Endokrynologia Polska
DOI: 10.5603/EP.a2018.0036
Tom/Volume 69; Numer/Number 4/2018
ISSN 0423–104X

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

Dayan Cheng*, Han Gao*, Wentao Li

Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China
**Dayan Cheng and Han Gao contributed equally to this work.*

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 11RCTs 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

Wentao Li, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, 274 Zhijiang Road, Shanghai 200071, China, tel.: +861 333 188 2730; e-mail: 1037238853@qq.com (D.-y. Cheng), habika_gao@sina.com (H. Gao), 1132@szy.sh.cn (W-t. Li)

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 no 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

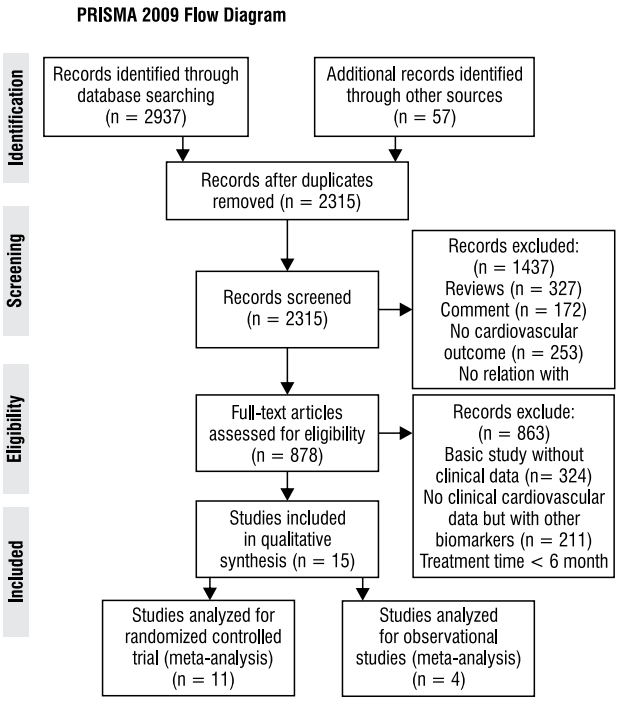
Trials were identified and subjected to the following inclusion criteria: controlled trial among adults with T2DM comparing any dose and preparation of oral rosiglitazone with no intervention, or with placebo and reporting mortality or a cardiovascular outcome (cardiovascular death, myocardial infarction, 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.



From: Moher O, Uberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and MetaAnalyses: The PRISMA Statement. PloS Med. 6 (7): e1000097. doi: 10.1371/journal.pmed1000097. For more information, visit www.prisma-state ment.org

Figure 1. *Flow chart of article selection*
Rycina 1. *Schemat działania podczas wyboru prac*

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], and the RCT participants tended to be overweight/obese (average baseline BMI ranged from 27.9 to 34.1 kg/m^2), 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 rozyglitazonu zawarta w analizie zdarzeń sercowo-naczyniowych*

Source	Study Design	Intervention group; ontrol 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	T2DM with NYHA class I or II HF LVEF ≤ 45%	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; ontrol 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 al.one, 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; ontrol 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
Mcguire 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 Exclusion: within past 6 mo and not taking any oral hypoglycemic drugr	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 Exclusion: within past 3 mo and not taking any oral hypoglycaemic drugs.	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	Endpoint was a composite of death, MI, or stroke	Blinded independent cardiologist checked listings of serious adverse events. CVD, HF,
Brown-stein 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 prespeci-fied diagnostic criteria
Mcafee 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; AMI, acute myocardial infarction; CHF, Congestive heart failure; CR, Coronary revascularization; CABG, Coronary artery bypass grafting surgery; PCI Percutaneous coronary intervention; NR, Not reported

