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# Effect and cardiovascular safety of adding rosiglitazone to insulin therapy in type 2 diabetes: A meta-analysis

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## ABSTRACT

**Aims/Introduction:** Recently, the use of rosiglitazone has been limited or withdrawn from the market as a result of cardiovascular risk. However, theoretically adding rosiglitazone to insulin could help insulin to decrease the glucose level. The present meta-analysis was designed to investigate the effect and safety of adding rosiglitazone to insulin therapy in type 2 diabetes.

**Materials and Methods:** We searched published and unpublished databases through to March 2012. Randomized controlled trials (RCTs) comparing rosiglitazone in combination with insulin (RSG + INS) vs insulin alone (INS) in type 2 diabetes with outcomes including glycated hemoglobin levels, insulin dose, lipid parameters, blood pressure, edema and cardiovascular adverse events were selected.

**Results:** Nine RCTs with durations of 24–26 weeks involving 1,916 patients were included. The RSG + INS group showed significantly decreased glycated hemoglobin levels by 0.89% ($P < 0.00001$) with an 8.48-U reduction in daily insulin dose ($P < 0.00001$). However, the risks of hypoglycemia and edema were more frequent in the RSG+INS group ($P < 0.0001$; $P = 0.03$, respectively). Total cholesterol level was significantly increased in the RSG+INS group ($P < 0.00001$), but none of the high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol or triglyceride levels were significantly different between groups. There were no significant differences between groups with regard to the risks of myocardial infarction, heart failure, cardiovascular death or all-cause death.

**Conclusions:** Rosiglitazone could help type 2 diabetes patients with poorly controlled glucose with insulin therapy to decrease glucose levels and reduce their daily insulin dose, but at the cost of increased total cholesterol level, hypoglycemia and edema risk. Compared with insulin therapy, adding rosiglitazone to insulin did not increase the risks of myocardial infarction, heart failure, cardiovascular death or all-cause death.

## INTRODUCTION

There are 346 million people worldwide with diabetes mellitus. Of those, 90% have type 2 diabetes[1]. Type 2 diabetes is a chronic metabolic disorder resulting from a progressive insulin secretary defect in the background of insulin resistance[2]. For patients diagnosed with type 2 diabetes, lifestyle modifications (including diet, exercise and weight loss) are recommended first; if patients have failed to adequately improve hyperglycemia, monotherapy with metformin as initial pharmacological therapy is recommended; if hyperglycemia persistently fails to be controlled, a second-line hyperglycemic drug is added to metformin (which drug is added to metformin firstly is not clearly recommended), insulin treatment should be started when it is necessary[3].

Rosiglitazone, an oral antidiabetic drug, was initially approved in 1999 in the USA, and was widely used for its great

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improvement of glycemic control; it was even once the world's best-selling antidiabetic drug, with a $3 billion bill in annual revenue. It is in a class of insulin sensitizers known as thiazolidinediones (TZDs), which reduce plasma glucose by mainly decreasing insulin resistance, and increasing insulin sensitivity in peripheral tissue (muscle and adipose tissue) and liver by activating the peroxisome proliferator-activated receptor-γ (PPAR-γ), and helps to preserve pancreatic β-cell function[4]. However, rosiglitazone is associated with weight gain, edema, heart failure, bone fractures and increased cardiovascular events. In September 2010, the US Food and Drug Administration (FDA) declared restrictions for rosiglitazone, whereas the European Medicines Agency (EMA) withdrew the drug from the market based on meta-analyses of mostly short-term randomized controlled trials (RCTs) suggesting that it could increase myocardial infarction (MI) risk[5,6]. In November 2013, the FDA removed the restrictions for rosiglitazone that were put in place in 2010 as a result of a recent re-evaluation of the data from a large, long-term clinical trial carried out by the Duke Clinical Research Institute[7].

Insulin therapy is a traditional and classical treatment that can be used in different types of diabetes. Almost two-third of individuals with type 2 diabetes receiving oral antidiabetic therapy only cannot achieve the glycemic target glycated hemoglobin (HbA1c) of 7% and require insulin therapy[8,9]. However, insulin therapy requires injection, which reduces patients' compliance, and is associated with increased incidence of hypoglycemia, weight gain, edema and insulin resistance, which would lead to an increased insulin dose.

Theoretically, adding rosiglitazone to insulin could help insulin decrease the glucose level by reducing insulin resistance. However, some studies suggested that rosiglitazone increases the risk of MI, especially in patients treated with insulin[5,10]. To date, there has been no large trial or meta-analysis on the combination therapy of rosiglitazone and insulin. The aim of the present meta-analysis was to investigate the effect and safety of adding rosiglitazone to insulin therapy in patients with type 2 diabetes, and to evaluate whether we should/should not use rosiglitazone anymore.

## MATERIALS AND METHODS

### Eligibility Criteria

We selected RCTs comparing the combination therapy of rosiglitazone and insulin with the same insulin therapy. The duration of trials was at least 24 weeks. Both therapies can be with or without the same additional intervention, such as other classes of oral medications/lifestyle programs. Participants were adults with type 2 diabetes of any sex or race. Trials had to report at least one of the following outcomes: HbA1c levels, daily insulin dose, lipid parameters (total cholesterol, high-density lipoprotein cholesterol [HDL-c], low-density lipoprotein cholesterol [LDL-c], very low-density lipoprotein cholesterol cholesterol [VLDL-c] and triglyceride), blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]), fluid retention events (weight gain and edema) and cardiovascular adverse events (MI, heart failure [HF], cardiovascular death [CV death] and all-cause death).

