazone arm and 37 in the control arm ($P < 0.50$).

*Applying these results to clinical practice*
The only secondary prevention trial in T2DM is PROactive. RECORD and ADOPT are primary prevention trials.

In spite of recent concerns about overall safety, PPAR agonists appear to maintain promise as a cardiovascular therapeutic; however, larger well-designed studies will undoubtedly clarify many issues. Safe and effective agents that control glucose in T2DM and reduce cardiovascular events would be a welcome addition to this dormant cardiovascular medication arena.

## PPARs and Surrogate Cardiovascular End Points
PPARs have recently been studied in the carotid artery by ultrasound to assess their potential benefit on atherosclerosis. Few small trials with TZDs have been done over the past decade. The largest study to date is the Carotid Intimal-medial Thickness in Atherosclerosis using Pioglitazone (CHICAGO) trial [52•]. This was a randomized, double-blind, multicenter trial comparing pioglitazone hydrochloride (15–45 mg/d) or glimepiride (1–4 mg/d) in 462 patients with T2DM who were randomized to two glycemic treatment arms over 18 months. Carotid artery intima-media thickness (CIMT) images were examined by a single ultrasonographer at one center and read by a single treatment-blinded reader using automated edge-detection technology. The primary outcome was the absolute change from baseline to final visit in mean posterior wall CIMT of the left and right common carotid arteries. The primary outcome at 72 weeks revealed less progression of mean CIMT with pioglitazone versus glimepiride ($P < 0.02$). Several points regarding atherosclerosis progression, high-density lipoprotein cholesterol, triglycerides, and cardiovascular end points require comments. There was less atherosclerosis progression in the TZD group than in the glimepiride arms of the study over 4 weeks. Furthermore, glucose control was not as good in the glimepiride arm compared with the pioglitazone group over 18 months. This reflects a common observation in clinical practice with these two agents. The second point is the significant increase in high-density lipoprotein cholesterol levels in the pioglitazone group, which could have had a significant effect on the progression of CIMT. Another significant change was in triglyceride levels (which decreased

13.5% in the pioglitazone group and increased 2.1% in the glimepiride arm; $P < 0.001$). Lastly, if one combines cardiovascular mortality, nonfatal MI, nonfatal stroke, coronary revascularization, carotid endarterectomy/ stenting, hospitalization for unstable angina, and hospitalization for heart failure, there were fewer patients in the pioglitazone-treatment group ($n = 4$) than in the group receiving glimepiride ($n = 10$). Although not statistically significant, this point again raises the question about the potential cardiovascular benefits of TZDs.

## PPAR Agents, Restenosis, and Coronary Artery Stenting

Only a few small trials involving coronary stents and TZDs have been performed. In one very tightly controlled study by Takagi et al. [53], bare metal stents were evaluated by intravascular ultrasound over a period of 6 months in 44 patients with T2DM. Patients were randomized to a pioglitazone-treatment group or placebo group. Multiple image slices within the stent were obtained every 1 mm. The stent area and lumen area were measured and the neointimal area was calculated. Measurements were averaged over the number of selected image slices. The neointimal index was calculated as the averaged neointimal area divided by the averaged stent area multiplied by 100 (and expressed as a percentage). Baseline characteristics were similar, with a significantly higher use of acarbose in the control arm. The most common stent used was an NIR (Medinol; Boston Scientific, Tel Aviv, Israel), placed at 10 atmospheres. The stent length was 15 mm, with reference vessel of 2.8 mm. The postprocedure minimal lumen diameter was 2.6 mm for TZD and 2.7 mm for placebo. Flow at the minimal lumen diameter at 6 months was 2.0 mm for TZD and 1.5 mm for placebo ($P < 0.006$). The neointimal index in the pioglitazone group was significantly smaller than that in the control group ($28\% \pm 9\%$ vs $48\% \pm 15\%$, respectively; $P < 0.0001$).

In another prospective, randomized, case-controlled trial involving 95 patients with diabetes and coronary artery disease randomly assigned to a control or rosiglitazone group (48 and 47 patients, respectively), Choi et al. [54] used quantitative coronary angiography to assess restenosis rate at study entry and again at 6-month follow-up. Intravascular ultrasound was not used. Patients underwent quantitative coronary angiography at study entry and again at 6 months and were assigned to either control or rosiglitazone groups (8 mg before undergoing catheterization and 4 mg/d thereafter). Stent diameter was 3.2 mm and length was 18 mm. At 6-month angiographic follow-up, the diameter of stenosis increased by 23% in the TZD arm and 40% in the placebo arm ($P < 0.004$).

Both of these small trials in patients with T2DM and bare metal stents reveal a significant reduction in in-stent restenosis with the use of TZDs. However, due to design limitations in trial length and inadequate sample size, potential cardiovascular event reductions were not observed.

