Efficacy and Safety of Novel Thiazolidinedione Rivoglitazone in Type-2 Diabetes a Meta-Analysis

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Abstract

No meta-analysis has analyzed the safety and efficacy of rivoglitazone in type-2 diabetes (T2DM). We undertook this meta-analysis to address this knowledge gap. Electronic databases were searched for RCTs involving T2DM patients receiving rivoglitazone in the intervention arm, and placebo/active comparator in the control arm. The primary outcome was to evaluate changes in HbA1c. Secondary outcomes were to evaluate alterations in glucose, lipids, and adverse events. From initially screened 24 articles, data from 3 RCTs (3591 patients) that fulfilled all criteria was analzsed. HbA1c was significantly lower with standard-dose (1 mg/d) [MD-0.86% (95%CI:-1.11–-0.61); $P < 0.01$; $I^2 = 87\%$] and high-dose (1.5-2 mg/d) [MD-0.97%(95%CI:-1.03–-0.90); $P < 0.01$; $I^2 = 19\%$] rivoglitazone compared to placebo. When compared to pioglitazone (30-45 mg/d), HbA1c lowering was comparable with standard-dose [MD 0.05%(95%CI:-0.01 – 0.11); $P = 0.08$; $I^2 = 11\%$], but superior with high-dose [MD -0.11%(95%CI:-0.18– -0.04); $P < 0.01$; $I^2 = 0\%$] rivoglitazone. Triglycerides were significantly lower with standard-dose [MD-17.95 mg/dl (95%CI:-34.23–-1.66); $P = 0.03$; $I^2 = 0\%$] and high-dose [MD-40.41 mg/dl (95%CI:-72.90– -7.93);$P = 0.01$;$I^2 = 71\%$] rivoglitazone compared to placebo. Adiponectin significantly improved with standard-dose [MD 7.94 ng/ml (95%CI: 5.48–10.39); $P < 0.01$;$I^2 = 98\%$] and high-dose [MD 13.82 ng/ml (95%CI: 8.16–19.48); $P < 0.01$; $I^2 = 100\%$] rivoglitazone compared to placebo. hsCRP was significantly lower with standard-dose [MD -1.00 mg/L (95% CI: -1.20 – -0.80); $P < 0.01$; $I^2 = 6\%$] and high-dose [MD -1.50 mg/L (95%CI:-1.59– -1.40); $P < 0.01$; $I^2 = 0\%$] rivoglitazone compared to placebo. Treatment-emergent adverse events with standard-dose [Risk ratio (RR) 1.16 (95%CI: 0.84 –1.60); $P = 0.38$; $I^2 = 0\%$] and high-dose [RR1.34 (95%CI: 0.99–1.83); $P = 0.06$; $I^2 = 0\%$] rivoglitazone was comparable to placebo. Severe adverse events with standard-dose [RR1.88 (95%CI: 0.69–5.12);$P = 0.22$;$I^2 = 0\%$] and high-dose [RR 1.27 (95% CI: 0.45 – 3.59); $P = 0.68$; $I^2 = 0\%$] rivoglitazone was comparable to placebo. This meta-analysis highlights the good glycaemic efficacy and safety of both standard and high-dose rivoglitazone, and appears to be better than lobeglitazone in T2DM.

Keywords: Lobeglitazone, meta-analysis, rivoglitazone, type-2 diabetes

Introduction

Thiazolidinediones (TZDs) are an established class of anti-diabetes medications whose primary mechanism of action is activating peroxisome proliferator-activated receptor γ (PPARγ) to reduce hepatic, muscular and adipose tissue insulin resistance, resulting in improved blood glucose disposition, leading to better diabetes control in people living with type-2 diabetes (T2DM).[1] Troglitazone was the first approved agent of this class withdrawn from clinical practice in the 2000s due to hepatoxicity.[2] Rosiglitazone and pioglitazone, subsequently approved for clinical use by US Food and Drug Administration (FDA) in 1999, have been demonstrated to have good glycaemic efficacy, and glycaemic durability

Supplementary material available online

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_17_23

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Submitted: 12-Jan-2023 **Revised:** 11-Mar-2023
Accepted: 24-Mar-2023 **Published:** 28-Aug-2023

How to cite this article: Dutta D, Kadian J, Maisnam I, Kumar A, Bhattacharya S, Sharma M. Efficacy and safety of novel thiazolidinedione rivoglitazone in type-2 diabetes a meta-analysis. Indian J Endocr Metab 2023;27:286-95.

with low hypoglycemia risk.[3,4] Fluid retention and weight gain have been issues associated with all approved TZDs to date. Following a meta-analysis published in 2007 linking rosiglitazone with myocardial infarction, it was withdrawn from Australia, South Africa, Europe, and many other countries across the world, except the USA.[5] Pioglitazone in contrast has been shown to improve cardiovascular outcomes and reduce cardiovascular events in people with established cardiovascular disease.[6] Because of the associated fluid retention, the use of pioglitazone is contraindicated only in people with heart failure.[6] Still, a suspect risk of bladder cancer, and osteoporosis, especially in post-menopausal women and the elderly have limited the use of pioglitazone and TZDs. Lobeglitazone, a TZD initially developed in the 2000s in South Korea was the third-ever glitazone approved for clinical use in South Korea.[7,8] We recently published a meta-analysis showing the glycaemic efficacy and side effect profile of a novel TZD lobeglitazone (0.5 mg/d) to be similar to that of half-maximum dose of pioglitazone (15 mg/d).[7] Hence lobeglitazone appears to be a weaker anti-diabetes medication with glycaemic efficacy lesser than a full dose of pioglitazone.[7]

Rivoglitazone has been developed as a potential alternative to the currently available TZDs.[9] In the in-vitro, rivoglitazone has shown 445-fold selectivity for PPARγ over PPARα or PPARδ isoforms. Early animal and clinical studies have demonstrated rivoglitazone to be a potent and effective blood glucose-lowering agent, with dose-proportional pharmacokinetics.[9,10] The plasma half-life of rivoglitazone is approximately 13 hours.[9,10] A 6-week proof-of-concept study demonstrated good glycemic effects in people living with type 2 diabetes.[11] Fluid retention was noted at supratherapeutic doses only.[11]

Several randomized controlled trials (RCTs) have been published evaluating the clinical efficacy and safety profile of rivoglitazone in T2DM.[12-14] However, to date no meta-analysis has been published which has holistically analyzed the glycaemic efficacy, glycaemic durability, and safety of rivoglitazone in managing T2DM. Hence the aim of this meta-analysis was to evaluate the efficacy and safety of rivoglitazone in T2DM and to find out how it compares to the currently available TZDs for clinical use.

