GUIDELINES BASIC SCIENCE

PPARγ activator, rosiglitazone: Is it beneficial or harmful to the cardiovascular system?

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Abstract

Rosiglitazone is a synthetic agonist of peroxisome proliferator-activated receptor γ which is used to improve insulin resistance in patients with type Ⅱ diabetes. Rosiglitazone exerts its glucose-lowering effects by improving insulin sensitivity. Data from various studies in the past decade suggest that the therapeutic effects of rosiglitazone reach far beyond its use as an insulin sensitizer since it also has other benefits on the cardiovascular system such as improvement of contractile dysfunction, inhibition of the inflammatory response by reducing neutrophil and macrophage accumulation, and the protection of myocardial injury during ischemic/reperfusion in different animal models. Previous clinical studies in type Ⅱ diabetes patients demonstrated that rosiglitazone played an important role in protecting against arteriosclerosis by normalizing the metabolic disorders and reducing chronic inflammation of the vascular system. Despite these benefits, inconsistent findings have been reported, and growing evidence has demonstrated adverse effects of rosiglitazone on the cardiovascular system, including increased risk of acute myocardial infarction, heart failure and chronic heart failure. As a result, rosiglitazone has been recently withdrawn from EU countries. Nevertheless, the effect of rosiglitazone on ischemic heart disease has not yet been firmly established. Future prospective clinical trials designed for the specific purpose of establishing the cardiovascular benefit or risk of rosiglitazone would be the best way to resolve the uncertainties regarding the safety of rosiglitazone in patients with heart disease.

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INTRODUCTION

Type Ⅱ diabetes mellitus (T2DM) is a disease whose incidence is dramatically increasing and requires continuing medical management in many countries[1,2]. T2DM is characterized by insulin resistance and impaired glucose tolerance[3]. The development of T2DM involves 3 metabolic defects that include insulin resistance, alterations in hepatic glucose production and β-cell deficiency[4]. The

earliest defect seen in the development of T2DM is insulin resistance[4]. In this state, the β-cells produce large amounts of insulin reaching a supraphysiologic level as a compensatory response to peripheral tissue insulin resistance. If insulin resistance is left untreated, the β-cells begin to fail to produce insulin, resulting in a state of relative insulin deficiency[4]. T2DM is known to develop after this phase. T2DM patients have a 2- to 4-fold increased risk of developing coronary artery disease, unstable angina and myocardial infarction (MI)[5,6]. Furthermore, T2DM patients have been shown to have a worse prognosis than non-diabetic patients after a cardiovascular event[7,8].

Thiazolidinediones (TZDs) are an oral medication developed to reduce insulin resistance in T2DM patients and have been used since 1997[9]. TZDs exert their properties by stimulating a nuclear hormone receptor, the peroxisome proliferator-activated receptor γ (PPARγ)[10]. Troglitazone was the first drug developed but was withdrawn from the market due to liver toxicity[9]. Currently, pioglitazone and rosiglitazone are the only compounds that are available for clinical use[9]. However, the effects of rosiglitazone have been controversial regarding cardiovascular effects in both animal and clinical studies[11-59]. On the positive side, rosiglitazone has been shown to exert its potent insulin sensitization by improving insulin resistance in T2DM[10,60]. Various studies demonstrated that the therapeutic effects of rosiglitazone could reach far beyond its action as an insulin sensitizer because it has other therapeutic effects on many organs especially in the cardiovascular system in both animal models and humans[11-59]. Nevertheless, in the past decade growing evidence from both basic and clinical studies indicates that rosiglitazone could be harmful to the heart[11-25]. Because of its serious undesired effects, rosiglitazone has been recently withdrawn from the EU market[61], and is under close monitoring by the US Food and Drug Administration[62,63].

In this review, we aim to summarize and discuss the overall benefits as well as the adverse effects of rosiglitazone on the heart from both pre-clinical and clinical reports. Understanding the inconsistent findings as well as the limitations found in each study using rosiglitazone should allow investigators to carefully design future studies that hopefully can clarify previous inconsistent findings, and to indicate whether rosiglitazone should be used in patients.

