Drug Class Review on Thiazolidinediones

Final Report

EVIDENCE TABLES

May 2006

The Agency for Healthcare Research and Quality has not yet seen or approved this report

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Boucher M 2002, 2003 COHTA Report	"To evaluate the evidence that compares rosiglitazone or pioglitazone with other oral antidiabetic agends…, either when used alone or when added to non-thiazolidionedione agent in the treatment of type 2 diabetes"	1999-2001	RCTs comparing the efficacy of ROSI or PIO with other anti-diabetic agents Adults(>18y) with DM2 requiring drug therapy; ROSI or PIO, either as montherapy or add-on therapy to a non-TZD drug; No language restrictions	ROSI: 11 studies (3 full-text, 8 abstracts) PIO: 8 studies	RCTs only Primary outcomes A1c and FPG

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Boucher M 2002, 2003 COHTA Report	Discussed for each study in narrative	Treatment duration PIO: 12-268w ROSI: 12-148w	ROSI A1c: monotherapy: -0.08%, NSD compared glyburide or repaglinide Add-on therapy: -1.29% (p<0.05 compared to various other drugs) FPG: monotherapy: -0.62 mmol/l (p<0.05 when compared to glyburide or repaglinide) Add-on therapy: -2.82 mmol/l (p<0.05 when compared to various other drugs) Lipids: ROSI produced a larger increase from baseline in total-cholesterol., LDL, HDL compared to other anti-diabetic agents; NSD TG levels PIO A1c: monotherapy: -0.46%, NSD compared glyburide or repaglinide Add-on therapy: -1.29% (p<0.05 when compared to various other drugs) FPG: monotherapy (1 study): 0.89 mmol/l (p<0.05 when compared to or repaglinide) add-on therapy: -2.87 mmol/l (p<0.05 when compared to various other drugs) Lipids: PIo produced larger increase from baseline in HDL compared to other anti-diabetic agents; NSD for total-cholesterol and LDL; significant decrease from baseline in TG

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Subgroups	Adverse events
Boucher M 2002, 2003 COHTA Report	NR	Both drugs are generlaly well tolerated ROSI Anemia: Hb change -3.9 to 12 g/l; rarely led to clinical anemia; 2 withdrawals due to anemia Hypoglycemia: ROSI monotherapy; 0.5 to 1.0%; then used as add-on: 2.6 to 6.1%; particularly common when combined with insulin; 4 withdrawals due to hypoglycemica Weight: increased with ROSI; 0.7 to 5.3 kf; higher increases with insulin Edema: 2.5 to 3.5% o nmonotherapy; 10.8% when combined with gliclazide, 13.1 to 16.2% when combined with insulin Liver function: vast majority of subjects in trials maintained normal liver enzyme levels; no serious liver AEs noted PIO Anemia: small decreases in Hb (-0.48 g/dl compared to SU, $p<0.05$) and hematocrit; stabilied within 12 weeks; no pateint wethdrew due to anemia Hypoglycemia: uncommon; increased occurrence when used as add-on, especially with insulin; no withdrawals for hypoglycemia Liver function: vast majority of subjects in trials maintained normal liver enzyme levels; no serious liver AEs noted Weight: gains 0.95 to 3.6 kg; highest occurrence of edema when used with insulin BP: small decrease in SBP

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Chilcott J 2001 overlaps with HTA report; examines Pio only	"presents a systematic review of the published literature on the effectiveness of pioglitazone in the treatment of type 2 diabetes…"	1966 (or start of database) - 3/2001	At least 1 outcome measures had to involve the effects of PIO on glycemic control, CV risk factors, or Aes; intervention involved Pio alone or in combination with other antidiabetic drugs; the comparator was another antidiabetic drug or placebo; patients with type 2 diabetes; was a systematic review or RCT; patients received >=12w of study drug	11 studies ; total 2669 patients	RCTs only

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Chilcott J 2001 overlaps with HTA report; examines Pio only	All adult populations, mean age 54-58y; 80% white; higher BMI in US than Japanese studies; PIO dosage 7.5-45mg qd; most had run-in period	6 monotherapy 5 combination therapy	Monotherapy A1c: US studies: decrease up to 2.6% in drug-naïve, less in 7.5 mg qd No studies directly compared Pio with other antidiabetic drugs TG: decrease significantly with PIO in 1 study; FDA 2000 also indicates decrease (no statistics); at dosages >30 mg/d PIO associated with reductions in TG of 30-70 mg/dL; increase in placebo groups HDL: increased in all patient groups, more with higher dosage; NR in FDA 2000 Weight: consistent increase in weight (2 studies); difference from placebo group up to 4.3 kg; dose-related BP: No data Combined therapy A1c: decrease up to 1.6% ($p<0.01$) in 3 US studies TG: all studies showed decrease with 30 and 45 mg/d; $p<0.05$ with all 45 mg studies HDL: consistent increase in all studies, up to 5.8 mg/dL LDL: little data; NSD when reported Total cholesterol: little data; NSD when reported Weight: increased significantly ($p<0.01$), dose-related; up to 3.9 kg; greater increase with insulin or SU+PIO BP: few data; 1 study no change

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Subgroups	Adverse events
Chilcott J 2001 overlaps with HTA report; examines Pio only	FDA 2000: decrease in A1c greater in women than men in 2 studies NSD between < or >65y	Hepatotoxicity: FDA 2000: incidence of alanine aminitransferase levels >3 times upper limit normal: NSD PIO and placebo; pio 0.26%; NSD in 3 Japanese studies Edema: more frequent in PIO than placebo; overall 'figures' 6.6% Pio, 2.3% placebo (FDA 2000); japanese studies 1.55 to 11.7%, more common treatment than placebo groups Reduction in Hb: small decrease noted with PIO monotherapy; thought to be due to hemodolutoin; clinical anemia not a concern Cardiac effects: (FDA 2000): 1 report LVH and LBBB; new ECG finds NSD placebo or PIO grroups; in Japanese studies NS cardiab abnormalities with PIO Elevation creatine phosphokinase: FDA 2000: 7/1510 patients in treatment arms had increased CPK >10 times normal; placebo data NR; other studies reported 9.6% vs 2.8% placebo and 6.0% vs 1.5% placebo; no information about skeletal muscle symptoms

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Chiquette E 2004	RCTs of PIO and ROSI "in patients with type 2 diabetes to evaluate their effect on glycemic control, lipids, blood pressure, and weight"	1966 (or start of database) - 1/2004	RCT; enrolled ≥30 adults with DM2; evaluated rosiglitazone 4 or 8 mg or pioglitazone 30 or 45 mg in montherapy or in combination with other anti-diabetic medications; examined A1c; minimum treatment duration 12w; published in English	23 studies	RCTs only Median duration of treatment: PIO 16w, ROSI 26w Minority of trials reported weight maintenance strategy

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Chiquette E 2004	PIO and ROSI: Mean age 5.6, 57.5y BMI: 29.3, 29.7 kg/m2 A1c at baseline: 9.5, 9.2%	Median duration of treatment: PIO 16w, ROSI 26w Minority of trials reported weight maintenance strategy	Results given as PIO 30 mg, 45 mg; ROSI 4mg, 8mg (mean change in outcome in treatment group minus placebo group) A1c (%): Monotherapy: -0.99, -1.21;-0.90, -1.50 (all p<0.05 vs placebo) Combination therapy: -1.16, -1.56; -1.05, -1.26 (all p<0.05 vs placebo) Lipids (mg/dL), monotherapy and combined therapy (Pio and Rosi combined) Results given as Pio; Rosi Total cholesterol: HDL: 4.6; 2.7 (both p<0.05 vs placebo) LDL: -0.4 (NSD from placebo); 15.3 (p<0.05 vs placebo) TG: -39.7 (p<0.05 vs placebo); -1.1 (NSD vs placebo) BP (mm Hg), monotherapy and combined therapy (Pio and Rosi combined) Results given as Pio; Rosi SBP: NR, -0.7 (NSD vs placebo) DBP: NR; -0.8 (NSD vs placebo) Weight (kg): drug did not predict effect (p>0.10) Pio and Rosi combined Japanese trials: 0.7 vs placebo (p<0.05) Non-Japanese trials: 3.3 vs placebo (p<0.05)

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Subgroups	Adverse events
Chiquette E 2004	None	NR

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Czoski-Murray 2004 HTA report	"to evaluate the use of pioglitazone and rosiglitazone, in terms of both clinical and cost-effectiveness in the treatment of type 2 diabetes"	1966 (or start of database) - 6/2002	At least 1 outcome measures had to involve the effects of PIO or ROSI on glycemic control, CV risk factors, or Aes; intervention involved PIO or ROSI in combination with other antidiabetic drugs; the comparator was another antidiabetic drug or placebo; patients with type 2 diabetes; was a systematic review or RCT; patients received >=12w of study drug	ROSI: 8 studies, data NR for 7/8 as proprietary (Table 6) PIO: 3 studies of combination therapy	RCTs only
Henry RR 2003	"focuses on the impact of insulin resistance on patients with type 2 diabetes and reviews the potential benefits of insulin-sensitizing agents…"	1966-4/2003	NR	NR	NR

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Czoski-Murray 2004 HTA report	Described Table 7 for PIO, reported for 1 ROSI study	ROSI: dosage 4 to 8 mg qd PIO: dosage 15-30 mg qd	A1c: both drugs reduce by approximately 1% and are more effective at higher doses Weight: increases for both drugs No long-term data of effects No head-to-head, prospective RCTs were identified comparing ROSI and PIO, but the available evidence indicates the 2 drugs have similar effects
Henry RR 2003	NR	NR; no information on dosages, duration, cointerventions	PIO improves glycemic control, reduces IR, lowers BP, shifts fat distribution from visceral to subcutaneous, raises HDL, no change LDL, reduces fasting TG ROSI: improvs glycemic control, decreases BP, decreases IR, reduces WBC counts and CRP, variable effect on TG, may increase HDL, increase LDL

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Subgroups	Adverse events
Czoski-Murray 2004 HTA report	None	Rosiglitazone Addition of ROSI to metformin was associated with a significant reduction in risk of hyperglycemica in 1 study; NS effect when added to SU ROSI+metformin increased hyperlipidemia in 1 study Anemia and edema higher with ROSI combination therapies than for controls Pioglitazone See Chilcott 2001 review
Henry RR 2003	None	NR

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Inzucchi SE 2002	To review the literature regarding the efficacy of oral antidiabetic agents, both as monotherapy and in combination	NR	English-language articles of unique RCTs involving recently available oral agents for DM2; follow-up at least 3m, each group at least 10 subjects at study conclusion, A1c reported	3 studies identified: ROSI vs placebo: 493+959 PIO vs placebo: 408 (3 trials of troglitazone also reported)	RCTs ROSI: 2 placebo-controlled studies PIO: 1 placebo-controlled study
Meriden T 2003	"reviews the evidence for the minimal effects of standard antidiabetic treatments on the macrovascular complications associated with type 2 diabetes, discussses the improvement in markers of CV risk seen with the TZDs, and explores the rationale for their earlier use"	1988-2003	NR	NR	Reported in narrative for individual studies

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Inzucchi SE 2002	NR	NR; no information on dosages, duration, cointerventions	In placebo-controlled trials, TZDs lower A1c as much as Sus and metformin and more than AGIs In head-to-head studies, TZDs produce equivalent reductions in A1c compared to metformin and Sus No long-term outcome studies on microvascular endpouts TZDs increase LDL, decrease TG TZD slightly reduce BP, enhance fibrinolysis and improve endothelial function PIO and ROSI "appear to have similar efficacy on glycemica" based on one citation (an opinion piece)
Meriden T 2003	Reported in narrative for individual studies	Reported in narrative for individual studies	TDZs appropriate for monotherapy or combination therapy; they exert beneficial CV effects; improve insulin sensitivity, vascular, inflammatory and coagulation defects; preserve beta-cell function; may reduce dyslipidemia and visceral obesity; preliminary data suggest that greater benefit may be derived when TZDs are used before substantial disease progression has occurred

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Subgroups	Adverse events
Inzucchi SE 2002	None	Weight gain, which can be as great or greater than with Sus; appears to involve mostly peripheral subcutaneous sites; edema; anemia; PIO and ROSI not coincidently associated with liver injury
Meriden T 2003	None	NR

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Noble J 2005	"we review the evidence supporting use of TZD(s)… for the treatment of DM2"	NR	NR	NR	NR
Stolar 2003 Review of Aes only	"provides an overview of the cardiovascular risk profile of patients with type 2 diabetes and discusses the cardiovascular	1966-4/2003	NR	NR; total number of studies NR	NR

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Noble J 2005	Discussed for each study in narrative	Discussed for individual studies; no summary data	TZDs lower A1c by as much as 1.0 to 1.5% Effects in 4w, full effect takes 6 to 12 w Effect complementary with Sus and metformin No evidence that TZDs reduce the long-term complications of DM2 No head-to-head data identified
Stolar 2003 Review of Aes only	Reported only for selected individual studies	Reported only for selected individual studies	A1c: ROSI and Pio act similarly to decrease A1c up to 1.1% with ROSI and 1.7% with PIO Additional research needed comparison ROSI and PIO, long-term safety, and long-term health outcomes

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Subgroups	Adverse events
Noble J 2005	None	NR
Stolar 2003 Review of Aes only	NR	Peripheral edema occurs in approximately 2 to 5% of patients receiving ROSI or PIO

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
van Wijk JPH 2003	To evaluate the effects of ROSI and PIO on blood lipids in patients with DM2	Start date NR; assume 1966; search completed 12/2002	Double-blind, placebo-controlled, RCTs that evaluated effects of ROSI or PIO on blood lipids in patients with DM2; follow-up at least 8w	ROSI: 3236 PIO: 2068	RCTs ROSI: 11 studies PIO: 8 studies

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
van Wijk JPH 2003	ROSI: mean values over all studies: age 58.6y, 39% female PIO: mean values over all studies: age 55.8y, 45% female	ROSI: mean values over all studies: duration treatment 22w; mean values for study-level variables: 56% maximal dose; weight-maintenance diet 34% of studies PIO: mean values over all studies: duration treatment 18w; mean values for study level variables: 8% maximal dose; weight-maintenance diet 52% of studies	Change intervention-control group (mmol.l): ROSI 4, 8 mg/d, PIO 15,30,45 mg/d Triglycerides: 0.13, 0.05, -0.44, -0.66, -0.38 Cholesterol: 0.52, 0.70, -0.01, 0.01, 0.10 HDL: 0.05, 0.06, 0.10, 0.09, 0.11 LDL: 0.34, 0.48, 0.08, -0.01, 0.15 Mean treatment effects of ROSI vs PIO: p <0.001 for all 4 lipid measures

Evidence Table 1. Systematic reviews of TZDs: data

Author Year	Subgroups	Adverse events
van Wijk JPH 2003	Monotherapy: PIO trials showed greater benefit on all lipid levels vs ROSI ($p<0.05$)	NR

Evidence Table 2. Systematic reviews of TZDs: quality assessment

Internal Validity

Author Year	Clear review question	Comprehensive sources?	Literature search strategy specified?	Important studies missing?	Explicit eligibility criteria?	Adequate detail about primary studies?
Boucheer M 2002, 2003 COHTA Report	Yes	Yes (MEDLINE, EMBASE, Cochrane, and others; grey literature, bibliographies	Yes	No	Yes	Yes
Chilcott J 2001 PIO review	Yes	Yes (MEDLINE, EMBASE, Cochrane, and others; grey literature, bibliographies	No; not in this publication, but may be the same as the Czoski-Murray HTA report	No	Yes	Yes
Chiquette E 2004	Yes	Yes (MEDLINE, EMBASE, Cochrane, and others; grey literature, bibliographies	Yes (HTA search strategy)	No	Yes	Yes
Czoski-Murray 2004 HTA report	Yes	Yes (MEDLINE, EMBASE, Cochrane, and others; grey literature, bibliographies	Yes	No	Yes	Yes

Evidence Table 2. Systematic reviews of TZDs: quality assessment

Internal Validity				External Validity	
Author Year	Standard method of appraisal of studies?	Exclusion criteria	Quality	Relevant to a key question?	Funding source and role of funder
Boucheer M 2002, 2003 COHTA Report	QA (Jadad scale)	Encompassed by inclusion criteria	Good	Addresses efficacy and Aes	Canadian Coordinating Orrice for health Technology Assessment, Ottawa, ON Canada
Chilcott J 2001 PIO review	QA performed, but no studies excluded on this basis as couldn't evaluate 5 incomplete reports; Jadad score used	Encompassed by inclusion criteria	Good	Addresses efficacy and Aes	UK National Health Service Research and Development Health Technology Assessment Programme
Chiquette E 2004	QA performed; no details on appriach; no studies excluded on this basis	Encompassed by inclusion criteria	Good	Addresses efficacy and Aes	Dr. Chiquette employed by Aventis Pharmaceuticals; Dr. DeFronzo has research grants from Takeda, GlaxosmithKline and other pharmaceutical companies
Czoski-Murray 2004 HTA report	Jadad used for RCTs	Encompassed by inclusion criteria	Good	Addresses efficacy and Aes	UK National Health Service Research and Development Health Technology Assessment Programme

Evidence Table 2. Systematic reviews of TZDs: quality assessment

Internal Validity

Author Year	Clear review question	Comprehensive sources?	Literature search strategy specified?	Important studies missing?	Explicit eligibility criteria?	Adequate detail about primary studies?
Henry RR 2003	No; "focuses on the impact of insulin resistance on patients with tyep 2 diabetes and reviews the potential benefits of insulin-sensitizing agents…"	MEDLINE only	Yes	Uncertain	No	No
Inzucchi SE 2002	Yes	MEDLINE plus bibliographies	No	No	Yes	No
Meriden T 2003	No; unfocused question which looks at the 'minimal effects' of treatment	MEDLINE plus bibliographies	Yes; specific drugs not included in search	No	No	Yes, in narrative
Noble J 2005	No; "we review the evidence supporting use of TZD(s)… for the treatment of DM2"	MEDLINE and cochrane Database of Systematic Reviews	Yes; MeSH terms given	Yes	No	Yes, in narrative
Stolar 2003 Review of Aes only	Yes	MEDLINE plus bibliographies	Yes	No	No	No, selected studies described in narrative fashion

Evidence Table 2. Systematic reviews of TZDs: quality assessment

Internal Validity				External Validity	
Author Year	Standard method of appraisal of studies?	Exclusion criteria	Quality	Relevant to a key question?	Funding source and role of funder
Henry RR 2003	No quality assessment	None reported	Poor No quality assessment, only MEDLINE, no duplicate abstraction	Addresses effects on insulin resistance only	NR
Inzucchi SE 2002	No quality assessment	Follow-up <3m, study groups <10 subjects	Poor No quality assessment, no duplicate abstraction	Addresses efficacy and Aes	NR
Meriden T 2003	No quality assessment	None reported	Poor No quality assessment; no details on abstraction	Addresses efficacy	Supported in part by a grant from GlaxoSmithKline, Research Triangle Park, North Carolina; Author affiliated with BlaxosmithKline and Takeda Pharmaceuticals America, Inc.
Noble J 2005	No quality assessment	None reported	Poor No quality assessment; no details on abstraction	Addresses efficacy and Aes	NR
Stolar 2003 Review of Aes only	No quality assessment	NR	Poor	Addresses efficacy and Aes	NR

Evidence Table 2. Systematic reviews of TZDs: quality assessment

Internal Validity

Author Year	Clear review question	Comprehensive sources?	Literature search strategy specified?	Important studies missing?	Explicit eligibility criteria?	Adequate detail about primary studies?
van Wijk JPH 2003	Yes	MEDLINE only	In part; used "placebo" with "type 2 diabetes", plus drug names; only 46 citations identified; search likely too narrow	No	Yes	Yes

Evidence Table 2. Systematic reviews of TZDs: quality assessment

Internal Validity				External Validity	
Author Year	Standard method of appraisal of studies?	Exclusion criteria	Quality	Relevant to a key question?	Funding source and role of funder
van Wijk JPH 2003	No quality assessment	Yes Combination therapy with lipid-lowering drugs excluded	Poor No quality assessment, only MEDLINE, no duplicate abstraction	Addresses effects on lipids only	NR Authors are at University of Utrecht, the Netherlands

Evidence Table 3. Head to head controlled trials

Derosa G, 2004, 2005 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** None **Setting:** Multicenter

Wash out : 30 days **Country:** Italy

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	91	4/	0/	87

Inclusion criteria:

White patients aged ≥18y with DM2 (according to ADA criteria) for ≥ 6m, A1c>7.5% or experienced ≥1 AE with diet and oral agents given up to maximum dose; patients also had metabolic syndrome by ATP III classification; TG ≥150mg/dL; hypertension (BP ≥130/85 mmg Hg); fasting C-peptide>1.0 ng/mL; BMI 23.6-25.2

Exclusion criteria:

Receiving glimepiride; history of ketoacidosis; unstable or rapidly progressive diabetic retinopathy, nethropathy, or neuropathy; impaired hepatic function; impaired renal function; severe anemia; history of MI or stroke; CHF New York Heart Association Class III or IV, cerebral vascular conditions in last 6m; pregnant women or breast-feeding or childbearing age and not using adequate contraceptive precautions

Comments:

Derosa 2004 and 2005 are companion papers (same population, different outcomes); information from both papers presented here.

Population: **Mean age:** 54 years **Ethnicity:** NR

Gender: 53% Female

Type 2 diabetes duration (SD), year: NR

Intervention: added to sulfonylurea

Duration: 12 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	15mg	Pio	45	8.2 (0.7)	68.9 (3.5)		
Rosiglitazone	4mg	Rosi	42	8.0 (0.8)	67.8 (3.1)		

Laboratory measures:

	Pio	Rosi
A1c, change from baseline to 12m: % (SD)		
	-1.4	-1.3
within-group change, both p<0.01; NSD between-groups		
FPG, change from baseline to 12m: mg/dL		
	-31	-21
PPG, change from baseline to 12m: mg/dL		
	-35	-29
Total cholesterol, change from baseline to 12m: mg/dL		
	-11	28
p vs Rosi	p<0.05	
LDL, change from baseline to 12m: mg/dL		
	-15	20
p vs Rosi	p<0.05	

Evidence Table 3. Head to head controlled trials

Derosa G, 2004, 2005			**Quality rating: Fair**
HDL, change from baseline to 12m: mg/dL			
	6	1	
p vs Rosi	NSD		
TG, change from baseline to 12m: mg/dL			
	-26	31	
p vs Rosi	p<0.05		
Physiologic outcomes:			
	Pio	**Rosi**	
BMI, change from baseline to 12m: mg/m2 (SD)			
	1.2	1.5	
NSd between groups			

P value NR if not specified.

Evidence Table 3. Head to head controlled trials

Durbin R, 2004 **Quality rating: Fair**

Design:

Study design: CT Ope Parallel **Run-in :** None **Setting:** Single Center

Wash out : None **Country:** USA

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed

NR/ NR/ 172

Inclusion criteria:

prediabetes (IGT and insulin resistance); clinic patients with normal or borderline A1c, elevated C-peptide (>2.0 mg/ml), FBS 100-125 mg/dl, 2-h PP BG 140-200 mg/dl

Exclusion criteria:

None reported

Comments:

Active treatment patients were initially treated with troglitazone 400 mg/d for average 10m, until withdrawn from the market. Then active treatment either Rosi or Pio. Follow-up 24-45m from baseline; mean duration TZD therapy 36m. Troglitazone treatment group (active or comparison) determined by which physician patient was seeing; Rio vs Pio determined by which information meeting was attended (when troglitazone was discontinued).

Population: **Mean age:** 56.4 years **Ethnicity:** White 52%; Black 1.1%; Hispanic 44%

Gender: 51% Female

Type 2 diabetes duration (SD), year: NR

Intervention: monotherapy

Duration: 36 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	30 mg qd	Pio	62	6.23 (0.74)	NR (NR)	NR (NR)	titrated up as needed
Rosiglitazone	4 mgqd	Rosi	39	6.12 (0.60)	NR (NR)	NR (NR)	titrated up as needed
No treatment	NA	Control	71				

Laboratory measures:

	Pio	Rosi	Control
A1c, change from start or ROSI or PIO: % (SD)			
	-0.12	-0.14	0.43
p vs Pio or rosi			p<0.01

Evidence Table 3. Head to head controlled trials

Durbin R, 2004 **Quality rating: Fair**

Laboratory measures:

	Pio	Rosi	Control
A1c, change from start or ROSI or PIO: % (SD)			
	-0.12	-0.14	0.43
p vs Pio or rosi			p<0.01

Physiologic outcomes:

	Pio	Rosi	Control
Weight, chagne from baseline to 3 years: kg (SD)			
	2.5(6.3)	0.3(5.5)	2.0(1.3)
p-value NR			

Health outcomes:

	Pio	Rosi	Control
Progression to diabetes at end of study: number of patients			
	2	1	19
Estimated cumulative incidence DM2 after 3y: %			
	2.97	2.97	26.8
Incidence DM2 88.9% lower in TZDs(combined) than control (p<0.001)			
NNT to prevent 1 case DM2 in 3y			
4.2 for TZDs			

P value NR if not specified.

Evidence Table 3. Head to head controlled trials

Goldberg RB, 2005 — Quality rating: Fair

Design:

Study design: RCT DB Parallel **Run-in :** 28 days **Setting:** Multicenter
Wash out : 28 days **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	4410/	802/	735	150/	15/	719

Inclusion criteria:

Men or women ≥35y with DM2 (by WHO criteria), fasting TG ≥150 mg/dl and <600 mg/dl; LDL <130mg/dl; C-peptide ≥1 ng/ml; A1c ≥7% and ≤11% if naïve to previous oral agents; or A1c ≥7% and ≤9.5% if previously treated with oral monotherapy

Exclusion criteria:

Treatment within 60d with insulin, systemic glucocorticoid therapy, combination oral antihyperglycemic therapy, any lipid-lowering agent, or any weight-loss agent; allergy to any TZD; serum creatinine ≥2.0 mg/dl; 2+ dipstick proteinuria; AAT or AST ≥1.5 times upper limit normal; significant clinical liver disease, Hb <10.5 g/dl (females) or <11.5 g/cl (males); abnormal thyrotropin; functional New York Heart Association Cardiac Disease Class III or IV; history of CVD or heart surgery within 6m; on renal dialysis or having renal transplant; current therapy for malignancy; HIV infection; signs or symptoms of drug or alcohol abuse; potential for pregnancy

Comments:

Sites in the US (78), Puerto Rico (11), Mexico 4), Columbia (7)
Quality assessment: patients withdrawn for protocol violation (Pio 17, Rosi 14), but did analyze these patients if ≥1 follow-up measure; therefore consider ITT analysis; although attrition high, no differential between groups

Population: **Mean age:** 56.1 years **Ethnicity:** Pio: 65% white, 295 Hispanic, 23% Asian; Rosi: 60% white, 21% Hispanic, 3% Asian
Gender: 46% Female
Type 2 diabetes duration (SD), year: 3.9 (4.5)

Intervention: monotherapy

Duration: 24 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	30-45mg qd	Pio	369	7.6 (1.2)	93.7 (20.6)		
Rosiglitazone	4mg qd - bid	Rosi	366	7.5 (1.2)	92.5 (21.0)		

Laboratory measures:

	Pio	Rosi
A1c, change from baseline: % (SE)		
	-0.7(-0.1)	-0.6(0.1)
p vs Rosi	p=0.129	
TG, change from baseline: mg/dL (SE)		
	-51.9(7.8)	13.1(7.8)
p vs Rosi	p<0.001	
HDL, change from baseline: mg/dL (SE)		
	5.2(0.5)	2.4(0.5)
p vs Rosi	p<0.001	
LDL, change from baseline: mg/dL (SE)		
	12.3(1.6)	21.3(1.6)
p vs Rosi	p<0.001	

Evidence Table 3. Head to head controlled trials

Goldberg RB, 2005		**Quality rating: Fair**
Total cholesterol, change from baseline: mg/dL (SE)		
	8.8(1.9)	28.2(1.9)
p vs Rosi	p<0.001	
Fasting plasma glucose, change from baseline: mg/dL (SE)		
	-33.2(2.2)	-36.6(2.2)
p vs Rosi	p=0.233	

Physiologic outcomes:

	Pio	**Rosi**
Weight, change from baseline: kg (Se)		
	2.0(0.2)	1.6(0.2)
p vs Rosi	p=0.164	

P value NR if not specified.

Evidence Table 3. Head to head controlled trials

Khan M, 2002 **Quality rating: Fair**

Design:

Study design: RCT Ope Parallel **Run-in :** None **Setting:** Single Center

Wash out : 14 days **Country:** US

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed

NR/ NR/ 186 30/ 29/ 127

Inclusion criteria:

Patients currently taking troglitazone and with stable liver function assessed by liver enzymes (alanine and aspartate aminotransferase).

Exclusion criteria:

NR

Comments:

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: NR% Female

Type 2 diabetes duration (SD), year: NR

Intervention: monotherapy

Duration: 4 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	2-4mg	Rosi	60	7.9 (1.9)	103.3 (24.8)	NR (NR)	
Pioglitazone	15-45mg	Pio	67	80.0 (1.7)	101.4 (24.2)	NR (NR)	

Laboratory measures:

	Pio	Rosi
Total cholesterol, change from baseline to 4m: mg/dL		
	-19	4
p vs Rosi	p<0.01	
HDL, change from baseline to 4m: mg/dL		
	2	1
p vs Rosi	NSD	
LDL, change from baseline to 4m: mg/dL		
	-17	-2
p vs Rosi	p<0.01	
TG, change from baseline to 4m: mg/dL		
	-15	6
p vs Rosi	NSD	
A1c, change from baseline to 4m: mg/dL		
	NR	NR

No significant change from baseline was noted between or within groups

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Aronoff S, 2000 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 42-56 days **Setting:** Multicenter
Wash out : 42-56 days **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	408	NR/	unclear/	399

Inclusion criteria:
A1c ≥7.0%, FPG ≥140 mg/dl, fasting C-peptide >1 ng/ml

Exclusion criteria:
Chronic insulin users; history of ketoacidosis; unstable or rapidly progressive diabetic retinopathy, nethropathy, or neuropathy; impaired LFT (>2.4 times upper limit of normal; impaired renal function with serum creatinine >1.8 mg/dl; anemia; MI, TIA, CVA, coronary angioplasty or bypass graft in last 6m

Comments:

Population: **Mean age:** 53.7 years **Ethnicity:** Caucasian 78%, Hispanic 12%, African-American 8%, Asian 2%
Gender: 42% Female
Type 2 diabetes duration (SD): NR (NR) years

Intervention: monotherapy

Duration:

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	7.5mg	Pio-7.5		10.0 (1.97)	93.5 (14.2)	NR (NR)	
Placebo	NA	Placebo		10.4 (1.96)	90.4 (13.1)	NR (NR)	
Pioglitazone	15mg	Pio-15		10.2 (1.96)	91.2 (16.0)	NR (NR)	
Pioglitazone	30mg	Pio-30		10.2 (1.94)	90.3 (14.6)	NR (NR)	
Pioglitazone	45mg	Pio-45		10.3 (1.92)	90.8 (13.6)	NR (NR)	

Laboratory measures:

	Pio-7.5	Pio-15	Pio-30	Pio-45	Placebo
A1c, change from baseline to 26 weeks: % (SEM)	0.2(0.17)	-0.3(0.17)	-0.3(0.17)	-0.9(0.18)	0.7(0.17)
p<0.05 vs placebo for 15, 30, 45 mg					
FPG, change from baseline to 26 weeks: % (SEM)	-18.1(6.77)	-29.6(31.8)	-31.8(6.66)	-55.9(6.9)	9.4(6.72)
p<0.05 vs placebo for 15, 30, 45 mg					
HDL, LS meam % change from baseline to 26 weeks: % (SEM)	7.9(2.05)	14.1(2.05)	12.2(2.04)	19.1(2.07)	8.1(2.03)
p<0.05 vs placebo for 45 mg					
TG, LS mean % change from baseline to 26 weeks: % (SEM)	8.9(4.73)	-9.0(4.74)	-9.6(4.65)	-9.3(4.81)	4.8(4.7)
p-value unclear					
LDL, LS mean % change from baseline to 26 weeks: % (SEM)	1.0(2.67)	7.2(2.67)	5.2(2.47)	6.0(2.69)	4.8(2.62)
NSD vs placebo for any group					

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Aronoff S, 2000				**Quality rating: Poor**
Total cholesterol, LS mean % change from baseline to 26 weeks: % (SEM)				
2.3(1.56)	4.6(1.56)	3.3(1.54)	6.4(1.59)	4.4(1.55)
NSD vs placebo for any group				

Physiologic outcomes:

Pio-7.5	**Pio-15**	**Pio-30**	**Pio-45**	**Placebo**
Weight, change from baseline to 26 weeks: kg (SEM)				
-0.6(0.29)	1.3(0.33)	1.3(0.38)	2.8(0.39)	-1.3(0.36)
NSD vs placebo for any group				

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Dormandy JA, 2005 **Quality rating: Good**

Design:

Study design: RCT DB Parallel **Run-in :** None **Setting:** Multicenter

Wash out : None **Country:** Multiple European

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	5602/	5238/	5238	363/	2/	5238

Inclusion criteria:

Patients with DM2 who were aged 35-75 years; A1c >6.5% (or local laboratory equivalent) despite treatment with diet or oral agents, with or without insulin; evidence of extensive macrovascular disease (1 or more of MI, stroke, coronary artery bypass surgery, percutaneous coronary intervention, ≥ 6m prior to study; or acute coronary syndrome ≥3m prior to study; or objective evidence of coronary artery disease or arterial disease of the leg)

Exclusion criteria:

DM1, taking only insulin, had planned coronary or peripheral revascularization; New York Heart Association Class II/III heart failure or above; ischaemic ulcers, gangrene or chest pain in the leg; had hemodialysis; >2.5 times the upper limit of normal concentrations of alanine aminotransferase

Comments:

PROactive (PROspective pioglit Azone Clinical Trial in macro Vascular Events); 321 centers in 19 European countries.
Primary endpoint: time from randomization to: all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle.
Secondary endpoint: time to death from any cause, non-fatal myocardial infarction (excluding silent myocardial infarction), or stroke.
Analyzed by ITT principles; no cross-overs; 2 patients lost to follow-up; 16% or PIO and 17% of placebo group discontinued study medication before death or final visit.

