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REVIEW ARTICLE

The forgotten type 2 diabetes mellitus medicine: rosiglitazone

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Abstract
Type 2 diabetes mellitus (T2DM) is a chronic disease prevalent in the world, and it is also one of the overall factors leading to overall morbidity and mortality. Throughout Asia, the proportion of people with T2DM and obesity has increased and this growth rate shows no signs of slowing down. Thiazolidinediones (TZDs) can specifically treat insulin resistance and improve metabolic syndrome, including rosiglitazone, troglitazone and pioglitazone, which are peroxisome proliferator-activated receptor (PPAR) agonists. These drugs have been shown to have better therapeutic effect and glycemic control, but also accompanied by a series of adverse reactions. Cardiovascular events are currently the most serious adverse events of rosiglitazone, which cardiovascular toxicity is higher than pioglitazone. Rosiglitazone has been restricted or even withdrawal from the market in most countries owing to concerns about its cardiovascular safety, while its beneficial effect on insulin resistance has been demonstrated. New data on rosiglitazone-mediated heart failure, myocardial infarction and fractures provide clinicians with prescriptions with fewer side effects to treat patients. Studies have shown that rosiglitazone is the most effective treatment in TZDs (in vivo study), not only hypoglycemic effect but with some additional effects, such as anti-inflammatory and anti-cancer capabilities, retinopathy (animal models) and ischemia–reperfusion injury protection effects, lipid regulation and blood pressure reduction, etc. Although rosiglitazone shows the highest risk of arrhythmia in diabetes management while has the capacity to reduce the risk of atrial fibrillation.

Keywords Type 2 diabetes mellitus · Rosiglitazone · Thiazolidinedione · Cardiovascular disease · PPAR-γ agonist · Insulin resistance

Introduction

Type 2 diabetes mellitus (T2DM) is a global epidemic disease that may cause serious complications and premature death [1, 2]. Thiazolidinediones (TZDs) are oral hypoglycemic drugs which effectively treat T2DM. As a result of concerns about liver toxicity that troglitazone has been withdrawal from markets and existing glitazone drugs include rosiglitazone and pioglitazone. The therapeutic effect of oral hypoglycemic drugs on T2DM will be weakened with the prolongation of treatment time [3, 4].

Rosiglitazone peroxisome proliferator-activated receptor-γ (PPARγ) agonist which increases the incidence rate or may increase morbidity and mortality caused by cardiovascular diseases. The US Food and Drug Administration (FDA) introduced rosiglitazone to black box warning and restriction and held several meetings on the risk of cardiovascular disease of rosiglitazone to review the safety data of rosiglitazone and make suggestions. An advisory committee voted 20:3 to show that there was evidence that rosiglitazone increased the risk of cardiovascular events and thus restricted rosiglitazone usage [1, 3, 5]. At one meeting in June 2013, thirteen members voted to modify the highly restrictive risk evaluation and mitigation strategy (REMS) and final meeting relaxed the use of rosiglitazone [5, 6]. The use rate of rosiglitazone decreased from 39.1 to 1% or even less from 2007 to 2013 after removing the black box warning and restriction [7]. TZD's use in T2DM patients is interrelated with an increased risk of heart failure and

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edema, even if recommendations are followed [8]. T2DM is a risk factor for heart disease and congestive heart failure (CHF). Patients should be warned to use rosiglitazone or pioglitazone because they will lead to the occurrence and deterioration of CHF. TZDs are not recommended in combination with insulin and cannot be used in patients with NYHA class II, III or IV cardiac function [9].

Excessive liver glucose production and peripheral insulin resistance are the main defects of the pathophysiological basis of T2DM [10]. Additionally, PPAR-γ participates in the regulation of lipid metabolism and carbohydrate, promotes the synthesis of glucose transporters and activates the differentiation of adipocytes [11, 12]. PPAR-γ is highly expressed in adipose tissue, which is the regulator of insulin sensitivity, lipid metabolism and adipogenesis [13]. Rosiglitazone achieves glycemic control by reducing insulin resistance and increasing liver and peripheral insulin sensitivity while without causing obvious hypoglycemia (not promoting insulin secretion) [14]. Early application of rosiglitazone improved oxidative stress and inflammation of T2DM patients [15, 16].

Previously, rosiglitazone was widely used to treat T2DM patients while its impact on mortality and morbidity of cardiovascular events had not yet been determined. Early meta-analysis confirmed that rosiglitazone increased the risk of heart failure, cardiovascular death and myocardial infarction [17, 18]. Clinical trial RECORD is required by the European Medicines Agency after the launch of rosiglitazone. However, it reported an increase in the risk of heart failure which resulted a sharp decline in sales of rosiglitazone in Europe and even delisting [19].

Rosiglitazone is closely related to fractures caused by bone loss and bone mineral density (BMD) reduction in T2DM patients [20–23]. Rosiglitazone-mediated fractures mainly occur in women, most of them are upper and lower extremities. Of course, the increased risk of fracture is also present in male group [21, 24].

The main purpose of this review is to elaborate the clinical benefits (Table 1) and review the adverse reactions [25] of rosiglitazone, newly discovered effects of rosiglitazone and comparison with pioglitazone will be introduced and discussed.

Methods

We used the following keywords to search literature as of May 2021 on China Knowledge Network, Web of Science, PubMed: peroxisome proliferator-activated receptors, adverse reactions, thiazolidinedione, rosiglitazone, pioglitazone, heart failure, cardiovascular events, cardiovascular safety, myocardial infarction, cardiovascular mortality, weight gain, cancer, edema, fractures, stroke and type 2 diabetes. Main original papers, randomized controlled trials and review articles are included. Research on rosiglitazone on arrhythmia and ischemia—reperfusion injury has been reviewed in recent years. References of these articles were reviewed in detail. For non-English articles, only the abstract is considered.

Clinical benefits of rosiglitazone

TZDs have a major effect on adipose tissue by activating PPARγ as well as act on liver and muscle to improve β-cell function and lipid distribution, improve insulin sensitivity and reduce insulin resistance to improve glycemic control. To reduce HbA1c level and glycotoxic effect on β-cells, the problem of fasting blood glucose increase should be solved before postprandial blood glucose increase and TZDs notably reduced glycosylated hemoglobin (HbA1c) level and fasting blood glucose in diabetic patients [3, 4, 26]. Additionally, TZDs can increase transactivation of PPAR, thereby reducing insulin resistance (i.e, reducing gluconeogenesis and increasing the utilization of glucose and lipid metabolism in peripheral tissues), which in turn leads to an increase in endogenous insulin to maintain blood glucose levels [11]. Using rosiglitazone 8 mg daily for 3 years to treat T2DM can conspicuously reduce the incidence of T2DM and increase the likelihood that adults with impaired fasting glucose or impaired glucose tolerance or with both, will return to normal blood glucose [27]. Since TZDs bring about cardiovascular disease and T2DM results in high mortality, treatment for dyslipidemia, hypertension and hypercoagulability ought to be carried out to minimize the risk of death [26].

