

A Meta-analysis Comparing the Effect of Thiazolidinediones on Cardiovascular Risk Factors

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Background: In patients with type 2 diabetes mellitus, all therapeutic options should be evaluated for their effect on cardiovascular risk factors, in addition to glycemic control. We conducted a meta-analysis of randomized controlled trials of pioglitazone hydrochloride and rosiglitazone maleate in patients with type 2 diabetes to evaluate their effect on glycemic control, lipids, blood pressure, and weight.

Methods: Randomized controlled trials of patients with type 2 diabetes that compared pioglitazone or rosiglitazone with placebo for 12 weeks were included. Primary analysis was to compare thiazolidinediones with placebo. Secondary analysis was to identify whether treatment with pioglitazone differed from rosiglitazone in any outcomes. We calculated weighted mean differences and 95% confidence intervals.

Results: Twenty-three randomized controlled trials were identified. Both thiazolidinediones demonstrated similar hemoglobin A_{1c} level decreases of 1.0% to 1.5% and similar increases in body weight of approximately 3.0 kg. Pioglitazone significantly lowered triglyceride level (−40 mg/dL [−0.45 mmol/L]; 95% confidence interval [CI], −53 to −26 mg/dL [−0.60 to −0.29 mmol/L]), increased high-density lipoprotein cholesterol (HDL-C)

level (+4.6 mg/dL [+0.12 mmol/L]; 95% CI, 3.6 to 5.5 mg/dL [0.09 to 0.14 mmol/L]), and showed neutral effect on low-density lipoprotein cholesterol (LDL-C) and total cholesterol levels. Rosiglitazone significantly increased HDL-C level (+2.7 mg/dL [+0.07 mmol/L]; 95% CI, 2.0 to 3.4 mg/dL [0.05 to 0.09 mmol/L]), but increased LDL-C level (+15 mg/dL [+0.39 mmol/L]; 95% CI, 13 to 17 mg/dL [0.34 to 0.44 mmol/L]), total cholesterol level (+21 mg/dL [+0.54 mmol/L]; 95% CI, 18 to 25 mg/dL [0.47 to 0.65 mmol/L]), and demonstrated neutral effect on triglyceride level (−1.1 mg/dL [−0.12 mmol/L]; 95% CI, −14 to 12 mg/dL [−0.16 to 0.14 mmol/L]). No data were available on pioglitazone and blood pressure. Rosiglitazone had a neutral effect on systolic (−0.7 mm Hg; 95% CI, −2.6 to 1.1 mm Hg) and diastolic (−0.8 mm Hg; 95% CI, −1.8 to 0.3) blood pressure.

Conclusions: Thiazolidinediones have similar effects on glycemic control and body weight. Pioglitazone produced a more favorable lipid profile. Head-to-head comparative trials as well as longer-term cardiovascular outcome studies are needed to determine whether there are differences in efficacy between the 2 thiazolidinediones.

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TYPE 2 DIABETES MELLITUS IS an increasingly common disease whose prevalence is closely aligned with the growing epidemic of obesity.¹ Diabetes affects nearly 16 million Americans and contributes to almost 200 000 deaths a year, primarily from cardiovascular disease (CVD).² Strategies that improve known cardiovascular risk factors in patients with diabetes are desirable if the increased risk of CVD is to be prevented. Because obesity is an independent risk factor for CVD³⁻⁶ as well as for diabetes,⁷ one might predict an increase in CVD as the obesity-induced diabetes epidemic spreads.¹

The results of the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that improved glycemic control, regardless of the pharmacological intervention (metformin, first and second generation sulfonylureas, or insulin) used to achieve the reduction in hemoglobin A_{1c}

(HbA_{1c}) level, can significantly reduce microvascular complications but fails to significantly alter the incidence of CVD.⁸ Since antihypertensive and lipid-lowering therapies have been shown to decrease the incidence of CVD in patients with type 2 diabetes,^{9,10} there is a compelling need for anti-diabetic medications that also address the problem of accelerated CVD through their impact on cardiovascular risk factors.

In the late 1990s, the insulin-sensitizing thiazolidinediones were approved for the treatment of type 2 diabetes mellitus in the United States. There are 2 drugs in this class: rosiglitazone maleate (Avandia; GlaxoSmithKline, Research Triangle Park, NC) and pioglitazone hydrochloride (Actos; Takeda Chemical Industries Ltd, Osaka, Japan). We conducted a meta-analysis of randomized controlled trials of pioglitazone and rosiglitazone in patients with type 2 diabetes to evaluate their effect on glycemic control, lipids, blood pressure, and weight.

METHODS

We identified the citations using a comprehensive search strategy developed by the National Institute for Clinical Excellence for identifying randomized controlled trials pertinent to the thiazolidinediones of interest (rosiglitazone and pioglitazone).^{11,12} We searched all electronic bibliographic databases from inception to January 2004: MEDLINE, Cochrane Controlled Trials Register, Cochrane database of systematic reviews, and National Health Service Centre for Reviews and Dissemination. In addition, we reviewed New Drug Application submissions from rosiglitazone and pioglitazone available on the Food and Drug Administration Web site and abstracts from recent meetings (ie, American Diabetes Association). Reference lists of all relevant articles also were checked. To be included, the citation had to meet the following 6 criteria: (1) was randomized controlled trial (blind or open), (2) enrolled at least 30 adults with type 2 diabetes, (3) evaluated the effect of rosiglitazone maleate (4 or 8 mg) or pioglitazone hydrochloride (30 or 45 mg) in monotherapy or in combination with other antidiabetic medication (eg, sulfonylureas, metformin, or insulin), (4) evaluated the effect of the drug on HbA_{1c} (lipids and weight were collected but were not a requirement for inclusion), (5) had a minimum treatment duration of 12 weeks, and (6) was published in English.