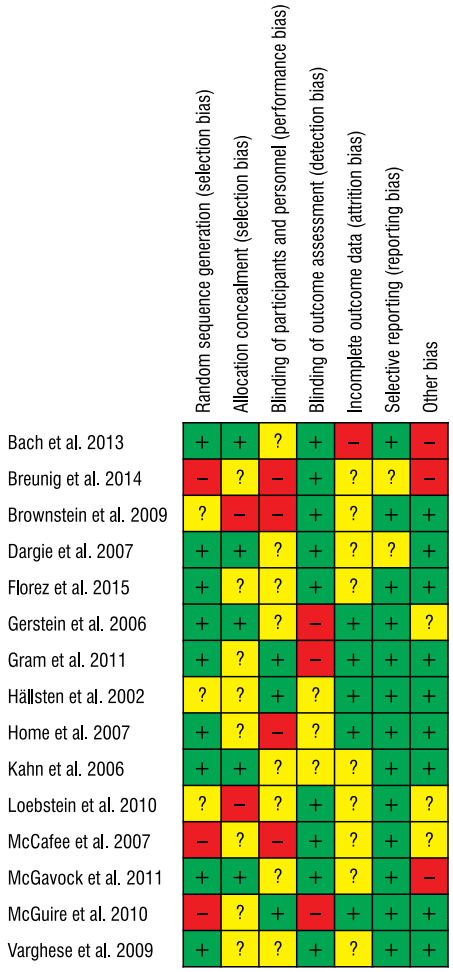


Figure 2. *Risk of bias summary*

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 (I2 = 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 (I2 = 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 (I2 = 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 (I2 = 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 (I2 = 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 (I2 = 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 (I2 = 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 rozyglitazonu*

		No. (To.) of Participants				
Source	**Treatment groups**	**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

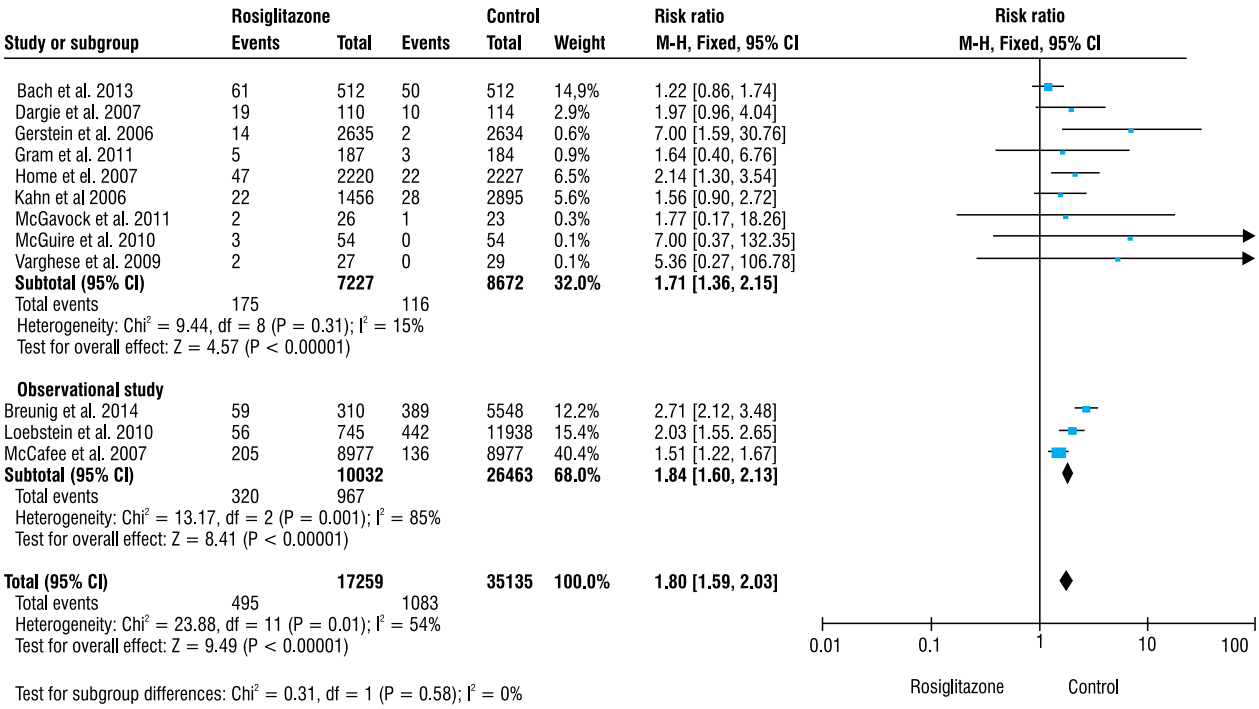


Figure 3. *Forest plot showing the effect of rosiglitazone on risk of heart failure*