## TZDs in the Media and Regulatory Implications

TZDs have received much attention recently in the scientific literature and lay press. Nissen and Wolski [55] purported that the incidence of MI was increased in individuals with T2DM who were taking rosiglitazone. As expected, an outcry ensued, with patients urgently calling their physicians and asking if they should discontinue their therapy. Within the medical community, it resulted in a series of debates as to the type of statistical analysis used in the report, the way it was reported, the relevance of the data that were included, and more importantly, those that were excluded. A special session by the US Food and Drug Administration (FDA) was held to study the validity of the implications from this meta-analysis. The results of the FDA hearing did not support those reported by Nissen and Wolski, and the FDA released a special report to physicians and placed a boxed warning on the risks of heart failure for the entire TZD class of antidiabetes drugs: "This class includes Avandia (rosiglitazone), Actos (pioglitazone), Avandaryl (rosiglitazone and glimepiride), Avandamet (rosiglitazone and metformin), and Duetact (pioglitazone and glimepride)." It was also recommended that these drugs not be used by individuals with serious or severe heart failure who have marked limits on their activity and who are comfortable only at rest or who are confined to either a bed or chair. Accordingly, physicians were warned that patients prescribed this class of agents should be carefully monitored for signs and symptoms of heart failure, including excessive and rapid weight gain, shortness of breath, and edema, after starting drug therapy. As with any standard of care, medical vigilance is always necessary and risk ratios must be considered when tailoring treatment to individual prescriptions.

## Conclusions

As with all prescription medications, careful selection of patients and close observation for adverse effects are paramount. Clearly, from a purely basic science view, TZDs warrant strong consideration in patients with diabetes and atherosclerosis. Clinically, this class of compounds has significant advantages for glucose control in patients, with potential for β-cell preservation. Another frequently overlooked aspect in the treatment of T2DM is the rarity of hypoglycemia in patients treated with TZDs unless they are combined with an insulin secretagogue or insulin. However, concerns such as heart failure, MI, and increased risk of bone fracture continue to plague the TZD class. The question of whether cardiovascular side effects vary by agent between the classes will require more research to answer. At present and based on existing

data, pioglitazone may have fewer cardiovascular risks and more potential benefits for patients with T2DM.