Two reviewers independently performed the screening of studies, selection, validation, data extraction, and the assessment of methodological quality. Disagreements were resolved by consensus. No studies were excluded on the basis of methodological quality.

The primary analysis was to compare of pioglitazone and rosiglitazone with placebo for all outcomes (HbA_{1c}, fasting blood glucose [FBG], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], total cholesterol, triglyceride, systolic and diastolic blood pressure, and weight). The secondary analysis was to identify whether treatment effects with pioglitazone differed from that with rosiglitazone in any outcomes.

We calculated the weighted mean difference (WMD) and 95% confidence interval (CI) for all variables. The treatment effects were calculated as mean changes from baseline for thiazolidinedione treatment minus those of placebo for each outcome. A fixed-effects model approach was used, but in case of heterogeneity, a random-

effects model was used. Heterogeneity was diagnosed using the χ^2 test at a $P \leq .10$.

To develop parsimonious meta-regression models, we used simple linear regression to identify significant association between clinical outcomes and their baseline values. Analyses were performed with the statistical package Stata (version 6; Stata Corp, College Station, Tex), using the "metan" and "metareg" routines.¹³ The routine metareg extends a random effects meta-analysis to estimate the extent to which 1 covariate (in this case pioglitazone or rosiglitazone) explains heterogeneity in the treatment effects.¹³

RESULTS

Twenty-three randomized controlled trials met the inclusion criteria.¹⁴⁻³⁶ The design of each trial included is presented in **Table 1**. More than 3000 subjects were enrolled in 10 randomized controlled trials evaluating pioglitazone and more than 5000 subjects were enrolled in studies evaluating rosiglitazone. The subjects enrolled in the pioglitazone and rosiglitazone trials were of similar age (56.6 vs 57.5 years) and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) (29.3 vs 29.7). At baseline, subjects in the pioglitazone trials had a slightly higher HbA_{1c} level (9.6% vs 9.2%; $P < .05$), triglyceride level (245 vs 211 mg/dL [2.77 vs 2.38 mmol/L]; $P < .05$), LDL-C level (127 vs 121 mg/dL [3.29 vs 3.13 mmol/L]; $P \geq .05$), and slightly lower HDL-C level (43.9 vs 45.1 mg/dL [1.14 vs 1.17 mmol/L]; $P \geq .05$). The median duration of treatment with the study drug was 16 and 26 weeks for pioglitazone and rosiglitazone, respectively. In most trials, subjects who were receiving prior oral antidiabetic medication were required to discontinue their use at the beginning of the run-in/washout phase. The median duration of the run-in/washout phase was 6 weeks for pioglitazone and 4 weeks for rosiglitazone. A minority of trials reported a weight maintenance strategy within their protocol.

The linear regression results were not significant between any clinical outcome and their respective baseline. Therefore, these variables were kept out of the meta-regression model.

GLYCEMIC CONTROL

The effects of thiazolidinediones on glycemic control, as measured by HbA_{1c} and fasting blood glucose, are presented in **Table 2** and **Table 3**. Both doses of pioglitazone hydrochloride (30 mg/d and 45 mg/d) when used as monotherapy significantly reduced HbA_{1c} level by -0.99% (95% CI, -1.32 to -0.66) and -1.21% (95% CI, -1.79 to -0.62) compared with placebo. The addition of pioglitazone hydrochloride (30 mg/d) to other antihyperglycemic agents (metformin or sulfonylureas) led to greater reductions in HbA_{1c} level by -1.16% (95% CI, -1.41 to -0.90) compared with placebo. Only 1 trial used the maximum dose of pioglitazone hydrochloride (45 mg) in combination with sulfonylurea (HbA_{1c}, -1.56% ; 95% CI, -1.96 to -1.16). Both doses of rosiglitazone maleate (4 mg/d and 8 mg/d), when used as monotherapy, resulted in significant reductions in HbA_{1c} level by -0.90% (95% CI, -1.42% to -0.38%) and -1.50% (95% CI, -1.75% to -1.24%), respectively, compared with placebo. The combination of rosiglitazone maleate with metformin, with sulfonylureas or with insulin also resulted in greater reductions in HbA_{1c} level compared with placebo at low (4 mg/d) ($\Delta = -1.05\%$; 95% CI, -1.19% to -0.90%) and high (8 mg/d) ($\Delta = -1.26\%$; 95% CI, -1.48% to -1.04%) doses. In the pioglitazone hydrochloride monotherapy studies (30 mg/d and 45 mg/d combined), fasting plasma glucose (FBG) concentration decreased on average by 51 mg/dL (-2.83 mmol/L) (95% CI, -62 to -39 mg/dL [-3.44 to -2.16 mmol/L]). When pioglitazone was added to another antidiabetic agent, FBG concentration fell approximately 47 mg/dL (-2.61 mmol) (95% CI, -55 to -39 mg/dL [-3.05 to -2.16 mmol/L]). Rosiglitazone, as monotherapy, decreased FBG level by 57 mg/dL (-3.16 mmol/L) (95% CI, -89 to -25 mg/dL [-4.94 to -1.39 mmol/L]) when used as combination therapy, rosiglitazone reduced the FBG by 50 mg/dL (-2.78 mmol/L) (95% CI, -55 to -45 mg/dL [-3.05 to -2.50 mmol/L]).

