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The Glitazars Paradox: Cardiotoxicity of the Metabolically Beneficial Dual PPARα and PPARγ Activation

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Abstract

The most common complications in patients with type-2 diabetes are hyperglycemia and hyperlipidemia that can lead to cardiovascular disease. Alleviation of these complications constitutes the major therapeutic approach for the treatment of diabetes mellitus. Agonists of peroxisome proliferator-activated receptor (PPAR) alpha and *PPARγ* are used for the treatment of hyperlipidemia and hyperglycemia, respectively. PPARs belong to the nuclear receptors super-family and regulate fatty acid metabolism. PPARα ligands, such as fibrates, reduce circulating triglyceride levels, and PPARγ agonists, such as thiazolidinediones, improve insulin sensitivity. Dual-PPARα/γ agonists (glitazars) were developed to combine the beneficial effects of PPARα and PPARγ agonism. Although they improved metabolic parameters, they paradoxically aggravated congestive heart failure in patients with type-2 diabetes via mechanisms that remain elusive. Many of the glitazars, such as muraglitazar, tesaglitazar, and aleglitazar, were abandoned in phase-III clinical trials. The objective of this review article pertains to the understanding of how combined PPARα and PPARγ activation, which successfully targets the major complications of diabetes, causes cardiac dysfunction. Furthermore, it aims to suggest interventions that will maintain the beneficial effects of dual PPARα/γ agonism and alleviate adverse cardiac outcomes in diabetes.

Keywords

glitazars; dual PPARα/γ agonists; cardiovascular effects; diabetes; heart failure

INTRODUCTION

Diabetes is the seventh leading cause of death worldwide.[1] It is classified into two major forms, type 1 and 2. Type-2 diabetes (T2D) melitus affects the majority of the diabetic population, and it is associated with obesity and insulin resistance combined with insufficient compensatory insulin secretion.[2] For patients in whom the recommended

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lifestyle changes[3] are not adequate to control the complications of the disease, pharmacotherapy is required to preserve glycemic control. Besides the noninsulin antihyperglycemic drugs, such as biguanides, sulfonylureas, meglitinides, glitazones alpha-glucosidase inhibitors, glucagon-like peptide-1, dipeptidyl peptidase 4 inhibitors, and sodium/glucose cotransporter 2 inhibitors, drugs that regulate both glucose and lipid metabolism have been generated. The dual-PPARα/γ coactivators or "glitazars" combine the insulin-sensitizing effect of PPARγ agonists with the lipid- and triglyceride-lowering effects of PPARα agonists, which are additionally accompanied by an increase in the high-density lipoprotein (HDL)-cholesterol levels (Fig. 1).[4] The dual actions of these agents come in varying degrees of PPARα and PPARγ activation, depending on their chemical structure (Fig. 2). Some of the glitazars, when compared with the single PPARγ agonists, which are also used in antidiabetic treatment, were more efficient in lowering hyperglycemia and hyperlipidemia.[5,6] However, although glitazars improved clinical efficacy on glucose control and lipid metabolism, they were discontinued because of major cardiovascular events, such as stroke, myocardial infarction (MI), peripheral edema, and heart failure (Fig. 1 and Table 1).[7–10] This review aims to summarize the basic and clinical research findings to date on glitazars and contribute to the understanding of the mechanisms that involve PPARα and PPARγ activation and underlie their cardiovascular adverse effects.

Clinical Applications of PPAR Agonists PPARα Agonists

Several studies and clinical trials on PPARα agonists (fibrates) have also attempted to investigate their benefits versus adverse effects. The FIELD study showed that fibrates reduce total cardiovascular events, specifically reducing nonfatal MIs and revascularizations. This decrease however was not significant in the lowering of the primary outcome of coronary events in the general population.[11] Another study showed that long-term use of fenofibrate reduced microvascular-associated complications and was generally well-tolerated, specifically in patients with T2D. However, it had no significant effect on mortality or on other adverse cardiovascular outcomes.[12] The positive effect of fibrates has been suggested to be mediated by increased expression of HDL proteins (AI, AII), reverse cholesterol transport factors (ABCA1, SR-BI), lipid-remodeling factors (lipoprotein lipase), and anti-inflammatory functions. It has also been suggested that fibrates alter the composition of the atheromatic plaque in a way that leads to regression of atherosclerosis.[13,14] Although the magnitude of the benefits of fibrates is intermediate, it can have high clinical significance in high-risk individuals and in those with combined dyslipidemia. Despite their partially beneficial role, fibrates are accompanied by several other adverse effects due to non–lipid-related differential regulation on homocysteine, creatinine, and hemoglobin A1c (HbA1c). Specifically, fibrates have been shown to increase homocysteine with gemfibrozil, increasing it less than fenofibrate.[15] The ACCORD lipid trial studied whether a coadministration of fibrates and statins (another lipid-lowering drug) is more efficient in reducing the risk of cardiovascular events by either of the drugs used alone. The outcome of the study indicated that combination therapy could not effectively reduce cardiovascular disease in most high-risk adults with T2D. In addition, the researchers noted that men may experience a more robust benefit from the combination therapy, whereas women on combined fibrates and statins therapy seemed to have more cardiovascular problems than those on statins alone.[16] Furthermore, the combination of fibrates and statins

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has also been reported to increase the incidence of rhabdomyolysis.[17] However, a recently developed fibrate, permafibrate (K-877), when coadministered with statins showed milder side effects.[18,19] Further research on this drug is currently in phase-III clinical trials (PROMINENT, NCT03071692, started in 2017).