Population: **Mean age:** 61.8 years **Ethnicity:** 98.5% Caucasian

Gender: 34% Female

Type 2 diabetes duration (SD): 9.5 (NR) years

Intervention: monotherapy

Duration:

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	15-45mg qd	Pio	2605	7.8 (NR)	NR (NR)	30.7 (4.7)	
Placebo	NA	Placebo	2633	7.9 (NR)	NR (NR)	31.0 (4.8)	

Laboratory measures:

	Pio	Placebo
A1c, change from baseline to study end: % (CI)	-0.8(-1.6, -0.1)	-0.3(-1.1, 0.4)
between-group p<0.0001		
TG, change from baseline to study end: % change (CI)	-11.4(-34.4, 18.3)	1.8(-23.7, 33.9)
between-group p<0.0001		
LDL, change from baseline to study end: % change (CI)	7.2(-11.2, 27.6)	4.9(-13.9, 23.8)
between-group p<0.0001		
HDL, change from baseline to study end: % change (CI)	19.0(6.6, 33.3)	10.1(-1.7, 21.4)
between-group p<0.0001		

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Dormandy JA, 2005 **Quality rating: Good**

Laboratory measures:

	Pio	Placebo
A1c, change from baseline to study end: % (CI)	-0.8(-1.6, -0.1)	-0.3(-1.1, 0.4)
between-group p<0.0001		
TG, change from baseline to study end: % change (CI)	-11.4(-34.4, 18.3)	1.8(-23.7, 33.9)
between-group p<0.0001		
LDL, change from baseline to study end: % change (CI)	7.2(-11.2, 27.6)	4.9(-13.9, 23.8)
between-group p<0.0001		
HDL, change from baseline to study end: % change (CI)	19.0(6.6, 33.3)	10.1(-1.7, 21.4)
between-group p<0.0001		

Physiologic outcomes:

	Pio	Placebo
SBP, change from baseline to end of study: mm Hg	-3	0
between-group p=0.03		
Weight, change from baseline to end of study: kg	3.6	-0.4
p vs Placebo	p<0.0001	

Health outcomes:

	Pio	Placebo
Hospitalizations: %	44	46

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Herz M, 2003 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 21-35 days **Setting:** Multicenter

Wash out : None **Country:** Canada and Spain

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	297	20/	5/	287

Inclusion criteria:

Diagnosis of DM2 that was not controlled by diet and exercize; no previous treatment with insulin or oral antihyperglycemic medications

Exclusion criteria:

Cardiac disease with marked limitation of functional capacity (NYHA Class III or IV clinical status); serum TG >500 mg/dL or total cholesterol >300 mg/dL; serum creatinine ≥1.8 mg/dL; renal transplant or current renal dialysis; serum alanine aminotransferase or aspartate aminotransferase >2.5 times the upper limit of normal for the central laboratory; clinical signs or symptoms of liver disease; hemoglobin or hematocrit below the lower limit of normal for the central laboratory; previous HIV infection; treatment with systemic glucocorticoids (excluding topical and inhaled preparations) within the previous 4 weeks; BMI ≤25; signs or symptoms of substance abuse; or life expectancy <3 years.

Comments:

Population: **Mean age:** 58.4 years **Ethnicity:** White 96.3%, Asian 2.4%, Hispanic 1.3%

Gender: 46% Female

Type 2 diabetes duration (SD): 1.67 (3.12) years

Intervention: monotherapy

Duration: 16 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	30mg	Pio-30	99	7.5	86.6 (15.9)		
Pioglitazone	45mg	Pio-45	99	7.6	84.1 (16.8)		
Placebo	NA	Placebo	99	7.5	86.3 (17.4)		

Laboratory measures:

	Pio-30	Pio-45	Placebo
HbA1c, change from baseline at week 16: %			
	-0.8	-0.9	-0.2
p vs Placebo	<0.001	<0.001	NA
HbA1c, proportion of patients achieving ADA target of <7%: % (n)			
	70.5(67)	68.8(66)	42.7(41)
p vs Placebo	<0.001	0.001	NA
Fasting plasma glucose, change from baseline at week 16: %			
	-15.7	-18.6	-1.1
p vs Placebo	<0.001	<0.001	NA
HDL-c, change from baseline at week 16, mg/dL: %			
	+16	+20	+9
p vs Placebo	0.028	<0.001	
Triglycerides, change from baseline at week 16: %			
	5	16	NR
p vs Placebo	NS	0.007	NA

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Herz M, 2003 **Quality rating: Fair**

Total cholesterol, change from baseline at week 16: %			
	+4	NR	NR
p vs Placebo	NS	NS	NA
LDL-C, change from baseline at week 16: %			
	7	NR	NR
p vs Placebo	NS	NS	NR

Physiologic outcomes:

	Pio-30	Pio-45	Placebo
Weight, change from baseline at week 16: kg			
	+0.35	+0.82	-1.58
p vs Placebo	<0.001	<0.001	NA

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Kipnes M, 2001 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 21 days **Setting:** Multicenter
Wash out : 42 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	638/	NR/	560	75/	7/	539

Inclusion criteria:

Patients were required to have been receiving a stable dose of a sulfonylurea for 30 days or longer and to have a BMI of 25 to 45, and to have HbA1c 8.0% or greater and a fasting C-peptide level >1.0 ng/mL.

Exclusion criteria:

Patients with a history of ketoacidosis or with unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy were excluded, as were those with imparied hepatic or renal function, or with anemia. Patients with unstable cardiovascular conditions (e.g., NYHA Class III or IV congestive heart failure), or a history of myocardial infarction, stroke, or cerebrovascular conditions within 6 months of study enrollment.

Comments:

Population: **Mean age:** 56.7 years **Ethnicity:** 79.1% White; 11.1% Black; 8.2% Hispanic; 1.6% Asian
Gender: 41% Female
Type 2 diabetes duration (SD): NR (NR) years

Intervention: Added to sulfonylurea

Duration: 20-23 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	15mg	Pio-15	184	10.0 (NR)	NR (NR)	31.4 (5.0)	
Pioglitazone	30mg	Pio-30	189	9.9 (NR)	NR (NR)	32.4 (7.2)	
Placebo	NA	Placebo	187	9.9 (NR)	NR (NR)	32.0 (4.9)	

Laboratory measures:

	Pio-15	Pio-30	Placebo
HbA1c, change from baseline at week 16: % (95% CI)			
	-0.8(-1.0, -0.6)	-1.2(-1.4, -1.0)	+0.1(-0.1, 0.2)
p vs Placebo	<=0.05	<=0.05	NA
Fasting plasma glucose, change from baseline at week 16: mg/dL (95% CI)			
	-33.8(-41.4, -26.3)	-52.3(-59.7, -44.8)	+5.6(-1.9, +13.1)
p vs Placebo	<=0.05	<=0.05	NA
Total cholesterol, change from baseline at week 16: mg/dL			
	+2.0	+2.0	+9
p vs Placebo	NS	NS	NA
LDL-c, change from baseline at week 16: mg/dL			
	+4	+3	+7
p vs Placebo	<=0.05	<=0.05	NA
HDL-c, change from baseline at week 16: mg/dL			
	+3	+4	-2
p vs Placebo	NS	NS	NA

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Kipnes M, 2001 **Quality rating: Fair**

Triglycerides, change from baseline at week 16: mg/dL			
	-42	-62	+8
p vs Placebo	NS	<=0.05	NA

Physiologic outcomes:

	Pio-15	Pio-30	Placebo
Weight, change from baseline at week 16: kg			
	+1.9	+2.9	-0.8
p vs Placebo	<0.5	<0.5	NA

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Mattoo V, 2005 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 90 days **Setting:** Multicenter

Wash out : no days **Country:** Multiple (US, Europe, Canada)

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	385/	308/	289	26/	NR/	276

Inclusion criteria:

DM2 diagnosed according to WHO criteria, used insulin therapy (with or without an oral antihyperglycemic medication for 3 months or longer, had HbA1c value 7.5% or higher at screening, and were 30 years or older at the time of diabetes diagnosis.

Exclusion criteria:

DM1, clinical signs or symptoms of any chronic systemic condition (liver disease, diminished cardiac function, renal impairment, transplantation or dialysis, HIV infection), or signs or symptoms of drug or alcohol abuse. Previous TZD use, systemic glucorticoid therapy, nicotinic acid at a dose >500 mg.d, or therapy for a malignancy other than basal cell or squamous cell skin cancer. Women who were breastfeeding or pregnant, women of childbearing potential not actively practicing birth control.

Comments:

Population: **Mean age:** 58.9 years **Ethnicity:** 96.5% white, 3.5% other

Gender: 57% Female

Type 2 diabetes duration (SD): 162.1 (NR) years

Intervention: Added to insulin

Duration: 6 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	30	Pio	142	8.85 (0.11)	NR (NR)	32.5 (4.8)	
Placebo	NA	Placebo	147	8.79 (0.10)	NR (NR)	31.8 (5.0)	

Laboratory measures:

	Pio	Placebo
HbA1c, change from baseline at month 6: %		
	0.74	0.13
p vs Placebo	<0.002	NA
HbA1c, proportion of patients who attained <7.0% at month 6: N (%)		
	26(18.0)	10(6.9)
	NR	NR
P-value NR		
Fasting plasma glucose, change from baseline at month 6: mmol/l		
	-1.22	+0.68
p vs Placebo	<0.002	NA
HDL-c, change from baseline at month 6: mmol/l		
	+0.12	-0.03
p vs Placebo	<0.002	NA
LDL-c, change from baseline at month 6: mmol/l		
	-0.02	-0.08
p vs Placebo	NS	NR

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

McMahon G, 2005 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** None **Setting:** NR
Wash out : None **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	20	4/	NR/	16

Inclusion criteria:
"Insulin-requiring DM2".

Exclusion criteria:
Clinical evidence of heart disease (i.e., angina or heart failure symptoms), evidence of obstructive coronary artery disease on rest-stress myocardial perfusion PET imaging, ischemic changes or left ventricular hypertrophy on resting EKG, overt clinical evidence of cerebrovascular or peripheral vascular disease, history of more than mild hypertension (<160/95 mm Hg), overt nephropathy, glycohemoglobin level of ≤7%, or history of cardiomyopathy, valvular heart disease, or liver dysfunctioin.

Comments:

Population: **Mean age:** 54.5 years **Ethnicity:** NR
Gender: 44% Female
Type 2 diabetes duration (SD): 14.8 (NR) years

Intervention: added to insulin

Duration: 3 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	45mg	Pio	8	7.35 (0.64)	NR (NR)	35.1 (7.1)	
Placebo	NA	Placebo	8	7.65 (0.64)	NR (NR)	32.3 (4.1)	

Laboratory measures:

	Pio	Placebo
A1C, change from baseline at week 12: %		
	-0.68	+0.17
p vs Placebo	<0.05	NA
Fasting plasma glucose, change from baseline at week 12: mg.dL		
	-18.7	+2.4
p vs Placebo	NS	NA
Total cholesterol, change from baseline at week 12" mg.dL		
	-12.0	-6.6
p vs Placebo	NS	NA
LDL-c, change from baseline at week 12: mg.dL		
	+4.1	-28.5
p vs Placebo	NS	NA
HDL-c, change from baseline at week 12: mg.dL		
	+4.8	-6.0
p vs Placebo	<0.05	NA

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

McMahon G, 2005 **Quality rating: Poor**

Triglycerides, change from baseline at week 12: mg.dL		
	-92.9	-38.7
p vs Placebo	<0.05	NA

Physiologic outcomes:

	Pio	Placebo
Systolic BP (resting), change from baseline at week 12: mmHg		
	-8.3	+7.4
	NR	NR
p-value NR		

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Miyazaki Y, 2001; Miyazaki Y, 2004 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Single Center
Wash out : NR **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	NR	NR/	NR/	23

Inclusion criteria:
Age 30-70 years, BMI <36, stable body weight for at least 3 months before the study, and fasting plasma glucose 140-240 mg/dl. In good general health without cardiac, hepatic, renal, or other chronic diseases.

Exclusion criteria:
Patients who had previously received insulin, metformin, another TZD, or acarbose.

Comments:

Population: **Mean age:** 54.5 years **Ethnicity:** White (34.8%); Black (8.7%); Hispanic (56.5%)
Gender: 26% Female
Type 2 diabetes duration (SD): 5.3 (NR) years

Intervention: added to sulfonylurea, Pio

Duration: 16 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	45mg	Pio	12	8.9 (0.3)	84.8 (3.6)		
Placebo	NA	Placebo	11	7.9 (0.3)	81.4 (5.0)		

Laboratory measures:

	Pio	Placebo
HbA1c, change from baseline at week 16: % (SD)		
	-1.7(0.3)	0(0.2)
p vs Placebo	<0.001	NA
Fasting plasma glucose, change from baseline at week 16: mg/dL (SD)		
	-50.0(12.0)	+25.0(22.0)
p vs Placebo	0.006	NA
Total cholesterol, change from baseline at week 16: mg/dL (SD)		
	-7.0(6.0)	-1.0(5.0)
	NR	NR
p-value NR		
LDL-c, change from baseline at week 16: mg/dL (SD)		
	-2.0(6.0)	0(4.0)
	NR	NR
p-value NR		
HDL-c, change from baseline at week 16: mg/dL (SD)		
	+1.0(2.0)	-1.0(1.0)
	NR	NR
p-value NR		

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Miyazaki Y, 2001; Miyazaki Y, 2004		**Quality rating: Poor**
Triglycerides, change from baseline at week 16: mg/dL (SD)		
	-33.0(11.0)	+1.0(11.0)
p vs Placebo	0.047	NA

Physiologic outcomes:

	Pio	**Placebo**
Weight, change from baseline at week 16: kg (SD)		
	3.6(1.4)	0.3(0.4)
p vs Placebo	0.44	NA
BMI, change from baseline at week 16: kg/m2 (SD)		
	1.3(0.5)	0.1(0.2)
p vs Placebo	0.037	

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Miyazaki Y, 2002 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter

Wash out : 48-64 days **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	58	0/	0/	58

Inclusion criteria:

Patients were required to have HbA >7.0%, fasting plasma glucose (FPG) > 140 mg/dl, fasting C-peptide >1 ng/ml.

Exclusion criteria:

Patients who used insulin or have unstable proliferative retinopathy, impaired liver function, impaired kidney function (serum creatine >1.8 mg/dl), or anemia. Patients taking previous antidiabetic therapy underwent a 6-8 week single-blind washout.

Comments:

Population: **Mean age:** 54 years **Ethnicity:** Caucasian: 42(72.4%%); African-American: 4(6.8%%); Mexican-American: 8(13.7%%); Asian: 2(3.4%%)

Gender: 41% Female

Type 2 diabetes duration (SD): NR (NR) years

Intervention: monotherapy, Pio

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	15mg	Pio-15	12	8.0 (0.3)	93 (5)	NR (NR)	
Pioglitazone	30mg	Pio-30	11	8.5 (0.5)	97 (4)	NR (NR)	
Pioglitazone	45mg	Pio-45	11	9.1 (0.3)	86 (3)	NR (NR)	
Placebo	NA	Placebo	11	8.6 (0.5)	90 (4)	NR (NR)	

Laboratory measures:

	Pio-7.5	Pio-15	Pio-30	Pio-45	Placebo
HbA1c, change from baseline at week 26: % (SEM)					
	+0.3(0.4)	-0.1(0.4)	-0.8(0.3)	+1.8(0.4)	+1.2(0.5)
p vs Placebo	0.14	0.05	0.003	0.002	NA
Fasting plasma glucose, change from baseline at week 26: mg/dL (SEM)					
	+13.0(17.0)	+10.0(0.8)	-46.0(19.0)	-77.0(13.0)	+21.0(25.0)
p vs Placebo	0.3	0.2	0.04	0.002	NA
Total cholesterol, change from baseline at week 26: mg/dL (SEM)					
	+4.0(5.0)	+3.0(7.0)	-8.0(10.0)	+5.0(7.0)	+1.0(14.0)
p vs Placebo	0.8	0.9	0.6	0.8	NA
HDL-c, change from baseline at week 26: mg/dL (SEM)					
	+2.0(1.0)	+5.0(2.0)	+6.0(1.0)	+4.0(1.0)	+3.0(2.0)
p vs Placebo	0.7	0.6	0.2	0.3	NA
LDL-c, change from baseline at week 26: mg/dL (SEM)					
	-1.0(6.0)	-3.0(5.0)	-6.0(1.0)	+5.0(8.0)	-12.0(13.0)
p vs Placebo	0.4	0.5	0.7	0.3	NA

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Miyazaki Y, 2002					**Quality rating: Fair**
Triglycerides, change from baseline at week 26: mg/dL (SEM)					
	+16.0(17.0)	-19.0(21.0)	-53.0(39.0)	-24.0(22.0)	+53.0(56.0)
p vs Placebo	0.3	0.09	0.05	0.08	NA
Physiologic outcomes:					
	Pio-7.5	**Pio-15**	**Pio-30**	**Pio-45**	**Placebo**
Weight, change from baseline at week 26: kg (SEM)					
	+0.2(0.5)	+2.0(0.9)	+3.0(1.1)	+4.5(0.7)	-0.4(1.4)
p vs Placebo	0.7	0.17	0.07	0.006	NA
-0.1 (SEM)					
	+0.1(0.2)	+0.7(0.3)	+1.0(0.4)	+1.0(0.3)	0.5
p vs Placebo	0.8	0.18	0.11	0.006	NA

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Negro R, 2004 **Quality rating: Poor**

Design:

Study design: RCT NR Parallel **Run-in :** None **Setting:** Single Center

Wash out : None **Country:** Italy

Sample:

Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
NR/	NR/	NR	NR/	NR/	40

Inclusion criteria:

DM2 patients on metformin (up to 3000mg/d); mean SBP <140 and mean DBP <90mm Hg and nocturnal BP falling less than 10% compared to diurnal hours on 24h BP recording at beginning of study.

Exclusion criteria:

Taking antihypertensive medication, diabetic neuropathy and micro- or macroalbuminuria; pancratitis; gastrointestinal and/or malabsorption conditions; heart disease or insufficiency, malignant disease; any liver or renal impairment; history of drug or alcohol abuse; pregnancy or lactation.

Comments:

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: NR% Female

Type 2 diabetes duration (SD): NR

Intervention: added to metformin; non-dippers

Duration: 8 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	30mg qd	Pio	20	7.7 (0.4)	NR (NR)	26.8 (2.4)	
Placebo	NA	Placebo	20	7.7 (0.63)	NR (NR)	26.7 (2.4)	

Laboratory measures:

	Pio	Placebo
A1c, change from baseline to 8w: %		
	-0.5	-0.1
p vs Placebo	NSD	
pre and post values given witih SE		
Total cholesterol, change from baseline to 8w: mg/dL		
	-9.0	-4.2
p vs Placebo	NSD	
pre and post values given witih SE		
HDL, change from baseline to 8w: mg/dL		
	2.15	-0.1
p vs Placebo	p=0.009	
pre and post values given witih SE		
LDL, change from baseline to 8w: mg/dL		
	8.4	-7.5
p vs Placebo	NSD	
pre and post values given witih SE		

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Negro R, 2004			**Quality rating: Poor**
TG, change from baseline to 8w: mg/dL			
	-8.5	6.5	
p vs Placebo	NSD		
pre and post values given witih SE			

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Rosenblatt S, 2001 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 35 days **Setting:** Multicenter

Wash out : None **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	197	54/	NR/	197

Inclusion criteria:

BMI of 25-40, diagnosis of DM2 using diagnostic criteria of the National Diabetes Data Group, a HbA1c >=8.0%, endogenous insulin production as measured by a fasting C-peptide >0.33 nmol/l (1ng/ml) and normal thyroid function.

Exclusion criteria:

Patients who used insulin chronically, had a history of ketoacidosis, or had advanced, unstable, or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy, patients with abnormal thyroid function, impaired hepatic function (AST, ALT, total bilirubin, or alkaline phosphatase >2.5 X ULN), impaired renal function, anemia, pregnancy, left ventricular hypertrophy, NYHA class III or greater congestive heart failure, uncontrolled hypertension, or known sensitivity to Pio. Documented history of transient ischemic attacks, MI, coronary angioplacty or CABG, or unstable angina within the 6 months prior to study entry.

Comments:

Population: **Mean age:** 54.4 years **Ethnicity:** White (66%); Black (10.2%); Hispanic (21.8%); Other (2.5%)

Gender: 47% Female

Type 2 diabetes duration (SD): NR (NR) years

Intervention: monotherapy

Duration: 16 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	30mg	Pio	101	10.65 (1.77)	89.8 (18.0)	31.5 (4.7)	
Placebo	NA	Placebo	96	10.42 (1.7)	87.2 (18.4)	30.7 (5.0)	

Laboratory measures:

	Pio	Placebo
HbA1c, change from baseline at week 16: % (SD)		
	-0.60(0.17)	+0.76(0.17)
p vs Placebo	<=0.05	NA
Fasting plasma glucose, change from baseline at week 16: mmol/l (SD)		
	-2.77(0.38)	+0.43(0.39)
p vs Placebo	<=0.05	NA
Triglycerides, change from baseline at week 16: mmol/l		
	-0.67	+0.07
p vs Placebo	0.0178	NA
HDL-C, change from baseline at week 16: mmol/l		
	+1.63	NR
p vs Placebo	0.0001	NA
LDL-C, change from baseline at week 16: mmol/l		
	NR	NR
NS vs placebo		

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Rosenblatt S, 2001 **Quality rating: Fair**

Total cholesterol, change from baseline at week 16: mmol/l		
	NR	NR
NS vs placebo		

Physiologic outcomes:

	Pio	Placebo
Weight, change from baseline to week 16 (kg)		
	+1.35	-1.87
p vs placebo	<0.0001	NA

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Rosenstock J, 2002 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 21 days **Setting:** Multicenter

Wash out : 42 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	566	58/	11/	566

Inclusion criteria:

Ages 30-75, with DM2, required to have received insulin treatment (≥30 units/day) for ≥4 months, with a stable dosage for at least 30 days; HbA1c ≥8.0% and fasting C-peptide >0.7 mcg/l.

Exclusion criteria:

Patients with a history of ketoacidosis, unstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy; impaired hepatic function; impaired kidney function; anemia, or unstable or symptomatic cardiovascular or cerebrovascular conditions.

Comments:

Population: **Mean age:** 57.1 years **Ethnicity:** White (73%); other ethnicity information NR

Gender: 53% Female

Type 2 diabetes duration (SD): NR (NR) years

Intervention: added to insulin

Duration: 16 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	15mg	Pio-15	191	9.75 (0.10)	95.4 (17.6)	33.2 (5.4)	
Pioglitazone	30mg	Pio-30	188	9.84 (0.10)	98.7 (17.7)	34.3 (6.2)	
Placebo	NA	Placebo		9.75 (0.10)	95.4 (17.0)	33.2 (5.2)	

Laboratory measures:

	Pio-15	Pio-30	Placebo
HbA1c, least squares mean change from baseline at week 16: % (SD)			
	-0.99(0.08)	-1.26(0.08)	-0.26(0.08)
p vs Placebo	<0.0001	<0.0001	NA
Triglycerides, least squares mean change from baseline at week 16: mg/dL			
	+12.3	-27.2	+32.25
p vs Placebo	NS	<=0.05	NA
HDL-c, least squares mean change from baseline at week 16: mg/dL			
	+3.1	+3.9	-0.1
p vs Placebo	<=0.05	<=0.05	NA
Total cholesterol, least squares mean change from baseline at week 16: mg/dL			
	+3.0	+0.8	-1.4
p vs Placebo	NS	NS	NA
LDL-c, least squares mean change from baseline at week 16: mg/dL			
	+6.4	+3.4	-1.8
p vs Placebo	<=0.05	NS	NA

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Rosenstock J, 2002 **Quality rating: Fair**

Laboratory measures:

	Pio-15	Pio-30	Placebo
HbA1c, least squares mean change from baseline at week 16: % (SD)			
	-0.99(0.08)	-1.26(0.08)	-0.26(0.08)
p vs Placebo	<0.0001	<0.0001	NA
Triglycerides, least squares mean change from baseline at week 16: mg/dL			
	+12.3	-27.2	+32.25
p vs Placebo	NS	<=0.05	NA
HDL-c, least squares mean change from baseline at week 16: mg/dL			
	+3.1	+3.9	-0.1
p vs Placebo	<=0.05	<=0.05	NA
Total cholesterol, least squares mean change from baseline at week 16: mg/dL			
	+3.0	+0.8	-1.4
p vs Placebo	NS	NS	NA
LDL-c, least squares mean change from baseline at week 16: mg/dL			
	+6.4	+3.4	-1.8
p vs Placebo	<=0.05	NS	NA

Physiologic outcomes:

	Pio-15	Pio-30	Placebo
Weight, change from baseline at week 16: kg			
	2.3	3.7	-0.4
p-values NR			

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Satoh N, 2003 **Quality rating: Poor**

Design:

Study design: CT Ope Parallel **Run-in :** None **Setting:** Multicenter
Wash out : None **Country:** Japan

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	136	NR/	NR/	136

Inclusion criteria:
Persons in the outpatient clinics with DM2, stable and relatively high blood glucose, A1c 7.0-9.0%.

Exclusion criteria:
Persons taking ACE inhibitors or angiotensis II receptor antagonists

Comments:
If taking SU prior to study, continued at same dosage.
SEM are given in paper; converted to SD for reporting of demographic data; left as SEM for outcomes data

Population: **Mean age:** 59.9 years **Ethnicity:** NR
Gender: 53% Female
Type 2 diabetes duration (SD): NR (NR) years

Intervention: CCT, poor Q, Kevin

Duration: 13 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	30mg qd	Pio	70	8.1 (0.8)	NR (NR)	23.4 (3.3)	
No treatment	NA	Control	66	8.0 (1.6)	NR (NR)	23.0 (4.1)	

Laboratory measures:

	Pio-Base	Control-Base	Pio-F/U	Control-F/U
A1C, baseline and 3-month follow-up: % (SE)				
	8.1(0.1)	8.0(0.2)	7.1(0.1)	7.9(0.2)
	NR	NR	NR	NR
FPG, baseline and 3-month follow-up: mmol/l (SE)				
	9.6(0.4)	9.4(0.3)	8.0(0.3)	9.2(0.3)
p vs no treatment	NR	NR	p<0.01	NR
Total cholesterol, baseline and 3-month follow-up: mmol/l (SE)				
	5.46(0.1)	5.45(0.16)	5.33(0.1)	5.46(0.17)
p vs no treatment	NR	NR	NS	NR
LDL, baseline and 3-month follow-up: mmol/l (SE)				
	3.30(0.08)	3.32(0.11)	3.17(0.08)	3.33(0.12)
p vs no treatment	NR	NR	NS	NR
p vs pioglitazine ba	NR	NR	0.05	NR
HDL, baseline and 3-month follow-up: mmol/l (SE)				
	1.44(0.05)	1.47(0.10)	1.47(0.05)	1.43(0.11)
p vs no treatment	NR	NR	NR	NR
Triglycerides, baseline and 3-month follow-up: mmol/l (SE)				
	1.56(0.04)	1.55(0.04)	1.50(0.04)	1.55(0.04)
p vs no treatment	NR	NR	NS	NR

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Satoh N, 2003 **Quality rating: Poor**

Laboratory measures:

	Pio-Base	Control-Base	Pio-F/U	Control-F/U
A1C, baseline and 3-month follow-up: % (SE)				
	8.1(0.1)	8.0(0.2)	7.1(0.1)	7.9(0.2)
	NR	NR	NR	NR
FPG, baseline and 3-month follow-up: mmol/l (SE)				
	9.6(0.4)	9.4(0.3)	8.0(0.3)	9.2(0.3)
p vs no treatment	NR	NR	p<0.01	NR
Total cholesterol, baseline and 3-month follow-up: mmol/l (SE)				
	5.46(0.1)	5.45(0.16)	5.33(0.1)	5.46(0.17)
p vs no treatment	NR	NR	NS	NR
LDL, baseline and 3-month follow-up: mmol/l (SE)				
	3.30(0.08)	3.32(0.11)	3.17(0.08)	3.33(0.12)
p vs no treatment	NR	NR	NS	NR
p vs pioglitazine ba	NR	NR	0.05	NR
HDL, baseline and 3-month follow-up: mmol/l (SE)				
	1.44(0.05)	1.47(0.10)	1.47(0.05)	1.43(0.11)
p vs no treatment	NR	NR	NR	NR
Triglycerides, baseline and 3-month follow-up: mmol/l (SE)				
	1.56(0.04)	1.55(0.04)	1.50(0.04)	1.55(0.04)
p vs no treatment	NR	NR	NS	NR

Physiologic outcomes:

	Pio-Base	Control-Base	Pio-F/U	Control-F/U
SBP, baseline and 3-month follow-up (SE)				
	144(2)	146(2)	145(2)	146(3)
p vs no treatment	NR	NR	NS	NR
DBP, baseline and 3-month follow-up (SE)				
	81(2)	82(2)	81(2)	82(2)
p vs no treatment	NR	NR	NS	NR
BMI, baseline and 3-month follow-up: kg/m2 (SE)				
	23.4(0.4)	23.0(0.5)	23.5(0.4)	23.2(0.5)
	NR	NR	NR	NR
SBP, baseline and 3-month follow-up (SE)				
	144(2)	146(2)	145(2)	146(3)
	NR	NR	NR	NR
DBP, baseline and 3-month follow-up (SE)				
	81(2)	82(2)	81(2)	82(2)
	NR	NR	NR	NR

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Satoh N, 2003 **Quality rating: Poor**

Laboratory measures:

	Pio-Base	Control-Base	Pio-F/U	Control-F/U
A1C, baseline and 3-month follow-up: % (SE)				
	8.1(0.1)	8.0(0.2)	7.1(0.1)	7.9(0.2)
	NR	NR	NR	NR
FPG, baseline and 3-month follow-up: mmol/l (SE)				
	9.6(0.4)	9.4(0.3)	8.0(0.3)	9.2(0.3)
p vs no treatment	NR	NR	p<0.01	NR
Total cholesterol, baseline and 3-month follow-up: mmol/l (SE)				
	5.46(0.1)	5.45(0.16)	5.33(0.1)	5.46(0.17)
p vs no treatment	NR	NR	NS	NR
LDL, baseline and 3-month follow-up: mmol/l (SE)				
	3.30(0.08)	3.32(0.11)	3.17(0.08)	3.33(0.12)
p vs no treatment	NR	NR	NS	NR
p vs pioglitazine ba	NR	NR	0.05	NR
HDL, baseline and 3-month follow-up: mmol/l (SE)				
	1.44(0.05)	1.47(0.10)	1.47(0.05)	1.43(0.11)
p vs no treatment	NR	NR	NR	NR
Triglycerides, baseline and 3-month follow-up: mmol/l (SE)				
	1.56(0.04)	1.55(0.04)	1.50(0.04)	1.55(0.04)
p vs no treatment	NR	NR	NS	NR

Physiologic outcomes:

	Pio-Base	Control-Base	Pio-F/U	Control-F/U
DBP, baseline and 3-month follow-up (SE)				
	81(2)	82(2)	81(2)	82(2)
	NR	NR	NR	NR

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Scherbaum W, 2002 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** None **Setting:** Multicenter

Wash out : 70 days **Country:** Germany

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	509/	492/	252	52/	NR/	235

Inclusion criteria:

Men and women ages 35-70 years with DM2. At screening, BMI values between 25 and 35, HbA1c values between 7.5% and 12%, and FBG levels between 140 mg/dl and 300 mg/dl (≤250 mg/dl at the end of the washout period). Female participants had to be postmenopausal, surgically sterilized, or using appropriate contraceptive methods to avoid pregnancy.

Exclusion criteria:

DM1, secondary failure to treatment with sulphonylureas, or requirement for other antidiabetic treatment. History of ketoacidosis, malabsorption, acute or chronic pancreatitis, liver disease, significant ventricular hypertrophy, complex cardiac arrhythmias, angina pectoris, heart failure, MI, hypertension, stroke, or hypothyroidism. History of TIA or stroke, significant anemia of any etiology, clinically relevant hematological or malignant disease in the last 10 years, HIV infection, alcohol or drug abuse, or participation in a clinical trial in the 3 months prior to the study.

Comments:

Population: **Mean age:** 58.9 years **Ethnicity:** NR

Gender: 46% Female

Type 2 diabetes duration (SD): 5.2 (NR) years

Intervention: monotherapy

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	15 mg	Pio-15	89	9.33 (NR)	87.2 (NR)	29.9 (NR)	
Pioglitazone	30 mg	Pio-30	78	9.06 (NR)	82 (NR)	29.3 (NR)	
Placebo	NA	Placebo	84	8.75 (NR)	84.8 (NR)	29.2 (NR)	

Laboratory measures:

	Pio-15	Pio-30	Placebo
HbA1c, change from baseline at week 26: % (SD)			
	-0.92(1.5)	-1.05(1.25)	-0.34(0.98)
p vs Placebo	NS	>0.003	NA
Fasting blood glucose, change from baseline at week 26: mg/dl (SD)			
	-34.3(50.8)	-36.0(62.6)	+2.4(46.3)
p vs Placebo	0.004	<0.001	NA

Physiologic outcomes:

	Pio-15	Pio-30	Placebo
Weight, change from baseline at week 25: kg (SD)			
	+0.3(NR)	+0.8(NR)	-1.1(NR)
p-values NR			

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Smith S, 2004; Bogacka I, 2004 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** None **Setting:** NR
Wash out : None **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	48/	48	6/	NR/	42

Inclusion criteria:

Ages 35-75 years, with DM2 as defined by a fasting plasma glucose of 125 mg/kl or higher at entry or fasting plasma glucose of more than 115 mg/dl and a 2h oral glucose tolerance test glucose of 200 mg/dl or higher. FPG at entry of 200 mg/dl or less. For women, use of adequate contraceptive control (oral contraceptives, hysterectomy, tubal ligation, or postmenopausal status).

Exclusion criteria:

Significant renal, cardiac, liver, lung, or neurological disease, although controlled hypertension was acceptable if baseline blood pressure was less than 140/90 mmHg on medications. Patients with prior use of TZDs, beta blockers, current pregnancy, smokers, alcohol or other drug abuse, or unwilling to abstain from caffeine for 48 hours and alcohol for 24 hours before metabolic rate measurements. Liver function tests at baseline greater than 2.5 times the ULN; metal objects that would interfere with the measurement of visceral fat with CT such as implanted rods or surgical clips. Taking drugs known to affect lipid metabolism, energy metabolism, or body weight, such as orlistat, sibutramine, ephedrine, phenylpropanolamine, or corticosteroids.

