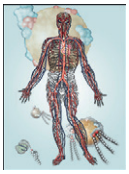

Thematic Review Series: New Lipid and Lipoprotein Targets for the Treatment of Cardiometabolic Diseases

PPAR-γ as a therapeutic target in cardiovascular disease: evidence and uncertainty

Janice V. Huang, Clifford R. Greyson, and Gregory G. Schwartz[1]

Cardiology Section, Denver VA Medical Center, US Department of Veterans Affairs, Denver, CO; and School of Medicine, University of Colorado, Denver, CO

Abstract Peroxisome proliferator-activated receptor γ (PPAR-γ) is a key regulator of fatty acid metabolism, promoting its storage in adipose tissue and reducing circulating concentrations of free fatty acids. Activation of PPAR-γ has favorable effects on measures of adipocyte function, insulin sensitivity, lipoprotein metabolism, and vascular structure and function. Despite these effects, clinical trials of thiazolidinedione PPAR-γ activators have not provided conclusive evidence that they reduce cardiovascular morbidity and mortality. The apparent disparity between effects on laboratory measurements and clinical outcomes may be related to limitations of clinical trials, adverse effects of PPAR-γ activation, or off-target effects of thiazolidinedione agents. This review addresses these issues from a clinician's perspective and highlights several ongoing clinical trials that may help to clarify the therapeutic role of PPAR-γ activators in cardiovascular disease.—Huang, J. V., C. R. Greyson, and G. G. Schwartz. **PPAR-γ as a therapeutic target in cardiovascular disease: evidence and uncertainty. *J. Lipid Res.* 2012.** 53: **1738–1754.**

Supplementary key words peroxisome proliferator-activated receptor gamma • diabetes • insulin resistance • fatty acids • atherosclerosis • randomized clinical trials

The nuclear transcription factor peroxisome proliferator-activated receptor γ (PPAR-γ) is highly expressed in adipose tissue and plays a central role in adipocyte function, fat storage, and lipid metabolism (1–4). PPAR-γ activators are commonly used to treat patients with type 2 diabetes who share metabolic abnormalities that include excessive and inflamed adipose tissue (5), particularly in visceral depots (6); elevated circulating concentrations of nonesterified fatty acids (NEFA), triglycerides, glucose, insulin, and inflammatory mediators; and reduced concentrations of adiponectin and high-density lipoprotein cholesterol (HDL-C). Each of these abnormalities is associated with and may contribute to increased cardiovascular risk (7–9).

PPAR-γ promotes adipogenesis in subcutaneous fat, stimulating the differentiation of preadipocytes into adipocytes with capacity for incremental lipid filling (1, 2). Consequently, treatment with a PPAR-γ activator shifts fat stores toward subcutaneous adipose tissue and away from visceral adipose tissue (**Fig. 1**), liver, and skeletal muscle cells (10–14). The resulting metabolic effects, discussed below, include enhanced insulin sensitivity; improved glycemic control; decreased plasma NEFA, triglycerides, and inflammatory markers; and increased plasma adiponectin and HDL-C (15–17). Moreover, both experimental and clinical evidence indicate that PPAR-γ mobilizes endothelial progenitor cells, promotes vascular endothelial repair, improves endothelium-mediated vasodilator function, decreases vascular smooth muscle proliferation, lowers blood pressure, retards the progression of atherosclerosis, and mitigates ischemia/reperfusion injury (18–21).

This portfolio of metabolic and vascular effects would lead to a reasonable expectation that treatment with a PPAR-γ activator would have substantial, favorable effects on cardiovascular morbidity and mortality. However, evidence from clinical trials conducted to date has not substantiated this prediction, possibly because other, undesirable cardiovascular actions of PPAR-γ mitigate its beneficial effects. For example, renal salt and water retention may cause intravascular and extracellular volume expansion, edema, and risk of congestive heart failure (22); increased adipose tissue mass contributes to weight gain (13); some

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Abbreviations: ACS, acute coronary syndrome; CDK, cyclin-dependent kinase; CHD, coronary heart disease; cIMT, carotid intima-media thickness; CV, cardiovascular; EPC, endothelial progenitor cell; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MI, acute myocardial infarction; PPAR-γ, peroxisome proliferator-activated receptor γ; TZD, thiazolidinedione.

