Original Article

Therapeutic Roles of Peroxisome Proliferator–Activated Receptor Agonists

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Peroxisome proliferator–activated receptors (PPARs) play key roles in the regulation of energy homeostasis and inflammation, and agonists of PPARα and -γ are currently used therapeutically. Fibrates, first used in the 1970s for their lipid-modifying properties, were later shown to activate PPARα. These agents lower plasma triglycerides and VLDL particles and increase HDL cholesterol, effects that are associated with cardiovascular benefit. Thiazolidinediones, acting via PPARγ, influence free fatty acid flux and thus reduce insulin resistance and blood glucose levels. PPARγ agonists are therefore used to treat type 2 diabetes. PPARα and -γ agonists also affect inflammation, vascular function, and vascular remodeling. As knowledge of the pleiotropic effects of these agents advances, further potential indications are being revealed, including roles in the management of cardiovascular disease (CVD) and the metabolic syndrome. Dual PPARα/γ agonists (currently in development) look set to combine the properties of thiazolidinediones and fibrates, and they hold considerable promise for improving the management of type 2 diabetes and providing an effective therapeutic option for treating the multifactorial components of CVD and the metabolic syndrome. The functions of a third PPAR isoform, PPARδ, and its potential as a therapeutic target are currently under investigation. *Diabetes* **54:2460–2470, 2005**

The three peroxisome proliferator–activated receptor (PPAR) isoforms PPARα, -γ, and -δ are nuclear receptors activated by fatty acids and fatty acid–derived eicosanoids. PPARα is expressed mainly in tissues where active fatty acid catabolism occurs (e.g., liver, brown fat, kidney, heart, and skeletal muscle), and PPARγ is restricted largely to white and brown adipose tissue, with lower levels in cardiac and skeletal muscle. PPARα and -γ are also expressed in vascular endothelium, vascular smooth muscle, and macrophages/foam cells. PPARδ is expressed in most tissues.

Activation of PPARs leads to the formation of heterodimers with retinoid-X receptors (RXRs). These PPAR-RXR dimers bind to DNA-specific sequences called peroxisome proliferator–response elements, thus stimulating or dampening the transcription of target genes. In addition to being differentially distributed, PPAR isoforms vary in their selectivities and sensitivities to ligands and recruit distinct coactivator proteins, resulting in the regulation of different sets of genes (1). In general, PPARα regulates genes involved in fatty acid uptake and oxidation, inflammation, and vascular function, whereas PPARγ regulates genes involved in fatty acid uptake and storage, inflammation, and glucose homeostasis. PPARδ regulates genes involved in fatty acid metabolism, inflammation, and macrophage lipid homeostasis.

Because PPARs have key roles as regulators of energy homeostasis and inflammation, much research has been directed toward development of synthetic PPAR ligands. In the 1990s, it was realized that the lipid-modifying properties of fibrates were attributable to the selective activation of PPARα. Subsequently, the thiazolidinediones, which are structural analogs of fibrates, were shown to activate PPARγ. Synthetic PPARδ agonists have recently been developed, and preclinical work is clarifying the function of this receptor. In addition, agents that activate multiple PPAR isoforms are now in development: dual PPARα/γ agonists and pan-PPAR agonists (PPARα/γ/δ).

This review examines the efficacy of PPAR agonists in conditions for which they are currently indicated (dyslipidemia and type 2 diabetes) and discusses their potential in the treatment of other conditions, including cardiovascular disease (CVD) and the metabolic syndrome.

PPAR AGONISTS IN THE TREATMENT OF DYSLIPIDEMIA

Fibrates were introduced for treatment of hyperlipidemia. Trials with fibrates have shown a reduction in coronary heart disease (CHD) risk through modification of atherogenic dyslipidemia. Fibrates are now recommended for the treatment of patients with dyslipidemia who are at high risk of CHD (2).

PPARα potentiates fatty acid oxidation in the liver,

heart, kidney, and skeletal muscle. Activation of PPARα leads to an increase in expression of lipoprotein lipase and apolipoprotein A-V (apoA-V) and to a decrease in hepatic apoC-III. These actions lower plasma triglycerides in chylomicrons and VLDL particles, thus liberating fatty acids, which are taken up and stored as fat in adipocytes or metabolized in skeletal muscle (3). In addition, PPARα activation increases hepatic apoA-I and -II expression, which raises HDL cholesterol levels, and promotes HDL-mediated cholesterol efflux from macrophages by inducing ATP-binding cassette A1 transporter (4). In addition to the efficacy of fibrates in the clinical management of atherogenic dyslipidemias involving reduced HDL cholesterol and elevated triacylglycerol-rich lipoprotein levels, they are effective in shifting the LDL subclass distribution toward larger particle species (5). Evidence of their beneficial effect on CVD has been obtained from several large clinical trials (6–11) (Table 1).

Bezafibrate. The Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) (6) investigated the effect of bezafibrate and dietary intervention on atherosclerosis in survivors of myocardial infarction (MI) who had dyslipidemia (predominantly hypertriglyceridemia). Bezafibrate slowed the progression of focal coronary atherosclerosis to a degree comparable to that achieved with statins and reduced the incidence of coronary events in young postinfarct patients. It also led to improvements in lipid profile (Table 1).

The Bezafibrate Infarction Prevention (BIP) study (7) investigated the effect of bezafibrate on fatal/nonfatal MI or sudden death in patients with stable angina or previous MI and high total cholesterol. The probability of an event was not significantly reduced, but post hoc analysis of a subgroup of patients with high baseline triglycerides revealed a significant reduction in the cumulative risk of coronary events. Bezafibrate treatment increased HDL cholesterol and lowered triglyceride levels. It should be noted that bezafibrate is an unusual member of the fibrate class in that although it acts primarily as a PPARα agonist, it also has some effect on PPARδ (12).

Gemfibrozil. The Helsinki Heart Study (HHS) (8) assessed the reduction in CHD risk produced by elevating HDL cholesterol and lowering non-HDL cholesterol concentrations with gemfibrozil in asymptomatic middle-aged men with primary dyslipidemia. Marked improvements in lipid profile in the gemfibrozil group compared with placebo were associated with a significant reduction in the incidence of CHD.

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) (9) examined the effect of gemfibrozil on nonfatal MI and coronary death in men with CHD and low HDL cholesterol. Gemfibrozil significantly reduced the risk of an event compared with placebo. The risk of stroke was also significantly reduced compared with placebo. Although LDL cholesterol levels did not differ significantly in the two groups, the reductions in coronary events and death with gemfibrozil treatment were accompanied by an increase in HDL cholesterol and reductions in total cholesterol and triglyceride levels. Although the increase in HDL cholesterol was associated with reduced risk, it did not account for all of the risk

reduction, suggesting that gemfibrozil may have pleiotropic effects.

The complementary lipid-altering effects of fibrates have led to their increased use as combination therapy. However, a statin/fibrate, particularly gemfibrozil, combination may be associated with increased risk of rhabdomyolysis. In vitro studies have highlighted that gemfibrozil may increase the myotoxic effects of statins (13,14) and that use of gemfibrozil results in higher plasma concentrations of statins (15–18). Possible mechanisms for this include inhibition of statin glucuronidation (13), which may then reduce statin elimination in vivo. Inhibition of the P450 enzyme CYP2C8 by gemfibrozil (13,19) may also impede elimination of statins (13). In contrast to the findings for gemfibrozil, the use of fenofibrate in combination with statins is associated with myotoxic effects to a lesser extent. During a survey in 1998–2002 on total reports of rhabdomyolysis in patients on statin/fibrate combination therapy, fenofibrate/cerivastatin was associated with a small proportion of cases (2.3%), whereas gemfibrozil/cerivastatin accounted for the majority of reports (88%) (20). Thus, it should be recommended that gemfibrozil not be used in combination with the current generation of statins, while combinations of other fibrates with statins should be used with caution. Furthermore, it is important that the effects of new PPAR agonists on statin glucuronidation and cytochrome P450 metabolism be investigated.