Comments:

Population: **Mean age:** 54.7 years **Ethnicity:** White (73.8%); Other (26.2%)
Gender: 55% Female
Type 2 diabetes duration (SD): NR (NR) years

Intervention: added to metformin or sulfonylurea

Duration: 24 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	45mg	Pio	21	6.88 (1.35)	93.5 (19.6)	NR (NR)	
Placebo	NA	Placebo	21	6.46 (0.72)	91.5 (14.9)	NR (NR)	

Laboratory measures:

	Pio	Placebo
HbA1c, change from baseline at week 24: % (SD)		
	-0.96(1.11)	-0.11(0.79)
p vs Placebo	0.0054	NA
Fasting blood glucose, change from baseline at week 12: % (SD)		
	-27.05(31.47)	-6.41(40.25)
p-value not reported for week 12		
Fasting blood glucose, change from baseline at week 24: % (SD)		
	-25.10(25.69)	+2.40(33.65)
p vs Placebo	0.0031	NA
Triglycerides, change from baseline at week 12: mg/dl (SD)		
	-54.18(134.85)	-18.23(77.35)
p-value not reported for week 12		

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Smith S, 2004; Bogacka I, 2004 **Quality rating: Poor**

Triglycerides, change from baseline at week 24: mg/dl (SD)		
	-58.52(123.26)	-2.36(59.87)
p vs Placebo	0.0035	NA
HDL-c, change from baseline at week 12: mg/dl (SD)		
	+6.68(6.10)	+2.34(4.25)
p-value not reported for week 12		
HDL-c, change from baseline at week 24: mg/dl (SD)		
	+7.77(5.22)	+1.44(3.77)
p vs Placebo	0.0003	NA
LDL-c, change from baseline at week 12: mg/dl (SD)		
	+10.81(37.71)	+1.65(14.21)
p-value not reported for week 12		
LDL-c, change from baseline at week 24: mg/dl (SD)		
	+18.29(26.86)	+6.78(18.97)
p vs Placebo	0.3538	NA
Total cholesterol, change from baseline at week 12: mg/dl (SD)		
	+11.50(38.82)	+3.36(20.12)
p-value not reported for week 12		
Total cholesterol, change from baseline at week 24: mg/dl (SD)		
	+19.57(26.14)	+8.19(20.88)
p vs Placebo	0.3822	NA

Physiologic outcomes:

	Pio	**Placebo**
Weight, change from baseline at week 24: kg (SD)		
	+3.88(3.11)	-0.79(3.36)
p-value NR		

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Takagi T, 2003 **Quality rating: Poor**

Design:

Study design: RCT NR Parallel **Run-in :** None **Setting:** Single Center

Wash out : None **Country:** Japan

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed

NR/ NR/ NR NR/ NR/ 44

Inclusion criteria:

Patients with DM2 who underwent successful coronary stent implantation between 12/1999 and 9/2000 in Kobe General Hospital; on oral hypoglycemic agents or insulin; FPG ≥126 mg/dl; plasma glucose ≥200 mg/dl 2h after 75-g oral glucose load

Exclusion criteria:

Patients with liver or renal dysfunction; unsuccessful reperfusion after coronary stent implantation; cardiogenic shock or congestive heart failure

Comments:

No information on attrition; only data on completers presented (including baseline data)

Population: **Mean age:** 64 years **Ethnicity:** NR

Gender: 23% Female

Type 2 diabetes duration (SD): NR (NR) years

Intervention: monotherapy

Duration: 6 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	30mg	Pio	23	6.8 (0.6)	NR (NR)	25.6 (2.8)	
No treatment	NA	Control	21	6.5 (1.3)	NR (NR)	24.5 (2.9)	

Laboratory measures:

	Pio	Control
A1c, change from baseline to 6 months: % (SD)		
	-0.3(NR)	-0.2(NR)
p vs no treatment	NSD	NA
HDL, change from baseline to 6 months: mg/dl (SD)		
	5(NR)	2(NR)
p vs no treatment f	0.3003	NA
TG, change from baseline to 6 months: mg/dl		
	-30(NR)	0(NR)
p vs no treatment f	0.5334	NA
LDL, change from baseline to 6 months: mg/dl		
	2(NR)	-10(NR)
p vs no treatment f	0.9813	NA
Total cholesterol, change from baseline to 6 months: mg/dl		
	0(NR)	-9(NR)
p vs no-treatment f	0.7156	NA

P value NR if not specified.

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Wallace T, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** None **Setting:** Single Center
Wash out : None **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	30	NR/	NR/	30

Inclusion criteria:
Ages 45-74 with diet-treated DM2

Exclusion criteria:
Cardiac failure, previous MI, abnormal liver function tests, or impaired renal function

Comments:

Population: **Mean age:** 61.8 years **Ethnicity:** NR
Gender: 27% Female
Type 2 diabetes duration (SD): 2.6 (NR) years

Intervention: monotherapy

Duration: 12 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	45mg	Pio	19	6.7 (0.9)	90.7 (3.6)	NR (NR)	
Placebo	NA	Placebo	11	6.7 (0.9)	85.2 (4.3)	NR (NR)	

Laboratory measures:

	Pio	Placebo
HbA1c, change from baseline to week 12: % (SE)		
	-0.3(0.1)	+0.3(0.1)
p vs Placebo	0.003	NA
Fasting blood glucose, change from baseline to week 12: mmol/l (SE)		
	-1.1(0.2)	+0.1(0.2)
p vs Placebo	0.001	NA
Total cholesterol, change from baseline to week 16: mmol/l (SE)		
	-0.02(0.11)	-0.02(0.13)
p vs Placebo	NS	NA
HDL-c, change from baseline to week 16: mmol/l (SE)		
	+0.14(0.03)	+0.02(0.04)
p vs Placebo	0.02	NA
LDL-c, change from baseline to week 16: mmol/l (SE)		
	+0.04(0.12)	+0.1(0.14)
p vs Placebo	NS	NA
Triglycerides, change from baseline to week 16: mmol/l (SE)		
	-0.62(0.31)	+0.36(0.14)
p vs Placebo	NS	NA

Evidence Table 4. Efficacy - Placebo-controlled trials type 2 diabetes, pioglitazone

Wallace T, 2004 **Quality rating: Fair**

Laboratory measures:

	Pio	Placebo
HbA1c, change from baseline to week 12: % (SE)		
	-0.3(0.1)	+0.3(0.1)
p vs Placebo	0.003	NA
Fasting blood glucose, change from baseline to week 12: mmol/l (SE)		
	-1.1(0.2)	+0.1(0.2)
p vs Placebo	0.001	NA
Total cholesterol, change from baseline to week 16: mmol/l (SE)		
	-0.02(0.11)	-0.02(0.13)
p vs Placebo	NS	NA
HDL-c, change from baseline to week 16: mmol/l (SE)		
	+0.14(0.03)	+0.02(0.04)
p vs Placebo	0.02	NA
LDL-c, change from baseline to week 16: mmol/l (SE)		
	+0.04(0.12)	+0.1(0.14)
p vs Placebo	NS	NA
Triglycerides, change from baseline to week 16: mmol/l (SE)		
	-0.62(0.31)	+0.36(0.14)
p vs Placebo	NS	NA

Physiologic outcomes:

	Pio	Placebo
Weight, change from baseline to week 16: kg (SE)		
	+0.7(0.6)	+1.1(0.5)
p vs Placebo	NS	NA
BMI, change from baseline to week 16: kg/m2 (SE)		
	+0.2(0.2)	+0.4(0.2)
p vs Placebo	NS	NA

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Agrawal A, 2003 **Quality rating: Fair, based on 2' data**

Design:

Study design: RCT DB Parallel **Run-in :** 14-28 days **Setting:** Multicenter
Wash out : NR **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	824	NR/	NR/	801

Inclusion criteria:
Patients currently treated with sulfonylureas.

Exclusion criteria:
Patients of child-bearing potential, serum creatinine level >1.8 mg/dl

Comments:
Rosi added to glibenclamide, gliclazide or glipizide.
This paper is a post hoc analysis of the results of 3 similar RCTs obtained from a literature review; no citations given.

Population: **Mean age:** 61.6 years **Ethnicity:** NR
Gender: 38% Female
Type 2 diabetes duration (SD), year: 9.3 (NR)

Intervention: added to sulfonylurea, 2' data

Duration: 6 months

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	2mg	Rosi	405	9.2 (1.3)	NR (NR)	31.0 (4.0)	
Placebo	NA	Placebo	419	9.2 (1.4)	NR (NR)	30.7 (4.0)	

Laboratory measures:

	Rosi	Placebo
A1c, renally impaired, change from baseline at 6 months: %	-0.7	+0.4
A1c, non-renally impaired, change from baseline to 6m: %	-0.6	+0.5
FPG, renally impaired, change from baseline to 6m: mmol/l	-2.1	-1.6
FPG, non-renally impaired, change from baseline to 6m: mmol/l	+0,5	+1.0

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Barnett A, 2003 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : NR **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	177/	171	0/	0/	171

Inclusion criteria:
Patients with DM2, taking sulphonylurea for at least 4 months with dose unchanged within 2 months before start of study, those taking medications that affect glucose or lipids were eligile if doses remained constant at screening and during study period

Exclusion criteria:
Patients of child-bearing potential, severe hypertension, anemia or blood disorders, congestive heart failure, significant liver disease, a weight variance of >5% between screening and baseline

Comments:

Population: **Mean age:** 54.2 years **Ethnicity:** Indian: 60%; Pakistani: 27%; Bangladeshi: 9.5%; Sri Lankan: 3%; Mauritian: less than 1%
Gender: 22% Female
Type 2 diabetes duration (SD), year: NR (NR)

Intervention: added to sulfonylurea

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg	Rosi	84	9.21 (1.27)	NR (NR)	26.8 (NR)	
Placebo	NA	Placebo	87	9.06 (1.30)	NR (NR)	26.4 (NR)	

Laboratory measures:

	Rosi	Placebo
A1c, change from baseline to 26 weeks: %		
	-1.16	+0.26
p vs Placebo	0.001	NR
Fasting plasma glucose, change from baseline to 26 weeks: mmol/l		
	-2.5	+0.2
p vs Placebo	0.001	

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Choi D, 2004 **Quality rating: Poor**

Design:

Study design: RCT Ope Parallel **Run-in :** no days **Setting:** Single Center

Wash out : no days **Country:** Korea

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	95	4/	8/	83

Inclusion criteria:

Previously treated diabetes on oral agents or insulin who had recent acute MI or stable or unstable angina and underwent coronary stent implantation at the study university hospital.

Exclusion criteria:

Previously treated with TZDs, ejection fraction <35%, liver or renal dysfunciotn or a pregnancy, lesions of reference vessel diameter <2.75 mm.

Comments:

Population: **Mean age:** 59.9 years **Ethnicity:** Not reported

Gender: 39% Female

Type 2 diabetes duration (SD), year: 7.4

Intervention: added to various

Duration: 6 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosi-4	4 mg qd	Rosi-4	38	7.79 (1.3)	67.6 (10.0)	24.9 (2.96)	
Usual care			45	7.72 (1.13)	68.1 (11.0)	24.8 (3.35)	

Laboratory measures:

	Rosi-4	Usual care
A1c, change from baseline to 6 months: % (SD)		
	-0.61(1.15)	-0.75(1.07)
p vs usual care	NS	NA
FPG, change from baseline to 6 months: mmol/l (SD)		
	-1.68(1.17)	-2.03(1.43)
p vs usual care	NS	NA
Fasting insulin, change from baseline to 6 months: pmol/l (SD)		
	-5.8(16.4)	-1.4(15.3)
p vs usual care	NS	NA
analyses excluded insulin-treated patients		
Total cholesterol, change from baseline to 6 months: mmol/l (SD)		
	-0.59(0.93)	-0.50(0.94)
p vs usual care	NS	NA
HDL-c, change from baseline to 6 months: mmol/l (SD)		
	0.11(0.21)	0.08(0.22)
p vs usual care	NS	NA
Triglycerides, change from baseline to 6 months: mmol/l (SD)		
	-0.55(0.56)	-0.29(0.57)
p vs usual care	NS	NA

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Choi D, 2004 **Quality rating: Poor**

Laboratory measures:

	Rosi-4	Usual care
A1c, change from baseline to 6 months: % (SD)		
	-0.61(1.15)	-0.75(1.07)
p vs usual care	NS	NA
FPG, change from baseline to 6 months: mmol/l (SD)		
	-1.68(1.17)	-2.03(1.43)
p vs usual care	NS	NA
Fasting insulin, change from baseline to 6 months: pmol/l (SD)		
	-5.8(16.4)	-1.4(15.3)
p vs usual care	NS	NA
analyses excluded insulin-treated patients		
Total cholesterol, change from baseline to 6 months: mmol/l (SD)		
	-0.59(0.93)	-0.50(0.94)
p vs usual care	NS	NA
HDL-c, change from baseline to 6 months: mmol/l (SD)		
	0.11(0.21)	0.08(0.22)
p vs usual care	NS	NA
Triglycerides, change from baseline to 6 months: mmol/l (SD)		
	-0.55(0.56)	-0.29(0.57)
p vs usual care	NS	NA

Health outcomes:

	Rosi-4	Usual care
Death at 6 months: n (%) (%)		
	0(0)	0(0)
p vs usual care	NS	NA
Target lesion revascularization at 6 months: n (%) (%)		
	4(10.5)	9(20)
p vs usual care	0.244	NA
Major adverse cardiac events (deathm Q-wasve MI, or target lesion revascularization) : n (%)		
	4(10.5)	9(20)
p vs usual care	0.244	NA

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Fonseca V, 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 28 days **Setting:** Multicenter

Wash out : 28 days **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	443/	410/	348	51/	7/	348

Inclusion criteria:

Persons with DM2 between 40 and 80 years of age, with FPG 7.8-16.7 mmol/L at screening and during the placebo-maintenance period while taking 2.5 g/d of metformin; fasting C-peptide ≥ 0.27 nmol/L; BMI 22-38; weight change of no more than 10% between screening and baseline

Exclusion criteria:

Significant renal or hepatic disease, angina, New York Heart Association Class III or IV cardiac insufficiency, symptomatic diabetic neuropathy, significant clinical ECG abnormality, abnormal laboratory test results (blood chemistry, hematology, urinalysis); chronic use of insulin therapy; participated in any Rosi-related study; used an investigational drug (excluding metformin) within 30d of study; anorectic agents were discontinued ≥ 30d before screening; lipid-lowering agents were maintained at same dosage level throughout the study

Comments:

Setting:
36 sites in USA.

Population: **Mean age:** 58 years **Ethnicity:** 80% White, 7% Black, 13% other

Gender: 32% Female

Type 2 diabetes duration (SD), year: 7.3 (5.7)

Intervention: added to metformin

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg	Rosi-4	119	8.9 (1.3)	NR (NR)	30.2 (4.2)	
Rosiglitazone	8mg	Rosi-8	110	8.9 (1.5)	NR (NR)	29.8 (3.9)	
Placebo	NA	Placebo	113	8.6 (1.3)	NR (NR)	30.3 (4.4)	

Laboratory measures:

	Rosi-4	Rosi-8	Placebo
A1c, change from baseline at week 26: %			
	-0.56	-0.78	0.45
p vs Placebo	p<0.001	p<0.001	
% who achieved 1% reduction in A1c: %			
	-32.8	37.3	7.1
FPG, change from baseline to week 26: mg/dl			
	-33.0	-48.4	5.9
p vs Placebo	p<0.001	p<0.001	
Total cholesterol, change from baseline to week 26: mmol/L			
	0.72(0.74)	0.82(1.07)	0.18(0.61)
p vs Placebo	p<0.0001	p<0.0001	

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Fonseca V, 2000				**Quality rating: Fair**
HDL, change from baseline to week 26: mmol/L				
	0.13(0.19)	0.16(0.24)	0.06(0.14)	
p vs Placebo	p=0.0002	p=0.0002		
LDL, change from baseline to week 26: mmol/L				
	0.46(0.58)	0.53(0.76)	0.1(0.44)	
p vs Placebo	p<0.0001	p<0.0001		
TG, change from baseline to week 26: mmol/L				
	0.08(1.35)	-0.0003(1.72)	0.008(1.32)	
p vs Placebo	0.53	0.98		

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Gomez-Perez F, 2002 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 28 days **Setting:** Multicenter
Wash out : None **Country:** Mexico

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed
169/ NR/ 116 26/ 5/ 105

Inclusion criteria:
Men and women of non-childbearing potential with type DM2, 40 to 80, fasting C-peptide level ≥ 0.8 ng/ml at screening, FPG level ≥140 mg/dl and ≤300 mg/dl at weeks 0 and 2 of the metformin maintenance period, respectively.

Exclusion criteria:
Clinically significant renal or hepatic disease, anemia, severe cardiac disease, left ventricular hypertrophy, and hypertension.

Comments:

Population: **Mean age:** 53.1 years **Ethnicity:** White (4.8%); Hispanic (76.2%); Other (19.0%)
Gender: 74% Female
Type 2 diabetes duration (SD), year: 10.3 (NR)

Intervention: added to metformin

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg	Rosi-4	35	10.2 (NR)	NR (NR)	28.0 (4.0)	
Rosiglitazone	8mg	Rosi-8	36	9.7 (Nr)	NR (NR)	27.6 (3.2)	
Placebo	NA	Placebo	34	9.8 (NR)	NR (NR)	28.5 (3.9)	

Laboratory measures:

	Rosi-4	Rosi-8	Placebo
A1c, change from baseline to 26 weeks: %			
	-0.7	-1.2	+0.3
p vs Placebo	0.0132	0.0002	NA
FPG, change from baseline to 26 weeks: mg/dl			
	-45.1	-62.5	+3.7
p vs Placebo	0.0019	<0.001	NA
A1c, proportion of patients who achieved response (>=0.7% reduction from baseline) at 26 weeks: %			
	54.3	61.1	23.5
p vs Placebo	<0.05	<0.05	NA
Total cholesterol, change from baseline to 26 weeks: mg/dL (SD)			
	+14.6(28.2)	+21.6(26.8)	+2.0(28.8)
LDL cholesterol, change from baseline to 26 weeks: mg/dL (SD)			
	+6.1(22.5)	+16.6(24.7)	-1.0(20.9)
HDL cholesterol, change from baseline to 26 weeks: mg/dL (SD)			
	+5.2(7.9)	+6.4(7.0)	-0.5(7.2)
p vs Placebo	<0.05	<0.05	NA

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Gomez-Perez F, 2002 **Quality rating: Fair**

Laboratory measures:

	Rosi-4	Rosi-8	Placebo
A1c, change from baseline to 26 weeks: %			
	-0.7	-1.2	+0.3
p vs Placebo	0.0132	0.0002	NA
FPG, change from baseline to 26 weeks: mg/dl			
	-45.1	-62.5	+3.7
p vs Placebo	0.0019	<0.001	NA
A1c, proportion of patients who achieved response (>=0.7% reduction from baseline) at 26 weeks: %			
	54.3	61.1	23.5
p vs Placebo	<0.05	<0.05	NA
Total cholesterol, change from baseline to 26 weeks: mg/dL (SD)			
	+14.6(28.2)	+21.6(26.8)	+2.0(28.8)
LDL cholesterol, change from baseline to 26 weeks: mg/dL (SD)			
	+6.1(22.5)	+16.6(24.7)	-1.0(20.9)
HDL cholesterol, change from baseline to 26 weeks: mg/dL (SD)			
	+5.2(7.9)	+6.4(7.0)	-0.5(7.2)
p vs Placebo	<0.05	<0.05	NA

Physiologic outcomes:

	Rosi-4	Rosi-8	Placebo
Weight, change from baseline to 26 weeks: kg (95% CI)			
	+0.26(-0.87, +1.38)	+2.42(+1.22, +3.62)	-0.86(-1.88, +0.16)

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Honisett S, 2003 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** NR
Wash out : NR **Country:** Austrialia

Sample:

Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
NR/	NR/	31	0/	0/	31

Inclusion criteria:
Women, diagnosed with DM2 (1-12y prior)

Exclusion criteria:
None reported

Comments:

Population: **Mean age:** NR years **Ethnicity:** NR
Gender: 100% Female
Type 2 diabetes duration (SD), year: 1-12

Intervention: monotherapy

Duration:

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg qd	Rosi	21	7.6 (0.7)	NR (NR)	NR (NR)	
Placebo	NA	Placebo	10	NR (NR)	NR (NR)	NR (NR)	

Laboratory measures:

	Rosi-4	Placebo
Fasting plasma glucose, change baseline to 12weeks: mmol (SD)		
	-2.3(NR)	NR(NR)
	0.001	NSD
HbA, change from baseline to 12weeks: % (SD)		
	-1.2(NR)	NR(NR)
	0.001	NSD

Physiologic outcomes:

	Rosi-4	Placebo
Brachial systolic blood pressure, change from baseline to 12 weeks: mmHg (SD)		
	-12(NR)	NR(NR)
	0.003	NSD
Central systolic blood pressure, change from baseline to 12 weeks: mmHg (SD)		
	-7.0(NR)	NR(NR)
	0.02	NSD
Diastolic blood pressure, change from baseline to 12 weeks: mmHg (SD)		
	-6.0(NR)	NR(NR)
	0.004	NSD

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Jones T, 2003 **Quality rating: Fair**

Design:

Study design: RCT DB Open **Run-in :** 28 days **Setting:** NR
Wash out : NR **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	550	NR/	NR/	548

Inclusion criteria:

Patients of non-child-bearing potential, aged 40-80 years, diagnosed with DM2, fasting C-peptide >0.8 ng/ml at screening, maintaining a FPG level (between >140 mg/dL- <300 mg/dL) prior to randomization.

Exclusion criteria:

Patients with clinically significant renal or hepatic disease, angina, cardiac insufficiency, symptomatic diabetic neuropathy, significant clinical abnormality on electocardiogram, history of chronic insulin therapy, participation in any previous RSG-related studies, use of any investigational drug within 30 days of study.

Comments:

Population: **Mean age:** 59.9 years **Ethnicity:** NR
Gender: 32% Female
Type 2 diabetes duration (SD), year: NR (NR)

Intervention: added to metformin

Duration: 6 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg	Rosi-4	116	8.8 (1.3)	NR (NR)	27.7 (1.3)	+2.5g/day metformin
Rosiglitazone	8mg	Rosi-8	215	8.8 (1.3)	NR (NR)	27.7 (1.3)	+2.5g/day metformin
Metformin	2.5 g qd	Met	NR	8.8 (1.4)	NR (NR)	27.7 (1.4)	

Laboratory measures:

	Met	Rosi-4	Rosi-8
A1c, change from baseline at week: %			
	+0.3	-0.43	-0.54
p vs metformin	NR	NR	NR
A1c, Non-overweight population, change from baseline to 6 months: %			
	+0.3(NR)	-0.50(NR)	-0.30(NR)
p vs Met	NR	NR	0.025
A1c, Overweight population, change from baseline to 6 months: % (SD)			
	+0.10(NR)	-0.50(NR)	-0.75(NR)
p vs Met	NR	0.025	0.025
A1c, Obese population, change from baseline to 6 months: % (SD)			
	+0.2(NR)	-0.70(NR)	-0.90(NR)
p vs Met	NR	0.025	0.025
Fasting plasma glucose, Non-overweight population, change from baseline to 6 months: mmol/L (SD)			
	+0.30(NR)	--1.50(NR)	-1.50(NR)
p vs Met	NR	0.025	0.025

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Jones T, 2003 **Quality rating: Fair**

Fasting plasma glucose, Overweight population, change from baseline to 6 months: mmol/L (SD)			
	+0.50(NR)	-1.60(NR)	-2.5(NR)
p vs Met	NR	0.025	0.025
Fasting plasma glucose, Obese population, change from baseline to 6 months: mmol/L (SD)			
	-0.30(NR)	-1.75(NR)	-3.5(NR)
p vs Met	NA	0.025	0.025

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Kim Y, 2005 **Quality rating: Fair**

Design:

Study design: RCT NR Open **Run-in :** NR **Setting:** Single Center

Wash out : NR **Country:** South Korea

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed

NR/ NR/ 125 NR/ NR/ 120

Inclusion criteria:

Patients with fasting C-peptide level >1.1 ng/ml, taking metformin and/or sulfonylurea therapy at least 3 months, with unchanged dose for at least 2 months

Exclusion criteria:

Patients currently using insulin, having congestive heart failure, significant liver disease, impaired kidney function and anemia.

Comments:

Population: **Mean age:** 58.4 years **Ethnicity:** NR

Gender: 65% Female

Type 2 diabetes duration (SD), year: 11.0 (6.4)

Intervention: monotherapy

Duration: 12 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg qd	Rosi	63	9.7 (1.7)	61.5 (8.8)	23.9 (2.5)	
Control	NA	Control	62	9.3 (1.3)	62.3 (11.0)	24.5 (3.0)	

Laboratory measures:

	Rosi	Control
Fasting plasma glucose, change from baseline to 12 weeks: mmol/l (SD)		
	-3.4(NR)	-1.2(NR)
	0.001	0.05
p vs control	NR	NR
A1c, change from baseline to 12 weeks: % (SD)		
	-1.1(NR)	-0.10(NR)
	0.001	NSD
p vs control	NR	NR
Total cholestrol, change from baseline to 12 weeks: mmol/l (SD)		
	+0.14(NR)	-0.11(NR)
	NSD	NSD
p vs control	NR	NR
HDL cholestrol, change from baseline to 12 weeks: mmol/l (SD)		
	+0.20(NR)	-0.10(NR)
	NSD	NSD
p vs control	NR	NR

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Kim Y, 2005 **Quality rating: Fair**

LDL cholestrol, change from baseline to 12 weeks: mmol/l (SD)		
	+0.13(NR)	0.06(NR)
	NSD	NSD
p vs control	NR	NR
Triglycerides, change from baseline to 12 weeks: mmol/l (SD)		
	-0.01(NR)	-0.06(NR)
	NSD	NSD
p vs control	NR	NR

Physiologic outcomes:

	Rosi	Control
BMI, change from baseline to 12 weeks: kg/m (SD)		
	+0.5(NR)	0.0(NR)
	0.01	NSD
p vs control	NR	NR
Weight, change from baseline to 12 weeks: kg (SD)		
	+1.2(NR)	+0.1(NR)
	0.01	NSD
p vs control	NR	NR
SBP, change from baseline to 12 weeks: mmHg (SD)		
	-2.4(NR)	-1.9(NR)
	NSD	NSD
p vs control	NR	NR
DBP, change from baseline to 12 weeks: mmHg (SD)		
	-2.9(NR)	-1.7(NR)
	0.05	NSD
p vs control	NR	NR

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Lebovitz H, 2001 **Quality rating: Poor**

Design:

Study design: RCT DB Parallel **Run-in :** 28 days **Setting:** Multicenter
Wash out : NR **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	623	90/	NR/	493

Inclusion criteria:

Patients with a fasting glucose between 7.8-16.7 mmol/l, fasting plasma C-peptide level greater than 0.26 nmol/l, BMI between 22-38 kg/m at screen.

Exclusion criteria:

Patients with angina or cardiac insufficiency, renal impairment, hepatic disease, history of diabetic ketoacidosis, history of chronic insulin use, symptomatic diabetic neuropathy, a serious major illness compromising study participation, women of child-bearing potential.

Comments:

Population: **Mean age:** 60 years **Ethnicity:** White 74.2%; Black 8.7%; Other 17.0%
Gender: 48% Female
Type 2 diabetes duration (SD), year: 4.93 (NR)

Intervention: monotherapy

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Placebo	NA	Placebo	158	9.0 (1.7)	NR (NR)	NR (NR)	
Rosiglitazone	2mg qd	Rosi-2	166	9.0 (1.5)	NR (NR)	NR (NR)	
Rosiglitazone	4mg qd	Rosi-4	169	8.8 (1.6)	NR (NR)	NR (NR)	

Laboratory measures:

	Rosi-2	Rosi-4	Placebo
Patients achieving a mean HbA of <8% at 26 weeks: %			
	42.8	58.6	20.3
	NR	NR	NR
Fasting glucose level, change from baseline at 26 weeks: % (SD)			
	-2.11(2.91)	-3.0(2.85)	+1.05(3.58)
	0.05	0.05	NR
p vs Placebo	0.0001	0.0001	
Total cholestrol, change from baseline at 26 weeks: mmol/l (SD)			
	+0.66(1.17)	+0.73(1.13)	+0.15(0.72)
	0.05	0.05	0.05
HDL cholestrol, change from baseline at 26 weeks: mmol/l (SD)			
	+0.11(0.18)	+0.11(0.23)	+0.06(0.19)
	0.05	0.05	0.05
LDL cholestrol, change from baseline at 26 weeks: mmol/L (SD)			
	+0.43(0.70)	+0.61(0.81)	+0.15(0.65)
	0.05	0.05	0.05

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Lebovitz H, 2001 **Quality rating: Poor**

Laboratory measures:

	Rosi-2	Rosi-4	Placebo
Patients achieving a mean HbA of <8% at 26 weeks: %			
	42.8	58.6	20.3
	NR	NR	NR
Fasting glucose level, change from baseline at 26 weeks: % (SD)			
	-2.11(2.91)	-3.0(2.85)	+1.05(3.58)
	0.05	0.05	NR
p vs Placebo	0.0001	0.0001	
Total cholestrol, change from baseline at 26 weeks: mmol/l (SD)			
	+0.66(1.17)	+0.73(1.13)	+0.15(0.72)
	0.05	0.05	0.05
HDL cholestrol, change from baseline at 26 weeks: mmol/l (SD)			
	+0.11(0.18)	+0.11(0.23)	+0.06(0.19)
	0.05	0.05	0.05
LDL cholestrol, change from baseline at 26 weeks: mmol/L (SD)			
	+0.43(0.70)	+0.61(0.81)	+0.15(0.65)
	0.05	0.05	0.05

Physiologic outcomes:

	Rosi-2	Rosi-4	Placebo
Weight, change from baseline at 26 weeks: kg kg (SD)			
	+1.6(3.1)	+3.5(3.6)	-1.0(2.9)
	NR	NR	NR

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Miyazaki Y, 2001 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 42 days **Setting:** NR
Wash out : NR **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	29	0/	0/	29

Inclusion criteria:
Patients with DM2, fasting plasma glucose between 140-260 mg/dl.

Exclusion criteria:
Previous treatment with insulin or other TZD, evidence of cardiac, hepatic, renal or other chronic diseases, other medications that affect glucose metabolism, performing excessive physical exercise, stable body weight for 3 months before study.

Comments:

Population: **Mean age:** 55 years **Ethnicity:** NR
Gender: 45% Female
Type 2 diabetes duration (SD), year: 5 (NR)

Intervention: monotherapy, Rosi

Duration: 12 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Placebo	NA	Placebo	14	8.3 (1.5)	87.5 (18.7)	30.1 (3.7)	
Rosiglitazone	8mg qd	Rosi	15	8.7 (1.5)	86 (15.5)	30.0 (4.3)	

Laboratory measures:

	Rosi	Placebo
Fasting plasma glucose, change from baseline at 12 weeks: % (SD)		
	21.0(NR)	2.0(NR)
	0.01	NR
p vs Placebo	0.003	
A1c, change from baseline at 12 weeks: % (SD)		
	-1.3(NR)	-2.0(NR)
	0.01	NR
p vs Placebo	0.0001	
Total cholestrol, change from baseline at 12 weeks: mg/dL (SD)		
	+15.0(8.0)	-3.0(0.4)
	NR	NR
LDL cholestrol, change from baseline at 12 weeks: mg/dl (SD)		
	+8.0(NR)	+1.0(NR)
	NR	NR
HDL cholestrol, change from baseline at 12 weeks: mg/dL (SD)		
	+4.0(2.0)	-3.0(2.0)
p vs Placebo	0.01	NR

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Miyazaki Y, 2001 **Quality rating: Fair**

Triglycerides, change from baseline at 12 weeks: mg/dl (SD)		
	-2.0(NR)	48.0(NR)
	NR	NR

Physiologic outcomes:

	Rosi	Placebo
BMI, change from baseline at 24 weeks: kg/m (SD)		
	+1.3(NR)	0(NR)
p vs Placebo	0.0004	
Weight, change from baseline at 24 weeks: kg (SD)		
	+3.7(NR)	0(NR)
p vs Placebo	0.0003	

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Nolan J, 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 21 days **Setting:** Multicenter
Wash out : NR **Country:** Ireland

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	541/	NR/	380	NR/	NR/	348

Inclusion criteria:
Patients with DM2, with fasting plasma glucose of 7-15 mmol/l.

Exclusion criteria:
Patients treated with insulin, with diabeteic complications, serious renal, hepatic or hematological impairment, severe heart failure, pregnant or lactating women, women of child-bearing potential.

Comments:

Population: **Mean age:** 62.8 years **Ethnicity:** White: (94.2%); Black: (0%); Other: (2.6%)
Gender: 40% Female
Type 2 diabetes duration (SD), year: 5.47 (6.26)

Intervention: monotherapy

Duration: 8 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg qd	Rosi-4	95	NR (NR)	80.0 (12.6)	29.4 (4.3)	
Rosiglitazone	8 mg qd	Rosi-8	90	NR (NR)	81.2 (11.7)	29.1 (3.74)	
Rosiglitazone	12 mg qd	Rosi-12	91	NR (NR)	81.1 (13.6)	29.4 (4.0)	
Placebo	NA	Placebo	93	NR	81.3 (0.49)	29.6 (4.4)	

Laboratory measures:

	Rosi-4	Rosi-8	Rosi-12	Placebo
Fasting glucose, change from baseline to 8 weeks: mmol/l (SD)				
	-0.9(2.1)	-2.0(2.6)	-1.7(2.3)	0.4(3.1)
p vs Placebo	0.0003	0.0001	0.0001	
Fructosamine, change from baseline to 8 weeks: mmol/l (SD)				
	+10(48)	-10(56)	-9(43)	+24(44)
p vs Placebo	0.05	0.0001	0.0001	

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Patel J, 1999 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : 21 days **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	763/	NR/	380	69/	NR/	311

Inclusion criteria:
Patients with a fasting plasma glucose concentration >7.8 - <13.3 mmol/L, fasting C-peptide concentration >0.27.

Exclusion criteria:
Patients with clinically significant renal, hepatic disease, symptomatic angina pectoris, cardiac insufficiency, haematologic abnormalities, requirement of insulin therapy.

Comments:

Population: **Mean age:** 57.7 years **Ethnicity:** White 91.3%; Black 6.7%; Other 24.1%
Gender: 32% Female
Type 2 diabetes duration (SD), year: 5.2 (NR)

Intervention: monotherapy

Duration: 12 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	0.05 mg bid	Rosi-0.05	74	9.1 (NR)	NR (NR)	29.4 (3.8)	
Rosiglitazone	0.25mg bid	Rosi-0.25	72	8.9 (NR)	NR (NR)	28.6 (4.1)	
Rosiglitazone	1mg bid	Rosi-1	79	9.0 (NR)	NR (NR)	29.5 (4.1)	
Rosiglitazone	2mg bid	Rosi-2	80	9.0 (NR)	NR (NR)	28.4 (4.1)	
Placebo	NA	Placebo	75	9.1 (NR)	NR (NR)	28.9 (4.0)	

Laboratory measures:

	Rosi-0.05	Rosi-0.25	Rosi-1	Rosi-2	Placebo
			0.0001	0.0001	
A1c, change from baseline at 12 weeks: %					
	+0.6(0.14)	+0.6(0.14)	+0.1(0.13)	-0.1(0.13)	+0.3(0.13)
p vs Placebo	0.0569	0.0565	0.4716	0.0287	
Total cholestrol, change from baseline at 12 weeks: mg/dL (SD)					
	+5.9(3.41)	+10.4(3.34)	+9.0(3.21)	+26.9(3.15)	+5.7(3.29)
	NR	NR	NR	NR	NR
HDL, change from baseline at 12 weeks: mg/dL (SD)					
	-0.1(NR)	+1.2(NR)	+1.9(NR)	+5.6(NR)	+2.1(NR)
	NR	NR	NR	NR	NR
LDL, change from baseline at 12 weeks: mg/dL (SD)					
	+0.7(2.73)	+3.0(2.69)	+3.3(2.60)	+16.9(2.52)	+1.6(2.60)
	NR	NR	NR	NR	NR

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Patel J, 1999				**Quality rating: Fair**
Triglycerides, change from baseline at 12 weeks: mg/dL				
+26.7(16.30)	+23.8(16.0)	+6.9(15.36)	+17.3(15.13)	+16.1(15.7)

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Phillips S, 2001 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 28 days **Setting:** Multicenter
Wash out : NR **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	1503/	NR/	959	NR/	NR/	908

Inclusion criteria:
Patients aged 40-80 years, BMI 22-38 kg/m2, with DM2, FPG 7.8-16.7 mmol/l (140-300 mg/dl), fasting C-peptide > 0.27 nmol/l at screening.

Exclusion criteria:
Clinically significant renal disease, coronary insufficiency or congestive heart failure, symptomatic diabetic neuropathy, or elevations in total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), or aspartate aminotransferase >2.5 times the upper limit of the reference range.

