



Long-term risk of rosiglitazone on cardiovascular events — a systematic review and meta-analysis

Wpływ długotrwałego stosowania rozyglitazonu na zdarzenia sercowo-naczyniowe
— przegląd systematyczny i metaanaliza

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Abstract

Rosiglitazone has been proposed as a treatment strategy for type 2 diabetes mellitus (T2DM), and it could provide robust glucose-lowering capability with risk of cardiovascular events. We thus performed a systematic review and meta-analysis of controlled trials to assess the effect of this treatment on glycaemic control and cardiovascular events in patients with T2DM. We systematically search PubMed, Embase, and the Cochrane Central Register of Controlled Trials comparing rosiglitazone to other anti-diabetic treatments. These studies included randomised controlled trials (RCTs), cohort studies, and case-control studies that had treatment with at least six months of follow-up in patients with T2DM. We aimed to evaluate the long-term effect on cardiovascular risk of rosiglitazone compared with a basal insulin drug. The main outcomes included myocardial infarction, heart failure, stroke, cardiovascular mortality, and all-cause mortality. We included 11 RCTs and four observational studies involving 20,079 individuals with T2DM allocated to rosiglitazone and a similar number to comparison groups of which only five compared rosiglitazone with placebo and collected data on cardiovascular outcomes. Among patients with T2DM, rosiglitazone is associated with a significantly increased risk of heart failure, with little increased risk of myocardial infarction, without a significantly increased risk of stroke, cardiovascular mortality, and all-cause mortality compared with placebo or active controls. Alternative methods to reduce the uncertainty in long-term pragmatic evaluations, inclusion of rosiglitazone in factorial trials, publication of cardiovascular outcome data from adverse event reporting in trials of rosiglitazone and a cardiovascular endpoint trial of rosiglitazone among people without diabetes. (*Endokrynol Pol* 2018; 69 (3): 381–394)

Key words: cardiovascular disease, rosiglitazone, type 2 diabetes mellitus, systematic review

Streszczenie

Rozyglitazon został zaproponowany jako strategia leczenia cukrzycy typu 2 (*type 2 diabetes mellitus*; T2DM). Ma on zdolność do silnego obniżenia stężenia glukozy z jednoczesnym ryzykiem wystąpienia zdarzeń sercowo-naczyniowych. Autorzy przeprowadzili przegląd systematyczny i metaanalizę kontrolowanych badań, aby ocenić wpływ leczenia rozyglitazonem na kontrolę glikemii i zdarzenia sercowo-naczyniowe u pacjentów z cukrzycą typu 2. Systematycznie przeszukano bazy PubMed, Embase oraz Centralny Rejestr Badań z Grupą Kontrolną im. Cochrane'a (*Cochrane Central Register of Controlled Trials*), porównując rozyglitazon z innymi terapiami przeciwcukrzycowymi. Badania te obejmowały randomizowane badania kontrolowane, badania kohortowe oraz badania kliniczno-kontrolne, które obejmowały leczenie z co najmniej 6-miesięcznym okresem badań kontrolnych u pacjentów z cukrzycą typu 2. Celem była ocena długoterminowego wpływu rozyglitazonu na ryzyko sercowo-naczyniowe w porównaniu z podstawowym lekiem przeciwcukrzycowym. Główne zdarzenia obejmowały zawał serca, niewydolność serca, udar, śmiertelność z powodu chorób sercowo-naczyniowych oraz śmiertelność niezależnie od przyczyny. Uwzględniono 11 randomizowanych badań kontrolowanych i 4 badania obserwacyjne obejmujące 20 079 pacjentów z cukrzycą typu 2 przypisanych do rozyglitazonu i podobną liczbę w grupach porównawczych, w których tylko 5 badań porównywało rozyglitazon z placebo i gromadziło dane dotyczące zdarzeń sercowo-naczyniowych. Wśród pacjentów z cukrzycą typu 2 rozyglitazon jest powiązany ze znacznie zwiększonym ryzykiem niewydolności serca, z nieznacznie zwiększonym ryzykiem zawału serca, bez istotnie zwiększonego ryzyka udaru, śmiertelności z powodu chorób sercowo-naczyniowych i śmiertelności niezależnie od przyczyny w porównaniu z placebo lub aktywną grupą kontrolną. Alternatywne metody zmniejszania niepewności w długoterminowych ocenach pragmatycznych, włączanie rozyglitazonu do badań czynnikowych, publikacja danych dotyczących zdarzeń sercowo-naczyniowych z doniesień o zdarzeniach niepożądanych w badaniach dotyczących rozyglitazonu i próba z udziałem rozyglitazonu w kierunku zdarzeń sercowo-naczyniowych wśród osób bez cukrzycy. (*Endokrynol Pol* 2018; 69 (3): 381–394)

Słowa kluczowe: choroba sercowo-naczyniowa, rozyglitazon, cukrzyca typu 2, przegląd systematyczny

Introduction

Type 2 diabetes mellitus is considered an epidemic in the world [1]. Complications of diabetes included

stroke, blindness, kidney failure, and lower-extremity amputations; the most common developments are heart disease [2], stroke [3, 4], and associated metabolic abnormalities, such as lipid abnormalities and chronic



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vascular inflammation [5], which are significant cardiovascular risk factors. The treatment options for diabetic patients are limited and the costs are high. To meet the demand for newer and more effective drug treatments for T2DM, the prescribing medication to lower glucose among people with T2DM aims to reduce the symptoms of hyperglycaemia and the risk of macrovascular complications. Rosiglitazone is one member of the thiazolidinedione class of peroxisome proliferation-activated receptor gamma (PPAR- γ) antidiabetic agents, mainly metabolised by liver, which have reduced insulin resistance so as to effectively control blood glucose [6], which is also a key factor in hyperglycaemia in patients with T2DM. However, subsequent randomised trials evaluating the effects of intensive treatment for the regulation of blood glucose have highlighted concerns about adverse effects, in particular hypoglycaemia and mortality [7], and demonstrated inconsistent findings for risk of macrovascular complications [8]. Clinical data show that rosiglitazone can improve insulin sensitivity, and it is an effective treatment for glycated haemoglobin production and fasting, with significant reductions in plasma glucose for T2DM [9, 10]. Synchronously, rosiglitazone suggests potentially beneficial effects on overall cardiovascular risk; it can reduce blood pressure, improve vascular endothelial dysfunction and lipid metabolism disorders [9, 11, 12]. In addition, the other benefits have included reduced serum matrix metalloproteinases-9, C-reactive protein [13, 14], and serum levels [15]. There have been some reports of severe adverse drug reactions, such as heart failure, in the early stages of rosiglitazone treatment [16].

The cardiovascular safety of rosiglitazone in patients with diabetes has become a major concern [17]. Since then, several articles have reviewed the efficacy of rosiglitazone for the treatment of T2DM in controlled trials on cardiovascular safety [18]. There is not enough clinical trial evidence that rosiglitazone-induced glycaemic control leads to a reduction in the macrovascular complications of T2DM. Therefore, our objective was to qualitatively and quantitatively evaluate the benefits (e.g. myocardial infarction and stroke) and risks (e.g. heart failure, cardiovascular mortality, all-cause mortality) of rosiglitazone therapy in patients with T2DM. We have conducted a systematic review and meta-analysis to date.