Insulin resistance is the basis of pathogenesis of hyperglycemia and cardiovascular disease [14]. Capabilities of rosiglitazone to reduce insulin resistance, increase liver and peripheral insulin sensitivity, improve inflammation, oxidative stress and metabolic syndrome has been confirmed, the reason that does not increase the risk of hypoglycemia is without promoting insulin secretion [14, 15, 27–31]. The early use of TZDs will delay or prevent progression of T2DM. Impaired fasting glucose and/or impaired glucose tolerance are risk factors for cardiovascular disease, T2DM and renal disease. In a prospective study, 172 T2DM patients with impaired glucose tolerance and insulin resistance were treated with TZDs. Mean HbA1c and C-peptide levels in patients receiving TZDs were lower than those in the control group over a 2-year period and were maintained at the end of study. The incidence of T2DM related to TZDs decreased by 88.9% ($P < 0.001$) compared with the control group after 3 years [4, 32]. Moreover, inflammation is also a characteristic of T2DM [33]. Patients after intensive insulin therapy can continue to take insulin sensitizer rosiglitazone to improve inflammation and oxidative stress [15, 28, 34,

Table 1 Clinical benefits or effect and risk associated with rosiglitazone therapy [4, 14, 16, 24, 26–28, 32, 38, 55, 85, 86, 127]

Clinical benefits or effect of rosiglitazone	
Reduce insulin resistance (16.0–24.6%) and increase insulin sensitivity. Homeostasis model assessment was about 13.4–33.0% (18 months)	
Improve and maintain beta cell function (49.5–60.0%)	
Increase the mass of subcutaneous fat tissue by about 2.9%, especially in the abdomen subcutaneous fat tissue cavity	
Ingredients to improve lipid profile	
Plasma HDL cholesterol increased about 0.12 mmol/l	
Improve LDL concentration (21.4 mg/dl) and particle size, reduced weak dense LDL cholesterol	
Reduce the concentration of free fatty acids (−0.12 mEq/dl)	
Lower plasma triglycerides about 12.3 mg/dl	
Increase serum adiponectin level 2–3 times	
Effect on glycemic control	
Lower fasting glycemic levels, approximately 37.2 mg/dl	
Reduce HbA1c level (1.1% ± 0.3%)	
Assist reduce the daily insulin dose for T2DM patients with poor glycemic control	
The durability of glycemic control was higher than other oral hypoglycemic drugs (such as metformin and glibenclamide)	
Effects on blood vessels and blood pressure	
Decrease vascular adhesion molecules	
Lower systolic 1.5 mmHg and diastolic blood pressure 3.5 mmHg	
Prevent in-stent restenosis	
Increase vasodilation	
Effect on inflammation	
Decrease plasma CRP levels (36–41%, 18 months)	
Improve the expression of matrix metalloproteinases	
Effect on procoagulant state	
Reduce plasminogen activator inhibitor 1 (5.7–11.1%, 18 months)	
Decrease platelet aggregation	
Decrease plasma fibrinogen (2.1–3.2%) at 18 months	
Compared with those without TZDs, the prevention or delay of the progression of T2DM was approximately 88.9%, while that of rosiglitazone was about 60%.	
Reduce urine albumin excretion to protect renal	
Improve LFT level and histological parameters of NASH, T2DM patients with NAFLD or NASH will benefit from it	
Risk of rosiglitazone	
Cardiovascular events	Heart failure, myocardial infarction and cardiovascular death (less evidence, Nissen's meta-analysis)
Fracture	Exist in both men and women
Bladder cancer	Bladder cancer
Weight gain	Weight gain
Stroke	Higher risk than pioglitazone (large-scale observational study published by Graham et al. [58])
Edema	Peripheral edema/macular edema
Arrhythmia	Low-level evidence suggested that rosiglitazone was associated with high-risk arrhythmia
Anemia	ADOPT trial

TZDs thiazolidinediones, *LFT* liver function test, *T2DM* Type 2 diabetes mellitus, *NASH* non-alcoholic steatohepatitis, *NAFLD* non-alcoholic fatty liver disease, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *CRP* C-reactive protein

35]. T2DM is one of the main causes of hypertension. After rosiglitazone treatment, systolic/diastolic blood pressure of patients decreased [16, 19, 36, 37].

Compared with metformin or sulfonylurea, homeostasis model assessment of rosiglitazone has higher insulin sensitivity, lower C-reactive protein (CRP) and causes significant weight gain [16]. The decrease of HbA1c level in patients treated with rosiglitazone is inevitable with an average reduction of 1% ± 0.3%, and the number of patients with HbA1c reaching ≤ 6.5 and ≤ 7.0% will increase. If

other therapies with HbA1c levels below 7.0% cannot be maintained, insulin therapy should be started [26, 36, 37]. Besides, the 5-year mean HbA1c level of the rosiglitazone group in the RECORD trial was lower than the control group [19]. The ADOPT trial showed that compared with metformin and glibenclamide, the risk of rosiglitazone treatment was reduced by 32% and 63% ($P < 0.001$). Moreover, rosiglitazone was better than metformin and glibenclamide in the endurance of glycemic control in T2DM after 5 years of treatment [24, 38]. In DREAM trial, three years of median treatment with rosiglitazone reduced prediabetes diabetes progression/death by 60% and maintained β-cell function [27, 32]. Metformin and TZDs have overlapping effects on a series of atherosclerotic thrombosis factors and markers. These include a decrease in several vascular adhesion molecules, a decrease in platelet aggregation, a decrease in plasminogen activator inhibitor 1 (PAI-1) and a decrease in markers of low-grade inflammation (such as CRP) (Table 1) [14]. Metformin and rosiglitazone increase level of serum adiponectin to regulate lipid metabolism and glycemic control to achieve target blood glucose [14, 39]. Compared with metformin, rosiglitazone has a greater effect on the absorption of peripheral glucose [14]. Furthermore, both improved the composition of lipid mass spectrometry. Rosiglitazone reduces the concentration of free fatty acids (FFA) and the proportion of weak dense low-density lipoprotein without interfering with the pharmacokinetics with each other [14]. Unlike metformin, rosiglitazone can be used in patients with impaired renal function and is well tolerated without obvious gastrointestinal side effects [40]. Rosiglitazone helps T2DM patients with poor glycemic control to lower glycemic levels and reduce daily insulin doses through insulin therapy. However, a meta-analysis reported that adding rosiglitazone to insulin-treated T2DM patients will increase the risk of edema ($P = 0.03$) and hypoglycemia ($P < 0.0001$), cholesterol levels will also increase [41, 42].

Rosiglitazone reduced Homaβ, PAI-1 activity, CRP, fibrinogen, TGF-β, FFA and triglyceride levels compared to nateglinide [28]. Rosiglitazone has a positive effect on anti-atherosclerosis paraoxonase activity, as well as better control of blood glucose concentration, increases paraoxonase activity, high-density lipoprotein (HDL) cholesterol levels, ApoA-1 and PON1, reduces serum homocysteine, weak dense LDL cholesterol and malondialdehyde levels in T2DM patients (Table 1) [14, 16, 19, 43, 44]. Moreover, rosiglitazone improved cardiovascular function by modulating the PPAR signaling pathway targeting ApoA1 and ApoA5. After rosiglitazone treatment, ApoA1, ApoA5, Cyp2b9, Cyp2b10, Cyp2c37 and Cyp2J5 are differentially expressed, which was responsible for the cardiovascular outcome and glycemic control of T2DM [44, 45]. Furthermore, despite pioglitazone and rosiglitazone treatment similarly improved metabolic parameters, diastolic function and blood pressure values, in patients with T2DM only rosiglitazone significantly improved systolic myocardial function [46].