### Search Strategy

We searched the Pubmed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) for studies published in English up to March 2012. The following search terms were used: "rosiglitazone", "insulin", "randomized controlled trial" or "clinical trial". To identify unpublished data, we reviewed the websites of the drug manufacturer GlaxoSmithKline, FDA and ClinicalTrials.gov.

In addition, bibliographies of included studies, meta-analyses and recent reviews were checked.

### Study Selection and Data Extraction

Two researchers independently checked titles and abstracts for studies that could potentially meet the inclusion criteria. Full-text articles of these studies were retrieved and reviewed for detailed assessment. If there were both published and unpublished data for the same trial, the unpublished data was considered to be superior after comparison. From the included studies, we extracted types of interventions, baseline characteristics of participants and relevant outcomes on to a preformatted spreadsheet. Any uncertainties or disagreements between the two researchers were resolved through discussion or consultation with a third person by checking the original articles.

### Assessing Risk of Bias

In accordance with the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions*, we used the following features to assess risk of bias for included studies: sequence generation, allocation concealment, blinding of participants and outcome assessors, withdrawal rate, and intention-to-treat (ITT) analysis[11]. The features were graded as adequate (or yes), unclear or inadequate (or no). If all features were adequate (or yes), the information from the study was at low risk of bias. If one or more features were unclear, it was at unclear risk of bias. If one or more features were inadequate (or no), it was at high risk of bias[12]. Funnel plots were used to evaluate publication bias only if there were at least 10 studies included for some outcome and no significant between-study heterogeneity[13].

### Statistical Analysis

Statistical analysis was carried out using RevMan 5.0 software (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Danish) provided by the Cochrane Collaboration. For continuous data, we calculated the weighted mean difference (WMD) or the standard mean difference (SMD) with 95% confidence intervals (95% CI) for the change of parameters from baseline to the end of the study. WMD was used when the data were measured by the same unit, and SMD was used when the data were measured by different units. For

dichotomous data, we calculated the risk ratio (RR) with 95% CI. *P*-values <0.05 were considered to be statistically significant. The pooled results of studies included in the meta-analysis and statistical homogeneity between trials were assessed using the fixed-effects model where a $\chi^2$-test $P > 0.1$ indicated no heterogeneity. The random-effects model of meta-analysis was used when statistical heterogeneity exited ($\chi^2$-test $P \leq 0.1$)[14]. If there was considerable variation in results ($I^2 > 75\%$), we only used descriptive analysis[15].

## RESULTS

### Trial Flow

The process of study selection is shown in Figure 1.

A total of 39 articles were identified as potentially relevant RCTs, and full-texts were reviewed. Of these, nine RCTs[16–19] that fulfilled the inclusion criteria were included in the present meta-analysis. The remaining trials were excluded as a result of different reasons listed in Figure 1.

### Study Characteristics

The characteristics of the included studies are summarized in Table 1.

Nine RCTs with a duration of 24–26 weeks involving 1,916 patients were included. Studies were from all over the world with different races and reported in English. Four studies were published[16–19], whereas the other five were unpublished and available from the GlaxoSmithKline website. The number of participants among the studies varied from 18 to 630. Most participants were middle to old-aged type 2 diabetes patients with inadequate glucose control (HbA1c > 7.0%) on previous insulin treatment with/without oral antidiabetic medications. Rosiglitazone doses varied from 2 to 8 mg/day. Eight studies used large doses of rosiglitazone (4–8 mg/day), except one with <4 mg/day. Only one trial used additional lifestyle intervention (diet change and physical activity) besides rosiglitazone[17]. Insulin doses could be regulated as a result of the blood glucose level or HbA1c level, or if hypoglycemia occurred.