Methods

Methodology

The meta-analysis was done as per the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.[15] The predefined protocol is registered with the international prospective register of systematic reviews (PROSPERO) having a registration number of CRD42022367396. All RCTs satisfying inclusion criteria, published till September 2022 were considered for this meta-analysis. This meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[16] No separate ethics committee approval was required for this meta-analysis as ethical approval already exists for the individual RCTs included in this study.

The PICOS criteria were used to screen and select the studies for this meta-analysis with patients (P) being individuals with T2DM; intervention (I) being the use of rivoglitazone over the background of standard care for T2DM; control (C) being patients with diabetes on standard care for managing T2DM but not receiving rivoglitazone but receiving any placebo or any other anti-diabetes medication in place of rivoglitazone; outcomes (O) being evaluated were impact on HbA1c, fasting plasma glucose (FPG), lipid parameters and any adverse effects noted. Only patients with T2DM were considered for this meta-analysis. Only those RCTs which had at least 2 arms were included, with the intervention arm receiving rivoglitazone on the background of standard care for T2DM and the non-intervention or control arm receiving a placebo or any other approved anti-diabetes medication for T2DM.

The primary outcome was to evaluate the changes in HbA1c. The secondary outcomes of this study were to evaluate the alterations in FPG, lipid parameters, bone mineral density parameters, and adverse events. Analysis of the outcomes was done based on whether the control group received an active comparator (any other anti-diabetes/blood glucose lowering medication) – labeled here as the active control group (ACG) or a placebo/any other non-diabetes medication – labeled as passive control Group (PCG).

Search method for identification of studies

A detailed search of electronic databases for RCTs published till September 2022 was done at Cochrane register, Medline, PubMed, Embase (Ovid SP), clinicaltrials.gov, ctri.nic.in, global health, and Google Scholar using Boolean search strategy: ((rivoglitazone) AND ((diabetes) OR ("diabetes mellitus")).

Data extraction, study selection, and risk of bias assessment

Data extraction was carried out independently by two authors using standard data extraction forms. The details have been elaborated on elsewhere.[17] Three authors independently assessed the risk of bias using Review Manager (Revman) Version 5.4 (The Cochrane Collaboration, Oxford, UK 2014) software. We specifically looked for selection bias, performance bias, detection bias, attrition bias, reporting bias, and any other bias like publication bias. The details of how the risk of bias assessment was done have already been elaborated elsewhere.[17]

Measures of treatment effect, heterogeneity assessment, grading of results, and data synthesis

For continuous variables, outcomes were expressed as mean differences (MD). Conventional units were used for analysis. Dichotomous outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CI). Adverse events were

expressed as absolute risk differences. RevMan 5.4 was used for comparing the outcomes.[16,17] Heterogeneity was assessed by studying the forest plot generated for the primary and secondary outcomes. Subsequently, heterogeneity was analyzed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance with the I^2 test.[18,19] The details have been elaborated elsewhere.[17] The random effect model was used for the analysis of outcomes expressed as 95% confidence intervals (95%CI). Forrest plots were plotted with the left side favoring rivoglitazone and the right-side favoring control.

Results

A total of 24 articles were found after the initial search [Figure 1]. Following the screening of the titles, and abstracts, the search was reduced to 14 studies, as 10 duplicates were removed. Further evaluation of the remaining 14 articles in detail led left us with 6 studies. Finally, three RCTs in people with T2DM were included in this meta-analysis as they fulfilled all the criteria.[12-14] Three studies were removed as they were either reviews or proof of concept studies.[9-11]

Rivoglitazone was used at doses ranging from 0.5 mg/d – 3 mg/d in different studies.[12-14] We used rivoglitazone 1 mg/d (standard dose) and 1.5 or 2 mg/d (high dose) doses for primary analysis in our meta-analysis as they were the most commonly used dose across all the studies. Chou (2012) *et al.*[12] and Kong (2011) *et al.*[13] evaluated rivoglitazone 1 mg/d and 1.5 mg/d in their studies. Truitt (2010) *et al.*[14] evaluated rivoglitazone 1 mg/d and 2 mg/d in their study. The duration of follow-up in the studies by Chou (2012) *et al.*,[12] Kong (2011) *et al.*[13] and Truitt (2010) *et al.*[14] was 26 weeks, 12 weeks, and 26 weeks respectively. All the 3 RCTs analyzed in this meta-analysis had both a placebo control group as well an active (anti-diabetes medication) control group.[12-14] Hence the outcomes of rivoglitazone compared to placebo have been presented by Chou 2012a, Kong 2011a, and Truitt 2010a. The active controls in the studies by Chou (2012) *et al.*,[12] Kong (2011) *et al.*[13] and Truitt (2010) *et al.*[14] were pioglitazone 45 mg/day, pioglitazone 30 mg/d and pioglitazone 45 mg/d respectively. The outcomes of rivoglitazone compared to active controls have been presented in Chou 2012b, Kong 2011b, and Truitt 2010b. The details of the studies included in this meta-analysis have been elaborated in Table 1.

Risk of bias in the included studies

The summaries of the risk of bias of the 3 studies included in the meta-analysis have been elaborated in Figure 2a and b and Supplementary Table 1. Random sequence generation, allocation concealment bias (selection bias), performance bias (blinding of participants and investigators), detection

