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Modulating peroxisome proliferator–activated receptors for therapeutic benefit? Biology, clinical experience, and future prospects

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Abstract

Clinical trials of cardiovascular disease (CVD) prevention in patients with type 2 diabetes mellitus primarily have been directed at the modification of a single major risk factor; however, in trials that enroll patients with and without diabetes, the absolute risk in CVD events remains higher in patients with diabetes. Efforts to reduce the macrovascular and microvascular residual risk have been directed toward a multifactorial CVD risk-factor modification; nonetheless, long-term complications remain high. Dual-peroxisome proliferator–activated receptor (PPAR) α/γ agonists may offer opportunities to lower macrovascular and microvascular complications of type 2 diabetes mellitus beyond the reductions achieved with conventional risk-factor modification. The information presented elucidates the differentiation of compound-specific vs class-effect properties of PPARs as the basis for future development of a new candidate molecule. Prior experience with thiazolidinediones, an approved class of PPAR γ agonists, and glitazars, investigational class of dual-PPAR α/γ agonists, also provides important lessons about the risks and benefits of targeting a nuclear receptor while revealing some of the future challenges for regulatory approval.

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Worldwide trends in certain deleterious lifestyles are associated with an epidemic in disorders of insulin resistance manifested by the phenotypic expression of obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM).^{1,2} The transition to T2DM heralds an increased risk of macrovascular and microvascular diseases,³ and these cardiovascular disease (CVD) events continue to increase in the ensuing years after the diagnosis of T2DM.^{4–6} Often, multiple risk factors contribute to macrovascular events in patients with T2DM,⁷ whereas glycemic status is the main risk factor for microvascular disease.⁸

Clinical trials of CVD prevention in patients with T2DM primarily have been directed at the modification of a single major risk factor, as seen in trials of antihypertensive agents⁹ and lipid-lowering therapies.^{10–17} In these trials that enroll both nondiabetic and diabetic patients, relative risk reductions with cholesterol-lowering therapies are similar in both groups; however, the absolute risk in CVD events remains markedly higher in patients with diabetes.^{15,18} The difference in macrovascular and microvascular events in “treated” diabetic patients has been described as *residual risk*.⁷ A multifactorial CVD risk-factor modification intervention program in T2DM is a rational and efficacious treatment strategy for the prevention of macrovascular and microvascular complications in patients with type 2 diabetes and microalbuminuria¹⁹; however, the risk of recurrent macrovascular events and microvascular complications remains high. The residual risk is enhanced by inadequate remediation of multiple risk factors^{20–22} and poor treatment adherence to multidrug regimens.^{23,24} Improved use of evidence-based therapy in the United States have been accompanied by reductions in CVD events.²⁵

With this perspective as background, we discuss the actions of dual-peroxisome proliferator-activated receptor (PPAR) α/γ agonists and the implications for the prevention of macrovascular and microvascular complications of T2DM. With past experience in this class of agents, we present information that regards differentiation of compound-specific vs class-effect properties as the basis for future development of a new candidate molecule. However, prior experience with thiazolidinediones (TZDs), an approved class of PPAR γ agonists, and glitazars, investigational class of dual-PPAR α/γ agonists, also provides important lessons about the risks and benefits of targeting a nuclear receptor and revealing some of the future challenges for regulatory approval.

Peroxisome proliferator-activated receptor biology: implications for practice

Peroxisome proliferator-activated receptors are ligand-activated transcription factors and members of the nuclear receptor family, which also includes the estrogen receptor and the thyroid hormone receptor. Three PPAR isotypes exist: PPAR α , PPAR γ , and PPAR δ . All 3 PPARs have both shared and distinct aspects of their biology. When activated by specific ligands, nuclear receptors become transcription factors that regulate the expression of distinct target genes. This control of gene expression occurs through the assembly of a transcriptional complex. For PPARs, this complex includes the retinoid X receptor (RXR), another nuclear receptor that is an obligate heterodimeric partner for various nuclear receptors. Retinoid X receptor has its own ligand, which is thought to be 9-*cis*-retinoic acid.