The cardiovascular safety of rosiglitazone led the U.S. FDA to initially implement black box warnings and restrictions on it making most T2DM patients vigilant and prejudiced, leading to a sharp decline in sales of rosiglitazone despite the FDA reassessed its cardiovascular safety in 2013 and released its restrictions that had not been able to increase its sales. In view of the low price of rosiglitazone and drugs mainly for insulin resistance, which indicate the clinical use of rosiglitazone is reasonable.

Adverse reactions and events

Fracture and bone mineral density

T2DM women have normal or higher BMD, but overall risk of bone fracture is approximately twice that of non-diabetic subjects [20, 22]. Epidemiological studies have confirmed that T2DM in women is an independent risk factor for fractures. PPAR-γ is expressed in bone marrow stromal cells, osteoclasts, osteoblasts and adipocytes [22]. Rosiglitazone may increase bone loss at the expense of osteoblast formation by increasing adipogenesis [23]. Several clinical trials related to rosiglitazone have shown that rosiglitazone changed bone metabolism, increased bone loss and the risk of bone fracture in T2DM patients. A number of research data have shown that fracture has a direct relationship with gender. In a 2-year clinical trial, metformin plus rosiglitazone was associated with serum procollagen type I N-terminal propeptide, but rosiglitazone plasma concentration was not associated with fasting bone turnover markers. No cause of rosiglitazone associated with increased bone resorption may be the combination with insulin [47]. Another randomized, double-blind study of postmenopausal T2DM women showed that rosiglitazone was related to a reduction in BMD of femoral neck from baseline to week 52 (−1.47%). During 52 weeks of rosiglitazone or metformin treatment, the BMD of total hip joint decreased (−1.62 and −0.72%, respectively). After switching to metformin, total hip BMD loss caused by rosiglitazone was reduced [22]. Furthermore, a study of skeleton of postmenopausal female showed that patient's average femoral neck BMD, spine average BMD and hip total BMD all decreased after treatment with rosiglitazone [20].

ADOPT trial showed that without obvious difference in fracture rate between male treatment groups while at least 60 cases of rosiglitazone were reported in the female patients, the cumulative incidence of rosiglitazone treatment for 5 years in the female patients was 15.1%, metformin 7.3% and glibenclamide 7.7%. Rosiglitazone increased the risk of fracture compared with glibenclamide and metformin,

with a relative risk ratio of 2.13 and 1.81, respectively. The increased fracture of rosiglitazone occurred in premenopausal and postmenopausal women as well as mainly occurred in upper and lower limbs [24]. Furthermore, in a typical study, in metformin plus rosiglitazone group 46.5% of diabetic men had a higher incidence of vertebral fracture compared with the control group ($P=0.06$) and the incidence of vertebral fracture was higher compared with patients receiving metformin monotherapy (66.7 vs. 27.3%; $P=0.01$) [21].

In RECORD [19], the incidence of fractures in the rosiglitazone group was higher than the control group (risk ratio [RR] = 1.57, 95% confidence interval [CI] = 1.26–1.97, $P<0.0001$) and the RR in women was higher than in men (RR = 1.82 vs. 1.23; interaction $P=0.10$). The most common sites were upper extremity (RR = 1.57, $P=0.0095$) and lower extremity (RR = 2.60, $P<0.0001$). In ACCORD, during a 4.8-year follow-up, 262 men and 287 women were discovered to have experienced at least one non-spinal fracture. The fracture rate of women using TZDs for 1–2 years (HR = 2.32) or using TZDs for > 2 years (HR = 2.01) was higher than women without TZDs. The use of TZDs increased the incidence of non-spinal fractures in women with T2DM and decreased the incidence of fractures after discontinuation. In addition, male non-spinal fractures were not related to the use or discontinuation of TZDs [48].

The second-largest adverse event of rosiglitazone is fracture, the main reason is clinical use will reduce the BMD of patient. Patients exposed to rosiglitazone for one to two years tend to have fractures (Especially upper and lower limbs) and is most commonly observed in women, while a small number of studies have indicated that men exposed to rosiglitazone also increase the risk of fractures. Fractures that occur from one year of exposure are commonly peripheral and may be time-dependent and dose-dependent.

Cardiovascular events

Cardiovascular events are the first adverse reaction of rosiglitazone. Several meta-analyses and clinical trials investigated the effects of rosiglitazone on cardiovascular outcomes, unlike pioglitazone which is trusted by people, the high cardiovascular risk of rosiglitazone makes it biased. In recent years, many studies have shown that pioglitazone has cardiovascular benefits while rosiglitazone is rarely related.

The cardiovascular diseases related to rosiglitazone include heart failure, myocardial infarction and cardiovascular death, which are also the most concerned problems of users [29, 49, 50]. Rosiglitazone-mediated myocardial infarction and heart failure have been confirmed in several early clinical trials, while cardiovascular mortality has different outcomes [29, 51]. Several trials have reported different outcomes for rosiglitazone-mediated cardiovascular disease in recent years, which is a denial of previous trials [42, 51–54]. An investigation of edema and heart failure was conducted in the French Pharmacovigilance Database (FPVD), finally 161 (7%) of 2295 cases of T2DM who were exposed to TZDs had heart failure conspicuously higher than other patients (7.4 vs. 0.1%, $P<0.001$) [8]. A retrospective study from a health maintenance organization database reported that rosiglitazone was only related to CHF after 30 months of treatment (HR = 2.23), while the risk of myocardial infarction did not increase (HR = 1.13) [30]. Table 2 lists available data on rosiglitazone therapy and the development of myocardial infarction, heart failure and cardiovascular death in clinical trials.

Several early clinical trials involving rosiglitazone treated pre-diabetic or T2DM participants showed that there was more imbalance of cardiovascular events in the rosiglitazone group compared with placebo [54]. Nissen and Wolski published a meta-analysis of 42 clinical trials in 2007 reported that rosiglitazone increased the risk of myocardial infarction (Odds ratio (OR) = 1.43, 95% CI = 1.03–1.98; $P=0.03$) and cardiovascular death (OR = 1.64, 95% CI = 0.98–2.74; $P=0.06$) compared with the control group (comparison drugs or placebo) [17]. A meta-analysis of four randomized controlled trials ($n=14,291$, rosiglitazone: 6421 and control treatment: 7870, followed up for 1–4 years) published in the same year reported that rosiglitazone significantly increased heart failure (RR = 2.09; $P<0.001$) and myocardial infarction (RR = 1.42; $P=0.02$), without significant increase in cardiovascular mortality (RR = 0.90; $P=0.53$) [18]. Data from a meta-analysis in 2015 displayed that pioglitazone and rosiglitazone were associated with increased risk of myocardial infarction and heart failure (except cardiovascular death) in T2DM patients [55]. Additionally, in RECORD [19], 14.4% in rosiglitazone group ($n=2220$) and 14.5% in active control group (metformin or sulfonylurea, $n=2227$) experienced major outcomes over a mean of 5.5 years of follow-up. The addition of rosiglitazone increased the risk of heart failure and a small increase in myocardial infarction (hazard ratio (HR) = 1.14). Rosiglitazone did not increase the overall morbidity or mortality of cardiovascular disease compared to standard hypoglycemic agents (HR = 0.84). But the RECORD trial had flaws (No comparison with placebo but with active treatment) [19]. RECORD faced criticism at the 2010 Advisory Committee meeting because its design was an open label, and GlaxoSmithKline employees had access to the data, it seemed that some data were missing [6]. Although, RECORD showed no difference in myocardial infarction or cardiovascular mortality between rosiglitazone and sulfonylurea or metformin treatment. However, the European Marketing Authority still suggested that rosiglitazone should be withdrawn from the European market on 23 September 2010 [54]. Additionally, on 25 November 2013, the FDA reduced the REMS requirements for the RECORD trial and removed certain prescriptions and restrictions for