Overall, studies indicate that by increasing the level of HDL cholesterol and lowering plasma triglycerides, fibrates can reduce the incidence of CHD. Currently, evidence that fibrates affect clinical outcome in patients with vulnerable plaques is predominantly associated with gemfibrozil. However, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, an ongoing prospective 5-year study in 9,795 patients with type 2 diabetes, will provide evidence as to whether fibrates are effective for primary prevention of CVD.

Fibrates in patients with type 2 diabetes. Patients with type 2 diabetes are at particularly high risk of atherosclerotic events. Post hoc analyses of completed trials such as the VA-HIT and the HHS suggest that patients with diabetes derive greater benefits from fibrate therapy than nondiabetic subjects (21–25). Two studies that have prospectively investigated the impact of fibrate-mediated lipoprotein modification on CVD risk in patients with type 2 diabetes, the Diabetes Atherosclerosis Intervention Study (DAIS) and the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) study, support the benefit of PPARα therapy in the management of type 2 diabetes.

The DAIS (10) was designed to assess the effects of correcting lipoprotein abnormalities using fenofibrate on coronary atherosclerosis. Patients with good glycemic control, mild lipoprotein abnormalities typical of type 2 diabetes, and at least one visible coronary lesion were randomized to micronized fenofibrate or placebo. The increase in percentage diameter stenosis and the decrease in minimum lumen diameter were significantly smaller in the fenofibrate group than in the placebo group. The reduction in angiographic progression of coronary artery disease was related, at least in part, to significant changes in total cholesterol, HDL cholesterol, LDL cholesterol, and

TABLE 1
Summary of clinical trials of fibrates

Study	Intervention	Patients	Follow-up/treatment duration	Lipid outcome	Cardiovascular outcome
Bezafibrate					
BECAIT: de Faire et al. (6)	Bezafibrate 200 mg three times a day vs. placebo	81 men post-MI, <45 years old, dyslipidemia (predominantly hypertriglyceridemia)	5 years of treatment	↓Total cholesterol, ↓triglycerides, ↑HDL cholesterol, no change in LDL cholesterol	↓Progression focal coronary atherosclerosis ($P = 0.049$), ↓incidence of coronary events (3 vs. 11, $P = 0.02$)
BIP: BIP Study Group (7)	Bezafibrate 400 mg/day vs. placebo	3,090 patients, post-MI/stable angina, 45–74 years old, total cholesterol 180–250 mg/dl, HDL cholesterol ≤45 mg/dl, triglyceride ≤300 mg/dl, LDL cholesterol ≤180 mg/dl	6.2 years (mean follow-up)	↓Triglycerides (21%), ↑HDL cholesterol (18%)	No difference in probability of coronary events (13.6 vs. 15.0%, $P = 0.26$), subgroup post hoc analysis in patients with triglyceride ≥200 mg/dl: ↓cumulative risk of coronary events (39.5%, $P = 0.02$)
Gemfibrozil					
HHS: Frick et al. (8)	Gemfibrozil 600 mg twice daily vs. placebo	4,081 men, asymptomatic, 40–55 years old, primary dyslipidemia (non-HDL cholesterol ≥200 mg/dl)	5 years of treatment	↓Total cholesterol, ↓triglycerides, ↓LDL cholesterol, ↓non-HDL cholesterol, ↑HDL cholesterol	↓Incidence of CHD (34%, $P < 0.02$)
VA-HIT: Rubins et al. (9)	Gemfibrozil 1,200 mg/day vs. placebo	2,531 men, CHD, veterans >74 years old, HDL cholesterol ≤40 mg/dl, LDL cholesterol ≤140 mg/dl, triglycerides ≤300 mg/dl	5.1 years (median follow-up)	↓Total cholesterol, ↓triglycerides, ↑HDL cholesterol, no change in LDL cholesterol	↓Risk of coronary events (RR ↓ 22%, $P = 0.006$, absolute risk ↓ 4.4%, ↓risk of death from CHD, nonfatal MI, stroke (24%, $P < 0.001$)
Fibrates in patients with type 2 diabetes					
DAIS: DAIS Investigators (10)	Fenofibrate 200 mg/day vs. placebo	Type 2 diabetes (mean A1C 7.5%), 418 patients, ≥1 coronary lesion	≥3 years of treatment	Significant changes in total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol	Less ↑ in stenosis diameter (2.11 vs. 3.65%, $P = 0.02$), smaller ↓ in lumen diameter (−0.06 vs. −0.10 mm, $P = 0.029$)
SENDCAP: Elkeles et al. (11)	Bezafibrate 400 mg/day vs. placebo	Type 2 diabetes, 164 patients, no CVD	≥3 years of treatment	↓Total cholesterol (−7 vs. −0.3%, $P = 0.004$), ↓triglycerides (−32 vs. 4%, $P = 0.001$), ↓total-to-HDL cholesterol ratio (−12 vs. −0.0%, $P = 0.001$), ↑HDL cholesterol (6 vs. −2%, $P = 0.02$)	↓Combined incidence of probable ischemic change on resting electrocardiogram and MI ($P = 0.01$), no change in arterial disease

BECAIT, Bezafibrate Coronary Atherosclerosis Intervention Trial; BIP, Bezafibrate Infarction Prevention; DAIS, Diabetes Atherosclerosis Intervention Study; HHS, Helsinki Heart Study.

triglyceride concentrations, even in individuals previously judged not to need treatment.

The SENDCAP study (11) was also conducted to determine whether intervention with a fibrate (combined with conventional management) could improve cardiovascular outcomes in patients with type 2 diabetes. Patients with no history of clinical CVD were randomized to bezafibrate or placebo. Compared with placebo, those treated with bezafibrate had significantly greater reductions in median serum triglycerides, total cholesterol, and total-to-HDL cholesterol ratio, and they had significantly greater increases in HDL cholesterol. Although there was no significant difference between groups in the progression of ultrasonically measured arterial disease, those treated with bezafibrate experienced a significant reduction in the combined incidence of probable ischemic change on resting electrocardiogram and documented MI.

PPAR AGONISTS IN THE MANAGEMENT OF INSULIN RESISTANCE AND TYPE 2 DIABETES

Insulin sensitivity and glycemic control. Insulin resistance occurs long before the clinical onset of diabetes. Onset of insulin resistance is often accompanied by obesity, in particular visceral obesity. Resistance of dysfunctional fat cells to the antilipolytic effects of insulin leads to chronic elevations in plasma free fatty acid (FFA) levels. This, in turn, induces insulin resistance in the liver and skeletal muscle, resulting in reduced glucose uptake and increased gluconeogenesis. Dysfunctional fat cells also produce excessive amounts of cytokines (e.g., tumor necrosis factor-α [TNF-α], interleukin [IL]-6, and resistin) that further induce insulin resistance, inflammation, and atherosclerosis and that secrete reduced amounts of insulin-sensitizing cytokines such as adiponectin. The obesity that characterizes this pathological state is also frequently associated with nonalcoholic steatohepatitis, a progressive liver condition that carries a risk for fibrosis, cirrhosis, and end-stage liver disease and that is augmented by insulin resistance (26).