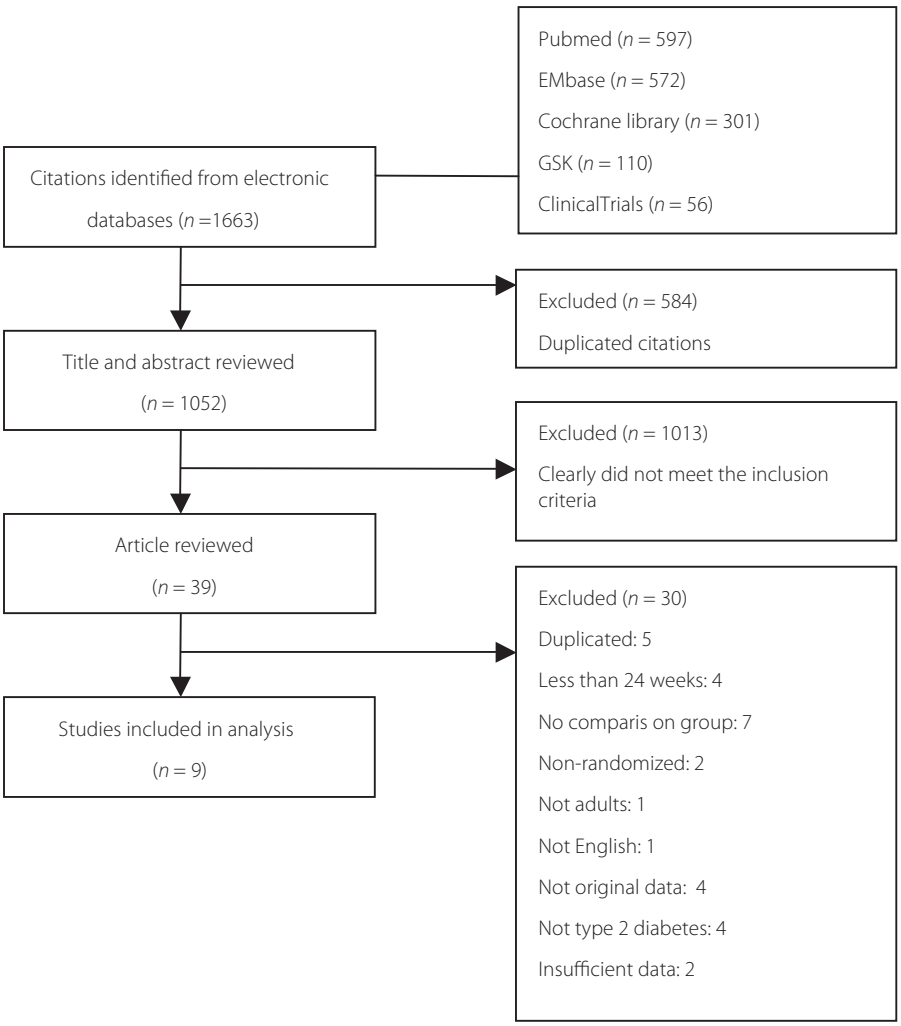


**Figure 1** | Flow chart of included studies.

**Table 1** | Characteristics of included studies

| Study | Intervations | | Participants | | | | |
|---|---|---|---|---|---|---|---|
| | Study arms | Duration (weeks) | Population | *n* | Age (years) | Male sex (%) | Country |
| 49653/082 | RSG (4 mg/day) + INS | 26 | T2DM poorly controlled on | 107 | 57.1 | 56.6 | USA |
| | RSG (8 mg/day) + INS | | insulin monotherapy | 105 | 57.7 | 54.4 | |
| | PBO + INS | | | 107 | 55.6 | 55.8 | |
| 49653/085 | RSG (4–8 mg/day) + INS | 26 | T2DM poorly controlled on | 138 | 61.3 | 54.0 | Europe |
| | PBO + INS | | insulin monotherapy | 139 | 61.5 | 46.8 | |
| 49653/095 | RSG (4 mg/day) + INS | 26 | T2DM poorly controlled on | 99 | 57.8 | 63.9 | USA |
| | RSG (8 mg/day) + INS | | insulin monotherapy | 97 | 57.4 | 58.9 | |
| | PBO + INS | | | 96 | 58.9 | 45.3 | |
| 49653/347 | RSG (2 mg/day) + INS | 24 | T2DM poorly controlled on | 209 | 52.7 | 57.0 | USA |
| | RSG (2–4 mg/day) + INS | | insulin monotherapy | 209 | 52.6 | 48.1 | |
| | PBO + INS | | | 212 | 53.8 | 46.2 | |
| AVD102209 | RSG (4 mg/day) + INS | 24 | T2DM poorly controlled on | 132 | 56.8 | 48.0 | China |
| | PBO + INS | | insulin monotherapy | 131 | 55.9 | 52.4 | |
| Naka 2011 | RSG (4 mg/day) + INS | 24 | T2DM poorly controlled on | 17 | 64.7 | 17.6 | Greece |
| | INS | | insulin monotherapy | 14 | 67.3 | 28.6 | |
| Reynolds 2002 | RSG (4 mg/day) + INS + LP | 24 | Obese T2DM poorly controlled | 8 | NR | NR | USA |
| | PBO + INS + LP | | on insulin theropy with/ without oral antidiabetic medications | 10 | NR | NR | |
| Wong 2005 | RSG (4 mg/day) + INS | 24 | Insulin treated T2DM with stable glycemic control on | 26 | 62.9 | NR | China (Hong Kong) |
| | INS | | peritoneal dialysis therapy | 26 | 61.6 | NR | |
| Yilmaz 2007 | RSG (8 mg/day) + INS | 24 | T2DM poorly controlled on | 15 | 57.6 | 46.7 | Turkey |
| | INS | | insulin monotherapy | 19 | 61.5 | 63.2 | |

INS, Insulin; LP,lifestyle program; MET, metformin; NR, not reported; PBO, placebo; RSG, rosiglitazone; T2DM, type 2 diabetes mellitus.

### Risk of Bias

The details of the risk of bias are summarized in Table 2.

The randomization procedure was not reported or was unclear for eight studies, except one that was adequately randomized[18]. None of the studies reported on allocation concealment. A double-blinded method was used for clinical data in six studies, whereas two studies were open-labeled. The participant dropout rate ranged from 0% to 27.8%. ITT analysis was carried out in six studies. In summary, five of the nine studies were at unclear risk of bias, whereas the other four were at high risk.