Table 2 Rosiglitazone and the development of HF, MI and CV death: randomized controlled clinical trials of patients with no diabetes or T2DM. Additional

Study	Population	Drug	Number	Duration of trial	HF occurrence	MI occurrence	CV death occurrence
RECORD [19]	T2DM patients	Rosiglitazone	2220	Mean 5.5 years	61 (2.7%)	64 (2.9%)	60 (2.7%)
		Sulfonylurea/metformin	2227		29 (1.3%)	56 (2.5%)	71 (3.2%)
		P value			<0.001	0.47	0.32
DREAM [27, 32]	Patients with IFG and/or IGT	Rosiglitazone	2635	Median 3 years	14 (0.53%)	16 (0.61%)	12 (0.5%)
		Placebo	2634		2 (0.08%)	9 (0.34%)	10 (0.4%)
		P value			<0.01		
ADOPT [38]	T2DM patients	Rosiglitazone	1456	Median 4 years	22 (1.5%)	27 (1.9%)	0
		Glyburide	1441		9 (0.6%)	18 (1.2%)	Total 1
		Metformin	1454		19 (1.3%)	23 (1.6%)	Total 1
		P value			0.26		
APPROACH [71]	T2DM with known coronary atherosclerosis	Rosiglitazone	333	Median 18 months	8 (2.4%)	8 (2.4%)	4 (1.2%)
		Glipizide	339		3 (0.9%)	7 (2.1%)	3 (0.9%)
		P value			0.14		0.5
Graham et al. [58]	Geriatric medical insurance	Rosiglitazone	67,593	Mean 3 years	1125 (3.94%)	523 (1.83%)	2593 (9.10%)
	T2DM patients	Pioglitazone	159,978		2182 (3.00%)	1223 (1.68%)	5386 (7.42%)
		P value			<0.001	0.18	
BARI 2D [59]	T2DM with known coronary atherosclerosis	Rosiglitazone	992	Mean 4.5 years	3.31%	2.16%	1.88%
		No Thiazolidinedione	1199		3.07%	3.16%	2.56%
		P value			0.62	0.06	0.08
STARR [50]	Patients with IFG and/or IGT	Rosiglitazone	709	Mean 3 years	1 (0.14%)	3 (0.42%)	2 (0.28%)
		Placebo	716		0	1 (0.14%)	1 (0.14%)
		Ramipril	715		2 (0.28%)	2 (0.28%)	1 (0.14%)
		Placebo	710		1(0.14%)	2 (0.28%)	2 (0.28%)

diabetic drugs containing rosiglitazone in 2010 [1, 3]. At the same time, DREAM trial reported that rosiglitazone increased heart failure compared with placebo [0.53 vs. 0.08%, HR = 7.04, $P = 0.01$] [32]. In a cohort study, it was observed that the risk of myocardial infarction and coronary revascularization in patients using rosiglitazone may be lower than the risk associated with sulfonylureas, but higher than the risk associated with metformin [56]. A retrospective cohort study of coronary revascularization and myocardial infarction conducted in the PharMetrics database following this cohort study [56] showed that the risk of coronary heart disease in patients using TZDs appeared to be between the risks associated with metformin and sulfonylurea [57]. In the case of continuous treatment with rosiglitazone or pioglitazone in a shorter period of time without interruption, the risk of myocardial infarction alone was as high as 21% [57].

Graham in a large observational study involving 227,571 subjects and followed up for 3 years, the risk of stroke, heart failure and death related to rosiglitazone were higher than pioglitazone, and were related to the increased risk of stroke, myocardial infarction, heart failure or death. Although the overall results were not novel, this study was large-scale, rigorous and timely. But their coverage had limitations. As with all observational studies, since the treatment allocation (in this case pioglitazone or rosiglitazone) was not randomized, the results may reflect an unrecognized bias or confusion—potential threats to effectiveness can only be reliably mitigated by randomization [3, 58].

In 2014, relationship between rosiglitazone usage and cardiovascular results was evaluated in the Veterans Affairs Diabetes Trial (VADT). Rosiglitazone was associated with a reduction in the risk of major composite cardiovascular outcomes [4 mg: HR = 0.63 and 8 mg: HR = 0.60] and a reduction in cardiovascular death (HR = 0.25 for rosiglitazone 4 and 8 mg/day, $P < 0.001$), and did not result in a higher risk of myocardial infarction [51]. Since cardiovascular disease did not increase but decreased, which supported the FDA's final decision: experts recommended relaxing the restriction on rosiglitazone [51]. In the BARI 2D trial, in patients with coronary artery disease and T2DM, neither on-treatment nor propensity matching analysis supported the association of rosiglitazone treatment with an increase in major ischemic

cardiovascular events (myocardial infarction, stroke, heart failure, cardiovascular death) [59], similar to the results of VADT and BARI 2D in two meta-analyses in recent years [42, 52]. In 2015, a meta-analysis of four randomized trials that repeated more than 12 months of follow-up, the relative risk of no myocardial infarction in rosiglitazone group was 0.997, the relative risk of no cardiovascular death was 1.001. Authors attributed these findings to the fact that original analysis may have exaggerated results owing to the low risk of cardiovascular diseases involved at the baseline [52]. According to the meta-analysis ($n=1{,}916$) published in 2014, there was without significant difference in heart failure, myocardial infarction or cardiovascular death between patients treated with rosiglitazone and those treated with insulin alone. The short duration of the study did not result in prudent outcomes and the combination with insulin were two defects in this meta-analysis [9, 42].

More interestingly, a recent meta-analysis of cardiovascular events of rosiglitazone published in 2018 showed that rosiglitazone compared to placebo or active control ($n=20{,}079$) with a significant increase in the risk of heart failure (RR = 1.71; $P<0.001$) and a small increase in the risk of myocardial infarction (RR = 1.12; $P=0.30$), while rosiglitazone and cardiovascular mortality (RR = 0.93; $P=0.55$) with no statistical difference [60]. Although meta-analysis provides a means for inferring conclusions by combining individual trials/studies, the outcomes commonly carry several inherent weaknesses. In fact, in view of factors, for instance, the selection of criteria to include studies, research endpoints, patient demographics included in various trials or statistical models and adjustments applied to the data, etc., results of different meta-analyses may be weakened [29]. Furthermore, differences in study duration included in different meta-analyses may also affect the observed results. This is especially true in meta-analyses that assess cardiovascular disease outcomes, in which case longer exposures to effective treatments are required to produce differential changes. Additionally, the inclusion of rosiglitazone trials in non-diabetic populations, such as DREAM trial [32] included not T2DM patients but prediabetes patients, which may add another confusing factor. Another important issue to consider when interpreting the meta-analysis of the effects of rosiglitazone on cardiovascular disease is the inclusion of studies without and with rosiglitazone comparators. In fact, the effects of rosiglitazone or additional treatments with rosiglitazone in individual studies may result overestimation or underestimation of rosiglitazone-related cardiovascular disease effects [29].