Comments:
Setting: 65 US centers

Population: **Mean age:** 57.5 years **Ethnicity:** White: 72.7%; Black: 9%; Other: 12.8%
Gender: 40% Female
Type 2 diabetes duration (SD), year: 5.9 (6.14)

Intervention: monotherapy

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4 mg qd	Rosi-4qd	181	8.9 (1.6)	NR (NR)	29.9 (4.1)	
Rosiglitazone	4 mg bid	Rosi-4bid	187	9.0 (1.5)	NR (NR)	29.9 (4.3)	
Rosiglitazone	2 mg bid	Rosi-2bid	186	8.9 (1.5)	NR (NR)	30.0 (4.2)	
Rosiglitazone	8 mg qd	Rosi-8qd	181	8.9 (1.5)	NR (NR)	30.0 (4.3)	
Placebo	NA	Placebo	173	8.9 (1.5)	NR (NR)	29.1 (4.2)	

Laboratory measures:

	Rosi				
LDL, change from baseline to 26w, mmol/l: Median %					
	-1.6	+7.1	+6.2	+12.6	+10.3
	NR				
HDL, change from baseline to 26w, mmol/l: Median %					
	+5.3	+7.8	+7.7	+8.9	+10.9
	NR				
Total cholesterol, change from baseline to 26w, mmol/l: Median %					
	+0.8	+9.8	+7.2	+13.9	+10.6
	NR				
TG, change from baseline to 26w, mmol/l: Median %					
	+0.3	+12.5	+4.2	+8.4	-2.1
	NR				

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Phillips S, 2001				**Quality rating: Fair**
A1c, change from baseline to 26w: Median %				
NR	-0.8	-0.9	-1.1	-1.5
p vs Placebo	P<0.0001	p<0.0001	p<0.0001	p<0.0001
Physiologic outcomes:				
Rosi				
Weight, change from baseline to 26w: kg				
-0.9	1.2	1.5	2.6	3.3
p vs Placebo/baseli	p<0.0001	p<0.0001	p<0.0001	p<0.0001

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Raskin P, 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 14 days **Setting:** Multicenter
Wash out : 14 days **Country:** Usa

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	529/	NR/	303	NR/	NR/	284

Inclusion criteria:
Patients aged 40-80 years, DM2, fasting plasma glucose concentration 7.8 mmol/l or more, fasting C-peptide concentration 0.27nmol/l or more

Exclusion criteria:
Patients with clincally important renal or hepatic disease, symptomatic angina pectoris or cardiac insufficiency, hematologic abnormalities, requirement of insulin therapy

Comments:

Population: **Mean age:** 58.54 years **Ethnicity:** White 69.3%; Black 7.2%;; Other 17.1%
Gender: 43% Female
Type 2 diabetes duration (SD), year: 5.3 (NR)

Intervention: monotherapy

Duration: 8 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	2mg bid	Rosi-2	73	.087 (0.0144	NR (NR)	30.2 (4.7)	
Rosiglitazone	4mg bid	Rosi-4	66	.089 (0.0145	NR (NR)	30.5 (3.8)	
Rosiglitazone	6mg bid	Rosi-6	76	.087 (0.0149	NR (NR)	30.0 (4.3)	
Placebo	NA	Placebo	69	.087 (0.0163	NR (NR)	30.4 (4.2)	

Laboratory measures:

	Placebo	Rosi-2	Rosi-4	Rosi-6
FPG, change from baseline at 8 weeks: mmol/l (SD)				
	+1.1(NR)	-2.0(NR)	-2.4(NR)	-22.5(NR)
A1c, change from baseline at 8 weeks: % (SD)				
	+.010(NR)	+.004(NR)	NR(NR)	NR(NR)
	0.0001	0.0025	NS	NS
Total cholesterol, change from baseline at 8 weeks: mg/dL (SD)				
	+0.10(NR)	+0.8(NR)	+0.8(NR)	+0.8(NR)
HDL, change from baseline at 8 weeks: mg/dL (SD)				
	+0.5(NR)	+0.7(NR)	+0.8(NR)	+0.13(NR)
LDLI, change from baseline at 8 weeks: mg/dL (SD)				
	0(NR)	+0.5(NR)	+0.4(NR)	+0.6(NR)
TG, change from baseline at 8 weeks: mg/dL (SD)				
	0(NR)	+0.1(NR)	+0.2(NR)	+0.3(NR)

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Raskin P, 2001 **Quality rating: Good**

Design:

Study design: RCT DB Parallel **Run-in :** 56 days **Setting:** Multicenter
Wash out : NR **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	370/	367/	319	48/	7/	313

Inclusion criteria:
Patients with mean baseline HbA > 7.5%, receiving >30 U insulin/day, fasting C-peptide level >0.13 nmol/l, HbA >7.5%

Exclusion criteria:
Elevated liver enzymes (>2.5 times the upper limit of the reference range), serum creatine >160 mmol/l, anemia (Hb<11 g/dl for men or <10 g/dl for women), BMI <22 or >42 kg/m, history of ketoacidosis, angina, cardiac insufficiency, electrocardiographic evidence of marked left venticular hypertrophy, uncontrolled hypertension or hemoglobinopathy, variation in body weight >10% during run-in period, FPG >19.4 mmol/l on 2 more more study visits

Comments:

Population: **Mean age:** 56.8 years **Ethnicity:** White 73.3%; Black 18.3%; Other 12.6%
Gender: 45% Female
Type 2 diabetes duration (SD), year: 12.3

Intervention: added to insulin

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	2 mg bid	Rosi-4	106	9.1 (1.3)	NR (NR)	32.1 (4.8)	
Placebo	NA	Placebo	104	8.9 (1.1)	NR (NR)	32.7 (4.5)	
Rosiglitazone	4 mg bid	Rosi-8	103	9.0 (1.3)	NR (NR)	32.3 (4.9)	

Laboratory measures:

	Rosi-4	Rosi-8	Placebo
A1c, change from baseline at 26 weeks: % (SD)			
	-0.6(1.1)	-1.2(1.1)	+0.1(1.0)
	0.0001	0.0001	0.2032
p vs Placebo	0.0001	0.0001	
Fasting plasma glucose, change from baseline at 26 weeks: mmol/l (SD)			
	-2.3(3.9)	-2.5(3.3)	+0.6(3.8)
	0.0001	0.0001	0.1273
p vs Placebo	0.0001	0.0001	
Triglycerides, change from baseline at 26 weeks: mg/dL (SD)			
	+0.25(3.24)	+0.05(1.72)	+0.53(2.3)
	0.4253	0.7527	0.0211
Total cholestrol, change from baseline at 26 weeks: mg/dL (SD)			
	+0.51(1.15)	+0.75(1.36)	+0.19(0.85)
	0.0001	0.0001	0.0262
HDL cholestrol, change from baseline at 26 weeks: mg/dL (SD)			
	+0.17(0.36)	+0.16(0.46)	+0.06(0.2)
	0.00674	0.0005	0.0006

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Raskin P, 2001			**Quality rating: Good**
LDL cholestrol, change from baseline at 26 weeks: mg/dL (SD)			
+0.28(NR)	+0.38(NR)	+0.01(NR)	
0.0001	0.0001	0.7598	

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Reynolds L, 2002 **Quality rating: Poor**

Design:

Study design: RCT NR Parallel **Run-in :** NR **Setting:** Multicenter

Wash out : 42 days **Country:** US

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	21	3/	0/	17

Inclusion criteria:

Patients with DM2 requiring insulin therapy. All subjects were considered to have inadequate glycemic control with hemoglobin A1c>7%, and to be overweight with a BMI >27.

Exclusion criteria:

Not reported

Comments:

Population: **Mean age:** NR years **Ethnicity:** NR

Gender: NR% Female

Type 2 diabetes duration (SD), year: NR

Intervention: monotherapy

Duration: 24 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Placebo	NA	Placebo	NR	9.8 (NR)	234.5 (NR)		
Rosiglitazone	4mg qd	Rosi	8	8.0 (9.8)	241.6 (20.2)		

Laboratory measures:

	Rosi	Placebo
A1c, change from baseline at week 24: %	-1.1	-2.9
Total cholestrol, change from baseline at week 24: %	-16.6	-24.8
Triglycerides, change from baseline at week 24: %	-40.9	-105
LDL cholestrol, change from baseline at week 24: %	-8.9	-15.7
HDL cholestrol, change from baseline at week 24: %	-0.7(+2.3)	

Physiologic outcomes:

	Rosi	Placebo
BMI, change from baseline at week 24: %	-4.4	-2.9
Weight, change from baseline at week 24: lbs	-26.2	-16.0

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Tan G, 2005a **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR
Wash out : NR **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	24	NR/	NR/	18

Inclusion criteria:
Patients aged 30-70, a fasting plasma glucose of 7-12 mmol/l and a BMI >24 kg/m2

Exclusion criteria:
Previous treatment with oral hypoglycaemic agents, cardiac, hepatic, renal or other chronic diseases, without microvascular complications

Comments:

Population: **Mean age:** 52.3 years **Ethnicity:** NR
Gender: 46% Female
Type 2 diabetes duration (SD), year: NR (NR)

Intervention: monotherapy

Duration: 12 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg bid	Rosi	18	7.0 (0.2)	NR (NR)	32.8 (4.9)	
Placebo	NA	Placebo	18	7.4 (0.2)	NR (NR)	32.8 (4.9)	

Laboratory measures:

	Rosi	Placebo
Insulin sensitization, change from baseline, at 12 weeks: % (SD)		
	-6.6(NR)	NR(NR)
p vs Placebo	0.16	NA
NEFA concentrations, change from baseline, at 12 weeks: % (SD)		
	NR(NR)	-21(NR)
p vs Placebo	0.04	NA
Plasma glucose concentrations, change from baseline at 12 weeks: % (SD)		
	-6.6(NR)	NR(NR)
p vs Placebo	0.16	NA

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

van Wijk J, 2005 **Quality rating: Fair**

Design:

Study design: RCT DB Crossover **Run-in :** NR **Setting:** NR

Wash out : 42 days **Country:** Netherlands

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	22/	20/	19	0/	0/	19

Inclusion criteria:

Patients aged 35-70 years, diagnosed with DM2.

Exclusion criteria:

Smokers, women of child-bearing potential, taking insulin treatment, current or previous treatment with TZD, HbA >9%, serum creatinin >200 mean mol/l, abnormal thyrotropin, apartate aminotransferase, or alanine aminotransferase >2 times the upper limit of normal, congestive cardiac failure, blood pressure >160/>95 mmHg, total cholestrol >8mmol/l and/or triglycerides >5 mmol/l, alcohol intake >3 units/day.

Comments:

Population: **Mean age:** 60 years **Ethnicity:** NR

Gender: 26% Female

Type 2 diabetes duration (SD), year: NR (NR)

Intervention: monotherapy

Duration: 8 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4 mg bid	Rosi	19	6.2 (0.9)	NR (NR)	29.2 (4.8)	
Placebo	NA	Placebo	19	6.2 (0.9)	NR (NR)	29.2 (4.8)	

Laboratory measures:

	Rosi	Placebo
Total cholestrol to HDL cholestrol (SD)		
	5.63(0.40)	5.54(0.34)
p vs Placebo	NS	NA
Fasting plasma levels: Change from baseline to endpoint (SD)		
	5.39(0.24)	4.96(0.20)
p vs Placebo	0.05	NR
Triglycerides levels: Change from baseline to endpoint (SD)		
	1.97(0.22)	1.88(0.20)
p vs Placebo	NS	NR
HDL cholestrol		
	1.05(0.21)	0.98(0.09)
	NS	NR

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Wang G, 2005 **Quality rating: Fair**

Design:

Study design: RCT Not r Parallel **Run-in :** None **Setting:** Single Center

Wash out : None **Country:** China

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	71	1/	NR/	70

Inclusion criteria:

Ages 50 to 73, with a diagnosis of coronary artery disease (>50% stenosis as proven on angiography) and established DM2. all patients had undergone angiography and percutansous coronary intervention.

Exclusion criteria:

Acute MI during the preceding 12 weeks, cardiac insufficiency, renal function impairment, liver function impairment, systemic inflammatory disease, infectious disease, cancer, or a serious illness that would affect participation; insulin treatment.

Comments:

Population: **Mean age:** 61.2 years **Ethnicity:** NR

Gender: 18% Female

Type 2 diabetes duration (SD), year: NR (NR)

Intervention: monotherapy; subgroup: pts w/CAD afte

Duration: 6 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg qd	Rosi	35	7.29 (0.17)	NR (NR)	26.1 (2.5)	
No treatment	NA	Control	35	7.33 (0.17)	NR (NR)	25.6 (2.7)	

Laboratory measures:

	Rosi	Control

Health outcomes:

	Rosi	Control
Coronary events, total number at 6 months (%)		
	4(11.4)	12(34.3)
p vs control	<0.05	NA

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Wolfenbuttel B, 2000 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 14-28 days **Setting:** Multicenter

Wash out : None **Country:** Multiple European

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	829/	639/	593	175/	NR/	574

Inclusion criteria:

30-80 years of age, BMI 22-38 kg/m2, and DM2, FPG ≤15.0 mmol.l, A1c ≥7.5% and evidence of insulin secretory capacity, treated with SU for at least 6 months.

Exclusion criteria:

Clinically significant renal or hepatic disease, symptomatic diabetic neuropathy requiring treatment, clinically significant abnormalities identified during the screening physical examinaion, on OCG, or in any laboratory tests; patients who required insulin therapy or blood glucose-lowering medications other than SU.

Comments:

Population: **Mean age:** 61.2 years **Ethnicity:** White (96.9%); Black (1.0%); Other (2.1%)

Gender: 43% Female

Type 2 diabetes duration (SD), year: 7.3 (range 0-34)

Intervention: added to sulfonylurea

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	1 mg bid	Rosi-2	199	9.20 (1.19)	NR (NR)	28.0 (3.9)	
Rosiglitazone	2 mg bid	Rosi-4	183	9.23 (1.18)	NR (NR)	28.3 (3.9)	
Placebo	NA	Placebo	192	9.21 (1.30)	NR (NR)	28.1 (4.1)	

Laboratory measures:

	Rosi-2	Rosi-4	Placebo
A1c, change from baseline to 26 weeks: % (SD)			
	-0.59(NR)	-1.03(NR)	NR(NR)
p vs Placebo	<0.0001	<0.0001	NA
A1c, patients achieving reduction of >=0.7% at week 26: % (SD)			
	39(NR)	60(NR)	19(NR)
p vs Placebo	0.0001	0.0001	NA
FPG, decrease from baseline to 26 weeks: mmol/l (SD)			
	-0.95(NR)	-2.09(NR)	-0.32(NR)
p vs Placebo			
p-value vs placebo NR, both ROSI groups p<0.0001 vs baseline, placebo p=0.1054 vs baseline			
Total cholesterol, change from baseline to week 26: mmol/l (SD)			
	+0.3(NR)	+0.4(NR)	+0.1(NR)
p vs Placebo	0.0081	<0.0001	NA
HDL, change from baseline to week 26: mmol/l (SD)			
	+0.1(NR)	+0.1(NR)	0(NR)
p vs Placebo	0.7971	0.0019	NA

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Wolfenbuttel B, 2000				**Quality rating: Fair**
LDL, change from baseline to week 26: mmol/l (SD)				
	+0.1(NR)	+0.2(NR)	0(NR)	
p vs Placebo	0.7921	0.0030	NA	
TG, change from baseline to week 26: mmol/l (SD)				
	+0.4(NR)	+0.2(NR)	+0.1(NR)	
p vs Placebo	0.0020	0.1393	NA	

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Yang W, 2002 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 28 days **Setting:** NR

Wash out : NR **Country:** Taiwan

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	64	0/	0/	64

Inclusion criteria:

Patients with DM2, with fasting plasma glucose 7-15 mmol/l, and HA >7.5%, those stable on sulfonylurea for at least 2 months before study,

Exclusion criteria:

Other severe micorovascular complications requiring immediate medical attention, those stable on sulfonylurea for at least 2 months before study,

Comments:

Population: **Mean age:** 58.3 years **Ethnicity:** NR

Gender: 59% Female

Type 2 diabetes duration (SD), year: NR (NR)

Intervention: added to sulfonylurea

Duration: 6 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	2 mg bid	Rosi	30	9.5 (1.1)	64.9 (11.8)	25.8 (2.9)	
Placebo	NA	Placebo	34	9.7 (1.4)	65.3 (11.2)	25.8 (3.5)	

Laboratory measures:

	Rosi	Placebo
A1c, change from baseline to 6m: % (SD)		
	-0.7(1.0)	0.4(1.3)
p vs Placebo	0.005	NS
FPG, change from baseline to 6m: mtmol/l (SD)		
	-10.6(41.0)	+17.8(58.5)
p vs Placebo	0.05	NS

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Yang W, 2002 **Quality rating: Fair**

Laboratory measures:

	Rosi	Placebo
A1c, change from baseline to 6m: % (SD)		
	-0.7(1.0)	0.4(1.3)
p vs Placebo	0.005	NS
FPG, change from baseline to 6m: mtmol/l (SD)		
	-10.6(41.0)	+17.8(58.5)
p vs Placebo	0.05	NS

Physiologic outcomes:

	Rosi	Placebo
Weight, change from baseline to 6m: kg (SD)		
	3.0(2.4)	-0.4(1.9)
p vs Placebo	p<0.0005	NR
BMI, change from baseline to 6m: kg/m2 (SD)		
	1.2(1.0)	-0.18(0.79)
p vs Placebo	p<0.0005	NR
SBP, change from baseline to 6m: mmHg (SD)		
	-0.3(15.7)	-8.1(16.3)
p vs Placebo	p<0.01	NR
DBP, change from baseline to 6m: mmHg (SD)		
	-0.4(8.0)	-1.1(7.4)
p vs Placebo	NS	NR

P value NR if not specified.

Evidence Table 5. Efficacy - Placebo-controlled trials, type 2 diabetes, rosiglitazone

Zhu X, 2003 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** 14 days **Setting:** Multicenter
Wash out : NR **Country:** China

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	771/	554/	NR	NR/	NR/	530

Inclusion criteria:
Patients with DM2, BMI of 19-38 kg/m, fasting plasma glucose 7.5-12.9 mmol/l at screening, glucosylated hemoglobin of >7.5%, received a sulfonylurea for at least 6 months, at a constant dose for at least 2 months before screening

Exclusion criteria:
Clinically significant abnormalities at physical exam, diabetic neuropathy, abnormal blood cell counts

Comments:

Population: **Mean age:** 59 years **Ethnicity:** NR
Gender: 55% Female
Type 2 diabetes duration (SD), year: NR (NR)

Intervention: added to sulfonylurea

Duration: 24 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg bid	Rosi-4	215	9.8 (1.5)	NR (NR)	NR (NR)	
Rosiglitazone	8mg bid	Rosi-8	210	9.9 (1.6)	NR (NR)	NR (NR)	
Placebo	NA	Placebo	105	9.8 (1.3)	NR (NR)	NR (NR)	

Laboratory measures:

	Rosi-4	Rosi-8	Placebo
A1c, change from baseline to 2 weeks: % (SD)			
	-1.04(NR)	-1.44(NR)	-0.4(NR)
p vs Placebo	0.0001	0.0001	NR
Fasting plasma glucose, change from baseline to 2 weeks: mg/dl (SD)			
	-21.6(NR)	-36.0(NR)	+0.5(NR)
p vs Placebo	0.0001	0.0001	NR

P value NR if not specified.

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Belcher 2004, Khan 2004 **Quality rating: NA (4 trials combined**

Design:

Study design: RCT DB Parallel **Run-in :** None **Setting:** Multicenter
Wash out : None **Country:** Multiple European

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed
NR/ NR/ 3713

Inclusion criteria:

This study is a reporting of 4 primary trials listed in Kahn: Matthews 2004, Hanefeld 2004, and 2 studies from Takeda Europe Research and Development Center, Ltd.
Adults 35-75 years with DM2 and A1c between 7.5% and 11.0% despite therapy with diet or stable SU or metformin regimen

Exclusion criteria:

MI or CVA in prior 6m; symptomatic heart failure; DBP ≤100 mg Hg

Comments:

Belcher 2004 combines 4 included studies, but no citations for the original studies. Investigators overlap (but are not identical with) Schernthaner.
Appears to overlap with Hanefeld 2004, Matthews 2004; number of patients identical to these 3 studies; to Belcher 2004 report of 4 primary studies; awaiting Charbonnel 2005 study
Patients were in 4 RCTs comparing treatment with Pio, metformin, or gliclazide; 2 trials were monotherapy, 2 were add-on therapy (1 to SU, other to metformin).
Unable to assess quality of Belcher or Khan; has no information; appear to come from 4 fair-quality primary studies.

Population: **Mean age:** 57 years **Ethnicity:** NR
Gender: 44% Female
Type 2 diabetes duration (SD), year: 4.2

Intervention: combined, 4 trials

Duration: 52 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	30-34mg	Pio	1857	8.7 (1.0)			+/- other
Metformin or Glicl	variable	Met/Glic	1856	8.7 (1.0)			

P value NR if not specified.

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Charbonnel BH, 2004 — Quality rating: Poor

Design:

Study design: RCT DB Parallel **Run-in :** None **Setting:** Multicenter
Wash out : None **Country:** Multiple European

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed
2412/ NR/ 1270

Inclusion criteria:
Patients 35-75y with DM2 inadequately treated with diet alone; A1c 7.5-11%, stable or worsening glycemic control over at least 3m

Exclusion criteria:
Previously used glucose-lowering agents; contraindications to either study drug; long-term treatment with corticosteroids during study was prohibited; no beta-blockers in last 4w or during study

Comments:
Setting; 209 centers in 14 European countries, Australia, Canada, South Africa, and Israel

Population: **Mean age:** NR years **Ethnicity:** NR
Gender: NR% Female
Type 2 diabetes duration (SD), year: 9.5

Intervention: monotherapy, gliclazide
Duration: 52 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	42 mg qd mean	Pio	NR	8.7 (NR)	NR (NR)	Nr (NR)	
Gliclazide	198 mg qd mean	Glic	NR				

Laboratory measures:

	Pio	Glic
A1c, change from baseline to 52w: %		
	-1.4	-1.4
p vs Glic	NSD	
TG, change from baseline to 52w: mmol/l		
	-0.51	-0.44
p vs Glic	p=0.413	
HDL, change from baseline to 52w: mmol/l		
	0.22	0.06
p vs Glic	p<0.001	
LDL, change from baseline to 52w: mmol/l		
	0.12	-0.17
p vs Glic	p<0.001	
FPG, change from baseline to 52w: mmol/l		
	-2.4	-2.0
p vs Glic	p=0.002	

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Charbonnel BH, 2004 **Quality rating: Poor**

Laboratory measures:

	Pio	Glic
A1c, change from baseline to 52w: %		
	-1.4	-1.4
p vs Glic	NSD	
TG, change from baseline to 52w: mmol/l		
	-0.51	-0.44
p vs Glic	p=0.413	
HDL, change from baseline to 52w: mmol/l		
	0.22	0.06
p vs Glic	p<0.001	
LDL, change from baseline to 52w: mmol/l		
	0.12	-0.17
p vs Glic	p<0.001	
FPG, change from baseline to 52w: mmol/l		
	-2.4	-2.0
p vs Glic	p=0.002	

Physiologic outcomes:

	Pio	Glic
Weight, change from baseline to 52w: kg		
	2.8	1.9
	NR	

P value NR if not specified.

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Hanefeld M, 2004 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** None **Setting:** Multicenter
Wash out : None **Country:** Multiple European and Canada

Sample:

Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
952/	NR/	639	11/	100/	639

Inclusion criteria:

Subjects aged 35-75 years; DM2 inadequately managed with sulfonylurea monotherapy (at ≥ 50% maximal dose or maximal tolerated dosage for ≥3m); stable or worsening glycemic control for ≥3m; 7.5%<A1c<11.0%; C-peptide ≥1.5 ng/ml at screening; females: post-menopausal, sterlized, or using satisfactory contraception

Exclusion criteria:

DM1 or ketoacidosis; history of MI, TIA, stoke in prior 6m; symptomatic heart failure; malabsorption or pancreatitis; familial polyposis coli; malignant disease in prior 10y; history of lacticacidosis or hypoxemia or substance abuse; pregnant or lactating; prior treatment with metformin or any TZD

Comments:

Trial conducted in 12 European countries plus Canada

Population: **Mean age:** 60 years **Ethnicity:** Baseline characteristics reported in the metformin + SU group 98.9% Caucasian
Gender: 50% Female
Type 2 diabetes duration (SD), year: 7.1 (5.6)

Intervention: added to sulfonylurea

Duration: 52 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	15-45mg qd	Pio	319	8.82 (0.98)	85.3 (15.1)		
Metformin	850-2550mg qd	Met	320	8.8 (0.97)	84.9 (14.5)		

Laboratory measures:

	Pio+SU	Met+SU
A1c, change from baseline to 52 weeks: %		
	-1.2	-1.36
p vs Met + SU	0.065	
% patients achieving A1c<7.0% at 52 weeks		
	39	40
p vs Met + SU	p NR	
C-peptide, change from baseline to week 52: ng/ml		
	-0.2	0.0
p vs p==0.160		
Triglycerides, change from baseline to week 52: mmol/l		
	-0.42(p=0.008)	-0.28
HDL, change from baseline to week 52: mmol.l		
	0.16	0.09
p vs p<0.0001		
LDL, change from baseline to week 52: mmol.l		
	0.08(p=0.0002)	-0.16

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Hanefeld M, 2004		Quality rating: Fair
Urinary albumin-to-creatinine ratio, change from baseline to week 52: mmol.l		
	-15	2
between-group p=0.017		
FPG, change from baseline to 52 weeks: mmol/l		
	-2.2	-2.3
p vs Met + SU	0.529	
Triglycerides, change from baseline to 104 weeks: mmol/l		
p vs Met + SU	0.008	
HDL, change from baseline to 104 weeks: mmol/l		
p vs Met	<0.0001	
LDL, change from baseline to 104 weeks: mmol/l		
p vs Met	0.0002	
A1c <7.0%c at 104 weeks: % patients		
	30.2	28.4
p vs Met	p=0.635	
A1c, change from baseline to 104 weeks: %		
	-1.03	-1.16
p vs Met	p=0.173	
FPG, chagne from baseline to 104 weeks: mmol/l		
	2.0	1.9
p vs Met	p=0.506	

P value NR if not specified.

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Matthews DR, 2005 **Quality rating: Fair**

Design:

Study design: RCT DB Parallel **Run-in :** None **Setting:** Multicenter
Wash out : None **Country:** Europe and Australia

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed
NR/ NR/ 630 NR/ 99/ 620

Inclusion criteria:

Male and female patients with DM2 inadequately managed with metformin at 50% of maximum tolerated dose for ≥3m; 35-75y; a1c ≥7.5% of ≤11%; fasting C-peptide ≥1.5 ng/mL; stable or worsening glycemic control for ≥3m.

Exclusion criteria:

DM1; ketoacidoses, MI, TIA or stroke in last 6m; symptomatic heart failure; acute malabsorption or chronic pancreatitis; familial polyposis coli, malignant disease in the last 10y; substance abuse; potential of pregnancy; breast-feeding; rpior treatment with insulin gliclazide; prioglitazone or other SU or TZDs.

Comments:

Setting: 75 centers in 9 European countries and Australia

Population: **Mean age:** 56 years **Ethnicity:** Caucasian: 99.7%
Gender: 50% Female
Type 2 diabetes duration (SD), year: 5.7 (NR)

Intervention: added to metformin

Duration: 11 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	39 mg qd mean	Pio	317	8.71 (1.00)	91.8 (16.2)	32.6 (5.0)	
gliclazide	212 mg qd mean	Glic	313	8.53 (0.9)	92.7 (17.4)	32.6 (5.8)	

Laboratory measures:

	Pio	Glic
A1c, change from baseline to 52 weeks: % (SD)		
	-0.99	-1.01
p vs Glic	p=0.837	
FPG, change from baseline to 52 weeks: mg/dL (SD)		
	-34.2	-30.6
p vs Glic	p=0.506	
TG, change from baseline to 52 weeks: mg/dL (SD)		
	-53.1	-19.5
p vs Glic	p<0.001	
HDL, change from baseline to 52 weeks: mg/dL		
	6.9	0
p vs Glic	p<0.001	
LDL, change from baseline to 52 weeks: mg/dL		
	10.4	-4.2
p vs Glic	p<0.001	

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Matthews DR, 2005		Quality rating: Fair
A1c, change from baseline to 104 weeks: % (SD)		
	-0.89	-0.77
	NR	NR
Achieved target A1c <7.0% at 104 weeks: % patients		
	30.6	25.2
p vs Glic	0.128	
FPG, change from baseline to 104 weeks: mg/dL (SD)		
	-1.8	-1.1
p vs Glic	p<0.001	
Physiologic outcomes:		
	Pio	**Glic**
Weight, change from baseline at 52 weeks: kg		
	1.5	1.4
	NR	NR

P value NR if not specified.

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Saad MF, 2004 **Quality rating: Fair**

Design:

Study design: RCT Ope Parallel **Run-in :** None **Setting:** Multicenter
Wash out : 28 days **Country:** USA

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed
NR/ NR/ 177 52/ NR/ 125

Inclusion criteria:
Patients with DM2 18-73 years old; fasting C-peptide >0.4 mg/ml; BMI 25-42 kg/m2; TG 151-500 mg/dl; previously treated for at least 2m with diet or an oral agents; FPG 126-240 mg/dl at time of randomization

Exclusion criteria:
Received lipid-lowering drugs within 3w, or a thiazolidinedione within 3m; clinically significant cardiovascular, hepatic, or renal disease

Comments:
Setting: 31 sites in the USA
Pio arm was open-label, others double blind
LOCF used in analysis

Population: **Mean age:** 54 years **Ethnicity:** NR
Gender: 52% Female
Type 2 diabetes duration (SD), year: NR (NR)

Intervention: monotherapy

Duration: 12 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	45mg qd	Pio	28	8.5 (NR)	NR (NR)	31 (NR)	
Ragaglitazar	0.1mg qd	Rag-0.1	26	8.0 (NR)	NR (NR)	33 (NR)	
Ragaglitazar	1mg qd	Rag-1	30	8.4 (NR)	NR (NR)	31 (NR)	
Ragaglitazar	4mg qd	Rag-4	32	8.6 (NR)	NR (NR)	31 (NR)	
Ragaglitazar	10mg qd	Rag-10	31	7.7 (NR)	NR (NR)	32 (NR)	
Placebo	NA	Placebo	30	8.1 (NR)	NR (NR)	31 (NR)	

Laboratory measures:

	Rag-0.1	Rag-1	Rag-4	Rag-10	Pio	Placebo
A1c, change from baseline to 12w: % (SD)						
	0.5(NR)	-0.5(NR)	-1.3(NR)	-1.1(NR)	-0.3(NR)	0.8(NR)
p vs Placebo	NS	0.05	0.05	0.05	0.05	NA
FPG, change from baseline to 12w: mg/dl (SD)						
	-9.3(NR)	-48.3(NR)	-74.1(NR)	-77.0(NR)	-43.1(NR)	22.5(NR)
p vs Placebo	0.05	0.05	0.05	0.05	0.05	NA
TG, change from baseline to 12w: % change (SD)						
	-12.6(NR)	-40.4(NR)	-61.7(NR)	-51.4(NR)	--39.7(NR)	5(NR)
p vs Placebo	NS	0.05	0.05	0.05	0.05	NA
LDL, change from baseline to 12w: % change (SD)						
	10.1(NR)	-5.4(NR)	-13.8(NR)	-19.0(NR)	11.6(NR)	0.2(NR)
p vs Placebo	NS	NS	0.05	0.05	NS	NS

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Saad MF, 2004				Quality rating: Fair		
HDL, change from baseline to 12w: % change (SD)						
	5.3(NR)	19.8(NR)	30.6(NR)	10.2(NR)	15.1(NR)	2.7(NR)
p vs Placebo	NS	0.05	0.05	NS	NS	NA

P value NR if not specified.

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Schernthaner G, 2005 — Quality rating: Fair

Design:

Study design: RCT DB Parallel **Run-in :** None **Setting:** Multicenter
Wash out : None **Country:** Multiple European

Sample: Number Screened/ Eligible/ Enrolled: 2145/ NR/ 1199 Number Withdrawn/ Lost to follow-up/ Analyzed: 194/ 15/ 1194

Inclusion criteria:
Aged 35-75 years with DM2 inadequately controlled with diet alone; A1c 7.5% to 11% with stable or worsening glycemic control for ≥3m

Exclusion criteria:
Prior use of glucose-lowering drugs; contraindication to either study drug; corticosteroids were permitted if treatment commenced >=4w before screening; thiazides were not allowed.

Comments:
Setting: 167 centers in 12 European countries

Population: **Mean age:** 57 years **Ethnicity:** NR
Gender: 45% Female
Type 2 diabetes duration (SD), year: 3.3 (NR)

Intervention: monotherapy
Duration: 52 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	43 mg qd	Pio	597	8.7 (1.0)	88.2 (15.5)	NR (NR)	
Metformin	2124 mg qd	Met	597	8.7 (1.0)	89.7 (16.6)	NR (NR)	

Laboratory measures:

	Pio	Met
A1c, change from baseline to 52 weeks: % (SD)		
	-1.41(NR)	-1.50(NR)
p vs Met	NSD	NA
FPG, change from baseline to 52 weeks: mg/dl		
	-8.9	-9.1
p vs Met	p=0.016	
TG, change from baseline to 52 weeks: mg/dl		
	-54.0	-26.6
p vs Met	p=0.001	
HDL, change from baseline to 52 weeks: mg/dl		
	6.18	3.09
p vs Met	p=0.001	
LDL, change from baseline to 52 weeks: mg/dl		
	10.4	-4.25

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Schernthaner G, 2005 **Quality rating: Fair**

Laboratory measures:

	Pio	Met
A1c, change from baseline to 52 weeks: % (SD)		
	-1.41(NR)	-1.50(NR)
p vs Met	NSD	NA
FPG, change from baseline to 52 weeks: mg/dl		
	-8.9	-9.1
p vs Met	p=0.016	
TG, change from baseline to 52 weeks: mg/dl		
	-54.0	-26.6
p vs Met	p=0.001	
HDL, change from baseline to 52 weeks: mg/dl		
	6.18	3.09
p vs Met	p=0.001	
LDL, change from baseline to 52 weeks: mg/dl		
	10.4	-4.25

Physiologic outcomes:

	Pio	Met
Weight, change form baseline to 52 weeks: kg (SD)		
	1.9(NR)	-2.5(NR)

P value NR if not specified.

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Tan G, 2005 **Quality rating: Poor**

Design:

Study design: RCT DB Crossover **Run-in :** None **Setting:** Multicenter
Wash out : None **Country:** USA, Europe

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	567	293/	6/	293

Inclusion criteria:
Patients with DM2 inadequately controlled with A1c 7.5-11.0% with diet alone, 35-75 years, no prior use of oral agents

Exclusion criteria:
NR

Comments:
Setting: 98 centers in US, Canada, Europe, South Africa.
Mention of a 1-year parent study, but no citation; patients who finished 1-year study were asked to participate in 2-year study, but all patients were included in this study, regardless of whether they continued treatment for second year.
Reference made to Charbonnel study 2005 (pending)

QA:
Data right-censored when drop-out if A1c<8.0% (threshold for failure); called failure if ≥8.0%; DOES THIS BIAS RESULTS?
UNCLEAR if ITT (for above reason)
Protocol violation in 3.9%; removed from study

Population: **Mean age:** 56 years **Ethnicity:** NR
Gender: NR% Female
Type 2 diabetes duration (SD), year: 2.8 (NR)

Intervention: monotherapy

Duration: 2 year

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	25-30mg	Pio	270	NR (NR)	91.7 (19.9)	NR (NR)	
Gliclazide	80-320mg	Glic	297	NR (NR)	89.2 (18.2)	NR (NR)	

Laboratory measures:

	Pio	Glic
Maintain glycemic control at 2 years (A1c<8.0%): % (SD)	47.8%(NR)	37.0%(NR)

P value NR if not specified.