PPARγ Agonists

Most of the antidiabetic drugs that activate PPARγ exhibit cardiovascular risk in a direct or indirect manner. The thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, have been associated with fluid retention and increased risk for cardiac dysfunction and heart failure.[20–22] A meta-analysis of randomized trials and the PROactive study showed that although diabetic patients treated with pioglitazone had lower all-cause mortality, they had a higher heart failure incidence.[23,24] Rosiglitazone has been associated with even higher risk of heart failure and other cardiovascular events[25,26] and MI.[27] In contrast, the RECORD trial showed that rosiglitazone treatment increased the risk for heart failure but did not reveal any association with MIs.[28,29] In accordance to the RECORD trial, the AHA/ACCF Science Advisory in 2010, upon reevaluation of the cardiovascular effects of TZDs, acknowledged that the association of rosiglitazone with increased risk for heart failure still remains uncertain[30]. Afterward, in 2013, rosiglitazone was reapproved without any restrictions by the United States Food and Drug Administration.

Dual PPARα/γ Agonists

The effort to develop PPAR agonists without adverse effects led to the development of dual agonists (glitazars) that activate both PPARα and PPARγ, thus combining the lipid-lowering effects of PPARα with the insulin-sensitizing effects of PPARγ. Depending on their molecular structure, these molecules exert varying degrees of PPARα and PPARγ activation. Although glitazars lower plasma glucose and triglycerides,[4] they have been associated with ischemic events[31] and congestive heart failure.[32] A precautionary statement for an approved dual agonist, saroglitazar, was issued for patients with diabetes and congestive heart failure.[32] Other glitazars, such as tesaglitazar, aleglitazar, muraglitazar, and cevoglitazar have been discontinued due to adverse side effects, including heart failure and myocardial ischemia.[31]

The first dual agonist was farglitazar, which was discontinued in phase-III clinical trials due to evidence of edema.[33] Farglitazar had also been tested in phase-II clinical trials for the treatment of hepatic fibrosis but failed to show significant therapeutic effects.[34] The retraction of farglitazar was followed by discontinuation of ragaglitazar,[35] imiglitazar, and tesaglitazar trials,[36] due to carcinogenicity in rodent toxicity models, elevated creatinine levels in serum, and cardiac dysfunction, respectively. Imiglitazar treatment increased HDL cholesterol levels. This was associated with higher apolipoprotein A-I levels, larger HDL particles, and suppression of small-density HDL particles. Imiglitazar decreased plasma triglycerides and apolipoprotein B-100 levels. However, evidence of liver enzyme abnormalities led to its withdrawal from phase-III clinical trials.[37,38]

Tesaglitazar decreases hyperglycemia and dyslipidemia[9] and prevents atherosclerosis in mice with low-density lipoprotein (LDL) receptor deficiency.[21] Later, two series of phase-III clinical trials, named GALLANT and GALEX, tested tesaglitazar versus common

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antidiabetic drugs, such as metformin, pioglitazone, and placebos. All studies were terminated due to side effects, such as congestive heart failure and renal toxicity, that occurred despite tesaglitazar's strong antihyperlipidemic and antihyperglycemic effects.[21,39–42]

Similarly, muraglitazar development was discontinued due to higher rates of all-cause mortality compared with pioglitazone. Higher mortality was associated with edema, cardiac dysfunction, stroke, heart failure, and increased weight gain rate.[22,43] A double-blind randomized clinical trial that compared muraglitazar and pioglitazone showed that muraglitazar decreased hemoglobin A1c (HbA1c), cholesterol, apolipoprotein B, and triglycerides ($P < 0.0001$) and increased HDL-C.[43]

Muraglitazar and tesaglitazar failure was followed by the development of glitazars with slightly modified chemical structures. However, all alternatives were eventually abandoned due to various cardiovascular and other adverse effects. Naveglitazar, a dual PPARα/γ agonist with γ-dominance, was also discontinued due to carcinogenic effects in the urinary bladder of rats, which were preceded by urothelial hypertrophy, inflammation, and changes in urinary composition.[44] Three more dual agonists, sipoglitazar, cevoglitazar, and AVE-0847, were also discontinued due to adverse effects.

Another attempt with aleglitazar portrayed a protective role of the drug in mouse cardiomyocytes exposed to high glucose levels in vitro.[45] Aleglitazar protects the heart against ischemia–reperfusion injury by suppressing myocardial apoptosis and decreasing infarct size.[46] However, aleglitazar was discontinued in phase-III trials due to other side effects, including severe gastrointestinal bleeding and bone fractures.[47]

Another PPARα/γ agonist, CG301269, also had beneficial metabolic effects in animal studies with rodents.[48] Furthermore, administration of CG301269 in a mouse model of myocardial ischemia/reperfusion did not exacerbate heart failure. Conversely, another dual PPARα/γ agonist, LY510929, which treated hyperlipidemia and hyperglycemia in rats, caused left ventricular hypertrophy after treatment for 2 weeks.[49]

The most recently developed dual PPARα/γ agonists are chiglitazar and saroglitazar. Specifically, chiglitazar is a PPARα/γ/δ panagonist that improves insulin sensitivity and glucose tolerance, and reduces the homeostatic model assessment index, plasma triglycerides, total cholesterol, low-density lipoprotein cholesterol levels, alanine gluconeogenesis, and hepatic glycogen levels in monosodium glutamate (MSG) obese rats.[50] Two phase-III trials concluded that chiglitazar is a safe treatment option against T2D (NCT02121717), although adverse events, such as weight gain, edema, and hypoglycemia, were reported.