Material and methods

We undertook a systematic review and meta-analysis in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [19] and the Meta-Analysis of observational Studies in Epidemiology (MOOSE) [20].

Search strategy

We searched PubMed (1966 to 17 May 2017), EMBASE, and the Cochrane Central Register (1966 to 17 May 2017) for RCTs and observational studies using the search words rosiglitazone or thiazolidinediones or TZDs and myocardial infarction or cardiovascular or stroke or heart failure and type 2 diabetes, or T2DMs, and limited our search to investigations that were randomised clinical trials involving humans. We also completed the papers with meta-analysis and rosiglitazone in the title. We restricted the search to studies in humans and clinical trials using filters provided by PubMed and EMBASE. There was no language restriction. We retrieved further information by a manual search of references from recent reviews and relevant published original studies. Finally, we manually screened the reference list of a recent systematic review of cardiovascular endpoint trials of glucose-lowering medication [21].

The included trials had to state their intention to monitor cardiovascular adverse events in the "Aims" or "Methods" section, and to explicitly report data (including zero events) on MI, HF, stroke, and cardiovascular mortality. The studies also included a cohort or case-control design that enrolled participants with T2DM. The inclusion criteria for trials were as follows: 1. rosiglitazone treatment of at least six months duration; 2. study participants with T2DM; 3. rosiglitazone as the intervention drug vs. a control, which could be placebo or other oral hypoglycaemic drugs.

Study selection

Trials were identified and subjected to the following inclusion criteria: controlled trial among adults with T2DM comparing any dose and preparation of oral rosiglitazone with no intervention, or with placebo and reporting mortality or a cardiovascular outcome (cardiovascular death, myocardial infarction, stroke, or HF) as a primary or secondary outcome. Published reports were reconciled with trials in the Prospective Register of Systematic Reviews register when possible. We also extracted the following data from each selected study: total number of participants, age, sex, trial duration, mean HbA1c, body weight, FPG and any cardiovascular adverse events were subjected to adjudication to assess the adverse drug reaction. We excluded quasi-experimental studies and crossover, patients with NYHA class II–III heart failure, studies including children, pregnant women, and people with impaired glucose tolerance, and follow-up was less than six months.

Statistical analysis

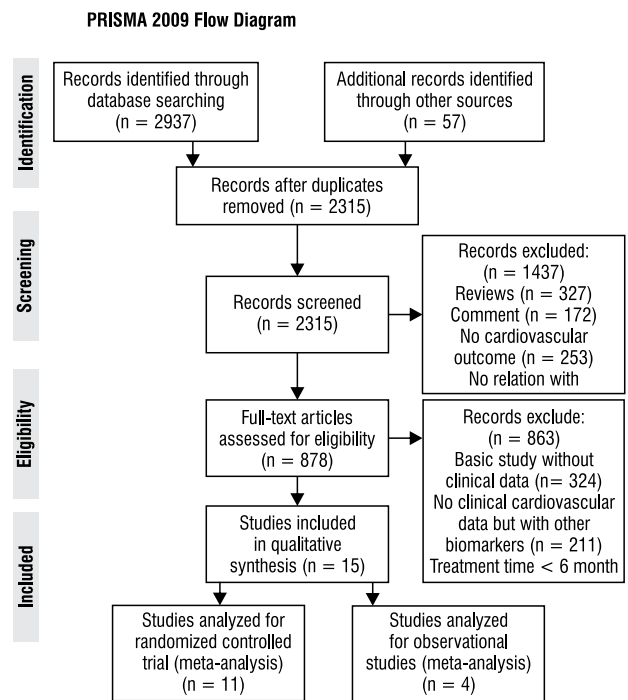
We assessed rosiglitazone on five outcomes: myocardial infarction, heart failure, stroke, cardiovascular mortality,

and all-cause mortality. For analysis of cardiovascular events of participants, we calculated an overall relative risk (RR). For categorical outcomes we also calculated pooled estimates of the relative risk with a random-effects model. In the analyses of each outcome, we performed pre-planned sensitivity analyses restricted to trials that compared PPAR- γ agonist treatment to basal-bolus insulin regimens. The risks of cardiovascular were more significant for rosiglitazone treatment.

We assessed the possibility of publication bias by constructing a funnel plot of each trial's effect size against the standard error (appendix). The assessed funnel plot asymmetry using Begg and Egger tests, and defined significant publication bias as $P < 0.1$. We use the Cochran Q test to assess heterogeneity between studies. We also did I² testing to assess the magnitude of the cardiovascular events between studies, with values greater than 50% regarded as being indicative of moderate-to-high heterogeneity. These data were processed using Review Manager (RevMan), version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) to calculate relative risks (RRs). We assessed the risk of publication bias by producing a funnel plot for all-cause mortality. We performed sensitivity analyses to explore the influence on effect size of statistical models, trial duration, and adjudication of cardiovascular events.

Results

We identified 2994 potentially relevant studies for our analysis (Fig. 1). Following screening of titles and abstracts, we reviewed the full text of 878 articles and included 15 trials that met all the inclusion criteria for the meta-analysis. The full text stage that absence of the collection of data or clinical data for cardiovascular events were excluded. The characteristics of the included studies are shown in Table I. Studies were reported between 2002 and 2015. Four of 15 studies were observational studies, and the other studies were randomised, controlled trials. Two studies were open-label [42, 44], and of the seven placebo-controlled trials, 10 included other glucose-lowering drugs. We identified five trials including 3136 patients allocated to rosiglitazone, which simply compared rosiglitazone with placebo and collected data on cardiovascular outcomes [36, 37, 39, 46, 47]. In total, 20,079 patients with type 2 diabetes were allocated to rosiglitazone, and a similar number to comparison groups, in the included studies. Duration of follow-up ranged from six to 72 months; three studies followed patients up for more than four years [6, 34, 36]. No studies were assessed as having low risk of bias (Fig. 2). Participants' mean age ranged from 50 to 64.3 years and exceeded 60 years in six studies [34, 36, 37, 38, 43, 47],



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Figure 1. Flow chart of article selection

Rycina 1. Schemat działania podczas wyboru prac

and the RCT participants tended to be overweight/obese (average baseline BMI ranged from 27.9 to 34.1 kg/m²), with longstanding (average duration ranged from 0 years in one study [41] to 11.5 years [38] and poorly controlled diabetes [HbA1c was less than 8%] in seven studies [6, 35, 41, 42, 45–47] and ranged from 6.8% to 9.3%; average baseline FPG was less than 150 mg/dl in three studies [39, 41, 45], and unclear in four studies and ranged from 105.5 to 184 mg/dl). The RRs for our pooled analyses of the effects of rosiglitazone for MI, heart failure, stroke, cardiovascular mortality and all-cause mortality are shown in Figure 3. Data on cardiovascular events and mortality in the included trials are shown in Table II. The appendix also shows the assessment of risk of bias in the trials. Eleven randomised, controlled trials reported adequate randomisation, none was stopped early, eight were multicentre, five studies did not specify whether data collectors and outcome assessors were masked to treatment allocation, and only three were not funded by industry.