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

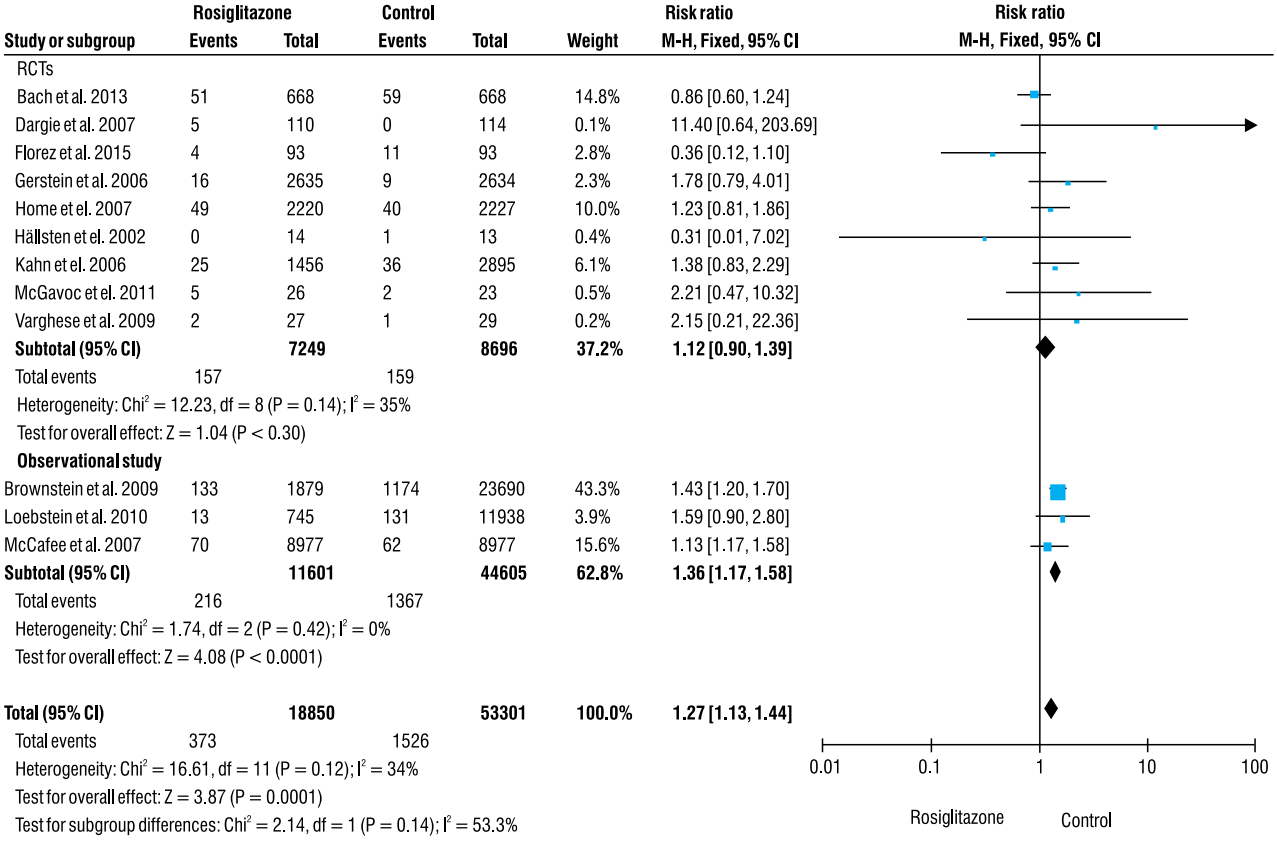


Figure 4. *Forest plot showing the effect of rosiglitazone on risk of myocardial infarction*