BENEFICIAL EFFECTS OF ROSIGLITAZONE ON THE CARDIOVASCULAR SYSTEM

Previous studies reported that rosiglitazone had beneficial effects on the cardiovascular system in *in vitro*, *in vivo* and clinical studies. These beneficial effects of rosiglitazone are summarized in Table 1. In rat models of ischemic/reperfusion (I/R) injury, pretreatment with rosiglitazone

reduced the infarct size and improved ischemia/reperfusion-induced myocardial contractile dysfunction[26,46,48]. Rosiglitazone treatment also improved left ventricular (LV) systolic pressure and positive and negative maximal values of the first derivative of LV pressure (dP/dt) during I/R injury[32,46]. In addition, in both obese and normal rats rosiglitazone could decrease systolic blood pressure, improve contractile function and normalize the insulin level[31,44,45]. These findings suggested that rosiglitazone could prevent the development of hypertension associated with insulin resistance. This notion was supported by the finding that rosiglitazone treatment could enhance nitric oxide (NO)-mediated arteriolar dilation[28]. Furthermore the accumulation of neutrophils and macrophages and expression of monocyte chemoattractant factor (MCP)-1 in the ischemic heart was diminished by rosiglitazone[46]. Likewise, rosiglitazone treatment in diabetic rat and mouse models reduced the blood levels of glucose, triglycerides, and free fatty acids, and enhanced cardiac glucose oxidation in the ischemic myocardium[26,50]. Rosiglitazone treatment also reduced myocardial apoptosis and infarction size post I/R injury by restoring the balance between the pro-apoptotic and anti-apoptotic mitogen-activated protein kinase (MAPK) signaling pathway, increasing phosphatidylinositol-3-kinase-Akt phosphorylation, and inhibiting p42/44 MAPK[26,35,38,41,59].

In *in vitro* studies, incubation of a rat cardiomyoblast cell line with rosiglitazone demonstrated cardioprotective effects against oxidative stress, and the antioxidant enzyme heme oxygenase 1 was upregulated in these cells after rosiglitazone treatment[40]. Furthermore, rosiglitazone could inhibit cardiac fibroblast proliferation, increase connective tissue growth factor expression and decrease NO production induced by advanced glycation endproducts in cultured neonatal rat cardiac fibroblasts[37]. In addition, rosiglitazone could prevent cardiac hypertrophy by inhibiting angiotensin Ⅱ[27,32,54].

Many clinical studies reported that the beneficial effects of rosiglitazone on the cardiovascular system were similar to those from animal studies. Rosiglitazone therapy has been shown to reduce cardiovascular complications associated with T2DM[47,49,58]. Data from preliminary studies in patients who underwent coronary angioplasty and stent implantation demonstrated that rosiglitazone treatment for 6 mo led to a lower occurrence of restenosis and a lower degree of stenosis of the luminal diameter after angioplasty[64]. Furthermore, a study in patients with T2DM demonstrated that treatment with 4 mg/d of rosiglitazone for 12 wk decreased not only insulin resistance but also pulse wave velocity, which is a direct parameter of arterial stiffness in patients with diabetes and coronary arteries disease (CAD)[58]. Rosiglitazone has been shown to reduce plasma levels of C-reactive protein[5,51,56,58], matrix metalloproteinase-9 and MCP-1[58] in T2DM patients, suggesting that rosiglitazone plays an important role in protecting against arteriosclerosis by normalizing metabolic disorders and reducing chronic inflammation of the vascular system. Rosiglitazone treat-

Table 1 Reports of the beneficial effects of rosiglitazone on the cardiovascular system in pre-clinical and clinical studies