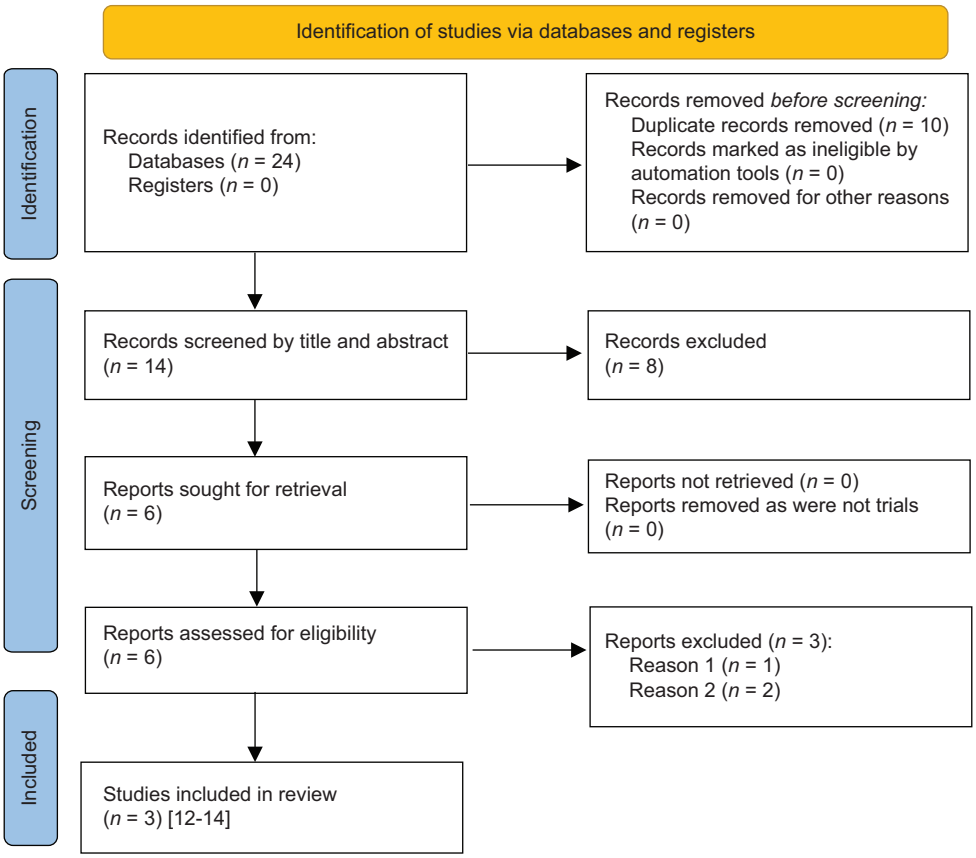

Figure 1: Flowchart elaborating on study retrieval and inclusion in the meta-analysis. Reason-1: three studies were excluded as their were either proof of concept studies or review[9-11]; RCT: randomized controlled trial

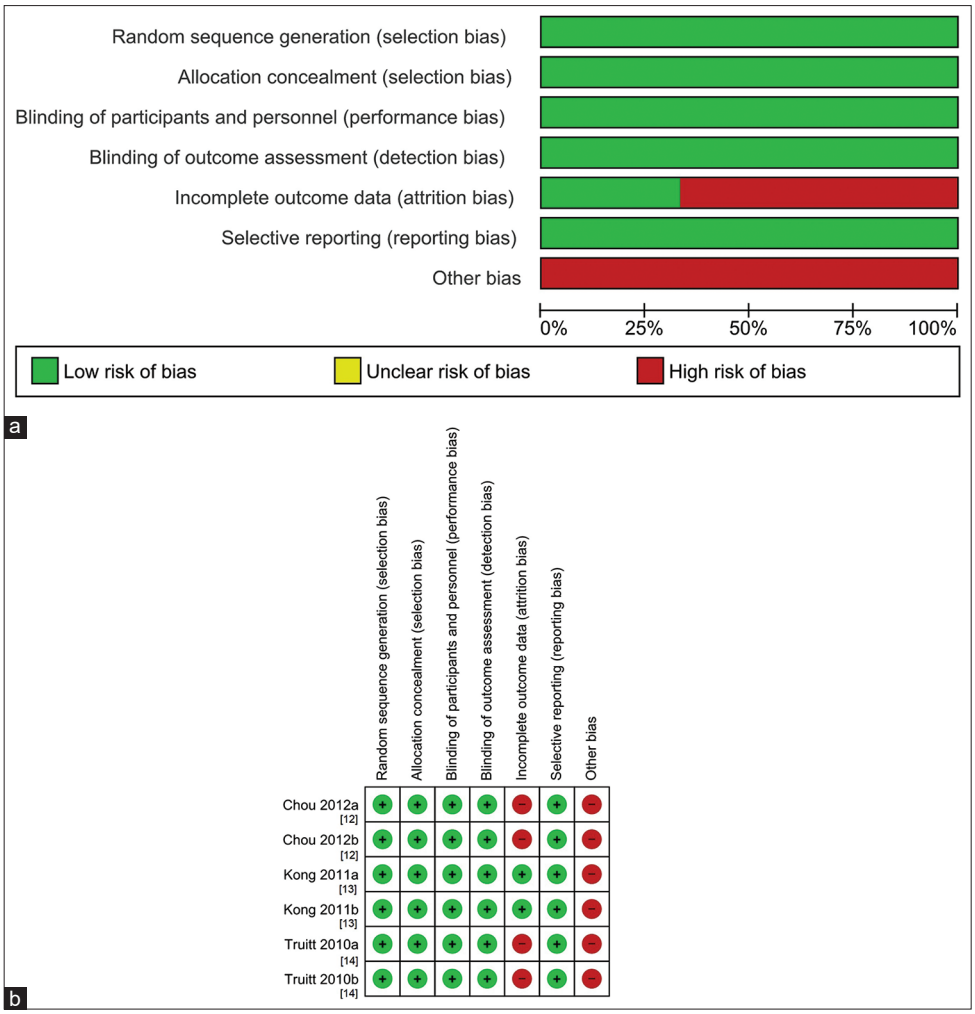

Figure 2: (a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; (b) Risk of bias summary: review authors' judgements about each risk of bias item for each included study

bias (blinding of outcome assessors), and, reporting bias were judged to be low in all the 3 studies (100%). Incomplete outcome data (attrition bias) was judged to be low in 1 out of 3 studies (33.33%). Source of funding, especially pharmaceutical, authors from the pharmaceutical organizations, and conflict of interests were looked into in the "other bias" section. Another bias was judged to be high in all the 3 studies (100%) [Figure 2a and b].

Effect of lobeglitazone on primary outcomes

HbA1c

Data from 3 studies involving 638 and 1,103 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on HbA1c as compared to placebo. Individuals receiving standard dose rivoglitazone [MD -0.86% (95% CI: -1.11 – -0.61); $P < 0.01$; $I^2 = 87\%$ (considerable heterogeneity); Figure 3a] and high dose rivoglitazone [MD -0.97% (95% CI: -1.03 – -0.90); $P < 0.01$; $I^2 = 19\%$ (low heterogeneity); Figure 3b] had a significantly higher lowering of HbA1c as compared to PCG.

Data from 3 studies involving 1,233 and 1,701 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on HbA1c as compared to ACG. Individuals receiving standard dose rivoglitazone [MD 0.05% (95% CI: -0.01 – 0.11); $P = 0.08$; $I^2 = 11\%$ (low heterogeneity); Figure 3c] had a comparable lowering of HbA1c as compared to ACG. Individuals receiving high dose rivoglitazone [MD -0.11% (95% CI: -0.18 – -0.04); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity); Figure 3d] had a significantly higher lowering of HbA1c as compared to active controls.