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

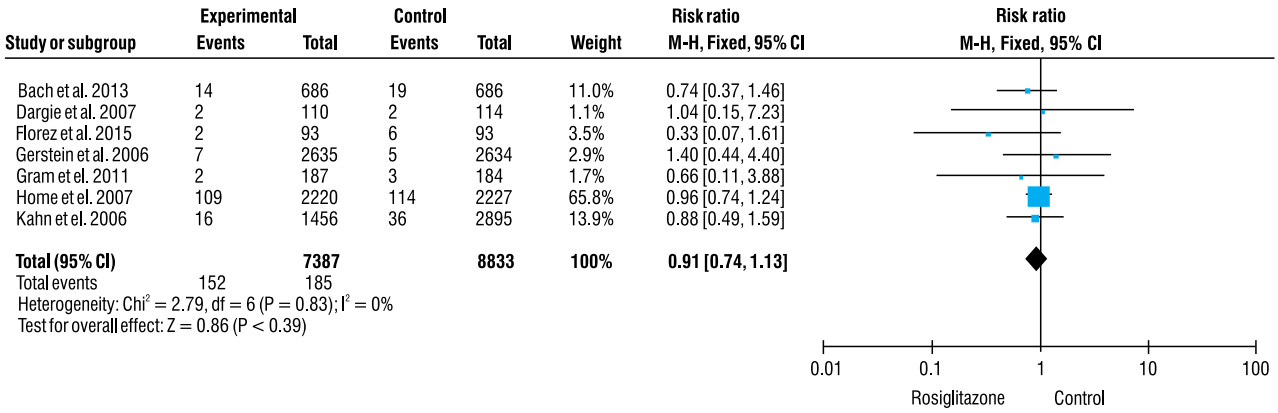


Figure 5. *Forest plot showing the effect of rosiglitazone on risk of stroke*

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

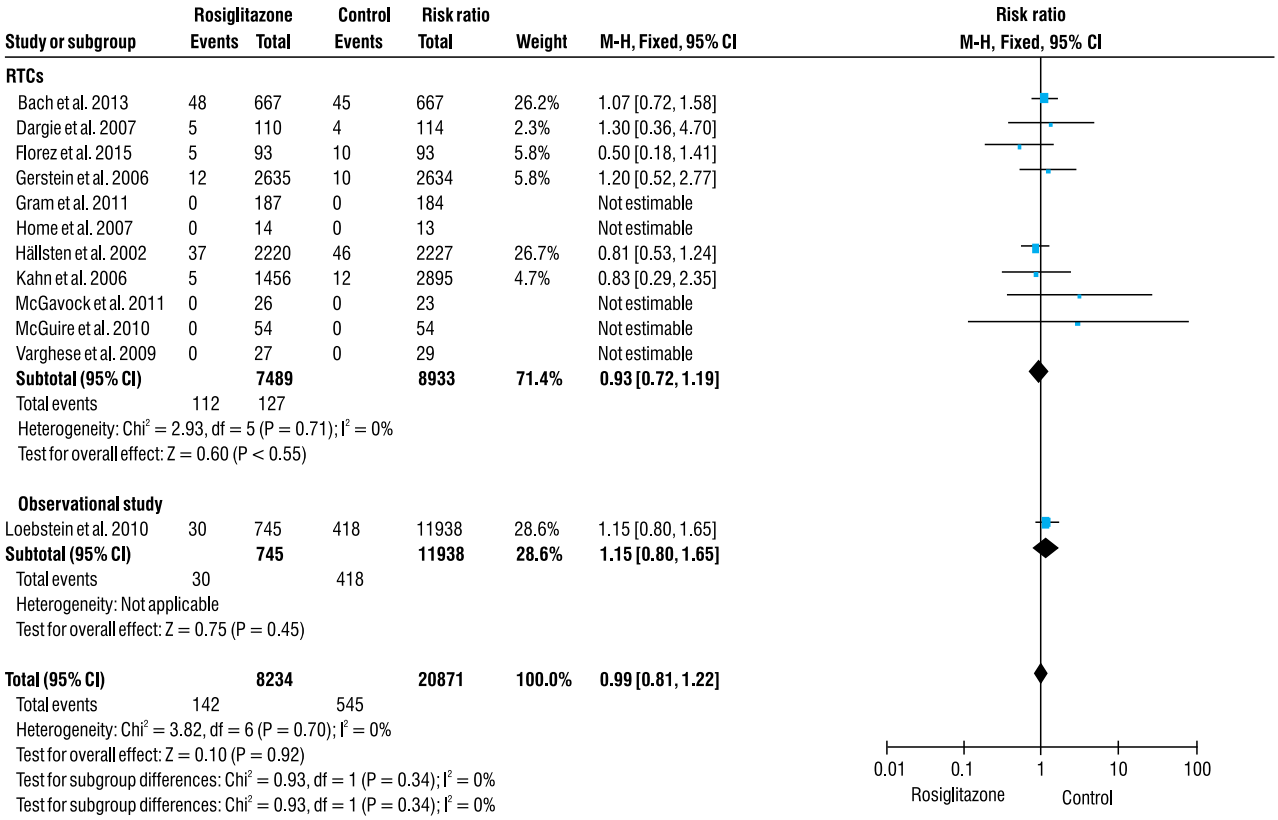


Figure 6. *Forest plot showing the effect of rosiglitazone on risk of cardiovascular death*