The effect of rosiglitazone on risks of heart failure (Fig. 3), myocardial infarction (Fig. 4), stroke (Fig. 5), cardiovascular death (Fig. 6), and all-cause mortality (Fig. 7) are shown. All outcomes, except for the risk of heart failure, favoured rosiglitazone, with limited heterogeneity between studies, but none achieved statistical

Table I. Characteristics of rosiglitazone included in the analysis of cardiovascular events
 Tabela I. Charakterystyka rosiglitazonu zawarta w analizie zdarzeń sercowo-naczyniowych

Source	Study Design	Intervention group; /control group	Intervention /control (n)	Follow-up (months)	Duration of Treatment, Mean, y	Age, Mean, y	BMI [kg/m ²]	FPG [mg/dl]	HbA1c (%)	Male, %	Inclusion criteria	Participants	Monitoring for Adverse Cardiovascular Outcomes	Adjudication/Review of Adverse Cardiovascular Outcomes
Randomized controlled trials														
Bach et al. 2013 [34]	Double-blind	Ros; con	992/1199	72	NR	62	32	NR	NR	70	T2DM, CVD, Age ≥ 62 y NYHA-Class II/III HF,		Secondary endpoint was a composite of death, MI, or stroke	Blinded independent cardiologist checked listings of serious adverse events. CVD, HF, PCI
Dargie et al. 2007 [37]	Double-blind	Ros; Pla	110/114	12	1	64.3	28.8	163.6	7.8	84	FPG: 126–216 mg/dl BMI ≤ 35 kg/m ² LVEF ≤ 45%	T2DM with NYHA class I or II HF	Prespecified aim to compare cardiovascular morbidity and mortality; secondary outcomes included cardiovascular events	Cardiovascular end points reported to independent adjudication committee of 3 consultant cardiologists
Florez et al. 2015 [38]	Nr	Ros; con	447/447	29	11.5	62	31.5	NR	9.3	98	HbA1c < 7.5%, BMI > 27 kg/m ²	T2DM, aged ≥ 41 y, class III/IV HF	Individual events from the composite cardiovascular CV outcome, CV death, MI and coronary revascularization	Cox proportional hazards models were conducted for all outcome evaluations, and crude and fully adjusted and their corresponding 95% (CIs)
Gerstein et al. 2006 [39]	Single-blind	Ros; Pla	2635/2634	36	3	54.6	30.8	109.8	8.7	41.7	OGTT(FPG:6.1–7.0 mmol/l and 2-h PG ≥ 7.8 mmol/l); IGT(FPG < 7.0 mmol/l and 2-h PG: 7.8–11.1 mmol/l)	Impaired glucose tolerance and/or fasting glucose Exclusions: history of diabetes cardiovascular disease and HF	Prespecified secondary outcomes were MI and HF	Adjudicated by blinded independent monitoring committee using prespecified diagnostic criteria

Source	Study Design	Intervention group; control group	Intervention /control (n)	Follow-up (months)	Duration of Treatment, Mean, y	Age, Mean, y	BMI [kg/m ²]	FPG [mg/dl]	HbA1c (%)	Male, %	Inclusion criteria	Participants	Monitoring for Adverse Cardiovascular Outcomes	Adjudication/Review of Adverse Cardiovascular Outcomes
Gram et al. 2011 [40]	Double-blind	Ros ± Asp Ins ± Met ± NPH Ins; Plac ± Asp Ins ± Met ± NPH Ins	187/184	24	8.9	56.5	33.5	184	8.5	55.1	HbA1c > 7.0% (53.0 BMI > 25 kg/m ²)	T2DM, All prior antidiabetic treatments were stopped received a starting dose of 12 IU	Serious hypoglycaemia was defined as any hypoglycaemic episode requiring assistance	Safety data were reviewed unblinded during the study by an independent academic diabetologist.
Hällsten et al. 2002 [41]	Double-blind	Ros; Met	14/13	6	0.0	58.6	29.3	129.6	6.8	71.4	New diagnosis or diet alone, FBG 6.1–11.0 mmol/l	T2DM, Excluded: cardiovascular disease, blood pressure 160/100 mmHg	Primary outcome was whole-body and skeletal muscle glucose uptake, blood flow, and oxygen consumption	Arterial and plasma glucose was determined in duplicate by the glucose oxidase method
Home et al. 2007 [42]	Open-label	Ros; Met Or gly	2220/2227	45	3.75	58.4	31.6	177	7.9	51.4	BMI ≥ 25 HbA1c: 7.0–9.0%	T2DM, Age 40–75,y. Exclusions: recent hospitalization for CVD,PCIHF	Primary outcome measure was hospitalization for cardiovascular events (MI and HF)	Blinded end-point committee adjudicated using prespecified diagnostic criteria; about 85% of all reported events have been adjudicated
Kahn et al. 2006 [6]	Double-blind	Ros; Met or gly	1456/2895	57.6	4	57	32.2	151.5	7.4	55.7	FPG:126–18 mg/dl, Lifestyle management,	T2DM, diagnosed within past 3 y and not taking any oral hypoglycaemic drugs. Exclusions: unstable or severe angina, any degree of HF	Adverse event categories of special interest prespecified in analysis plan, including HF and MI	Blinded independent cardiologist checked listings of serious adverse events. HF, reports then reviewed by second blinded independent cardiologist, with third cardiologist arbitrating in case of disagreement; ongoing external review by FDA did
Mcgavock et al. 2011 [45]	Double-blind	Ros; Pla	26/23	6	10.7	58	33.2	105.5	7.7	60.7	NR	T2DM and either CVD or ≥ 1 other CVD risk factor Exclusion: within past 6 mo and not taking any oral hypoglycaemic drug	Primary outcome measure for the trial was integrated cardiovascular performance	All images and spectra were collected and analysed by a single investigator blinded to study treatment assignment using a commercially available workstation