Overall, the meta-analysis showed a significant reduction in HbA_{1c} and FBG levels for all

Table 1. Summary of Included Trials

Source	Design	Diet	Baseline Values						Groups
			Age, y	HbA _{1c} , %	LDL-C, mg/dL	TG, mg/dL	HDL-C, mg/dL	BMI	
Pioglitazone									
Kaneko et al, ¹⁵ 1997 (N = 273)	RDBP for 12 wk; run-in/washout: 4 wk; previously diet controlled	No change	56	9.3	NR	150	50	25	Placebo; P 15 mg/d; P 30 mg/d; P 45 mg/d
Aronoff et al, ¹⁴ 2000 (N = 408)	RDBP for 26 wk; run-in/washout: 8 wk; 69% stopped OHA prior to entry	None	54	10.3	134	261	41	NR	Placebo; P 7.5 mg/d; P 15 mg/d; P 30 mg/d; P 45 mg/d
Scherbaum and Goke, ²³ 2002 (N = 251)	RDBP for 26 wk; run-in/washout: 10 wk; 61% stopped OHA prior to entry	DNSG EASD*	59	8.9	NR	NR	NR	29	Placebo; P 30 mg/d
Herz et al, ²¹ 2003 (N = 297)	RDBP for 16 wk; run-in/washout: 3-5 wk; previously diet controlled	No change	58	7.5	NR	168	46	31	Placebo; P 30 mg/d; P 45 mg/d
Rosenblatt et al, ²² 2001 (N = 197)	RDBP for 16 wk; run-in/washout: 6 wk; 60% stopped OHA prior to entry	None	54	10.5	131	318	40	31	Placebo; P 30 mg/d
Einhorn et al, ¹⁸ 2000 (N = 328)	RDBP for 16 wk; run-in/washout: 3-6 wk; 30% stopped OHA prior to entry	Weight maintenance	56	9.8	119	299	42	32	Placebo + Met; P 30 mg/d + Met
Kaneko et al, ¹⁶ 1997 (N = 149)	RDBP for 12 wk; run-in/washout: 4 wk; none stopped OHA prior to entry	No change	58	9.8	NR	147	51	24	Placebo + SU; P 30 mg/d + SU
Kaneko et al, ¹⁷ 1997 (N = 276)	RDBP for 12 wk; run-in/washout: 4 wk; none stopped OHA prior to entry	No change	57	9.9	NR	150	50	24	Placebo + SU; P 15 mg/d + SU; P 30 mg/d + SU; P 45 mg/d + SU
Kipnes et al, ²⁰ 2001 (N = 560)	RDBP for 16 wk; run-in/washout: 3-6 wk; 13% stopped OHA prior to entry	Weight maintenance	57	9.9	125	263	42	32	Placebo + SU; P 15 mg/d + SU; U; P 30 mg/d + SU
Rosenstock et al, ¹⁹ 2002 (N = 566)	RDBP for 16 wk; run-in/washout: 3-6 wk; 12% stopped OHA prior to entry	No change	57	9.8	127	245	43	33	Placebo + Ins; P 15 mg/d + Ins; P 30 mg/d + Ins
Rosiglitazone									
Lebovitz et al, ²⁵ 2001 (N = 493)	RDBP for 26 wk; run-in/washout: 4 wk; 73% stopped OHA prior to entry	Weight maintenance	60	8.9	122	NR	42	30	Placebo; R 2 mg/d; R 4 mg/d
Phillips et al, ²⁶ 2001 (N = 959)	RDBP for 26 wk; run-in/washout: 4-6 wk; 75% stopped OHA prior to entry	NR	57	8.9	127	176	43	30	Placebo; R 4 mg/d; R 2 mg bid; R 8 mg/d; R 4 mg bid
Patel et al, ²⁸ 1999 (N = 380)	RDBP for 12 wk; run-in/washout: 4 wk; ? % stopped OHA prior to entry (not given)	Weight maintenance	58	9.0	126	209	48	29	Placebo; R 0.1 mg/d; R 0.5 mg/d; R 2 mg/d; R 4 mg/d
Xixing et al, ²⁹ 2001 (N = 554)	RDBP for 24 wk; run-in/washout not given; ? % stopped OHA prior to entry (not given)	NR	NR	9.8	NR	NR	NR	NR	Placebo + SU; R 4 mg/d + SU; R 8 mg/d + SU
Wolffenbittel et al, ³¹ 2000 (N = 574)	RDBP for 26 wk; run-in/washout: 2-4 wk; ? % stopped OHA prior to entry (not given)	NR	61	9.2	136	168	44	28	Placebo + SU; R 2 mg/d + SU; R 4 mg/d + SU
Barnett et al, ²⁷ 2003 (N = 177)	RDBP for 26 wk; run-in/washout (not given); ? % stopped OHA prior to entry (not given)	NR	54	9.1	114	177	47	27	Placebo + SU; R 8 mg/d + SU
Vongthavaravat et al, ³² 2002 (N = 348)	ROL for 20 wk; run-in/washout: 2-4 wk; ? % stopped OHA prior to entry (not given)	Weight maintenance	55	9.0	130	NR	42	27	SU alone; R 4 mg/d + SU
Gomez-Perez et al, ³⁰ 2002 (N = 116)	RDBP for 26 wk; run-in/washout: 10 wk; 40% stopped OHA prior to entry	NR	53	9.9	110	210	50	28	Placebo + Met; R 4 mg/d + Met; R 8 mg/d + Met
Fonseca et al, ³³ 2000 (N = 348)	RDBP for 26 wk; run-in/washout: 4-7 wk; ? % stopped OHA prior to entry (not given)	Weight maintenance	58	8.8	115	232	45	30	Placebo + Met; R 4 mg/d + Met; R 8 mg/d + Met
Raskin et al, ²⁴ 2001 (N = 319)	RDBP for 26 wk; run-in/washout: 8 wk; all subjects receiving insulin monotherapy prior to entry	NR	57	9.0	122	226	46	32	Placebo + Ins; R 4 mg/d + Ins; R 8 mg/d + Ins
Hutchman et al, ³⁶ 2000 (N = 346)	RDBP for 26 wk; run-in/washout: 4 wk; approximately 30% stopped OHA prior to entry	NR	60	9.1	122	243	45	30	Placebo + SU; R 2 mg/d + SU; R 4 mg/d + SU
Moran et al, ³⁴ 2000 (N = 309)	RDBP for 26 wk; run-in/washout: 4 wk; approximately 50% stopped OHA prior to entry	NR	58	9.2	126	261	44	30	Placebo + SU; R 4 mg/d; R 4 mg/d + SU
Lowry et al, ³⁵ 2000 (N = 322)	RDBP for 26 wk; run-in/washout: 4-10 wk; approximately 50% stopped OHA prior to entry	NR	59	9.2	107	227	46	30	Placebo + Met; R 8 mg/d; R 8 mg/d + Met