Nuclear receptors including PPARs and RXRs have a generally conserved overall domain structure:

1. DNA-binding domain, which governs the receptor binding to RXR and PPAR response elements in target gene promoters;
2. a ligand-binding domain, which determines how specific pharmacologic and endogenous nuclear receptor ligands bind to and modulate receptor activity; and
3. activation domains, which help determine receptor activity.

In response to a specific ligand, PPARs undergo a conformational change, allowing recruitment or release of accessory molecules (known as coactivators or corepressors, respectively) that are key determinants of the functional state of the PPAR-RXR transcriptional complex.²⁶

The clinical relevance of this brief summary of PPAR biology rests in the fact that the complexity of this mechanism identifies multiple variables that could influence the responses to any given clinical agonist. First, the DNA-binding domains of PPARs are exceptionally large. Thus, different synthetic PPAR agonists, or their metabolites, can attach to the ligand-binding domain in a distinctive way, resulting in different conformational states and differential accessory molecule recruitment. The formation of endogenous ligands or the catabolism of synthetic agonists may vary, directly influencing responses. Accessory molecules can differ in specific tissues, a potential contributor to why a PPAR agonist has unique effects in different tissues. Promoter regions may vary, particularly as a function of genetics, resulting in different responses. Other modifications of PPARs can occur through phosphorylation. Finally, it is important to keep in mind that all of these factors also vary for RXR, ultimately influencing the PPAR response seen.²⁶

Within the context of this basic science, there has been extensive work through multiple lines of evidence that PPARs act as key regulators of energy balance. Peroxisome proliferator-activated receptor activation regulates the expression of multiple target genes involved in glucose homeostasis, fatty acid oxidation, and lipid metabolism. Importantly, because each PPAR isotype controls not just 1 but rather multiple target genes, PPAR activation allows for coordinated regulation of programs of functional responses. In the same way that insulin regulates multiple responses by binding to and activating the insulin receptor, all of which coordinate how the body responds to a meal or glucose load, PPAR activation affords a systematic response through gene regulation. It is important to note that PPARs can both induce or repress expression of target genes. In addition to their actions on metabolism, PPARs also have been shown to repress inflammation and modulate responses relevant to atherosclerosis (discussed further for each PPAR isotype later). These general observations in regard to PPAR action are derived from various lines of evidence, including the cellular responses to synthetic PPAR agonists, which contributed to the Food and Drug Administration's (FDA's) approval of PPARs for clinical use.²⁷

Although most of the effects attributed to PPAR action is through their regulation of gene expression, ongoing basic science work also has identified other mechanisms that can influence or help explain PPAR responses. For example, in response to a PPAR ligand such

as a TZD, PPAR γ can undergo a posttranslational modification known as SUMOylation, in which the Small Ubiquitin Modifier (SUMO) is linked to PPAR γ , resulting in stabilization of a conformation with a transcriptional corepressor that blocks gene expression. Because PPAR γ SUMOylation can repress transcription of inflammatory target genes, as has been suggested in macrophages, this could help explain PPAR effects in atherosclerosis and inflammation.²⁸

Peroxisome proliferator–activated receptor α

Peroxisome proliferator–activated receptor α , expressed in the skeletal muscle and liver, is a master regulator of fatty acid oxidation. Peroxisome proliferator–activated receptor α –activating fibrates were in use as agents that lower triglycerides and raise high-density lipoprotein (HDL) before PPAR α was even known to exist.²⁹ The effects of fibrates provide a robust example of how PPARs induce coordinated programs of gene expression. Peroxisome proliferator–activated receptor α activation increases the expression of lipoprotein lipase, which hydrolyzes fatty acids from triglycerides; represses the expression of apolipoprotein (Apo) C3, the endogenous lipoprotein lipase repressor; increases expression of fatty acid repressors such as CD36; and increases multiple β -oxidation enzymes. Thus, PPAR α regulates a series of steps, all oriented toward triglyceride lowering and fatty acid oxidation. Indeed, lipoprotein lipase action even generates endogenous PPAR α ligands.³⁰ Peroxisome proliferator–activated receptor α increases expression of ApoA1, the major lipoprotein of HDL. Peroxisome proliferator–activated receptor α also is expressed in vascular smooth muscle cells, endothelial cells, monocytes/macrophages, and T cells, with evidence for decreased proatherosclerotic responses and inflammation.^{31,32}