Models	Dose of rosiglitazone	Major findings	Interpretation	Ref.
Cultured neonatal rat cardiomyocytes	5 μmol/L; pretreated for 30 min before stimulation with Ang II (1 μmol/L) for 48 h	Inhibited Ang II-induced upregulation of skeletal α-actin and ANP genes, and prevent an increase in cell surface area	Rosiglitazone involved in the inhibition of cardiac hypertrophy	[27]
Isolated and cultured neonatal rat ventricular myocytes	1, 5, 10 μmol/L; pretreated for 48 h	Accelerated Ca^{2+} transient decay rates Increased SERCA2 mRNA levels Upregulation of IL-6 secretion Enhanced TNF-α- and lipopolysaccharide-induced NF-κB-dependent transcription	Cardioprotective effects of rosiglitazone may be mediated *via* NF-κB	[43]
Isolated and cultured adult rat ventricular myocytes	10^{-8}-10^{-5} mol; pretreated for 24 h	Did not increase protein synthesis Did not attenuate hypertrophic response to noradrenaline, phorbol-12-myristate13-acetate and endothelin-1	Rosiglitazone did not directly induce cardiomyocyte hypertrophy in cardiomyocytes	[30]
Cultured neonatal rat ventricular myocytes	10 μmol/L; pretreated for 24 h	Inhibited the endothelin-1-induced increase in protein synthesis, surface area, calcineurin enzymatic activity, and protein expression Inhibited the nuclear translocation of NFATc4 Enhanced the association between PPARγ and calcineurin/nuclear factor of activated T-cells	Rosiglitazone inhibited endothelin-1-induced cardiac hypertrophy *via* calcineurin/nuclear factor of activated T-cells pathway	[29]
Cultured rat cardiomyoblast cell line H9c2(2-1)	100 μmol/L; pretreated for 24 h	Increased expression of heme oxygenase 1 Increased cell viability under oxidative stress induced by H_2O_2	Rosiglitazone had cardioprotective effects against oxidative stress	[40]
Cultured neonatal rat cardiac fibroblasts	0.1, 1, 10 μmol/L pretreated for 48 h	Inhibited cardiac fibroblast proliferation Increased connective tissue growth factor expression Decreased nitric oxide production induced by advanced glycation endproducts	Rosiglitazone could prevent myocardial fibrosis	[37]
Cultured neonatal rat ventricular myocytes	1 μmol/L; pretreated for 30 min prior to H_2O_2 treatment	Decrease cell apoptosis Increase Bcl-2 protein content	Rosiglitazone protected cells from oxidative stress through upregulating Bcl-2 expression	[42]
Cultured neonatal rat cardiac myocytes	0.1, 1, 3, 10, 30 μmol/L; pretreated for 30 min before hypoxia	Decreased cytoplasmic accumulation of histone-associated DNA fragments Increased reoxygenation-induced rephosphorylation of Akt Did not alter phosphorylation of the MAP kinases ERK1/2 and c-Jun N-terminal kinase	Rosiglitazone protected cardiac myocytes against I/R injury by facilitating Akt rephosphorylation	[35]
Fatty Zucker rats	7-7.5 μmol/L per kilogram po; 9-12 wk	Decreased systolic blood pressure Decreased fasting hyperinsulinemia Improved mesenteric arteries contraction and relaxation	Rosiglitazone prevented the development of HT and endothelial dysfunction associated with insulin resistance	[45]
Rats with I/R injury	3 mg/kg per day po; pretreated for 7 d; 1 and 3 mg/kg iv given during I/R	Improved left ventricular systolic pressure, dP/dt_{max} and dP/dt_{min} Reduced neutrophils and macrophages accumulation Reduced the infarct size Downregulation of CD11b/CD18 Upregulation of L-selectin on neutrophils and monocytes	Rosiglitazone decreased infarct size and improved contractile dysfunction during I/R possibly *via* inhibition of the inflammatory response	[46]
Fatty Zucker rats with I/R injury (*Ex vivo* model)	3 mg/kg po; 7 or 14 d prior to isolated perfuse heart study	Normalized the insulin resistance Restored GLUT4 protein levels Improved contractile function Prevented greater loss of ATP	Rosiglitazone protected obese rat heart from I/R injury	[44]
I/R injury in isolated perfused normal and STZ- induced diabetic rat hearts (*Ex vivo* model)	1 μmol/L given prior to ischemia; 10 μmol/kg per day po after STZ injection for 4 wk	Inhibited activating protein-1 DNA-binding activity Inhibited of Jun NH₂-terminal kinase phosphorylation Reduced lactate levels and lactate dehydrogenase activity	Rosiglitazone attenuated postischemic myocardial injury in isolated rat heart	[34]
Sprague-Dawley rats	5 mg/kg per day po; 7 d	Reduced systolic blood pressure reduced vascular DNA synthesis, expression of cyclin D1 and cdk4, AT₁ receptors, vascular cell adhesion molecule-1, and platelet and endothelial cell adhesion molecule, and NF-κB activity	Rosiglitazone prevented the development of hypertension and endothelial dysfunction	[31]
T2DM mice	3 mg/kg per day po; 7 d	Did not affect serum glucose and insulin Increased serum 8-isoprostane and dihydroethydine-detectable superoxide production Enhanced catalase and reduced NAD(P)H oxidase activity Did not affect SOD activity	Rosiglitazone enhanced nitric oxide mediation of coronary arteriolar dilations *via* attenuating oxidative stress in T2DM mice	[28]