Saroglitazar is the only glitazar still in clinical development. It is a dual PPARα/γ agonist with significant lowering effects on serum lipids and glucose. A study with 23 male and 11 female patients with T2D and dyslipidemia, who were treated with saroglitazar, showed significant reduction in total cholesterol, LDL cholesterol, and plasma triglycerides.[4] Saroglitazar incurs moderate PPARγ activation and more robust activation of PPARα,[51] even in comparison with the PPARα activator, WY14,643.[52] A recent study showed that

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saroglitazar diminishes hypertriglyceridemia and improves insulin sensitivity and β-pancreatic cell function by alleviating glucolipotoxicity, possibly through direct PPARγ activation in patients with T2D and high blood triglyceride levels.[7] The substance was approved in June 2013 for clinical use in India.[53] Saroglitazar has never been associated with cardiovascular complications, although its product information contains a precautionary statement for its use in patients with T2D and congestive heart failure. These findings combined with those from older studies for other dual PPARα/γ agonists presented the high efficiency of dual PPARα/γ agonists against hyperglycemia and hyperlipidemia.[54–56]

Molecular Mechanisms of Cardiac Toxicity by Single or Dual PPARα–PPARγ Activation

Since the beginning of clinical development for both single PPAR agonists and dual PPARα/γ agonists, there have been concerns about their potential association with cardiovascular complications.[57] Therefore, elucidation of the mechanisms that underlie adverse outcomes is warranted. Accordingly, various studies have focused on the molecular basis of these unexplained effects.

PPARs are nuclear receptors that act as transcriptional factors by forming heterodimers with retinoid X receptors and binding to cis-acting DNA elements (PPREs). Endogenous ligands, such as steroids, retinoids, cholesterol metabolites, and dietary lipids, can activate PPARs.[58] PPARs transcriptional activity can be increased or decreased depending on interaction with either coactivators, including the CBP/p300, the p160/SRC family (SRC-2/GRIP1/TIF2, SRC-3/Pcip/rac3/ACTR/AIB1/TRAM-1), and the PPARγ coactivator 1 (PGC-1) family (PGC-1α, PGC-1β)[59] or corepressors, such as nuclear receptor corepressor protein (NCoR)[60] and the silencing mediator of retinoid and thyroid hormone receptors (SMRT).[61] There are three PPAR isoforms: PPAR-α (*NR1C1*), PPAR-γ (*NR1C3*), and PPAR-β/δ (*NR1C2*).[62]

PPARα

PPARα is predominantly expressed in tissues with high capacity for fatty acid oxidation (FAO), including the heart, liver, macrophages, muscle, and kidneys,[63] and regulates the expression of proteins that are involved in this process.[64] PPARα ligands, such as fibrates, lower plasma triglyceride levels and increase HDL levels.[65]

PPARα regulates the expression of genes that encode for proteins that are involved in FAO, such as cluster of differentiation (*Cd*)36, carnitine palmitoyl transferase I (*Cpt1*), diacylglycerol acyltransferase (*Dgat*), malonyl-CoA decarboxylase (*Mcd*), and fatty acid-binding protein (*Fabp*).[66] Mice with global deletion of PPARα have lower levels of FAO, higher glucose oxidation, and increased hepatic lipid content.[67] Cardiomyocyte PPARα is activated by fatty acids released from intracellular triglyceride stores to be catabolized for mitochondrial ATP synthesis.[68,69] Accordingly, overexpression of PPARα increases FAO and decreases glucose oxidation.[64] Constitutive cardiomyocyte-specific expression of PPARα (αMHC-PPARα) increases oxidation rate, as shown by increased palmitate turnover from triglyceride stores.[70] Interestingly, along with increased lipid oxidation, constitutive cardiomyocyte PPARα expression leads to cardiac lipid accumulation.[64] This is likely accounted for by increased fatty acid uptake through CD36,[71] which also stimulates a

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positive-feedback PPARα activation loop that is constituted by phosphorylation of PPARα by GSK3α.[72] The ventricular hypertrophy and dysfunction phenotype of these mice resembles diabetic cardiomyopathy because they have profound accumulation of intramyocardial triglycerides after short-term fasting.[64] It has been shown that PPARα cooperates synergistically with KLF15 to induce gene expression,[73] whereas binding of Sirtuin (SIRT) 1 on PPARα has the opposite effect.[74] In conclusion, PPARα plays a central role in stimulating fatty acid uptake and oxidation.

Various factors activate PPARα expression, such as glucocorticoids,[75] farnesoid X receptor (FXR),[76] AMP-activated protein kinase (AMPK),[77–79] estrogen-related receptor (EER)α,[80] retinoic acid,[81] retinoid X receptor (RxR),[82] phorbol-12-myristate-13-acetate,[83] branched chain amino acids,[84] nitrate,[85] heat shock factor-1,[86] diabetes,[64,87] and exercise training.[88] On the other hand, cardiac PPARα expression is reduced during heart failure,[89] MI,[90] hypoxia,[91,92] endotoxemia,[93,94] and polymicrobial sepsis.[95] The details of the mechanisms that lead to this reduction remain elusive. The JNK signaling pathway has been associated with reduced cardiac PPARα gene expression.[96] Many factors, such as IL-1β,[97] IL-6,[97] PPARδ,[98,99] NF-κ?,[100] glucose,[101,102] insulin,[103] Akt,[104] c-Myc,[105] the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway,[106] periostin,[107] reactive oxygen species,[100] growth hormone,[108] androgens,[109] and angiotensin II,[110] have been reported to downregulate *Ppara* expression.