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Tan M (glimepiride), 2004 — Quality rating: Fair

Design:

Study design: RCT DB Parallel **Run-in :** 7-21 days **Setting:** Multicenter
Wash out : None **Country:** Mexico

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	584/	244/	244	51/	17/	208

Inclusion criteria:

Patients with DM2 with A1c >7.5% and ≤11.0% in patients who were not receiving oral hypoglycemic agents, and >7.5% and ≤ 9.5% in patients who were receiving oral agents. Patients must have had a trial of diet and lifestyle interventions before study enrollment.

Exclusion criteria:

Treatment with a TZD or insulin within the previous 3 months, current prescription for a maximum dose of an oral agent or for combination oral therapy; treatment with oral or parenteral glucocorticosheroids within the last 30 days; cardiac disease with significant functional limitation (NR Heart Association Class III or IV; triglycerides >400 mg/dl; serum creatinine >2.0 mg/dl; renal transplantation or current renal dialysis; ALT or AST > 2.5 times upper limit of normal; clinical signs or symptoms of liver disease; Hg<115 g/l for women and <115g/l for men; BMI <25 or >35 kg/m2; signs or symptoms of substance abuse

Comments:

Data are reported for ITT: all randomized patients who received ≥1 dose of study medication and had a baseline and ≥1 efficacy measurement; completers also reported (data not abstracted)

Population: **Mean age:** 55.3 years **Ethnicity:** Hispanic 99%, white 1%
Gender: 51% Female
Type 2 diabetes duration (SD), year: 6.7 (NR)

Intervention: monotherapy

Duration:

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	37 mg qd	Pio	121	8.54 (0.9)	74.2 (10.5)	29.3 (3.3)	
Glimepiride	6mg qd	Glim	123	8.45 (1.0)	74.5 (10.8)	28.8 (3.2)	

Laboratory measures:

	Pio	Glim
A1c, change from baseline to 52-week follow-up: % (SE)		
	-0.78(0.162)	-0.68(0.169)
p vs Glim	0.638	
FPG, change from baseline to 52-week follow-up: mmol/l (SE)		
	-0.6(0.36)	-0.6(0.38)
p vs Glim	0.012	NA
HDL, change from baseline to 52-week follow-up: mmol/l (SD)		
	0.07(NR)	NR
p vs Glim	NS	NA
LDL, change from baseline to 52-week follow-up: mmol/l (SD)		
	0.42(NR)	NR(NR)
p vs Glim	0.002	NA
Total cholesterol, change from baseline to 52-week follow-up: mmol/l (SD)		
	0.48(NR)	NR(NR)
p vs Glim	0.024	NA

Evidence Table 6. Efficacy - Selected active-controlled trials type 2 diabetes, pioglitazone

Tan M (glimepiride), 2004 **Quality rating: Fair**

Laboratory measures:

	Pio	Glim
A1c, change from baseline to 52-week follow-up: % (SE)		
	-0.78(0.162)	-0.68(0.169)
p vs Glim	0.638	
FPG, change from baseline to 52-week follow-up: mmol/l (SE)		
	-0.6(0.36)	-0.6(0.38)
p vs Glim	0.012	NA
HDL, change from baseline to 52-week follow-up: mmol/l (SD)		
	0.07(NR)	NR
p vs Glim	NS	NA
LDL, change from baseline to 52-week follow-up: mmol/l (SD)		
	0.42(NR)	NR(NR)
p vs Glim	0.002	NA
Total cholesterol, change from baseline to 52-week follow-up: mmol/l (SD)		
	0.48(NR)	NR(NR)
p vs Glim	0.024	NA

Physiologic outcomes:

	Pio	Glim
SBP, change from baseline at week 52: mmHg (SD)		
	-3.5(NR)	-1.4(NR)
p vs baseline	=0.027	NR
Pio vs basline p=0.027		
DBP, change from baseline at week 52: mmHg (SD)		
	-3.9(NR)	1.3(NR)
p vs Baseline	p<0.001	NR
p vs Pio at 52w	NR	p=0.028
Pio vs baseline p<0.001		

P value NR if not specified.

Evidence Table 7. Efficacy - Selected active-controlled trials type 2 diabetes, rosiglitazone

Hallsten K, 2002 — Quality rating: Fair

Design:

Study design: RCT DB Parallel **Run-in :** 28 days **Setting:** Multicenter
Wash out : NR **Country:** Finland

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	43	2/	0/	41

Inclusion criteria:
Patients diagnosed with DM2, but with no diabetic complication.

Exclusion criteria:
Patients with a fasting glucose value <6.1 mmol/l or >11.0 mmol/l after run-in period, cardiovascular disease, blood pressure >160/100 mmHg, previous or current abnormal hepatic or renal function, antidiabetic medication, anemia or oral corticosteroids.

Comments:

Population: **Mean age:** 58.0 years **Ethnicity:** NR
Gender: 32% Female
Type 2 diabetes duration (SD): NR (NR) years

Intervention: monotherapy

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	2-4mg bid	Rosi	14	6.8 (0.7)	83.7 (7.9)	NR (NR)	
Metformin	500-1000mg bid	Met	13	6.9 (0.7)	88.8 (10.8)	NR (NR)	
Placebo	NA	Placebo	14	6.3 (0.4)	88.3 (9.4)	NR (NR)	

Laboratory measures:

	Rosi	Met	Placebo
Fasting A1c, change from baseline to 26 weeks: % (SD)	-0.3(NR)	-0.7(NR)	-0.5(NR)
Fasting plasma glucose, change from baseline to 26 weeks: mmol/l (SD)	-0.4(NR)	-1.2(NR)	0(NR)

Physiologic outcomes:

	Rosi	Met	Placebo
Weight, change from baseline to 26 weeks: kg (SD)	+0.6(NR)	+2.0(NR)	-0.1(NR)
Systolic blood pressure, change from baseline to 26 weeks: mmHg (SD)	-3.0(5.0)	-3.2(4.1)	-2.8(3.2)
Diastolic blood pressure: change from baseline to 26 weeks: mmHg (SD)	-6.3(2.4)	-5.9(2.6)	+0.3(2.7)

P value NR if not specified.

Evidence Table 7. Efficacy - Selected active-controlled trials type 2 diabetes, rosiglitazone

Iozzo P, 2003 — Quality rating: Fair

Design:

Study design: RCT DB Parallel **Run-in :** 28 days **Setting:** NR
Wash out : NR **Country:** Finland

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	30	0/	0/	30

Inclusion criteria:
Patients diagnosed with DM2 for 1-3y before study, no prior pharmacotherapy for DM2

Exclusion criteria:
Patients with a fasting glucose value of <6.1 mmol/l or >11.0 mmol/l after run-in, cardiovascular disease, blood pressure >160/100 mmHg, abnormal hepatic or renal function, proliferative retinopathy, anemia, corticosteroid treatment.

Comments:

Population: **Mean age:** 58 years **Ethnicity:** NR
Gender: 33% Female
Type 2 diabetes duration (SD): NR (NR) years

Intervention: monotherapy

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg qd	Rosi	9	66.8 (0.99)	NR (NR)	29.2 (4.2)	
Metformin	1000mg bid	Met	11	6.95 (0.9)	NR (NR)	28.2 (3.6)	
Placebo	NA	Placebo	10	6.11 (0.7)	NR (NR)	30.5 (4.7)	

Laboratory measures:

	Rosi	Met	Placebo
Fasting glucose levels, change from baseline to 26 weeks: mmol/l (SD)			
	-0.9(NR)	-1.1(NR)	NR(NR)
	0.05	0.05	
p vs Placebo	0.09	0.01	
A1c, change from baseline to 26 weeks: % (SD)			
	-0.36(NR)	-0.68(NR)	+0.01(NR)
	NR	0.05	NR
p vs Placebo	NR	0.03	NR
Triglycerides, change from baseline to 26 weeks: mol/l (SD)			
	-0.11(NR)	-0.09(NR)	-0.67(NR)
Cholestrol, change from baseline to 26 weeks: mol/l (SD)			
	+0.33(NR)	-0.12(NR)	-0.06(NR)
LDL cholestrol, change from baseline to 26 weeks: mol/l (SD)			
	+0.35(NR)	-0.20(NR)	+0.28(NR)
HDL cholestrol, change from baseline to 26 weeks: mol/l (SD)			
	+0.10(NR)	+0.11(NR)	+0.08(NR)
	0.05	NR	NR

Evidence Table 7. Efficacy - Selected active-controlled trials type 2 diabetes, rosiglitazone

Iozzo P, 2003 **Quality rating: Fair**

P value NR if not specified.

Evidence Table 7. Efficacy - Selected active-controlled trials type 2 diabetes, rosiglitazone

Natali A, 2004 Quality rating: Fair

Design:

Study design: RCT DB Parallel **Run-in :** 28 days **Setting:** Multicenter
Wash out : NR **Country:** Italy and UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	74	0/	0/	74

Inclusion criteria:
Patients with fasting plasma glucose between 7.0-15.0 mmol/l, A1c <10% after washout.

Exclusion criteria:
Patients with BMI>35mg/m, presence of clinically significant renal or hepatic disease, anemia, diabetic retinopathy or symptomatic neuropathy, cardiac failure, angina pectoris, or recent myocardial infarction, change in dose of ACE inhibitors, B-blockers, diuretics, stains or fibrates in the 4 weeks before screening, current treatment with vitamins, nitrates or calcium channelblockers, women of childbearing potential.

Comments:

Population: **Mean age:** 58.3 years **Ethnicity:** NR
Gender: 16% Female
Type 2 diabetes duration (SD): 5.4 (NR) years

Intervention: monotherapy

Duration: 16 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg bid	Rosi	24	7.7 (1.2)	NR (NR)	27.6 (2.8)	
Metformin	500mg tid	Met	28	7.8 (1.1)	NR (NR)	28.0 (3.5)	
Placebo	NA	Placebo	22	7.6 (0.8)	NR (NR)	30.2 (3.1)	

Laboratory measures:

	Rosi	Met	Placebo
Fasting blood sugar, change from baseline at 16 weeks: mmol/ (SE)			
	-2.3(0.5)	-2.3(0.5)	+0.4(0.6)
	0.005	0.005	NSD
A1c, change from baseline at 16 weeks: % (SE)			
	-1.2(0.3)	-1.6(0.3)	+1.3(NR)
	NSD	0.07	0.001
Triglycerides, change from baseline at 16 weeks: mg/dl (SE)			
	+36.0(32.0)	-44(41.0)	+6.0(17.0)
	NR	NR	NR
HDL cholestrol, change from baseline at 16 weeks: mg/dl (SE)			
	+4.0(3.0)	+3.0(2.0)	+1.0(1.0)
	NR	NR	NR
LDL cholestrol, change from baseline at 16 weeks: mg/dl (SE)			
	+11.0(6.0)	+2.0(6.0)	-3.0(2.0)
	NR	NR	NR

Evidence Table 7. Efficacy - Selected active-controlled trials type 2 diabetes, rosiglitazone

Natali A, 2004 **Quality rating: Fair**

Laboratory measures:

	Rosi	Met	Placebo
Fasting blood sugar, change from baseline at 16 weeks: mmol/ (SE)			
	-2.3(0.5)	-2.3(0.5)	+0.4(0.6)
	0.005	0.005	NSD
A1c, change from baseline at 16 weeks: % (SE)			
	-1.2(0.3)	-1.6(0.3)	+1.3(NR)
	NSD	0.07	0.001
Triglycerides, change from baseline at 16 weeks: mg/dl (SE)			
	+36.0(32.0)	-44(41.0)	+6.0(17.0)
	NR	NR	NR
HDL cholestrol, change from baseline at 16 weeks: mg/dl (SE)			
	+4.0(3.0)	+3.0(2.0)	+1.0(1.0)
	NR	NR	NR
LDL cholestrol, change from baseline at 16 weeks: mg/dl (SE)			
	+11.0(6.0)	+2.0(6.0)	-3.0(2.0)
	NR	NR	NR

Physiologic outcomes:

	Rosi	Met	Placebo
SBP, 24-H, change from baseline at week 16: mmHg (SE)			
	-4.0(2.0)	-3.0(2.0)	+0.3(2.0)
	NR	NR	NR
DBP, 24-H, change from baseline at week 16: mmHg (SE)			
	-2.0(1.0)	-1.0(1.0)	+0.1(1.0)
	0.05	NR	NR
p vs Placebo	0.005	NR	
Weight, change from baseline at week 16: kg (SE)			
	+0.5(0.5)	-0.6(0.4)	-0.3(0.8)
	NR	NR	NR

P value NR if not specified.

Evidence Table 7. Efficacy - Selected active-controlled trials type 2 diabetes, rosiglitazone

Virtanen K, 2003 — Quality rating: Fair

Design:

Study design: RCT DB NR | **Run-in :** 28 days | **Setting:** NR
Wash out : NR | **Country:** Finland

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	44	3/	1/	41

Inclusion criteria:
Patients with BMI 23-39 kg/m and presence of endogenous insulin production (fasting C-peptide >0.2 nmol/l).

Exclusion criteria:
Patients with fasting plasma glucose <6.1 or >10.0 mmol/l after screening period, cardiac disease, blood pressure >160/100 mmHg, hepatic or renal diseses, symptoms of complications of diabetes, history of lactate acidosis, antidiabetic medication or oral corticosteroid treatment and recent changes in antihypertensive medication or use of B-adrenergic blocking agents.

Comments:

Population: **Mean age:** 58 years **Ethnicity:** NR
Gender: 32% Female
Type 2 diabetes duration (SD): NR (NR) years

Intervention: monotherapy

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg bid	Rosi	14	6.8 (0.74)	83.7 (7.9)	30.4 (3.7)	
Metformin	500mg bid	Met	13	6.9	88.8	29.9	
Placebo	NA	Placebo	14	6.3 (0.4)	88.3 (9.7)	30.3 (4.9)	

Laboratory measures:

	Rosi	Met	Placebo
Fasting plasma glucose, change from baseline to 26 weeks: % (SD)			
	NR(NR)	15.0(NR)	NR(NR)
	0.10	NR	NR
p vs Placebo	NR	0.01	
A1c, change from baseline to 26 weeks: % (SD)			
	NR(NR)	-10.0(NR)	NR(NR)
p vs Placebo	NR	0.05	NR

Physiologic outcomes:

	Rosi	Met	Placebo
Weight, change from baseline 26 weeks: kg			
	0.0(NR)	-2.0(NR)	NR(NR)
p vs Placebo	NR	0.05	NA

P value NR if not specified.

Evidence Table 7. Efficacy - Selected active-controlled trials type 2 diabetes, rosiglitazone

Vongthavaravat Vm 2002 Quality rating: Fair

Design:

Study design: RCT Ope Parallel **Run-in :** 14 days **Setting:** Multicenter
Wash out : None **Country:** Various

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	348/	334/	334	96/	NR/	334

Inclusion criteria:

Patients with DM2 (as defined by the National Diabetes Data group criteria) who had been receiving SU therapy (glibenclamide, glipizide, gliclazide, chlorpropamide, tolbutamide, or glimepiride) for at least 6 months and if SU dose had been constant for at least 2 months before the screening visit; between 40 and 80 years of age and have a fasting plasma glucose concentration between 126 and 270 mg/dl (7 and 15 mmol/l) at screening.

Exclusion criteria:

Significant renal or hepatic impairment, hypertension, anemia, abnormal blood cell counts or hypertension; severe angina, coronary insufficiency, heart failure, EKG evidence of left ventricular hypertrophy; patients requiring insulin or who had taken investigational drugs within 30 days of screening.

Comments:

Patients from India, Brazil, The Philippines, Thailand, Argentina, and Tunisia.
Compared Rosi + sulphonlyurea to sulphonyurea alone.

Population: **Mean age:** 56.0 years **Ethnicity:** White (38.3%); Black (3.0%); Asian (57.5%); Other (1.2%)
Gender: 56% Female
Type 2 diabetes duration (SD): <1 to 41 years (NR) years

Intervention: added to sulfonylurea; subgroup (ethnici

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg qd	Rosi	164	9.1 (NR)	69.0 (NR)	NR (NR)	
SU alone	NR	SU	170	8.9 (NR)	68.8 (NR)	NR (NR)	

Laboratory measures:

	Rosi	SU
A1c, change from baseline to 26 weeks: % (95% CI)		
	-1.1(-1.37, -0.89)	+0.1(-0.1, +0.2)
p vs SU alone	0.0001	NR
FPG, change from baseline to 26 weeks: mg/dl (95% CI)		
	-38.4(-47.1, -19.7)	+5.3(-1.8, +12.5)
p vs SU alone	0.0001	NR
FPG, proportion of patients with >30 mg/dl reduction at 26 weeks: N (%)		
	89(54.3)	40(23.5)
p vs SU alone	0.0001	NR
FPG, proportion of patients with <140 mg/dl at 26 weeks: N (%)		
	68(41.5)	26(15.3)
p vs SU alone	0.0001	NR
A1c, proportion of patients with >= 0.7% reduction at 26 weeks: N (%)		
	101(64.7)	31(18.8)
p vs SU alone	0.0001	NR

Evidence Table 7. Efficacy - Selected active-controlled trials type 2 diabetes, rosiglitazone

Vongthavaravat Vm 2002		Quality rating: Fair
Total cholesterol, change from baseline to 26 weeks: mg/dL (SD)		
+13(NR)	-2(NR)	
p-value not reported		
HDL-c, change from baseline to 26 weeks: mg/dl (SD)		
+4(NR)	+2(NR)	
p-value not reported		
LDL-c, change from baseline to 26 weeks: mg/dl (SU alone)		
+5(NR)	-5(NR)	
p-value not reported		

P value NR if not specified.

Evidence Table 8. Efficacy - Placebo-controlled trials in prediabetes or metabolic syndrome, rosiglitazone

Bennett S, 2004 **Quality rating: Fair**

Design:

Study design: RCT NR NR **Run-in :** 28 days **Setting:** Multicenter

Wash out : NR **Country:** UK

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	58/	NR/	40	NR/	NR/	18

Inclusion criteria:

Patients with consistent IGT, BMI 22-39 kg/m

Exclusion criteria:

Significant anemia, renal or hepatic disease, congestive heart failure, BP >180 mm Hg or BP >110 mm Hg

Comments:

Population: **Mean age:** 59.7 years **Ethnicity:** White 100%

Gender: 90% Female

Type 2 diabetes duration (SD): NR

Intervention: monotherapy

Duration: 12 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg bid	Rosi	9	NR (NR)	79.6 (12.3)	30.2 (5.0)	
Placebo	NA	Placebo	9	NR (NR)	81.9 (13.5)	28.8 (5.0)	

Laboratory measures:

	Rosi	Placebo
Fasting plasma glucose, change from baseline to week 12: mmol/l		
	-0.28(0.68)	-0.05(0.77)
p vs Placebo	0.1816	
A1c, change from baseline to follow-up: %		
	0.4	
change relative to placebo (p=0.76)		

Evidence Table 8. Efficacy - Placebo-controlled trials in prediabetes or metabolic syndrome, rosiglitazone

Bennett S, 2004 **Quality rating: Fair**

Laboratory measures:

	Rosi	Placebo
Fasting plasma glucose, change from baseline to week 12: mmol/l		
	-0.28(0.68)	-0.05(0.77)
p vs Placebo	0.1816	
A1c, change from baseline to follow-up: %		
	0.4	
change relative to placebo (p=0.76)		

Physiologic outcomes:

	Rosi	Placebo
Weight, change from baseline to follow-up: kg (SD)		
	1.3(2.5)	-0.2(1.5)
p vs placebo	p=0.17	

Health outcomes:

	Rosi	Placebo
24-h SBP, change from baseline at 12 weeks: mmHg		
	-7.0	+2.6
p vs Placebo	0.0066	
24-h DBP, change from baseline at 12 weeks: mmHg		
	-6.4	+2.5
p vs Placebo	0.0126	

P value NR if not specified.

Evidence Table 8. Efficacy - Placebo-controlled trials in prediabetes or metabolic syndrome, rosiglitazone

Hung Y, 2005 **Quality rating: Poor**

Design:

Study design: RCT SB Parallel **Run-in :** NR **Setting:** Single Center

Wash out : NR **Country:** Taiwan

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	30	0/	0/	30

Inclusion criteria:

Patients with IGT, BMI <27 kg/m, FPG >7.0 mmol/l, 2-hr plasma glucose between 7.8-11.1 mmol/l

Exclusion criteria:

Patients using insulin/oral hypoglycemic agents, lipid-lowering agents within 3m before study, pregnant or nursing, impaired renal function, abnormal serum aspartate/alanine aminotransferase, acute/chronic pancreatitis, history of cerebrovascular accident or heart failure, taking concomitant drugs such as beta-blockers, diuretics, cholestyramine or systemic steroids

Comments:

Population: **Mean age:** 54.8 years **Ethnicity:** NR

Gender: 57% Female

Type 2 diabetes duration (SD): NR

Intervention: monotherapy

Duration: 12 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg qd	Rosi	15	6.4 (0.2)	NR (NR)	24.6 (2.3)	
Placebo	NA	Placebo	15	6.3 (0.2)	NR (NR)	24.2 (2.3)	

Laboratory measures:

	Rosi	Placebo
Total cholesterol, change from baseline at 12 weeks: mmol/l		
	+0.15	-.18
	0.001	NSD
HDL, change from baseline at 12 weeks: mmol/l		
	+0.18	0
	0.05	NR
LDL, change from baseline at 12 weeks: mmol/l		
	+0.67	-.08
	0.05	NR
A1c, change from baseline to 12 weeks: %		
	-0.1	-0.1

Evidence Table 8. Efficacy - Placebo-controlled trials in prediabetes or metabolic syndrome, rosiglitazone

Hung Y, 2005 **Quality rating: Poor**

Laboratory measures:

	Rosi	Placebo
Total cholesterol, change from baseline at 12 weeks: mmol/l		
	+0.15	-.18
	0.001	NSD
HDL, change from baseline at 12 weeks: mmol/l		
	+0.18	0
	0.05	NR
LDL, change from baseline at 12 weeks: mmol/l		
	+0.67	-.08
	0.05	NR
A1c, change from baseline to 12 weeks: %		
	-0.1	-0.1

Physiologic outcomes:

	Rosi	Placebo
Progression to DM2: cases		
	0	1

Health outcomes:

	Rosi	Placebo
Reversal to normal oral glucose tolerance test: (%) Rosi 33%, placebo 13% Progression to DM2: Rosi: 0 cases; placebo 1 case		
	33	13
P-value NR		

P value NR if not specified.

Evidence Table 8. Efficacy - Placebo-controlled trials in prediabetes or metabolic syndrome, rosiglitazone

Wang T, 2004 **Quality rating: Fair**

Design:

Study design: RCT NR NR **Run-in :** 56 days **Setting:** Multicenter

Wash out : NR **Country:** Taiwan

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	50	0/	0/	50

Inclusion criteria:

Patients had to show presence of metabolic syndrome, and meet at least of the following 3 criteria: waist circumference of >90 cm in men and >80 cm in women, serum triglycesides of > 150 mg/dl, high density lipo-protein cholesterol levels <40 mg/dl in men and <50 mg/dl in women, impaired fasting glucose of 110-125 mg/dl, blood presure of >130/85 mmHg or treated hypertension.

Exclusion criteria:

Patients with acute coronary events, stroke or coronary revascularization within the preceding 3 months; diabetes mellitus according to the criteria of the American Diabetes Association, overt liver disease, chronic renal failure, hypothyroidism, myopathy, alcohol/drug abuse, several other signficant diseases, use of other lipid-lowering therapy, immunosuppresants, erythromycin, hormone replacement therapy.

Comments:

Population: **Mean age:** 59.5 years **Ethnicity:** NR

Gender: 42% Female

Type 2 diabetes duration (SD): NR

Intervention: monotherapy

Duration: 8 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	4mg qd	Rosi	25	NR (NR)	NR (NR)	25.2 (3.4)	
Placebo	NA	Placebo	25	NR (NR)	NR (NR)	25.6 (3.0)	

Laboratory measures:

	Rosi	Placebo
FPG, change from baseline to 8 weeks: mmol/l (SD)		
	-2.0(NR)	-1.0(NR)
p vs placebo	0.370	
Total cholesterol, change from baseline to 8 weeks: mg/dl (SD)		
	+22(NR)	-5.0(NR)
p vs placebo	0.014	
TG, change from baseline to 8 weeks: mg/dl (SD)		
	-22.0(NR)	-11.0(NR)
p vs placebo	0.717	

Evidence Table 8. Efficacy - Placebo-controlled trials in prediabetes or metabolic syndrome, rosiglitazone

Wang T, 2004 **Quality rating: Fair**

LDL, change from baseline to 8 weeks: mg/dl (SD)		
	+20(NR)	-5.0(NR)
p vs placebo	0.025	

HDL cholestrol, change from baseline to 8 weeks: mg/dl (SD)		
	+2.0(NR)	0(NR)
p vs placebo	0.032	

Physiologic outcomes:

	Rosi	Placebo
SBP, change from baseline at week 8: mm Hg (SD)		
	-10.0(NR)	+1.0(NR)
p vs placebo	p=0.002	
DBP, change from baseline at week 8: mm Hg (SD)		
	-7.0(NR)	-1.0(NR)
p vs placebo	p=0.080	

P value NR if not specified.

Evidence Table 9. Efficacy - Active-controlled trials in prediabetes or metabolic syndrome, pioglitazone

Lester JW, 2005 — Quality rating: Fair

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : NR **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	NR	NR/	NR/	3186

Inclusion criteria:
Male and female patients with DM2 inadequately managed with metformin at ≥50% of maximum tolerated dose for ≥3m; 35-75y; a1c ≥7.5% of ≤11%; fasting C-peptide ≥1.5 ng/ml; stable or worsening glycemic control for ≥3m.

Exclusion criteria:
DM1; ketoacidoses, MI, TIA or stroke in last 6m; symptomatic heart failure; acute malabsorption or chronic pancreatitis; familial polyposis coli, malignant disease in the last 10y; substance abuse; potential of pregnancy; breast-feeding.

Comments:
Report of 4 other RCTs: Hanefeld 2004, Matthews 2004, Schernthaner, Charbonnel 2005
This study is reported separately, although overlaps other reports, as examines subgroup with DM2 and metabolic syndrome
Quality assessment: based on 4 primary studies, all of fair quality
Contains data on subset of 4 original studies with DM2 and metabolic syndrome: 3186 out of original 3713 patients (86%)

Population: **Mean age:** NR years **Ethnicity:** NR
Gender: NR% Female
Type 2 diabetes duration (SD): NR

Intervention: 4 other studies, DM2 +MS

Laboratory measures:

	Pio 15-45	Met	SU	Pio+SU	Met+SU	Pio+Met
A1c, change from baseline to 52w: % (SE)						
	-1.6(0.03)	-1.7(0.05)	-1.4(0.05)	-1.3(0.06)	-1.4(0.06)	-1.1(0.06)
	NR	NR	NR	NR	NR	NR
PIO group had greater decrease than SU (p<0.05) and decrease similar to metformin group						
FPG, change from baseline to 52w: mmol/l (SE)						
	-2.8(0.077)	-2.5(0.11)	-2.2(0.11)	-2.2(0.15)	-2.2(0.15)	-2.0(0.15)
	NR	NR	NR	NR	NR	NR
PIO group had greater decrease than metformin, SU, and metformin+SU (p<0.05)						
TG, change from baseline to 52w: mmol/l (SE)						
	-12.8(1.38)	-2.6(1.97)	-5.1(1.94)	-12.2(2.70)	-6.0(2.67)	-12.8(2.66)
	NR	NR	NR	NR	NR	NR
PIO and PIO+metformin had greater decrease than other groups (p<0.05)						
HDL, change from baseline to 52w: mmol/l (SE)						
	20.1(0.59)	11.1(0.84)	7.1(0.83)	17.4(1.15)	11.6(1.13)	19.8(1.13)
	NR	NR	NR	NR	NR	NR
PIO and PIO+others had greater increase than comparators (p<0.05)						
LDL, change from baseline to 52w: mmol/l (SE)						
	8.9(0.73)	-0.8(1.04)	-3.4(1.02)	5.1(1.41)	-0.9(1.39)	9.7(1.4)
	NR	NR	NR	NR	NR	NR
PIO and PIO+others had greater increase than comparators (p<0.05)						

Evidence Table 9. Efficacy - Active-controlled trials in prediabetes or metabolic syndrome, pioglitazone

Lester JW, 2005 — Quality rating: Fair

Total cholesterol, change from baseline to 52w: mmol/l (SE)					
5.8(0.49)	-0.4(0.69)	-4.2(0.68)	3.2(0.95)	-1.3(0.94)	5.9(0.94)
NR	NR	NR	NR	NR	NR
PIO and PIO+others had greater increase than comparators (p<0.05)					

Physiologic outcomes:

Pio 15-45	Met	SU	Pio+SU	Met+SU	Pio+Met
Weight, change from baseline to 52w: kg (SE)					
2.5	-2.8	1.9	3.0	-1.2	NR
NR	NR	NR	NR	NR	NR
Increased weight (p<0.05) in Pio group compared to metformin and SU					

P value NR if not specified.

Evidence Table 9. Efficacy - Active-controlled trials in prediabetes or metabolic syndrome, pioglitazone

Rasouli N, 2005 — Quality rating: Poor

Design:

Study design: RCT DB Parallel **Run-in :** 14 days **Setting:** Single Center
Wash out : None **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NR/	NR/	NR	NR/	NR/	23

Inclusion criteria:
Subjects in good health with IGT were recruited by local advertisement; FPG <110 mg/dl; 2h OGTT (75-g load) 140-199 mg/dl; age 35-65y; stable weight for 3m

Exclusion criteria:
History of coronary artery disease, use of fibrates, ACE inhibitors, angiotensin II receptor blockers

Comments:
No information on attrition.

Population: **Mean age:** NR years **Ethnicity:** NR
Gender: NR% Female
Type 2 diabetes duration (SD): NR

Intervention: monotherapy
Duration: 12 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	45 mg qd	Pio	11	5.3 (0.1 SE)	90.7 (13.9)	33.6 (4.6)	
Metformin	2000 mg qd	Met	12	5.3 (0.7 SE)	93.9 (14.9)	33.3 (3.1)	

Laboratory measures:

	Pio	Met
A1c, change from baseline to 10w: %		
	0.1	-0.1
p vs baseline	NSD	NSD
TG, change from baseline to 10w: mmol/l		
	-0.2	0.3
p vs baseline	NSD	NSD
LDL, change from baseline to 10w: mmol/l		
	-0.3	0.1
p vs baseline	NSD	NSD
HDL, change from baseline to 10w: mmol/l		
	0.1	0
p vs baseline	NSD	NSD
Total cholesterol, change from baseline to 10w: mmol/l		
	-0.4	0
p vs baseline	NSD	NSD

Evidence Table 9. Efficacy - Active-controlled trials in prediabetes or metabolic syndrome, pioglitazone

Rasouli N, 2005 **Quality rating: Poor**

Laboratory measures:

	Pio	Met
A1c, change from baseline to 10w: %		
	0.1	-0.1
p vs baseline	NSD	NSD
TG, change from baseline to 10w: mmol/l		
	-0.2	0.3
p vs baseline	NSD	NSD
LDL, change from baseline to 10w: mmol/l		
	-0.3	0.1
p vs baseline	NSD	NSD
HDL, change from baseline to 10w: mmol/l		
	0.1	0
p vs baseline	NSD	NSD
Total cholesterol, change from baseline to 10w: mmol/l		
	-0.4	0
p vs baseline	NSD	NSD

Physiologic outcomes:

	Pio	Met
Weight, change from baseline to follow-up: kg		
	2.7	0.7
p vs baseline	p<0.005	NSD
BMI, change from baseline to follow-up: kg/m2		
	0.9	-0.3
p vs baseline	p<0.05	NSD

P value NR if not specified.