Hypercholesterolemic New Zealand rabbits with I/R injury	3 mg/kg per day po; 5 wk prior to I/R	Attenuated postischemic myocardial nitrative stress Restored a beneficial balance between pro- and anti-apoptotic MAPK signaling Reduced postischemic myocardial apoptosis Improved cardiac functional recovery	Rosiglitazone attenuated arteriosclerosis and prevented I/R-induced myocardial apoptosis	[38]
Zucker diabetic fatty rats with I/R injury	3 mg/kg per day po; 8 d prior to I/R	Reduced blood glucose, triglycerides, and free fatty acids levels Enhanced cardiac glucose oxidation Increased Akt phosphorylation (Akt-pS473) and its downstream targets (glycogen synthase kinase-3β and FKHR-pS256) (forkhead transcription factor) Reduced apoptotic cardiomyocytes and myocardial infarct size	Rosiglitazone protected heart against I/R injury	[26]
Sprague-Dawley rats with I/R injury	3 mg/kg per day po; 7 d prior to I/R	Reduced infarct size Decreased myocardial expression of AT_1 receptors Increased AT_2 mRNA and protein expression Inhibited p42/44 MAPK Did not alter Akt1 expression	Rosiglitazone attenuated myocardial I/R injury possibly *via* increase expression of AT_2 and inhibition of p42/44 MAPK	[41]
Sprague-Dawley rats with I/R injury	3 mg/kg per day po for 8 wk prior to I/R	Improved left ventricular dP/dt_{max} and dP/dt_{min} Inhibited myocardial angiotensin Ⅱ and aldosterone No significant effects on myocardial AT_1 and AT_2 mRNA	Rosiglitazone had a beneficial effect on post-infarct ventricular remodeling, but had a neutral effect on mortality	[32]
WT and eNOS knockout mice with I/R injury	3 mg/kg ip; pretreated for 45 min prior to I/R	WT mice: increased the recovery of left ventricular function and coronary flow following ischemia eNOS knockout mice: suppressed the recovery of myocardial function following ischemia	Rosiglitazone protected the heart against I/R injury *via* nitric oxide by phosphorylation of eNOS	[48]
Isolated perfused hearts from T2DM mice	23 mg/kg per day po; pretreated for 5 wk	Normalized plasma glucose and lipid concentrations Restored rates of cardiac glucose and fatty acid oxidation Improved cardiac efficiency due to decrease in unloaded myocardial oxygen consumption Improved functional recovery after low-flow ischemia	Rosiglitazone improved cardiac efficiency and ventricular function	[50]
WT and APN knockdown/knockout mice with myocardial infarction	20 mg/kg per day po; pretreated 72 h prior to MI and continuously treated until 7 and 14 d	Improved the postischemic survival rate of WT mice at 14 d of treatment Increased adipocyte APN expression Elevated plasma APN levels Reduced infarct size Decreased apoptosis and oxidative stress Improved cardiac function	APN was crucial for cardioprotective effects of rosiglitazone in myocardial infarction	[57]
Hypercholesterolemic rats	4 mg/kg per day po; pretreated for 5 mo	Reduced Ang Ⅱ level Upregulated AT_2 Improved lipid metabolism	Rosiglitazone protected the heart against cardiac hypertrophy *via* improved lipid profile, reduced Ang-Ⅱ and increase AT_2 expression	[54]
Mice with I/R injury	3 mg/kg per day po; pretreated for 14 d prior to I/R	Reduced ratio of infarct size to ischemic area (area at risk) Reduced the occurrence ventricular fibrillation Attenuated cardiac apoptosis Increased levels of p-Akt and p-GSK-3α	Cardioprotective effects of rosiglitazone against I/R injury were mediated *via* a PI3K/Akt/GSK-3α-dependent pathway	[59]
T2DM patients (*n* = 21)	4 mg/d; 6 mo	Weight loss (first 12 wk) Decreased waist circumference Decreased systolic and diastolic blood pressure Reduced HbA1c	Rosiglitazone amplified some of the positive benefits of lifestyle intervention	[55]
Randomized, double-blind, placebo-controlled study in T2DM (*n* = 357)	4 or 8 mg/d; 26 wk	Reduced C-reactive protein, matrix metalloproteinase-9 and white blood cell levels Did not alter interleukin-6 level	Rosiglitazone had beneficial effects on overall cardiovascular risk	[49]
Randomized, double-blind in CAD patients without diabetes (*n* = 40, control = 44)	4 mg/d for 8 wk followed by 8 mg/d for 4 wk	Reduced E-selectin Reduced von Willebrand Reduced C-reactive protein & fibrinogen Reduced homeostasis model of insulin resistance index Elevation of LDL and triglyceride level	Rosiglitazone reduces markers of endothelial cell activation and levels of acute-phase reactants in CAD patients without DM	[56]
Randomized, double-blind, placebo-controlled study in T2DM with CAD patients (*n* = 54)	4-8 mg/d; 16 wk	Improved glycemic control and whole-body insulin sensitivity Increased myocardial glucose uptake in both ischemic and non-ischemic regions	Rosiglitazone facilitated myocardial glucose storage and utilization in T2DM with CAD patients	[36]
Randomized controlled trial in patients with impaired glucose tolerance (*n* = 2365, control = 2634)	8 mg/d; 3 yr	Facilitated normoglycemic Did not alter cardiovascular event	Rosiglitazone reduced incidence of T2DM and increased normoglycemia	[47]