Peroxisome proliferator–activated receptor γ

Peroxisome proliferator–activated receptor γ is present in adipocytes and is well established as a master regulator of adipogenesis and, in vivo, as an insulin sensitizer, as evidenced by the effects of TZDs as PPAR γ agonists.³³ Peroxisome proliferator–activated receptor γ is expressed throughout the vasculature and in inflammatory cells where it decreases inflammation and atherosclerosis in multiple models and settings.^{34–36}

Peroxisome proliferator–activated receptor δ

Peroxisome proliferator–activated receptor δ also is widely expressed, but it is the least-studied PPAR, in part perhaps from the lack of any studied PPAR δ agonist to ever reach clinical approval. Like PPAR α , PPAR δ activation can increase fatty acid oxidation, repress inflammation, and increase ApoA1 and HDL levels. However, PPAR δ activation also results in actions distinct from PPAR α .²⁷

As previously pointed out, PPAR biology is complex, incompletely understood, and dependent on the specific nature of a given agonist. The selective PPAR modulator concept derives from this notion and the idea that specific PPAR modulating agents might be developed that limit known adverse effects of the current or prior PPAR agonists while retaining their benefit. Certainly, selective estrogen modulators exist, with distinct effects between raloxifene, tamoxifen, and estrogen itself. We also know that 2 TZDs, rosiglitazone and pioglitazone, are free of the irreversible liver failure that led to the withdrawal of the

first approved TZD agent troglitazone. Pioglitazone also has been shown to have distinct clinical effects from rosiglitazone, as well as different patterns of regulated gene expression. As one example of such distinctions, pioglitazone has effects on endothelial responses in vitro and in vivo that appear dependent on PPAR α , arguing for “cross-talk” between PPAR γ -activating pioglitazone or 1 of its metabolites on PPAR α . Moreover, recent studies have uncovered novel aspects that may contribute to PPAR responses including protein modification through SUMOylation, decreased phosphorylation of cyclin-dependent kinase 5, and modulation of RXR activation, all of which contribute to distinct effects of any given PPAR agonist.²⁷

Peroxisome proliferator–activated receptor therapies in current practice

Despite the controversy around the clinical actions of PPAR agonists, ongoing preclinical work has continued to explore PPARs in terms of metabolism and atherosclerosis. It is worth noting that those preclinical studies have shown, in a fairly consistent manner, that PPAR activation improves metabolism, limits inflammation, and/or decreases atherosclerosis. Multiple studies have shown decreased inflammation and atherosclerosis in mouse models and in human surrogate studies.²⁷

Peroxisome proliferator–activated receptor agonists

Thiazolidinediones are a class of PPAR γ agonists that improve insulin resistance³⁷ and certain biomarkers associated with atherosclerosis and CVD events.^{38–40} For this reason, this class of antidiabetic agents had been considered as targeted therapy for the underlying cause of T2DM in the era when these agents received regulatory approval for their effects on glycemic status. However, reports of congestive heart failure raised concerns about the risks of this class of agents.^{38,41} Furthermore, the presumed superiority of TZDs on atherothrombotic CVD was theoretical due to the lack of evidence on CVD events that would be acquired from large-scale, double-blind, randomized, placebo-controlled trials. Although the efficacy of pioglitazone was investigated in a placebo-controlled trial of high-risk diabetic patients with atherosclerotic vascular disease,⁴² the primary composite end point that comprised macrovascular events and revascularization procedures was not reduced significantly. Although clinical events were reduced by pioglitazone therapy, this effect was not observed in those patients receiving statin therapy.⁴³ Thus, the one purported favorable clinical trial with a TZD agent is not satisfactory evidence because of the lack of contemporary treatment.