Bladder cancer

According to reports, TZDs increased the risk of bladder cancer, which was limited to pioglitazone, but for rosiglitazone, two reviews in recent years did not discuss this in detail [29, 54]. According to literature screening, we have observed two literatures which have been investigated in recent years, rosiglitazone, like pioglitazone, increases the risk of bladder cancer. In a national nested case–control study, the use of rosiglitazone increased the incidence of bladder cancer (Odds ratio [OR] = 3.07) and occurred mostly in men (81.2%). Less than one year of continuous use was associated with a higher risk of bladder cancer than the absence of TZDs (OR = 4.48) [61, 62]. In another nested case–control study observed, the OR of rosiglitazone < 1 year was 0.98, OR of 1–2 years was 1.78 and OR of > 2 years was 2.00. A higher probability of bladder cancer was associated with long-term exposure to rosiglitazone, and users who had been exposed for more than 2 years had the highest probability [63]. The anticancer effect of rosiglitazone is only applicable to cancers other than bladder cancer, such as thyroid cancer, breast cancer and gastric cancer. On the other hand, some studies also indicated that rosiglitazone did not increase the risk of bladder cancer compared to pioglitazone or had nothing to do with the increased risk of bladder cancer. Only the above evidence can explain to a certain extent that rosiglitazone increases the risk of bladder cancer.

Rosiglitazone causes weight gain

Several clinical trials have shown that rosiglitazone often causes weight gain when it plays its pharmacological role in recent years. The main reasons for the use of rosiglitazone in the treatment of T2DM patients with decreased aerobic exercise capacity may be weight gain and increased subcutaneous fat [35]. Weight gain caused by rosiglitazone does not affect heart rate variability of patients with T2DM and coronary heart disease [43]. In the ADOPT monotherapy trial, the median weight change increased by 3.5 kg at 4 years [24, 38]. Compared with sulfonylureas [1.2 kg difference, $P=0.003$] and metformin [4.3 kg difference, $P<0.001$] in RECORD, the weight of patients in the rosiglitazone group increased significantly [16]. The possible reasons are rosiglitazone enhanced insulin sensitivity, increased sugar accumulation, adipocyte differentiation and appetite under the stimulation of drugs, increased LDL cholesterol levels, decreased hemoglobin, increased subcutaneous fat mass, unchanged or slightly decreased visceral fat mass, fluid retention and a positive calorie balance due to improved glycemic control [15, 54, 64]. Fortunately, the weight gain caused by rosiglitazone can be combined with metformin during monotherapy to suppress [14].

Stroke

It seems that the current research on the adverse effects of rosiglitazone rarely shifts attention to whether rosiglitazone increases the risk of stroke. In RECORD, the rosiglitazone group had fewer hospital admissions and probability of stroke compared with the active control group. However, the RECORD trial is an exception, because the lack of control with the placebo group results in different conclusions from other experimental results [19]. Subsequently, the research boom of rosiglitazone came, several trials have involved the increased risk of stroke (DREAM, APPROACH, Graham et al.) [27, 32, 58]. In a meta-analysis, rosiglitazone increased the risk of stroke (NNH = 28) compared with patients without TZDs treatment, and rosiglitazone had a higher risk than pioglitazone (overall, NNH = 36) [55]. But this was limited to meta-analysis of observational studies rather than meta-analysis of clinical trials, the risk of stroke did not increase [60]. On the whole, the stroke probability of rosiglitazone is not high (< 2%) [19, 59], but this problem cannot be ignored.

Edema

Soon after rosiglitazone and pioglitazone went on sale, data showed edema and CHF were important complications of TZDs treatment of diabetic patients [65]. For example, on 30 November 2001, Health Canada received more and more reports of CHF, pulmonary edema and pleural effusion related to rosiglitazone and pioglitazone [9]. The severity of the problem was sufficiently important that the American Heart Association and the American Diabetes Association convened a consensus meeting to discuss then published a consensus statement on TZDs usage, peripheral edema and CHF [65]. Although the exact cause of macular edema is unclear, it is speculated that TZDs can cause peripheral edema by affecting renal and intestinal ion transport, increasing plasma volume and sympathetic nerve activation, and causing growth factor-related vascular permeability [66]. Macular edema is also a risk factor for diabetic retinopathy [66]. Confusingly, rosiglitazone exhibits an ameliorating effect on retinopathy in rodent models, which will be discussed in the following chapters. Moreover, other studies have reported that with the popularity of rosiglitazone and pioglitazone, peripheral edema occurred during the treatment, when pioglitazone/rosiglitazone is used in combination with other oral hypoglycemics (such as sulfonylurea, metformin and insulin), peripheral edema is most common [3, 9, 25, 65]. Seek medical attention as soon as possible due to rosiglitazone causes edema [9]. In FPVD, 7% T2DM patients exposed to TZDs had a notably higher edema risk than other patients (18 and 0.8%, respectively). A multiple logistic regression model considering potential confounding factors (sex, age, comorbidities and drug exposure) indicated that TZDs exposure was still associated with edema [8].

The results of a retrospective cohort study of 103,368 T2DM patients showed that TZDs treatment was associated with an increased risk of diabetic macular edema during 1-year and 10-year follow-up assessments. There was no direct difference between rosiglitazone and pioglitazone (pioglitazone OR = 3.6; rosiglitazone OR = 3.1) [67]. Another prospective cohort study involving approximately 170,000 diabetic patients showed that users of TZDs (98% using pioglitazone) were more likely to develop macular edema (OR = 2.6). After excluding patients with no drug benefit, no ophthalmological examination, and HgA1c < 7.0, the use of TZDs was still associated with an increased risk of macular edema (OR = 1.6) [68].

Coronary atherosclerosis

Rosiglitazone has several properties that can affect the progression of atherosclerosis. Two trials of the effect of rosiglitazone on T2DM patients with coronary atherosclerosis have yielded similar results. The safety and efficacy of saphenous vein graft atherosclerosis in 193 T2DM patients after coronary artery bypass grafting (CABG) were evaluated in VICTORY, but without conspicuous statistical difference between rosiglitazone and placebo ($P = 0.22$) [69]. Therefore, In VICTORY trial, rosiglitazone did not limit the progression of coronary atherosclerosis [69, 70]. In addition, in APPROACH, rosiglitazone did not obviously reduce the primary outcome of percentage of atherosclerotic volume (−0.64%; 95% CI 1.46–0.17; $P = 0.12$) compared to glipizide [71]. However, a prospective study reported a significantly lower incidence of in-stent restenosis at 6 months in the rosiglitazone group compared with the control group (stent lesion: 17.6 vs. 38.2%, $P = 0.030$), and the degree of diameter stenosis was notably lower than that in the control group (23.0 ± 23.4 vs. 40.9 ± 31.9%, $P = 0.004$). This effect of rosiglitazone in preventing in-stent restenosis is partly attributed to its anti-inflammatory properties and may be an important way to inhibit any undiscovered or diffuse atherosclerotic process found in T2DM patients [72]. In the STARR trial, compared with the placebo group, the rosiglitazone group reduced the main carotid intima-media thickness (CIMT) outcome of patients with impaired glucose tolerance and/or impaired fasting blood glucose while the difference was not statistically significant ($P = 0.08$) and significantly reduced the secondary CIMT outcome ($P = 0.01$), while ramipril had only a neutral outcome for CIMT compared with placebo [50].