## Disclosures

Dr. Chilton has received money from or conducted work for Bristol-Myers Squibb, Pfizer, GlaxoSmithKline, Takada, and Merck Sharp & Dohme. The other authors report no potential conflicts of interest relevant to this article.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Hamman RF, Wing RR, Edelstein SL, et al.: **Effect of weight loss with lifestyle intervention on risk of diabetes.** *Diabetes Care* 2006, **29:**2102–2107.
2.• Semple RK, Chaterjee VK, O'Rahilly S: **PPARa and human metabolic disease.** *J Clin Invest* 2006, **116:**581–589.
This is an excellent article that discusses in detail the metabolism of PPAR in humans.
3. Auboeuf D, Rieusset J, Fajas L, et al.: **Tissue distribution and quantification of the expression of mRNAs of peroxisome proliferator-activated receptors and liver X receptor-alpha in humans: no alteration in adipose tissue of obese and NIDDM patients.** *Diabetes* 1997, **46:**1319–1327.
4. Finck BN: **The PPAR regulatory system in cardiac physiology and disease.** *Cardiovasc Res* 2007, **73:**269–277.
5. Gearing KL, Göttlicher M, Teboul M, et al.: **Interaction of the peroxisome-proliferator-activated receptor and retinoid X receptor.** *Proc Natl Acad Sci U S A* 1993, **90:**1440–1444.
6. Tugwood JD, Issemann I, Anderson RG, et al.: **The mouse peroxisome proliferator activated receptor recognizes a response element in the 5' flanking sequence of the rat acyl CoA oxidase gene.** *EMBO J* 1992, **2:**433–439.
7. Krogsdam AM, Nielsen CA, Neve S, et al.: **Nuclear receptor corepressor-dependent repression of peroxisome-proliferator-activated receptor delta-mediated transactivation.** *Biochem J* 2002, **363(Pt 1):**157–165.
8. Dichtl W, Nilsson L, Goncalves I, et al.: **Very low-density lipoprotein activates nuclear factor-kappaB in endothelial cells.** *Circ Res* 1999, **84:**1085–1094.
9. Ricote M, Li AC, Willson TM, et al.: **The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation.** *Nature* 1998, **391:**79–82.
10. Marx N, Schönbeck U, Lazar MA, et al.: **Peroxisome proliferator-activated receptor gamma activators inhibit gene expression and migration in human vascular smooth muscle cells.** *Circ Res* 1998, **83:**1097–103.
11. Takeda K, Ichiki T, Tokunou T, et al.: **Peroxisome proliferator-activated receptor gamma activators downregulate angiotensin II type 1 receptor in vascular smooth muscle cells.** *Circulation* 2000, **102:**1834–1839.
12. Goetze S, Xi XP, Graf K, et al.: **Troglitazone inhibits angiotensin II-induced extracellular signal-regulated kinase 1/2 nuclear translocation and activation in vascular smooth muscle cells.** *FEBS Lett* 1999, **452:**277–282.
13. Wang CC, Goalstone ML, Draznin B: **Molecular mechanisms of insulin resistance that impact cardiovascular biology.** *Diabetes* 2004, **53:**2735–2740.
14. Hsueh WA, Law RE: **Insulin signaling in the arterial wall.** *Am J Cardiol* 1999, **84(1A):**21J–24J.
15. Miyazaki Y, He H, Mandarino LJ, et al.: **Rosiglitazone improves downstream insulin receptor signaling in type 2 diabetic patients.** *Diabetes* 2003, **52:**1943–1950.
16. Arslanian SA, Lewy V, Danadian K, et al.: **Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance.** *J Clin Endocrinol Metab* 2002, **87:**1555–1559.
17. Bailey CJ, Turner RC: **Metformin.** *N Engl J Med* 1996, **334:**574–579.
18. Kim JK, Fillmore JJ, Gavrilova O, et al.: **Differential effects of rosiglitazone on skeletal muscle and liver insulin resistance in A-ZIP/F-1 fatless mice.** *Diabetes* 2003, **52:**1311–1318.
19. Norris AW, Chen L, Fisher SJ, et al.: **Muscle-specific PPARgamma-deficient mice develop increased adiposity and insulin resistance but respond to thiazolidinediones.** *J Clin Invest* 2003, **112:**608–618.
20. Hevener AL, He W, Barak Y, et al.: **Muscle-specific PPARg deletion causes insulin resistance.** *Nat Med* 2003, **9:**1491–1497.
21. Sethi S, Eastman AY, Eaton JW: **Inhibition of phagocyte-endothelium interactions by oxidized fatty acids: a natural anti-inflammatory mechanism?** *J Lab Clin Med* 1996, **128:**27–38.
22. Sethi S, Ziouzenkova O, Ni H, et al.: **Oxidized omega-3 fatty acids in fish oil inhibit leukocyte-endothelial interactions through activation of PPAR alpha.** *Blood* 2002, **100:**1340–1346.
23. Nohé B, Johannes T, Dieterich HJ: **Antiinflammatory effects of omega-3 fatty acids vary at different stages of inflammation.** *Am J Physiol Heart Circ Physiol* 2003, **285:**H2248–H2249.
24. Murray AJ, Panagia M, Hauton D, et al.: **Plasma free fatty acids and peroxisome proliferator-activated receptor alpha in the control of myocardial uncoupling protein levels.** *Diabetes* 2005, **54:**3496–3502.
25. Neubauer S, Horn M, Cramer M, et al.: **Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy.** *Circulation* 1997, **96:**2190–2196.
26.• Belfort R, Harrison SA, Brown K, et al.: **A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis.** *N Engl J Med* 2006, **355:**2297–2307.
This paper examines the use of TZDs and their beneficial effects on organ lipotoxicity.
27. Schlierf G, Dorow E: **Diurnal patterns of triglycerides, free fatty acids, blood sugar, and insulin during carbohydrate-induction in man and their modification by nocturnal suppression of lipolysis.** *J Clin Invest* 1973, **52:**732–740.
28. Szczepaniak LS, Dobbins RL, Metzger GJ, et al.: **Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging.** *Magn Reson Med* 2003, **49(3):**417–423.
29. Bocos C, Göttlicher M, Gearing K, et al.: **Fatty acid activation of peroxisome proliferator-activated receptor (PPAR).** *J Steroid Biochem Mol Biol* 1995, **53(1–6):**467–473.
30. Rodríguez VM, Portillo MP, Picó C, et al.: **Olive oil feeding up-regulates uncoupling protein genes in rat brown adipose tissue and skeletal muscle.** *Am J Clin Nutr* 2002, **75:**213–220.
31. McGavock JM, Victor RG, Unger RH, et al.: **Adiposity of the heart, revisited.** *Ann Intern Med* 2006, **144:**517–524.
32. Collins AR, Meehan WP, Kintscher U, et al.: **Troglitazone inhibits formation of early atherosclerotic lesions in diabetic and nondiabetic low density lipoprotein receptor-deficient mice.** *Arterioscler Thromb Vasc Biol* 2001, **21:**365–371.
33. Zierath JR, Ryder JW, Doebber T, et al.: **Role of skeletal muscle in thiazolidinedione insulin sensitizer (PPARgamma agonist) action.** *Endocrinology* 1998, **139:**5034–5041.
34. Kim SY, Kim HI, Park SK, et al.: **Liver glucokinase can be activated by peroxisome proliferator-activated receptor-gamma.** *Diabetes* 2004, **53(Suppl 1):**S66–S70.