### Results of Meta-Analysis

The results of different outcomes are summarized in Table 3.

#### *Glycemic Control (HbA1c) and Insulin Dose Reduction*

The pooled data from eight studies reporting on HbA1c values showed that the combination therapy of rosiglitazone and insulin (RSG + INS group) significantly reduced HbA1c values compared with insulin therapy (INS group; WMD −0.89, 95% CI −1.19 to −0.58, $P < 0.00001$; Appendix S1). Meanwhile, the daily insulin dose was significantly reduced in the RSG + INS group than in INS group from seven studies (WMD −8.48, 95% CI −11.68 to −5.27, $P < 0.00001$; Appendix S2. However, there was significant heterogeneity among studies ($I^2 = 78\%$, $P < 0.0001$; $I^2 = 62\%$, $P = 0.01$).

#### *Hypoglycemia*

Compared with the INS group, the RSG + INS group was associated with a significantly increased risk of hypoglycemia from six studies (RR 1.33, 95% CI 1.16–1.52, $P < 0.0001$; Appendix S3). We found no evidence of statistical heterogeneity for this outcome ($I^2 = 0\%$, $P = 0.48$).

#### *Lipid Parameters*

Based on the pooled results of six studies, there was a significant increase in total cholesterol level in the RSG + INS group compared with the INS group (SMD 0.44, 95% CI 0.27–0.61, $P < 0.00001$; Appendix S4). There were no significant differences between two groups in the levels of HDL-c, LDL-c, VLDL-c or triglyceride (Appendix S5–S8). However, significant heterogeneity existed among studies for LDL-c and triglyceride ($I^2 = 95\%$, $P < 0.00001$; $I^2 = 59\%$, $P = 0.03$, respectively).

#### *Blood Pressure*

The pooled data from three studies showed there were no significant differences between the RSG + INS group and the INS group in improvement in SBP or DBP (WMD −3.16, 95% CI

**Table 2** | Bias of included studies

| Study | Sequence generation | Allocation concealment | Double-blind | Withdrawal (%) | ITT analysis | Risk of bias |
|---|---|---|---|---|---|---|
| 49653/082 | Unclear | Unclear | Yes | 21.0 | Yes | Unclear |
| 49653/085 | Unclear | Unclear | Yes | 14.8 | Yes | Unclear |
| 49653/095 | Unclear | Unclear | Yes | 21.6 | Yes | Unclear |
| 49653/347 | Unclear | Unclear | Yes | 27.8 | Yes | Unclear |
| AVD102209 | Unclear | Unclear | Yes | 9.1 | Yes | Unclear |
| Naka 2011 | Unclear | Unclear | No | 8.8 | No | High |
| Reynolds 2002 | Unclear | Unclear | Yes | 14.3 | No | High |
| Wong 2005 | Yes | Unclear | No | 9.6 | Yes | High |
| Yilmaz 2007 | Unclear | Unclear | Unclear | 0.0 | No | High |

ITT, Intention-to-treat.

–9.76 to 3.43, $P = 0.35$; –0.39, 95% CI –13.34 to 12.56, $P = 0.95$; Appendix S9–S10). However, there was significant heterogeneity among studies for diastolic blood pressure ($I^2 = 87\%$, $P = 0.0005$).

*Fluid Retention*

Compared with the INS group, the RSG + INS group significantly increased the risk of edema (RR 1.44, 95% CI 1.03–2.01, $P = 0.03$; Appendix S11). Among 1,846 patients from seven studies that reported edema, there was only one patient that experienced serious edema. There was no significant increase in the risk of weight gain associated with rosiglitazone (RR 1.96, 95% CI 0.88–4.33, $P = 0.10$; Appendix S12). No heterogeneity existed among studies for these outcomes.

*Cardiovascular Adverse Events*

Based on the pooled results, the risks of MI, heart failure, CV death and all-cause death between the RSG + INS group and the INS group were not significantly different (RR 2.46, 95% CI 0.52–11.70, $P = 0.26$; RR 1.82, 95% CI 0.49–6.74, $P = 0.37$; RR 0.77, 95% CI 0.22–2.65, $P = 0.68$; 0.70, 95% CI 0.25–1.95, $P = 0.50$, respectively; Appendix S13–S16). No heterogeneity existed among studies for these outcomes.