Evidence Table 10. Quality assessment of efficacy trials

Internal validity **External validity**

Agrawal A, 2003

Design: **Trial type:** Placebo **Quality rating:** Fair, based on 2' data

1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 824
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	14-28 / NR
3. Groups similar at baseline?	No	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	No	Contamination	No	5. Controlled group standard of care?	NR
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: NR for this paper and primary studies not cited	
6. Care provider masked?	Unclear, reported as double blind				
7. Patients masked?	Unclear, reported as double blind				
10. Intention-to-treat analysis?	Yes, low attrition, LOCF				
11. Postrandomization exclusions?	Unable to determine				

Aronoff S, 2000

Design: **Trial type:** Placebo **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 408
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	42-56 / 42-56
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	Unclear
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR
9. Loss to follow-up, differential?	High			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Unclear, described as double blind			6. Funding: Takeda America	
6. Care provider masked?	Unclear, described as double blind				
7. Patients masked?	Unclear, described as double blind			Comment: Described as using an ITT approach, but no explanation; 399/408 were anlyazed, using LOCF. % Completing study: 33% in placebo and 44-58% in Pio groups.	
10. Intention-to-treat analysis?	No				
11. Postrandomization exclusions?	Unable to determine				

Baksi A, 2004

Design: **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 473
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	28 / none
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: supported by a grant from GlaxosmithKline	
6. Care provider masked?	Unclear, reported as double blind				
7. Patients masked?	Unclear, reported as double blind				
10. Intention-to-treat analysis?	No, high attrition				
11. Postrandomization exclusions?	No				

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity			
Barnett A, 2003	**Design:**		**Trial type:** Placebo	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	177 /	171
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Uncl			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: SmithKlineBeecham Pharmaceuticals			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Yes			Comment: Power calculation estimated target of 210 patients.			
10. Intention-to-treat analysis?	Not clear						
11. Postrandomization exclusions?	Unable to determine						
Belcher 2004, Khan 2004	**Design:**		**Trial type:** Active	**Quality rating:** NA (4 trials combined			
1. Randomization adequate?		8. Reporting of Attrition		1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	3713
2. Allocation adequate?		Crossover		3. Run-in/ Wash out (days):	None /	None	
3. Groups similar at baseline?		Adherence		4. Class naive patients only?			
4. Eligibility criteria specified?		Contamination		5. Controlled group standard of care?			
9. Loss to follow-up, differential?				2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?				6. Funding:			
6. Care provider masked?							
7. Patients masked?							
10. Intention-to-treat analysis?							
11. Postrandomization exclusions?							
Bennett S, 2004	**Design:**		**Trial type:** Placebo	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	58 /	NR /	40
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	28 /	NR	
3. Groups similar at baseline?	Not c	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: GlaxoSmithKline			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No: 17/18 (94.4%) analyzed						
11. Postrandomization exclusions?	No						

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity			
Charbonnel BH, 2004	**Design:**		**Trial type:** Active	**Quality rating:** Poor			
1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	2412 /	NR /	1270
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	None /	None	
3. Groups similar at baseline?	Yes	Adherence	Yes,	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear; reported as double blind			6. Funding: Takeda Euro R&D and Eli Lilly, USA			
6. Care provider masked?	Unclear; reported as double blind						
7. Patients masked?	Unclear; reported as double blind						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	NR						
Choi D, 2004	**Design:**		**Trial type:** Active	**Quality rating:** Poor			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	95
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	no /	no	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?			
5. Outcome assessors masked?	No			6. Funding: Korea Science & Engineering Foundation			
6. Care provider masked?	No						
7. Patients masked?	No						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Yes						
Derosa G, 2004, 2005	**Design:**		**Trial type:** H2H	**Quality rating:** Fair			
1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	91
2. Allocation adequate?	Yes	Crossover	No	3. Run-in/ Wash out (days):	None /	30	
3. Groups similar at baseline?	Yes	Adherence	Yes	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	NR			6. Funding: NR			
6. Care provider masked?	Double blind, unclear who						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusions?	Yes						

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity	
Dormandy JA, 2005	**Design:**		**Trial type:** Placebo	**Quality rating:** Good	
1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	5602 / 5238 / 5238
2. Allocation adequate?	Yes	Crossover	Yes	3. Run-in/ Wash out (days):	None / None
3. Groups similar at baseline?	Yes	Adherence	Yes	4. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	No
9. Loss to follow-up, differential?				2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Yes			6. Funding: Takeda Pharmaceutical Company and Eli Lilly Company	
6. Care provider masked?	Yes				
7. Patients masked?	Yes				
10. Intention-to-treat analysis?	Yes				
11. Postrandomization exclusions?	No				
Durbin R, 2004	**Design:**		**Trial type:** H2H	**Quality rating:** Fair	
1. Randomization adequate?	NA	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 172
2. Allocation adequate?	NA	Crossover	Yes	3. Run-in/ Wash out (days):	None / None
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	NR
5. Outcome assessors masked?	NR			6. Funding: NR	
6. Care provider masked?	No; open label				
7. Patients masked?	No				
10. Intention-to-treat analysis?	Yes				
11. Postrandomization exclusions?	No				
Fonseca V, 2000	**Design:**		**Trial type:** Placebo	**Quality rating:** Fair	
1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	443 / 410 / 348
2. Allocation adequate?	Yes	Crossover	No	3. Run-in/ Wash out (days):	28 / 28
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: SmithKline Beecham Pharmaceuticals	
6. Care provider masked?	Unclear, reported as double blind				
7. Patients masked?	Unclear, reported as double blind				
10. Intention-to-treat analysis?	Yes				
11. Postrandomization exclusions?	No				

Evidence Table 10. Quality assessment of efficacy trials

Internal validity **External validity**

Goldberg RB, 2005

Design: **Trial type:** H2H **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Unclear; reported as double blind		
6. Care provider masked?	Unclear; reported as double blind		
7. Patients masked?	Unclear; reported as double blind		
10. Intention-to-treat analysis?	Yes		
11. Postrandomization exclusions?	Yes		

1. Number Screened/ Eligible/ Enrolled:	4410 / 802 / 735
3. Run-in/ Wash out (days):	28 / 28
4. Class naive patients only?	No
5. Controlled group standard of care?	Yes
2. Exclusion criteria reported?	Yes
6. Funding:	Study jointly funded by Eli Lilly and Takeda Pharmaceuticals North America

Gomez-Perez F, 2002

Design: **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	NR	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Unclear, reported as double blind		
6. Care provider masked?	Unclear, reported as double blind		
7. Patients masked?	Yes (placebo)		
10. Intention-to-treat analysis?	No (105/111 analyzed)		
11. Postrandomization exclusions?	Yes		

1. Number Screened/ Eligible/ Enrolled:	169 / NR / 116
3. Run-in/ Wash out (days):	28 / None
4. Class naive patients only?	NR
5. Controlled group standard of care?	Yes
2. Exclusion criteria reported?	Yes
6. Funding:	Not reported; 3 authors (including corresponding author) from GlaxoSmithKline

Hallsten K, 2002

Design: **Trial type:** Placebo/Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	NR	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	Unclear, reported as double blind		
6. Care provider masked?	Unclear, reported as double blind		
7. Patients masked?	Yes (placebo)		
10. Intention-to-treat analysis?	No: 41 of 45 (91.1%) analyzed		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	NR / NR / 43
3. Run-in/ Wash out (days):	28 / NR
4. Class naive patients only?	NR
5. Controlled group standard of care?	Yes
2. Exclusion criteria reported?	Yes
6. Funding:	Academy of Finland, Novo Nordisk Foundation, Finnish Diabetes Research Society, and GlaxoSmithKline

Evidence Table 10. Quality assessment of efficacy trials

Internal validity | **External validity**

Hanefeld M, 2004 — Design: — Trial type: Active — Quality rating: Fair

1. Randomization adequate?	NR	8. Reporting of Attrition		Yes
2. Allocation adequate?	NR		Crossover	No
3. Groups similar at baseline?	Yes		Adherence	No
4. Eligibility criteria specified?	Yes		Contamination	No
9. Loss to follow-up, differential?	Yes			
5. Outcome assessors masked?	Unclear; reported as double blind			
6. Care provider masked?	Unclear; reported as double blind			
7. Patients masked?	Unclear; reported as double blind			
10. Intention-to-treat analysis?	No			
11. Postrandomization exclusions?	Unable to determine			

1. Number Screened/ Eligible/ Enrolled: 952 / NR / 639
3. Run-in/ Wash out (days): None / None
4. Class naive patients only? Yes
5. Controlled group standard of care? NR
2. Exclusion criteria reported? Yes
6. Funding: Work supported by Takeda Europe R&D Centre and Eli Lilly and Company

Herz M, 2003 — Design: — Trial type: Placebo — Quality rating: Fair

1. Randomization adequate?	NR	8. Reporting of Attrition		Yes
2. Allocation adequate?	NR		Crossover	No
3. Groups similar at baseline?	Yes		Adherence	No
4. Eligibility criteria specified?	Yes		Contamination	No
9. Loss to follow-up, differential?	No			
5. Outcome assessors masked?	Yes			
6. Care provider masked?	NR			
7. Patients masked?	Yes			
10. Intention-to-treat analysis?	No (287/297)			
11. Postrandomization exclusions?	Yes			

1. Number Screened/ Eligible/ Enrolled: NR / NR / 297
3. Run-in/ Wash out (days): 21-35 / None
4. Class naive patients only? Yes
5. Controlled group standard of care? Yes
2. Exclusion criteria reported? Yes
6. Funding: Eli Lilly and Company

Honisett S, 2003 — Design: — Trial type: Placebo — Quality rating: Poor

1. Randomization adequate?	NR	8. Reporting of Attrition		No
2. Allocation adequate?	NR		Crossover	No
3. Groups similar at baseline?	NR		Adherence	No
4. Eligibility criteria specified?	No		Contamination	No
9. Loss to follow-up, differential?	NR			
5. Outcome assessors masked?	Unclear, reported as double blind			
6. Care provider masked?	Unclear, reported as double blind			
7. Patients masked?	Yes (placebo)			
10. Intention-to-treat analysis?	NR			
11. Postrandomization exclusions?	Unable to determine			

1. Number Screened/ Eligible/ Enrolled: NR / NR / 31
3. Run-in/ Wash out (days): NR / NR
4. Class naive patients only? NR
5. Controlled group standard of care? NR
2. Exclusion criteria reported? NR
6. Funding: Not reported

Comment: Brief report: insufficient information to assess quality.

Evidence Table 10. Quality assessment of efficacy trials

Internal validity | **External validity**

Hung Y, 2005

Design: | **Trial type:** Placebo | **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 30
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR / NR
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	Yes
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	No			6. Funding: Not reported	
6. Care provider masked?	No				
7. Patients masked?	Yes			Comment: Outcome assessors not masked; not clear if intention-to-treat analysis because no information on withdrawals is provided.	
10. Intention-to-treat analysis?	Unable to determine				
11. Postrandomization exclusions?	Unable to determine				

Iozzo P, 2003

Design: | **Trial type:** Placebo/Active | **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 30
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	28 / NR
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	Yes
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: GlaxoSmithKline	
6. Care provider masked?	Unclear, reported as double blind				
7. Patients masked?	Yes (placebo)			Comment: Unable to determine if patients were analyzed selectively (I.e., if not ITT), because no information is provided about withdrawals. States "30 patients were recruited."	
10. Intention-to-treat analysis?	Unable to determine				
11. Postrandomization exclusions?	Unable to determine				

Jones T, 2003

Design: | **Trial type:** Placebo | **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 550
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	28 / NR
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	Uncl			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	No			6. Funding: Not reported; 3 of 4 authors from GlaxoSmithKline	
6. Care provider masked?	No				
7. Patients masked?	No				
10. Intention-to-treat analysis?	No				
11. Postrandomization exclusions?	Unable to determine				

Evidence Table 10. Quality assessment of efficacy trials

Internal validity | **External validity**

Kerenyi Z, 2004

Design: | **Trial type:** Active | **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	Yes
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind		
6. Care provider masked?	Unclear, reported as double blind		
7. Patients masked?	Unclear, reported as double blind		
10. Intention-to-treat analysis?	No, high attrition		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	450 /	439 /	340
3. Run-in/ Wash out (days):	28 /	none	
4. Class naive patients only?	NR		
5. Controlled group standard of care?	NR		
2. Exclusion criteria reported?			

6. Funding: Funding NR; several authors affiliated with GlaxoSmithKlinePharmaceuticals, UK and USA

Khan M, 2002

Design: | **Trial type:** H2H | **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	NR; open label trial		
6. Care provider masked?	No		
7. Patients masked?	No		
10. Intention-to-treat analysis?	No		
11. Postrandomization exclusions?	Yes		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	186
3. Run-in/ Wash out (days):	None /	14	
4. Class naive patients only?	No		
5. Controlled group standard of care?	NR		
2. Exclusion criteria reported?	NR		

6. Funding: NR

Comment: Quality assessment: patients with incomplete or unusable data were excluded (12 in Rosi and 17 in Pio group); reported that drop-outs not different from completers.

Kim Y, 2005

Design: | **Trial type:** Active | **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes
2. Allocation adequate?	NR	Crossover	No
3. Groups similar at baseline?	Yes	Adherence	No
4. Eligibility criteria specified?	Yes	Contamination	No
9. Loss to follow-up, differential?	No		
5. Outcome assessors masked?	No		
6. Care provider masked?	No		
7. Patients masked?	No		
10. Intention-to-treat analysis?	No: 120/125 (96%) analyzed		
11. Postrandomization exclusions?	No		

1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	125
3. Run-in/ Wash out (days):	NR /	NR	
4. Class naive patients only?	NR		
5. Controlled group standard of care?	Yes		
2. Exclusion criteria reported?	Yes		

6. Funding: National R&D program, Ministry of Science Technology, Republic of Korea

Evidence Table 10. Quality assessment of efficacy trials

Internal validity **External validity**

Kipnes M, 2001

Design: **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	638 /	NR /	560
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	21 /	42	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding: Takeda Pharmaceuticals			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusions?	No						

Langenfeld MR, 2005

Design: **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	192
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	Yes		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	NR			6. Funding: Study supported by an unrestricted grant from takeda Pharma GmbH, Germany			
6. Care provider masked?	No, open label						
7. Patients masked?	No, open label						
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusions?	Unable to determine						

Lebovitz H, 2001

Design: **Trial type:** Placebo **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	623
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	28 /	NR	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Not reported. 5 of 6 authors from SmithKline Beecham Pharmaceuticals			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Yes			Comment: Unable to determine if randomization was successful because methods not reported and baseline characteristics not reported for randomized population. Not ITT; cannot rule out bias in selection of patients for analysis.			
10. Intention-to-treat analysis?	No: 472/533 (88.6%) randomized wer						
11. Postrandomization exclusions?	Yes- excluded 21 patients for protocol						

Evidence Table 10. Quality assessment of efficacy trials

Internal validity | **External validity**

Matthews DR, 2005

Design: | **Trial type:** Active | **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 630
2. Allocation adequate?	Yes	Crossover	No	3. Run-in/ Wash out (days):	None / None
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	Yes
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	DB, but unclear who blinded			6. Funding: Takeda Euro R&D and Eli Lilly and Company	
6. Care provider masked?	DB, but unclear who blinded				
7. Patients masked?	Yes			Comment: Quality assessment: allocation concealment adequate (reported in Charbonnel 2005), used centralized telephone system 104-week outcomes were abstracted from Charbonnel 2005	
10. Intention-to-treat analysis?	Yes				
11. Postrandomization exclusions?	Unable to determine				

Mattoo V, 2005

Design: | **Trial type:** Placebo | **Quality rating:** Fair

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	385 / 308 / 289
2. Allocation adequate?	Yes	Crossover	No	3. Run-in/ Wash out (days):	90 / no
3. Groups similar at baseline?	Yes	Adherence	Yes	4. Class naive patients only?	Yes
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Yes, but not described			6. Funding: Eli Lilly and Takeda	
6. Care provider masked?	Yes, but not described				
7. Patients masked?	Yes				
10. Intention-to-treat analysis?	No				
11. Postrandomization exclusions?	Yes (1 patient)				

McMahon G, 2005

Design: | **Trial type:** Placebo | **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 20
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	None / None
3. Groups similar at baseline?	No	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	NR ('double-blind')			6. Funding: Takeda (partial), American Heart Association, NHLBI	
6. Care provider masked?	NR ('double-blind')				
7. Patients masked?	Yes				
10. Intention-to-treat analysis?	No				
11. Postrandomization exclusions?	Yes				

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity			
Miyazaki Y, 2001	**Design:**		**Trial type:** Placebo	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	29
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	42 /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	Yes		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: SmithKline Beecham			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Yes (placebo)						
10. Intention-to-treat analysis?	NR						
11. Postrandomization exclusions?	Unable to determine						
Miyazaki Y, 2001; Miyazak	**Design:**		**Trial type:** Placebo	**Quality rating:** Poor			
1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	NR
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	NR	
3. Groups similar at baseline?	No	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Takeda America (in part)			
6. Care provider masked?	NR						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	NR						
11. Postrandomization exclusions?	Unable to determine						
Miyazaki Y, 2002	**Design:**		**Trial type:** Placebo	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	58
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	48-64	
3. Groups similar at baseline?	No	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	NR ('double blind')			6. Funding: Takeda			
6. Care provider masked?	NR ('double blind')						
7. Patients masked?	Yes (placebo)						
10. Intention-to-treat analysis?	NR						
11. Postrandomization exclusions?	Unable to determine						

Evidence Table 10. Quality assessment of efficacy trials

Internal validity **External validity**

Natali A, 2004

Design: **Trial type:** Active/Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 74
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	28 / NR
3. Groups similar at baseline?	No	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: GlaxoSmithKline	
6. Care provider masked?	Unclear, reported as double blind				
7. Patients masked?	Yes				
10. Intention-to-treat analysis?	No: 6/74 (8.1%) not analyzed)				
11. Postrandomization exclusions?	Yes				

Negro R, 2004

Design: **Trial type:** Placebo **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	NR	1. Number Screened/ Eligible/ Enrolled:	NR / NR / NR
2. Allocation adequate?	NR	Crossover	NR	3. Run-in/ Wash out (days):	None / None
3. Groups similar at baseline?	Yes	Adherence	NR	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	NR	5. Controlled group standard of care?	NR
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	NR			6. Funding: NR	
6. Care provider masked?	NR				
7. Patients masked?	NR				
10. Intention-to-treat analysis?	Uncertain				
11. Postrandomization exclusions?	NR				

Nolan J, 2000

Design: **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	541 / NR / 380
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	21 / NR
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	Yes
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Not reported; 3 of 4 authors from SmithKline Beecham Pharmaceuticals	
6. Care provider masked?	Unclear, reported as double blind				
7. Patients masked?	Yes (placebo)				
10. Intention-to-treat analysis?	No: 369/380 analyzed (97.1%)				
11. Postrandomization exclusions?	No				

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity			
Patel J, 1999	**Design:**		**Trial type:** Placebo	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	763 /	NR /	380
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	21	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Authors from SmithKline Beecham and VA; funding source NR			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Yes (placebo)						
10. Intention-to-treat analysis?	No: 375/380 (98.7%) analyzed						
11. Postrandomization exclusions?	No						
Phillips S, 2001	**Design:**		**Trial type:** Placebo	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	1503 /	NR /	959
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	28 /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear; reported as double blind			6. Funding: NR, author affiliations include SmithKline Beecham Pharmaceuticals, USA			
6. Care provider masked?	Unclear; reported as double blind						
7. Patients masked?	Unclear; reported as double blind						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	Unable to determine						
Raskin P, 2000	**Design:**		**Trial type:** Placebo	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	529 /	NR /	303
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	14 /	14	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Not reported; 5 of 6 authors from SmithKline Beecham Pharmaceuticals			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No: 284/303 (93.7%) analyzed						
11. Postrandomization exclusions?	No						

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity	
Raskin P, 2001	**Design:**		**Trial type:** Placebo	**Quality rating:** Good	
1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	370 / 367 / 319
2. Allocation adequate?	Yes	Crossover	No	3. Run-in/ Wash out (days):	56 / NR
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Yes			6. Funding: Not reported; individual authors have received support from SmithKline Beecham	
6. Care provider masked?	Yes				
7. Patients masked?	Yes				
10. Intention-to-treat analysis?	No 6/319 (1.9%) randomized had no v				
11. Postrandomization exclusions?	Yes: 6/319 (1.9%) randomized had no				
Rasouli N, 2005	**Design:**		**Trial type:** Placebo	**Quality rating:** Poor	
1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / NR / NR
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	14 / None
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	NR			6. Funding: Merit Review Grant from the Veterans Administration; grant from ADA, and grant from Takada Pharmadeuticals; grant from NIH (National	
6. Care provider masked?	NR				
7. Patients masked?	NR				
10. Intention-to-treat analysis?	Unable to determine				
11. Postrandomization exclusions?	NR				
Reynolds L, 2002	**Design:**		**Trial type:** Placebo	**Quality rating:** Poor	
1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 21
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR / 42
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	Unab			2. Exclusion criteria reported?	NR
5. Outcome assessors masked?	NR			6. Funding: Health Management Resources and GlaxoSmithKline	
6. Care provider masked?	NR				
7. Patients masked?	Yes (placebo)			Comment: Number completing is reported, but not number enrolled, so unable to determine if ITT analysis or followup rate; blinding of outcome assessment not specified (patients conducted blood glucose monitoring but data were reviewed by study personnel).	
10. Intention-to-treat analysis?	Unable to determine				
11. Postrandomization exclusions?	Unable to determine				

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity			
Rosenblatt S, 2001	**Design:**			**Trial type:** Placebo	**Quality rating:** Fair		
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	197
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	35 /	None	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes, but not described			6. Funding: Takeda Pharmaceuticals			
6. Care provider masked?	Yes, but not described						
7. Patients masked?	NR						
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusions?	No						
Rosenstock J, 2002	**Design:**			**Trial type:** Placebo	**Quality rating:** Fair		
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	566
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	21 /	42	
3. Groups similar at baseline?	Yes	Adherence	Yes	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Yes			6. Funding: Takeda Pharmaceuticals			
6. Care provider masked?	NR ('double blind')						
7. Patients masked?	Yes (placebo)						
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusions?	No						
Saad MF, 2004	**Design:**			**Trial type:** Active and placebo	**Quality rating:** Fair		
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	177
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	None /	28	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Unclear		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Funding NR; one author affiliation Novo-Nordisk Pharmaceuticals, Princeton, NJ			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Not for PIO						
10. Intention-to-treat analysis?	No, high attrition						
11. Postrandomization exclusions?	None reported						

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity			
Satoh N, 2003	**Design:**			**Trial type:** Placebo		**Quality rating:** Poor	
1. Randomization adequate?	Not r	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	136
2. Allocation adequate?	Not r	Crossover	No	3. Run-in/ Wash out (days):	None /	None	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	Unce			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	No			6. Funding: Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Research			
6. Care provider masked?	No			Comment: Poor quality: Attrition NR; can't determine if ITT; open label			
7. Patients masked?	NR						
10. Intention-to-treat analysis?	Uncertain						
11. Postrandomization exclusions?	NR						
Scherbaum W, 2002	**Design:**			**Trial type:** Placebo		**Quality rating:** Poor	
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	509 /	492 /	252
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	None /	70	
3. Groups similar at baseline?	No	Adherence	No	4. Class naive patients only?	0		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Takeda Pharmaceuticals, Europe			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Yes						
Schernthaner G, 2005	**Design:**			**Trial type:** Active		**Quality rating:** Fair	
1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	2145 /	NR /	1199
2. Allocation adequate?	Yes	Crossover	No	3. Run-in/ Wash out (days):	None /	None	
3. Groups similar at baseline?	Yes	Adherence	Yes	4. Class naive patients only?	Yes		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear; reported as double blind			6. Funding: NR			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Yes, placebo used						
10. Intention-to-treat analysis?	No, LOCF and exclusions						
11. Postrandomization exclusions?	Yes, 3% for protocol violation						

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity	
Smith S, 2004; Bogacka I,	**Design:**		**Trial type:** Placebo	**Quality rating:** Poor	
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 48 / 48
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	None / None
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	Yes
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Unclear
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Takeda Pharmaceuticals, Inc, USA	
6. Care provider masked?	Unclear, reported as double blind				
7. Patients masked?	Yes				
10. Intention-to-treat analysis?	No				
11. Postrandomization exclusions?	Yes				
St John Sutton M, 2002	**Design:**		**Trial type:** Active	**Quality rating:** Fair	
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / 351 / 203
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	28 / none
3. Groups similar at baseline?	No	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Funding NR; several authors are affiliated with GlaxoSmithKline	
6. Care provider masked?	Unclear, reported as double blind				
7. Patients masked?	Unclear, reported as double blind				
10. Intention-to-treat analysis?	Yes				
11. Postrandomization exclusions?	No				
Takagi T, 2003	**Design:**		**Trial type:** No treatment	**Quality rating:** Poor	
1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / NR / NR
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	None / None
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	No
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	Attriti			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	NR			6. Funding: NR	
6. Care provider masked?	Yes				
7. Patients masked?	NR				
10. Intention-to-treat analysis?	No				
11. Postrandomization exclusions?	Unclear				

Evidence Table 10. Quality assessment of efficacy trials

Internal validity **External validity**

Tan G, 2005

Design: **Trial type:** Active **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	
2. Allocation adequate?	NR	Crossover	No	
3. Groups similar at baseline?	Yes	Adherence	No	
4. Eligibility criteria specified?	Yes	Contamination	No	
9. Loss to follow-up, differential?	High			
5. Outcome assessors masked?	Unclear, reported as double-blind			
6. Care provider masked?	Unclear, reported as double blind			
7. Patients masked?	Unclear, reported as double blind			
10. Intention-to-treat analysis?	No			
11. Postrandomization exclusions?	Yes			

1. Number Screened/ Eligible/ Enrolled: NR / NR / 567
3. Run-in/ Wash out (days): None / None
4. Class naive patients only? Yes
5. Controlled group standard of care? nr
2. Exclusion criteria reported? NR
6. Funding: Takeda Europe Research and Development Centre, London, UK, and Eli Lilly and Company

Tan G, 2005a

Design: **Trial type:** Placebo **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	
2. Allocation adequate?	NR	Crossover	No	
3. Groups similar at baseline?	Yes	Adherence	No	
4. Eligibility criteria specified?	Yes	Contamination	No	
9. Loss to follow-up, differential?	Yes			
5. Outcome assessors masked?	Unclear, reported as double blind			
6. Care provider masked?	Unclear, reported as double blind			
7. Patients masked?	Yes (placebo)			
10. Intention-to-treat analysis?	No			
11. Postrandomization exclusions?	Unable to determine			

1. Number Screened/ Eligible/ Enrolled: NR / NR / 24
3. Run-in/ Wash out (days): NR / NR
4. Class naive patients only? Yes
5. Controlled group standard of care? Yes
2. Exclusion criteria reported? Yes
6. Funding: GlaxoSmithKline

Tan M (glimepiride), 2004

Design: **Trial type:** Active **Quality rating:** Fair

1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	
2. Allocation adequate?	Yes	Crossover	No	
3. Groups similar at baseline?	Yes	Adherence	No	
4. Eligibility criteria specified?	Yes	Contamination	Yes	
9. Loss to follow-up, differential?	Yes			
5. Outcome assessors masked?	Unclear, "double blind"			
6. Care provider masked?	Unclear, "double blind"			
7. Patients masked?	Unclear, "double blind"			
10. Intention-to-treat analysis?	No, as high attrition			
11. Postrandomization exclusions?	Yes, for protocol violation			

1. Number Screened/ Eligible/ Enrolled: 584 / 244 / 244
3. Run-in/ Wash out (days): 7-21 / None
4. Class naive patients only? No; but no TZD in last
5. Controlled group standard of care?
2. Exclusion criteria reported? Yes
6. Funding: Several authors affiliated with Eli Lilly and Co.

Comment: Randomization by central randomization table generated by the sponsor; administered by an automated interactive voice response system. Randomization stratified by oral agent-naïve and experienced patients; blocked by site

Evidence Table 10. Quality assessment of efficacy trials

Internal validity | **External validity**

Tan MH, 2004a

Design: | **Trial type:** Active | **Quality rating:** Poor

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	200
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	none /	7-21	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	Yes		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	No		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?			
5. Outcome assessors masked?	NR			6. Funding: Eli Lilly and company			
6. Care provider masked?	NR						
7. Patients masked?	NR			Comment: Poor quality due to high attrition			
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Unable to determine						

van Wijk J, 2005

Design: | **Trial type:** Placebo | **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	22 /	20 /	19
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	NR /	42	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	Yes		
4. Eligibility criteria specified?		Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: GlaxoSmithKline			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Yes (placebo)						
10. Intention-to-treat analysis?	Unable to determine						
11. Postrandomization exclusions?	Unable to determine						

Virtanen K, 2003

Design: | **Trial type:** Active/Placebo | **Quality rating:** Fair

1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	44
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	28 /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	Yes		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	NR		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Academy of Finland, Novo Nordisk Foundation, Finnish Diabetes Research Society, and GlaxoSmithKline			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Unclear, reported as double blind			Comment: Companion Hallsten 2002			
10. Intention-to-treat analysis?	Yes						
11. Postrandomization exclusions?	No						

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity	
Vongthavaravat Vm 2002	**Design:**		**Trial type:** No treatment control	**Quality rating:** Fair	
1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	348 / 334 / 334
2. Allocation adequate?	Yes	Crossover	No	3. Run-in/ Wash out (days):	14 / None
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	No			6. Funding: SmithKlineBeecham	
6. Care provider masked?	No				
7. Patients masked?	No				
10. Intention-to-treat analysis?	Yes				
11. Postrandomization exclusions?	No				
Wallace T, 2004	**Design:**		**Trial type:** Placebo	**Quality rating:** Fair	
1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 30
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	None / None
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	Yes
4. Eligibility criteria specified?	No (v	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	NR			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	NR ('double-blind')			6. Funding: Takeda UK	
6. Care provider masked?	NR ('double-blind')				
7. Patients masked?	Yes (placebo)				
10. Intention-to-treat analysis?	Unable to determine				
11. Postrandomization exclusions?	Unable to determine				
Wang G, 2005	**Design:**		**Trial type:** No treatment control	**Quality rating:** Fair	
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR / NR / 71
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	None / None
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes
5. Outcome assessors masked?	NR			6. Funding: Major National Basic Research Program of China, Chinese National Natural Science Foundation	
6. Care provider masked?	NR				
7. Patients masked?	NR				
10. Intention-to-treat analysis?	Yes				
11. Postrandomization exclusions?	No				

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity			
Wang T, 2004	**Design:**		**Trial type:** Placebo	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	50
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	56 /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	NR ('double blind')			6. Funding: Not reported			
6. Care provider masked?	NR ('double blind')						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	Yes (no dropouts)						
11. Postrandomization exclusions?	Unable to determine						
Watanabe I, 2005	**Design:**		**Trial type:** Active	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	30
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	none /	none	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?			
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?			
5. Outcome assessors masked?	NR			6. Funding: NR			
6. Care provider masked?	NR						
7. Patients masked?	NR						
10. Intention-to-treat analysis?	Yes, with attrition						
11. Postrandomization exclusions?	No						
Wolfenbuttel B, 2000	**Design:**		**Trial type:** Placebo	**Quality rating:** Fair			
1. Randomization adequate?	NR	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	829 /	639 /	593
2. Allocation adequate?	NR	Crossover	Yes	3. Run-in/ Wash out (days):	14-28 /	None	
3. Groups similar at baseline?	NR	Adherence	No	4. Class naive patients only?	Not reported		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	No			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: Not reported. One of 5 authors from SmithKlineBeecham			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Yes (placebo)						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Yes						

Evidence Table 10. Quality assessment of efficacy trials

Internal validity				External validity			
Yang W, 2002	**Design:**			**Trial type:** Placebo		**Quality rating:** Fair	
1. Randomization adequate?	NR	8. Reporting of Attrition	No	1. Number Screened/ Eligible/ Enrolled:	NR /	NR /	64
2. Allocation adequate?	NR	Crossover	No	3. Run-in/ Wash out (days):	28 /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	NR ('double blind')			6. Funding: Smith-Kline Beecham Pharmaceuticals and a grant from the Department of Education of the Republic of China			
6. Care provider masked?	NR ('double blind')						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No						
11. Postrandomization exclusions?	Unable to determine						
Zhu X, 2003	**Design:**			**Trial type:** Placebo		**Quality rating:** Fair	
1. Randomization adequate?	Yes	8. Reporting of Attrition	Yes	1. Number Screened/ Eligible/ Enrolled:	771 /	554 /	NR
2. Allocation adequate?	Yes	Crossover	No	3. Run-in/ Wash out (days):	14 /	NR	
3. Groups similar at baseline?	Yes	Adherence	No	4. Class naive patients only?	NR		
4. Eligibility criteria specified?	Yes	Contamination	No	5. Controlled group standard of care?	Yes		
9. Loss to follow-up, differential?	Yes			2. Exclusion criteria reported?	Yes		
5. Outcome assessors masked?	Unclear, reported as double blind			6. Funding: SmithKlineBeecham Research & Development			
6. Care provider masked?	Unclear, reported as double blind						
7. Patients masked?	Yes						
10. Intention-to-treat analysis?	No: 530/554 (95.7%) analyzed						
11. Postrandomization exclusions?	No						

Evidence Table 11. Adverse events head-to-head trials

Derosa G, 2004, 2005

Total withdrawals: Number

Pio	Rosi
2	2

Withdrawals due to AEs: Number

Pio	Rosi
0	0

Adverse events:

Pio	Rosi
Transient, mild to moderate Aes, % (SD)	
6.7	11.9
Increase ALT or AST 2.0 X ULN: Number	
0	2
LFT regressed to normal after 15d	

Comments: P value NR if not specified.
Headache: 1 patient on Pio, 1 on Rosi
Transaminases: NSD from baseline either treatment group
Overall treatment compliance rate 97.5%

Durbin R, 2004

Total withdrawals: %

Pio	Rosi	Control
0	0	0

Withdrawals due to AEs: %

Pio	Rosi	Control
0	0	0

Adverse events:

Pio	Rosi	Control
Weight, change from baseline (lb), Number (SD)		
5.4 (13.8)	0.7 (12.0)	4.5 (3.5)
Appear to be changes from start of study (ie trog)		

Comments: P value NR if not specified.

Evidence Table 11. Adverse events head-to-head trials

Goldberg RB, 2005

Total withdrawals: Number (%)

Pio	Rosi
70(19.0)	80(21.9)
p= NR	

Withdrawals due to AEs: Number

Pio	Rosi
10	10
p= NSD	

Comments: P value NR if not specified.

LFT, creatine phosphokinase, BP, HB hematocrit: NSD
Edema, CHF: NSD

Hanefeld M, 2004

Adverse events:

Pio	Met
Withdrawals due to Aes (%): %	
3.6	5.9
Incidence of Aes: %	
59.9	61.9
Serious Aes, %: %	
6.6	9.7
Gastrointestinal disorders (%): %	
12.2	23.4
3.1	4.1
Hypoglycemic episodes: (%)	
14.7	10.7
6.9	1.6
Weight, change from baseline (kg): Number	
2.8	-1.0

Comments: P value NR if not specified.

104 weeks: Pio group had consistently improved liver enzyme function vs metformin
Aes results; no change aspartate aminitransferase in either group; decrease GTP, alanine aminotransferase and alkaline phosphatase in both groups (p NR)
decrease HB and hematocrit both groups (p NR)

Evidence Table 11. Adverse events head-to-head trials

Herz M, 2003

Total withdrawals: Number (%)

Pio-30	Pio-45	Placebo
7(7)	7(7)	11(11)
p= NS		

Withdrawals due to AEs: Number (%)

Pio-30	Pio-45	Placebo
1(1)	0(0)	5(5)
p= NS		

Adverse events:

	Pio-30	Pio-45	Placebo
Treatment-emergent adverse events, incidence, Number (%)			
	63 (63.6)	79 (79.8)	68 (68.7)
p vs placebo	NSD	NSD	
Arthralgia, incidence, Number (%)			
	3 (3)	10 (10)	2 (2)
p vs placebo	NSD	0.017	NA
Hypoglycemic episodes, incidence, Number (%)			
	11 (11)	10 (10)	11 (11)
p vs placebo	NSD	NSD	
Edema, incidence, Number (%)			
	14 (14)	16 (16)	16 (16)
p vs placebo	NSD	NSD	NA

Comments: P value NR if not specified.

Khan M, 2002

Total withdrawals: NR

Withdrawals due to AEs: NR

Comments: P value NR if not specified.
NR

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Aronoff S, 2000

Total withdrawals: %

Pio-All	Placebo
42 to 56	67
p= NR	

Withdrawals due to AEs: Number (%)

Pio-7.5	Pio-15	Pio-30	Pio-45	Placebo	Placebo
2(2)	3(4)	4(5)	3(4)	2(3)	
p= NR					

Adverse events:

	Pio-All	Placebo
Overall rate of AEs: %		
	76	85
NSD between these 2 groups		
URTI: %		
	15.2	11.4
p vs placebo	>0.05	NA
Headache: %		
	12.5	10.1
Cardiac adverse events, Number (%)		
	12 (3.6)	5 (6.3)
NSD		
Edema or peripheral edema, Number (%)		
	12 (3.6)	0 (0)
p-value NR		
Hypoglycemia, Number (%)		
	4 (1.2)	0 (0)
p vs placebo	>0.05	NA

Comments: P value NR if not specified.

Most common reason for withdrawal was lack of glycemic control as established by provider, symptomatic hypoglycemia, patient perception of lack of control.
Withdrawals for poor glycemic control: placebo 49%, 29-35% in Pio groups
Most commonly reported A

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Belcher 2004, Khan 2004

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse events:

	Pio	Other
Cardiac deaths: %		
	0.2	0.3
Hospitalizations, all causes: %		
	0.2	0.3
p vs other	NSD	
MI: %		
	0.5	0.4

Comments: P value NR if not specified.

Charbonnel BH, 2004

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse events:

	Pio	Glic
Edema (%): %		
	8.7	4.5
Hypotlycemia: %		
	3.5	10.1
Hemoglobin, change from baseline to 52w (g/dl): Number		
	-0.7	-0.2
Abnormal LFT during study (%): %		
	0.5	1.6

Comments: P value NR if not specified.