[1]To whom correspondence should be addressed.
e-mail: Gregory.Schwartz@va.gov

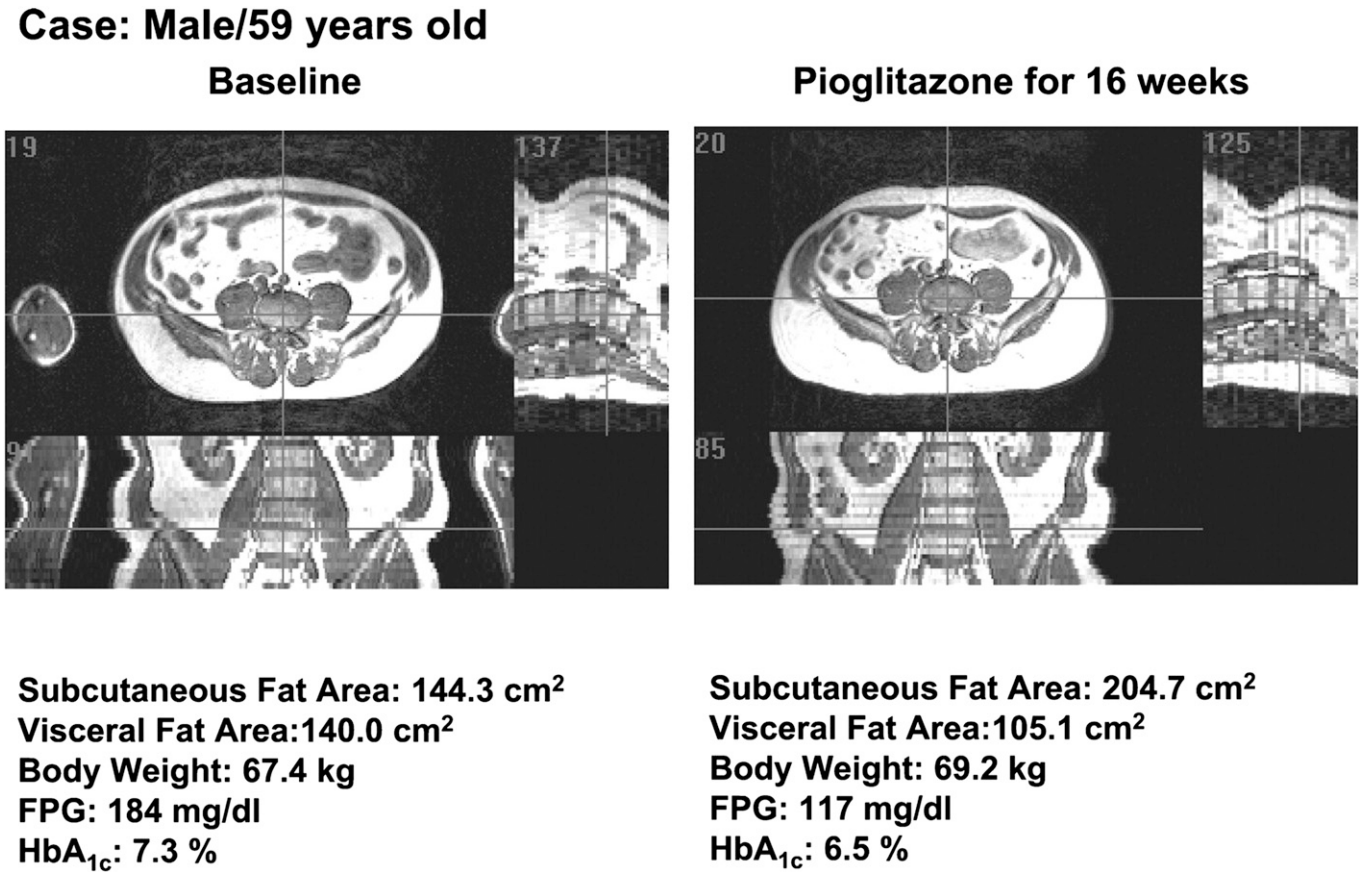

Fig. 1. Changes in body fat distribution induced by short-term treatment with thiazolidinedione. MRI images demonstrating changes in visceral and subcutaneous abdominal fat depots with 16 weeks of treatment with pioglitazone in a 59-year-old individual with type 2 diabetes. Transverse (left upper), sagittal (right upper), and coronal (left lower) views show that pioglitazone increased subcutaneous fat and decreased visceral fat, with increased total body weight. Reproduced from Ref. 13 with permission.

PPAR-γ activators may increase concentrations of low density lipoprotein cholesterol (LDL-C) (23); and in vitro and animal studies suggest that thiazolidinedione (TZD) PPAR-γ activators may interact with cardiac ion channels to promote arrhythmias (24–26). While some studies have shown that PPAR-γ activation retards atherosclerosis (18), others have indicated a greater propensity for plaque necrosis (27, 28). Thus, the net balance of favorable and unfavorable effects of PPAR-γ activation on cardiovascular outcomes remains uncertain (**Table 1**).

This article reviews metabolic and cardiovascular effects of PPAR-γ activation that might influence cardiovascular outcomes, in juxtaposition to the results of major completed clinical trials and observational studies of TZD drugs. Key questions are posed for ongoing and future clinical investigation of PPAR-γ as a therapeutic target in cardiovascular disease.

BLOOD GLUCOSE AND INSULIN SENSITIVITY

Experimental and clinical data from transgenic animal models and studies in patients with dominant negative PPAR-γ polymorphisms indicate that the action of PPAR-γ is crucial to insulin sensitivity of adipose tissue, liver, and skeletal muscle (29–32). In clinical therapy of type 2 diabetes, the use of a TZD PPAR-γ agonist as monotherapy or add-on therapy improves insulin sensitivity, manifest by reduced fasting plasma glucose and insulin concentrations, lowering of hemoglobin A1c (HbA1c) by 0.5–1.5%, and improvement in indices of insulin sensitivity determined by euglycemic hyperinsulinemic clamp, glucose tolerance testing, or homeostasis model (33–36).

A large body of experimental evidence implicates insulin resistance as a driver of atherosclerosis (37). Insulin-resistant states, including type 2 diabetes, impaired glucose tolerance, and/or metabolic syndrome substantially increase the incident risk of cardiovascular disease and worsen the prognosis of established cardiovascular disease (38–41). The severity of hyperglycemia, marked by average HbA1c levels, correlates with the risk of macrovascular atherosclerotic events (42). However, a critical but unanswered question is whether pharmacologic treatment that increases insulin sensitivity thereby reduces cardiovascular risk. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) trial, the effect of pioglitazone on cardiovascular endpoints was not related to its effect on HbA1c (43). Several large trials in patients with type 2 diabetes found no significant difference in cardiovascular morbidity and mortality among patients treated with more intensive or less intensive glycemic control regimens

TABLE 1. Tissue-specific actions of PPAR-γ with potential to influence cardiovascular outcomes

Tissue	Favorable Effects (Refs.)	Evidence	Unfavorable Effects (Refs.)	Evidence
Arterial wall	Decrease arterial wall inflammation, retard progression of atherosclerosis (18,123–125,128–139)	E, C	Plaque hemorrhage and necrosis (27,28)	E
	Mobilize endothelial progenitor cells, promote endothelial repair, improve endohelial function (20,102–110,112,113)	E, C		
	Lower blood pressure (92–95)	C		
	Prevent vascular smooth muscle proliferation, prevent restenosis after angioplasty (115–121)	E, C		
Adipose	Redistribute mass from visceral to subcutaneous depots (1–4,12,13)	E, C	Weight gain (13,92,190,191,193)	E, C
	Anti-inflammatory (80–83)	E, C		
	Increase adiponectin secretion (17,73–75)	E, C		
	Enhance insulin sensitivity (29,30,32)	E, C		
Circulating lipids and lipoproteins	Raise HDL-C, reduce triglycerides (23,43,84,92)	C	Increase LDL-C (rosiglitazone) (23,91,193)	C
	Reduce NEFA (60,62–65,67)	C		
Liver and muscle	Reduce steatosis, enhance local and systemic insulin sensitivity (10,11,14,29,31–36)	E, C		
Kidney			Sodium and fluid retention (163,166–171)	E, C
Heart	Mitigate ischemia/reperfusion injury (140–150)	E	Congestive heart failure (22,92,94,191,193).	C
			Block cardiac ion channels, promote ischemic arrhythmias (24–26,180)	E
Brain	Reduce infarct size (156–161)	E		

C, clinical evidence; E, experimental evidence.

(44–46). The frequency of use and/or dosage of TZDs (predominantly rosiglitazone) was higher in the intensive control arms of these trials (45, 46). However, because the trials did not employ a uniform treatment regimen in each arm, but rather adjusted treatment for each patient according to HbA1c levels, the data do not elucidate the relations among TZD use, insulin sensitivity, and cardiovascular outcomes.