Synthetic ligands for PPARγ are of particular interest for treating patients with type 2 diabetes because they restore sensitivity to insulin. This property has been attributed to the direct effects of PPAR agonists on lipid metabolism in adipose tissue and to secondary effects on lipid and glucose metabolism in liver and skeletal muscle (27,28). PPARγ agonists promote adipocyte differentiation, and they promote FFA uptake and storage in subcutaneous adipose rather than visceral adipose tissue. This reduces FFA levels, with associated reductions in insulin resistance. In addition, activation of PPARγ is believed to increase the expression and translocation to the cell surface of the glucose transporters GLUT1 and -4, thus increasing glucose uptake into liver and skeletal muscle cells and reducing plasma glucose levels (29). PPARγ agonists may also restore insulin sensitivity by decreasing TNF-α (30) and increasing adiponectin expression (31).

The value of PPARγ agonists in the management of insulin resistance and type 2 diabetes is demonstrated by a number of important clinical trials with thiazolidinediones (32–37) (Table 2). Although troglitazone has now been withdrawn from the market because of rare but serious cases of hepatotoxicity, studies with pioglitazone and rosiglitazone indicate that this is not a class effect. Class effects associated with these agents include weight gain, edema (38), and increased lipoprotein(a) concentrations (39,40). Because of concerns about fluid retention, thiazolidinediones are not recommended for use in patients with New York Health Association class III or IV cardiac status (38). Despite these warnings, thiazolidinediones are increasingly prescribed to patients with diabetes and heart failure. A recent cohort study suggested that thiazolidinediones are not associated with risk of death from heart failure in patients with diabetes and heart failure (41). However, such patients should be monitored closely. The results of cardiovascular outcome studies with pioglitazone and rosiglitazone will establish the long-term benefits and risks of these agents.

Troglitazone. The Troglitazone Study Group carried out a dose-ranging study of troglitazone in patients with type 2 diabetes (32). Levels of HbA$_{1c}$ (A1C) fasting plasma glucose (FPG), plasma nonesterified fatty acids, triglycerides, and fasting plasma insulin were significantly lower in troglitazone-treated patients than in control subjects, and the troglitazone-treated group demonstrated increased insulin sensitivity. HDL cholesterol concentrations increased with higher doses of troglitazone (>600 mg/day).

The Troglitazone in the Prevention of Diabetes (TRIPOD) study found that troglitazone improved insulin sensitivity in two-thirds of Hispanic women with previous gestational diabetes. Troglitazone also provided protection against development of type 2 diabetes (33), thought to be associated with preservation of pancreatic β-cell function. Recent results of the Diabetes Prevention Program also showed that troglitazone reduced the incidence of diabetes, even though it was given for a limited period of time because of its discontinuation (42).

Pioglitazone. In patients with type 2 diabetes (34), pioglitazone decreased A1C and FPG levels, without changing fasting or glucose-stimulated insulin/C-peptide concentrations. Fasting plasma FFA and triglyceride concentrations were also significantly reduced. During an insulin clamp, pioglitazone significantly reduced basal endogenous glucose production, whereas insulin-stimulated total and nonoxidative glucose disposal during a second insulin clamp were significantly increased (34). Pioglitazone-induced improvements in hepatic insulin sensitivity are associated with reductions in hepatic fat content (43).

Several larger studies have confirmed the effects of pioglitazone on blood glucose and lipid profiles in patients with type 2 diabetes. In the placebo-controlled Pioglitazone 026 study, pioglitazone significantly reduced A1C, FPG, fasting insulin, C-peptide, and triglyceride concentrations, and it increased HDL cholesterol. Total cholesterol and LDL cholesterol levels were unaffected (35). Furthermore, a recent trial specifically investigating the lipid-lowering effects of thiazolidinediones found that pioglitazone was associated with significant improvements in triglycerides, HDL cholesterol, non-HDL cholesterol, and LDL particle size compared with rosiglitazone (44). The ongoing Pioglitazone Prevention of Type 2 Diabetes (PIPOD) trial (an extension of TRIPOD) is investigating whether 4 years of pioglitazone treatment offers continued protection from diabetes in women who had normal/

TABLE 2
Summary of clinical trials of thiazolidinediones

| Study	Intervention	Patients	Follow up/ treatment duration	Blood glucose outcome	Lipid outcome
Troglitazone					
Troglitazone Study Group: Kumar et al. (32)	Troglitazone 200/400/600/800 mg/day vs. placebo	330 patients with type 2 diabetes	12 weeks of treatment	↓A1C (mean 7.0–7.4 vs. 8.0%, $P = 0.055$ to <0.001), ↓FPG (360–426 vs. 499 mg/dl, $P < 0.001$), ↓ fasting insulin, ↑insulin sensitivity (HOMA 34.3–42.8 vs. 29.9%, $P < 0.05$)	↓Nonesterified Fas, ↓ triglycerides, ↑HDL cholesterol (for 600 and 800 mg/day)
TRIPOD: Buchanan et al. (33)	Troglitazone 400 mg/day vs. placebo	266 women with previous gestational diabetes	30 months (median follow-up)	↓Diabetes incidence rates ($P < 0.01$), ↑ preservation of pancreatic β-cell function	
Pioglitazone					
Miyazaki et al. (34)	Pioglitazone 45 mg/day vs. placebo	23 patients with type 2 diabetes	16 weeks of treatment	↓A1C (−1.7%, $P < 0.001$), ↓FPG (−49 mg/dl, $P < 0.01$), no change in C-peptide levels	↓FFA (change from baseline −168 vs. 13 μEq/l, $P = 0.02$), ↓triglyceride (change from baseline −33 vs. 1 mg/dl, $P = 0.047$)
Pioglitazone 026 Study: Rosenblatt et al. (35)	Pioglitazone 30 mg/day vs. placebo	197 patients with type 2 diabetes	16 weeks of treatment	↓A1C (−1.4%, $P = 0.001$), ↓FPG (−57.5 mg/dl, $P = 0.001$), ↓C-peptide (−0.08 nmol/l, $P = 0.001$), ↓ fasting insulin (−11.9 pmol/l, $P = 0.001$), ↓insulin resistance (HOMA −12.4%, $P < 0.001$), ↑β-cell function (HOMA +47.7%, $P < 0.001$)	↓Triglyceride (−16.6%, $P = 0.018$). ↑HDL cholesterol (+12.6%, $P = 0.007$)
Rosiglitazone					
Mayerson et al. (36)	Rosiglitazone 4 mg twice daily	9 patients with type 2 diabetes	10–12 weeks of treatment	↑Insulin-stimulated glucose metabolism (from baseline), low dose 68% ($P < 0.02$), high dose 20% ($P < 0.016$)	From baseline: ↓FFA (~40%, $P < 0.005$), ↓hepatic triglyceride (~40%, $P < 0.005$), ↑extramyocellular lipids (39%, $P < 0.05$), ↑ adipocyte lipolysis in response to insulin (52% $P < 0.04$)
Patel et al. (37)	Rosiglitazone 1 and 2 mg twice daily vs. placebo	380 patients with type 2 diabetes	12 weeks of treatment	From baseline: ↓FPG ($P = 0.001$), ↓fructosamine (2 mg twice daily, $P = 0.003$), ↓plasma insulin (2 mg twice daily, $P = 0.004$)	From baseline: ↓FFA ($P = 0.001$); 2 mg twice daily: ↑HDL cholesterol ($P = 0.0009$), ↑total cholesterol ($P = 0.0001$), ↑LDL cholesterol ($P = 0.0001$)