Pharmacologic activation or constitutive cardiomyocyte expression of PPARα causes intramyocardial lipid accumulation and cardiac dysfunction[64,111] accompanied by the activation of protein kinase C signaling and β-adrenergic receptor desensitization.[112] Adrenergic signaling attenuation may also be accounted for by phosphodiesterase 1C, which is stimulated by PPARα.[113] PPARα$^{-/-}$ mice have decreased myocardial fatty acid metabolism.[114–116] Despite the importance of FAO for cardiac function,[117] these mice have normal cardiac function at baseline according to some studies.[116,118,119] This suggests the activation of other proteins that may substitute PPARα in stimulating FAO. Conversely, other studies showed that PPARα$^{-/-}$ mice have reduced cardiac function at baseline, which was attributed to fibrosis,[115,120] abnormal mitochondrial structure, and oxidative stress.[121,122] Following metabolic stress, such as starvation, exposure to high temperature, and high workload, PPARα$^{-/-}$ mice had lower levels of cardiac ATP[115,119] and lower contractile performance.[119] Stimulation of β_1-adrenergic receptors by isoproterenol reduced positive inotropic effect.[120] Short-term starvation[67,118] and CPT1 inhibition[114] caused hepatic and cardiac lipid accumulation and hypoglycemia.

These studies indicate that PPARα is important for activation of cardiac FAO and inhibition of glucose utilization. It is possible that PPARα$^{-/-}$ mice do not develop cardiac dysfunction at baseline because of either compensatory activation of other PPAR isoforms or higher glucose utilization.[118] Nevertheless, activation of PPARγ may act as an insulin-sensitizing process that promotes glucose uptake. However, this compensation is not sufficient when prolonged during myocardial stress.

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PPARγ

PPARγ is expressed mainly in adipose tissue. It has a pivotal role in adipogenesis, thermogenesis, and fatty acid and triglyceride storage.[63,123,124] TZDs, recognized as "glitazones," are PPARγ ligands, which act as insulin sensitizers that lower plasma glucose.[125] However, until today, there is a lot of controversy about the association of PPARγ agonists with cardiovascular risk and whether they can cause heart failure via direct actions on the heart or indirectly via increased salt and water retention.[20]

There is a broad range of transcriptional factors and physiological stimuli that upregulate PPARγ expression, such as C/EBPs,[126,127] estrogen,[128] Krüppel-like factor (KLF)5,[129] KLF15,[130] MEK/ERK signaling,[131] c-Fos[132] TGF-β,[133] Smad1,[134] p38 kinase, early growth-response factor-1 (Egr-1),[135] FGF21,[136,137] ghrelin,[138] polyunsaturated fatty acids,[102,139,140] the orphan nuclear receptor RORα,[141] the zinc-finger protein Zfp423,[142] and vitamin E.[143] Transcriptional factors and stimuli that suppress PPARγ expression are lipopolysacharides,[144,145] JNK,[146–148] TNFα,[149–152] IL-11,[151] CCAAT/enhancer-binding protein homologous protein (CHOP),[153] retinoic acid,[81,154] estrogen receptor (ER)-α,[155] KLF2,[146,156] KLF7,[157] the JAK/STAT pathway,[106,126,127] interferon-gamma,[144,158] leptin,[159] angiotensin II,[110] fasting,[160] and androgens.[161]

Both gain and loss of PPARγ function mouse models have been generated. Mice with cardiomyocyte-specific constitutive PPARγ1 expression have increased cardiac lipid accumulation, abnormal mitochondrial structure, and dilated cardiomyopathy.[124] This mouse model has also been described as a model of arrhythmia and sudden death, which is attributed to prolongation of the QRS and QT intervals, polymorphic ventricular tachycardia, and ventricular fibrillation.[162] The level of PPARγ overexpression seems to influence the timing and severity of the phenotype.[124]

Although constitutive expression of cardiomyocyte PPARγ is clearly cardiotoxic, ablation of PPARγ does not seem to be protective either. Mice with global PPARγ deletion are lethal, and the embryos have cardiac abnormalities caused by placental defects.[163] Cardiomyocyte-specific PPAγ$^{-/-}$ mice develop cardiac hypertrophy with preserved systolic cardiac function, which is not associated with altered cardiac metabolism.[164–166] Hypertrophy has been attributed to elevated NF-κB expression,[164] macrophage infiltration,[165] and cardiomyocyte elongation.[167] Cardiomyocyte-specific PPARγ$^{-/-}$ mice have increased oxidative damage, mitochondrial abnormalities, and die from dilated cardiomyopathy.[168] Interestingly, PPARγ ablation was not accompanied by changes in the expression profile of PPARγ target genes. This implies that compensatory mechanisms, likely via the activation of other PPAR isoforms, are activated when PPARγ is blocked. Inducible cardiomyocyte-specific PPARγ deletion decreases the expression of FAO-related genes and proteins and lowers fatty acid utilization, whereas glucose utilization does not change.[169] Thus, although activation of PPARγ has been attributed to cardiotoxicity, its inhibition also compromises cardiomyocyte biology and leads to cardiac dysfunction.