The BARI-2D trial took an additional step to address the hypothesis that an insulin-sensitizing treatment strategy would provide greater cardiovascular benefit than an insulin-providing strategy. It included 2,368 patients with type 2 diabetes and coronary heart disease (CHD) (47). The insulin-providing strategy utilized insulin (61% of patients) and/or sulfonylurea (52% of patients). The insulin-sensitizing strategy involved metformin (75% of patients) and/or TZD (62% of patients). In both arms, a target of HbA1c less than 7% was set. In attempting to achieve this target, there was substantial crossover use of insulin and sulfonylurea in the insulin-sensitizing arm and metformin in the insulin-providing arm. The insulin-sensitizing arm, compared with the insulin-providing arm, achieved lower mean HbA1c (7 versus 7.5%) and median fasting insulin levels (6 versus 10 μU/ml), suggesting greater insulin sensitivity, and it resulted in fewer hypoglycemic episodes. Nonetheless, after mean follow-up of 5 years, the occurrence of death, myocardial infarction (MI), or stroke was nearly identical in both arms. The results of BARI-2D do not support the conclusion that insulin sensitization reduces cardiovascular risk in type 2 diabetes. However, as with the trials discussed above, the use of multiple glycemic control agents in a nonstandardized fashion in both arms of the trial precludes inferences regarding the efficacy of TZDs or any other specific drug class.

NEFA

High plasma NEFA concentrations may be deleterious to vascular function, intermediary metabolism, and cardiovascular outcomes. At high concentrations, NEFA are toxic to endothelial cells. High circulating NEFA can cause oxidant stress and inflammatory responses in endothelium and are associated clinically with hypertension and endothelial dysfunction (48, 49). Moreover, endothelial dysfunction can be induced in normal subjects by acute elevation of circulating NEFA from infusion of triglyceride emulsion and heparin (50, 51). High NEFA levels can cause or exacerbate β cell dysfunction (52) and are central in the pathogenesis of skeletal muscle and liver insulin resistance (53) and hepatic steatosis (54). A positive feedback loop

can develop whereby insulin resistance causes NEFA levels to rise, and elevated NEFA in turn worsens insulin resistance. High levels of NEFA, particularly saturated fatty acids, may alter electrophysiologic properties of cardiac myocytes, predisposing to ventricular arrhythmias (55). Prospective studies have related high NEFA levels to risk of sudden cardiac death (56).

Plasma NEFA concentrations are elevated in patients with diabetes, insulin resistance, or metabolic syndrome. In normal subjects, fasting NEFA concentration averages 300–400 μmol/l. In patients with type 2 diabetes, NEFA concentrations are typically 50–100% higher, in the 500–800 μmol/l range (57, 58). Similar elevations are observed in nondiabetic, insulin-resistant patients (59). TZD PPAR-γ activators are among the most effective available pharmacologic agents to reduce plasma NEFA concentrations, with effects similar in magnitude to therapeutic doses of insulin (60). Decreases in NEFA are apparent as soon as 4 weeks after initiation of treatment (61). TZD drugs reduce both fasting and postprandial NEFA levels by 20–40% in both type 2 diabetic and nondiabetic, insulin-resistant subjects (11, 62, 63). Reductions in postprandial NEFA presumably reflect an improvement in adipose tissue insulin sensitivity, allowing greater insulin suppression of lipolysis. Reductions produced by rosiglitazone and pioglitazone are similar (64). Moreover, using [1-^{14}C]palmitate as a tracer, rosiglitazone was shown to reduce NEFA turnover rate by 15% in type 2 diabetic patients (62). Pioglitazone and rosiglitazone each produce 20–25% reductions in NEFA when added to sulfonylurea and/or metformin therapy in type 2 diabetes (60, 65). The effect of TZD treatment on fasting NEFA is strongly correlated with the effect of treatment on glycemic control, marked by reduction of hemoglobin A1c (66). TZDs reduce NEFA to a greater extent than metformin, sulfonylurea agents, statins, or fibrates (66–69).

ADIPONECTIN

Adipose tissue serves important autocrine, paracrine, and endocrine functions. Among its secretory products, adiponectin plays a key role in maintaining insulin sensitivity and may exert anti-inflammatory and cardioprotective effects (70). Low adiponectin levels are associated with traditional cardiovascular risk factors, including diabetes, hypertension, and dyslipidemia. Experimental administration of adiponectin improves insulin sensitivity, glycemic control and lipoprotein profile (71, 72). TZD PPAR-γ activators are the most effective class of approved drugs to raise circulating adiponectin concentrations. In patients with type 2 diabetes or other insulin-resistant conditions, TZD treatment typically produces a doubling of plasma adiponectin concentration (17, 73–75). In contrast, other antidiabetic or lipid-modifying drugs produce much smaller or no changes in adiponectin (76–79). In parallel with increased adiponectin production by adipose tissue, activation of PPAR-γ in adipocytes or in mononuclear inflammatory cells resident in adipose tissue reduces local inflammation and inhibits release of inflammatory mediators from adipose tissue (80–83).

CIRCULATING LIPOPROTEINS

TZD PPAR-γ activators may exert favorable effects on plasma lipoproteins, with increased HDL-C and decreased triglyceride concentration. Lipoprotein changes are more favorable with pioglitazone than with rosiglitazone (23, 84), possibly due to the additional action of the former as a weak PPAR-α activator (85–87). Although a relationship between circulating triglyceride concentration and cardiovascular risk remains uncertain, a large body of observational data relates higher HDL-C to lower cardiovascular risk. Among patients treated with statins, the risk of adverse cardiovascular events diminishes by 1–1.5% with each 1 mg/dl increment in HDL-C (88). If that relation applies when HDL-C is raised pharmacologically, assuming a baseline HDL-C concentration of 40 mg/dl and a 10% increase with TZD treatment, one might expect TZDs to reduce cardiovascular risk by approximately 5% on the basis of increased HDL-C alone. Indeed, in the PROACTIVE study, a beneficial effect of pioglitazone on the risk of death, MI, or stroke was related to increases in HDL-C, but not decreases in HbA1c (43), and favorable effects of pioglitazone on progression of carotid intima-media thickness (cIMT) and coronary atherosclerosis have also been related to the drug's effects on HDL-C or HDL-C/triglyceride ratio (89, 90). Pioglitazone and rosiglitazone have similar effects on HDL-C, and both agents increase LDL particle size (23); however, the compounds differ in their effects on LDL-C and apolipoprotein B concentration: Pioglitazone generally has minimal effect (23), whereas rosiglitazone can produce increases of 10–20% (23, 91). It remains uncertain whether differential effects of pioglitazone and rosiglitazone on lipoproteins account for differences in clinical efficacy of these agents.