Adverse event report surveillance after the specific TZD agents was approved, providing the earliest concern about potential hazards of TZD therapy on CVD morbidity and mortality and non-CVD conditions such as hepatotoxicity with troglitazone,⁴⁴ bone fractures with rosiglitazone⁴⁵ and pioglitazone,⁴⁶ and bladder cancer with pioglitazone.⁴⁷ In meta-analyses, rosiglitazone was associated with a higher risk of myocardial infarction (MI) and CVD mortality,⁴⁸ and both rosiglitazone and pioglitazone were accompanied by an increased risk of congestive heart failure.⁴⁵ In the Medicare database, differences in CVD morbidity with rosiglitazone and pioglitazone were explored.⁴⁹ In these reports, rosiglitazone use was associated with more MI and more hospitalizations for congestive

heart failure. The CVD hazards associated with rosiglitazone therapy promoted its withdrawal by the European Medicines Agency,⁵⁰ and its use was restricted by the FDA.⁵¹ Recent concerns about the risk of bladder cancer with pioglitazone therapy have presented another concern related to this therapeutic agent that resulted in labeling changes, which advised that pioglitazone not be used in patients with active bladder cancer and used with caution in patients with history of bladder cancer.⁵²

Further exploration of mechanisms may lead to novel ways to achieve PPAR activation effects without some of the adverse effects. For example, inhibition of CDK5 phosphorylation has been suggested to be the mechanism through which some of PPAR γ effects occur.⁵³

The angiotensin receptor antagonist telmisartan is a partial agonist of PPAR γ that may have antiatherogenic effects in hypertensive patients. Treatment with telmisartan results in an increase of PPAR γ gene expression in peripheral monocytes and significant inhibition of monocyte chemoattractant protein-1 gene expression.⁵⁴ Other antiatherosclerotic effects of telmisartan reported in experimental animals include induced messenger RNA expression of ATP-binding cassette transporters A1 and G1 (ABCA1/G1), reduced proinflammatory cytokine gene activation, and antifibrotic effects that are mediated through inhibition of hepatocyte growth factor, a downstream effector of PPAR γ activation, that regulates the expression of transforming growth factor- β 1 and other profibrotic cytokine genes.^{55,56}

Peroxisome proliferator-activated receptor α agonists

Fibric acid derivatives have been investigated in multiple clinical trials that have included patients with T2DM.¹⁴ In these trials, gemfibrozil therapy reduced incident CVD events including in subgroups of T2DM patients with and without established CVD.^{57,58} In contrast, the more potent PPAR α agonist, fenofibrate, has not shown any reduction in macrovascular events in T2DM when used as monotherapy¹⁶ or in combination with simvastatin.¹³ One limitation of these clinical trials with fenofibrate may relate to the inclusion of patients with a broad range of fasting triglycerides and HDL cholesterol levels, after it had been established that fibrates are substrate specific, requiring a certain level of triglycerides for their clinical efficacy.⁵⁹ In contrast with the lack of overall efficacy in the prevention of macrovascular disease, fenofibrate therapy has shown consistent benefits in the prevention of microvascular complications of diabetes.^{60–63}

Dual-PPAR agonists

Several dual-PPAR agonists (eg, muraglitazar and tesaglitazar) have been investigated in late-phase trials. The clinical trial development of both agents has been terminated for different adverse events that included an increase in congestive heart failure with muraglitazar and renal toxicity with tesaglitazar. Other glitazar programs (ragaglitazar/KRP-297, KRP 0767/MK-0767) have been concluded due to carcinogenicity in preclinical studies. Overall, the failed development of several glitazars represents increased awareness and focus concerning potential toxicities with this class of agents.⁶⁴