Randomized, double-blind, placebo-controlled trial in patients with T2DM (*n* = 70, control =16)	8 mg/d; 6 mo	Decreased plasma glucose and HbA1c with a trend to decrease HOMA index Decreased C-peptide and fasting insulin Reduced C-reactive protein Improved endothelium-dependent dilation	Rosiglitazone improved endothelial function and C-reactive protein in patients with T2DM	[51]
Randomized, controlled trial in patient with T2DM with CAD (Rosiglitazone; *n* = 25)	4 mg/d; 12 wk	Decreased insulin resistance Decreased pulse wave velocity Reduced plasma levels of C-reactive protein and monocyte chemoattractant protein 1	Rosiglitazone prevented arteriosclerosis by normalizing metabolic disorders and reducing chronic inflammation of the vascular system	[58]
Prospective and cross-sectional study in T2DM (Rosiglitazone; *n* = 22, metformin/rosiglitazone; *n* = 100)	Treated with rosiglitazone 6 mo	Decreased endotoxin Increased adiponectin levels	Lower endotoxin and higher adiponectin in the groups treated with rosiglitazone may be responsible for the improved insulin sensitivity	[39]
Comprehensive meta-analysis of randomized clinical trials (*n* = 42922, control = 45483)	Results of 164 trials with duration > 4 wk	The OR for all-cause and cardiovascular mortality with rosiglitazone was 0.93 and 0.94, respectively The OR for nonfatal MI and heart failure with rosiglitazone was 1.14 (0.9-1.45) and 1.69 (1.21-2.36), respectively The risk of heart failure was higher when rosiglitazone was administered as add-on therapy to insulin	Rosiglitazone did not increase risk of MI or cardiovascular mortality	[52]