Rycina 6. *Wykres typu forest plot, przedstawiający wpływ rozyglitazonu 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

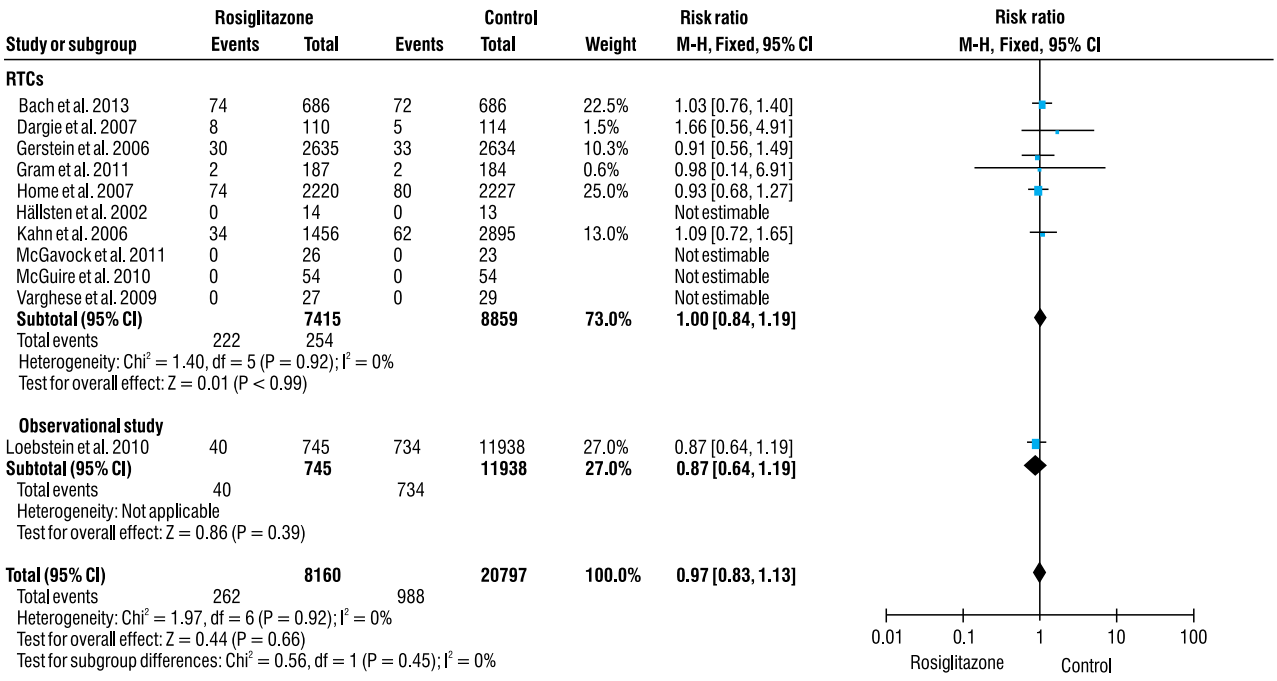


Figure 7. *Forest plot showing the effect of rosiglitazone on risk of all-cause mortality*

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

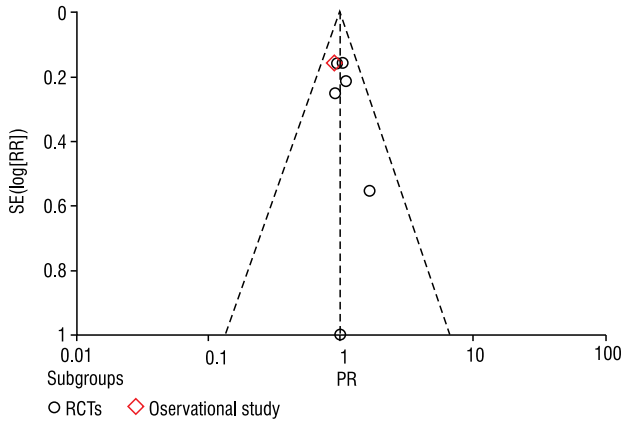


Figure 8. *Funnel plot of effect size estimates for all-cause mortality*

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.