BLOOD PRESSURE

Large clinical trials of TZDs demonstrate small but consistent reductions in blood pressure. For example, in the PROACTIVE study, in which 75% of subjects had a history of hypertension, pioglitazone reduced systolic blood pressure by a mean of 3 mm Hg, compared with placebo (92). In a Diabetes Outcome Progression Trial (ADOPT), in which 78% of patients had a history of hypertension, monotherapy with rosiglitazone, compared with metformin or glyburide, was associated with 1–2 mm Hg lower systolic and diastolic blood pressure after 4 years of treatment (93). In the open-label Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy (RECORD) trial, there was no difference in office blood pressure when rosiglitazone was added to sulfonylurea or metformin, compared with the combination of sulfonylurea and metformin (94). However, in a subset of 759 patients (85% with a history of hypertension) who underwent ambulatory blood pressure monitoring, 24 h mean systolic and diastolic blood pressure were 2–3 mm Hg lower in the rosiglitazone arm after 1 year of treatment (95). A reduction of blood pressure by 2–3 mm Hg, if sustained over the long term, might be expected to

significantly reduce the risk of adverse renal and cardiovascular events, particularly congestive heart failure (96). However, in clinical trials with a relatively brief duration of observation, early effects of PPAR-γ activators to increase plasma volume and promote heart failure might dominate before any long-term beneficial effect to reduce heart failure through blood pressure reduction became evident.

ENDOTHELIAL FUNCTION, VASCULAR SMOOTH MUSCLE CELL PROLIFERATION, AND RESTENOSIS

PPAR-γ is expressed in human vascular endothelial cells (97). Vascular endothelial dysfunction usually accompanies type 2 diabetes and metabolic syndrome. Both animal models and clinical studies of these conditions are characterized by reduced number and functionality of endothelial progenitor cells (EPC) (98–100). In turn, reduced EPC number has been related to the degree of impairment of flow-mediated vasodilation in type 2 diabetes (101). In experimental animal models and clinical studies, TZD drugs have been shown to stimulate production of EPCs and promote endothelial repair after vascular injury (102–106).

Activation of PPAR-γ with TZDs increases endothelial nitric oxide bioavailability by direct actions on endothelium, including suppression of inflammatory gene expression or activation of endothelial AMP-activated protein kinase, or indirect mechanisms related to increased adiponectin and decreased circulating NEFA concentrations (20, 107–109). In patients with type 2 diabetes or other insulin-resistant states, TZD treatment improves brachial artery endothelial function, as marked by greater flow or acetylcholine-mediated vasodilation (75, 110–112). Improvements in coronary endothelium-dependent vasodilation have been demonstrated with pioglitazone (113, 114).

PPAR-γ is expressed in vascular smooth muscle, where its activation may inhibit proliferation and migration (115–118). These effects, along with those to promote endothelial repair, have raised interest in PPAR-γ activators as a potential strategy to prevent restenosis after percutaneous coronary revascularization. Several small, randomized trials have been performed in diabetic and nondiabetic patients after bare metal stent implantation, with clinical and angiographic endpoints. Meta-analyses of these trials suggest that TZDs may reduce late lumen loss and need for further target vessel revascularization, with more convincing effects in diabetics and with pioglitazone than in nondiabetics or with rosiglitazone (119–121). It has also been hypothesized that salutary endothelial effects of PPAR-γ activation might reduce the risk of stent thrombosis after drug-eluting stent implantation (122), but to date there are no data to either corroborate or refute this.

DEVELOPMENT AND PROGRESSION OF ATHEROSCLEROSIS

Because PPAR-γ is expressed in vascular tissues, including endothelium and smooth muscle, as well as in macrophages that reside in atherosclerotic lesions, a role of PPAR-γ in modulating the development and progression of atherosclerosis has been postulated. Most, but not all, experimental evidence indicates an antiatherogenic effect. Most animal studies have shown that PPAR-γ ligands retard progression of atherosclerosis (18), whereas genetic deletion of PPAR-γ from macrophages accelerates atherosclerosis (123, 124). In rabbits with atherosclerosis induced by high-cholesterol diet and balloon arterial injury, 3 months of treatment with pioglitazone reduced lesion inflammation, as gauged noninvasively by ^{18}F-deoxyglucose positron emission tomography and dynamic contrast-enhanced magnetic resonance imaging and pathologically by lesion macrophage density and neovascularization (125). However, a study of advanced atherosclerotic lesions in LDL-receptor knockout mice showed that TZD drugs promoted plaque necrosis (27), and a recent study determined that atheromatous human aortas are enriched in soluble lipid mediators that may induce neovascularization of the arterial wall through a PPAR-γ dependent mechanism (28). Clinically, such effects might predispose to plaque hemorrhage and rupture.

A potential synthesis of these seemingly contradictory data is that PPAR-γ may oppose atherosclerosis in its early stages but exert different and deleterious effects in advanced atherosclerotic lesions. Studies examining whether vascular PPAR-γ expression is altered in human atherosclerosis also provide conflicting evidence. In one study, PPAR-γ mRNA expression was lower in atheromatous carotid endarterectomy and abdominal aortic aneurysm specimens than in normal inferior mesenteric arteries excised during colectomy (126). In contrast, another study of human aortas sampled at autopsy found increased expression of PPAR-γ mRNA and protein in areas of atherosclerosis (127). These studies leave open the question of whether vascular PPAR-γ favorably modulates the progression of atherosclerosis, unfavorably modulates this process, or plays no direct pathophysiologic role. The first possibility is suggested by a study that demonstrated the potential of PPAR-γ agonists to promote differentiation of human monocytes into anti-inflammatory M2 macrophages and that showed a positive correlation between expression of PPAR-γ mRNA and M2 markers in human carotid atherosclerotic lesions (128).

Clinical studies have utilized vascular imaging techniques to evaluate the effects of TZD agents on atherosclerosis progression, as marked by cIMT, coronary atheroma volume by intravascular ultrasound (IVUS), coronary artery calcification by computed tomography, or arterial pulse wave velocity. Major trials are summarized in **Table 2**. In aggregate, these studies suggest that TZDs retard atherosclerosis progression, with more convincing evidence for pioglitazone than rosiglitazone.

The Study of Atherosclerosis with Ramipril and Rosiglitazone (STARR) (129) compared effects of rosiglitazone with placebo on cIMT progression in 1,256 subjects with impaired glucose tolerance or impaired fasting glucose, but without diabetes or overt cardiovascular disease. The primary outcome was an aggregate measure of cIMT in 12 carotid arterial segments. After 3 years of follow-up,