Ang: Angiotensin; ANP: Atrial natriuretic peptide; OR: Odds ratio; T2DM: Type 2 diabetes mellitus; Hb: Hemoglobin; HOMA: Homeostatic Model of Insulin Resistance; CAD: Coronary artery disease; WT: Wild-type; APN: Adiponectin; eNOS: Endothelial nitric oxide synthase; GSK: Glycogen synthase kinase; LDL: Low density lipoprotein; AT: Angiotensin receptor type; SOD: Superoxide dismutase; MAPK: Mitogen-activated protein kinase; PI3K: Phosphatidyl inositol-3-kinase; STZ: Streptozotocin; I/R: Ischemia/reperfusion; TNF: Tumor necrosis factor; IL: Interleukin; NF: Nuclear factor; SERCA: sarcoendoplasmic reticulum calcium ATPase; HT: Hypertension; NFAT: nuclear factor of activated T cells; ERK: Extracellular signal-regulated kinase; PPAR: Peroxisome proliferator-activated receptor; MI: Myocardial infarction.

ment in patients with T2DM with/without CAD has also been shown to improve myocardial glucose uptake and utilization[36,47]. Rosiglitazone decreased both systolic and diastolic pressure[53,55], suggesting that this drug could improve systolic and diastolic function. All of these findings indicate that in addition to improving insulin resistance in T2DM patients, rosiglitazone also has the beneficial effects on overall cardiovascular risk.

ADVERSE EFFECTS OF ROSIGLITAZONE ON THE CARDIOVASCULAR SYSTEM

Despite these previously mentioned beneficial effects of rosiglitazone on the cardiovascular system, growing evidence indicates other adverse cardiovascular outcomes. The effect of rosiglitazone in increasing mortality in post-MI rats was first reported by Lygate *et al*[21] in 2003. Later, more studies, including clinical trials, demonstrated undesirable effects of rosiglitazone on the cardiovascular system. These findings suggested that rosiglitazone treatment may be harmful and should be used with caution in cardiovascular patients. A summary of reports on the adverse effects of rosiglitazone in various models as well as clinical studies are shown in Table 2.

Rosiglitazone treatment has been shown to induce apoptotic cell death in cultured vascular smooth muscle cell by increasing caspase 3 activity and the cytoplasmic histone-associated DNA fragmentation *via* the proapototic extracellular signal-regulated kinase 1/2-independent pathway[17]. Likewise, in an *in vivo* I/R injury model, it has been demonstrated that rosiglitazone therapy for 8 wk in non-diabetic rats with MI did not reduce either LV in-

farct size or LV hypertrophy, and increased mortality rate after I/R injury[21]. These findings suggested that rosiglitazone did not have cardioprotective effects in myocardial I/R injury. Furthermore, rosiglitazone treatment has been shown to increase cardiac phosphorylation of the p38MAPK signaling pathway[15], suggesting that rosiglitazone could facilitate cardiomyocyte apoptosis. In addition, rosiglitazone has been shown to be associated with an increased incidence of cardiac hypertrophy due to the increased expression of atrial natriuretic peptide, B-type natriuretic peptide, collagen I and III and fibronectin[16], leading to cardiac hypertrophy. The deterioration in cardiac function was also found in mice and rats when treated with rosiglitazone[12,24].

In a large animal model, which is more similar to a human, a recent study in swine has demonstrated that intravenous administration of rosiglitazone at clinically relevant doses attenuated epicardial monophasic action potential shortening during ischemia, possibly *via* blockade of cardiac ATP-sensitive potassium channels, and increased the propensity for ventricular fibrillation[20].

Growing evidence from recent clinical trials suggest that rosiglitazone could have serious harmful effects on the cardiovascular system[11,13,14,18,19,22,23,65]. The meta-analysis by Nissen *et al*[11] was the first report raising concerns about the cardiovascular safety profile of rosiglitazone. In a meta-analysis, Nissen *et al*[11] demonstrated that T2DM patients who received rosiglitazone treatment had a significantly increased risk of MI, heart failure and cardiovascular mortality. Although the method and statistical analysis used in this study have been criticized[14,52,66], the subsequent meta-analyses showed similar concerns

Table 2 Reports of the adverse effects of rosiglitazone on the cardiovascular system in pre-clinical and clinical studies