Acknowledgements
We thank Wentao Li, Encephalopathy Department, Shanghai municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, for his help in developing the revision strategy.

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.

No funding.

References

1. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. Lancet Diabetes Endocrinol. 2015; 3(2): 105–113, doi: 10.1016/S2213-8587(14)70219-0, indexed in Pubmed: 25466521.
2. Haffner SM, Lehto S, Rönnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998; 339(4): 229–234, doi: 10.1056/NEJM199807233390404, indexed in Pubmed: 9673301.
3. Lee M, Saver JL, Hong KS, et al. Effect of pre-diabetes on future risk of stroke: meta-analysis. BMJ. 2012; 344: e3564, doi: 10.1136/bmj.e3564, indexed in Pubmed: 22677795.
4. Kernan WN, Inzucchi SE, Viscoli CM, et al. Insulin resistance and risk for stroke. Neurology. 2002; 59(6): 809–815, doi: 10.1212/wnl.59.6.809.
5. Di Pino A, Urbano F, Zagami RM, et al. Low Endogenous Secretory Receptor for Advanced Glycation End-Products Levels Are Associated With Inflammation and Carotid Atherosclerosis in Prediabetes. J Clin Endocrinol Metab. 2016; 101(4): 1701–1709, doi: 10.1210/jc.2015-4069, indexed in Pubmed: 26885882.
6. Kahn SE, Haffner SM, Heise MA, et al. ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006; 355(23): 2427–2443, doi: 10.1056/NEJMoa066224, indexed in Pubmed: 17145742.
7. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med. 2010; 170(14): 1191–1201, doi: 10.1001/archinternmed.2010.207, indexed in Pubmed: 20656674.
8. Home PD, Pocock SJ, Beck-Nielsen H, et al. RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009; 373(9681): 2125–2135, doi: 10.1016/S0140-6736(09)60953-3, indexed in Pubmed: 19501900.
9. Lebovitz HE, Dole JF, Patwardhan R, et al. Rosiglitazone Clinical Trials Study Group. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. J Clin Endocrinol Metab. 2001; 86(1): 280–288, doi: 10.1210/jcem.86.1.7157, indexed in Pubmed: 11232013.
10. Phillips LS, Grunberger G, Miller E. Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes. Diabetes Care. 2001; 24(2): 308–315, doi: 10.2337/diacare.24.2.308, indexed in Pubmed: 11213884.
11. Parulkar AA, Pendergrass ML, Granda-Ayala R, et al. Nonhypoglycemic effects of thiazolidinediones. Ann Intern Med. 2001; 134(1): 61–71, doi: 10.7326/0003-4819-134-1-200101020-00014, indexed in Pubmed: 11187421.
12. Lautamaki R, Airaksinen K, Seppanen M, et al. Rosiglitazone Improves Myocardial Glucose Uptake in Patients With Type 2 Diabetes and Coronary Artery Disease: A 16-Week Randomized, Double-Blind, Placebo-Controlled Study. Diabetes. 2005; 54(9): 2787–2794, doi: 10.2337/diabetes.54.9.2787, indexed in Pubmed: 16123370.
13. Lautamäki R, Nuutila P, Airaksinen KE, et al. The effect of PPARgamma-agonism on LDL subclass profile in patients with type 2 diabetes and coronary artery disease. Rev Diabet Stud. 2006; 3(1): 31–38, doi: 10.1900/RDS.2006.3.31, indexed in Pubmed: 17491710.