Abbreviations: bid, twice daily; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; Ins, insulin; LDL-C, low-density lipoprotein cholesterol; Met, metformin; RDBP, randomized, double-blind, placebo-controlled; OHA, oral hypoglycemic agent; NR, not reported; P, pioglitazone hydrochloride; R, rosiglitazone maleate; ROL, randomized open label; SU, sulfonyleureas; TG, triglycerides.

SI conversions: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

*DNSG EASD indicates the nutritional recommendations of the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes.

Table 2. Mean Change in HbA_{1c} Level

Source	Treatment Length, wk	Control, (n) Mean ± SD % Change in HbA _{1c} From Baseline	Treatment, (n) Mean ± SD % Change in HbA _{1c} From Baseline	Placebo Subtracted Effect, Change in HbA _{1c} , % (95% CI)
Pioglitazone monotherapy				
Aronoff et al ¹⁴ (P 30 mg/d vs placebo)	26	(79) +0.7 ± 1.5	(85) -0.3 ± 1.6	-1.0 (-1.5 to -0.5)
Aronoff et al ¹⁴ (P 45 mg/d vs placebo)	26	(79) +0.7 ± 1.5	(76) -0.9 ± 1.6	-1.6 (-2.1 to -1.1)
Herz et al ²¹ (P 30 mg/d vs placebo)	16	(99) -0.2 ± 1.2	(99) -0.8 ± 1.3	-0.6 (-0.9 to -0.3)
Herz et al ²¹ (P 45 mg/d vs placebo)	16	(99) -0.2 ± 1.2	(99) -0.9 ± 1.3	-0.7 (-1.0 to -0.4)
Scherbaum and Goke ²³ (P 30 mg/d vs placebo)	26	(76) -0.3 ± 1.0	(76) -1.1 ± 1.3	-0.7 (-1.1 to -0.4)
Rosenblatt et al ²² (P 30 mg/d vs placebo)	23	(93) +0.7 ± 1.6	(100) -0.6 ± 1.7	-1.4 (-1.8 to -0.9)
Kaneko et al ¹⁵ (P 30 mg/d vs placebo)	12	(55) +0.4 ± 0.9	(54) -1.0 ± 1.2	-1.4 (-1.8 to -1.0)
Kaneko et al ¹⁵ (P 45 mg/d vs placebo)	12	(55) +0.4 ± 0.9	(49) -1.0 ± 1.6	-1.4 (-1.9 to -0.9)
Pioglitazone combination therapy				
Rosenstock et al ¹⁹ (P 30 mg/d + Ins vs Ins + placebo)	16	(177) -0.3 ± 1.1	(185) -1.3 ± 1.1	-1.0 (-1.2 to -0.8)
Einhorn et al ¹⁸ (P 30 mg/d + Met vs Met + placebo)	16	(160) +0.2 ± 1.3	(168) -0.7 ± 1.3	-0.8 (-1.1 to -0.6)
Kaneko et al ¹⁷ (P 30 mg/d + SU vs SU + placebo)	12	(59) +0.5 ± 0.9	(52) -1.2 ± 1.2	-1.6 (-2.0 to -1.2)
Kaneko et al ¹⁷ (P 45 mg/d + SU vs SU + placebo)	12	(59) +0.5 ± 0.9	(58) -1.1 ± 1.3	-1.6 (-2.0 to -1.2)
Kaneko et al ¹⁶ (P 30 mg/d + SU vs SU + placebo)	12	(49) -0.1 ± 1.2	(56) -1.2 ± 1.3	-1.2 (-1.6 to -0.7)
Kipnes et al ²⁰ (P 30 + SU vs SU + placebo)	16	(182) +0.1 ± 1.5	(182) -1.2 ± 1.5	-1.3 (-1.6 to -1.0)
Rosiglitazone monotherapy				
Lebovitz et al ²⁵ (R 4 mg/d vs placebo)	26	(158) +0.9 ± 1.9	(169) -0.6 ± 3.0	-1.5 (-2.0 to -1.0)
Phillips et al ²⁶ (R 2 mg bid vs placebo)	26	(173) +0.8 ± 1.1	(187) -0.1 ± 1.4	-0.9 (-1.2 to -0.6)
Phillips et al ²⁶ (R 4 mg bid vs placebo)	26	(173) +0.8 ± 1.1	(186) -0.7 ± 1.4	-1.5 (-1.8 to -1.2)
Patel et al ²⁸ (R 2 mg bid vs placebo)	12	(74) +0.3 ± 1.1	(74) -0.1 ± 1.1	-0.4 (-0.8 to 0.0)
Rosiglitazone combination therapy				
Barnett et al ²⁷ (R 8 mg/d + SU vs SU + placebo)	26	(87) +0.3 ± 1.7	(84) -1.2 ± 1.7	-1.4 (-1.9 to -0.9)
Raskin et al ²⁴ (R 4 mg/d + Ins vs Ins + placebo)	26	(104) +0.1 ± 1.0	(106) -0.6 ± 1.1	-0.7 (-1.0 to -0.4)
Raskin et al ²⁴ (R 8 mg/d+Ins vs Ins+placebo)	26	(104) +0.1 ± 1.0	(103) -1.2 ± 1.1	-1.3 (-1.6 to -1.0)
Vongthavaravat et al ³² (R 2 mg bid + SU vs SU)	26	(170) +0.1 ± 1.3	(164) -1.1 ± 1.4	-1.2 (-1.5 to -0.9)
Woffenbittel et al ³¹ (R 4 mg/d + SU vs SU + placebo)	26	(192) +0.2 ± 1.1	(183) -0.9 ± 1.1	-1.1 (-1.3 to -0.9)
Xixing et al ²⁹ (R 4 mg/d + SU vs SU + placebo)	26	(105) -0.4 ± 1.2	(215) -1.4 ± 1.2	-1.0 (-1.3 to -0.7)
Xixing et al ²⁹ (R 8 mg/d + SU vs SU + placebo)	26	(105) -0.4 ± 1.2	(210) -1.9 ± 1.4	-1.5 (-1.8 to -1.2)
Moran et al ³⁴ (R 4 mg/d + SU vs SU + placebo)	26	(99) +0.9 ± 1.2	(98) -0.5 ± 1.1	-1.4 (-1.7 to -1.1)
Hutchmann et al ³⁶ (R 4 mg/d + SU vs SU + placebo)	26	(115) +0.6 ± 1.6	(116) -0.3 ± 1.8	-0.9 (-1.4 to -0.5)
Fonseca et al ³³ (R 4 mg/d + Met vs Met + placebo)	26	(113) +0.5 ± 1.2	(116) -0.6 ± 1.0	-1.0 (-1.3 to -0.7)
Fonseca et al ³³ (R 8 mg/d + Met vs Met + placebo)	26	(113) +0.5 ± 1.2	(110) -0.8 ± 1.2	-1.2 (-1.5 to -0.9)
Gomez-Perez et al ³⁰ (R 4 mg/d + Met vs Met + placebo)	26	(34) +0.3 ± 1.5	(35) -0.7 ± 1.5	-1.0 (-1.7 to -0.3)
Gomez-Perez et al ³⁰ (R 8 mg/d + Met vs Met + placebo)	26	(34) +0.3 ± 1.5	(36) -1.2 ± 1.9	-1.5 (-2.3 to -0.7)
Lowry et al ³⁵ (R 8 mg/d + Met vs Met + placebo)	26	(106) +0.1 ± 1.2	(103) -0.7 ± 1.3	-0.8 (-1.1 to -0.5)