Frequency of AE: Pio 75%, gliclazide 71%
Other reported Aes for Pio vs gliclazide: diarrhea (2.9 vs 3.4%); nausea (4.3 vs 5.1%); dizziness (4.0 vs 6.5%), headache (8.7 vs 8.9%), hypertension (3.4 vs 3.8%); no statistics

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Dormandy JA, 2005

Total withdrawals: Number

Pio	Placebo
854	876

Withdrawals due to AEs: Number

Pio	Placebo
235	202

Adverse events:

	Pio	Placebo
Any serious AE (% of patients): %		
	46	48
p vs placebo	p=0.110	
Any report of heart failure (% of patients): %		
	11	8
p vs placebo	p<0.0001	
Edema without heart failure (% of patients): %		
	573 (22)	342 (13)
Symptomatic hypoglycemia (% of patients): %		
	28	20
p vs placebo	p<0.0001	
NSD hypoglycemia requiring hospitalization		
Angina pectoris: %		
	3	5
p vs placebo	0.025	NA
Hospital admission for diabetes control: %		
	2	3
p vs placebo	0.003	NA
Accident: %		
	2	2
p vs placebo	0.798	NA
Pneumonia: %		
	2	1
p vs placebo	0.047	NA
Transient ischemic attack: %		
	1	2
p vs placebo	0.587	NA

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Dormandy JA, 2005

Neoplasms: %		
	4	4
NSD		

Comments: P value NR if not specified.

Serious Aes defined as: resulting in death, life-threatening, needing or prolonging in-patient admission, resulting in persistent or significant disability, or needing intervention to prevent any of the above.
Fatal heart failure: NSD
No cases of acute

Kipnes M, 2001

Total withdrawals: Number (%)

Pio	Placebo
42(11.3)	26(13.9)

p= NR

Note: rates reported for Pio 15 mg and 30 mg groups combined

Withdrawals due to AEs: Number (%)

Pio	Placebo
11(3.0)	5(3.0)

p= NR

Note: rates reported for Pio 15 mg and 30 mg groups combined

Adverse events:

	Pio-All	Placebo
Drug-related adverse events, overall incidence, Number (%)		
	83 (22)	34 (18)
p vs placebo	NSD	NA
Edema, incidence, Number (%)		
	27 (7)	4 (2)
p vs placebo	0.0109	NA
Hypoglycemic epidsodes, incidence, Number (%)		
	7 (1.9)	1 (0.53)
	NR	NR
Cardiac events, Number (%)		
	22 (5.9)	10 (5.3)
	NR	NR

Comments: P value NR if not specified.

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Matthews DR, 2005

Total withdrawals: %

Pio	Glic
17.7	13.4
p= NR	

Withdrawals due to AEs: %

Pio	Glic
13	14
p= NSD	

Adverse events:

Pio	Glic
Total AES reported: %	
55.5	58.1
NR	NR
Total no. events: PIO 533 (140 study-related), gliclazide 628 (210 study-related)	
Number Serious Aes: Number	
17	27
NR	NR
P NR	
Hypoglycemia: Number	
1.3	11.2
NR	NR
None of the events was severe; 2 patients withdrawn in gliclazide group	
Peripheral edema: %	
6.3	2.2
NR	NR
One patient on PIO withdrew due to edema	
Hemoglobin, change from baseline at 52 weeks (g/L): Number	
-6.0	-3.0
NR	NR

Comments: P value NR if not specified.

In Pio group, 2 patients develoled pulmonary edema; 1 felt related to Pio
Dizziness and vertigo were reported more frequently with Pio
Hypertension, arthralgia, diarrhea, paresthesia and dyspepsia were reported in the gliclazide group
Liver enzymes sho

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Mattoo V, 2005

Total withdrawals: Number (%)

Pio	Placebo
14(9.9)	12(8.2)
p= NR	

Withdrawals due to AEs: Number (%)

Pio	Placebo
7(4.9)	3(2.0)
p= NR	

Adverse events:

Pio	Placebo
Adverse events, total patients with, Number (%)	
109 (76.8)	98 (66.7)
p-value NR	
Subjective hypoglycemic episodes, incidence, Number (%)	
90 (63.4)	75 (51.0)
p vs placebo <0.05	NA
NS difference in rate of hypoglycemic episodes per 30 days or number of clinical hypoglycemic episodes (blood glucose <2.8 mmol/L)	
Edema, incidence of, Number (%)	
20 (14.1)	5 (3.4)
p-value NR	

Comments: P value NR if not specified.

Evidence Table 12. Adverse events efficacy trials, pioglitazone

McMahon G, 2005

Total withdrawals: Number (%)

Pio	Placebo
2(20)	2(20)
p= NR	

Withdrawals due to AEs: Number (%)

Pio	Placebo
1(10)	0(0)
p= NR	

Adverse events:

Pio	Placebo
Hypoglycemic events req'ing assistance, incidence, Number (%)	
3 (37.5)	1 (12.5)
p vs placebo 0.26	NA
Edema, incidence, Number (%)	
1 (12.5)	0 (0)
p-value NR	
Congestive heart failure, incidence, Number (%)	
1 (12.5)	0 (0)
p-value NR	

Comments: P value NR if not specified.

Miyazaki Y, 2001; Miyazaki Y, 2004

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

Comments: P value NR if not specified.

Miyazaki Y, 2002

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

Comments: P value NR if not specified.

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Negro R, 2004

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

Comments: P value NR if not specified.
No information on Aes reported; attrition NR

Rasouli N, 2005

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

Comments: P value NR if not specified.
No information on Aes provided.

Rosenblatt S, 2001

Total withdrawals:

Note: 54/197 (27.4%) overall withdrew; not reported per group

Withdrawals due to AEs: Number (%)

Pio	Placebo
1(1.0)	1(1.0)

p= NR
Note: placebo: severe angina, Pio: mild ECG abnormality

Adverse events:

Pio	Placebo
hypoglycemic episodes, incidence, Number (%)	
0 (0)	0 (0)
Edema, incidence, Number (%)	
5 (5.0)	1 (1.0)

p-value NR

Comments: P value NR if not specified.

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Rosenstock J, 2002

Total withdrawals: Number (%)

Pio-15	Pio-30	Placebo
23(12.0)	30(16.0)	16(8.6)
p= NR		

Withdrawals due to AEs:

Pio-15	Pio-30	Placebo
5(2.6)	6(3.2)	3(1.6)
p= NR		

Adverse events:

Pio-15	Pio-30	Placebo	Pio-All
Adverse events, overall, Number (%)			
		132 (74.3)	284 (78.4)
p-value NR			
Edema, incidence, Number (%)			
		12 (7.0)	55 (15.3)
p-value NR			
Hypoglycemia, incidence, Number (%)			
15 (8)	29 (15)	9 (5)	
p-value NR			
Congestive heart failure, Number (%)			
2 (1.0)	2 (1.1)	0 (0)	

Comments: P value NR if not specified.

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Saad MF, 2004

Total withdrawals: Number (%)

Rag-0.1	Rag-1	Rag-4	Rag-10	Pio	Pio
6(NR)	7(NR)	9(NR)	13(NR)	7(NR)	10(NR)

p= NR

Withdrawals due to AEs: Number (%)

Rag-0.1	Rag-1	Rag-4	Rag-10	Pio	Pio
NR(NR)	NR(NR)	5(NR)	10(NR)	0(NR)	0(NR)

p= NR

Adverse events:

Rag-0.1	Rag-1	Rag-4	Rag-10	Pio	Placebo
Hemoglobin, % change from baseline, Number (SD)					
	-6.7	-13.3	-19.4	-7.3	

p-value NR

Comments: P value NR if not specified.

Edema: led to withdrawal of 2 and 8 patients in the 4 and 10-mg groups
Weight gain: 22% in 4- and 10-mg groups; 5.7 and 5.9 kg, respectively
WBC: decreased from baseline compared to placebo in 4- and 10-mg groups (p<0.05)
Most common AEs (>4% of subjec

Satoh N, 2003

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

Comments: P value NR if not specified.

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Scherbaum W, 2002

Total withdrawals: Number (%)

Pio-15	Pio-30	Placebo
2(2.2)	0(0)	2(2.4)
p= NR		

Withdrawals due to AEs: Number (%)

Pio-15	Pio-30	Placebo
22(24.7)	8(10.3)	22(26.2)
p= NR		

Adverse Events: NR
Adverse events:

Pio-15	Pio-30	Placebo
Influenza-like symptoms, incidence, Number (%)		
22 (2)	7 (9)	7 (8)
p-value NR		
Back pain, incidence, Number (%)		
0 (0)	3 (4)	4 (5)
Bronchitis, incidence, Number (%)		
3 (3)	3 (4)	5 (6)
Cystitis, incidence, Number (%)		
4 (5)	1 (1)	2 (2)
Urinary tract infection, incidence, Number (%)		
2 (2)	2 (3)	4 (5)
Edema, incidence, Number (%)		
0 (0)	2 (3)	0 (0)
Weight gain >5%, incidence, Number (%)		
6 (7)	9 (12)	1 (1)

Comments: P value NR if not specified.

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Schernthaner G, 2005

Total withdrawals: Number (%)

Pio	Met
98(NR)	96(NR)

p= NR

Withdrawals due to AEs: Number (%)

Pio	Met
42(NR)	39(NR)

p= NR

Note: Reasons for withdrawal in PIO and metformin: GI 1.5%, 2.5%; general disorders 1.5%, 0.3%; headache, dizziness 1.7%, 0.3%

Adverse events:

	Pio	Met
Severe AEs, % (SD)	4.9 (NR)	7.4 (NR)
Hb, change from baselin to 52 weeks (g/dl), Number (SD)	-0.59 (NR)	-0.44 (NR)
Cardiovascular Aes, % (SD)	3.7 (NR)	3.9 (NR)
Alanine transaminase, change from baseline to 52w, Number (SD)	6.4 (NR)	2.8 (NR)
U/l		
Increase in lanine transaminase to 3x normal (%), Number (SD)	0.9 (NR)	2.2 (NR)
U/l		

Comments: P value NR if not specified.

AEs reported: Pio 316, metformin 346; NSD
LFT: GGT: decreased more in Pio than metformin (NSD); AP: decreaed both groups, NSD
Hepatotoxicity with drug discontinuation: 2 in Pio, 1 in metformin:

Smith S, 2004; Bogacka I, 2004

Total withdrawals: Number (%)

Pio	Placebo
3(12.5)	3(12.5)

p= NR

Withdrawals due to AEs: NR

Adverse Events: NR

Comments: P value NR if not specified.

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Takagi T, 2003

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

Comments: P value NR if not specified.

No patient had abnormalities in laboratory variables, including LFT to ≥2 times upper limit normal; 2 patients in Pio group and 3 in control group had transient increase LFT <2-times upper limit normal
Mild edema in 2 Pio patients; no severe congestive h

Tan G, 2005

Total withdrawals: % (%)

Pio	Glic
45.6(NR)	57(NR)
p= NR	

Withdrawals due to AEs: Number (%)

Pio	Glic
25(NR)	33(NR)
p= NR	

Comments: P value NR if not specified.

Study withdrawal due to weight gain: Pio 6 of 33 patients, gliclazide 1 of 25 patients
Withdrawal due to headaches: Pio 0%, gliclazide 3 of 25 patients

Evidence Table 12. Adverse events efficacy trials, pioglitazone

Tan M (glimepiride), 2004

Total withdrawals: Number (%)

	Pio	Glim
	34(28)	34(27)
	p= NSD	

Withdrawals due to AEs: NR

Adverse events:

	Pio	Glim
Weight, Number (SD)		
	1.49 (NR)	0.79 (NR)
p vs Pioglitazone	0.001	0.045
Peripheral edema, % (SD)		
	28.9 (NR)	13.8 (NR)
Pio vs glimipiride p0.005		
Hypoglycemia, >=1 episode, % (SD)		
	15.7 (NR)	30.9 (NR)
p=0.024		
ALT or Ast: neither treatment affected levels: Number		
Incidence treatment-emergent Aes, % (SD)		
	86.8 (NR)	76.4 (NR)
p vs Glim	NSD	NA

Comments: P value NR if not specified.

3 Aes in Pio considered treatment-related, 2 in gl

Wallace T, 2004

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse events:

	Pio-45	Placebo
Headache and lightheadedness, Number (%)		
	1 (5.3)	0 (0)

Comments: P value NR if not specified.

Monthly liver function tests remained normal; one patient taking Pio reported increased incidence of headaches and lightheadedness, resolved after 2 weeks

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Agrawal A, 2003

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse events:

	Rosi	Placebo
URTI: %		
	8.6	7.8
p-value NR		
Injury: %		
	6.6	5.7
p-value NR		
Hypoglycemia: %		
	5.1	2.8
p-value NR		
Edema: %		
	4.1	0
p-value NR		
Anemia: %		
	1.9	0.7
p-value NR		
Headache: %		
	4.9	5.4
p-value NR		

% AEs was similar for patients in both treatment groups when comparing those with renal impairment and those without, including incidence of hypoglycemia; edema more common in patients with normal renal function in both treatment groups (no statistics)
L

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Barnett A, 2003

Total withdrawals: NR

Withdrawals due to AEs: Number (%)

Rosi	Placebo
4(5)	9(10)

Adverse events:

	Rosi	Placebo
Influenza-like symptoms, total: %	10	14
Hypoglycemia, total: %	12	6
Headache, total: %	6	9
Dizziness, total: %	5	8
Coughing, total: %	7	5
Hyperglycaemia, total: %	1	9
p vs placebo	0.0345	
Upper respiratory infection, total: %	8	2
Hypercholestrolaemia, total: %	6	3
Flatulence, total: %	7	2
Leg Pain, total: %	2	7
Paraesthesia, total: %	6	3
Rhintitis, total: %	6	3
Myalgia, total: %	6	1

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Bennett S, 2004

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

P value NR if not specified.

Choi D, 2004

Total withdrawals: Number (%)

Rosi-4	usual care
9(19.1)	3(6.3)

p= 0.07

Withdrawals due to AEs: Number (%)

Rosi-4	usual care
0(0)	0(0)

p= NS

Adverse events:

"No patient had significant side effects, such as an elevation in liver enzyme levels."

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Fonseca V, 2000

Total withdrawals: Number

	Rosi-4	Rosi-8	Placebo

Withdrawals due to AEs: Number (%)

	Rosi-4	Rosi-8	Placebo
	7(5.9)	6(5.3)	5(4.3)

Adverse events:

	Rosi-4	Rosi-8	Placebo
% patients with >=1 AE: %			
	75.2	78.2	76.7
p vs placebo	NSD	NSD	
Serious non-fatal AEs (%): %			
	4.2	4.4	4.3
Hb, change from baseline to 26 weeks (g/L): Number			
	-5.0	-8.0	NR
p vs baseline	p<0.0001	p<0.0001	NSD
Edema at 26w (%): %			
	2.5	3.5	0.9
BMI, change from baseline to 26w (mg/m2): Number			
	-0.7	-1.9	1.2
p vs baseline	p=0.001	p=0.001	

Most frequently reported Aes: URTI, diarrhea, headache; 1 death in Pio 4 mg due to MI judged to be unrelated to study medication.
Symptomatic hypoglycemia: Pio 4mg: 3 patients, Pio 8mg: 5, placebo: 2; no third-party asssistance required for any episode.

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Gomez-Perez F, 2002

Total withdrawals: Number (%)

Rosi-4	Rosi-8	Placebo
8(21.6)	8(20.0)	10(25.6)

Withdrawals due to AEs: Number (%)

Rosi-4	Rosi-8	Placebo
2(5.4)	3(7.5)	1(2.6)

Adverse events:

Rosi-4	Rosi-8	Placebo
At least one adverse event, patients with, Number (%)		
31 (83.8)	28 (70.0)	27 (69.2)
Edema, total: %		
5.2	NR	
Cardiac-related adverse events, total: Number		
1	2	1
Serious adverse events, total: Number		
0	1	0
hemolysis		

P value NR if not specified.

Hallsten K, 2002

Total withdrawals: Number (%)

Rosi	Met	Placebo
0(0)	2(15.4)	0(0)

Withdrawals due to AEs: Number (%)

Rosi	Met	Placebo
0(0)	1(7.7)	0(0)

Adverse Events: NR

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Honisett S, 2003

Total withdrawals: Number

Rosi	Placebo
0	0

Withdrawals due to AEs: Number

Rosi	Placebo
0	0

Adverse Events: NR

P value NR if not specified.

Hung Y, 2005

Total withdrawals: Number

Rosi	Placebo
0	0
p= NR	

Withdrawals due to AEs:

Rosi	Placebo
0	0
p= NR	

Adverse events:

Rosi	Placebo
Aes: Number	
0	0

P value NR if not specified.

Iozzo P, 2003

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Jones T, 2003

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse events:

	Met alone	Rosi+Met
Upper respiratory tract infection, total, % (SD)	8.9 (NR)	16.0 (NR)
Diarrhoea, total, % (SD)	15.6 (NR)	12.7 (NR)
Injury, total, % (SD)	7.6 (NR)	8.0 (NR)
Fatigue, total, % (SD)	4.0 (NR)	5.9 (NR)
Anaemia, total, % (SD)	2.2 (NR)	7.1 (NR)
Sinusitis, total, % (SD)	5.3 (NR)	6.2 (NR)
Headache, total, % (SD)	8.9 (NR)	6.5 (NR)

P value NR if not specified.

Kim Y, 2005

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

P value NR if not specified.

Lebovitz H, 2001

Total withdrawals: Number (%)

Placebo	Rosi-2	Rosi-4
77(44)	46(26)	45(25)

p= NR

Withdrawals due to AEs: NR

Adverse Events: NR

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Miyazaki Y, 2001

Total withdrawals: Number (%)

Rosi	Placebo
0(0)	0(0)

p= NR

Withdrawals due to AEs: Number (%)

Rosi	Placebo
0(0)	0(0)

p= NR

Adverse Events: NR

No data on Aes reported

P value NR if not specified.

Natali A, 2004

Total withdrawals: Number

Rosi	Met	Placebo
0	0	0

p= NR

Withdrawals due to AEs:

Rosi	Met	Placebo
0	0	0

p= NR

Adverse Events: NR

P value NR if not specified.

Nolan J, 2000

Total withdrawals: Number

Rosi	Placebo
7	7

Withdrawals due to AEs: Number (%)

Rosi	Placebo
7(3.8)	7(7.5)

Adverse Events: NR

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Patel J, 1999

Total withdrawals: Number (%)

Rosi 0.05	Rosi-0.25	Rosi-1	Rosi-2	Placebo	Placebo
8(10.8)	11(15.2)	6(7.5)	5(6.2)	5(6.6)	
p= NR					

Withdrawals due to AEs: Number (%)

Rosi-0.05	Rosi-0.25	Rosi-1	Rosi-2	Placebo	Placebo
4(0.5)	1(0.1)	5(0.6)	3(0.3)	2(0.2)	
p= NR					

Adverse Events: NR

P value NR if not specified.

Phillips S, 2001

Total withdrawals: %

Rosi	Placebo
20.7	38.4
p= NR	

Withdrawals due to AEs: Number (%)

Rosi	Placebo
41(5.6)	19(10.8)
p= NR	

Adverse events:

Rosi	Placebo			
Patients reporting at least 1 AE (%): %				
75	71			
Edema (%): %				
3 (1.6)	9 (5.2)	12 (6.4)	7 (4.1)	12 (6.6)
NR	NR			
p-value NR				

Assessments based on observed data for all randomized patients
Withdrawal from placebo group for edema
Asymptomatic increase in serum ALT more than 3 times upper limit normal, 1 placebo 1 Rosi group
Hemoglobin: decrease in all Rosi groups, p<=0.0001 (r

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Raskin P, 2000

Total withdrawals: Number

Placebo	Rosi-2	Rosi-4	Rosi-6
10	5	8	4

p= NR

Withdrawals due to AEs:

Placebo	Rosi-2	Rosi-4	Rosi-8
6(9.3)	4(5.1)	3(4.2)	3(3.8)

p= NR

Adverse Events: NR

P value NR if not specified.

Raskin P, 2001

Total withdrawals: NR

Withdrawals due to AEs: Number (%)

Placebo	Rosi-All
5(4.7)	17(8.0)

p= NR

Adverse Events: NR

P value NR if not specified.

Reynolds L, 2002

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

P value NR if not specified.

Tan G, 2005a

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

P value NR if not specified.

van Wijk J, 2005

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Virtanen K, 2003

Total withdrawals: Number (%)

Rosi	Met	Placebo
1(NR)	2(NR)	0(NR)
p= NR		

Withdrawals due to AEs: Number (%)

Rosi	Met	Placebo
0(NR)	0(NR)	0(NR)
p= NR		

Adverse Events: NR

P value NR if not specified.

Vongthavaravat Vm 2002

Total withdrawals: Number (%)

Rosi	SU alone
36(30.0)	60(35.3)
p= 0.007 (calculated)	

Withdrawals due to AEs: Number (%)

Rosi	SU alone
7(4.3)	2(1.2)
p= <0.001	

Adverse events:

	Rosi	SU alone
Any adverse event, patients reporting at least one, Number (%)		
	104 (63.4)	90 (52.9)
Hypoglycemia, patients with occurrence of, Number (%)		
	19 (11.6)	2 (1.2)
p vs SU alone	<0.001	NR
Hyperglycemia, patients with occurrence of, Number (%)		
	4 (2.4)	16 (9.4)
Upper respiratory tract infection, patients with, Number (%)		
	12 (7.3)	12 (7.1)
Urinary tract infection, patients with, Number (%)		
	12 (7.3)	11 (6.5)

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Wang G, 2005

Total withdrawals: Number (%)

Rosi	Control
1(2.8)	0(0)

p= NR

Withdrawals due to AEs: NR

Adverse Events: NR

P value NR if not specified.

Wang T, 2004

Total withdrawals:

Rosi	Placebo
0	0

p= 0

Withdrawals due to AEs:

Rosi	Placebo
0	0

p= NR

Adverse Events: NR

Adverse events reported as none

P value NR if not specified.

Wolfenbuttel B, 2000

Total withdrawals: % (%)

Rosi-2	Rosi-4	Placebo
28(NR)	24(NR)	36(NR)

p= NR

Note: Number randomized to each group NR; RR for placebo vs Rosi 4 mg 0.68 (95% CI 0.49, 0.92)

Withdrawals due to AEs: Number (%)

Rosi-2	Rosi-4	Placebo
10(5.0)	10(5.5)	23(12.0)

p= NR

Adverse events:

Rosi-2	Rosi-4	Placebo
Hyperglycemia, incidence, % (SD)		
9.3 (NR)	5.3 (NR)	17.2 (NR)
p-value NR		
Hypoglycemia, incidence, % (SD)		
3.4 (NR)	5.3 (NR)	2.0 (NR)
p-value NR		

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Yang W, 2002

Total withdrawals: NR

Withdrawals due to AEs: NR

Adverse Events: NR

Patients with at least 1 AE probably related to Rosi: 13.6%; including URTI (1 case), edema (3), diarrhea (3)
LFT: no patient had increase LFT greater than 3 times upper limit normal
Total of 5 lost to follow-up; group and reason NR

P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Zhu X, 2003

Total withdrawals: % (%)

Rosi-4	Rosi-8	Placebo
11.8(NR)	11.3(NR)	34.8(NR)
p= NR		

Withdrawals due to AEs: Number (%)

Rosi-4	Rosi-8	Placebo
2(NR)	12(NR)	3(NR)
p= NR		

Adverse events:

	Rosi-4	Rosi-8	Placebo
report of adverse event, % (SD)	70.1 (NR)	79.6 (NR)	43.8 (NR)
Injury, % (SD)	2.0 (NR)	3.0 (NR)	6.0 (NR)
Hyperlipidemia, % (SD)	17.0	25.0	4.0
Edema, legs, % (SD)	21.0 (NR)	27.0 (NR)	0 (NR)
Edema, face, % (SD)	9.0 (NR)	11.0 (NR)	0 (NR)
Thrombocytpenia, % (SD)	9.0 (NR)	17.0 (NR)	4.0 (NR)
Urinary tract infection, % (SD)	20.0 (NR)	24.0 (NR)	8.0 (NR)
Upper respiratory tract infection, % (SD)	37.0 (NR)	22.0 (NR)	6.0 (NR)
Vision abnormal, % (SD)	5.0 (NR)	5.0 (NR)	6.0 (NR)
Weight increase, % (SD)	21.0 (NR)	37.0 (NR)	1.0 (NR)

P value NR if not specified.

Evidence Table 14. Subgroups, non-randomized studies, piogitazone and rosiglitazone

Chan NN, 2004 **Quality rating: Observational study**

Design:

Study design: NA NA NA **Run-in :** **Setting:** Single Center
Wash out : **Country:** USA

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed
NA/ NA/ NA 12

Inclusion criteria:
Insulin-treated DM2 patients with nephropathy who were started on Rosi due to suboptimal glycemic control and progressive weight gain

Exclusion criteria:
None reported

Comments:
Design: retrospective cohort
Quality assessment form NA

Population: **Mean age:** 65 years **Ethnicity:**)
Gender: 58% Female
Type 2 diabetes duration (SD): 16.5 (8.6) years

Intervention: monotherapy

Duration: mean 15.5 +/- 2.9 month

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone	2-4mg qd	Rosi	12	8.6 (1.4)	71.7 (13.6)		

Laboratory measures:

	Baseline	Rosi
A1c, baseline and follow-up: % (SD)		
	8.57(1.42)	7.48(1.3)
p vs follow-up		p=0.01
Total cholesterol, baseline and follow-up: mmol/l		
	5.06(1.39)	5.16(1.31)
p vs Rosi, baseline		p=0.82
HDL, baseline and follow-up: mmol/l		
	1.22(0.37)	1.29(0.32)
p vs baseline		p=0.14
LDL, baseline and follow-up: mmol/l		
	2.80(1.04)	2.93(1.03)
p vs baseline		p=0.74
TG, baseline and follow-up: mmol/l		
	2.34(1.3)	2.07(0.87)
p vs baseline		p=0.31

Evidence Table 14. Subgroups, non-randomized studies, piogitazone and rosiglitazone

Chan NN, 2004 **Quality rating: Observational study**

Laboratory measures:

	Baseline	Rosi
A1c, baseline and follow-up: % (SD)		
	8.57(1.42)	7.48(1.3)
p vs follow-up		p=0.01
Total cholesterol, baseline and follow-up: mmol/l		
	5.06(1.39)	5.16(1.31)
p vs Rosi, baseline		p=0.82
HDL, baseline and follow-up: mmol/l		
	1.22(0.37)	1.29(0.32)
p vs baseline		p=0.14
LDL, baseline and follow-up: mmol/l		
	2.80(1.04)	2.93(1.03)
p vs baseline		p=0.74
TG, baseline and follow-up: mmol/l		
	2.34(1.3)	2.07(0.87)
p vs baseline		p=0.31

Physiologic outcomes:

	Baseline	Rosi
Weight, baseline and follow-up: kg (SD)		
	71.7(13.6)	73.9(13.1)
p vs baseline		p=0.08

P value NR if not specified.

Evidence Table 14. Subgroups, non-randomized studies, piogitazone and rosiglitazone

Jun JK, 2003 **Quality rating: Fair, for case series**

Design:

Study design: NA NA NA **Run-in :** None **Setting:** Single Center

Wash out : None **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	143/	54/	54	0/	0/	54

Inclusion criteria:

Hispanic, >18y, have DM2, have uncontrolled hyperglycemia with A1c ≥8.0%; have taken Pio for at least 6m; have A1c within 1m before start of Pio; have at least 2 A1c measures at 3-m intervals during the 6-m period; have a lipid panel within 1m before start of Pio; have at least 2 lipid panels performed at 3m interval during study

Exclusion criteria:

Noncompliant with Pio as noted in chart

Comments:

Retrospective chart review

Population: **Mean age:** 54.6 years **Ethnicity:** Hispanic: 100%

Gender: 83% Female

Type 2 diabetes duration (SD): 10.3 (5.7) years

Intervention: monotherapy

Duration:

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	15-45mg qd	Pio					

Laboratory measures:

	Pio
A1c, change from baseline to 6m: %	
	-2.0
p vs baseline	p<0.0001
FPG, change from baseline to 6m: % change	
	-21.2
p vs baseline	p<0.0001
TG, change from baseline to 6m: % change	
	-5.6
p vs baseline	p=0.038
HDL, change from baseline to 6m: % change	
	6.5
p vs baseline	p=0.008
LDL, change from baseline to 6m: % change	
	-4.2
p vs baseline	NSD
Total cholesterol, change from baseline to 6m: % change	
	-5.6
p vs baseline	p=0.038

Evidence Table 14. Subgroups, non-randomized studies, piogitazone and rosiglitazone

Jun JK, 2003 **Quality rating: Fair, for case series**

Laboratory measures:

	Pio
A1c, change from baseline to 6m: %	
	-2.0
p vs baseline	p<0.0001
FPG, change from baseline to 6m: % change	
	-21.2
p vs baseline	p<0.0001
TG, change from baseline to 6m: % change	
	-5.6
p vs baseline	p=0.038
HDL, change from baseline to 6m: % change	
	6.5
p vs baseline	p=0.008
LDL, change from baseline to 6m: % change	
	-4.2
p vs baseline	NSD
Total cholesterol, change from baseline to 6m: % change	
	-5.6
p vs baseline	p=0.038

Physiologic outcomes:

	Pio
SBP, change from baseline to 6m: %	
	-2.2
p vs baseline	NSD
DBP, change from baseline to 6m: %	
	-6.3
p vs baseline	p=0.006
Weight, change from baseline to 6m: %	
	4.3
p vs baseline	p<0.0001

P value NR if not specified.

Evidence Table 14. Subgroups, non-randomized studies, piogitazone and rosiglitazone

King AB, 2003 **Quality rating: Fair, for cohort study**

Design:

Study design: NA NA NA **Run-in :** NA **Setting:** Single Center
Wash out : NA **Country:** USA

Sample:	Number Screened/	Eligible/	Enrolled	Number Withdrawn/	Lost to follow-up/	Analyzed
	NA/	179/	179	NA/	NA/	179

Inclusion criteria:
Clinic patients with DM2, treated with Pio 45mg/d for 6m or more without interruption; A1c and lipids available on the chart within 4w of starting treatment and approximately 4m into treatment

Exclusion criteria:
Patients whose lipid-lowering medication was changed during study period.

Comments:
Retrospective chart review of non-Hispanic Caucasians compared to Mexican-Americans

Population: **Mean age:** NR years **Ethnicity:** Non-Hispanic Caucasians: 54.7%; Mexican-Americans: 45.2%
Gender: NR% Female
Type 2 diabetes duration (SD): NR (NR) years

Intervention: subgroup

Duration:

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
PIO, Native-Amer	NR	Pio-NA	81	8.2 (1.9)	NR (NR)	NR (NR)	
PIO, White	NR	Pio-White	98	8.0 (1.9)	NR (NR)	NR (NR)	

Laboratory measures:

	Pio-White	Pio-NA
A1c, change from baseline to 3m: % (SD)		
	-1.2(1.8)	-1.1(1.4)
p vs PIO-NA	p=0.616	
HDL, change from baseline to 3m: % (SD)		
	17.0(21.0)	16.0(18.8)
p vs PIO-NA	p=0.748	
LDL, change from baseline to 3m: % (SD)		
	5.1(25.2)	6.5(48.1)
p vs PIO-NA	p=0.826	
TG, change from baseline to 3m: % change (SD)		
	10.1(47.1)	8.4(47.3)
p vs PIO-NA	p=0.802	

Physiologic outcomes:

	Pio-White	Pio-NA
Weight, change from baseline to 3m: kg (SD)		
	1.64	1.41
p vs PIO-NA	p=0.540	

P value NR if not specified.

Evidence Table 14. Subgroups, non-randomized studies, piogitazone and rosiglitazone

Kreider M, 2002 **Quality rating: NA (8 other studies)**

Design:

Study design: RCT DB Parallel **Run-in :** NR **Setting:** Multicenter
Wash out : NR **Country:** USA

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed
NR/ NR/ NR NR/ NR/ 3127

Inclusion criteria:
DM2, FPG varied among studies, range 7.8-16.9 mmol/l; age varied, range 30-80y; BMI 22-38 kg/m2

Exclusion criteria:
Significant renal disease; angina or cardiac insufficiency, symptomatic diabetic neruopathy, hepatic disease, history of diabetic ketoacidosis, history of chronic insulin use, other serious major illness

Comments:
Setting: 8 sites in USA
Design: analyzes data from 8 other studies: Patel 1999, Lebovitz 2001, Phillips 2001, Charbonnel 1999 (abstract), Raskin 2000, Nolan 2000
Patients stratified by < or >=70y
Efficacy data pooled from 3 montherapy studies of 26w duration; safety data pooled from all 8 studies
Quality assessment not performed as is report of 8 primary studies.
All primary studies funded by SmithKline Beecham Pharmaceuticals.

Population: **Mean age:** NR years **Ethnicity:** NR
Gender: 36% Female
Type 2 diabetes duration (SD): NR (NR) years

Intervention: monotherapy, elderly, 8 other studies

Duration: 26 week

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Rosiglitazone <70	4-12mg	Rosi <70	2099	8.8 (1.5)	NR (NR)	29.8 (4.1)	
Rosiglitazone >70	4-23mg	Rosi >70	427	8.6 (1.4)	NR (NR)	28.3 (3.9)	
Placebo <70	NA	Placebo <70	497	9.0 (1.7)	NR (NR)	29.8 (4.2)	
Placebo >70	NA	Placebo >70	104	8.9 (1.5)	NR (NR)	28.4 (4.1)	

Laboratory measures:

	Rosi-4<70	Rosi-4>70	Rosi-8<70	Rosi-8>70	Placebo<70	Placebo>70
A1c, change from baseline to 26w: %						
	-0.2	-0.1	-0.5	-0.4	0.8	1.0
	NR	NR	NR	NR	NR	NR
data derived from graphs, p-values NR						
FPG, change from baseline to 26w: mmol/l						
	-1.8	-2.2	-2.7	-2.6	0.7	0.5
	NR	NR	NR	NR	NR	NR
data derived from graphs, p-values NR						

Evidence Table 14. Subgroups, non-randomized studies, piogitazone and rosiglitazone

Kreider M, 2002 **Quality rating: NA (8 other studies)**

Laboratory measures:

	Rosi-4<70	Rosi-4>70	Rosi-8<70	Rosi-8>70	Placebo<70	Placebo>70
A1c, change from baseline to 26w: %						
	-0.2	-0.1	-0.5	-0.4	0.8	1.0
	NR	NR	NR	NR	NR	NR
data derived from graphs, p-values NR						
FPG, change from baseline to 26w: mmol/l						
	-1.8	-2.2	-2.7	-2.6	0.7	0.5
	NR	NR	NR	NR	NR	NR
data derived from graphs, p-values NR						

Physiologic outcomes:

	Rosi-4<70	Rosi-4>70	Rosi-8<70	Rosi-8>70	Placebo<70	Placebo>70
Weight, change from baseline to 26w, kg: %						
	2.14	1.66			-0.41	-1.34
	NR	NR	NR	NR	NR	NR
Rosi <70 vs Rosi >70 vs Placebo<70 vs Placevo >70; p-values NR						

P value NR if not specified.