Source	Study Design	Intervention group; control group	Intervention /control (n)	Follow-up (months)	Duration of Treatment, Mean, y	Age, Mean, y	BMI, [kg/m ²]	FPG [mg/dl]	HbA1c (%)	Male, %	Inclusion criteria	Participants	Monitoring for Adverse Cardiovascular Outcomes	Adjudication/Review of Adverse Cardiovascular Outcomes
Mcquire et al. 2010 [46]	Double-blind	Ros; Pla	54/54	6	9.5	57	34.1	NR	7.6	59.6	C-reactive protein 0.3 mg/L	T2DM and either CVD, (CAD, stroke, CPA) or ≥ 1 other CVD risk factor	Key secondary measures included new HF, BNP and MRI	All images analysed by a single-investigator blinded to study treatment, Systolic function was estimated by ejection fraction and diastolic function estimated by early diastolic peak filling rate
Varghese et al. 2009 [47]	Double-blind	Ros; Pla	27/29	12	NR	62.2	27.9	NR	NR	78	HbA1c < 10%	T2DM, Age 30–75 y, diet and exercise alone	All scans for analysis were made perpendicular to the long-axis of the carotid artery	Adjudicated by blinded independent committees all outcomes and selected safety events
Observational control studies														
Breunig et al. 2014 [35]	NR	Ros; Met	310/5548	19.2	NR	50	NR	NR	NR	33.6	Age ≥ 18 year, T2DM	Age ≥ 18 year, T2DM	Endpoint was a composite of death, MI, or stroke	Blinded independent cardiologist checked listings of serious adverse events. CVD, HF,
Brownstein et al. 2009 [36]	Double-blind	Ros; Met	1879/12490	48	NR	64	NA	NR	8	51.7	HbA1C > 6.0%	T2DM, Age ≥ 18 y, Exclusion: within past 6 mo and not taking any oral hypoglycaemic drug	Adjusted for in multivariate models and used for stratified analysis end point MI, CAD, HF, angina, PCI CABGS.	Blinded independent cardiologist checked listings of serious adverse events. CVD, HF, PCI
Loebstein et al. 2010 [43]	Double-blind	Ros; Met	745/11938	6	2.5	60	NA	NR	8.8	55.3	FPG ≥ 126 mg/dlor CPG ≤ 200 mg/dl HbA1C ≥ 7.25%	T2DM, Exclusion: within past 6 mo and not taking any oral hypoglycaemic drug	Primary outcome AMI, ACS, CR, CABGS, CHF, All-cause mortality	Adjudicated by blinded independent monitoring committee using prespecified diagnostic criteria
Mcatee et al. 2007 [44]	Open-blind	Ros; Met or sul	8977/17954	31	NR	52	NA	NA	NR	55	NR	T2DM, Age > 18 y, diagnosed within past 6 mo and not taking any oral hypoglycaemic drugs.	Composite outcome variable for MI and/or CR	Adjusted for baseline covariates, using prespecified diagnostic criteria

*Characteristics of total patients
Abbreviation: FPG, Fasting plasma glucose; HbA1c, Haemoglobin A1c; GFR, Glomerular filtration rate; Ros, Rosiglitazone; Met, Metformin; Plac, Placebo; Ros, Rosiglitazone; Sul, Sulfonylurea; Con, Control; Asp Ins, Insulin aspart; T2DMs, Type 2 diabetes mellitus; CVD, Cardiovascular disease; CAD, Coronary artery disease; CHF, Congestive heart failure; CR, Coronary revascularization; CABG, Coronary artery bypass grafting surgery; PCI Percutaneous coronary intervention; NR, Not reported

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bach et al. 2013	+	+	?	+	-	+	-
Breunig et al. 2014	-	?	-	+	?	?	-
Brownstein et al. 2009	?	-	-	+	?	+	+
Dargie et al. 2007	+	+	?	+	?	?	+
Florez et al. 2015	+	?	?	+	?	+	+
Gerstein et al. 2006	+	+	?	-	+	+	?
Gram et al. 2011	+	?	+	-	+	+	+
Hällsten et al. 2002	?	?	+	?	+	+	+
Home et al. 2007	+	?	-	?	+	+	+
Kahn et al. 2006	+	+	?	?	?	+	+
Loebstein et al. 2010	?	-	?	+	?	+	?
McCafee et al. 2007	-	?	-	+	?	+	?
McGavock et al. 2011	+	+	?	+	?	+	-
McGuire et al. 2010	-	?	+	-	+	+	+
Varghese et al. 2009	+	?	?	+	?	+	+

Figure 2. Risk of bias summary

Rycina 2. Podsumowanie ryzyka wystąpienia błędu

significance. Meta-analysis showed that rosiglitazone treatment increased the risk of cardiovascular events (Table III).

Heart failure

The data from 12 trials involving 52,394 patients, and nine RCT trials showed that the RR of heart failure with rosiglitazone significantly increased compared with placebo or active controls (175/7227 vs. 116/8672; RR 1.71; 95% CI 1.36–2.15; $P < 0.001$) (Fig. 3). There was no evidence of substantial statistical heterogeneity among the trials ($I^2 = 9\%$). The three observational studies trials showed that the RR of heart failure with rosiglitazone were (320/10032 vs. 967/26463; RR 1.84; 95% CI 1.60–2.13; $P < 0.001$). There was significant statistical heterogeneity among the trials ($I^2 = 87\%$).

MI

From the data from 12 trials involving 72,151 patients, nine RCT trials showed that the RR of myocardial infarction with rosiglitazone did not significantly increase

compared with placebo or active controls (157/7249 vs. 159/8696; RR 1.12; 95% CI 0.90–1.39; $P = 0.30$) (Fig. 4). There was no evidence of substantial statistical heterogeneity among the trials ($I^2 = 0\%$). The three observational trials showed that the RR of myocardial infarction with rosiglitazone was 216/11601 vs. 1367/44605; RR 1.36; 95% CI 1.17–1.58; $P < 0.001$. There was no evidence of substantial statistical heterogeneity among the trials ($I^2 = 0\%$).

Stroke

From the data from seven RCT trials involving 16,220 patients, nine RCT trials showed that the RR of stroke with rosiglitazone did not significantly increase compared with placebo or active controls (152/7387 vs. 185/8833; RR 0.91; 95% CI 0.74–1.13; $P = 0.39$) (Fig. 5). There was no evidence of substantial statistical heterogeneity among the trials ($I^2 = 0\%$).

Cardiovascular mortality

From the data from 12 trials involving 29,105 patients, 11 RCT trials showed that the RR of cardiovascular mortality with rosiglitazone was not significantly increased compared with placebo or active controls ($n = 112/7489$ vs. 127/8933; RR 0.93; 95% CI 0.72–1.19; $P = 0.55$) (Fig. 6). There was no evidence of substantial statistical heterogeneity among the trials ($I^2 = 0\%$). One observational study trials showed that the RR of cardiovascular mortality with rosiglitazone was (30/745 vs. 418/11938; RR 1.15; 95% CI 0.80–1.65; $P = 0.45$). There was no evidence of substantial statistical heterogeneity.

All-cause mortality

From the data from 11 trials involving 28,957 patients, 10 RCT trials showed that the RR of all-cause mortality with rosiglitazone was not significantly increased compared with placebo or active controls (222/7415 vs. 254/8859; RR 1.00; 95% CI 0.84–1.19; $P = 0.99$) (Fig. 7). There was no evidence of substantial statistical heterogeneity among the trials ($I^2 = 0\%$). The observational study trials showed that the RR of all-cause mortality with rosiglitazone was 40/745 vs. 734/11938; OR 0.87; 95% CI 0.64–1.19; $P = 0.39$. There was no evidence of substantial statistical heterogeneity.