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Combined Activation of PPARα and PPARγ

Controversial conclusions have been reported about the effects of dual PPARα/γ agonists on atherosclerotic plaque formation. Despite findings suggesting that treatment with a dual PPARα/γ agonist (tesaglitazar) stabilizes atherosclerotic plaque in diabetic LDLr$^{-/-}$ mice,[170] an experimental model of insulin resistance and dyslipidemia showed increased macrophage-rich plaque formation in apolipoprotein E–knockout mice receiving the dual PPARα/γ agonist (S)-3-(4-(2-carbazol(phenoxazin)-9-yl-ethoxy)phenyl)-2-ethoxypropionic acid (compound 3q).[171] The latter was associated with higher vascular expression of P-selectin, MCP-1, VCAM-1, and CD36, which are markers of endothelial activation and inflammation associated with plaque complexity.[171] These findings provided a potential framework for investigation on whether dual α/γ agonists are associated with high risk for cardiovascular adverse effects, when used by individuals with insulin resistance.[22]

A study in rats showed that daily treatment with suprapharmacological doses of the PPARα/γ agonist LY510929 increases heart weight, left ventricular lumen volume, and wall thickness in male and female rats on a dose-dependent manner. This study identified plasma aminoterminal proatrial natriuretic peptide (NTproANP) levels as a potential biomarker of the progression of PPARα/γ agonist–induced left ventricular hypertrophy in rats.[49]

A possible explanation for the observed heart failure pertains to glucolipotoxicity that is driven by the combined increase of PPARγ-driven insulin sensitization and glucose uptake in the setting of higher PPARα-induced activation of fatty acid uptake and oxidation.[172] This hypothesis corroborated previous studies showing that PPARγ can induce cardiac FAO-related gene expression[124] without causing cardiac dysfunction when PPARα is inhibited.[173,174]

Newer studies[124,173,174] indicated that combined PPARα and PPARγ activation compromise cardiac function. Constitutive cardiomyocyte-specific overexpression of PPARγ causes intramyocardial lipid accumulation and cardiac dysfunction[124] characterized by ventricular tachycardia and fibrillation.[162] Interestingly, cardiac dysfunction seems to occur when both cardiomyocyte PPARα and PPARγ are present. Along these lines, constitutive PPARγ expression in cardiomyocytes of PPARα-knockout mice did not result in cardiac dysfunction, despite the increased myocardial lipid content.[173] Pharmacologic activation of PPARγ with TZDs promotes cardiomyocyte hypertrophy in vitro.[175] However, it has also been proposed that the cardiotoxic effect of rosiglitazone may be independent to cardiomyocyte PPARγ activation as shown in mice with cardiomyocyte-specific deletion of PPARγ, which develop cardiac hypertrophy that is further exacerbated by treatment with rosiglitazone.[164,176] Availability of fatty acids that follows lipoprotein-derived or intracellular triglyceride hydrolysis is a critical component for the activation of PPARs.[68,177]

PPARγ-mediated cardiac toxicity occurs primarily in the presence of PPARα. Therefore, cardiac dysfunction of mice that overexpress cardiomyocyte PPARγ may be due to fatty acid–mediated PPARα activation, which does not occur in the aMHC-*Pparg;Ppara*$^{-/-}$ mice.[173] Nevertheless, there are mixed results on PPARγ-driven activation of PPARα with some studies showing that rosiglitazone increases PPARα expression,[178] although others showing reduced expression of PPARα-target genes.[179] Along these lines, previous studies have

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shown that activation of either PPARα or PPARγ in cardiomyocytes is associated with accumulation of acyl-carnitines and diacylglycerols in cardiomyocytes that lead to cardiac dysfunction,[112,173] although cardiac acyl-carnitine content was reduced in the aMHC-*Pparg;Ppara*$^{-/-}$ mice.[173]

In accordance with those studies, a recent one focusing on tesaglitazar has confirmed that cardiac dysfunction is associated with alterations in cardiac content of triglycerides, acyl-carnitines, diacylglycerols, and phosphatidic acid.[180] Combined treatment with tesaglitazar and resveratrol, which blocked the cardiotoxic effect of tesaglitazar, restored normal levels of acyl-carnitines, phosphatidic acid, and phosphatidylcholine.[180] In a similar context, activation of different PPAR isoforms seems to alter representation of lipid species in total lipidome. Specifically, rats treated with a PPARα agonist had higher hepatic saturated fatty acids and monounsaturated fatty acids and lower ω−6 and ω−3 polyunsaturated fatty acids.[181] On the other hand, treatment with a PPARγ agonist resulted in lower plasma triglycerides and phospholipids, higher hepatic phospholipids, lower total cardiac fatty acids and saturated fatty acids, and higher cardiac ω−6 polyunsaturated fatty acids.[181] Thus, the modulation of relative activation of PPARα and PPARγ by different dual PPARα/γ agonists may result in differential organ lipid content that may eventually protect or compromise organ function.

Combined PPARα/γ activation by tesaglitazar suppresses gene expression of SIRT1 and activation of PGC1α, which eventually leads to lower mitochondrial abundance.[180] Inhibition of PGC1α expression also occurs in aMHC-*Pparg* when treated with a PPARα agonist.[173] PGC-1α is the main coactivator for PPARs that serves as a scaffold, recruiting regulatory proteins for chromatin remodeling and transcription activation.[182–184] PGC1a controls FAO-related gene expression[185] and mitochondrial biogenesis.[186] Cardiac PGC1α gene expression is decreased in rodents and humans with heart failure.[187] Similarly, PGC1α-knockout mice develop cardiac dysfunction,[185] and they aggravate heart failure following pressure overload.[188] Surprisingly, overexpression of cardiomyocyte PGC1α also leads to cardiac dysfunction.[186] The mechanism behind the toxic effect of increased levels of PGC1α is attributed to the impairment of mitochondrial biogenesis and function.[186] On the other hand, short-term PGC1α overexpression in cardiomyocytes improves mitochondrial biogenesis and oxidative respiration and cardiac function. Thus, dilated cardiomyopathy of the αMHC-PGC1α transgenic mice is most likely due to the profound and long-term increase of PGC1α expression. Nevertheless, the same study[186] reported that transgenic lines with constitutive but not extremely high expression of PGC1α have normal cardiac function. Thus, the level of PGC1α activity seems to be a critical factor for the protective or aggravating role of this protein.