HOMA, homeostasis model assessment.
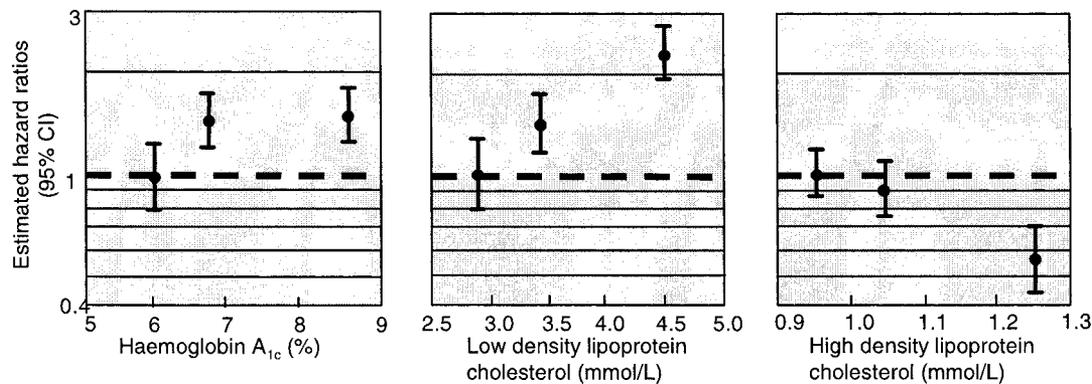
FIG. 1. High LDL cholesterol and low HDL cholesterol were better indicators of absolute cardiovascular risk (estimated hazard ratios for coronary artery disease) than A1C in the U.K. Prospective Diabetes Study trial (46). From Turner RC: The U.K. Prospective Diabetes Study: a review. *Diabetes Care* 21 (Suppl. 3):C35–C38, 1998.

impaired glucose tolerance or "mild diabetes" at the end of TRIPOD.

Rosiglitazone. In a 3-month study in patients with type 2 diabetes, rosiglitazone improved insulin-stimulated glucose metabolism during low- and high-dosage insulin clamps and led to reductions in plasma FFA concentration and hepatic triglyceride level (36). These changes were associated with increases in extramyocellular lipid content and in the sensitivity of peripheral adipocytes to insulin. The increase in insulin sensitivity elicited by rosiglitazone is associated with improvements in the clinical and histological severity of nonalcoholic steatohepatitis (26).

In a larger study, rosiglitazone significantly reduced FPG, fructosamine, FFAs, and plasma insulin from baseline, and it increased HDL cholesterol levels. Although the total-to-HDL cholesterol ratio and triglyceride level did not change, rosiglitazone treatment increased total cholesterol and LDL cholesterol (37).

As for pioglitazone, the effect of rosiglitazone on progression of type 2 diabetes is under investigation in a number of trials. One of these, the Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications (DREAM) trial, is currently assessing whether 3 years of rosiglitazone, alone or in combination with ramipril, delays or prevents the progression of type 2 diabetes in subjects with impaired glucose tolerance.

Benefits beyond glycemic control. In patients with diabetes, PPAR agonists have demonstrated several other potential benefits, in addition to their effects on insulin sensitivity and glucose homeostasis.

Over 70% of patients with type 2 diabetes have some degree of dyslipidemia (45), typically increased triglycerides and reduced HDL cholesterol levels. The U.K. Prospective Diabetes Study (UKPDS) demonstrated that lipid abnormalities were more important risk factors for CHD than A1C (Fig. 1) (46), a vital consideration given that up to 80% of patients with type 2 diabetes die from CVD complications (47). The ability of selective PPARα agonists, such as fibrates, to improve these abnormal lipid profiles is well established (48). There is also evidence that PPARγ agonists can impact positively on diabetic dyslipidemia, although currently available thiazolidinediones appear to have differential effects: whereas pioglitazone increases HDL cholesterol and lowers triglycerides (49),

rosiglitazone only provides improvements in HDL cholesterol levels. Indeed, rosiglitazone has been shown to increase total cholesterol and LDL cholesterol (50). Some evidence suggests that pioglitazone lowers triglycerides by enhancing the triglyceride fractional catabolic rate rather than decreasing hepatic production (51). In addition, thiazolidinedione treatment improves postprandial lipid metabolism. Rosiglitazone, troglitazone, and pioglitazone all induce a shift in LDL phenotype from dense to large buoyant subfractions (52–54).

Type 2 diabetes is also characterized by elevated levels of inflammatory markers, such as C-reactive protein (CRP), that are also closely linked to CVD risk. Thus, increasing interest is developing in the anti-inflammatory properties of PPARα and -γ agonists, and this is discussed in more detail below.

Ongoing clinical trials are investigating the ability of dual PPARα/γ agonists to provide type 2 diabetic patients with the collective benefits of effective sustained glycemic control, lipid management, and anti-inflammatory effects. Preliminary data from animal models of obesity and diabetes are encouraging (55), and early clinical trials have shown that these agents improve both the hyperglycemia and the dyslipidemia that are characteristic of type 2 diabetes (56). Because of caution surrounding possible carcinogenicity in animals, regulatory authorities have requested 2-year toxicology data before approving initiation of clinical trials of ≥6 months. Although there is currently no evidence of carcinogenicity in humans, and the cancer risk may be species-specific, it is important to establish the safety of PPAR agonists. Some dual PPARα/γ agonists, such as ragaglitazar and MK-0767, have been withdrawn from clinical trials. However, a number of other agents are undergoing preclinical evaluation, whereas tesaglitazar (Galida) and muraglitazar have completed the 2-year toxicity studies and are currently in clinical trials to clarify their efficacy and safety.