Model	Dose of rosiglitazone	Major findings	Interpretation	Ref.
Isolated and cultured vascular smooth muscle cells	1-10 μmol/L; incubated for 24 h	Induced cell death in a concentration-dependent manner Increased caspase 3 activity and the cytoplasmic histone-associated DNA fragmentation PD98059 (MAPKK inhibitor) did not abolish rosiglitazone induced ERK1/2 activation (proapoptotic effects)	Rosiglitazone induced apoptotic cell death through an ERK1/2-independent pathway	[17]
Rats with I/R injury	3 mg/kg per day po; pretreated for 14 d prior to I/R	Did not reduce left ventricular infarct size or hypertrophy Increased mortality rate Improved ejection fraction and prevented an increase left ventricular end diastolic pressure	Rosiglitazone did not prevent left ventricular remodeling, but was associated with increased mortality after myocardial infarction	[21]
Swine with I/R injury	3 mg/kg per day po; pretreated for 8 d prior to I/R	Increased expression of PPARγ Had no effect on myocardial contractile function Did not alter substrate uptake and proinflammatory cytokines expression	Rosiglitazone had no cardioprotective effects in a swine model of myocardial I/R injury	[25]
PPARγ-knockout (CM-PGKO) mouse	10 mg/kg per day po; 4 wk	Increased phosphorylation of p38 mitogen-activated protein kinase Induced phosphorylation of extracellular signal-related kinase 1/2 Did not affect phosphorylation of c-Jun N-terminal kinases Induced cardiac hypertrophy	Rosiglitazone caused cardiac hypertrophy at least partially independent of PPARγ in cardiomyocytes	[15]
Wild type and PPARγ overexpression mice	10 mg/kg per day po; 15 d	Increased lipid accumulation Increased size of the heart Decreased fractional shortening Increased CD36 expression	Rosiglitazone and PPARγ overexpression could be harmful to cardiac function	[24]
Swine with I/R injury	0.1, 1.0 10 mg/kg iv; pretreated for 60 min	Attenuated MAP shortening during ischemia by blocking cardiac KATP channels Increased propensity for ventricular fibrillation during myocardial ischemia	Rosiglitazone promoted onset of ventricular fibrillation during cardiac ischemia	[20]
Sprague-Dawley rats	15 mg/kg per day po; 21 d	Induced eccentric heart hypertrophy associated with increased expression of ANP, BNP, collagen I and III and fibronectin Reduced heart rate and increased stroke volume Increased heart glycogen content, myofibrillar protein content and turnover Reduced glycogen phosphorylase expression and activity	Rosiglitazone induced cardiac hypertrophy *via* the mTOR pathway	[16]
Meta-analysis in T2DM (n = 15 565, control = 12 282)	Received rosiglitazone more than 24 wk	Increased the risk of myocardial infarction Increased cardiovascular death incidence	Rosiglitazone increased in the risk of myocardial infarction and borderline increased in risk of cardiovascular death	[11]
RECORD study (n = 4447)	Received rosiglitazone with mean follow-up time of 3.75 yr	Increased the risk of heart failure	Rosiglitazone increased risk of heart failure, but did not increase the risk of cardiovascular death or all cause mortality	[18]
RECORD study (n = 4447)	Received rosiglitazone with mean follow-up time of 5.5 yr	Increased the risk of heart failure	Rosiglitazone increased risk of heart failure Suggestion of contraindication for rosiglitazone to be used in patients developing symptomatic heart failure	[65]
Case-control analysis of a retrospective cohort study (n = 159 026)	Treated with TZDs at least 1 yr	Increased risk of heart failure Increased mortality Increased risk of acute myocardial infarction	Rosiglitazone was associated with risk of heart failure, acute myocardial infarction, and mortality	[19]
Retrospective, double-blind, randomized clinical studies with rosiglitazone (n = 14 237)	Received rosiglitazone 24-52 wk	Increased heart failure incidence Increased events of myocardial ischemia	Rosiglitazone increased the risk of heart failure and myocardial infarction	[13]
A meta-analysis of randomized controlled trials (n = 6421, control = 7870)	Received rosiglitazone at least 12 mo	Increased risk of myocardial infarction and heart failure No increased risk of cardiovascular mortality	Rosiglitazone increased risk of myocardial infarction and heart failure, without increased risk of cardiovascular mortality	[23]