The activity of PGC1α is regulated by posttranslational mechanisms, including phosphorylation and acetylation. Acetylation of PGC1α is mainly controlled by the enzymatic activities of the acetyltransferase (general control of amino acid synthesis) GCN5 and the deacetylase SIRT1. A recent study showed that the dual PPARα/γ agonist (tesaglitazar) reduces cardiac SIRT1 expression and increases PGC1α acetylation. SIRT1 inhibition has been previously linked with cardiac dysfunction in several forms of cardiac stress. Resveratrol, which activates PPARγ,[189] SIRT1, and PGC1α,[190] maintained the

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beneficial antihyperlipidemic and antihyperglycemic effects of tesaglitazar and simultaneously negated the cardiotoxic effect of dual PPARα/γ activation while increasing mitochondrial abundance.[180] Conversely, treatment of PPARα$^{-/-}$ mice with tesaglitazar did not change PGC1α and SIRT1 expression and had a less profound effect in cardiac function compared with C57BL/6 mice that were also treated with tesaglitazar.[180] Thus, PPARα activation seems to account primarily for the cardiotoxic effects of dual PPARα/γ activation. Future studies on the role of PPARα in stimulating transcriptional and posttranslational repressors of PGC1α and SIRT1 would be useful to delineate the pathways that mediate the cardiotoxic effects of PPARα activation by single or dual agonists. Several factors that suppress PGC1α expression have been described so far in different tissues, including the histone methyltransferase Smyd1,[191] hypoxia inducible factor,[192] p160 myb binding protein[193], and various miRs, such as miR-23a,[194] miR-696,[195] miR-211,[196] miR-130b,[197] miR-494,[198] miR-29a,[199] miR-485–5p, miR-485–3p,[200] and miR-30b.[201] Accordingly, the role of combined activation of PAPRα and PPARγ in stimulating suppressors of SIRT1 or altering NAD^+/NADH ratio is another potential area for investigation that can delineate how dual PPARα/γ activation suppresses SIRT1 expression.[180]

Administration of rosiglitazone in mice with low levels of cardiac PPARα expression increases PGC1α expression,[174] whereas PPARγ activation in *LDLr*$^{-/-}$ mice fed with high-fat diet, which increases cardiac PPARα levels,[202,203] reduces PGC1α expression,[179] and causes cardiac hypertrophy. It has also been shown that treatment of mice with tesaglitazar increases PPARδ expression,[180] which regulates cardiac FAO.[204] PPARδ increases expression of UCP3 in the heart[204] and skeletal muscle.[205,206] Cardiomyocyte-specific overexpression of PPARδ increases glucose utilization and glycogen content without affecting fatty acid utilization, lipid content, and cardiac function.[207] Inducible cardiomyocyte-specific expression of constitutively active PPARδ also increases glucose utilization.[208] However, these mice have increased cardiac FAO, decreased glycogen content, and increased mitochondrial biogenesis without oxidative stress.[208] Thus, the level of activation of PPARδ seems to define the effect of this transcriptional factor independently from its expression levels.

These observations signify the importance of future studies focusing on the interplay between all three PPAR isoforms and their role in leading to PGC1α inhibition, when combined activation occurs. Furthermore, studies on potential cardioprotection by PPARα inhibition or activation of the SIRT1-PGC1α signaling in diabetes animal models that will be subjected to glitazars treatment are warranted.

CONCLUSIONS

Modulation of PPAR signaling has attracted a lot of interest for discovery and development of drugs for the treatment of diabetes. Single agonists of PPARα (fibrates) have been used as an adjunct therapy in the treatment of hypertriglyceridemia and hypercholesterolemia.[65] In addition, single PPARγ agonists (TZDs) have been used to treat hyperglycemia.[125] To alleviate toxicity of single PPAR agonists, dual PPARα/γ agonists (glitazars) were developed with the expectation to be an effective treatment for diabetic patients. Although these drugs were successful in improving insulin sensitivity and treating metabolic

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conditions associated with diabetes, most of glitazars have been suspended due to adverse effects on the urothelial, renal, and cardiovascular system (Fig. 3). Various studies have identified effects of combined PPARα and PPARγ activation on SIRT1 and PGC1γ expression and signaling. Interestingly, activation of the SIRT1-PGC1α metabolic network by resveratrol ameliorates the toxic effects of combined PPARα/γ activation.[180]

Up to date, saroglitazar seems to be the only dual PPARα/γ agonist with antihyperlipidemic and antihyperglycemic action that does not have serious adverse effects. However, it is accompanied by a warning and precautionary statement for use by patients at high risk for heart failure.[4] Investigation on whether saroglitazar is less toxic due to milder effects on SIRT1-PGC1α signaling and mitochondrial biology remains to be pursued. Additional studies are needed to explore whether combined use of glitazars with resveratrol or other SIRT1 activators will reduce the adverse effects of glitazars in humans. Also, further studies are necessary to elucidate whether combined PPARγ activation and PPARα inhibition can alleviate toxicity that has been speculated for the use of single PPARγ agonists, such as TZDs.

The goal of the present review article pertains primarily to understanding of the biological mechanisms that underlie cardiac toxicity of combined activation of PPARα and PPARγ, which materialized in several clinical applications of the dual PPARα/γ agonists. Undoubtedly, in the era of the use of sodium/glucose cotransporter 2 inhibitors and metformin, development of dual PPAR agonists is not of highest priority for the pharma industry. However, single PPARα or PPARγ agonists are still used. Importantly, in several cases, activation of a PPAR isoform may induce the expression of others, which eventually can resemble the situation of dual PPAR agonists, especially in the context of T2D that incurs aberrant load of tissues with lipids that can activate PPARs. Therefore, elucidation of the mechanisms, which underlie toxicity of single or multi-PPAR agonists, holds significant potential for the improvement of safety of existing treatments. Thus, understanding of critical pathophysiology aspects of dual PPARα/γ activation is important from the scientific point of view, as well as for the drug development industry.