35. Delerive P, De Bosscher K, Besnard S, et al.: **Peroxisome proliferator-activated receptor alpha negatively regulates the vascular inflammatory gene response by negative crosstalk with transcription factors NF-kappaB and AP-1.** *J Biol Chem* 1999, **274**:32048–32054.

36. de Winther MP, Kanters E, Kraal G, et al.: **Nuclear factor kappaB signaling in atherogenesis.** *Arterioscler Thromb Vasc Biol* 2005, **25**:904–914.

37. Calnek DS, Mazzella L, Roser S, et al.: **Peroxisome proliferator-activated receptor gamma ligands increase release of nitric oxide from endothelial cells.** *Arterioscler Thromb Vasc Biol* 2003, **23**:52–57.

38. Daynes RA, Jones DC.: **Emerging roles of PPARs in inflammation and immunity.** *Nat Rev Immunol* 2002, **2**:748–759.

39. Delerive P, Fruchart JC, Staels B: **Peroxisome proliferator-activated receptors in inflammation control.** *J Endocrinol* 2001, **169**:453–459.

40. Ricote M, Li AC, Willson TM, et al.: **The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation.** *Nature* 1998, **391**:79–82.

41. Pasceri V, Wu HD, Willerson JT, et al.: **Modulation of vascular inflammation in vitro and in vivo by peroxisome proliferator-activated receptor-gamma activators.** *Circulation* 2000, **101**:235–248.

42. Chen Z, Ishibashi S, Perrey S, et al.: **Troglitazone inhibits atherosclerosis in apolipoprotein E-knockout mice: pleiotropic effects on CD36 expression and HDL.** *Arterioscler Thromb Vasc Biol* 2001, **21**:372–377.

43. Nagashima K, Lopez C, Donovan D, et al.: **Effects of the PPARgamma agonist pioglitazone on lipoprotein metabolism in patients with type 2 diabetes mellitus.** *J Clin Invest* 2005, **115**:1323–1332.

44. Goldberg RB, Kendall DM, Deeg MA, et al.: **A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia.** *Diabetes Care* 2005, **28**:1547–1554.

45.• Ting HJ, Stice JP, Schaff UY, et al.: **Triglyceride-rich lipoproteins prime aortic endothelium for an enhanced inflammatory response to tumor necrosis factor-alpha.** *Circ Res* 2007, **100**:381–390.
This article revealed the marked amplification of inflammatory signals with triglycerides.

46. Nordestgaard BG, Benn M, Schnohr P, et al.: **Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women.** *JAMA* 2007, **298**:299–308.

47.• Wilcox R, Bousser MG, Betteridge DJ, et al.: **Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04).** *Stroke* 2007, **38**:865–873.
This study shows a significant benefit for secondary prevention of stroke in patients with T2DM when pioglitazone is used in conjunction with standard medical therapy for cardiovascular disease.

48. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators: **Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial.** *Lancet* 2006, **368**:1096–1105.

49.• Krall RL: **Cardiovascular safety of rosiglitazone.** *Lancet* 2007, **369**:1995–1996.
This article adds key information related to rosiglitazone trials not seen in other publications.

50. Kahn SE, Haffner SM, Heise MA, et al.: **Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy.** *N Engl J Med* 2006, **355**:2427–2443.

51. Home PD, Pocock SJ, Beck-Nielsen H, et al.: **Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD): study design and protocol.** *Diabetologia* 2005, **48**:1726–1735.

52.• Mazzone T, Meyer PM, Feinstein SB, et al.: **Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial.** *JAMA* 2006, **296**:2572–2581.
This study highlights the benefits of TZD therapy over glimepiride. There was statistically significant improvement in both serum triglyceride and high-density lipoprotein cholesterol concentrations, overall improved glycemic control, and slowed progression of atherosclerosis as measured by CIMT. Additionally, a trend toward improved cardiovascular outcomes was seen in the TZD group.

53. Takagi T, Yamamuro A, Tamita K, et al.: **Pioglitazone reduces neointimal tissue proliferation after coronary stent implantation in patients with type 2 diabetes mellitus: an intravascular ultrasound scanning study.** *Am Heart J* 2003, **146**:E5.

54. Choi D, Kim SK, Choi SH, et al.: **Preventative effects of rosiglitazone on restenosis after coronary stent implantation in patients with type 2 diabetes.** *Diabetes Care* 2004, **27**:2654–2660.

55. Nissen SE, Wolski K: **Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes.** *N Engl J Med* 2007, **356**:2457–2471.