Most recently, a novel dual-PPAR agonist, aleglitazar, has entered into phase III clinical development.⁶⁵ Aleglitazar is a balanced dual-PPAR agonist, equally stimulating *PPARα* and *PPARγ* genes. This PPAR agonist appears to be ideally suited for patients with T2DM and coronary artery disease, given its balance of *PPARα* and γ stimulation.⁶⁶ Effect of the dual peroxisome proliferator-activated receptor- α/γ agonist aleglitazar on risk of cardiovascular disease in patients with type 2 diabetes (SYNCHRONY)⁶⁷ was a 16-week, phase II, randomized, placebo-controlled trial designed to determine the optimal dose of aleglitazar with regard to the most efficacious treatment of diabetes and lipids. The study randomized 332 patients to 1 of 5 doses of aleglitazar, pioglitazone 45 mg once daily, or placebo. Treatment was continued for 16 weeks at 50 μg ($n = 55$), 150 μg ($n = 55$), 300 μg ($n = 55$), and 600 μg ($n = 55$) once daily of aleglitazar, 45 mg of pioglitazone ($n = 57$), or placebo ($n = 55$). The primary end point of the trial was change in hemoglobin A1C values from baseline until study end. The use of aleglitazar was associated with dose-dependent reductions in mean hemoglobin A1C values of -0.36% at the 150- μg dose, approximately -0.60% at the 300- μg dose, and up to -1.35% at the 600- μg dose compared with the use of placebo ($P < .05$ for all doses of aleglitazar vs placebo). The use of pioglitazone also reduced mean hemoglobin A1C values by approximately 0.30% compared with placebo. Aleglitazar appeared to lower hemoglobin A1C more than pioglitazone at the doses tested, but intergroup statistical testing was not reported.

Aleglitazar was associated with significant reductions in plasma triglycerides across all doses compared with placebo and with increased HDL cholesterol concentrations across all doses tested ($P < .01$). The 50- μg dose of aleglitazar reduced triglycerides approximately 15% , whereas higher doses of aleglitazar reduced triglycerides between 30% and 40% . Aleglitazar increased plasma HDL cholesterol levels approximately 13% at the 50- μg dose; at higher doses, the increase was in excess of 25% . Plasma low-density lipoprotein cholesterol concentrations were reduced by 4% at the 50- μg dose of aleglitazar and up to 20% at the highest dose of aleglitazar ($P < .01$), whereas ApoB values were reduced 10% to 30% across all doses of aleglitazar ($P < .01$). Although aleglitazar was associated with changes in these lipid parameters, pioglitazone had minimal effects on plasma lipids. In summary, the SYNCHRONY study demonstrated that use of aleglitazar was associated with more potent favorable changes in lipid parameters and enhanced glycemic control compared with pioglitazone.⁶⁷

With regard to safety, aleglitazar was very well tolerated and had a similar adverse-effect profile to that of pioglitazone. With both agents, there were reports of edema, with the highest doses of aleglitazar having 1 to 2 more subjects reporting edema than was reported from those randomized to pioglitazone. There were no statistically significant differences between the varying doses of aleglitazar and that of pioglitazone. There were a small number of patients reporting a drop in hemoglobin A1C in the aleglitazar group, whereas there were no reports of this in the pioglitazone group. There were only 2 cases of adjudicated congestive heart failure in the aleglitazar group. Serum creatinine levels rose by 5% to 16% across the escalating doses of aleglitazar, and estimated glomerular filtration rate fell 4% to 14% across those doses. The maximum changes in serum creatinine appeared to

plateau at 4 weeks, and the observed changes were reversible once the study drug was discontinued.⁶⁷

All in all, the preliminary data from the SYNCHRONY study and previous phase II studies suggest that aleglitazar is an effective dual-PPAR agonist associated with improved glycemic control, reduced plasma triglycerides and low-density lipoprotein cholesterol, and increased plasma HDL cholesterol. The changes exerted by aleglitazar appear favorable for treating diabetic patients and their associated dyslipidemia without any increase in reported adverse events or severe adverse events, except a reversible small decline in glomerular filtration rate.

Recommendations for the future: application of regulatory guidance

From the outset, it has been critical to briefly review the development of PPAR agonists to fully understand the major differences between agents. For CVD specialists, this came to the forefront after the publication of the meta-analysis of Nissen and Wolski⁴⁸ in 2007. In the pooling of the CVD safety data on rosiglitazone compared with usual care, there was a statistically significant excess of MI and CVD death in the rosiglitazone arm. A subsequent meta-analysis of the pioglitazone trials did not show the same trend and, in fact, demonstrated a trend toward a benefit with pioglitazone.⁶⁸ An excess of CVD ischemic events also was observed for muraglitazar, a dual- α/γ agonist.⁶⁹

Another CVD safety signal revolved around the PPAR γ -mediated effects of fluid accumulation, weight gain, and edema, leading to an increased incidence of congestive heart failure. In fact, what was consistent for both rosiglitazone and pioglitazone was the excess of heart failure episodes.⁷⁰ Unless a clinical trial is powered sufficiently and designed to adequately evaluate long-term effects, heart failure and other secondary outcome measures could be overlooked. Given these issues, a number of important observations related to the future of PPAR clinical development deserve mention. Of importance, dosing for chronic therapy may be quite different than it is for short-term trials, which may alter the identified CVD effects. Patients with New York Heart Classification classes 3 and 4 were excluded from previous trials, thus limiting the CVD risk in patients enrolled in these earlier trials.