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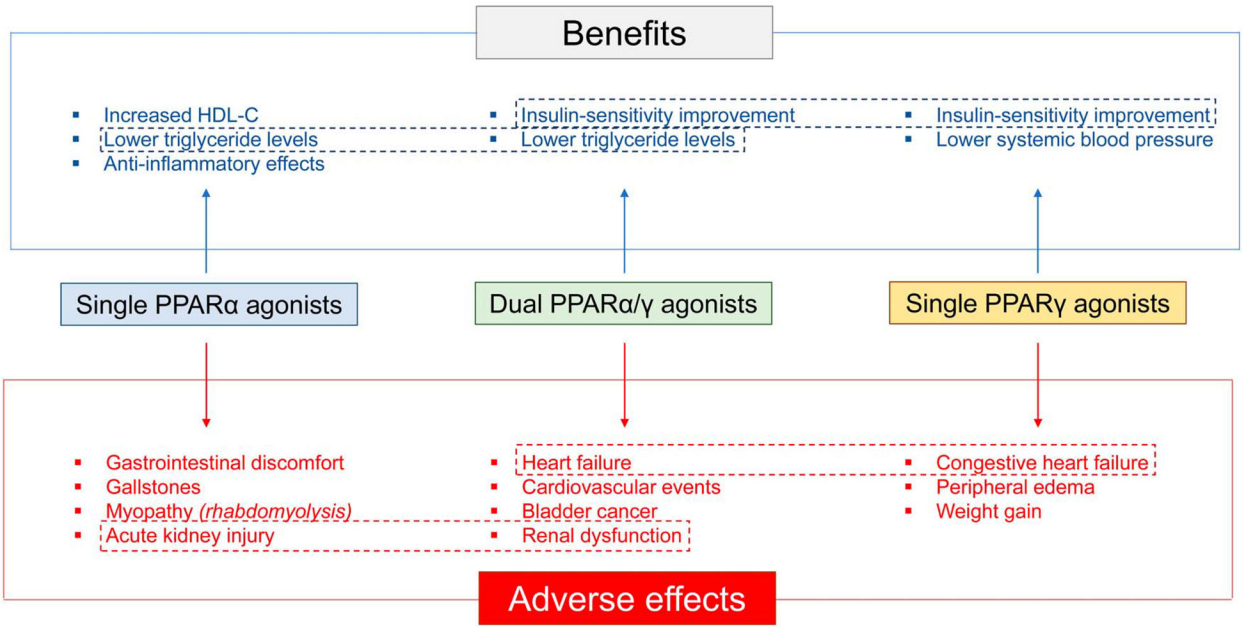

FIGURE 1.

Summary of benefits and adverse effects of single PPARα or PPARγ agonists and dual PPARα/γ agonists. Common effects of single and dual agonists are shown in frames.

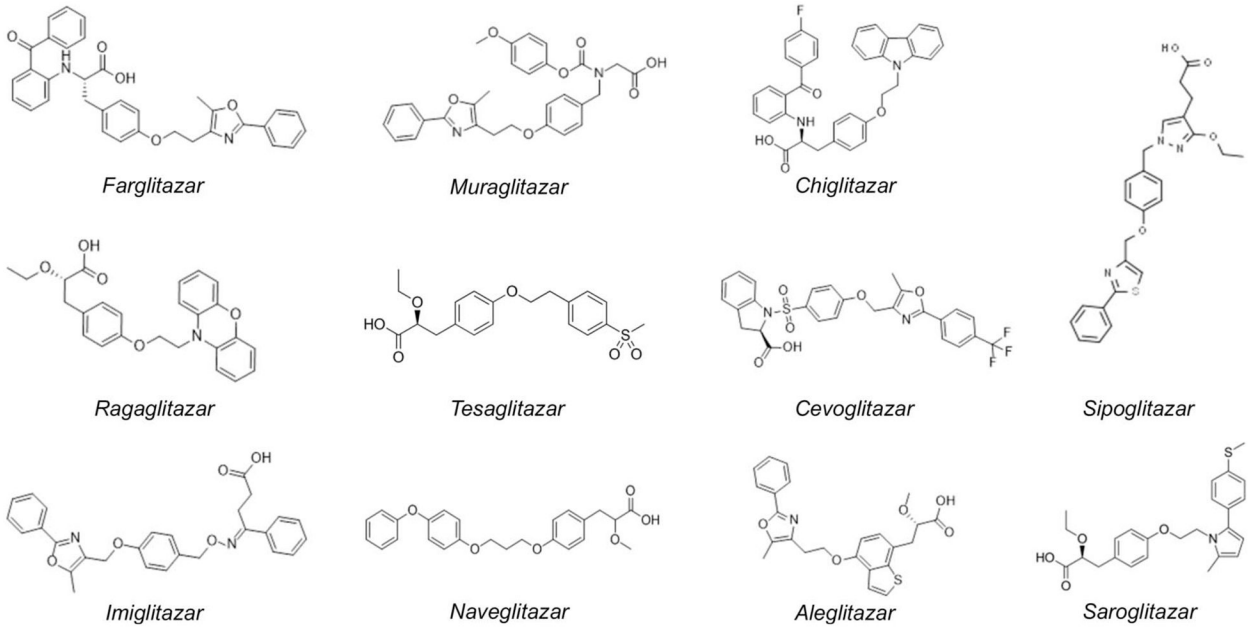

FIGURE 2.
Chemical structures of glitazars.