TABLE 2. Major randomized trials of TZD drugs with clinical or imaging outcomes

Trial, Year (Ref.)	Patient Population	Drug	Comparator	Design	Sample Size; Follow-up	Primary Outcome Measure	Key Results
Clinical outcomes							
PROACTIVE, 2005 (92)	Type 2 diabetes with evidence of macrovascular disease	Pioglitazone	Placebo	Double-blind	N = 5,248; 34.5 mo (mean)	Death, nonfatal acute MI, CVA, ACS, coronary or peripheral artery revascularization, or lower extremity amputation	Primary outcome: Pioglitazone 19.7%; placebo 21.7%; HR 0.90, $P = 0.095$. Principal secondary outcome (death, acute MI, or CVA): Pioglitazone 11.6%; placebo 13.6%; HR 0.84, $P = 0.027$.
DREAM, 2006 (191)	Impaired fasting glucose or impaired glucose tolerance without diabetes or prior CV disease	Rosiglitazone	Placebo	Double-blind; factorial design with ramipril/ placebo	N = 5,269; 3 yr (median)	Incident diabetes or death	Primary outcome: Rosiglitazone 11.6%; placebo 26% ; HR 0.40, $P < 0.0001$. Death: Rosiglitazone 1.1%; placebo 1.3%; NS. CV death, acute MI, or CVA: Rosiglitazone 1.2%; placebo 0.9%; HR 1.39, NS.
ADOPT, 2006 (193)	Recently diagnosed type 2 diabetes	Rosiglitazone	Metformin or glyburide	Double-blind	N = 4,360; 4 yr (median)	Failure of monotherapy to control diabetes	Primary outcome: Rosiglitazone 15%, metformin 21%, glyburide 34%. Serious CV events (fatal or nonfatal acute MI, CVA, or CHF): Rosiglitazone 3.4%, metformin 3.2%, glyburide 1.8% ($P < 0.05$ vs. rosiglitazone).
RECORD, 2009 (94)	Type 2 diabetes	Rosiglitazone added to metformin or SU	Combination of metformin and SU	Open-label, noninferiority	N = 4,447; 5.5 yr (mean)	CV hospitalization or CV death	Primary outcome: 14.5% both groups, HR 0.99.CV death, acute MI, or CVA: Rosiglitazone + metformin or SU 6.9%; metformin + SU 7.4%; HR 0.93, NS.
Imaging outcomes							
CHICAGO, 2006 (130)	Recently diagnosed type 2 diabetes without symptomatic atherosclerosis	Pioglitazone	Glimepiride	Double-blind	N = 361; up to 72 wk	cIMT: Change from baseline, posterior wall of common carotid arteries	Primary outcome: Pioglitazone mean −0.001 mm; glimepiride mean +0.012 mm, $P = 0.02$.
STARR, 2009 (129)	Substudy of DREAM	Rosiglitazone	Placebo	See DREAM	N = 1,256; up to 3 yr	cIMT: Aggregate change from baseline in 12 1-cm long carotid arterial segments	Primary outcome: Rosiglitazone mean 0.0064 mm; placebo mean 0.0088 mm; $P = 0.10$. Secondary outcome: Change of cIMT in posterior wall of common carotid arteries. Rosiglitazone mean 0.0017 mm; placebo mean 0.0054 mm, $P = 0.03$.
PERISCOPE, 2008 (133)	Type 2 diabetes with CHD	Pioglitazone	Glimepiride	Double-blind	N = 360; up to 18 mo	Coronary IVUS: Change from baseline in percentage atheroma volume	Primary outcome: Pioglitazone mean −0.16%; glimepiride +0.73%, $P = 0.002$.
APPROACH, 2010 (139)	Type 2 diabetes with CHD	Rosiglitazone	Glipizide	Double-blind	N = 462; up to 18 mo	Coronary IVUS: Change from baseline in percentage atheroma volume	Primary outcome: Rosiglitazone mean −0.21%; glipizide +0.43%, $P = 0.12$.

CVA, cerebrovascular accident; HR, hazard ratio; NS, not significant; SU, sulfonylurea.

there was a trend ($P = 0.10$) to less cIMT progression in the rosiglitazone group. A secondary outcome, cIMT progression in the posterior wall of the common carotid arteries, showed significantly less progression in the rosiglitazone group compared with placebo ($P = 0.03$). The Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial (130) compared effects of pioglitazone with glimepiride on posterior wall common carotid cIMT in 361 patients with type 2 diabetes. After observation up to 18 months, cIMT did not progress under pioglitazone treatment, but it increased with glimepiride ($P = 0.02$). However, in a subset of the CHICAGO cohort, pioglitazone had no effect on progression of coronary artery calcification (131). A meta-analysis of nine placebo or active comparator-controlled trials of pioglitazone or rosiglitazone (not including STARR and CHICAGO) in 1,400 patients with type 2 diabetes showed a significant favorable effect of TZD treatment on cIMT progression, without significant difference in the effects of the two drugs (132). A reduction of arterial pulse wave velocity was also demonstrated with TZD treatment, suggesting a favorable effect on arterial stiffness.

The Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial compared 18 months of treatment with pioglitazone or glimepiride on coronary atheroma volume in 360 diabetic patients. Percentage atheroma volume decreased slightly with pioglitazone but progressed with glimepiride (difference $P = 0.002$) (133). Several small trials, each with 54 or fewer participants, have examined the effects of 6–8 months of treatment with pioglitazone or placebo on coronary atheroma progression and ultrasonic tissue characteristics in patients with type 2 diabetes. These studies have shown that pioglitazone reduces coronary atheroma progression and/or volume of necrotic core (134–137). In contrast, a trial comparing 12 months of treatment with rosiglitazone versus placebo in 193 patients (138) showed no significant effect of rosiglitazone on saphenous vein bypass graft atherosclerosis assessed by IVUS, and the Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients with Cardiovascular History (APPROACH) trial found no difference in progression of coronary atheroma volume after up to 18 months of treatment with rosiglitazone or glipizide in 462 patients (139).

ISCHEMIA/REPERFUSION INJURY

Some experimental evidence suggests that PPAR-γ activation mitigates ischemia/reperfusion injury. In normal or insulin-resistant rodents, treatment with PPAR-γ activators improved contractile recovery and/or reduced infarct size after ischemia and reperfusion (140–149). Intravenous troglitazone reduced myocardial infarct size in dogs (150). Chronic, oral troglitazone suppressed inflammatory responses and improved postischemic contractile function in pigs (151), but the protective effects of troglitazone may have been due to its α-tocopherol moiety rather than PPAR-γ activation, as treatment with equimolar α-tocopherol recapitulated the beneficial effects of troglitazone, whereas treatment with rosiglitazone (which does not have a tocopherol moiety) did not. Other studies have investigated whether TZDs affect postinfarction left ventricular remodeling. The evidence is mixed, with some studies demonstrating reduced postinfarction fibrosis and improved systolic function (152, 153), while others show neutral or adverse effects on left ventricular remodeling and survival (154, 155).

Rodent studies suggest that cerebral ischemia/reperfusion injury may also be favorably modified by PPAR-γ activation, manifest by improved recovery of neurologic function and/or decreased infarct size (156–161). In these studies, postulated mechanisms of cerebral protection by PPAR-γ include attenuation of inflammatory responses in injured tissue, promotion of signaling through protective stress kinases, diminished apoptosis, and enhanced tissue availability of nitric oxide. Cerebral-protective effects of PPAR-γ activators have been demonstrated with either systemic or local treatment (161) and with either TZD or non-TZD agents (156).