The potential for carcinogenicity also has been raised with some of the PPAR agonists, including a recent report that bladder tumors may be associated with the use of pioglitazone.⁵² Mechanistic data to link PPAR agonists with carcinogenicity are lacking, making the importance of ongoing surveillance even more relevant. Are these findings the play of chance? Although this is outside the realm of this discussion, clearly the combined risks of CVD events and cancer need to be part of the overall safety profile of a PPAR compound.

Food and Drug Administration requirements for evaluation of cardiovascular risk with antidiabetic therapy

Recent developments and adverse event reports led to a wholesale evaluation of how diabetes drugs are approved by the FDA, which has direct relevance to the future of PPAR agents. In the past, the process was based on the premise that benefits outweighed the risks,

but evaluation did not principally address CVD safety. In December 2008, the FDA issued a broad and comprehensive statement regarding the development of new diabetes drugs, elaborating the means by which the CVD safety issue should be addressed.⁷¹ This document focused on CVD risk in phase II and III clinical trials and recommended the following:

1. Accruing a sufficient number of CVD events by enrolling patients at higher CVD risk.
2. Establishing independent CVD events adjudication committees to provide valid end point data for CVD death, nonfatal MI, nonfatal stroke, acute coronary syndrome requiring hospitalization, and urgent coronary revascularization.
3. Planning for meta-analyses of clinical trials to allow for a more robust assessment of CVD risk.
4. Demonstrating that new antidiabetic therapies do not increase CVD risk in comparison with existing therapies, especially when the drugs are used by the elderly or those with renal impairment. A proposed upper limit of the 95% confidence interval for the estimated risk ratio of less than 1.8 would have to be achieved before submission of the investigational drug for a new drug indication. This can be achieved either with a meta-analysis of phase II and III trials or by the addition of a large outcomes trial. For postmarketing safety, if the 2-sided upper bound of the 95% confidence interval for the estimated risk ratio lies between 1.3 and 1.8 from the premarketing data, then an additional outcomes trial will be required at the threshold of less than 1.3 to declare CVD safety.
5. Including long-term follow-up to at least 2 years, which is much longer than the 3 to 6 months seen in the past.

Future recommendations

The heterogeneity of clinical activity and toxicity demand that each PPAR agonist be evaluated on its own merits. The stimulation of the PPAR family of genes is complex and unpredictable, as previously discussed in this review. Indeed, it may be precisely the balance of α vs γ stimulation that determines efficacy and toxicity, including late toxicity. Within the PPAR family, there is no “class effect,” and each agent must be considered unique. The FDA has mandated that each agent within this class be evaluated individually in a variety of ways including clinical outcome studies.

Given the fact that the yardsticks have been moved to a more rigorous evaluation of antidiabetic therapy, it will be important to design trials that will be the most informative and efficient for the evaluation of safety and efficacy (Table).⁷²

Current large outcome-based clinical trials with incretin therapies as well as with a combined PPAR α / γ agent (ie, aleglitazar) are underway and have adopted many of these strategies. These data will be instrumental in determining the future clinical role of PPARs.

Mitigating risk in the patients with post-ACS: potential role for dual-agonists

The findings of the SYNCHRONY trial led to the design and implementation of the phase III aleglitazar to reduce cardiovascular risk CHD patients with a recent ACS event and type 2 diabetes mellitus (ALECARDIO) clinical trial.⁷³ The ALECARDIO study is a double-blind, placebo-controlled, multicenter, randomized trial testing the addition of aleglitazar on top of standard diabetic therapy and statin treatment in diabetic patients who have experienced a recent ACS. Approximately 6000 patients with recent ACS are being randomized to aleglitazar 150 µg daily or placebo. The study will continue for at least 2.5 years or until 950 events have occurred.