Abbreviations: bid, twice daily; CI, confidence interval; HbA_{1c}, hemoglobin A_{1c}; Ins, insulin; Met, metformin; P, pioglitazone hydrochloride; R, rosiglitazone maleate; SU, sulfonylureas.

thiazolidinedione doses whether used as monotherapy or in combination with other antihyperglycemic agents. The mean HbA_{1c} level at baseline was not significantly related to the observed HbA_{1c} level reduction at end of treatment. Mean baseline HbA_{1c} values were similar across studies, with a mean ± SD of 9.3 ± 0.63; the small variability explains why the relationship between baseline and end of treatment values was not significant at the study level, when a stronger relationship has been consistently observed within studies at the individual patient level. The meta-regression found that the drug grouping did not explain the heterogeneity (*P* = .84).

LIPIDS EFFECT

While both thiazolidinediones had similar effects on glycemic control, pioglitazone showed a neutral to beneficial impact on serum lipid levels, whereas rosiglitazone increased LDL-C, total cholesterol, and HDL-C levels and had a neutral effect on triglyceride level. The meta-regression found that the drug grouping was a significant predictor of heterogeneity for all lipid effects (*P* < .001); therefore, the results were presented and analyzed separately. Rosiglitazone, when used as monotherapy or in combination with other antihyperglycemic agents, was associated with a significant increase in LDL-C level (+15 mg/dL [+0.39 mmol/L]; 95% CI, 13 to 18

mg/dL [0.34 to 0.47 mmol/L]), whereas pioglitazone showed a neutral effect on LDL-C level (-0.4 mg/dL [-0.01 mmol/L]; 95% CI, -5 to 4 mg/dL [-0.13 to 0.10 mmol/L]). None of the pioglitazone studies showed a significant difference compared with placebo on LDL-C, whereas every rosiglitazone study showed a statistically significant increase in LDL-C level (Figure 1). Rosiglitazone treatment had no significant effect on the fasting plasma triglyceride concentration, whereas pioglitazone therapy significantly decreased the fasting triglyceride level (-40 mg/dL [-0.45 mmol]; 95% CI, -53 to -26 mg/dL [-0.60 to -0.29 mmol/L]). None of the rosiglitazone trials showed a statistically significant change in fasting plasma tri-

glyceride level, whereas 5 of 8 trials with pioglitazone demonstrated a statistically significant reduction in triglyceride level (**Figure 2**). Both thiazolidinediones significantly increased the HDL-C concentration (pioglitazone: $\Delta = +4.55$ mg/dL [$+0.12$ mmol/L] with 95% CI, 3.61 to 5.48 [0.09 to 0.14 mmol/L]; rosiglitazone: $\Delta = +2.71$ mg/dL [$+0.07$ mmol/L] with 95% CI, 2.01 to 3.42 mg/dL [0.05 to 0.09 mmol/L]) (**Figure 3**). Pioglitazone had no effect on total cholesterol (-0.1 mg/dL [-0.003 mmol/L]; 95% CI, -5 to 5 mg/dL [-0.13 to 0.13 mmol/L]), whereas rosiglitazone significantly increased the total cholesterol ($+21.3$ mg/dL [0.55 mmol/L]; 95% CI, 17.7 to 24.9 mg/dL [0.46 to 0.64 mmol/L]) (**Figure 4**). The treatment effects of pioglitazone on fasting plasma triglyceride, LDL-C, and total cholesterol levels were statistically significantly different than those of rosiglitazone (all $P < .01$).