ADVERSE AND/OR OFF-TARGET CARDIOVASCULAR ACTIONS OF PPAR-γ ACTIVATORS

As described in preceding sections, the portfolio of potentially beneficial cardiovascular effects of PPAR-γ activation might lead to the expectation that TZDs would provide clinical benefit to patients with or at risk for cardiovascular disease. However, as discussed in succeeding sections, clinical trials have not clearly demonstrated such benefit. The apparent divergence between metabolic and vascular actions of PPAR-γ activation and clinical outcomes with TZD treatment raises a pivotal question: Do adverse cardiovascular effects of PPAR-γ activation and/or off-target effects of TZDs attenuate or nullify the potential clinical benefit of this therapeutic approach?

Plasma volume expansion and heart failure

Effects of PPAR-γ activation on sodium retention and plasma volume have the potential to cause edema and significant heart failure (22). Treatment of patients without preexisting heart failure with TZD agents leads to an increase in circulating natriuretic peptides (162–164), plasma volume (164–166), and extracellular fluid volume (167, 168). PPAR-γ is expressed in the nephron, particularly in the collecting duct (169). Mice with collecting duct-specific deletion of PPAR-γ are resistant to rosiglitazone-induced plasma volume expansion (166). Mechanisms of sodium and volume retention via PPAR-γ may be enhanced transcription of the kinase SGK1 (170), which in turn activates the renal epithelial sodium channel, as well as nontranscriptional effects of PPAR-γ in the proximal tubule (171), with both actions promoting sodium retention (169). Patients with underlying systolic and/or diastolic cardiac dysfunction or a history of congestive heart failure may be particularly prone to develop heart failure in response to treatment with a PPAR-γ activator,

due to increased plasma volume. However, neither animal (151, 172) nor clinical studies (163, 173, 174) indicate that heart failure resulting from TZD treatment is due to direct, adverse effects of TZDs on left ventricular systolic function. Moreover, some studies indicate salutory effects of TZDs on diastolic function (175–177). Preclinical studies with novel, non-TZD PPAR-γ activators suggest that these agents may enhance insulin sensitivity to a similar degree as TZD agents, but with less expansion of plasma or extracellular volume (178, 179). Whether these novel PPAR-γ activators will pose a lower risk for congestive heart failure remains to be established.

Ion channels and electrophysiology

Increasing evidence suggests that TZD compounds may affect cardiac ion channels and arrhythmias through off-target mechanisms. In vitro studies indicate that TZDs block voltage-gated potassium channels and L-type calcium channels in isolated ventricular cardiomyocytes (25, 180) and block ATP-sensitive potassium current in channels from cardiac and noncardiac cells (181–185). Because these effects are immediate, they suggest nontranscriptional effects of the drugs rather than classical effects via nuclear PPAR-γ. In vivo studies indicate a potential for TZD drugs to influence cardiac arrhythmias. In dogs, troglitazone promotes dephosphorylation of connexin 43, a gap junction protein, in response to ischemia and reperfusion (150), an effect with possible pro-arrhythmic consequences. In pigs, acute treatment with troglitazone, rosiglitazone, or pioglitazone, resulting in clinically relevant plasma concentrations, blocks cardiac ATP-sensitive potassium (K_{ATP}) channels, promotes ischemic ventricular fibrillation, and impairs the success of defibrillation (24, 26). These pro-arrhythmic effects are recapitulated by the prototypical K_{ATP} blocker glyburide. The mechanism by which TZDs close the K_{ATP} channel may be via phosphorylation of its inward rectifying subunit (186). To date, no human cardiac electrophysiology studies have been performed before and after TZD treatment, and therefore, it remains unknown whether TZD treatment increases the propensity for cardiac arrhythmias in patients.

KEY CLINICAL TRIALS AND OBSERVATIONAL ANALYSES OF PIOGLITAZONE OR ROSIGLITAZONE IN PATIENTS WITH, OR AT RISK FOR CARDIOVASCULAR DISEASE

Although the balance of data from experimental studies and clinical studies with surrogate endpoints supports the plausibility of cardiovascular benefit from PPAR-γ activation, proof of efficacy depends on the results of large, randomized clinical trials that assess clinically relevant cardiovascular outcomes. To date, that proof remains elusive. This section draws inferences from key trials performed with pioglitazone and rosiglitazone (Table 2) and discusses limitations of the data.

PROACTIVE

PROACTIVE is the only completed trial to test a hypothesis of superiority of a TZD over placebo with regard to cardiovascular outcomes (92, 187). The trial compared pioglitazone 45 mg daily (or maximum tolerated dose) with placebo in 5,238 patients with type 2 diabetes, HbA1c greater than 6.5% despite treatment with other hypoglycemic agents, and evidence of macrovascular coronary, peripheral arterial, or cerebrovascular atherosclerotic disease. The primary outcome measure was the composite of all-cause mortality; nonfatal MI or acute coronary syndrome (ACS); stroke; coronary- or lower extremity arterial revascularization procedure; or amputation of a lower extremity above the ankle. At baseline, the median duration of diabetes was 8 years. Notably, only 43% of patients were treated with a statin at baseline and only 55% after randomization. In addition, imbalances in the use of insulin and metformin developed after randomization, with these agents used more often in the placebo group (46% and 64%) than in the pioglitazone group (36% and 58%). Insulin doses were also higher in the placebo group (188). After an average observation time of 34.5 months, the primary efficacy measure was not significantly affected by treatment with pioglitazone, with a hazard ratio of 0.90 (95% confidence interval 0.80–1.02, $P = 0.095$). Although no individual component of the primary composite endpoint was significantly affected by treatment assignment, there were trends toward reductions in nonfatal coronary events and stroke with pioglitazone. A prespecified secondary efficacy measure, time to first occurrence of death, MI (excluding silent), or stroke, was significantly reduced by pioglitazone with hazard ratio 0.84 ($P = 0.03$). Moreover, in a prespecified subgroup analysis, pioglitazone reduced the risk of recurrent MI by 28% among 2,445 patients with prior MI (189). However, investigator-reported heart failure and hospitalization for heart failure were significantly more frequent in the pioglitazone group.

Although PROACTIVE results support cardiovascular efficacy of pioglitazone, the evidence provided is inconclusive. First, although pioglitazone had a favorable effect on coronary events, an effect on the primary composite endpoint was diluted by null or negative-trending effects on lower extremity amputation or revascularization. Second, the Kaplan-Meier curves for the primary and key secondary cardiovascular efficacy measures showed no divergence for the first year but continuing divergence thereafter. This suggests that a longer observation period might have allowed a conclusive demonstration of efficacy of pioglitazone. Third, imbalances between the two treatment arms in the frequency and intensity of use of other diabetic therapies may have confounded the results if these agents also affected cardiovascular outcomes. Fourth, contemporary guidelines endorse statin use in the vast majority of patients who were included in PROACTIVE; however, only about half the patients in the trial were actually treated with a statin. In a posthoc analysis, the risk of death, MI, or stroke was reduced by 25% with pioglitazone among patients not treated with statin, but it was reduced by only 5% with pioglitazone among patients who were treated with a statin (43). Further studies will be required to address the question of whether pioglitazone or other PPAR-γ activators provide clinical benefit incremental to statins.