Effect of rivoglitazone on secondary outcomes

Fasting glucose

Data from 3 studies involving 638 and 1,103 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on fasting glucose as compared to placebo. Individuals receiving standard dose rivoglitazone [MD -36.96 mg/dl (95% CI: -47.52 – -26.40); $P < 0.01$; $I^2 = 81\%$ (considerable heterogeneity); Figure 3e] and high dose rivoglitazone [MD -46.40 mg/dl (95%

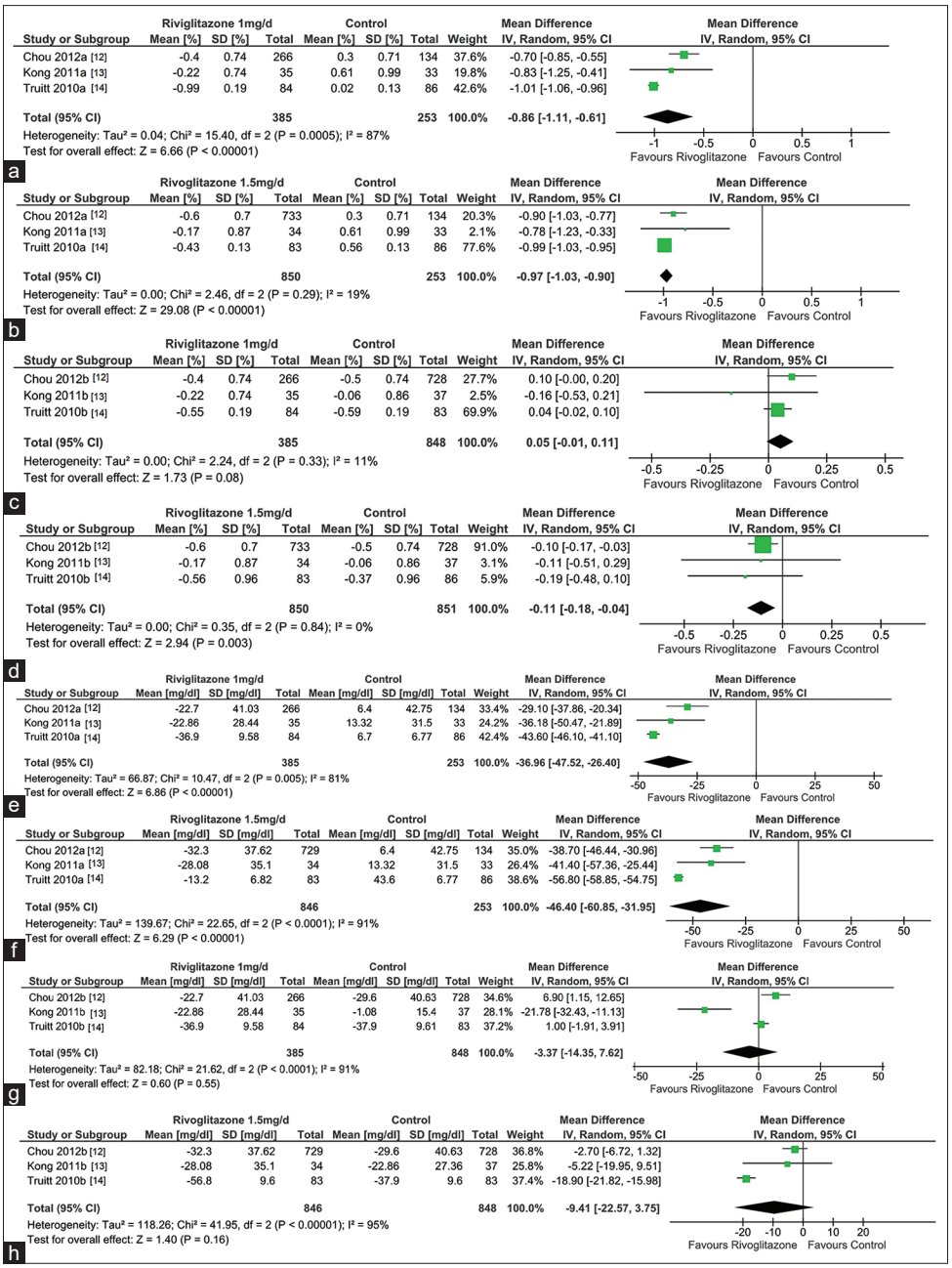

Figure 3: Forest plot highlighting the impact of (a) Standard dose rivoglitazone on HbA1c compared to placebo; (b) High dose rivoglitazone on HbA1c compared to placebo; (c) Standard dose rivoglitazone on HbA1c compared to pioglitazone; (d) High dose rivoglitazone on HbA1c compared to pioglitazone; (e): Standard dose rivoglitazone on fasting glucose compared to placebo; (f): High dose rivoglitazone on fasting glucose compared to placebo; (g): Standard dose rivoglitazone on fasting glucose as compared to pioglitazone; (h): High dose rivoglitazone on fasting glucose compared to pioglitazone

CI: -60.85 – -31.95); $P < 0.01$; $I^2 = 91\%$ (considerable heterogeneity); Figure 3f] had a significantly higher lowering of fasting as compared to PCG.

Data from 3 studies involving 1,233 and 1,701 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on fasting glucose as compared to ACG. Individuals receiving standard dose rivoglitazone [MD -3.37 mg/dl (95% CI: -14.35 – 7.62); $P = 0.55$; $I^2 = 91\%$ (considerable heterogeneity); Figure 3g] and high dose rivoglitazone [MD -9.41 mg/dl (95% CI: -22.57 – 3.75); $P = 0.16$; $I^2 = 95\%$ (considerable heterogeneity); Figure 3h] had a comparable lowering of fasting glucose as compared to ACG.

Lipid parameters

Data from 3 studies involving 631 and 1,095 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on serum triglycerides as compared to placebo. Individuals receiving standard dose rivoglitazone [MD -17.95 mg/dl (95% CI: -34.23 – -1.66);