Rosiglitazone and adiponectin

Adiponectin is secreted by adipose tissue and is down-regulated under obesity and insulin resistance [73]. It has been proved that the increase of adiponectin after rosiglitazone treatment is mainly related to its anti-inflammatory effect, rather than its metabolic effect [74]. Rosiglitazone significantly increased the expression of adiponectin and lipoprotein lipase in adipose tissue, and the reduction in liver fat caused by rosiglitazone was related to the increase in serum adiponectin concentration [75]. Genetic variation of adiponectin gene can affect circulating adiponectin levels in T2DM patients: the increase in serum adiponectin concentration of GG genotype in T2DM patients after rosiglitazone administration was less than that of other genotypes ($P=0.003$) [76]. In a double-blind, placebo-controlled crossover study, rosiglitazone treatment increased the adiponectin concentration by 69%. Skeletal muscle adipoR1 expression was down-regulated from 109.0 to 82.8 relative units ($P=0.04$) while adipoR1 expression in adipose tissue was up-regulated by rosiglitazone from 5.3 to 11.2 relative units ($P=0.02$). Contrary to the expression of adipoR1, rosiglitazone did not change the expression of adipoR2 in any tissue. Above data indicated that adipoR1 played a role in mediating the role of adiponectin in specific tissues related to insulin sensitization [77].

The plasma adiponectin concentration of T2DM patients treated with 2 mg rosiglitazone increased significantly in the second week and continued to increase during rosiglitazone treatment [74]. A randomized double-blind placebo-controlled trial showed that average plasma adiponectin level in the rosiglitazone group more than doubled compared with the placebo group ($P<0.0005$). The variation in plasma adiponectin levels explained by treatment was 24% ($r^2=0.24$) [78].

Corresponding meta-analysis outcomes showed that the serum adiponectin level after rosiglitazone in T2DM patients was higher than the pre-treatment level ($P<0.001$). A cohort study showed that rosiglitazone plus metformin contributed to increase the serum adiponectin level in patients with type 2 diabetes ($P<0.05$) [39]. Another clinical trial also showed that adiponectin levels in T2DM patients improved after rosiglitazone plus metformin treatment [79]. Compared with metformin, the serum adiponectin concentration of T2DM patients increased by 123% during rosiglitazone therapy, while remained unchanged in the metformin group and the reduction in serum adiponectin concentration was correlated with the decrease in liver fat ($r=-0.74$, $P<0.001$) [75].

Similar to rosiglitazone, pioglitazone also increased adiponectin levels in patients with T2DM [80–82]. In clinical trials, a significant increase in adiponectin was observed in both male and female patients with T2DM treated with pioglitazone ($P<0.001$) [80]. Adiponectin in the rosiglitazone ($P=0.026$) and pioglitazone ($P=0.004$) groups increased significantly from baseline, which was not seen in the placebo group [81].

Liver and renal function

Diabetic patients often suffer from progressive deterioration of proteinuria, which can eventually result in end-stage renal disease. The important beneficial effect of rosiglitazone is its renal protection which is the basis for rosiglitazone as an appropriate choice for anti-diabetic treatment for patients with renal failure [29]. In a meta-analysis of 15 studies (10 for pioglitazone and 5 for rosiglitazone) involving 2860 patients with normal and microalbuminuria, TZDs treatment was associated with a obvious reduction in urinary albumin excretion (SMD, standard deviation (SD) is -0.6 units). Similarly, TZDs were related to obvious reduction in urine protein excretion in patients with proteinuria (SMD, SD −1.1 units) [83]. Compared with glibenclamide, the urine albumin/creatinine of rosiglitazone plus petformin was significantly reduced (−22.7%; $P<0.01$) [84]. Compared with the placebo group in a randomized controlled trial, the ratio of urine albumin to creatinine in the rosiglitazone group was significantly lower [85]. In another large clinical trial, the urinary albumin excretion of the rosiglitazone (4 mg bd) group was significantly reduced, and the urinary albumin/creatinine ratio improved [86]. The reduction in the percentage of proteinuria was related to the decrease of free fatty acids, fasting plasma glucose, TNF-α, as well as the increase in fat mass, glucose clearance rate and plasma adiponectin [85].

Insulin resistance is commonly associated with non-alcoholic steatohepatitis (NASH) [87]. Patients with T2DM often suffer from impaired liver function tests (LFTs), which commonly reflects an increased prevalence of non-alcoholic fatty liver disease (NAFLD) in diabetic patients [88, 89]. The main feature of NAFLD is the accumulation of fat in liver cells, which in the case of NASH is also accompanied by fibrosis and inflammation [90, 91]. The corresponding meta-analysis reported that in NASH patients, TZDs and vitamin E improved liver histological scores, while metformin did not [91]. In a comparative study, rosiglitazone treatment has been shown to improve LFT levels and the histological parameters of NASH and one clinical trial have reported that improving insulin sensitivity after 48 weeks of rosiglitazone treatment improved the histological indicators of NASH [87, 92]. In view of the negative effect of hepatocyte PPARγ in NASH, the mechanism of inhibiting the promotion of endogenous PPARγ in hepatocytes may be a new strategy to increase the efficiency of NAFLD treatment [93].

Arrhythmia

Hypertension and diabetes have an important influence on the regulation of cardiac calcium (Ca^{2+}) [94]. 68,989 reports were for the arrhythmia of concern among 11.6 million in the FAERS database, of which rosiglitazone was the most frequently reported drug of all arrhythmias (OR = 6.02) [95]. When rosiglitazone was used for rat with diabetes and hypertension it can significantly alter the Ca^{2+} homeostasis and electrophysiological properties, which may have the possibility of causing arrhythmia [94]. Importantly, a prospective study provided realistic evidence to confirm that rosiglitazone and pioglitazone appeared to be associated with similar sudden cardiac arrest/ventricular arrhythmia risks and was gender-specific [96].

Arrhythmia: atrial fibrillation

According to current evidence, atrial remodeling is an important mechanism for the persistence and development of atrial fibrillation while inflammation and oxidative stress may be related to this process [97]. It can be inferred that the pleiotropic effect of rosiglitazone beneficially affects atrial remodeling thereby reducing the burden of arrhythmia [97, 98]. Rosiglitazone weakened the arrhythmic atrial fibrillation and atrial remodeling in diabetic rabbits induced by alloxan: rosiglitazone obviously reduced the duration of atrial fibrillation induction in rabbits ($P < 0.05$); rosiglitazone attenuated the remodeling of atrial structure as well as reduced the atrial activation time ($P < 0.05$) and atrial fibrosis ($P < 0.05$) [98]. Although rosiglitazone reduced the infarct size through external anti-apoptotic pathways and anti-inflammatory effects while it promoted fatal arrhythmias by reducing the phosphorylation of connexin43 and prolonging the attenuation rate of Ca^{2+} during ischemia–reperfusion, even if it had pro-arrhythmic effects but effectively reduced the size of myocardial infarction through anti-inflammatory effects and external apoptotic pathways [99]. In a pathology report study, two patients with T2DM were treated with rosiglitazone and paroxysmal atrial fibrillation was significantly improved [97]. Furthermore, a meta-analysis showed that the association between TZDs and the incidence of atrial fibrillation was not significant in the combined analysis of three randomized controlled trials (OR = 0.77, $P = 0.17$) while it was significant in the combined analysis of four observational studies (OR = 0.71, $P = 0.0003$) [100]. Additionally, a randomized controlled trial involving 2319 T2DM patients reported that subjects who received TZDs did not significantly decrease the incidence of atrial fibrillation in patients compared with patients who received insulin (HR = 0.75, $P = 0.30$) [101]. In a nationwide cohort study of 108,624 diabetic patients who had not previously had atrial fibrillation, diabetes increased the risk of atrial fibrillation by approximately 34%. The incidence of atrial fibrillation in TZDs treatment was significantly reduced ($P < 0.001$) compared with other second-line anti-diabetic drugs, after adjustment (HR = 0.76, $P = 0.047$) compared with other anti-diabetic drugs [102]. In another cohort study involving 12,065 patients with non-insulin-dependent diabetes, 1.6% of subjects had atrial fibrillation during a follow-up period of 63 ± 25 months (1.8% in the control group and 1.2% in the TZDs group). TZDs independently protected diabetic patients from new-onset atrial fibrillation (HR = 0.69; $P = 0.028$) [103].