The primary end point is the combination of CVD mortality, nonfatal MI, and nonfatal stroke. The ALECARDIO study is designed to meet the FDA requirement that new diabetic agents be tested in a major morbidity and mortality end point trial. Aleglitazar may offer unique benefit to diabetic patients with ACS, given the findings of SYNCHRONY with regard to improvement in glycemic control and favorable alterations in plasma lipids. Diabetic patients with an ACS event have elevated short- and long-term risks for recurrence. Furthermore, there is an elevated residual risk in the population despite optimal low-density lipoprotein cholesterol lowering with statin agents. In addition, recent data from diabetic treatment studies such as action to control cardiovascular risk in diabetes (ACCORD) leave open the possibility that the optimal degree of glycemic control remains unknown in patients with T2DM.

Certainly, additional studies will need to be undertaken with aleglitazar if it is approved by the FDA for the treatment of T2DM. The potential clinical benefit of balanced dual-PPAR activation ultimately may extend beyond diabetic populations with a recent ACS.⁷⁴ One can envision that patients with established coronary artery disease might benefit from an agent that improves glycemic control, reduces insulin resistance, promotes insulin sensitization, alters inflammation, and modulates plasma lipids away from a dyslipidemic pattern.^{21,65,66} The properties of aleglitazar suggest that it might favorably alter atherosclerotic progression similar to what has been observed in prior intravascular ultrasound studies with TZD agents.^{75,76} Finally, it may be that this class of therapy will prove beneficial in patients with metabolic syndrome, the precursor for diabetes. Much of the pathophysiology of metabolic syndrome is favorably altered through balanced dual-PPAR activation. Although it is easy to speculate about the potential clinical use of aleglitazar, prior experiences suggest that it will be essential to evaluate each scenario in several well-planned, carefully controlled trials to ensure both efficacy and safety.^{76–78}

Conclusions

Evidence-based CVD preventive therapies effectively reduce macrovascular events in patients with T2DM, but they are less effective in reducing the burden of microvascular complications. Activation of PPARs has been considered an important pharmacologic target for patients with T2DM, due to the established role these transcription factors play in the regulation of energy balance, as well as in the expression of multiple genes involved in the

metabolism of biomarkers intimately involved in the pathogenesis of both macrovascular and microvascular diseases. Although PPAR agonists improve glucose control and insulin sensitivity, reduce concentrations of atherogenic lipoproteins, and decrease inflammatory mediators, past experience with PPAR agonists shows that they can be accompanied by weight gain, heart failure, and bone fractures. From previous experience that focused on biomarkers, the quest for the cardiometabolic advantage with the next generation of PPAR agonists requires a reduction in negative cardiovascular outcomes and long-term safety with regard to bone fractures and cancer. Data from an ongoing cardiovascular outcome trial with the newest entry into the PPAR arena, aleglitazar, will help determine whether the right balance has been achieved.

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Table

Future trial design⁷²

Longer trials	In order to meet the FDA requirements, it is critical to conduct trials with longer-term follow-up—perhaps out to as long as 5 years. This would allow any safety signal to emerge and accrue the longest patient-year follow-up.
Larger trials	Trials that are larger in sample size should be conducted. Given the high prevalence of diabetes across the developed world, these patients are easy to identify. Designs that allow for a high proportion of patients to meet eligibility criteria will make these changes feasible. Global initiatives also will make it easier to recruit participants in these trials. Larger trials will allow investigators to tackle the safety issues head-on in a single study.
Patients with higher CVD risk	The enrichment of future trials in diabetes and CVD will require investigators to enroll patients at sufficiently high risk to confirm safety and efficacy for an investigational drug. Unlike the past, patients who are with post-ACS and those with a high Framingham score will need to be enrolled to confirm safety.
Using all the evidence	Large and simple postmarketing registries need to be created and conducted to take a “real-world” look at those not enrolled in clinical trials.
Evaluate more CVD outcomes	Heart failure, quality of life, and other measures cannot be overlooked. Important safety signals may emerge initially from secondary outcome measures.