**Table 3** | Results of meta-analysis: rosiglitazone vs insulin

| Outcomes | No. studies | No. participants | Overall effect | | | Heterogeneity test | |
|---|---|---|---|---|---|---|---|
| | | | Statistical method | Effect estimate [95% CI] | *P* | $I^2$ (%) | *P′* |
| HbAc1 | 8 | 1159 | WMD, random | –0.89 [–1.19, –0.58] | <0.00001 | 78 | <0.0001 |
| Insulin dose | 7 | 1152 | WMD, random | –8.48 [–11.68, –5.27] | <0.00001 | 62 | 0.01 |
| Hypoglycemia | 6 | 1815 | RR, fixed | 1.33 [1.16, 1.52] | <0.0001 | 0 | 0.48 |
| Lipid parameters | | | | | | | |
| Total cholesterol | 6 | 525 | SMD, fixed | 0.44 [0.27, 0.61] | <0.00001 | 0 | 0.64 |
| HDL-c | 6 | 525 | SMD, fixed | 0.14 [–0.03, 0.31] | 0.12 | 3 | 0.4 |
| LDL-c | 6 | 502 | SMD, random | 0.56 [–0.40, 1.52] | 0.25 | 95 | <0.00001 |
| VLDL-c | 2 | 389 | WMD, fixed | 3.55 [–1.04, 8.13] | 0.13 | 27 | 0.24 |
| Triglyceride | 6 | 525 | SMD, random | 0.17 [–0.15, 0.48] | 0.29 | 59 | 0.03 |
| Blood pressure | | | | | | | |
| SBP | 3 | 101 | WMD, fixed | –3.16 [–9.76, 3.43] | 0.35 | 35 | 0.22 |
| DBP | 3 | 101 | WMD, random | –0.39 [–13.34, 12.56] | 0.95 | 87 | 0.0005 |
| Fluid retention | | | | | | | |
| Edema | 7 | 1846 | RR, fixed | 1.44 [1.03, 2.01] | 0.03 | 40 | 0.12 |
| Weight gain | 4 | 1504 | RR, fixed | 1.96 [0.88, 4.33] | 0.10 | 0 | 0.48 |
| CV adverse events | | | | | | | |
| Myocardial infarction | 3 | 1226 | RR, fixed | 2.46 [0.52, 11.70] | 0.26 | 0 | 0.94 |
| Heart failure | 4 | 1518 | RR, fixed | 1.82 [0.49, 6.74] | 0.37 | 0 | 0.99 |
| Cardiovascular death | 5 | 1203 | RR, fixed | 0.77 [0.22, 2.65] | 0.68 | 0 | 0.72 |
| All-cause death | 6 | 1833 | RR, fixed | 0.70 [0.25, 1.95] | 0.50 | 0 | 0.72 |

CV adverse events, Cardiovascular adverse events; CI, confidence interval; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; RR, risk ratio; SBP, systolic blood pressure; SMD, standardized mean differece; VLDL-c, very low-density lipoprotein cholesterol; WMD, weighted mean difference.

## DISCUSSION

Nine RCTs involving 1,916 patients with type 2 diabetes were included in the present meta-analysis comparing adding rosiglitazone to insulin with insulin therapy. Five studies were at unclear risk of bias, whereas the other four were at high risk of bias. The results suggested that compared with the INS group, the RSG + INS group could effectively help insulin decrease HbA1c values by a mean of 0.89%; furthermore, with a mean reduction of 8.48 U daily insulin dose. Nevertheless, the RSG+INS group was associated with a 33% increased incidence of hypoglycemia. Total cholesterol level was increased in the RSG + INS group, but none of the levels of HDL-c, LDL-c, VLDL-c or triglyceride were significantly different. There were no significant changes of blood pressure (SBP or DBP) between the two groups. The RSG + INS group caused a 44% greater incidence of edema. The risks of MI, heart failure, CV death and all-cause death between the RSG + INS group and INS group were similar.

Insulin is a type of classical antidiabetic medication that has been used for almost 100 years. It can be used in every condition and different types of diabetes mellitus, but it also has some disadvantages. Hypoglycemia is a major treatment-associated complication of insulin, others include bruising, bleeding, lipohypertrophy, lipoatrophy, allergy, weight gain, edema, heart failure and potential cancer risk[20]. Besides, low compliance and a high withdrawal rate are common in insulin therapy. Some patients find daily insulin injection difficult and inconvenient, require training and are even fraught with some level of stigma. Type 2 diabetes is associated with insulin resistance, the long-term use of insulin might increase insulin resistance and a much higher dose of insulin injection is required, which would lead to elevated insulin adverse events. The synergistic effects of oral antidiabetic drugs with insulin might reduce the insulin dose, so insulin therapy is often accompanied with oral antidiabetic drugs. Common oral antidiabetic drugs and insulin combination therapy leads to a 0.3–0.6% decrease in HbA1c[21], and is associated with a 43% reduction in total daily insulin requirement compared with insulin monotherapy[22]. The present results showed that rosiglitazone could decrease HbA1c by 0.89% accompanied with an 8.48-U reduction in daily insulin dose. Therefore rosiglitazone and insulin combination therapy has significant benefits for glycemic control over insulin monotherapy. Rosiglitazone is an insulin-sensitizing drug that can decrease insulin resistance, and improve insulin sensitivity in the liver and muscle. The synergistic effect of rosiglitazone and insulin could greatly help patients decrease glucose level and reduce daily insulin dose. However, the addition of rosiglitazone to insulin was associated with a high proportion of patients experiencing hypoglycemia. However, most hypoglycemic events were not serious.