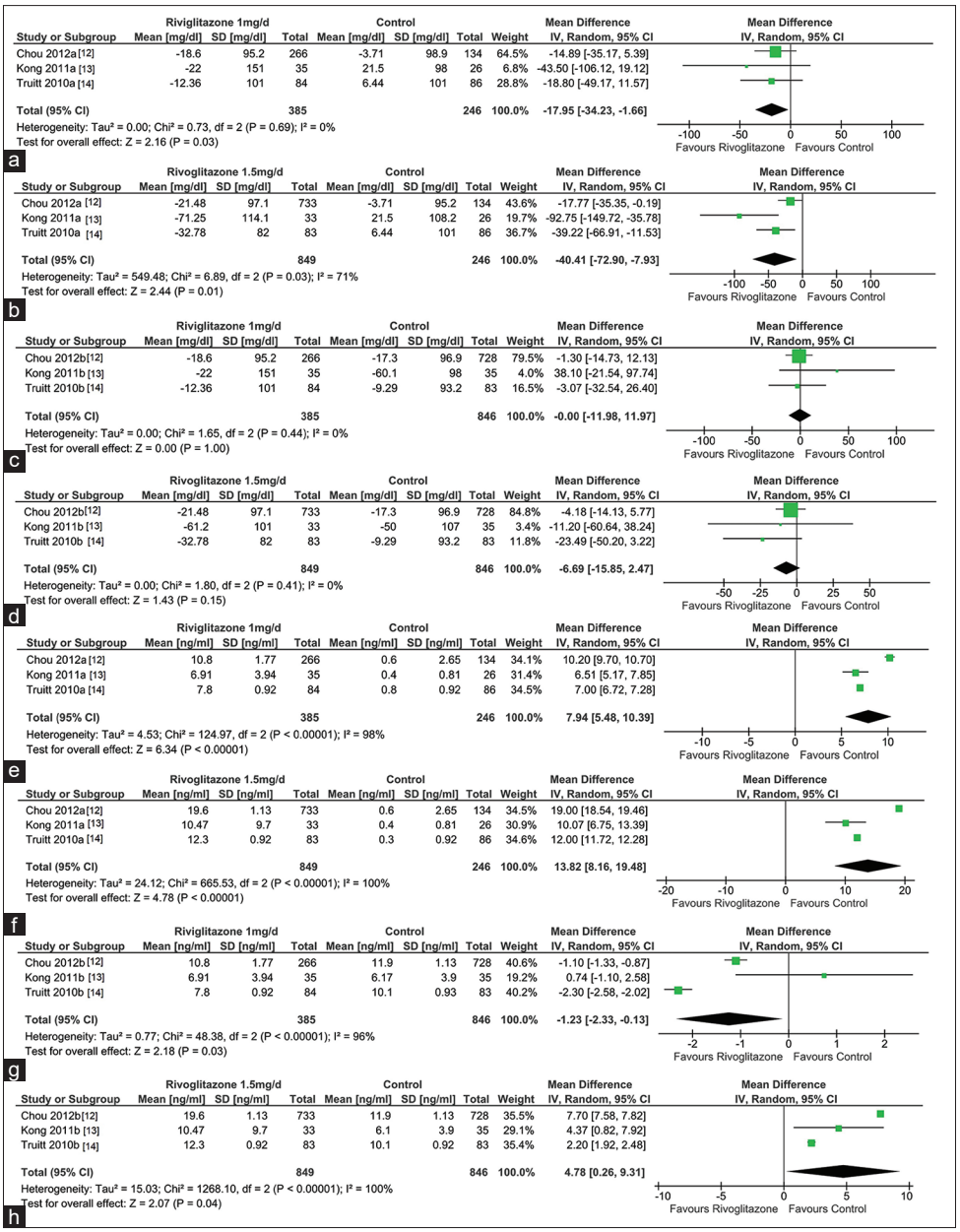

Figure 4: Forest plot highlighting the impact of (a) Standard dose rivoglitazone on serum triglycerides compared to placebo; (b) High dose rivoglitazone on serum triglycerides compared to placebo; (c) Standard dose rivoglitazone on serum triglycerides compared to pioglitazone; (d) High dose rivoglitazone on serum triglycerides compared to pioglitazone; (e): Standard dose rivoglitazone on serum adiponectin compared to placebo; (f): High dose rivoglitazone on serum adiponectin compared to placebo; (g): Standard dose rivoglitazone on serum adiponectin as compared to pioglitazone; (h): High dose rivoglitazone on serum adiponectin compared to pioglitazone

$P = 0.03$; $I^2 = 0\%$ (low heterogeneity); Figure 4a] and high dose rivoglitazone [MD -40.41 mg/dl (95% CI: -72.90 – -7.93); $P = 0.01$; $I^2 = 71\%$ (considerable heterogeneity); Figure 4b] had a significantly greater lowering of serum triglycerides as compared to PCG.

Data from 3 studies involving 1,231 and 1,695 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on serum triglycerides as compared to ACG. Individuals receiving standard dose rivoglitazone [MD -0.00 mg/dl (95% CI: -11.98 – 11.97); $P = 1$; $I^2 = 0\%$ (low heterogeneity); Figure 4c] and high dose rivoglitazone [MD -6.69 mg/dl (95% CI: -15.85 – 2.47); $P = 0.15$; $I^2 = 0\%$ (low heterogeneity); Figure 4d] had comparable lowering of serum triglycerides as a compared to active controls.

Adipocytokines

Adiponectin

Data from 3 studies involving 631 and 1,095 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on serum adiponectin as compared to placebo. Individuals receiving standard dose rivoglitazone [MD 7.94 ng/ml (95% CI: 5.48 – 10.39); $P < 0.01$;

I^2 = 98% (considerable heterogeneity); Figure 4e] and high dose rivoglitazone [MD 13.82 ng/ml (95% CI: 8.16 – 19.48); $P < 0.01$; I^2 = 100% (considerable heterogeneity); Figure 4f] had a significantly greater increase in serum adiponectin as compared to PCG.

Data from 3 studies involving 1,231 and 1,695 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on serum adiponectin as compared to ACG. Serum adiponectin was significantly lower in patients receiving standard dose rivoglitazone [MD -1.23 ng/ml (95% CI: -2.33 – -0.13); $P = 0.03$; I^2 = 96% (considerable heterogeneity); Figure 4g] as compared to active controls. Serum adiponectin in contrast was significantly higher in patients receiving high dose rivoglitazone [MD 4.78 ng/ml (95% CI: 0.26 – 9.31); $P = 0.04$; I^2 = 100% (considerable heterogeneity); Figure 4h] as compared to active controls.

High sensitivity C-reactive protein (hs-CRP)

Data from 3 studies involving 631 and 1,095 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on serum hsCRP as compared to placebo. Individuals receiving standard dose rivoglitazone [MD -1.00 mg/L (95% CI: -1.20 – -0.80); $P < 0.01$; I^2 = 6% (low heterogeneity); Supplementary Figure 1a] and high dose rivoglitazone [MD -1.50 mg/L (95% CI: -1.59 – -1.40); $P < 0.01$; I^2 = 0% (low heterogeneity); Supplementary Figure 1b] had a significantly greater decrease in serum hs-CRP as compared to PCG.

Data from 3 studies involving 1,231 and 1,695 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on serum hs-CRP as compared to ACG. Serum hs-CRP was significantly higher in patients receiving standard dose rivoglitazone [MD 0.10 mg/L (95% CI: 0.05 – 0.15); $P < 0.01$; I^2 = 0% (low heterogeneity); Supplementary Figure 1c] as compared to active controls. Serum hs-CRP in contrast was significantly lower in patients receiving high dose rivoglitazone [MD -0.40 mg/L (95% CI: -0.43 – -0.37); $P < 0.01$; I^2 = 0% (low heterogeneity); Supplementary Figure 1d] as compared to active controls.