BLOOD PRESSURE EFFECT

Only 5 trials were included in this outcome analysis. None of the pioglitazone trials reported blood pressure as an outcome. There were no significant differences between rosiglitazone and placebo in changes in systolic (-0.7 mm Hg; 95% CI, -2.6 to 1.1 mm Hg) or diastolic blood pressure (-0.8 mm Hg; 95% CI, -1.8 to 0.3 mm Hg).

WEIGHT EFFECT

Only 11 of 23 trials were included in this outcome analysis, since most trials did not report variance around the weight change value. Within 6 months of initiating therapy with thiazolidinediones, the average weight gain was $+2.7$ kg (95% CI, 1.8 to 3.7 kg). The studies were heterogeneous ($\chi^2 = 111.47$; $P < .001$), but drug grouping was not a predictor of the heterogeneity ($P > .10$). Additional analyses were done to examine the contribution of the Japanese trials to the heterogeneity. The Japanese trials⁵⁻⁷ included subjects with an average BMI of 25, whereas most studies outside of Japan were conducted in obese individuals (BMI = 30 in average for most studies). For Japanese trials only, the average weight gain was $+0.73$ kg (95% CI, 0.23 to 1.23 kg) and homogeneous ($\chi^2 = 0.67$; $P < .71$), whereas the non-

Table 3. Metabolic Effects of Thiazolidinediones*

Thiazolidinedione	No. of Studies	Weighted Mean Difference (95% CI)
Effect on glycemic control, HbA _{1c} , %		
Pioglitazone, 30 mg (monotherapy)	5	-0.99 (-1.32 to -0.66)
Pioglitazone, 45 mg (monotherapy)	3	-1.21 (-1.79 to -0.62)
Pioglitazone, 30 mg (combination therapy)	5	-1.16 (-1.41 to -0.90)
Pioglitazone, 45 mg (combination therapy)	1	-1.56 (-1.96 to -1.16)
Rosiglitazone, 4 mg (monotherapy)	3	-0.90 (-1.42 to -0.38)
Rosiglitazone, 8 mg (monotherapy)	1	-1.50 (-1.75 to -1.24)
Rosiglitazone, 4 mg (combination therapy)	8	-1.05 (-1.19 to -0.90)
Rosiglitazone, 8 mg (combination therapy)	6	-1.26 (-1.48 to -1.04)
Effect on glycemic control, FBG, mg/dL		
Pioglitazone, 30 mg (monotherapy)	4	-40.98 (-50.6 to -31.3)
Pioglitazone, 45 mg (monotherapy)	2	-53.9 (-73.5 to -34.4)
Pioglitazone, 30 mg (combination therapy)	5	-47.2 (-55.1 to -39.2)
Pioglitazone, 45 mg (combination therapy)	1	-47.2 (-61.7 to -32.7)
Rosiglitazone, 4 mg (monotherapy)	2	-56.9 (-88.8 to -25.2)
Rosiglitazone, 4 mg (combination therapy)	7	-45.3 (-50.5 to -40.2)
Rosiglitazone, 8 mg (combination therapy)	5	-55.1 (-62.4 to -47.9)
Effect on TG, mg/dL		
Pioglitazone	8	-39.71 (-53.0 to -26.4)
Rosiglitazone	9	-1.06 (-14.5 to 12.3)
Effect on HDL-C, mg/dL		
Pioglitazone	9	+4.55 (3.61 to 5.48)
Rosiglitazone	11	+2.71 (2.01 to 3.42)
Effect on LDL-C, mg/dL		
Pioglitazone	5	-0.37 (-4.68 to 3.94)
Rosiglitazone	11	+15.28 (13.0 to 17.5)
Effect on TC, mg/dL		
Pioglitazone	6	-0.09 (-5.33 to 5.14)
Rosiglitazone	11	21.3 (17.7 to 24.9)
Effect on SBP, mm Hg		
Pioglitazone	NA	NA
Rosiglitazone	5	-0.72 (-2.58 to 1.13)
Effect on DBP, mm Hg		
Pioglitazone	NA	NA
Rosiglitazone	5	-0.75 (-1.78 to 0.28)
Effect on weight, kg		
Pioglitazone and rosiglitazone	11	2.71 (1.76 to 3.66)

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

SI conversions: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert glucose to millimoles per liter, multiply by 0.0555; to convert triglycerides to millimoles per liter, multiply by 0.0113.

*More than 1 comparison of the study drugs (pioglitazone hydrochloride and rosiglitazone maleate) may be from the same study.

Japanese trials resulted in a $+3.3$ kg weight gain (95% CI, 2.5 to 4.2 kg) and remained heterogeneous ($\chi^2 = 43.54$; $P < .001$).

COMMENT

Type 2 diabetes mellitus is more than a disease of glucose metabolism, being associated with a number of metabolic abnormalities, including obesity, insulin resistance, hyperinsulinemia, increased waist circumference and visceral adipose tissue, hypertriglyceridemia, low HDL-C level, small dense LDL-C particles,

and high blood pressure.^{37,38} These abnormalities typically occur in clusters as part of the insulin resistance syndrome (the metabolic syndrome), which precede and predict the development of type 2 diabetes.³⁹ Since all of these abnormalities are recognized risk factors for CVD, it is not surprising that individuals with the insulin resistance syndrome, with or without type 2 diabetes, are at increased risk of CVD.⁴⁰⁻⁴³

Because 80% of patients with type 2 diabetes have the metabolic syndrome,⁴⁴ its components are appropriate targets to evaluate the ben-