RECORD, DREAM, ADOPT, and ACT NOW

The RECORD trial (94) tested a noninferiority hypothesis for rosiglitazone as second-line therapy in type 2 diabetes. In 4,447 subjects with type 2 diabetes not optimally controlled on monotherapy with metformin or sulfonylurea, the trial compared the addition of rosiglitazone to either metformin or sulfonylurea with the combination of metformin and sulfonylurea. The primary endpoint was time to cardiovascular hospitalization (including hospitalization for heart failure) or cardiovascular death. During open-label, randomized treatment there were significant imbalances in the use of diuretics and statins (both used more frequently in the rosiglitazone group). The rosiglitazone group exhibited lower levels of HbA1c and higher levels of LDL-C, HDL-C, and weight. After mean follow up of 5.5 years, primary endpoint events occurred in 321 patients in the rosiglitazone group and 323 patients in the metformin/sulfonylurea group, thus meeting the criterion for noninferiority of rosiglitazone. Fatal or nonfatal heart failure occurred more frequently in the rosiglitazone group than in the active control group (61 versus 29 patients). Limitations of RECORD include an event rate that was substantially lower than that projected in trial design with consequent reduction of statistical power, potential confounding by differential use of statins and diuretics, and open-label design.

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial (190, 191) was 2-factor, placebo-controlled study designed to determine whether rampril and/or rosiglitazone treatment prevents onset of diabetes among 5,269 nondiabetic patients with impaired fasting glucose or abnormal glucose tolerance. Rosiglitazone significantly reduced the progression to new onset diabetes during active treatment with the drug. Despite that benefit, a prespecified cardiorenal outcome measure, including cardiovascular events (MI, stroke, cardiovascular death, revascularization, heart failure, angina) and renal events (progression to microalbuminuria or macroalbuminuria), showed no difference between rosiglitazone and placebo over a mean 3 years of observation (rosiglitazone 15.7%, control 16%). Rosiglitazone was associated with more frequent development of heart failure. There was no interaction between rosiglitazone and ramipril on cardiovascular outcomes. The Actos Now for the Prevention of Diabetes (ACT NOW) trial (192) addressed a similar question to DREAM in 602 patients with impaired glucose tolerance who were randomized to receive either pioglitazone 45 mg or placebo. After a mean follow-up of 2.2 years, progression to diabetes occurred in 5% of the pioglitazone group compared with 16.7% of the placebo group, but too few cardiovascular events occurred (pioglitazone 26, placebo 23) to draw any inferences regarding effect of treatment on cardiovascular outcomes.

A Diabetes Outcome Progression Trial (ADOPT) (193) compared glycemic durability of rosiglitazone, metformin, and glyburide as first-line treatment in 4,360 patients with newly diagnosed type 2 diabetes. The primary outcome was monotherapy treatment failure, defined by a fasting blood glucose greater than 10 mmol/l after 6 weeks at maximum dose of assigned agent. At 5 years of follow-up, significantly fewer patients had failed rosiglitazone monotherapy (15%) compared with either metformin (21%) or glyburide (34%). HbA1c levels remained lower and insulin sensitivity higher in the rosiglitazone group, but with higher levels of LDL-C. In this relatively low-risk population, few cardiovascular events occurred. Notwithstanding this limitation, event frequencies, including heart failure, were similar in the rosiglitazone and metformin groups but lower in the glyburide group.

In composite, RECORD, DREAM, and ADOPT suggest that improved glycemic control with rosiglitazone is not accompanied by a corresponding reduction of cardiovascular risk. The findings again call into question whether insulin resistance and/or hyperglycemia are primary determinants of cardiovascular risk and/or whether glycemic benefits of rosiglitazone were negated by other actions of the drug, including a greater propensity for heart failure and increased LDL-C.

Meta-analyses

Meta-analyses of clinical trials with pioglitazone or rosiglitazone provide further insight into their cardiovascular effects. An analysis of 19 randomized controlled trials with pioglitazone, including PROACTIVE and comprising 16,390 patients, showed that the drug was associated with a significantly lower risk of death, MI, or stroke compared with corresponding control groups (4.4% versus 5.7%, hazard ratio 0.82, $P = 0.005$) (194). Similarly, a meta-analysis of 94 trials with pioglitazone, excluding PROACTIVE and comprising over 20,000 patients, showed that pioglitazone was associated with significantly lower all-cause mortality (195), with the caveat that the trials comprised only 57 deaths. In contrast, a meta-analysis of 56 randomized controlled trials with rosiglitazone comprising 35,531 patients showed that the drug was associated with an excess risk of MI (odds ratio 1.28, $P = 0.04$), albeit without excess cardiovascular mortality (196). These findings contributed to decisions by regulatory agencies to withdraw rosiglitazone in Europe and limit its use in the United States (197).

Observational analyses

Juxtaposition of generally favorable cardiovascular outcomes associated with pioglitazone with neutral to unfavorable outcomes associated with rosiglitazone suggests divergent effects on cardiovascular risk. Unfortunately, no randomized comparison of the two drugs has been performed to test this hypothesis. Instead, inferences must be drawn from analyses of observational databases. Six large, retrospective cohort studies compared treatment with rosiglitazone to treatment pioglitazone (as monotherapy or in combination with other hypoglycemic agents). After correction for potential confounders, each of these analyses found a greater incidence of major adverse cardiovascular events among patients treated with rosiglitazone than pioglitazone (198–203). A meta-analysis of 16 observational studies comparing rosiglitazone with pioglitazone

comprising 810,000 patients found significant adverse odds ratios associated with rosiglitazone (1.14 for death, 1.16 for MI, and 1.22 for congestive heart failure) (204). The implications of these findings are 2-fold: first, there is no reasonable basis for the ongoing use of rosiglitazone when pioglitazone provides a safer alternative, and second, the data reinforce the concept that safety and efficacy of new PPAR modulators must be evaluated on a compound-by-compound basis, rather than as a drug class. Compounds that nominally may be considered to be in the same class of PPAR activators may in fact exert very different effects on gene transcription, in part related to PPAR ligand-specific effects on coactivator or corepressor recruitment. Notwithstanding the limitations of an in vitro cell culture model, a recent study demonstrated that rosiglitazone, pioglitazone, and troglitazone regulated more genes discordantly than concordantly in adipocytes (**Fig. 2**) (205).