Safety

Data from 3 studies involving 645 and 1,095 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on treatment-emergent adverse events (TAEs) and severe adverse events (SAEs) as compared to placebo. The occurrence of TAEs with standard dose rivoglitazone [Risk ratio (RR) 1.16 (95% CI: 0.84 – 1.60); $P = 0.38$; I^2 = 0% (low heterogeneity); Figure 5a] and high dose rivoglitazone [RR 1.34 (95% CI: 0.99 – 1.83); $P = 0.06$; I^2 = 0% (low heterogeneity); Figure 5b] was comparable to

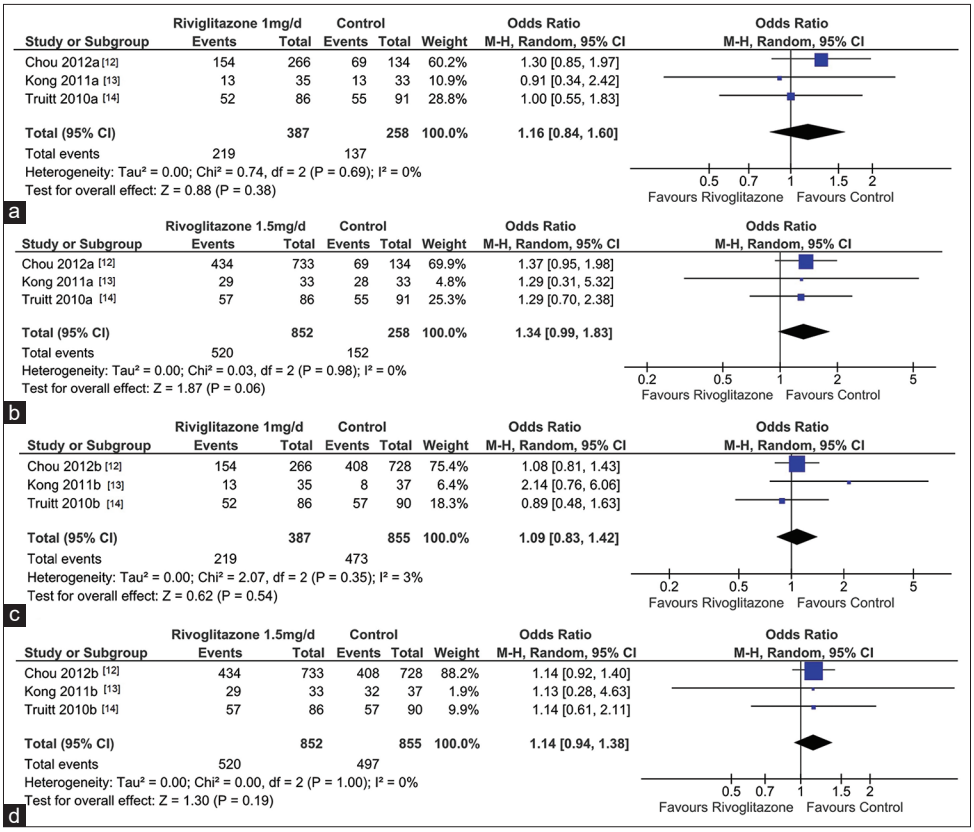

Figure 5: Forest plot highlighting the impact of (a) Standard dose rivoglitazone on occurrence of treatment-emergent adverse events (TAEs) compared to placebo; (b) High dose rivoglitazone on occurrence of TAEs compared to placebo; (c) Standard dose rivoglitazone on occurrence of TAEs compared to pioglitazone; (d) High dose rivoglitazone on occurrence of TAEs compared to pioglitazone

Table 1: Baseline characteristics of patients in the different randomized controlled trials evaluated in this meta-analysis

Parameter	Chou *et al.*[12]			Kong *et al.*[13]			Truitt *et al.*[14]			
	SDR	HDR	PCG	ACG	SDR	HDR	PCG	ACG	SDR	HDR	PCG	ACG
Number of patients	274	750	137	751	35	34	32	37	87	85	92	91
Age (years)	55.0±10.51	55.1±10.59	55.4±12.32	55.0±10.84	53.2±7.8	52.4±9.3	53.6±7.6	54.0±8.5	55.4±10.9	55.0±10.8	55.3±9.3	56.6±10.1
BMI (kg/m^2)	29.7±5.63	29.6±5.27	30.1±5.43	30.0±5.80	25.60±3.72	25.97±4.17	25.53±4.03	24.86±3.26	32.9±6.0	33.1±6.4	32.2±5.8	32.9±5.7
Weight (kg)	80.5±19.65	80.6±17.67	82.0±19.73	81.6±19.59	65.34±13.11	68.91±13.13	67.71±13.70	64.09±10.79	93.3±20.7	96.3±18.7	92.9±20.4	94.9±21.5
Duration of DM (years)	5.0±5.26	4.3±4.40	4.9±6.13	4.4±4.99	4.87±3.14	4.36±3.74	5.85±3.89	5.59±4.60	6.2±6.4	5.2±4.5	6.7±5.6	6.6±7.5
HbA1c (%)	7.7±0.53	7.7±0.57	7.7±0.54	7.7±0.58	7.45±0.72	7.40±0.70	7.35±0.62)	7.49±0.82	8.00±0.81	8.05±0.87	8.21±0.98	7.98±0.83
Fasting Glucose (mg/dl)	159.2±42.54	161.2±40.52	161.8±45.22	161.6±42.96	165.1±37.1	166.32±41.58	165.24±31.5	174.96±37.44	170.5±38.9	179.3±58.7	176.4±44.9	170.4±45.3
Triglycerides (mg/dl)	173.7±103.9	169.2±100.5	185.6±110.6	175.2±97.1	131.1±61.9	181.6±119.5	130.2±61.2	162.1±82.3	200.6±102.1	189.5±89.0	189.6±102.3	202.0±93.2
LDL-C (mg/dl)	112.9±32.2	112.0±32.31	108.4±29.5	110.7±33.6	135.3±35.9	131.1±27.8	118.7±30.9	123.4±35.57	109.1±27.2	108.8±31.2	112.6±38.6	109.5±34.5

Rv: rivoglitazone; SDR: Standard Dose Rivoglitazone group (1 mg/d); HDR: High Dose Rivoglitazone Group (1.5 mg/d or 2 mg/d); PCG: Placebo Control Group; ACG: Active Control Group (Pioglitazone 30-45 mg/d); BMI: body mass index; DM: diabetes; N/A: not available

those receiving placebo (PCG). The occurrence of SAEs with standard dose rivoglitazone [RR 1.88 (95% CI: 0.69 – 5.12); $P = 0.22$; $I^2 = 0\%$ (low heterogeneity); Supplementary Figure 1e] and high dose rivoglitazone [RR 1.27 (95% CI: 0.45 – 3.59); $P = 0.68$; $I^2 = 0\%$ (low heterogeneity); Supplementary Figure 1f] was comparable to those receiving placebo (PCG).