POTENTIAL THERAPEUTIC ROLES OF PPAR AGONISTS IN OTHER VASCULAR AND METABOLIC DISORDERS

Metabolic syndrome. The metabolic syndrome describes a complex of metabolic abnormalities, including obesity, diabetes, hypertension, and dyslipidemia, to which insulin resistance is central. The prevalence of this syndrome
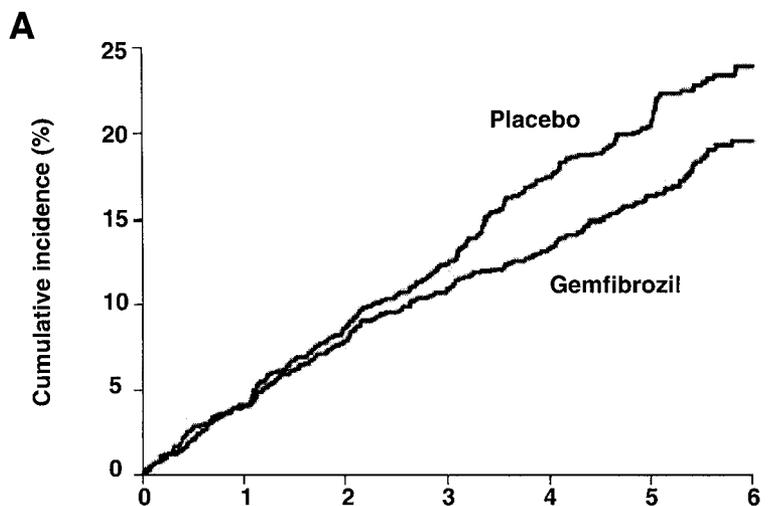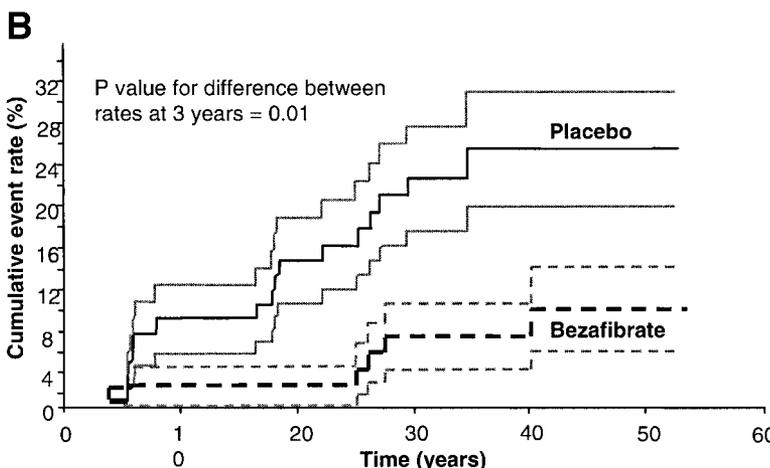
FIG. 2. Treatment with fibrates reduces cardiovascular risk versus placebo. *A*: VA-HIT study: Kaplan-Meier estimates showing reduced incidence of death from CHD and nonfatal MI in the gemfibrozil versus placebo groups. The relative risk reduction was 22% ($P = 0.006$), as derived from a Cox model. From Rubins et al. (9). *B*: The SENDCAP study: reduced rate of onset of definite CHD events in patients with type 2 diabetes treated with bezafibrate versus placebo. Lines show rates ±1 SE and *P* value by log-rank test for difference between placebo and bezafibrate-treated groups. n, subjects in study each year. From Elkeles et al. (11). Reproduced with permission from the Massachusetts Medical Society.

(currently 24% in the U.S.) is increasing across the globe (57). A substudy of the Botnia trial demonstrated that the effect of clustering of metabolic syndrome components on the risk of CHD morbidity in individuals with the metabolic syndrome appears greater than the relative risk associated with the individual components (58).

The data discussed in this review outline a compelling rationale for PPARα and -γ agonists as ideal agents for managing the metabolic syndrome. Thiazolidinediones improve glycemic control via their actions on insulin sensitivity, whereas fibrates improve a range of atherogenic dyslipidemias, including the dyslipidemic profile commonly associated with the metabolic syndrome. These agents also influence many other components of metabolic syndrome, including hypertension, inflammation, and vascular dysfunction and remodeling. If dual PPARα/γ agonists can bring together the beneficial effects of PPARα and -γ agonists, prospects for the management of patients with the metabolic syndrome will look brighter.

CVD. Although dyslipidemia is a central causative factor of atherosclerosis, processes such as inflammation, vascular dysfunction, and vascular remodeling are also involved.

The pleiotropic effects of PPAR agonists, therefore, take on extra significance in the management of CVD.

Fibrates are known to reduce cardiovascular risk (Fig. 2) (11,25). If successful, the FIELD trial, discussed earlier, will confirm that these PPARα agonists should be used to protect type 2 diabetic patients against heart disease.

Studies to determine whether the effects of thiazolidinediones translate into long-term cardiovascular benefits are also underway. These include two randomized trials: Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) and Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes (RECORD). The PROACTIVE is a double-blind, placebo-controlled trial that is assessing whether pioglitazone reduces total mortality and macrovascular morbidity in high-risk patients with type 2 diabetes. The RECORD study is evaluating the impact of open-label rosiglitazone on cardiovascular events and risk. In addition, the PPARγ Agonist for the Prevention of Late Adverse Events Following Percutaneous Coronary Revascularisation (PPAR) trial is assessing whether rosiglitazone re-

duces mortality, MI, and target vessel revascularization in obese individuals with hypertension or type 2 diabetes.

Inflammation. PPARα activation can inhibit inflammatory response genes by repressing nuclear factor-κB, signal transducer and activator of transcription, and activator protein-1 signaling. Downregulation of activator protein-1 leads to inhibition of thrombin-induced production of endothelin-1 in the arterial endothelium (59), decreased production of the inflammatory mediators IL-6 and cyclooxygenase-2 in response to IL-1, and downregulation of inducible nitric oxide (NO) synthase in macrophages (60). Inducible NO synthase is responsible for the generation of large amounts of NO, which can be toxic and proinflammatory. PPARα activation can also reduce tissue factor expression and activity in human monocytes/macrophages via inhibition of nuclear factor-κB (61,62). In the liver, PPARα activation decreases IL-1–induced CRP expression and IL-6–stimulated fibrinogen expression (63,64).

PPARα may activate a novel anti-inflammatory pathway. Fatty acids produced by LPL hydrolysis of VLDL (and to a lesser extent LDL and HDL) activate PPARα and thus reverse the increase in vascular cell adhesion molecule-1 expression induced by inflammatory stimuli such as TNF-α and lipoproteins (65). In addition to highlighting a novel anti-inflammatory pathway, these findings suggest different transcriptional responses dependent on the specific mechanism of fatty acid generation and uptake (66).

Activation of PPARγ also confers anti-inflammatory effects. In human monocytes, PPARγ is induced on exposure to oxidized LDL and is expressed at high levels in the foam cells of atherosclerotic lesions (66). Moreover, activation of PPARγ induces ATP-binding cassette A1 expression and cholesterol removal from macrophages, suggesting that PPARγ also regulates a pathway for cholesterol efflux (4). The anti-inflammatory properties of synthetic PPARγ agonists may also be explained, in part, by their ability both to inhibit production of TNF-α and other proinflammatory cytokines (30) and to increase adiponectin expression and secretion (31). In addition to increasing tissue sensitivity to insulin, adiponectin is known to inhibit inflammatory pathways.

CRP is an important marker of systemic inflammation and a powerful predictor of both diabetes and CVD risk (67,68). In a 26-week study of 357 patients with type 2 diabetes, rosiglitazone significantly reduced CRP levels (-26.8%, $P < 0.01$) compared with placebo; it also reduced matrix metalloproteinase-9, a useful marker of plaque stability (69). In another study, 84 nondiabetic patients with stable CHD were randomized to rosiglitazone or placebo for 12 weeks (70). Rosiglitazone significantly reduced several markers of endothelial activation and inflammation: E-selectin, von Willebrand factor, fibrinogen, and CRP. Plasminogen activator inhibitor type-1 (PAI-1) is another well-established inflammatory marker. Thiazolidinediones reduce PAI-1 protein expression in human preadipocytes and adipocytes (71). In addition, thiazolidinedione-mediated reduction in angiotensin II–induced PAI-1 expression is one suggested mechanism for a reduced incidence of microalbuminuria in diabetic nephropathy (72).

Endothelial function. The presence of NO, at low levels, is fundamental to endothelial health, and the ability of endothelial cells to synthesize this short-lived molecule is widely used as a marker of normal function. Agonists of PPARα and -γ have been shown to increase NO expression and release, respectively, from vascular endothelial cells (73,74), demonstrating that these agents may improve endothelial function in vivo.

Vascular remodeling. Vascular remodeling is now established as a key contributory factor in CVD. In vitro and in vivo studies have shown that thiazolidinediones inhibit the proliferation, hypertrophy, and migration of vascular smooth muscle cells (75–77). These agents also reduce the progression of intima-media thickness that commonly occurs in patients with atherosclerosis and, in some studies, decreases intima-media thickness per se (78,79). At least part of this action could be caused by interference with the mitogen-activated protein–kinase pathway (80).