Rosiglitazone reduces the incidence of atrial fibrillation in patients to a certain extent that specific effect and mechanism can be attributed to the regulation of rosiglitazone on inflammatory factors and changes in patients' oxidative stress state. Clinically, rosiglitazone may protect patients with T2DM from the harm of new-onset atrial fibrillation thereby improving its position in the management of diabetes drugs and may increase its usage.

Arrhythmia: ventricular fibrillation

The incidence of ventricular fibrillation was significantly increased (58 vs. 10%) compared with the vehicle group after receiving rosiglitazone during reperfusion in pigs and rats with cardiac ischemia, and the time to first ventricular fibrillation was reduced (3 ± 2 vs. 19 ± 1 min, $P < 0.05$). Rosiglitazone did not change the level of reactive oxygen species produced in cardiac mitochondria, nor can it prevent changes in mitochondrial membrane potential [104]. In pig model, TZDs promoted the onset of ischemic ventricular fibrillation and increased its mortality, which was related to the changes in conduction and spectral characteristics of ventricular fibrillation. Similar effects may adversely affect cardiovascular mortality in the clinical setting [105]. Importantly, TZDs blocked cardiac K_{ATP} channels at clinically relevant doses (K_{ATP} blockade promotes ischemic ventricular fibrillation) and promoted the onset of ventricular fibrillation during severe ischemia [106].

Retinopathy

To date, pioglitazone and rosiglitazone in the treatment of T2DM patients have other benefits of reducing endothelial dysfunction mediators. The increase in angiogenesis markers in patients receiving rosiglitazone may have different effects on diabetic retinopathy or nephropathy, which may increase

angiogenesis [107, 108]. Rosiglitazone may delay the onset of diabetic proliferative retinopathy, which may be owing to its anti-angiogenic activity: with an average follow-up of 2.8 years, in eyes with severe non-proliferative diabetic retinopathy at baseline 19.2% of the rosiglitazone group and 47.4% of the control group progressed to diabetic proliferative retinopathy within 3 years, relative risk was reduced by 59% (Wilcoxon, $P=0.045$; log-rank, $P=0.059$); fewer eyes in the rosiglitazone group experienced 3 or more lines of vision loss ($P=0.03$) [107]. Rosiglitazone up-regulated the effects of sestrin-1 and antioxidant enzyme superoxide dismutase 2 may increase the cell survival rate of retinal diseases and other neuronal diseases that may be oxidative stress as a key factor [108]. Rosiglitazone attenuated diabetes-induced ganglion cell retinal neuron apoptosis and mitochondrial metamorphosis, and reduced the expression of caspase-3 and p-STAT3 as well as increased the expression of SOCS3. Rosiglitazone may attenuate diabetes-induced retinal neuron apoptosis by inducing SOCS3 to inhibit the activity of p-STAT3, which prompted that rosiglitazone was capable of being used to prevent diabetic retinal neuron damage [109].

The combined use of semaglutide and rosiglitazone can reduce the expression of glial fibrillary acidic protein in diabetic retinopathy model rats, inhibit oxidative stress and PI3K/Akt/MTOR signal transduction thereby having a synergistic protective effect on retinal cells [110]. Troglitazone and rosiglitazone inhibited the phosphorylation of mitogen-activated protein kinase 1 regulated by extracellular signals in retinal endothelial cells. Intravitreal injection of troglitazone or rosiglitazone inhibited the development of retinal neovascularization ($P<0.01$), while did not obviously restrain the overexpression of vascular endothelial growth factor in ischemic retinal ganglion cell layer [111]. In contrast, systemic administration of pioglitazone rather than rosiglitazone can prevent ischemic retinal damage by negatively regulating the expression of TNF-α, which was mediated by up-regulation of anti-inflammatory adipogen adiponectin [112].

As mentioned above, rosiglitazone increased the risk of macular edema while it have been shown to improve retinopathy in animal models and whether it has similar effects for T2DM patients requires to be further confirmed in clinical trials.

Rosiglitazone and ischemia–reperfusion (IR) injury

Before PPARγ binds to the sequence-specific PPAR response element in the promoter region of the target gene, it regulates gene expression by forming a heterodimer with retinoid X receptor, thereby regulating a variety of metabolic pathways, including glucose metabolism and lipid biosynthesis [113]. Recent evidence suggests that PPARγ agonists can prevent IR injury [114]. Lung IR injury is a common clinicopathology related to high mortality [115]. PPARγ is constitutively activated in hepatocytes, and ischemia leads to a rapid decline in DNA binding, which is related to the decrease in ligand expression and co-activator binding [116].

Animals administered with a single dose of rosiglitazone (5 mg/kg) had functional and histomorphological beneficial effects in severe IR injury models after 24 h of reperfusion, which was the result that rosiglitazone can rebalance a number of key enzymes of the nitric oxide pathway (endothelial NO synthase and inducible NO synthase) to improve the renal outcome of IR injury [117, 118]. Besides, rosiglitazone induced endothelial NO synthase phosphorylation and prevented myocardial contractile dysfunction after IR and this effect was inhibited by the pharmacological inhibition of NO synthase and disappears after the gene encoding endothelial NO synthase was destroyed [118].

Administration of ACSL4 inhibitor rosiglitazone before ischemia can alleviate hypertrophic damage in IR-injured lung tissue, and was accompanied by the protective effect of ACSL4 knockdown on lung epithelial cells undergoing hypoxia/re-oxygenation [115]. The inhibitory effect of rosiglitazone on the production of reactive oxygen species was mainly superoxide anions, which may be produced by the activation of xanthine oxidase and/or neutrophils that is one of the mechanisms by which rosiglitazone reduces IR gastric injury [119]. Rosiglitazone inhibited IR-induced NF-κB activation and prevented blood-borne micro-metastasis in the liver by reducing strong IR stimulation, providing a promising strategy in metastasis therapy [120, 121]. In the investigation of rosiglitazone function in mice with liver IR injury, rosiglitazone increased PPARγ activation and reduced liver damage compared with untreated mice. Moreover, wild-type mice had less liver damage after IR than PPARγ-deficient mice [116]. The reduction of polymorphonuclear infiltration into reperfusion renal tissue reflected that rosiglitazone reduced the renal expression of ICAM-1 caused by IR, which was one of the potential mechanisms of the protective effect of rosiglitazone on renal IR injury [114]. Rosiglitazone had a protective effect on IR damage of rat testis through its antioxidant and anti-inflammatory properties [122].