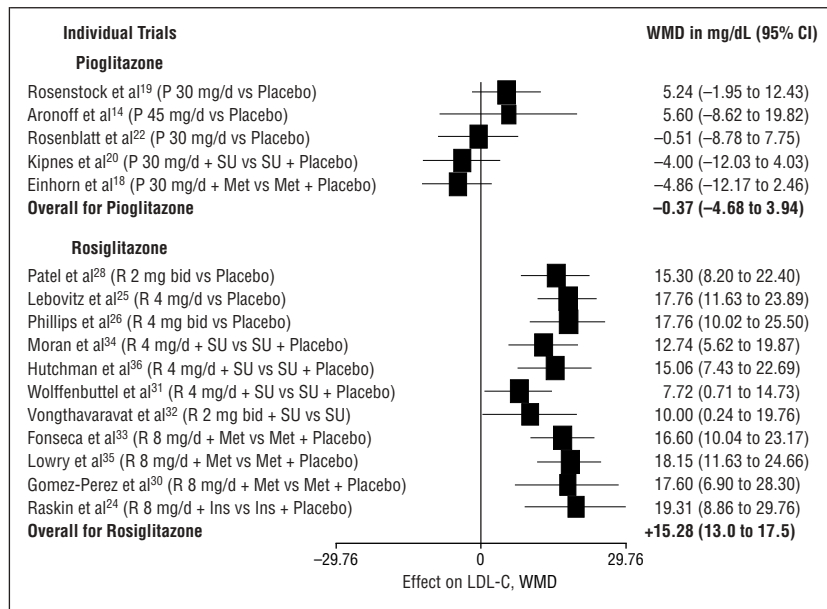


Figure 1. Effect of pioglitazone hydrochloride (P) or rosiglitazone maleate (R) vs placebo on low-density lipoprotein cholesterol (LDL-C) in patients with type 2 diabetes. To convert cholesterol to millimoles per liter, multiply by 0.0259. bid Indicates twice daily; CI, confidence interval; Ins, insulin; Met, metformin; SU, sulfonylureas; WMD, weighted mean difference.

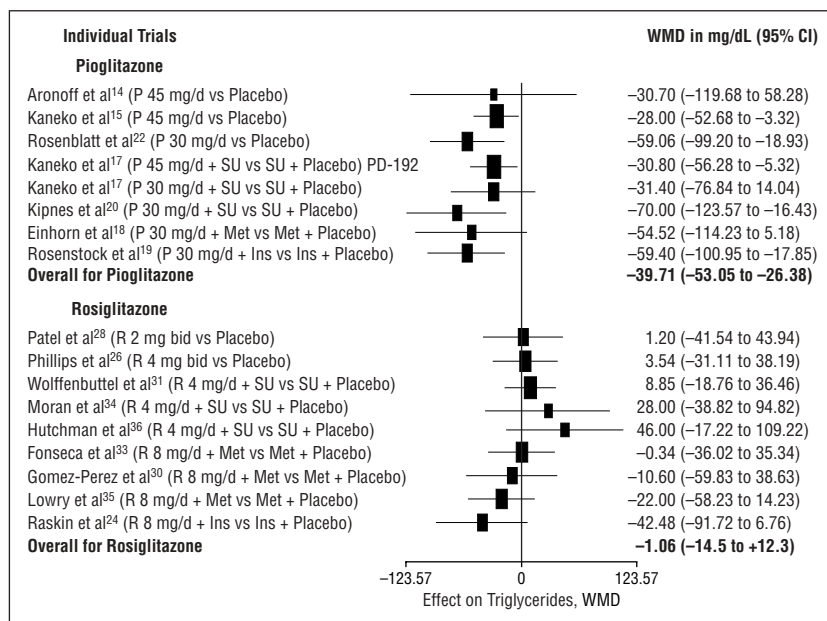


Figure 2. Effect of pioglitazone hydrochloride (P) or rosiglitazone maleate (R) vs placebo on triglycerides in patients with type 2 diabetes. To convert triglycerides to millimoles per liter, multiply by 0.0113. bid Indicates twice daily; CI, confidence interval; Ins, insulin; Met, metformin; SU, sulfonylureas; WMD, weighted mean difference.

efits of emerging therapies for type 2 diabetes.

The thiazolidinediones represent the newest class of drugs introduced into the United States for the treatment of type 2 diabetes mellitus. In this meta-analysis, we have evaluated the effects of pioglitazone and rosiglitazone on the following components of the insulin resistance syndrome: glycemia, triglycer-

ides, total cholesterol, LDL-C, HDL-C, blood pressure, and body weight. Both thiazolidinediones produced similar decreases in HbA_{1c} level of -1.0% to -1.5% and similar increases in body weight of approximately +3.0 kg. In contrast, pioglitazone had a more favorable effect on the plasma lipid profile, producing a significant reduction in plasma triglyceride levels compared with the

neutral effect of rosiglitazone on triglyceride level. Plasma levels of total cholesterol and LDL-C were significantly increased by rosiglitazone, whereas no changes in these lipid fractions were produced by pioglitazone. Plasma HDL-C concentration increased to a similar extent with both agents. The mechanism responsible for these beneficial effects of pioglitazone have yet to be established but may result from its modest agonistic effect on the peroxisome proliferator-activated receptor- α .⁴⁵ It also remains to be established whether these beneficial effects of pioglitazone on plasma lipid levels are sufficient to lower the risk of CVD. In addition, whether pioglitazone is superior to rosiglitazone in lipid lowering has not been tested in a head-to-head randomized trial.