Data from 3 studies involving 1242 and 1707 people with T2DM were analyzed to find out the impact of standard dose and high rivoglitazone respectively on TAEs and SAEs as compared to ACG. The occurrence of TAEs with standard dose rivoglitazone [RR 1.09 (95% CI: 0.83 – 1.42); $P = 0.54$; $I^2 = 3\%$ (low heterogeneity); Figure 5c] and high dose rivoglitazone [RR 1.14 (95% CI: 0.94 – 1.38); $P = 0.19$; $I^2 = 0\%$ (low heterogeneity); Figure 5d] was comparable to ACG. The occurrence of SAEs with standard dose rivoglitazone [RR 1.02 (95% CI: 0.54 – 1.94); $P = 0.07$; $I^2 = 0\%$ (low heterogeneity); Supplementary Figure 1g] and high dose rivoglitazone [RR 0.79 (95% CI: 0.46 – 1.37); $P = 0.41$; $I^2 = 0\%$ (low heterogeneity); Supplementary Figure 1h] was comparable to ACG.

A detailed evaluation of the TAEs revealed that weight gain and edema were the most common adverse events noted which were dose-dependent. Other adverse events noted in >3% of patients included fatigue, dizziness, arthralgia, cough, upper respiratory tract infections, dry eyes, blurry vision, palpitations, exertional dyspnea, hematuria, headache, and elevated brain natriuretic peptide.[9] The occurrence of most of these TAEs was similar in the study and the control groups except few which have been highlighted below.

The occurrence of weight gain was significantly higher in patients receiving rivoglitazone as compared to placebo (PCG) both with standard dose [MD 2.60 kg (95% CI: 1.65 – 3.55); $P < 0.01$; n = 170; Truitt 2010 *et al.*] as well as high dose rivoglitazone [MD 0.90 kg (95% CI: 0.09 – 1.71); $P = 0.03$; n = 164; Truitt 2010 *et al.*]. The quantum of weight gain was higher with the higher dose of rivoglitazone as compared to the placebo. Weight gain was significantly lower with standard dose rivoglitazone [MD -0.90 kg (95% CI: -1.70 – -0.10); $P = 0.03$; n = 167; Truitt 2010 *et al.*] as compared to active controls (ACG) receiving pioglitazone 45 mg/d. Weight gain in contrast, was significantly higher with high dose rivoglitazone [MD 0.90 kg (95% CI: 0.09 – 1.71); $P = 0.03$; n = 164; Truitt 2010 *et al.*] when compared to active controls (ACG) receiving pioglitazone 45 mg/d.

Discussion

Pioglitazone has been the flag-bearer for the thiazolidinediones class of anti-diabetes medications. In a meta-analysis evaluating the data from 26 studies with 19,645 participants, pioglitazone significantly reduced the risk of major adverse cardiovascular events in people with established cardiovascular disease (RR, 0.8 [95% CI, 0.7-0.9]), reduced albuminuria, without any effect on all-cause mortality (1.0 [0.8-1.1]).[9] An increased risk of hospitalization for heart failure (1.3 [1.1-1.6])

was noted and hence this drug is not recommended for clinical use in people with heart failure.[20]

Rivoglitazone has a higher potency to activate peroxisome proliferator-activated receptors gamma (PPAR-γ) as compared to pioglitazone and rosiglitazone (16.4-fold higher and 3.6-fold higher respectively).[21] Rivoglitazone has a longer half-life compared with that of rosiglitazone and pioglitazone (12.2, 4, and 7 hours respectively).[21] This meta-analysis provides re-assuring data on the glycaemic efficacy of standard dose (1 mg/d) and high dose (1.5-2 mg/d) rivoglitazone. HbA1c reduction with standard dose and high dose rivoglitazone as compared to placebo was -0.86% and -0.97% respectively. In addition, a high dose of rivoglitazone was superior to the full dose of pioglitazone (30-45 mg/d) with regards to glycaemic efficacy, providing an additional HbA1c reduction of -0.11%. Standard dose rivoglitazone has glycaemic efficacy comparable to full dose of pioglitazone (30-45 mg/d). The same was replicated with regard to fasting glucose reduction. Standard dose and high dose rivoglitazone had an impressive triglyceride lowering as compared to placebo (-17.95 and -40.41 mg/dl respectively), which was comparable to that of pioglitazone. Additional metabolic benefits of rivoglitazone include a significant improvement in the beneficial adipokine adiponectin levels along with a significant reduction in systemic inflammation as estimated by hsCRP. High dose rivoglitazone was superior to pioglitazone (30-45 mg/d), but standard dose rivoglitazone inferior to pioglitazone (30-45 mg/d) with regards to increase in adiponectin levels and reduction in hsCRP. Rivoglitazone was noted to be well tolerated without any increase in TAEs and SAEs when compared to placebo as well as active controls. Weight gain was noted with rivoglitazone which was dose-dependent, and was significantly higher with high-dose rivoglitazone as compared to standard dose rivoglitazone. When compared to the reference active control pioglitazone (30-45 mg/d), weight gain was noted to be higher with high dose rivoglitazone, but lower with standard dose rivoglitazone.

Although no head-to-head trial is available comparing rivoglitazone with lobeglitazone, rivoglitazone appears to be better than lobeglitazone with regards to glycaemic efficacy as well as side effect profile like weight gain. This is because full dose/high dose lobeglitazone (0.5 mg/d) had glycaemic efficacy similar to the half-maximal dose of pioglitazone (15 mg/d).[7] In contrast, our meta-analysis showed that high dose rivoglitazone (1.5-2 g/d) was superior to full dose pioglitazone (30-45 mg/d) with regards to HbA1c reduction. Data is lacking and hence trials are warranted to evaluate the role of rivoglitazone in metabolic dysfunction associated with fatty liver disease.

Based on the currently available clinical data, rivoglitazone at a starting dose of 1 mg by mouth can be used initially. If therapeutic goals are not met within 8-12 weeks with the 1-mg dose, the dosage could be increased to a maximum of 2 mg daily. Only one study evaluated doses of 3 mg daily or higher which was not associated with greater benefit but had greater side effects. Hence use of rivoglitazone at doses of more than 2 mg/day cannot be recommended at this point in time.