Microvascular effects. In addition, PPARs can also exert a therapeutic effect on the microvascular complications of diabetes. In patients with diabetic nephropathy, characteristic morphologic changes such as thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial expansion lead to microalbuminuria. PPARγ ligands ameliorate microalbuminuria in patients with early diabetic nephropathy (81), reduce urinary albumin excretion in microalbuminuric patients, and decrease the serum concentration of type IV collagen (82).

FUTURE APPLICATIONS OF PPAR AGONISTS

PPARα and -γ ligands are in widespread clinical use for the treatment of dyslipidemia and insulin resistance, respectively. In addition, preclinical studies suggest that ligands of the more recently identified PPAR isoform PPARδ may be beneficial in patients with these conditions. PPARδ agonists have been shown to reduce levels of triglycerides and small, dense LDLs and to increase HDL cholesterol in insulin-resistant animals (83,84). These agents may therefore be of benefit in patients with diabetic dyslipidemia or the metabolic syndrome. Treatment of obese mice with a PPARδ agonist reduces obesity and insulin resistance via an effect on fatty acid oxidation in skeletal muscle (85). Although investigation of PPARδ has not yet progressed beyond the preclinical stage, these findings have led to suggestions that PPARδ may be a useful pharmacological target for treatment of obesity and insulin resistance (86). Furthermore, although the precise role of PPARδ in the inflammatory process has not been fully elucidated, this receptor may also have anti-inflammatory effects, in particular in macrophages (87).

As investigation of the PPAR family continues, it is becoming apparent that PPARs are involved in a wide range of physiological processes and, as a result, are potential targets for a number of disease processes in addition to dyslipidemia and type 2 diabetes, such as psoriasis (88) and multiple sclerosis (89).

CONCLUSIONS

PPARs are central to the regulation of energy homeostasis, with each isoform controlling particular aspects. As a result, agents that activate individual PPARs have different clinical effects. PPARα agonists are used in clinical practice for the treatment of dyslipidemia (in particular low HDL cholesterol and elevated triglyceride levels) and

reducing cardiovascular risk, whereas PPARγ agonists are currently used for the treatment of type 2 diabetes; by reducing insulin resistance, these agents effectively ameliorate hyperglycemia. The roles played by PPARδ in control of lipid metabolism, glucose metabolism, and obesity are currently under investigation.

The finding that PPAR agonists play a role in regulating other processes, such as inflammation, vascular function, and vascular remodeling, has highlighted further potential indications for these agents, of which a few have been touched on in this article. Continued study of these agents will, no doubt, reveal new applications. Furthermore, initial studies suggest that the advent of dual PPARα/γ and pan-PPAR agonists is likely to broaden the therapeutic value of these agents.

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REFERENCES

1. Kersten S, Desvergne B, Wahli W: Roles of PPARs in health and disease. *Nature* 405:421–424, 2000
2. NCEP Panel: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
3. Gervois P, Torra IP, Fruchart JC, Staels B: Regulation of lipid and lipoprotein metabolism by PPAR activators. *Clin Chem Lab Med* 38:3–11, 2000
4. Chinetti G, Lestavel S, Bocher V, Remaley AT, Neve B, Torra IP, Teissier E, Minnich A, Jaye M, Duverger N, Brewer HB, Fruchart JC, Clavey V, Staels B: PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. *Nat Med* 7:53–58, 2001
5. Ruotolo G, Ericsson CG, Tettamanti C, Karpe F, Grip L, Svane B, Nilsson J, de Faire U, Hamsten A: Treatment effects on serum lipoprotein lipids, apolipoproteins and low density lipoprotein particle size and relationships of lipoprotein variables to progression of coronary artery disease in the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT). *J Am Coll Cardiol* 32:1648–1656, 1998
6. de Faire U, Ericsson CG, Grip L, Nilsson J, Svane B, Hamsten A: Secondary preventive potential of lipid-lowering drugs: the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT). *Eur Heart J* 17:37–42, 1996
7. The BIP Study Group: Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. *Circulation* 102:21–27, 2000
8. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V: Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 317:1237–1245, 1987
9. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol: Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 341:410–418, 1999
10. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 357:905–910, 2001
11. Elkeles RS, Diamond JR, Poulter C, Dhanjil S, Mahmood S, Richmond W, Mather H, Sharp P, Feher MD: Cardiovascular outcomes in type 2 diabetes: a double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. *Diabetes Care* 21:641–648, 1998
12. Peters JM, Aoyama T, Burns AM, Gonzalez FJ: Bezafibrate is a dual ligand for PPARalpha and PPARbeta: studies using null mice. *Biochim Biophys Acta* 1632:80–89, 2003
13. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH: Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos* 30:1280–1287, 2002
14. Prueksaritanont T, Zhao JJ, Ma B, Roadcap BA, Tang C, Qiu Y, Liu L, Lin JH, Pearson PG, Baillie TA: Mechanistic studies on metabolic interactions between gemfibrozil and statins. *J Pharmacol Exp Ther* 301:1042–1051, 2002
15. Kyrklund C, Backman JT, Neuvonen M, Neuvonen PJ: Gemfibrozil increases plasma pravastatin concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther* 73:538–544, 2003
16. Kyrklund C, Backman JT, Kivisto KT, Neuvonen M, Laitila J, Neuvonen PJ: Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther* 69:340–345, 2001
17. Backman JT, Kyrklund C, Neuvonen M, Neuvonen PJ: Gemfibrozil greatly increases plasma concentrations of cerivastatin. *Clin Pharmacol Ther* 72:685–691, 2002
18. Schneck DW, Birmingham BK, Zalikowski JA, Mitchell PD, Wang Y, Martin PD, Lasseter KC, Brown CD, Windass AS, Raza A: The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 75:455–463, 2004
19. Wang JS, Neuvonen M, Wen X, Backman JT, Neuvonen PJ: Gemfibrozil inhibits CYP2C8-mediated cerivastatin metabolism in human liver microsomes. *Drug Metab Dispos* 30:1352–1356, 2002
20. Jones PH, Davidson MH: Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* 95:120–122, 2005
21. Robins SJ: Cardiovascular disease with diabetes or the metabolic syndrome: should statins or fibrates be first line lipid therapy? *Curr Opin Lipidol* 14:575–583, 2003
22. Tenkanen L, Manttari M, Manninen V: Some coronary risk factors related to the insulin resistance syndrome and treatment with gemfibrozil: experience from the Helsinki Heart Study. *Circulation* 92:1779–1785, 1995
23. Robins SJ, Rubins HB, Faas FH, Schaefer EJ, Elam MB, Anderson JW, Collins D, Veterans Affairs HDL Intervention Trial (VA-HIT): Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes Care* 26:1513–1517, 2003
24. Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, Frick MH: Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 15:820–825, 1992
25. Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, Faas FH, Anderson JW: Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med* 162:2597–2604, 2002
26. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Oliver D, Bacon BR: Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. *Hepatology* 38:1008–1017, 2003
27. Jiang G, Dallas-Yang Q, Li Z, Szalkowski D, Liu F, Shen X, Wu M, Zhou G, Doebber T, Berger J, Moller DE, Zhang BB: Potentiation of insulin signaling in tissues of Zucker obese rats after acute and long-term treatment with PPARγ agonists. *Diabetes* 51:2412–2419, 2002
28. Way JM, Harrington WW, Brown KK, Gottschalk WK, Sundseth SS, Mansfield TA, Ramachandran RK, Willson TM, Kliewer SA: Comprehensive messenger ribonucleic acid profiling reveals that peroxisome proliferator-activated receptor gamma activation has coordinate effects on gene expression in multiple insulin-sensitive tissues. *Endocrinology* 142:1269–1277, 2001
29. Kramer D, Shapiro R, Adler A, Bush E, Rondinone CM: Insulin-sensitizing effect of rosiglitazone (BRL-49653) by regulation of glucose transporters in muscle and fat of Zucker rats. *Metabolism* 50:1294–1300, 2001
30. Cabrero A, Laguna JC, Vazquez M: Peroxisome proliferator-activated receptors and the control of inflammation. *Curr Drug Targets Inflamm Allergy* 1:243–248, 2002
31. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, Kuriyama H, Hotta K, Nakamura T, Shimomura I, Matsuzawa Y: PPAR-gamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 50:2094–2099, 2001
32. Kumar S, Boulton AJ, Beck-Nielsen H, Berthezene F, Muggeo M, Persson B, Spinas GA, Donoghue S, Lettis S, Stewart-Long P: Troglitazone, an insulin action enhancer, improves metabolic control in NIDDM patients: Troglitazone Study Group. *Diabetologia* 39:701–709, 1996
33. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological

treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51:2796–2803, 2002

34. Miyazaki Y, Mahankali A, Matsuda M, Glass L, Mahankali S, Ferrannini E, Cusi K, Mandarino L, DeFronzo RA: Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care* 24:710–719, 2001

35. Rosenblatt S, Miskin B, Glazer NB, Prince MJ, Robertson KE: The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. *Coron Artery Dis* 12:413–423, 2001

36. Mayerson AB, Hundal RS, Dufour S, Lebon V, Befroy D, Cline GW, Enocksson S, Inzucchi SE, Shulman GI, Petersen KF: The effect of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. *Diabetes* 51:797–802, 2002

37. Patel J, Anderson RJ, Rappaport EB: Rosiglitazone monotherapy improves glycaemic control in patients with type 2 diabetes: a twelve-week, randomized, placebo-controlled study. *Diabetes Obes Metab* 1:165–172, 1999

38. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LH, Kahn R, American Heart Association, American Diabetes Association: Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* 108:2941–2948, 2003

39. Matsumoto K, Miyake S, Yano M, Ueki Y, Tominaga Y: Relationships between apolipoprotein(a) phenotype and increase of lipoprotein(a) by troglitazone. *Metabolism* 48:1–2, 1999

40. Ko SH, Song KH, Ahn YB, Yoo SJ, Son HS, Yoon KH, Cha BY, Lee KW, Son HY, Kang SK: The effect of rosiglitazone on serum lipoprotein(a) levels in Korean patients with type 2 diabetes mellitus. *Metabolism* 52:731–734, 2003

41. Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM: Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation* 111:583–590, 2005

42. Knowler WC, Hamman RF, Edelstein SL, Barrett-Connor E, Ehrmann DA, Walker EA, Fowler SE, Nathan DM, Kahn SE, Diabetes Prevention Program Research Group: Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. *Diabetes* 54:1150–1156, 2005

43. Bajaj M, Suraamornkul S, Pratipanawatr T, Hardies LJ, Pratipanawatr W, Glass L, Cersosimo E, Miyazaki Y, DeFronzo RA: Pioglitazone reduces hepatic fat content and augments splanchnic glucose uptake in patients with type 2 diabetes. *Diabetes* 52:1364–1370, 2003

44. Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, Tan MH, Khan MA, Perez AT, Jacober SJ, the GLAI Study Investigators: A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 28:1547–1554, 2005

45. Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, Beckles GL, Saaddine J, Gregg EW, Williamson DF, Narayan KM: Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 136:664–672, 2000

46. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 316:823–828, 1998

47. Malmberg K, Yusuf S, Gerstein HC, Brown J, Zhao F, Hunt D, Piegas L, Calvin J, Keltai M, Budaj A: Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation* 102:1014–1019, 2000

48. Elisaf M: Effect of fibrates on serum metabolic parameters. *Curr Med Res Opin* 18:269–276, 2002

49. Peters Harmel AL, Kendall DM, Buse JB, Boyle PJ, Marchetti A, Lau H: Impact of adjunctive thiazolidinedione therapy on blood lipid levels and glycemic control in patients with type 2 diabetes. *Curr Med Res Opin* 20:215–223, 2004

50. Diamant M, Heine RJ: Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence. *Drugs* 63:1373–1405, 2003

51. Nagashima K, Lopez C, Donovan D, Ngai C, Fontanez N, Bensadoun A, Fruchart-Najib J, Holleran S, Cohn JS, Ramakrishnan R, Ginsberg HN: Effects of the PPARγ agonist pioglitazone on lipoprotein metabolism in patients with type 2 diabetes mellitus. *J Clin Invest* 115:1323–1332, 2005

52. Tack CJ, Smits P, Demacker PN, Stalenhoef AF: Troglitazone decreases the proportion of small, dense LDL and increases the resistance of LDL to oxidation in obese subjects. *Diabetes Care* 21:796–799, 1998

53. Freed MI, Ratner R, Marcovina SM, Kreider MM, Biswas N, Cohen BR, Brunzell JD: Rosiglitazone Study 108 investigators: Effects of rosiglitazone alone and in combination with atorvastatin on the metabolic abnormalities in type 2 diabetes mellitus. *Am J Cardiol* 90:947–952, 2002

54. Winkler K, Konrad T, Fullert S, Friedrich I, Destani R, Baumstark MW, Krebs K, Wieland H, Marz W: Pioglitazone reduces atherogenic dense LDL particles in nondiabetic patients with arterial hypertension: a double-blind, placebo-controlled study. *Diabetes Care* 26:2588–2594, 2003

55. Ljung B, Bamberg K, Dahllof B, Kjellstedt A, Oakes ND, Ostling J, Svensson L, Camejo G: AZ 242, a novel PPARa/g agonist with beneficial effects on insulin resistance and carbohydrate and lipid metabolism in ob/ob mice and obese Zucker rats. *J Lipid Res* 43:1855–1863, 2002

56. Skrumsager BK, Nielsen KK, Muller M, Pabst G, Drake PG, Edsberg B: Ragaglitazar: the pharmacokinetics, pharmacodynamics, and tolerability of a novel dual PPAR alpha and gamma agonist in healthy subjects and patients with type 2 diabetes. *J Clin Pharmacol* 43:1244–1256, 2003

57. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 287:356–359, 2002

58. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001

59. Delerive P, Martin-Nizard F, Chinetti G, Trottein F, Fruchart JC, Najib J, Duriez P, Staels B: Peroxisome proliferator-activated receptor activators inhibit thrombin-induced endothelin-1 production in human vascular endothelial cells by inhibiting the activator protein-1 signaling pathway. *Circ Res* 85:394–402, 1999

60. Fruchart JC, Duriez P, Staels B: Peroxisome proliferator-activated receptor-alpha activators regulate genes governing lipoprotein metabolism, vascular inflammation and atherosclerosis. *Curr Opin Lipidol* 10:245–257, 1999

61. Marx N, Mackman N, Schonbeck U, Yilmaz N, Hombach V, Libby P, Plutzky J: PPARalpha activators inhibit tissue factor expression and activity in human monocytes. *Circulation* 103:213–219, 2001