14. Haffner SM, Greenberg AS, Weston WM. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation. 2002; 106(6): 679–684, doi: 10.1161/01.CIR.0000025403.20953.23, indexed in Pubmed: 12163427.
15. Meisner F, Walcher D, Gizard F, et al. Effect of rosiglitazone treatment on plaque inflammation and collagen content in nondiabetic patients: data from a randomized placebo-controlled trial. Arterioscler Thromb Vasc Biol. 2006; 26(4): 845–850, doi: 10.1161/01.ATV.0000203511.66681.7f, indexed in Pubmed: 16410460.
16. Wooltorton E. Rosiglitazone (Avandia) and pioglitazone (Actos) and heart failure. CMAJ. 2002; 166(2): 219, indexed in Pubmed: 11826947.
17. Wang W, Zhou Xu, Kwong JSW, et al. Efficacy and safety of thiazolidinediones in diabetes patients with renal impairment: a systematic review and meta-analysis. Sci Rep. 2017; 7(1): 1717, doi: 10.1038/s41598-017-01965-0, indexed in Pubmed: 28496176.
18. Waksman JC. Cardiovascular risk of rosiglitazone: another perspective. J Pharm Pharmacol. 2008; 60(12): 1573–1582, doi: 10.1211/jpp.60.12.0002, indexed in Pubmed: 19000361.
19. Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med. 2009; 3(3): e123–e130, doi: 10.1016/j.jclinepi.2009.06.005, indexed in Pubmed: 21603045.
20. Bushe CJ, Bradley AJ, Wildgust HJ, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15): 2008–2012, doi: 10.1001/jama.283.15.2008, indexed in Pubmed: 10789670.
21. Holman RR, Sourij H, Califf RM, et al. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. Lancet. 2014; 383(9933): 2008–2017, doi: 10.1016/S0140-6736(14)60794-7, indexed in Pubmed: 24910232.
22. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007; 356(24): 2457–2471, doi: 10.1056/NEJMoa072761, indexed in Pubmed: 17517853.
23. Nathan DM. Rosiglitazone and cardiotoxicity--weighing the evidence. N Engl J Med. 2007; 357(1): 64–66, doi: 10.1056/NEJMe078117, indexed in Pubmed: 17551161.
24. Chiquette E, Ramirez G, Defronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. Arch Intern Med. 2004; 164(19): 2097–2104, doi: 10.1001/archinte.164.19.2097, indexed in Pubmed: 15505122.
25. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007; 370(9593): 1129–1136, doi: 10.1016/S0140-6736(07)61514-1, indexed in Pubmed: 17905165.
26. Berlie HD, Kalus JS, Jaber LA. Thiazolidinediones and the risk of edema: a meta-analysis. Diabetes Res Clin Pract. 2007; 76(2): 279–289, doi: 10.1016/j.diabres.2006.09.010, indexed in Pubmed: 17055103.
27. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA. 2007; 298(10): 1189–1195, doi: 10.1001/jama.298.10.1189, indexed in Pubmed: 17848653.
28. Koch A. [Benefits and harms - two sides of the same medal?]. Z Evid Fortbild Qual Gesundhwes. 2011; 105(3): 163–170, doi: 10.1016/j.zefq.2011.03.005, indexed in Pubmed: 21530904.