Summary estimates of 11 RCTs were based on a small number of events: 112 cardiovascular deaths in nine studies, 157 myocardial infarctions in nine studies, 175 heart failure events in seven studies, and 151 strokes in six studies. Two studies [34, 42] contributed the majority of data in the summary estimates, with weights of 61.7% for myocardial infarction, 81.4% for stroke, and 75%

Table II. Data on cardiovascular events and mortality in long-term use of rosiglitazone**Tabela II. Dane dotyczące zdarzeń sercowo-naczyniowych i śmiertelności podczas długotrwałego stosowania rosiglitazonu**

Source	Treatment groups	No. (To.) of Participants				
		Heart failure	Myocardial infarction	Stroke	Cardiovascular mortality	All-Cause mortality
Bach et al. 2013 [34]	Ros;	61 (512)	51 (668)	14 (686)	48 (667)	74 (686)
	con	50 (512)	59 (668)	19 (686)	45 (667)	72 (686)
Brownstein et al. 2009 [35]	Ros	NR	133 (1879)	NR	NR	NR
	Met	NR	1174 (23690)	NR	NR	NR
Breunig et al. 2014 [36]	Ros;	59 (310)	NR	NR	NR	NR
	Pla	389 (5548)	NR	NR	NR	NR
Dargie et al. 2007 [37]	Ros;	19 (110)	5 (110)	2 (110)	5 (110)	8 (110)
	Pla	10 (114)	1 (114)	2 (114)	4 (114)	5 (114)
Florez et al. 2015 [38]	Ros	NR	4 (93)	2 (93)	5 (93)	NR
	con	NR	11 (93)	6 (93)	10 (93)	NR
Gerstein et al. 2006 [39]	Ros	14 (2635)	16 (2635)	7 (2635)	12 (2635)	30 (2635)
	Pla	2 (2634)	9 (2634)	3 (2634)	10 (2634)	33 (2634)
Gram et al. 2011 [40]	Ros ± Asp Ins ± Met ± NPH In	5 (187)	NR	2 (187)	0 (187)	2 (187)
	Plac ± Asp Ins ± Met ± NPH In	3 (184)	NR	3 (184)	0 (184)	2 (184)
Hällsten et al. 2002 [41]	Ros	NR	0 (14)	NR	0 (14)	0 (14)
	Met	NR	1 (13)	NR	0 (13)	0 (13)
Home et al. 2007 [42]	Ros	47 (2220)	49 (2220)	109 (2220)	37 (2220)	74 (2220)
	Met or gly	22 (2227)	40 (2227)	114 (2227)	46 (2227)	80 (2227)
Kahn et al. 2006 [6]	Ros	22 (1456)	25 (1456)	16 (1456)	5 (1456)	34 (1456)
	Met or gly	28 (2895)	36 (2895)	36 (2895)	12 (2895)	62 (2895)
Loebstein et al. 2010 [43]	Ros	56 (745)	13 (745)	NR	30 (745)	40 (745)
	Met	442 (11938)	131 (11938)	NR	418 (11938)	734 (11938)
Mcafee et al. 2007 [44]	Ros	205 (8977)	70 (8977)	NR	NR	NR
	Met or Sul	136 (8977)	62 (8977)	NR	NR	NR
Mcgavocket al. 2011 [45]	Ros	2 (26)	5 (26)	NR	0 (26)	0 (26)
	Met or gly	1 (23)	2 (23)	NR	0 (23)	0 (23)
Mcguire et al. 2010 [46]	Ros	3 (54)	NR	NR	0 (54)	0 (54)
	Pla	0 (54)	NR	NR	0 (54)	0 (54)
Varghese et al. 2009 [47]	Ros	2 (27)	2 (27)	NR	0 (27)	0 (27)
	Pla	0 (29)	1 (29)	NR	0 (29)	0 (29)

Abbreviation: Ros, Rosiglitazone; Met, Metformin; Plac, Placebo; Ros, Rosiglitazone; Sul, Sulfonylurea; Con, Control

for heart failure. We undertook a sensitivity analysis replacing data from the longer-term follow-up of the two studies [33, 41] with the original published data [6]. This led to small changes in the pooled estimates that more strongly favoured rosiglitazone for risk of heart failure and the risk of myocardial infarction. The funnel map (Fig. 8) does not show that rosiglitazone has a risk of increasing mortality.

Sensitivity analysis

We performed sensitivity analyses using pooling methods and statistical models regarding heterogeneity, and the cardiovascular events (heart failure, MI, and stroke) were similar.

There was little or no heterogeneity in the meta-analysis of cardiovascular events, suggesting a consistent treatment effect. After excluding the trial with the

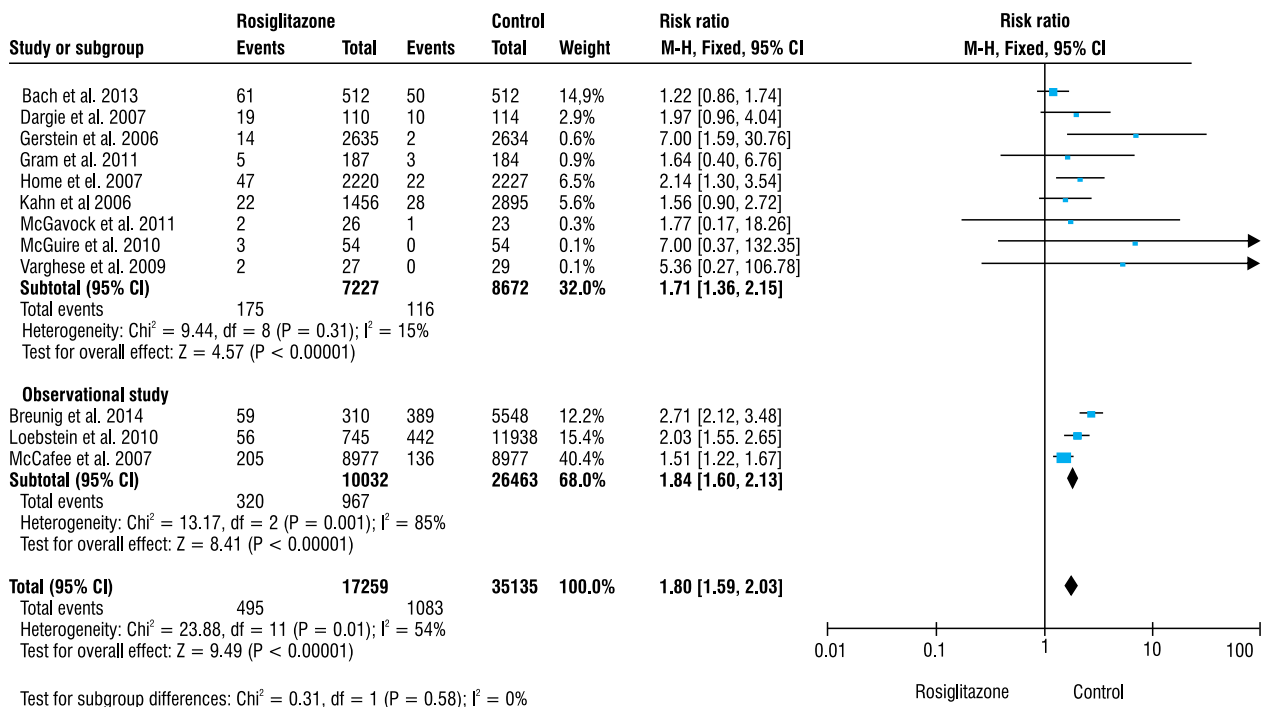


Figure 3. Forest plot showing the effect of rosiglitazone on risk of heart failure