Although the effect of both thiazolidinediones to increase body weight has raised some concern, many studies have demonstrated an inverse relationship between body weight and HbA_{1c}.^{25,28,46-49} Thus, the greater the increase in body weight, the greater the reduction in HbA_{1c} level. Moreover, despite the weight gain, pioglitazone reduced plasma triglyceride level, raised HDL-C level, and had a neutral effect on total cholesterol and LDL-C levels. Despite increased body weight, rosiglitazone therapy had a neutral effect on diastolic and systolic blood pressure, and both thiazolidinediones have been shown to reduce the blood pressure in hypertensive patients with type 2 diabetes.^{50,51} The weight gain associated with thiazolidinediones is therefore unlike the weight gain associated with increased caloric intake.⁵² The latter is associated with the development of insulin resistance and deterioration in glycemic control, a worsening of the dyslipidemia, and a rise in blood pressure.⁵³ Moreover, the thiazolidinediones have many in vivo and in vitro beneficial effects on a variety of measures of atherosclerosis^{52,54,55} and have been shown to slow progression of carotid intimal thickness^{56,57} and coronary stent restenosis.⁵⁸⁻⁶⁰ Nevertheless, the impact of this weight gain over many years can only be answered with long-term follow-up trials.

Finally, this meta-analysis should not be used to judge the ability of either

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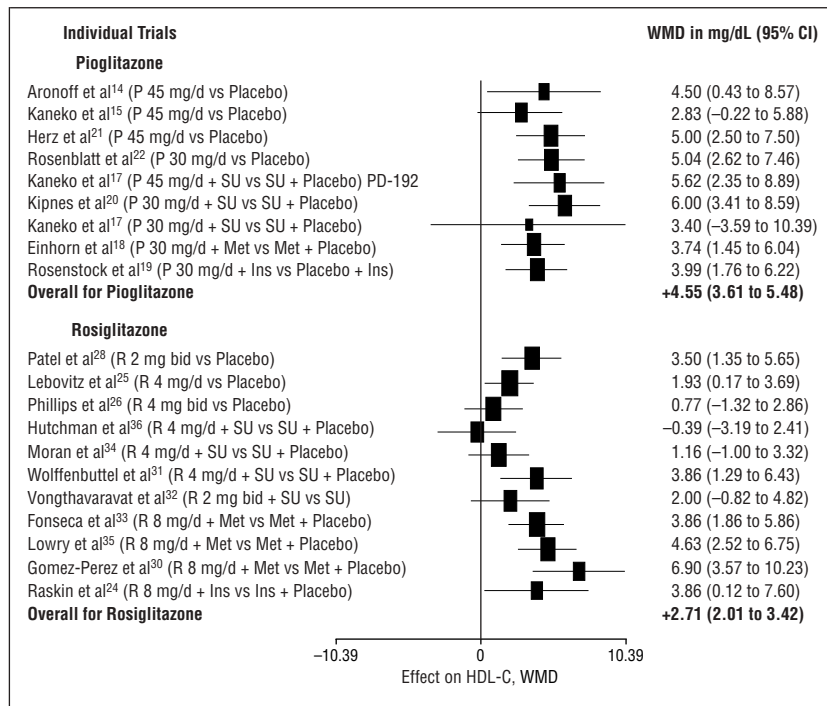


Figure 3. Effect of pioglitazone hydrochloride (P) or rosiglitazone maleate (R) vs placebo on high-density lipoprotein cholesterol (HDL-C) in patients with type 2 diabetes. To convert cholesterol to millimoles per liter, multiply by 0.0259. bid Indicates twice daily; CI, confidence interval; Ins, insulin; Met, metformin; SU, sulfonylureas; WMD, weighted mean difference.

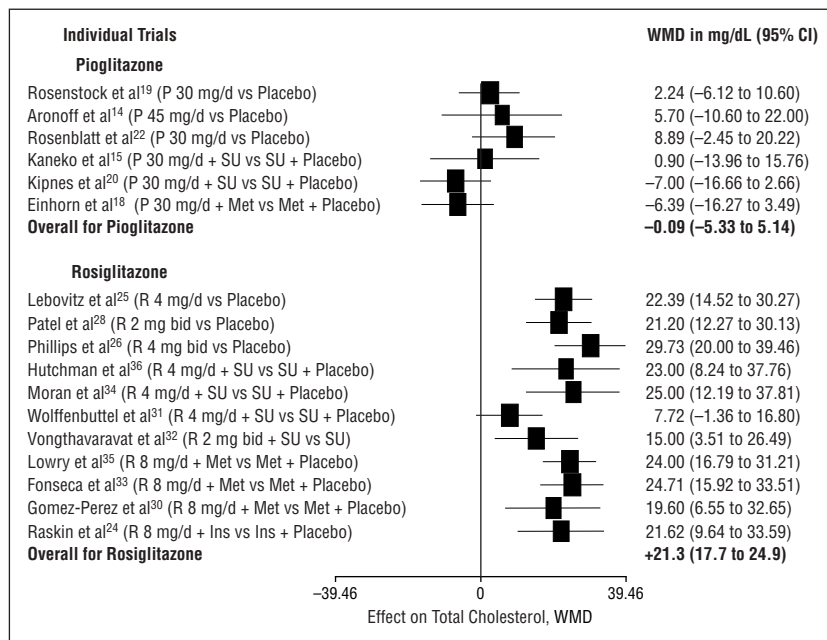


Figure 4. Effect of pioglitazone hydrochloride (P) or rosiglitazone maleate (R) vs placebo on total cholesterol in patients with type 2 diabetes. To convert cholesterol to millimoles per liter, multiply by 0.0259. bid Indicates twice daily; CI, confidence interval; Ins, insulin; Met, metformin; SU, sulfonylureas; WMD, weighted mean difference.

thiazolidinediones to reduce the incidence of cardiovascular events in patients with type 2 diabetes. The long-term effects of pioglitazone and rosiglitazone on cardiovascular morbidity and mortality currently are being evaluated in several large randomized con-

trolled trials: ADOPT (A Diabetes Outcome Progression Trial),⁶¹ RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes), and PROACTIVE (Prospective Pioglitazone Clinical Trial in Macrovascular Events).

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