29. Goldstein BJ. Differentiating members of the thiazolidinedione class: a focus on efficacy. Diabetes Metab Res Rev. 2002; 18 Suppl 2: S16–S22, doi: 10.1002/dmrr.251, indexed in Pubmed: 11921434.
30. Lebovitz HE. Differentiating members of the thiazolidinedione class: a focus on safety. Diabetes Metab Res Rev. 2002; 18 Suppl 2: S23–S29, doi: 10.1002/dmrr.252, indexed in Pubmed: 11921435.
31. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation. 2003; 108(23): 2941–2948, doi: 10.1161/01.cir.0000103683.99399.7e, indexed in Pubmed: 14662691.
32. Eng C, Kramer CK, Zinman B, et al. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet. 2014; 384(9961): 2228–2234, doi: 10.1016/S0140-6736(14)61335-0, indexed in Pubmed: 25220191.
33. Goldberg RB, Kendall DM, Deeg MA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005; 28(7): 1547–1554, doi: 10.2337/diacare.28.7.1547, indexed in Pubmed: 15983299.
34. Deeg MA, Buse JB, Goldberg RB, et al. GLAI Study Investigators. Pioglitazone and rosiglitazone have different effects on serum lipoprotein particle concentrations and sizes in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2007; 30(10): 2458–2464, doi: 10.2337/dc06-1903, indexed in Pubmed: 17595355.
35. Bach RG, Brooks MM, Lombardero M, et al. Rosiglitazone and outcomes for patients with diabetes and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Circulation. 2013; 128(8): 785–794, doi: 10.1161/circulationaha.112.000678, indexed in Pubmed: 23857320.
36. Breunig IM, Shaya FT, McPherson ML, et al. Development of heart failure in Medicaid patients with type 2 diabetes treated with pioglitazone, rosiglitazone, or metformin. J Manag Care Spec Pharm. 2014; 20(9): 895–903, doi: 10.18553/jmcp.2014.20.9.895, indexed in Pubmed: 25166288.
37. Brownstein JS, Murphy SN, Goldfine AB, et al. Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records. Diabetes Care. 2010; 33(3): 526–531, doi: 10.2337/dc09-1506, indexed in Pubmed: 20009093.
38. Dargie HJ, Hildebrandt PR, Riegger GAJ, et al. A randomized, placebo-controlled trial assessing the effects of rosiglitazone on echocardiographic function and cardiac status in type 2 diabetic patients with New York Heart Association Functional Class I or II Heart Failure. J Am Coll Cardiol. 2007; 49(16): 1696–1704, doi: 10.1016/j.jacc.2006.10.077, indexed in Pubmed: 17448371.
39. Florez H, Reaven PD, Bahn G, et al. VADT Research Group. Rosiglitazone treatment and cardiovascular disease in the Veterans Affairs Diabetes Trial. Diabetes Obes Metab. 2015; 17(10): 949–955, doi: 10.1111/dom.12487, indexed in Pubmed: 25964070.
40. Gerstein HC, Yusuf S, Bosch J, et al. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. The Lancet. 2006; 368(9541): 1096–1105, doi: 10.1016/s0140-6736(06)69420-8, indexed in Pubmed: 16997664.
41. Gram J, Henriksen JE, Grodum E, et al. Pharmacological treatment of the pathogenetic defects in type 2 diabetes: the randomized multicenter South Danish Diabetes Study. Diabetes Care. 2011; 34(1): 27–33, doi: 10.2337/dc10-0531, indexed in Pubmed: 20929990.
42. Hallsten K, Virtanen KA, Lonnqvist F, et al. Rosiglitazone but Not Metformin Enhances Insulin- and Exercise-Stimulated Skeletal Muscle Glucose Uptake in Patients With Newly Diagnosed Type 2 Diabetes. Diabetes. 2002; 51(12): 3479–3485, doi: 10.2337/diabetes.51.12.3479, indexed in Pubmed: 12453903.
43. Home PD, Pocock SJ, Beck-Nielsen H, et al. RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes--an interim analysis. N Engl J Med. 2007; 357(1): 28–38, doi: 10.1056/NEJMoa073394, indexed in Pubmed: 17551159.
44. Loebstein R, Dushinat M, Vesterman-Landes J, et al. Database evaluation of the effects of long-term rosiglitazone treatment on cardiovascular outcomes in patients with type 2 diabetes. J Clin Pharmacol. 2011; 51(2): 173–180, doi: 10.1177/0091270010368281, indexed in Pubmed: 20484611.
45. McAfee AT, Koro C, Landon J, et al. Coronary heart disease outcomes in patients receiving antidiabetic agents. Pharmacoepidemiol Drug Saf. 2007; 16(7): 711–725, doi: 10.1002/pds.1443, indexed in Pubmed: 17551989.
46. McGavock J, Szczepaniak LS, Ayers CR, et al. The effects of rosiglitazone on myocardial triglyceride content in patients with type 2 diabetes: a randomised, placebo-controlled trial. Diab Vasc Dis Res. 2012; 9(2): 131–137, doi: 10.1177/1479164111428628, indexed in Pubmed: 22067724.
47. McGuire DK, Abdullah SM, See R, et al. Randomized comparison of the effects of rosiglitazone vs. placebo on peak integrated cardiovascular performance, cardiac structure, and function. Eur Heart J. 2010; 31(18): 2262–2270, doi: 10.1093/eurheartj/ehq228, indexed in Pubmed: 20601395.
48. Varghese A, Yee MS, Chan CF, et al. Effect of rosiglitazone on progression of atherosclerosis: insights using 3D carotid cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2009; 11: 24, doi: 10.1186/1532-429X-11-24, indexed in Pubmed: 19635160.