I/R: Ischemia/reperfusion; PPAR: Peroxisome proliferator-activated receptor; T2DM: Type 2 diabetes mellitus; RECORD: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; ANP: Atrial natriuretic peptide; BNP: B-type natriuretic peptide; ERK: Extracellular signal-regulated kinase; TZD: Thiazolidinedione; mTOR: Mammalian Target of Rapamycin pathway.

regarding MI and heart failure, but not cardiovascular mortality[23,52,65].

Lipscombe *et al*[19] also demonstrated that rosiglitazone therapy in patients with T2DM was associated with a significantly increased risk of congestive heart failure, acute MI, and death. Similarly, results from a meta-analysis demonstrated that rosiglitazone treatment for at least 12 mo was associated with a significantly increased risk of MI and heart failure[23]. A retrospective analysis also suggested that rosiglitazone may increase the risk of heart failure[13]. These data from the clinical trials and meta-analysis in recent years strongly indicated that rosiglitazone could have adverse effects on the cardiovascular outcome due to increased risk of MI and heart failure, resulting in increased mortality in patients treated over a long period with rosiglitazone[14,18,22,23]. A meta-analysis demonstrated that patients treated with both rosiglitazone and pioglitazone had a 1.7-fold increase in risk of congestive heart failure with a slightly greater increase in risk with rosiglitazone than with pioglitazone (1.3-fold)[67].

The association between TZDs and heart failure is well recognized as a class effect. An increased plasma volume rather than direct effects on cardiac function is thought to be the mechanism responsible for heart failure[12]. Fluid retention is mediated through increased sodium reabsorption of the renal PPARγ-dependent pathway in the collecting tubules[68].

Unlike the mechanism responsible for heart failure, the mechanism of increased MI risk of rosiglitazone is still controversial. An unfavorable effect of the lipid profile has been proposed, in which rosiglitazone increases low density lipoprotein cholesterol to a greater extent than pioglitazone, and decreases the triglyceride level to a smaller extent than pioglitazone[69].

DISCREPANCY IN FINDINGS FROM ROSIGLITAZONE USE

As summarized in Table 1 for the beneficial effects and Table 2 for the adverse effects of rosiglitazone, these controversial reports are still debated. Although each side for and against the use of rosiglitazone has its own supporting documentation, the growing number of reports of serious adverse cardiovascular effects cannot be taken lightly. It is possible that the controversy on the cardiovascular effects of rosiglitazone could be due to differences in species which could have different drug metabolism, different experimental models, different drug administration methods as well as different time intervals of drug treatment which relates to the effects of the drug. The differences in patients' clinical characteristics may also contribute to the differences in outcomes, in which older patients with preexisting cardiovascular disease are more likely to have serious cardiovascular events.

Regardless of this controversy, since evidence from clinical reports indicated potential cardiovascular risks of rosiglitazone, the European Medicines Agency suggested that the anti-diabetes drug rosiglitazone (Avandia®)

should be suspended from the EU market due to its excessive cardiovascular risk[61,70]. As a result, rosiglitazone has been withdrawn from the EU market[61]. However, rosiglitazone is still available in the US but remains under close monitoring from the US Food and Drug Administration[61-63,71].

CONCLUSION

Rosiglitazone is a potent agent in the treatment of hyperglycemia in patients with T2DM because it is an insulin sensitizer and improves glucose uptake. Despite previous reports on its beneficial effects, growing evidence indicates that rosiglitazone increases cardiovascular risks in patients taking this drug. Although this drug has been withdrawn from the EU market, it is still can be used elsewhere. It is important that future large clinical trials should be done to evaluate the definitive cardiovascular outcome of the drug and the interplay between rosiglitazone and other available anti-hyperglycemic agents. In addition, large meta-analyses are also essential and must be carefully interpreted in order to elucidate the effects of rosiglitazone on cardiovascular risks and outcomes.

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