Rycina 3. Wykres typu forest plot, przedstawiający wpływ rozyglitazonu na ryzyko wystąpienia niewydolności serca

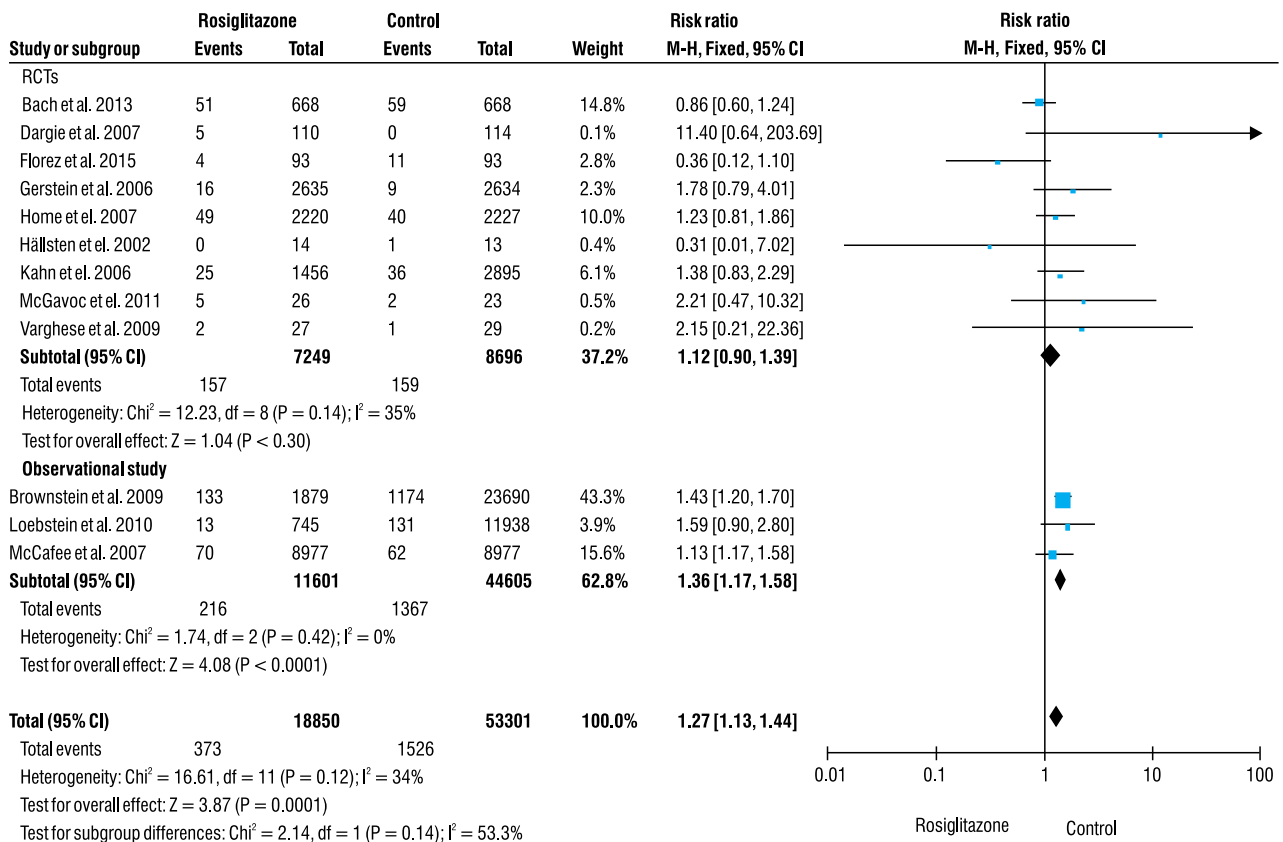


Figure 4. Forest plot showing the effect of rosiglitazone on risk of myocardial infarction

Rycina 4. Wykres typu forest plot, przedstawiający wpływ rozyglitazonu na ryzyko wystąpienia zawału mięśnia sercowego

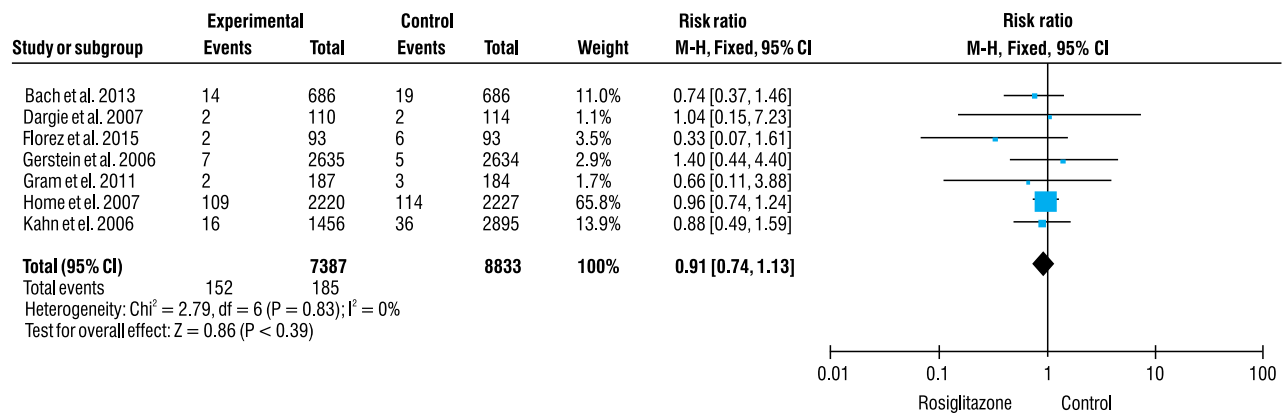


Figure 5. Forest plot showing the effect of rosiglitazone on risk of stroke

Rycina 5. Wykres typu forest plot, przedstawiający wpływ rosiglitazonu na ryzyko wystąpienia udaru