The cardioprotective effect of rosiglitazone-induced IR injury was mediated through PI3-K/Akt/GSK-3α-dependent pathways [123]. Rosiglitazone exerted an anti-apoptotic effect during hypoxia/re-oxygenation of isolated cardiomyocytes, at least in part by promoting the reactivation of prosurvival kinase Akt of which cardioprotective effect can decrease IR damage in patients undergoing cardiac surgery or suffering from myocardial infarction [124].

Rosiglitazone can reduce the IR damage of animal model tissues or organs via a variety of mechanisms (such as the balance of NO key enzymes) and has a certain protective effect which would bring greater benefits to patients during organ surgery. Cardiomyocytes are the direct targets of PPAR-γ agonists, at least to a certain extent by promoting Akt re-phosphorylation to promote their survival in IR, which may be related to clinically inhibiting reperfusion-induced injury in patients suffering from myocardial infarction or undergoing cardiac surgery. This cardioprotective effect of rosiglitazone can reduce reperfusion-induced injury in patients suffering from myocardial infarction or undergoing cardiac surgery [124].

Comparison of rosiglitazone and pioglitazone

There is no randomized controlled clinical trial comparing the safety and efficacy of rosiglitazone and pioglitazone [54]. To date, no research has shown rosiglitazone may actually be safer than pioglitazone. In fact, a large retrospective study by Graham et al. reported that rosiglitazone had a higher risk of heart failure, stroke and death compared with pioglitazone [58]. Their report will undoubtedly contribute to the FDA deliberations, which were likely to end with one of two possible actions for rosiglitazone. One option was to recommend that rosiglitazone be withdrawn from the US market and the TIDE trial should be terminated. The second option was to do nothing but wait for the results of the TIDE trial. The TIDE trial aimed at obtaining this information was terminated after 162 days due to US FDA was concerned the cardiovascular safety of rosiglitazone and the consequent public apprehension which may make recruitment hard and biased [125].

Rosiglitazone is a specific PPARγ activator, while pioglitazone is not only a selective human PPARγ1 but also a weak human PPARα activator [126]. PPARγ promotes the differentiation of stem cells into adipocytes and the storage of peripheral adipose tissue cells instead of releasing fatty acids [23]. In the transactivation analysis of PPARγ1, pioglitazone, rosiglitazone and troglitazone differentially activated PPARγ1, its efficacy grade was rosiglitazone > pioglitazone > troglitazone [126].

The beneficial effect of rosiglitazone on plasma lipid was less than pioglitazone: the total VLDL particle concentration of rosiglitazone was higher than pioglitazone, while the particle size reduction of VLDL was smaller than pioglitazone; pioglitazone decreased the total LDL particle concentration, while rosiglitazone increased its concentration; both increased the LDL particle size, the effect of pioglitazone was better; pioglitazone increased the concentration and size of total HDL particles, while rosiglitazone decreased them; both increased HDL cholesterol levels [127]. In other words, compared with pioglitazone, rosiglitazone has a smaller effect on blood lipid levels and is also a more effective PPARγ agonist; therefore, in view of rosiglitazone may have a greater risk of adverse events than pioglitazone is not far-fetched [3, 128]. The order of the effectiveness of TZDs as glucose transport stimulators in 3T3-L1 adipocytes and anti-hyperglycemic drugs in the body: rosiglitazone > pioglitazone > troglitazone [128]. The other proved inflammatory factor, rosiglitazone had less influence on pro-inflammatory factors than pioglitazone: the level of serum TNF-α of pioglitazone was reduced to a higher degree; pioglitazone had a greater effect on the levels of IL-8, vascular endothelial growth factor and angiogenin than rosiglitazone [129].

Database analysis and meta-analysis concluded that pioglitazone had a greater benefit on cardiovascular outcomes than rosiglitazone and had fewer side effects [54]. The same is true in stroke. Pioglitazone may reduce the risk of stroke attributable to its cardiovascular benefits. Just like PROactive [130], among PROactive participants with previous myocardial infarction ($n = 2445$) or previous stroke ($n = 948$) pioglitazone treatment was associated with 28 and 47% reductions in recurrent myocardial infarction and recurrent stroke, respectively, while rosiglitazone increased the risk of stroke in some studies. The most representative one is the retrospective study of David J. Graham compared with pioglitazone, rosiglitazone prescription increased the risk of stroke. Of course, rosiglitazone increased the risk of stroke compared with non-TZDs, but this was limited to the meta-analysis of observational studies rather than meta-analysis of clinical trials, which indicated that the risk of stroke did not increase. Secondly, the cardiovascular toxicity of rosiglitazone is obvious, which is higher than pioglitazone or other oral hypoglycemic drugs [55, 58]. Additionally, a meta-analysis of adverse reactions showed that rosiglitazone had a higher risk of weight gain (OR: 5.20; $P = 0.0001$) and peripheral edema (OR: 2.36; $P = 0.001$) than pioglitazone [25]. These analyses are problematic due to they are affected by selection bias [54], compared with pioglitazone, clinical trials conducted by rosiglitazone are suboptimal, for example, the quality of data provided by RECORD is lower than PROactive [19, 130].

Since the termination of the TIDE trial, no large-scale clinical trial has been able to compare the efficacy and safety of these two TZDs. It now appears that although in vivo studies have shown that rosiglitazone is a more effective PPARγ agonist while pioglitazone shows more clinical advantages, such as lipid effects, inflammatory factors and cardiovascular benefits, which is why people prefer pioglitazone rather than rosiglitazone.

Conclusion

In conclusion, PPAR-γ agonist rosiglitazone can specifically treat insulin resistance, improve peripheral insulin sensitivity, and will not cause hypoglycemia during the treatment process when without combining with other drugs. The general goal is to treat hyperglycemia in the management of T2DM [29]. Beneficial effects have been observed for many surrogate markers of cardiovascular disease, such as blood pressure, lipid profile, platelet aggregation and endothelial cell function. Subjects with visceral obesity and often with NASH or NAFLD may also benefit from fat redistribution associated with rosiglitazone treatment [29]. There are still worrying cardiovascular events (Especially myocardial infarction and heart failure), fractures and other adverse reactions. Judging from the current situation, there is not sufficient clinical trial evidence to confirm that rosiglitazone can inhibit the progression of coronary atherosclerosis in T2DM patients, which is contrary to the current view. During treatment, patients have a great chance of weight gain and edema. Rosiglitazone has the capability to reduce atrial fibrillation but not ventricular fibrillation, and patients with myocardial damage may show cardioprotection which can be attributed to the weakening of IR damage as well as it has the prevention and reduction capability of retinopathy in animal models. When edema or cardiovascular events occur, immediately stop using or switch to other hypoglycemic drugs. In fact, the diabetes drug rosiglitazone, which is currently only used in a few countries or regions and patients with uncontrolled glycemic, has better glycemic control effect—tolerability and durability are higher than metformin or glibenclamide, low price, lack of cardiovascular safety, which causes its use restriction and withdrawal from the market.

Although the FDA lifted the restriction on rosiglitazone, its use had actually ceased. Like TIDE trial, which was discontinued because the FDA was worried about the cardiovascular safety of rosiglitazone, since then, almost no country or region conducted high-quality clinical trials, which made it difficult to obtain comparative information between rosiglitazone and pioglitazone.

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