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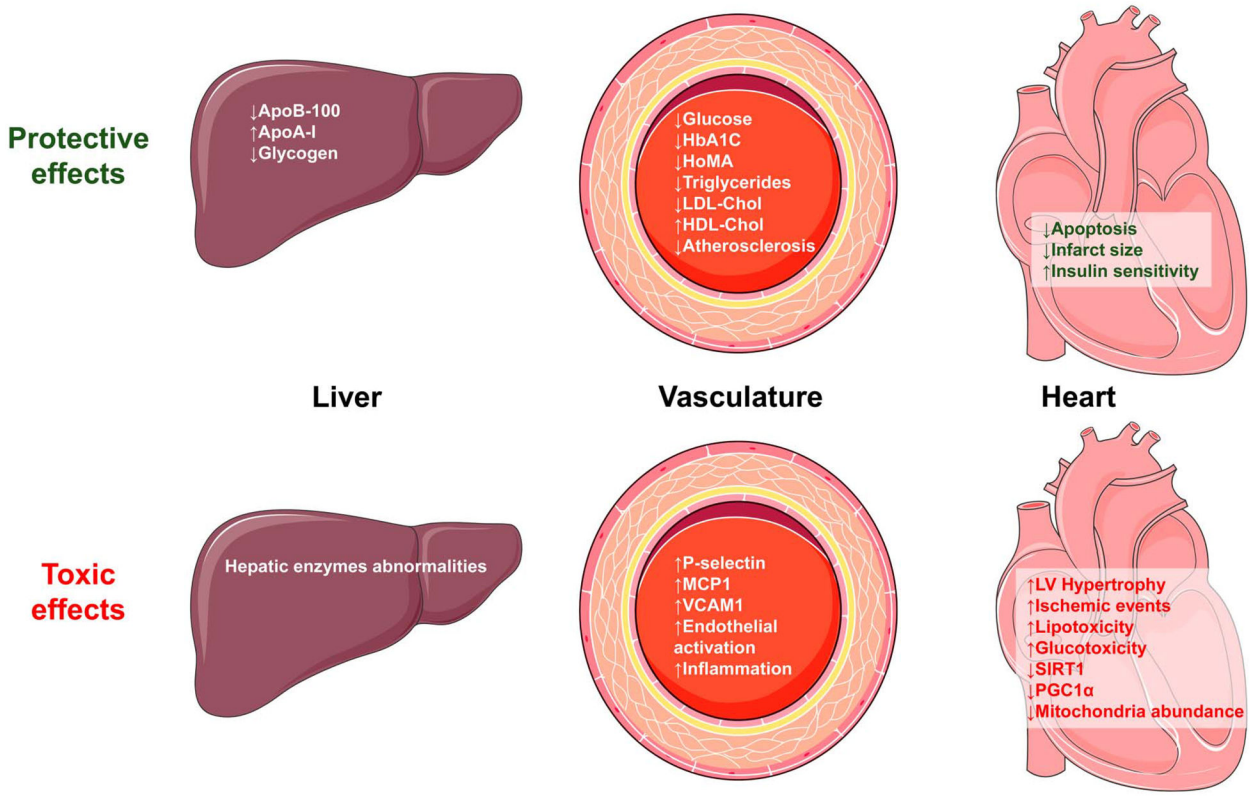

FIGURE 3.

Cardiovascular-related beneficial and toxic effects of glitazars. Figures were produced using Servier medical art (http://www.servier.com).

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TABLE 1.

Dual PPARα/γ agonists That Have Been Tested in Clinical Trials

Substance	Company	Disease	Discontinuation	Notes
Farglitazar	GlaxoSmithKline (London)	T2D	2003	Discontinued due to the evidence of edema
Ragaglitazar	Novo Nordisk (Denmark)	T2D	2004	Discontinued due to weight gain, anemia and bladder tumors in rodents
TAK-559/Imiglitazar	Takeda (Japan)	T2D	2004	Discontinued in phase III following abnormalities in liver enzymes
Muraglitazar (PARGLUVA)	Bristol-Myers Squibb (United States of America)	T2D	2006	Approved then discontinued due to CV events (heart failure)
Tesaglitazar *(GALIDA)*	AstraZeneca (United Kingdom)	T1D, T2D, Metabolic disorders	2006	Discontinued in phase III trials due to increased creatinine levels and decreased glomerular filtration rate
Naveglitazar (LY519818)	Eli Lilly (United States of America)	Cardiovascular disease, T2D, dyslipidemia	2006	Discontinued due to adverse preclinical findings in rodents
Sipoglitazar	Takeda (Japan)	T2D	2006	Discontinued due to safety concerns
Cevoglitazar	Novartis (Switzerland)	T2D, obesity	2008	Discontinued due to insufficient positive benefits
AVE-0847	Sanofi-Aventis (France)	T2D	2008	Termination of development due to reprioritization of product portfolio
Aleglitazar	Hoffman-La-Roche (Switzerland)	T2D	2013	Discontinued in phase III trials due to gastrointestinal bleeding, bone fractures, heart failure
Chiglitazar	Shenzhen Chipscreen, (China)	T2D	-	Safe and effective treatment for patients with T2D according to study results presented at the American Diabetes Association Scientific Sessions in 2019
Saroglitazar (LIPAGLYN)	Zydus Cadila (India)	T2D, dyslipidemia	-	Approved for use in India by the Drug Controller General of India

T1D, Type-1 diabetes; T2D, Type-2 diabetes.

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