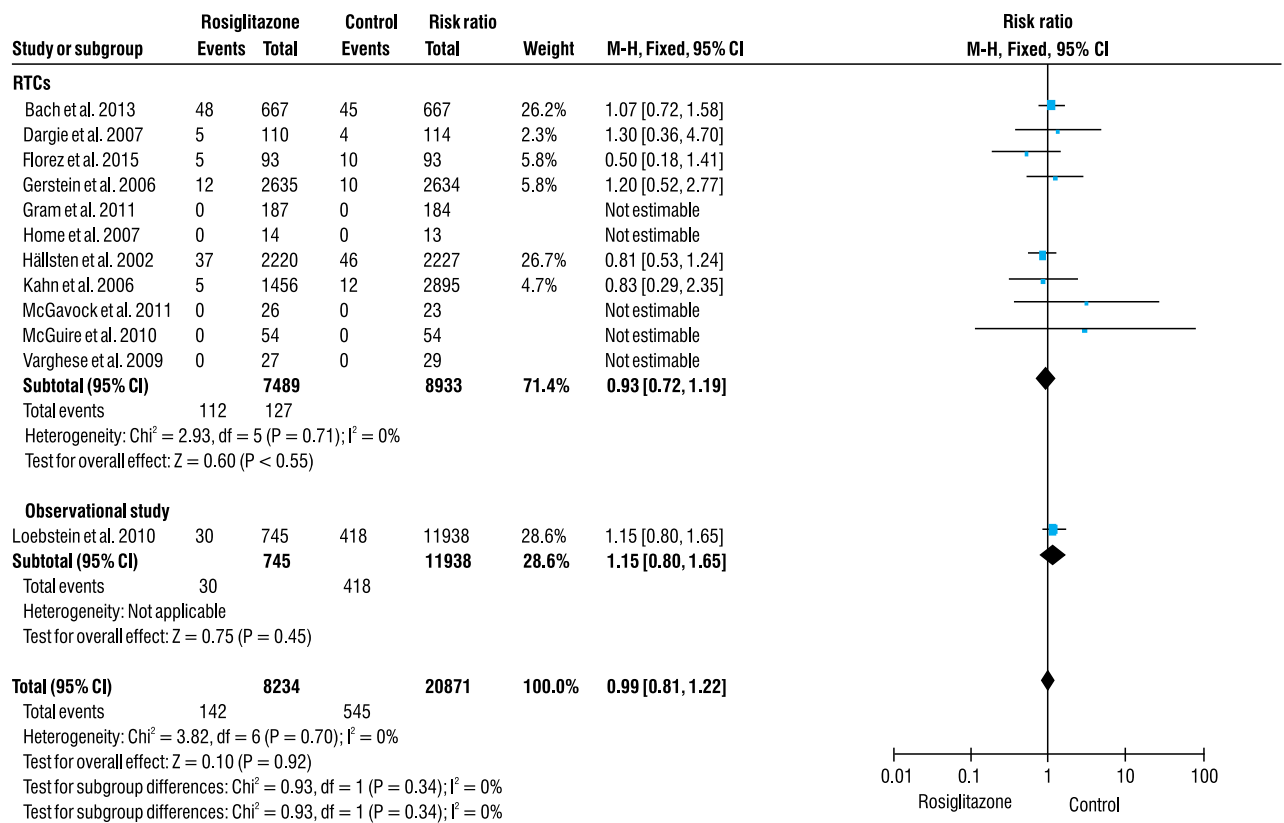


Figure 6. Forest plot showing the effect of rosiglitazone on risk of cardiovascular death

Rycina 6. Wykres typu forest plot, przedstawiający wpływ rosiglitazonu na ryzyko śmierci z powodu choroby sercowo-naczyniowej

smallest number of participants, observational studies, and shortest follow-up, the analysis of heart failure (RR 2.14; 95% CI 1.49–3.05; $P < 0.001$), MI (RR 1.35; 95% CI 1.00–1.83; $P = 0.05$), and stroke (RR 0.96; 95% CI 0.76–1.22; $P = 0.74$) with rosiglitazone from the three large trials of similar duration was similar.

Discussion

The meta-analysis included 11 randomised controlled trials and observational studies with over 20,000 participants with T2DM allocated to rosiglitazone. Though it was uncertainty about whether it reduces risk of

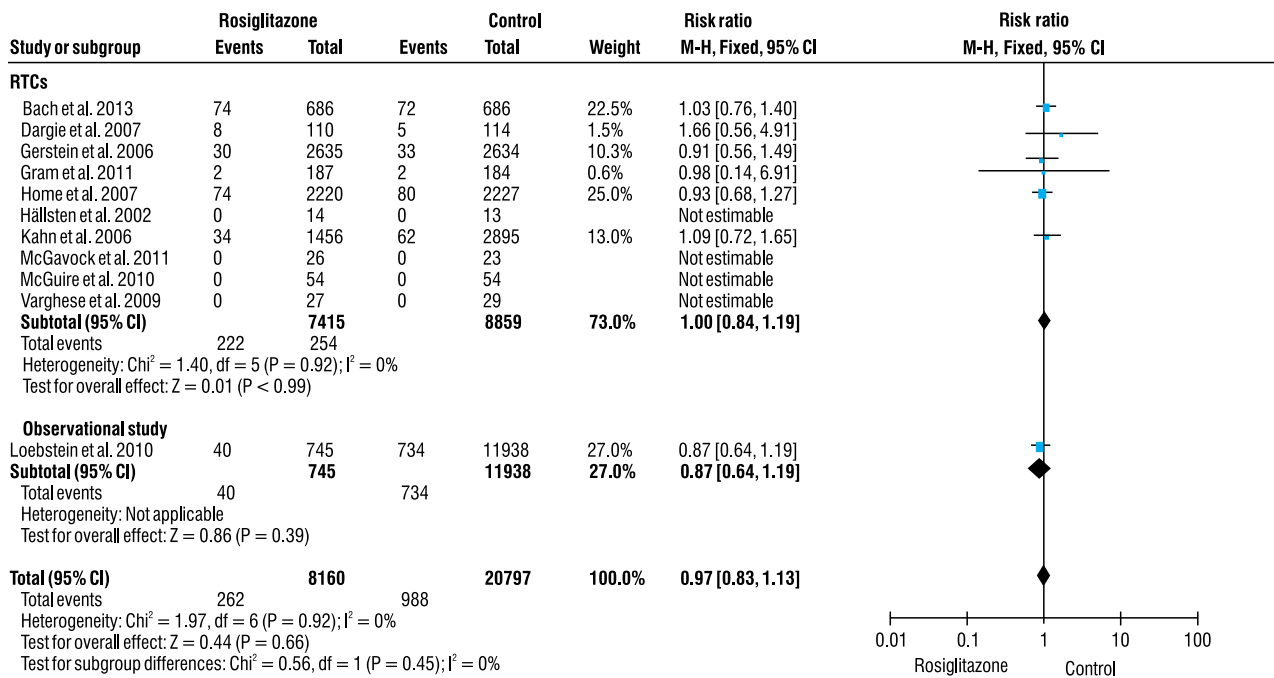


Figure 7. Forest plot showing the effect of rosiglitazone on risk of all-cause mortality

Rycina 7. Wykres typu forest plot, przedstawiający wpływ rosiglitazonu na ryzyko śmierci niezależnie od przyczyny

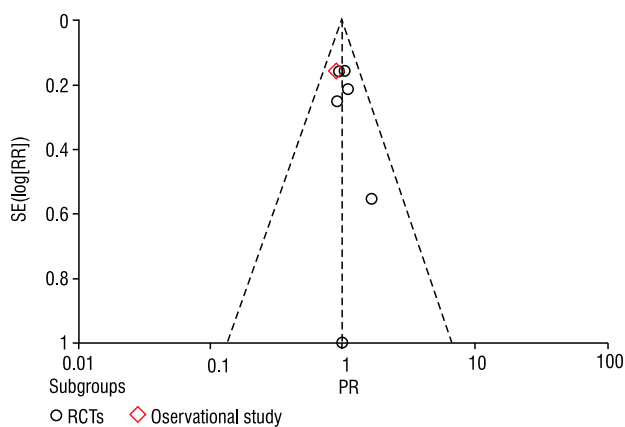


Figure 8. Funnel plot of effect size estimates for all-cause mortality

Rycina 8. Wykres lejkowy oszacowania wielkości efektu dla śmiertelności niezależnie od przyczyny

cardiovascular disease. In this review compared with a control group, we have summarised the adverse effects of the rosiglitazone group as an approximate doubling of the risk of heart failure, with an increase in the risk of the other cardiovascular events (e.g. MI and stroke), cardiovascular mortality, and all-cause mortality without any difference. In the results there are only five randomised, controlled cardiovascular endpoint trials simply comparing rosiglitazone with placebo among

patients with type T2DM. We found that rosiglitazone significantly increases the risk of heart failure and MI compared with other basal-bolus insulin regimens. These data show rosiglitazone and basal insulin combination treatment as a therapeutic strategy that can improve the management of T2DM. We analysed some cardiovascular events and used sensitivity analysis to adjudicated cardiovascular events that did not change the direction or magnitude of the effect.