To conclude it may be said that, this meta-analysis highlights the good glycaemic efficacy of both standard (1 mg/d) and high dose (1.5-2 mg/d) rivoglitazone. Non-glycaemic benefits of rivoglitazone is similar to pioglitazone. Weight gain remains a problem with rivoglitazone, as with pioglitazone, highlighting it to be a class effect. Further long-term follow-up studies are warranted to document the cardiovascular and bone health impact of rivoglitazone.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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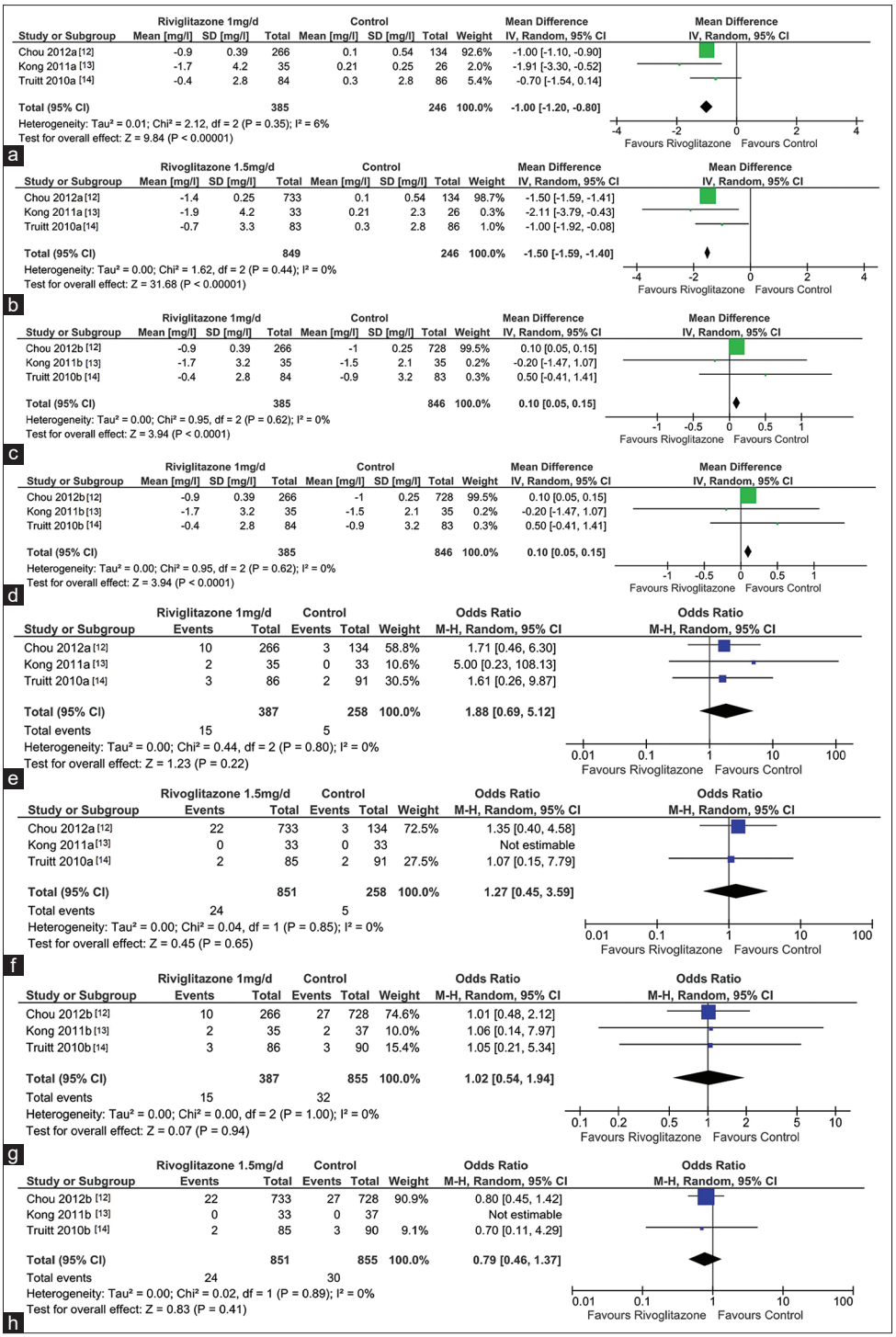
Supplementary Material

Supplementary Table 1: Risk of bias assessment table

Chou 2012	Risk Of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Randomized, double-blind, placebo and active comparator-controlled (RCT)
Allocation Concealment (Selection Bias)	Low Risk	Subjects were randomized 2 : 4 : 11:11 to receive double blind, double-dummy treatment with placebo, rivoglitazone 1.0 mg, rivoglitazone 1.5 mg or pioglitazone 45 mg per day.
Blinding Of Participants & Personal (Performance Bias)	Low Risk	Yes, double blinded RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Yes, double blinded RCT
Incomplete Outcome Data (Attrition Bias)	High Risk	1912 patients were randomized, of which data from 1482 patients who completed the study were analysed (attrition: 430; attrition rate: 22.48%). Any attrition rate of less than 15% was considered to be low.
Selective Reporting (Reporting Bias)	Low Risk	All pre-specified outcomes were reported
Other Biases	High Risk	This study was funded by Daiichi Sankyo, Inc. Drs Chou, Truitt and Choi were employed by Daiichi Sankyo Pharma Development, and Drs Moberly and Mun were employed by Daiichi Sankyo Pharma Development at the time the study was conducted. Dr Merante is employed by Daiichi Sankyo Development Ltd.
Kong 2011	**Risk Of Bias**	**Author Judgement**
Random Sequence Generation (Selection Bias)	Low Risk	Multicentre, double-blind, placebo and active controlled, parallel-group study
Allocation Concealment (Selection Bias)	Low Risk	Stratified randomization was done. Eligible patients were randomized into either one of the five treatment arms with 1 : 1 : 1 : 1 : 1 ratio in a double blinded fashion
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	174 patients were randomized, of which 160 patients completed the study. Hence attrition rate was 8.05%
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	This study was funded by Daiichi Sankyo, Inc. A. Y., H. S., T. A. and S. O. were employees of Daiichi Sankyo Co., Ltd.
Truitt 2010	**Risk Of Bias**	**Author Judgement**
Random Sequence Generation (Selection Bias)	Low Risk	Randomized, double-blind, double dummy, placebo- and active comparator-controlled study
Allocation Concealment (Selection Bias)	Low risk	Stratified randomization
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	High Risk	441 patients were randomized out of which 179 patients completed the study. Hence the attrition rate was 40.58%
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	This study was funded by Daiichi Sankyo, Inc. H.S.C., D.M., J.T., and A.C.W. are employees of Daiichi Sankyo, Inc



Supplementary Figure 1: Forest plot highlighting the impact of (a) Standard dose rivoglitazone on serum hsCRP compared to placebo; (b) High dose rivoglitazone on serum hsCRP compared to placebo; (c) Standard dose rivoglitazone on serum hsCRP compared to pioglitazone; (d) High dose rivoglitazone on serum hsCRP compared to pioglitazone; (e): Standard dose rivoglitazone on the occurrence of severe adverse events (SAEs) compared to placebo; (f) High dose rivoglitazone on the occurrence of SAEs compared to placebo; (g): Standard dose rivoglitazone on the occurrence of severe adverse events (SAEs) compared to active control group; (h) High dose rivoglitazone on the occurrence of SAEs compared to active control group