Fluid retention is an adverse event of both insulin and rosiglitazone. The present results showed that combination therapy of rosiglitazone and insulin was associated with an increased incidence of edema. Though most edema was mild to moderate. The incidence of weight gain and heart failure were similar between the groups. A double-blind RCT showed that the incidence of heart failure of rosiglitazone was 1.5%, significantly higher than glyburide (0.6%), but similar to metformin (1.3%)[23]. A meta-analysis of seven RCTs showed that TZDs increased the risk of heart failure compared with controls in patients with prediabetes or type 2 diabetes by 72% (RR 1.72, 95% CI 1.21–2.42, $P = 0.002$) [24]. Interestingly, TZDs-related heart failure would not increase the risk of CV death (RR 0.93, 95% CI 0.67–1.29, $P = 0.68$). Heart failure appeared to be a class effect, involving both rosiglitazone and pioglitazone, and was independent of dose or age or insulin use. TZDs-related heart failure was induced by fluid retention, but without the risk caused by progressive systolic or diastolic dysfunction of the left ventricle. In patients with type 2 diabetes and pre-existing chronic heart failure (New York Heart Association class I–II), 52 weeks with rosiglitazone therapy did not adversely affect left ventricular ejection fraction[25]. However, TZDs have been contraindicated in patients with all stages of heart failure (New York Heart Association class I–IV) in Europe and late stages (New York Heart Association III–IV) in the USA.

Over the past few years, the controversy about the cardiovascular safety of rosiglitazone has continued. In 2007, some meta-analyses ignited a firestorm about the ischemic cardiovascular risk of rosiglitazone. A meta-analysis by Nissen and Wolski including 42 trials with a duration of more than 24 weeks involving patients with type 2 diabetes, Alzheimer's disease and psoriasis reported a significant 43% increase risk of MI (odds ratio [OR] 1.43, 95% CI 1.03–1.98, $P = 0.03$) with rosiglitazone, with a borderline significant 64% increased risk in CV death (OR 1.64, 95% CI 0.98–2.74, $P = 0.06$)[26]. Similar results were seen in another meta-analysis including four long-term trials with a duration of at least 12 months. Among patients with impaired glucose tolerance or type 2 diabetes, rosiglitazone increased the risk of MI by 42%, but did not increase the risk of CV mortality[6]. Shortly thereafter, a patient-level meta-analysis carried out by the FDA showed that rosiglitazone was associated with a significant 40% increased risk of ischemic heart disease, but with no significant increase in the risks of MI or total mortality, or the composite end point of CV death, MI or stroke[27].

In contrast to meta-analyses, large clinical trials had more favorable results on the cardiovascular safety of rosiglitazone. To date, there has been only one large randomized clinical trial prospectively designed to evaluate the effect of rosiglitazone on cardiovascular outcomes for type 2 diabetes, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial. The primary end-point was cardiovascular hospitalization or CV death, with a hazard ratio (HR) non-inferiority margin of 1.20. After a mean 5.5-year follow up, the results showed that rosiglitazone increased the risk of heart failure (HR 2.10, $P = 0.01$), but with no significant increased

risk of MI (HR 1.14), CV death (HR 0.84), stroke (HR 0.72) or the composite of CV death, MI and stroke (HR 0.93)[28]. Large prospective randomized clinical trials designed to assess the macrovascular outcomes are the best approach to evaluate the relationship between rosiglitazone and cardiovascular events. Unfortunately, the weakness of the RECORD study was challenged. First, the open-label design introduced unavoidable biases that favored the rosiglitazone-treated group. Second, questions about the reliability of ascertainment and adjudication of the outcomes persisted. Therefore, the results from RECORD are inconclusive. Similar results were seen in another large RCT, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM), which focused on patients with impaired glucose tolerance or impaired fasting glucose, and no previous cardiovascular disease. There was no significant evidence that rosiglitazone might increase the risk of MI, CV death, stroke or death compared with placebo with a 3-year follow up[29]. Data from A Diabetes Outcome Progression Trial (ADOPT) showed that rosiglitazone was associated with a higher cardiovascular risk than glyburide, but similar to metformin[23].

In June 2010, Nissen and Wolski updated their meta-analysis by including 13 small trials and the recently completed RECORD trial in addition to their original 42 trials. Although the risk of MI remained statistically significant, it downgraded from 43% ($P = 0.03$) to 28% ($P = 0.04$). The previously borderline significant risk of CV death was no longer evident, from 64% ($P = 0.06$) to 3% ($P = 0.86$)[5].

Most evidence on cardiovascular risk of rosiglitazone was derived from meta-analyses, but there were deficiencies in these meta-analyses. First, rosiglitazone was compared with active controls on blood glucose (life program intervention, metformin, sulfonylurea, pioglitazone, insulin) or placebo or other controls (donepezil). Second, except for the RECORD trial, most trials were designed to evaluate the hypoglycemic effect of drugs, not cardiovascular outcomes. Third, participants were greatly varied among trials, including participants with type 2 diabetes, prediabetes, psoriasis, Alzheimer's disease and rheumatoid arthritis. These would lead to great clinical differences. Fourth, the meta-analyses included many "zero-event" trials. Some researchers applied different methodological approaches to reanalyze the data of a meta-analysis, and found a non-significant or significant increased risk for MI[30]. Thus, the evidence regarding the cardiovascular risk of rosiglitazone is inconsistent, fragile and methodologically deficient.