NEW PPAR-γ ACTIVATORS IN DEVELOPMENT

Pioglitazone and rosiglitazone act as full PPAR-γ agonists. Selective partial PPAR-γ agonists are being developed in the hope that they will produce similar insulin-sensitizing effects as TZDs but with fewer of the unwanted effects of a full agonist, including adipogenic weight gain, fluid retention, heart failure, and possibly pathologic bone remodeling and fractures. One such compound is INT-131, which has been evaluated in an 8-week, phase II, placebo-controlled monotherapy study in 70 patients with type 2 diabetes but without evident cardiovascular or renal disease (206). Doses of 1 mg or 10 mg daily were evaluated. At 1 mg, average fasting blood glucose was reduced from 163 to 142 mg/dl without an increase in body weight but also without significant changes in fasting insulin, adiponectin, or NEFA. At 10 mg, average fasting blood glucose was reduced from 183 to 137 mg/dl, an effect similar to monotherapy with maximum doses of pioglitazone or rosiglitazone, accompanied by significant reductions in insulin, adiponectin, and NEFA, but with a mean 1 kg increase in body weight. At present, it remains uncertain whether there will be any meaningful advantage of partial PPAR-γ activators at doses that provide glycemic control equivalent to approved doses of pioglitazone or rosiglitazone. In addition, at least two new TZD PPAR-γ agonists, rivoglitazone, a potent agonist (207), and balaglitazone, a partial agonist (208), are being evaluated in type 2 diabetes, but any advantages of these compounds over pioglitazone also remain uncertain.

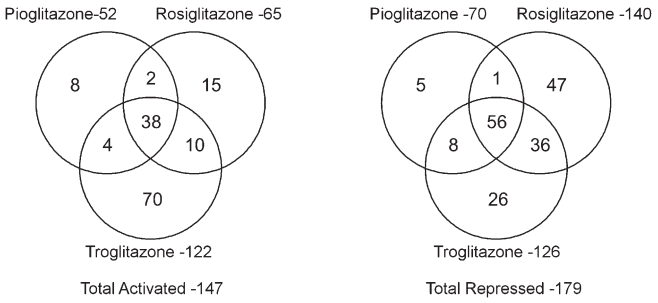

Fig. 2. Venn diagram of genes regulated by pioglitazone, rosiglitazone, and troglitazone. In cultured 3T3-L1 adipocytes, expression of mRNA was assessed using microarrays (GeneChip, Affymetrix) after 24 h of exposure to vehicle (DMSO), pioglitazone (20 μM), rosiglitazone (1 μM), or troglitazone (20 μM), concentrations known to elicit maximal biological effects. Despite significant overlap in genes activated or repressed by the three TZD agents, a substantial number of genes were regulated discordantly. The findings emphasize that each PPAR ligand induces a unique transcriptional effect, and they may provide an explanation for differences in clinical outcomes with pioglitazone and rosiglitazone. Reproduced from Ref. 205 with permission.

Considerable effort has been devoted to development of dual PPAR-α/γ activators that combine effects of PPAR-α to lower circulating triglycerides and raise HDL-C with effects of PPAR-γ to enhance insulin sensitivity. Glitazars are a class of drugs that activate both PPAR-α and PPAR-γ. Several glitazars progressed through phase II development but were then abandoned for various reasons, including development of bladder cancer in rodents (ragaglitazar), liver function abnormalities (imiglitazar), reduction in glomerular filtration rate (tesaglitazar), or an excess of adverse cardiovascular events in meta-analysis of small trials (muraglitazar) (211–213). Nonetheless, other dual PPAR-α/γ activators are in development. Among them, aleglitazar (214) has proceeded to phase III development.

PIVOTAL ONGOING CLINICAL TRIALS OF PPAR-γ ACTIVATORS IN PATIENTS WITH CARDIOVASCULAR DISEASE

Two large, ongoing multicenter international trials may provide important new information about the efficacy and safety of PPAR-γ activation in patients with cardiovascular disease. The Insulin Resistance Intervention after Stroke (IRIS) trial (www.clinicaltrials.gov NCT00091949) is a randomized comparison of pioglitazone (up to 45 mg daily) with placebo in nondiabetic, insulin-resistant patients with a recent ischemic stroke or transient ischemic attack. The criterion for insulin resistance is a HOMA-IR index greater than 3, measured 2 weeks to 6 months after the index event. Approximately 3,800 patients will be followed for a minimum of 3 years. The primary efficacy measure is time to first fatal or nonfatal stroke or MI. Recruitment will be completed in 2012, with results expected in 2015. IRIS

may provide important information in several respects. First, because approximately half of nondiabetic patients with acute coronary or cerebrovascular syndromes are insulin resistant (215, 216), potential efficacy of pioglitazone in such populations would have broad applicability. Second, because patients in IRIS are not diabetic at enrollment, the trial is less likely to be confounded by differential use of other diabetic medications in the two treatment arms than prior trials of TZDs in diabetic subjects. Third, IRIS should determine whether pioglitazone adds clinical benefit in patients treated with statins, a question left open by PROACTIVE (43).

Aleglitazar is the first dual PPAR-α/γ activator to proceed to phase III development. Because aleglitazar is believed to be a balanced PPAR-α/γ activator (i.e., relatively less PPAR-α activation than evaluated doses of tesaglitazar and relatively less PPAR-γ activation than evaluated doses of muraglitazar), it is hoped that renal and cardiovascular safety concerns with those previous agents will be avoided (217). The Alecardio trial (www.clinicaltrials.gov NCT01042769) compares aleglitazar with placebo in approximately 7,000 patients with type 2 diabetes and recent ACS. The primary efficacy measure is time to first occurrence of death or nonfatal MI or stroke. The trial will continue until 950 primary endpoint events have accrued.

SUMMARY AND FUTURE DIRECTIONS

Each PPAR ligand interacts differently with PPAR-retinoic acid dimers and attracts coactivators and corepressors in a ligand-specific manner. Therefore, transcriptional and clinical effects of each PPAR activator may differ from others. Inability to assume class effects adds complexity to preclinical and clinical development of new PPAR activator drugs. Although there is strong biological rationale for PPAR-γ activation to reduce cardiovascular risk, current clinical evidence leaves this hypothesis unproven. At present, supporting evidence is greatest for a clinical benefit of pioglitazone. However, to establish a secure role in cardiovascular therapeutics for pioglitazone, other selective PPAR-γ agonists, or dual PPAR agonists, ongoing and future clinical trials must go beyond the limitations of prior studies. Specifically, trials must evaluate agents on the basis of important clinical outcomes, including cardiovascular mortality, nonfatal MI, stroke, and heart failure; allow long enough exposure to observe modification of atherosclerotic risk; assess benefit in addition to statins; and avoid confounding by differential use of other diabetic medications.

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