62. Neve BP, Corseaux D, Chinetti G, Zawadzki C, Fruchart JC, Duriez P, Staels B, Jude B: PPARalpha agonists inhibit tissue factor expression in human monocytes and macrophages. *Circulation* 103:207–212, 2001

63. Kleemann R, Verschuren L, De Rooij BJ, Lindeman J, De Maat MM, Szalai AJ, Princen HM, Kooistra T: Evidence for anti-inflammatory activity of statins and PPAR{alpha}-activators in human C-reactive protein transgenic mice in vivo and in cultured human hepatocytes in vitro. *Blood* 103:4188–4194, 2004

64. Gervois P, Vu-Dac N, Kleemann R, Kockx M, Dubois G, Laine B, Kosykh V, Fruchart JC, Kooistra T, Staels B: Negative regulation of human fibrinogen gene expression by peroxisome proliferator-activated receptor alpha agonists via inhibition of CCAAT box/enhancer-binding protein beta. *J Biol Chem* 276:33471–33477, 2001

65. Ziouzenkova O, Asatryan L, Sahady D, Orasanu G, Perrey S, Cutak B, Hassell T, Akiyama TE, Berger JP, Sevanian A, Plutzky J: Dual roles for lipolysis and oxidation in peroxisome proliferation-activator receptor responses to electronegative low density lipoprotein. *J Biol Chem* 278:39874–39881, 2003

66. Tontonoz P, Nagy L, Alvarez JG, Thomazy VA, Evans RM: PPARgamma promotes monocyte/macrophage differentiation and uptake of oxidized LDL. *Cell* 93:241–252, 1998

67. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327–334, 2001

68. Ridker PM, Hennekens CH, Buring JE, Rifai N: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 342:836–843, 2000

69. Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI: Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation* 106:679–684, 2002

70. Sidhu JS, Cowan D, Kaski JC: The effects of rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein, and fibrinogen levels in non-diabetic coronary artery disease patients. *J Am Coll Cardiol* 42:1757–1763, 2003

71. Zirlik A, Leugers A, Lohrmann J, Ernst S, Sobel BE, Bode C, Nordt TK: Direct attenuation of plasminogen activator inhibitor type-1 expression in human adipose tissue by thiazolidinediones. *Thromb Haemost* 91:674–682, 2004

72. Nicholas SB, Kawano Y, Wakino S, Collins AR, Hsueh WA: Expression and function of peroxisome proliferator-activated receptor-gamma in mesangial cells. *Hypertension* 37:722–727, 2001

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

74. Goya K, Sumitani S, Xu X, Kitamura T, Yamamoto H, Kurebayashi S, Saito H, Kouhara H, Kasayama S, Kawase I: Peroxisome proliferator-activated receptor alpha agonists increase nitric oxide synthase expression in vascular endothelial cells. *Arterioscler Thromb Vasc Biol* 24:658–663, 2004

75. Dubey RK, Zhang HY, Reddy SR, Boegehold MA, Kotchen TA: Pioglitazone attenuates hypertension and inhibits growth of renal arteriolar smooth muscle in rats. *Am J Physiol* 265:R726–R732, 1993

76. Law RE, Meehan WP, Xi XP, Graf K, Wuthrich DA, Coats W, Faxon D, Hsueh WA: Troglitazone inhibits vascular smooth muscle cell growth and intimal hyperplasia. *J Clin Invest* 98:1897–1905, 1996

77. de Dios ST, Bruemmer D, Dilley RJ, Ivey ME, Jennings GL, Law RE, Little PJ: Inhibitory activity of clinical thiazolidinedione peroxisome proliferator activating receptor-gamma ligands toward internal mammary artery, radial artery, and saphenous vein smooth muscle cell proliferation. *Circulation* 107:2548–2550, 2003

78. Minamikawa J, Tanaka S, Yamauchi M, Inoue D, Koshiyama H: Potent inhibitory effect of troglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab* 83:1818–1820, 1998

79. Sidhu JS, Kaposzta Z, Markus HS, Kaski JC: Effect of rosiglitazone on common carotid intima-media thickness progression in coronary artery disease patients without diabetes mellitus. *Arterioscler Thromb Vasc Biol* 24:930–934, 2004

80. Graf K, Xi XP, Hsueh WA, Law RE: Troglitazone inhibits angiotensin II-induced DNA synthesis and migration in vascular smooth muscle cells. *FEBS Lett* 400:119–121, 1997

81. Imano E, Kanda T, Nakatani Y, Nishida T, Arai K, Motomura M, Kajimoto Y, Yamasaki Y, Hori M: Effect of troglitazone on microalbuminuria in patients with incipient diabetic nephropathy. *Diabetes Care* 21:2135–2139, 1998

82. Nakamura T, Ushiyama C, Suzuki S, Shimada N, Sekizuka K, Ebihara L, Koide H: Effect of troglitazone on urinary albumin excretion and serum type IV collagen concentrations in type 2 diabetic patients with microalbuminuria or macroalbuminuria. *Diabet Med* 18:308–313, 2001

83. Leibowitz MD, Fievet C, Hennuyer N, Peinado-Onsurbe J, Duez H, Bergera J, Cullinan CA, Sparrow CP, Baffic J, Berger GD, Santini C, Marquis RW, Tolman RL, Smith RG, Moller DE, Auwerx J: Activation of PPARdelta alters lipid metabolism in db/db mice. *FEBS Lett* 473:333–336, 2000

84. Oliver WR Jr, Shenk JL, Snaith MR, Russell CS, Plunket KD, Bodkin NL, Lewis MC, Winegar DA, Sznaidman ML, Lambert MH, Xu HE, Sternbach DD, Kliewer SA, Hansen BC, Willson TM: A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. *Proc Natl Acad Sci U S A* 98:5306–5311, 2001

85. Tanaka T, Yamamoto J, Iwasaki S, Asaba H, Hamura H, Ikeda Y, Watanabe M, Magoori K, Ioka RX, Tachibana K, Watanabe Y, Uchiyama Y, Sumi K, Iguchi H, Ito S, Doi T, Hamakubo T, Naito M, Auwerx J, Yanagisawa M, Kodama T, Sakai J: Activation of peroxisome proliferator-activated receptor delta induces fatty acid beta-oxidation in skeletal muscle and attenuates metabolic syndrome. *Proc Natl Acad Sci U S A* 100:15924–15929, 2003

86. Marx N, Duez H, Fruchart J-C, Staels B: Peroxisome proliferator-activated receptors and atherogenesis: regulators of gene expression in vascular cells. *Circ Res* 94:1168–1178, 2004

87. Lee CH, Chawla A, Urbiztondo N, Liao D, Boisvert WA, Evans RM, Curtiss LK: Transcriptional repression of atherogenic inflammation: modulation by PPARdelta. *Science* 302:453–457, 2003

88. Ellis CN, Varani J, Fisher GJ, Zeigler ME, Pershadsingh HA, Benson SC, Chi Y, Kurtz TW: Troglitazone improves psoriasis and normalizes models of proliferative skin disease: ligands for peroxisome proliferator-activated receptor-gamma inhibit keratinocyte proliferation. *Arch Dermatol* 136:609–616, 2000

89. Lovett-Racke AE, Hussain RZ, Northrop S, Choy J, Rocchini A, Matthes L, Chavis JA, Diab A, Drew PD, Racke MK: Peroxisome proliferator-activated receptor alpha agonists as therapy for autoimmune disease. *J Immunol* 172:5790–5798, 2004