On the contrary, pioglitazone has a more favorable effect on cardiovascular disease. A clinical trial designed to assess the effect of pioglitazone on macrovascular events, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial, showed that pioglitazone significantly reduced the composite of all-cause mortality, non-fatal MI and stroke (HR 0.84, 95% CI 0.72–0.98)[31]. A meta-analysis also showed the benefit of pioglitazone in regard to cardiovascular events, with an 18% reduced risk of the composite of death, MI and stroke[32]. An observational, retrospective, inception cohort study suggested that rosiglitazone was associated with increased risks of stroke, heart failure and the composite of MI, stroke, heart failure or death compared with pioglitazone[33]. Similar results for increased MI and death risks for rosiglitazone were obtained by a meta-analysis of 16 observational studies relative to pioglitazone[34]. The mechanism as to why the two TZDs have an opposite effect on cardiovascular events remains uncertain. The main potential factor might contribute to the different effect of the two TZDs on lipid metabolism. Some trials suggested pioglitazone had a more favorable effect on blood lipids. Pioglitazone was associated with a reduction in total cholesterol and triglycerides, and with an increase in HDL-c[35]. In contrast, rosiglitazone might increase total cholesterol and LDL-c compared with other therapies. In a comparative trial, pioglitazone produced less of an increase in LDL-c and triglyceride levels, a greater increase in HDL-c, reduced LDL particle concentration and increased LDL particle size compared with rosiglitazone[36]. The opposite effect between the two TZDs might be because pioglitazone is a PPAR-α/γ dual agonist, whereas rosiglitazone is a PPAR-γ agonist. The combination therapy of PPAR-α and PPAR-γ agonists led to a decrease in LDL-c levels, and might be of benefit in the treatment of type 2 diabetes patients with cardiovascular disease by downregulating cytokines[37]. PPAR-α agonist could improve cardiac dysfunction of adipose triglyceride lipase gene deletion mice[38].

Despite the controversy about the cardiovascular safety of rosiglitazone being inconclusive, in 2010, the FDA announced restrictions of access to rosiglitazone and the EMA withdrew the drug from the market as a result of the cardiovascular risk. The FDA required the GSK to develop a restricted access program for rosiglitazone under a risk evaluation and mitigation strategy: rosiglitazone-containing medicines should only be used in patients already being treated with these medicines, and new patients only if they are unable to achieve glucose control on other medications and are unable to take pioglitazone.

However, in November 2013, the FDA removed the prescribing and dispensing restrictions for rosiglitazone that were put in place in 2010 based on a comprehensive, outside, expert re-evaluation of the data of the RECORD study by Duke Clinical Research Institute[7]. The HR for rosiglitazone vs metformin/sulfonylurea of CV death/MI/stroke was 0.95 (95% CI 0.78–1.17) compared with 0.93 (95% CI 0.74–1.15) for the original RECORD results. Treatment comparisons for MI (HR 1.13, 95% CI 0.80–1.59) and mortality (HR 0.86, 95% CI 0.68–1.08) were also the same compared with the original RECORD results (HR 1.14, 95% CI 0.80–1.63 for MI; 0.86, 95% CI 0.68–1.08 for mortality). The re-evaluation results showed that the risk of MI of rosiglitazone was similar to the standard type 2 diabetes medicines, metformin and sulfonylurea.

Because type 2 diabetes is a chronic metabolic disease, the risks of macrovascular events and mortality as a result of rosiglitazone were intended to be seen in long-term trials. The studies included in the present meta-analysis were too short (just

24–26 weeks), and fewer than six trials were used to evaluate the cardiovascular events and mortality. There was a high risk of bias in four studies. As sequence generation and allocation concealment were clearly described in only one study, measurement bias existed. Blinding was not used in two studies, so selective bias existed. Attrition bias cannot be ignored in two studies, with withdrawals where ITT analysis was not carried out.

In conclusion, in patients with type 2 diabetes who were poorly glucose controlled, adding rosiglitazone to insulin therapy showed an advantage in the reduction in HbA1c of 0.89% compared with insulin therapy, but at the cost of increased total cholesterol level, hypoglycemia and edema risk. As a result of the existing limitation (e.g. short study duration), the conclusion should be drawn cautiously that adding rosiglitazone to insulin does not increase the risks of MI, heart failure, cardiovascular or all-cause death. Clinical physicians should weigh the potential benefits and risks of rosiglitazone in different patients.