Two previous meta-analyses showed that the risk of MI was significantly increased by rosiglitazone [22, 23]. One involving 42 RCTs with 14,237 participants determined the incidence of MI in the rosiglitazone compared with controls (RR 1.31; 95% CI 1.01–1.70) [22]. The other analysis involving 42 RCTs with 28,443 patients reported an increase in the risk of MI with rosiglitazone compared with controls (RR 1.43; 95% CI 1.03–1.98; $P = 0.03$) [23]. Our analyses included long-term trials showing that the RR estimate of 1.41 for MI is similar to the OR estimate of 1.43 obtained by two authors. A recent analysis reported that TZDs did not increase the risk of hypoglycaemia compared with controls; a possible mechanism for this is the fact that TZDs are mainly metabolized by the liver [17]. Several previous studies [24, 25] found, compared with active drugs, that metformin, rosiglitazone, and sulfonylurea had similar hypoglycaemic effect, which explained that the changes of HbA1c and FPG had no statistical significance. Our

Table III. Risk of cardiovascular events and mortality in patients with T2DMs**Tabela III.** Ryzyko zdarzeń sercowo-naczyniowych i śmiertelności u pacjentów z cukrzycą typu 2

Outcomes	No. of Study	Events/Total		RR (95% CI)	P Value	I2
		Rosiglitazone	Control			
Heart failure	9 RCTs	175/7227	116/8672	1.71 [1.36, 2.15]	< 0.0001	15%
	3 observational studies	320/10032	967/26463	1.84 [1.60, 2.13]	< 0.0001	85%
MI	9 RCTs	157/7249	159/8696	1.12 [0.90, 1.39]	0.30	34%
	3 observational studies	216/11601	1367/44605	1.36 [1.17, 1.58]	< 0.0001	0%
Stroke	7 RCTs	152/7387	185/8833	0.91 [0.74, 1.13]	0.39	0%
Cardiovascular Mortality	11 RCT	112/7489	127/8933	0.93 [0.72, 1.19]	0.55	0%
	1 observational studies	142/8234	545/20870	1.15 [0.80, 1.65]	0.45	0%
All-cause Mortality	10 RCTs	222/7415	254/8859	1.00 [0.84, 1.19]	0.99	0%
	1 observational studies	40/745	734/11938	0.87 [0.64, 1.19]	0.39	0%

Abbreviation: RCTs, Randomised, controlled trials; RR Relative risk; MI, myocardial infarction

findings were consistent with published meta-analyses that found that rosiglitazone can increase the risk of MI, stroke, or heart failure [8, 26].

All trials of the analyses suggested the possibility of bias or lack of information to evaluate the risk of bias. Most data for this review came from previous data [6, 39, 42, 43] that lacked recent experimental data. One study [35] shown patients with the bypass angioplasty revascularisation investigation T2DM, that had some limited for analysis. The data from the four observational studies [35, 36, 43, 44] were rather heterogeneous. Those were seminal trials concerning the effectiveness and safety of treatments for T2DM, albeit exhibiting a number of previously discussed limitations that might influence interpretation [27]. The analyses lack of placebo and double-blinding, 'subgroup' nature, lack of statistical significance of the update threshold, possible differences in the management of other cardiovascular risk factors between groups, and control of blood glucose levels in the control group the current standard is poor. In short, the research limitations included: 1. limited data on random trials, and inaccurate risk ratio. 2. Wide confidence intervals due to the small numbers. 3. Whether MI and heart failure have information on the time was unavailable, which affects the calculation of hazard ratios. 4. Whether patients with cardiovascular disease and severity before experimental study, which have consequences for the outcome.

Rosiglitazone can reduce the blood sugar in people with T2DM by increasing the sensitivity of the tissue to insulin. Rosiglitazone may increase the incidence of oedema, which raises concerns about the use of these drugs in heart failure patients [28]. In addition to the hypoglycaemic effect, rosiglitazone is beneficial to the cardiovascular system by activating the body fluid,

thrombus, and PPAR receptors on the endothelium [29]. Studies have suggested that rosiglitazone and pioglitazone are used in patients with heart failure or worsen, especially those that are in combination with insulin [30]. In the management of T2DM, the attainment of glycaemic targets is compromised by the limitation of available treatment. With some anti-diabetic treatments (e.g. sulfonylureas, insulin), there is an increased risk of hypoglycaemia as glucose concentrations approach the desired normal range. Other drugs (e.g. rosiglitazone, insulin) are associated with weight gain, an undesirable effect in patients with T2DM [31].

The use of cardio-protective drugs to control cardiovascular risk factors during the study may help reduce the risk of rosiglitazone damage. The cardiovascular differences between rosiglitazone and pioglitazone may be partly explained by different effects of lipids and lipoproteins, granules, and subclasses [32, 33]. If the excessive adverse effects of MI are mediated by LDL cholesterol and triglyceride rosiglitazone, it is possible to have sufficient fat to control statins, which can reduce the risk of MI. Aspirin also can reduce the risk of diabetes and coronary heart disease. The use, among patients with hypertension and diabetes, of angiotensin converting enzyme inhibitors or angiotensin receptor blockers may have an impact on cardiovascular adverse ketone, which can recede the protection of the heart. So the analysis should be based on the hierarchical use of these drugs as additional clinical data at lower risk of heart failure using Rogge column.

Although further research is needed to determine the best treatment method in practical application, our results clearly illustrate the effect of rosiglitazone on the cardiovascular system in the clinical treatment of patients with T2DM. The analyses have potential

regulatory and clinical implications. These data suggest that rosiglitazone reverses the hazard equilibrium. At present, clinical treatment of diabetes has a more secure program. Regulators should reassess the clinical value of rosiglitazone. Diabetes patients should avoid the risk of cardiovascular events associated with rosiglitazone in safer treatment.

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Authors' contributions

Conception and design: Dayan Cheng and Han Gao. Financial support: Wentao Li. Collection and assembly of data: Dayan Cheng and Han Gao. Data analysis and interpretation: Dayan Cheng and Wentao Li. Manuscript writing: All authors.

Data availability

The authors declare that the data supporting the findings of this study are available within the article.

Contribution statement

All authors were involved in the design of the review. Wentao Li, undertook analysis of the data. Dayan Cheng drafted the manuscript. All authors reviewed the manuscript and contributed to its revision. All authors approved the version to be published.

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