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## REFERENCES

1. World Health Organization. Media centre, Fact sheets, Diabetes. http://www.who.int/mediacentre/factsheets/fs312/en/. Accessed April 9, 2013.
2. American Diabetes Association. Standards of medical care in diabetes–2009. *Diabetes Care* 2009; 32 (Suppl 1): S13–S61.
3. Qaseem A, Humphrey LL, Sweet DE, *et al*. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2012; 156: 218–231.
4. Kahn SE, Lachin JM, Zinman B, *et al*. Effects of rosiglitazone, glyburide, and metformin on β-cell function and insulin sensitivity in ADOPT. *Diabetes* 2011; 60: 1552–1560.
5. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 2010; 170: 1191–1201.
6. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007; 298: 1189–1195.
7. Mahaffey KW, Hafley G, Dickerson S, *et al*. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. *Am Heart J* 2013; 166: 240.e1–249.e1.
8. Koro CE, Bowlin SJ, Bourgeois N, *et al*. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. *Diabetes Care* 2004; 27: 17–20.
9. Saydah S, Cowie C, Eberhardt MS, *et al*. Race and ethnic differences in glycemic control among adults with diagnosed diabetes in the United States. *Ethn Dis* 2007; 17: 529–535.
10. Monami M, Marchionni N, Mannucci E. Winners and losers at the rosiglitazone gamble A meta-analytical approach at the definition of the cardiovascular risk profile of rosiglitazone. *Diabetes Res Clin Pract* 2008; 82: 48–57.
11. Lewis JA, Machin D. Intention to treat–who should use ITT? *Br J Cancer* 1993; 68: 647–650.
12. Higgins JPT, Altman DG, Green S (eds). Chapter 8: assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions. John Wiley &Sons, Chichester, UK, 2008; 187–241.
13. Lau J, Ioannidis JP, Terrin N, *et al*. The case of the misleading funnel plot. *BMJ* 2006; 333: 597–600.
14. Deeks JJ, Higgins JPT, Altman DG, *et al*. (eds). Chapter 9: analysing data and undertaking meta-analyses. In: Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Chichester, UK, 2008; 243–296.
15. Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
16. Naka KK, Papathanassiou K, Bechlioulis A, *et al*. Rosiglitazone improves endothelial function in patients with type 2 diabetes treated with insulin. *Diab Vasc Dis Res* 2011; 8: 195–201.
17. Reynolds LR, Konz EC, Frederich RC, *et al*. Rosiglitazone amplifies the benefits of lifestyle intervention measures in long-standing type 2 diabetes mellitus. *Diabetes Obes Metab* 2002; 4: 270–275.
18. Wong TYH, Szeto CC, Chow KM, *et al*. Rosiglitazone reduces insulin requirement and C-reactive protein levels in type 2 diabetic patients receiving peritoneal dialysis. *Am J Kidney Dis* 2005; 46: 713–719.
19. Yilmaz H, Gursoy A, Sahin M, *et al*. Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and rosiglitazone or insulin and acarbose in type 2 diabetes. *Acta Diabetol* 2007; 44: 187–192.
20. Chan PF, Lai LK, Wong SN, *et al*. Review on the use of insulin in primary care. *Hong Kong Med J* 2013; 19: 52–60.
21. National Collaborating Centre for Chronic Conditions. Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update). Royal College of Physicians, London, 2008.
22. Goudswaard AN, Furlong NJ, Rutten GE, *et al*. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. *Cochrane Database Syst Rev*, 2004; (4): CD003418.
23. Kahn SE, Haffner SM, Heise MA, *et al*. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; 355: 2427–2443.
24. 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: 1129–1136.

25. Dargie HJ, Hildebrandt PR, Riegger GA, *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: 1696–1704.
26. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; 356: 2457–2471.
27. FDA Briefing Document: Advisory Committee meeting July 30th 2007 to discuss cardiovascular ischemic events with Avandia: Available at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-FDAbackgrounder.pdf. Accessed March 1, 2012.
28. Home PD, Pocock SJ, Beck-Nielsen H, *et al.* Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009; 373: 2125–2135.
29. Gerstein HC, Yusuf S, Bosch J, *et al.* Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006; 368: 1096–1105.
30. Claggett B, Wei LJ. Analytical issues regarding rosiglitazone meta-analysis. *Arch Intern Med*, 2011; 171: 179–180; author reply 180.
31. Dormandy JA, Charbonnel B, Eckland DJ, *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; 366: 1279–1289.
32. Lincoff AM, Wolski K, Nicholls SJ, *et al.* Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007; 298: 1180–1188.
33. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, *et al.* Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 2010; 304: 411–418.
34. Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. *BMJ*, 2011; 342: d1309.
35. Monami M, Vitale V, Ambrosio ML, *et al.* Effects on lipid profile of dipeptidyl peptidase 4 inhibitors, pioglitazone, acarbose, and sulfonylureas: meta-analysis of placebo-controlled trials. *Adv Ther* 2012; 29: 736–746.
36. 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: 1547–1554.
37. Wei J, Tang Q, Liu L, *et al.* Combination of peroxisome proliferator-activated receptor alpha/gamma agonists may benefit type 2 diabetes patients with coronary artery disease through inhibition of inflammatory cytokine secretion. *Exp Ther Med* 2013; 5: 783–788.
38. Wolkart G, Schrammel A, Dorffel K, *et al.* Cardiac dysfunction in adipose triglyceride lipase deficiency: treatment with a PPARalpha agonist. *Br J Pharmacol* 2012; 165: 380–389.

## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Appendix S1** | Forest plot of glycated hemoglobin.
**Appendix S2** | Forest plot of insulin dose.
**Appendix S3** | Forest plot of hypoglycemia.
**Appendix S4** | Forest plot of Total cholesterol.
**Appendix S5** | Forest plot of high-density lipoprotein cholesterol.
**Appendix S6** | Forest plot of low-density lipoprotein cholesterol.
**Appendix S7** | Forest plot of very low-density lipoprotein cholesterol.
**Appendix S8** | Forest plot of triglyceride.
**Appendix S9** | Forest plot of systolic blood pressure.
**Appendix S10** | Forest plot of diastolic blood pressure.
**Appendix S11** | Forest plot of edema.
**Appendix S12** | Forest plot of weight gain.
**Appendix S13** | Forest plot of myocardial infarction.
**Appendix S14** | Forest plot of heart failure.
**Appendix S15** | Forest plot of cardiovascular death.
**Appendix S16** | Forest plot of all-cause death.