Evidence Table 14. Subgroups, non-randomized studies, piogitazone and rosiglitazone

Manley HJ, 2003 **Quality rating: Observational study**

Design:

Study design: Cohort NA NA **Run-in :** NA **Setting:** Single Center
Wash out : NA **Country:** USA

Sample: Number Screened/ Eligible/ Enrolled Number Withdrawn/ Lost to follow-up/ Analyzed
NR/ NR/ NR NR/ NR/ NR

Inclusion criteria:
Chart review of patients receiving hemodialysis at a US clinic who were prescribed either Rosi or Pio from 4/2001 to 5/2002.

Exclusion criteria:
None reported.

Comments:
Retrospective chart review of patients on hemodialysis; quality assessment form NA
Quality: outcomes pre-specified. Participants appear to be all patients fulfilling inclusion criteria

Population: **Mean age:** 64.8 years **Ethnicity:** NR
Gender: 35% Female
Type 2 diabetes duration (SD): NR (NR) years

Intervention: ESRD

Duration:

Drug name	Total daily dosage	Drug-dosage	N	Baseline HbA1c, %	Baseline weight, kg	Baseline BMI, kg/m^2	Note
Pioglitazone	NR	Pio	NR	NR (NR)	NR (NR)	NR (NR)	
Rosiglitazone	NR	Rosi	NR	NR (NR)	NR (NR)	NR (NR)	

Laboratory measures:

	Pio	
A1c, baseline & follow-up, ROSI & PIO combined: %		
	8.59(2.18)	7.98(2.07)
p vs baseline		p=0.05
ROSI and PIO combined		
A1c, baseline and 3m follow-up: %		
	8.59(2.18)	7.98(2.07)
p vs baseline	p=0.05	

Physiologic outcomes:

	Pio	
SBP, baseline and 3m follow-up: mmHg		
	156.98(20.72)	151.41(18.32)
p vs baseline	p=0.01	
DBP, baseline and 3m follow-up: mmHg		
	77.55(10.10)	74.28(9.06)
p vs baseline	p=0.002	
Interdialytic weight change, baseline & 3m follow-up: kg		
	3.51(1.42)	3.61(1.36)
p vs baseline	p=0.1824	

Evidence Table 14. Subgroups, non-randomized studies, piogitazone and rosiglitazone

Manley HJ, 2003 **Quality rating: Observational study**

P value NR if not specified.

Evidence Table 15. Quality assessment of adverse events in efficacy trials

Author, year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately	Non-biased ascertainment methods?	Adequate duration of follow-up?	Overall adverse event assessment
Agrawal A 2003	Unclear; no information on patient selection	Yes	No	No	Method not reported	Yes, 6m	Fair; based on data presented; reports on 3 other RCTs but no citations
Bogacka, I. 2004	Yes	Not reported	No	No	Method not reported	Yes	Poor
Charbonnel 2004	Unclear; no information on patient selection	Uncertain; NR	No	No	Unclear; methods NR	Yes, 52w	Poor
Hallsten, K. 2002	Yes	Yes- (7% rosi, 8% metformin)	No	No	Method not reported	Yes	Poor
Herz, M. 2003	Yes	Yes	Yes	Yes	Yes (states double-blind, patient recorded or lab tests)	Yes	Good
Honisett, S. 2003	Not clear- little information on eligibility criteria	Not reported	No	No	Method not reported	Yes	Poor
Iozzo, P. 2003	Yes	Not reported	No	No	Method not reported	Yes	Poor

Evidence Table 15. Quality assessment of adverse events in efficacy trials

Author, year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately	Non-biased ascertainment methods?	Adequate duration of follow-up?	Overall adverse event assessment
Khan 2002	No information on Aes provided (except weight gain)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Kipnes, M. 2001	Yes	Yes- 15% withdrew, but low loss to followup	Some (labs)	Yes	Yes for labs, no for other (assessed by questionnaire, intensity determined by investigators, not specified if blinded)	Yes	Fair
Mattoo, V. 2005	Yes	Yes	No	No	Method not reported	Yes	Poor
McMahon, G. 2005	Yes	No- 4/20 (20%) did not complete and were not analyzed	No	No	Method not reported	Yes	Poor
Miyazaki, Y. 2001, 2004	Yes	Not reported	No	No	Method not reported	Yes	Poor
Miyazaki, Y. 2002	Yes	Not reported	No	No	Method not reported	Yes	Poor
Natali, A. 2004	Yes	Yes (8%)	No	No	Method not reported	Yes	Poor
Negro R 2004	No information on Aes provided	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Nolan, J. 2000	Yes	Yes	No	Yes	Not clear if blinded or independent.	Yes (8 weeks)	Fair
Phillips 2001	Unclear; no information on patient selection	Yes	No	No	Unclear; methods NR	Yes, 26w	Poor

Evidence Table 15. Quality assessment of adverse events in efficacy trials

Author, year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately	Non-biased ascertainment methods?	Adequate duration of follow-up?	Overall adverse event assessment
Phillips, L. 2001	No- did not randomize patients who experienced adverse events during run-in (7.5% of those screened) or who did not follow protocol (2.2%)	Yes	Some (labs)	Yes for labs, no for others	Lab tests performed at SmithKline Beecham Clinical Laboratories (assume blinded, but not explicitly stated), no information on other adverse events	Yes	Poor
Raskin, P. 2001	8 of 370 patients screened (2%) not randomized due to adverse events or protocol deviation	Yes	Yes for some (liver function tests); states "physical examination"	Yes	Yes	Yes	Fair
Rosenblatt, S. 2001	Yes	27% withdrew, loss to followup not reported	No	No	Method not reported	Yes	Poor
Rosenstock, J. 2002	Yes	Yes (2%)	Some (labs)	Yes for labs, no for others	Yes for labs, no for other (not specified if blinded or independent)	Yes	Fair

Evidence Table 15. Quality assessment of adverse events in efficacy trials

Author, year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately	Non-biased ascertainment methods?	Adequate duration of follow-up?	Overall adverse event assessment
Scherbaum, W. 2002	No- 240/492 (48.8%) patients enrolled in washout withdrawn before randomization for noncompliance	No	No	No: "AEs recorded at every visit"	Method not reported	Yes	Poor
Smith, S. 2004	Yes	Yes	No	No	Method not reported	Yes	Poor
van Wijk, J. 2005	Yes	Yes	No	No	Method not reported	Yes (8 weeks)	Poor
Wallace, T. 2004	Yes	Yes (1 patient in each group)	No, except for liver function tests	No	Method not reported	Yes	Poor

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Study design Setting	N	Adverse event(s) assessed	Data source	Population Inclusion criteria
Boyle P., 2002	Retrospective cohort	1115	Weight gain (not primary outcome)	Randomly selected medical records from 605 primary care practices in the US	Patients with type 2 diabetes who had started treatment with either PIO or ROSI between August 1, 1999 and August 31, 2000
Delea T., 2003	Retrospective cohort	5441 TZDs, 28,103 control	Heart failure	Database including information from pharmacy, provider, and facility claims for members enrolled in 35 US health plans	Patients with complete enrollment and demographic information, one or more paid provider or facility claims with a diagnosis of type 2 diabetes, and one or more pharmacy claims for an oral antihyperglycemic drug. From these patients, identified all those who had one or more pharmacy claims for a TZD and for whom information on therapy-days dispensed was available for all TZD prescriptions. Control group: for each patient in the TZD group, randomly selected five patients who were not in the TZD groups and who, during the preindex period of the corresponding TZD patient, 1) had one or more pharmacy claim for an oral antihyperglycemic agent, 2) had no diagnoses of heart failure, and 3) were continuously enrolled over this period
Frenchman, I.B., 2003	Retrospective cohort	182 total; Pio 11, rosi 13	All reported Aes	Chart review	Patients from long-term care facilities in New jersey and Pennsylvania with dibnosis of DM2 and who were prescribed metformin, a sulfonylurea, rosi, or pio either alone or in combination with insulin

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Exclusion criteria	Duration of exposure	Mean age (y) Gender (% male) Race/ethnicity
Boyle P., 2002	Timing of clinical laboratory testing, medication changes that could influence lipid profiles	PIO: 17.73 weeks (SD 3.83) ROSI: 17.41 weeks (SD 3.91)	60.3 55.1% male 72.3% White 14.7% Black 9.3% Hispanic 2.8% Asian 1.5% Other
Delea T., 2003	Patients with any claims with a diagnosis of heart failure during the 1-year period ending with the day before the index date	Maximum 40 months	58.5 57.1% male Ethnicity NR
Frenchman, I.B., 2003	None noted	NR	For whole group (182 patients): women 80.2 years, men 73.7 years % male NR Race NR

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Method and timing of AE assessment	Weight gain	Edema	Heart Failure
Boyle P., 2002	Chart review	Mean weight gain (kg), PIO vs ROSI: 1.97 vs 1.64 (NS)		
Delea T., 2003	Review of claims data			PIO vs ROSI Incidence of heart failure: 1.63% vs 2.39% Hazard ratio (95% CI) PIO (all): 1.92 (1.24 to 2.97) <45 mg: 1.81 (1.12 to 2.94) >=45 mg: 3.08 (1.14 to 8.31) ROSI (all): 2.27 (1.65 to 3.13) <8 mg: 2.25 (1.31 to 3.87) >=8 mg: 1.44 (1.07 to 1.94)
Frenchman, I.B., 2003	Chart records; no other details	NR	Pio: 1/11 Rosi: 0/13	No patient developed heart failure

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Liver Function	Hypoglycemia
Boyle P., 2002		
Delea T., 2003		
Frenchman, I.B., 2003	No patient had abnormal liver function tests	Hypoglycemia: Pio: 1/11 Rosi: 2/13 Overall Aes: Pio (alone or in combination) 8/11 (73%), nausea and vomiting, low FPG, edema Rosi (alone or in combination): 2/13 (15%) both had low FPG

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Study design Setting	N	Adverse event(s) assessed	Data source	Population Inclusion criteria
Gegick C., 2004	Retrospective cohort	100	Weight, liver function	Retrospective analysis of data from a previous prospective observational study.	Transition to PIO or ROSI after a recommended 1-week washout period, and lack of additional glycemic medication or dose change.
Harmel A., 2004	Retrospective cohort	829	Weight gain (not primary outcome)	Medical records from endocrinologist practices	Age >=18 with DM2 who had received anti-hyperglycemic treatment with either metformin (>=1000 mg/day), a SU agent, or the combination of metformin and a SU agent and subsequently were prescribed adjunctive therapy with either PIO (30-45 mg/day) or ROSI (4-8 mg/day)
Hussein Z., 2004	Retrospective cohort	203	Hypoglycemia, weight gain, edema	A prospectively recorded database at a hospital diabetes clinic	Patients with type 2 diabetes who had been prescribed TZDs (15, 30, or 45 mg PIO or 4 or 8 mg ROSI daily) fo rat least 2 months between May 1, 2000 and October 31, 2002 through the Royal Melbourne Hosptial diabetes clinic

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Exclusion criteria	Duration of exposure	Mean age (y) Gender (% male) Race/ethnicity
Gegick C., 2004	Receiving troglitazone for less than 4 months prior to the substitution, if they had not had at least two baseline A1c values while on maintenance troglitazone therapy, if there was a gap in therapy of greater than 3 weeks at the time of conversion, noncompliance, or if the patient left the practice or died prior to the completion of laboratory assessments	12 months	63.3 56% male Ethnicity NR
Harmel A., 2004	Patients received any other hyperglycemic medication(s) during the observation period; received any TZD for DM2 within 90 days prior to starting adjunct TZD therapy; received a systemic glucocorticosteroid at any time during the observation period	25 to 27 weeks	60.5 60% male Race: 83% white; 9% black, 4% Hispanic; 3% Asian, <1% other
Hussein Z., 2004	Not reported	At least 2 months	64.5 46.3% male Ethnicity NR

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Method and timing of AE assessment	Weight gain	Edema	Heart Failure
Gegick C., 2004	Body weight measured on a single scale at the time of office visits, and liver enzymes were obtained with a minimum frequency of every 2 months for the first 12 months according to guidelines	Mean weight gain after 12.6 months of treatment (kg), PIO vs ROSI: 4.1 (4.1%) vs 3.0 (2.8%) (NS)		
Harmel A., 2004	Medical record review	Mean weight gain (kg), PIO vs ROSI: 2.2 vs 1.6 (p=0.126)		
Hussein Z., 2004	Medical record review	Mean gain (kg) after 6 months of treatment, PIO vs ROSI: 2.3 vs 2.9; p=0.95	PIO vs ROSI Incidence of peripheral edema: 33% vs 21% (NS) Withdrawal due to periopheral edema: 7% vs 4% (NS) Pulmonary edema: 1.9% vs 3.1% (4 of these 5 patients had pre-existing heart failure treated with diuretics)	

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Liver Function	Hypoglycemia
Gegick C., 2004	No patient had an ALT value >=3 times the ULN, none above the ULN.	
Harmel A., 2004		
Hussein Z., 2004	1 patient in each group had elevated ALT.	Increased frequency of hypoglycemia: 17% PIO vs 11% ROSI (NS) All episodes were mild or moderate

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Study design Setting	N	Adverse event(s) assessed	Data source	Population Inclusion criteria
King A, 2000	Prospective cohort	101	Weight gain, edema	Patient data from one clinical practice	Not reported (patients started consectively on each of 3 TZDs "when clinically indicated")
King K., 2004	Retrospective cohort	79	Edema (primary outcome)	Pharmacy database (Veterans Integrated Service and Technology Architecture [VISTA])	Patients on either a TZD or insulin separately, and were later changed to TZD-plus-insulin therapy
LaCivita K., 2002	Retrospective cohort	20	Liver function, edema, weight gain (AEs not primary outcome)	Charts of 20 patients from one medical practice	All patients with type 2 diabetes who had received a minimum of 3 months therapy with ROSI 4 mg bid followed by treatment with PIO 45 mg once daily

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Exclusion criteria	Duration of exposure	Mean age (y) Gender (% male) Race/ethnicity
King A, 2000	Patients who were not on maximal recommended doses of TZDs (600 mg troglitazone, 8 mg rosiglitazone, 45 mg pioglitazone); patients also excluded if they started during the observation period on a medication that would influence their lipid profile or weight	4 months	59.8 51.5% male ethnicity NR
King K., 2004	Patients on any other medicines with known potential to cause edema (I.e., dihydropyridine calcium channel blockers and corticosteroids); on a loop diuretic or were edematous at the initiation of the combination therapy	Not reported	62 (range 41-93) 95% male Race: 84.8% white, 11.4% black, 3.8% Hispanic
LaCivita K., 2002	Patients excluded if dosages of any concomitant medications were changed during either treatment course; dosages of concomitant medications had to be stable by the time ROSI therapy was instituted. No patients were on insulin. Patients also excluded for noncompliance, unavailability for followup, and inability to tolerate the prescribed dosage	Mean 6 months (range 3-11 months)	66 20% male 100% Hispanic

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Method and timing of AE assessment	Weight gain	Edema	Heart Failure
King A, 2000	Method NR, baseline, and between 2 and 4 months of treatment	Mean weight gain (kg), PIO vs ROSI: 0.5 vs 2.6 (p-value NR, unable to calculate)	PIO vs ROSI: 6.7% vs 7.9% Edema as a reason for discontinuation NS for PIO vs ROSI	
King K., 2004	Medical record review		Prevalence of edema: PIO 4 mg: 12.7% PIO 8 mg: 5.1% ROSI 15 mg: 1.3% ROSI 30 mg: 6.3% Pulmonary edema: 1 patient taking ROSI	
LaCivita K., 2002	Review of medical records	Mean gain (kg) after mean 6 months of treatment, PIO vs ROSI: 1.6 (±2.4) vs 1.5 (±2.4)	1 patient in each group (5%) had ankle edema	

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Liver Function	Hypoglycemia
King A, 2000		
King K., 2004		
LaCivita K., 2002	No clinically significant changes in tests of liver function	

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Study design Setting	N	Adverse event(s) assessed	Data source	Population Inclusion criteria
Lebovitz H., 2002	Retrospective analysis of prospectively collected data from RCTs	10,209 (2319 from PIO trials, 4905 from ROSI trials, 2985 from troglitazone trials)	Liver function	Data obtained from 13 double-blind clinical trials of rosiglitazone monotherapy or combination therapy	Men and women between ages 30 and 80 with a diagnosis of DM2
Olansky L., 2003	Retrospective cohort	1115	Weight gain (not primary outcome)	Medical records of 605 primary care practices throughout the US	DM2, received either PIO (30 or 45 mg/day) or ROSI (4 or 8 mg/day) for >=12 weeks between August 1, 1999 and August 31, 2000. Age >=18; uninterrupted treatment for >=12 weeks; patient had >=2 office visits separated by 12 to 26 weeks, no change in antihyperlipidemic regimens at or between baseline and followup visits; >=2 rounds of clinical laboratory testing for study end points; dates of lab testing coincided approximately with the baseline and followup visits

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Exclusion criteria	Duration of exposure	Mean age (y) Gender (% male) Race/ethnicity
Lebovitz H., 2002	Not reported	8 to 12 weeks	Data not reported: most participants were white, age <65, gender NR
Olansky L., 2003	Patient failed previous non-TZD antihyperglycemic combination therapy and was switched to either PIO or ROSI monotherapy during the study period; received another TZD within 90 days before starting the study drug; started a medication (including beta-blockers and thiazide diuretics) at or between baseline and followup visits that could influence the lipid profile; change in medication regimen at or between baseline and followup that could influence the lipid profile; received a systemic glucorticosteroid during the study period.	>=12 weeks	60.5 55.3% male Race: 73% white, 15% black, 9% Hispanic, 3% Asian, 1% other

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Method and timing of AE assessment	Weight gain	Edema	Heart Failure
Lebovitz H., 2002	Routine laboratory safety tests were performed at screening, baseline, every 4 weeks for the first 3 months of treatment, and at 6- to 12-week intervals thereafter			
Olansky L., 2003	Abstracted from medical records	Mean weight gain (lbs), PIO vs ROSI: 2.0 (±0.4) vs 1.6 (±0.4) (NS) Differences between PIO and ROSI not significant in any subgroup (monotherapy, + metformin, +SU, +Met + SU)		

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Liver Function	Hypoglycemia
Lebovitz H., 2002	ALT >3 times ULN: troglitazone: 1.9% PIO: 0.26% ROSI: 0.17% No patients on PIO or ROSI discontinued due to abnormal liver function; no cases of jaundice	
Olansky L., 2003		

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Study design Setting	N	Adverse event(s) assessed	Data source	Population Inclusion criteria
Rajagopalan R., 2005	Retrospective analysis of claims data	8916	Incidence of liver failure or hepatitis	PharMetrics Patient-Centric Database, with claims for over 33 million unique patients from 58 health plans across the US.	Patients with one or more providers or facility claims with a diagnosis of type 2 diabetes; 18 years or older, who had initiated treatment either with a TZD, sulfonylurea, or metformin between 1/1/99 and 12/31/01. The index date was deemed as the date of the first antidiabetic pharmacy claim of interest for each patient. A pre-index period of 12-month duration preceding the index date was required so as to ensure that the index prescription was the patient's first prescription. Patients also had a minimum of 90 days of followup.
Tang W., 2003	Retrospective cohort	111	Edema in patients with heart failure; weight gain	Hospital heart failure registry	Outpatients with a documented clinical diagnosis of chronic, stable systolic heart failure (NYHA class I to III, LVEF <=45%) and a clinical diagnosis of DM2 (according to the latest American Diabetes Association guidelines) treated in one clinic between January 1999 and June 2001; patients who had received troglitazone, PIO, or ROSI at any point during their care. Non-TZD users served as a control group

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Exclusion criteria	Duration of exposure	Mean age (y) Gender (% male) Race/ethnicity
Rajagopalan R., 2005	Health plans without valid data on days supplied and quantity dispensed were excluded. Patients were excluded from the study sample if they met any of the following conditions: 1) were <age 18 as of the index date; 2) had a pre-index period with a duration of less than 12 months and/or a followup period with a duration of less than 3 months; 3) had evidence of the index therapy in the pre-index period; 4) had facility or professional service claim(s) with a diagnosis of liver failure or hepatitis at any time during their pre-index period; 5) had a prescription for troglitazone during any time during the pre-index or followup periods; 6) were not continuously eligible for health and pharmacy benefits during the entire pre-index and followup periods; 7) had less than 90 days of followup after the index date; or 8) were unsuccessfully matched based on propensity score.	Mean days of therapy (SD) by matched pairs group pio monotherapy: 310.3 (4.1) rosi monotherapy: 316.0 (4.2) pio monotherapy: 319.0 (4.8) SU monotherapy: 322.9 (4.9) pio monotherapy: 315.7 (5.4) metformin monotherapy: 320.5 (5.4)	53.9 52.0% male Race/ethnicity NR
Tang W., 2003	NR	12 months	55 68% male Ethnicity NR

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Method and timing of AE assessment	Weight gain	Edema	Heart Failure
Rajagopalan R., 2005	Primary measure was incidence of liver failure or hepatitis post-index date, defined as one or more providers or facility claims with a principal or secondary diagnosis of liver failure or hepatitis within the followup period.			
Tang W., 2003	Chart review	Overall maximal involuntary weight gain within first 12 months of therapy: 2.68 ± 3.76 kg (not reported separately by drug)	17.1% had documented fluid retention after TZD initiation. Fluid retention was seen with the use of all 3 TZDs, across all dosages (17% troglitazone, 15.6% PIO, 14.3% ROSI); 2 patients (11%) had documented physical signs of pulmonary edema (drug NR)	

Evidence Table 16. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Liver Function	Hypoglycemia
Rajagopalan R., 2005	Hazard ratio (95% CI) for risk of liver failure or hepatitis (primary or secondary diagnosis); pioglitazone monotherapy is index drug: pio monotherapy vs rosi monotherapy: 1.139 (0.439, 2.960) pio monotherapy vs SU monotherapy: 0.622 (0.272, 1.421) pio monotherapy vs metformin monotherapy: 0.580 (0.194, 1.733) Results for liver failure or hepatitis (principal diagnosis) and liver failure only also non-significant for all comparisons	
Tang W., 2003		

Evidence Table 17. Quality assessment of observational studies of adverse events

Author Year	Study design	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and accurate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Quality
Observational studies comparing pioglitazone and rosiglitazone							
Boyle P., 2002	Retrospective cohort	No	Yes	Not clear if blinded	No	Yes (mean 17 weeks)	Fair
Delea T., 2003	Retrospective cohort	Yes	Yes	Blinding not reported	Yes	Yes	Fair
Frenchman I.B., 2003	Retrospective cohort	No	No	Blinding not reported	No	Unclear	Poor Sample size only 24
Gegick C., 2004	Retrospective cohort	Yes	Yes	Blinding not reported	No	Yes (mean 12.6 months)	Fair
Harmel A., 2004	Retrospective cohort	No	No	Blinding not reported	No	Fair (12 weeks or more)	Poor
Hussein Z., 2004	Retrospective cohort	Yes	No	Methods not described	No	Fair (at least 2 months)	Fair
King A, 2000	Prospective cohort	No	No	Method NR	No	Fair (2-4 months)	Poor

Evidence Table 17. Quality assessment of observational studies of adverse events

Author Year	Study design	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and accurate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Quality
King K., 2004	Retrospective cohort	Yes	Chart review, no details	Blinding NR	No	Duration of followup not clear	Fair
LaCivita K., 2002	Retrospective cohort	Yes (weight), other AEs no	No	Blinding NR	No	Yes (at least 2 months; mean 6 months)	Fair-Poor
Lebovitz H., 2002	Retrospective analysis of prospectively collected data from RCTs	Yes	Yes	Blinding NR	No	Fair (ranged from 8 to 26 weeks)	Fair
Olansky L., 2003	Retrospective cohort	Not reported	Yes	Not clear if data abstraction blinded (data abstracted, then sent to a central location for review and analysis)	No	Yes (17-18 weeks)	Fair
Rajagopalan R., 2005	Retrospective cohort	Yes	Yes	Blinding NR	Yes	Yes (2 years)	Fair
Tang W., 2003	Retrospective cohort	Yes	Yes	No; unblinded	No	Yes (12 months)	Fair

Evidence Table 17. Quality assessment of observational studies of adverse events

Author Year	Study design	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and accurate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Quality
Safety-only studies, PIO							
Bajaj M., 2004	Before-after US Multicenter	Yes (weight)	Yes	Blinding not reported	Some	Yes (16 weeks)	Fair
Hayashi Y., 2003	Before-after	Yes (weight); others no	No	Not blinded	No	Yes (16 weeks)	Poor
Jun J., 2003	Prospective cohort with comparison Japan Single center	Some (liver function, BMI), other AEs not defined	Yes	Chart review, blinding not reported	No	Yes (6 months)	Fair
Jung W., 2005	Prospective cohort with comparison	Yes (hypoglycemic episodes)	Yes	Blinding not reported	No	Yes for hypoglycemic episodes (72 hours)	Fair
King A., 2003	Time series Japan Single center	Liver function only	No	Blinding not reported; timing not clear for assessment events other than liver function	No	Yes	Fair to Poor
King A., 2002	Retrospective cohort	Liver function only	Yes (for liver function)	No	No	Fair (2 months or longer)	Fair to Poor

Evidence Table 17. Quality assessment of observational studies of adverse events

Author Year	Study design	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and accurate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Quality
Kubo K., 2002	Prospective cohort with comparison Japan Single center	BMI yes, others no	No	Blinding not reported	No	Fair (12 weeks)	Fair to Poor
Ono M., 2005	Prospective cohort with comparison Germany Single center	Yes	No	Blinding not reported	No	Fair (12 weeks)	Fair
Rajagopalan R., 2004	Retrospective cohort (database analysis)	Yes	Yes	Yes	Some (age and preindex health care costs)	Fair (3 months or longer)	Fair
Schofl C., 2003	Postmarketing surveillance study (prospective cohort)	No	Yes	Not blinded or independent (AEs recorded by prescribing physician)	No	Fair (16 weeks)	Poor
Seino H., 2003	Time series Japan Single center	Yes for lab tests	Yes	Not blinded	No	Fair (16 weeks)	Fair to poor

Evidence Table 17. Quality assessment of observational studies of adverse events

Author Year	Study design	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and accurate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Quality
Safety-only studies, ROSI							
Chalasani N 2005	Cohort with comparison	Yes	Yes	Yes (based on laboratory values)	No	Yes (12m)	Fair
Freed MI 2002	RCT	Yes	No	AEs not described in detail, but study described as double-blind	No	Fair (16 weeks)	Fair
Kiayias 2002	Cohort with comparison Greece	No	No	Not blinded or independent (AEs recorded by prescribing physician)	No	Yes (20 weeks)	Poor
Marceille, J 2004	Retrospective cohort USA	Yes	Yes	Not clear, blinding not reported	No	Yes (6 months)	Fair
Miyazaki, Y 2005	Before-After Study. USA	Yes (body weight only)	Yes (weight only)	Blinding not reported	No for AEs	Fair (12 weeks)	Fair
Orbay, E 2004	Cohort Study Turkey	Yes	Yes	No	No	Yes (26 weeks)	Fair
Osei, K 2004	Cohort with comparison USA	Liver function only, not weight/edema	Yes for liver function, others no	Blinding not reported	No	Fair (3 months)	Fair to Poor
Pietruck, F 2005	Before-After Study	No	No	Methods not described	No	Yes (mean 10 months)	Poor
Roy, R 2004	Cohort Study USA	No	No	Methods not described	No	Fair (4 months)	Poor
Sarafidis, P 2004	Cohort Study Greece	Yes	Yes	Blinding not reported	No	Yes (6 months)	Fair

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Study design Setting	Population Inclusion criteria	Exclusion criteria
Bajaj M., 2004	Before-after US Multicenter	DM2, age 30 to 70 years, stable body weight for at least 3 months before the study, and FBG between 7.0 and 14.5 mmol/l	NR
Hayashi Y., 2003	Before-after	Adherence to a diet and exercise program for the treatment of DM2; treatment with a constant dosage of alpha-glucosidase inhibitors or alpha-glucosidase inhibitors plus SU for at least 8 weeks prior to the lead-in period and a medical history suggesting that alpha-glucosidase inhibitors would be effective; age 20 or older, treatment as an outpatient.	Type 1 DM or using antidiabetic drugs other than alpha-glucosidase inhibitors and SU within 4 weeks before the lead-in.
Jun J., 2003	Retrospective case series	DM2 Hispanic, >18y, have uncontrolled hyperglycemia with A1c>=8.0%; have taken PIO for at least 6m; have A1c within 1m before start of PIO; have at least 2 A1c measures at 3-m intervals during the 6-m period; have a lipid panel within 1m before start of PIO; have at least 2 lipid panels performed at 3-m interval during study	Noncompliant with PIO as noted in chart

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Age (y) Gender (% male) Race/ethnicity	Intervention	Other medications permitted	Method and timing of AE assessment
Bajaj M., 2004	51 (SD 2) 61.5% men Ethnicity NR	PIO 45 mg/day for 16 weeks	4 patients taking a stable dose of SU for at least 3 months prior to study, continued; 9 patients treated with diet alone.	Before and after 16 weeks of treatment.
Hayashi Y., 2003	57.1 (SD 8.1) 36.8% male Ethnicity NE	PIO 30 mg for 16 weeks	alpha-glucosidase inhibitors and SU that were previously being dispensed continued to be administered concurrently with a constant dosage and method of administratin throughout the study period.	NR
Jun J., 2003	54.6(8.5) 16.7 Hispanic: 100%	Received PIO treatment for at least 6m	Antihypertensives, antiepileptic agents, other diabetes medications	From chart review; no other details provided

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Adverse events
Bajaj M., 2004	Mean weight change from baseline to 16 weeks: +3.1 kg BMI: +1.1
Hayashi Y., 2003	Adverse signs and symptoms in 4/20 patients (20%), all women. Included 2 episodes each of edema and hypoglycemia-like reaction. All were mild and disappeared during or after treatment. No patient discontinued therapy because of adverse drug reactions. Abnormal changes in laboratory values, all mild, in 6/20 patients (30%). 2 myocardial infarctions; both patients were at risk for development of MI, "having angina pectoris and so on" before entry into the study.
Jun J., 2003	8 patients (5.6%) withdrew secondary to significant peripheral edema; 1 patient had exacerbation of congestive heart failure, 1 reported myalgias.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Study design Setting	Population Inclusion criteria	Exclusion criteria
Jung W., 2005	Prospective cohort with comparison Germany Single center	Patients with type 2 DM with A1c<=7%.	Not reported.
King A., 2002	Retrospective cohort	Among patients with DM2 treated with PIO at one diabetes clinic; the first 100 charts whose data met the following criteria: Patients treated with a maximum dose (45 mg/day) during the observation period and having baseline and 2 to 4 month followup lipid data.	NR
Kubo K., 2002	Prospective cohort with comparison Japan Single center	Patients with type 2 DM being treated at the diabetic outpatient clinic of one hospital.	Patients with diabetic nephropathy, nephropathy, neurological disease, arteriosclerotic disease, or hepatic dysfunction.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Age (y) Gender (% male) Race/ethnicity	Intervention	Other medications permitted	Method and timing of AE assessment
Jung W., 2005	61.1 years 50% male Race/ethnicity not reported	Pioglitazone 30 mg plus metformin 1700 mg or multiple-injection insulin therapy (mean dose 59.6 U/day).	Not reported; both groups monitored for 72 hours using Continuous Glucose Monitoring System.	Not reported.
King A., 2002	56.8 (SD 13.3) 45% male Race: 46% white, 39% Hispanic, 13% Asian, 2% black	PIO 45 mg/day for 2 to 4 months	Patients were allowed to be receiving concurrent lipid-lowering therapy with a staitn; however the dosage could not be changed, nor could another lipid-influencing medication be started within 6 weeks of baseline or during the observation period.	Medical record review.
Kubo K., 2002	Not reported	pioglitazone 30 mg, gliclazide 40 mg, or pioglitazone 30 mg in combination with gliclazide 40 mg for 12 weeks	Not reported; dietary and exercise therapy kept constant.	Not reported.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Adverse events
Jung W., 2005	ALT levels significantly decreased during treatment.
King A., 2002	No cases of hepatotoxicity or ALT elevations >3 times ULN during 8 month observation period. No cases of clinically significant edema, hypoglycemia, anemia or discontinuations of PIO therapy due to edema or other adverse effects. Mean weight increased 1.76 kg (SD 2.52; p<0.001) relative to baseline.
Kubo K., 2002	No patients developed hepatic dysfunction after treatment with pioglitazone. Edema was noted in 3 patients who received pioglitazone (mild, and treatment could be continued).

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Study design Setting	Population Inclusion criteria	Exclusion criteria
Ono 2005	Before-after Japan Multicenter	Type 2 DM, attending outpatient clinics at one hospital and its affiliated hospitals.	None of the patients were positive for hepatitis B or C virus, and all showed normal liver function tests.
Rajagopalan R., 2004	Retrospective cohort (database analysis)	Data (covering January 1, 1998 to March 31, 2002) from a national claims database comprising pharmacy, provider, and facility claims for 61 health plans in the US. Patients aged 18 or older with a diagnosis of type 2 DM (ICD-9 codes 250.x0, 250.x2) and/or evidence of use of antidiabetic medications who began receiving treatment with pioglitazone or insulin between January 1999 and December 2001. Data were required for 12 months or more before the index date and 3 months or more of followup. Included patients were required to be continuously enrolled for health and drug benefits and to have received the index therapy for 90 days or longer after the index date.	In addition to records not meeting inclusion criteria, medical claim with diagnosis of heart failure before index date; prescription for an OAD other than metformin or a SU in preindex period; prescription for digoxin in preindex period; use of troglitazone at any time; diabetes status (1 or 2) unknown; treatment with a TZD other than pioglitazone.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Age (y) Gender (% male) Race/ethnicity	Intervention	Other medications permitted	Method and timing of AE assessment
Ono 2005	Age, sex not reported 100% Japanese	pioglitazone 15 to 30 mg or troglitazone 400 mg	Not reported.	Liver function parameters (AST, ALT, y-GTP) measured before and at least 4 weeks (range 4 to 12 weeks) after the start of administration of pioglitazone or troglitazone. (also measured after withdrawal in cases treated with troglitazone)
Rajagopalan R., 2004	51.2 (SE 0.2) 50.9% men Race/ethnicity not reported	No intervention	NA	Incidence of congestive heart failure defined as either 1 or more provider or facility claim with a primary or secondary diagnosis of CHF or 1 or more hospital inpatient claiim with a diagnosis of CHF within the followup period. Followup period defined as the period beginning with the day after the index date and ending with the date of a change in index therapy, the last date on which claims data were available, or the date of health plan disenrollment, whichever occurred first, a minimum of 90 days after the index date.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Adverse events
Ono 2005	Change in liver function parameters in pioglitazone group from baseline to followup (IU/L) (N=12; 5 switched to pio after troglitazone treatment, 7 newly treated): AST: 17.0 ± 5.4 vs 16.2 ± 4.0 (NS) ALT: 23.8 ± 12.3 vs 19.9 ± 9.8 (p<0.05) y-GTP: 40.2 ± 31.1 vs 27.8 ± 20.7 (p<0.01) ALP: 127.9 ± 30.0 vs 116.8 ± 41.6 (NS)
Rajagopalan R., 2004	Crude incidence rate of CHF at 1 year, pioglitazone vs insulin: 2.0% vs 4.0% (p<0.001) Hazard ratio (95% CI) 0.501 (0.331 to 0.758) Crude incidence of CHF hospitalization at 1 year, pioglitazone vs insulin: 0.7% vs 2.5% (p<0.001) Hazard ratio (95% CI) 0.263 (0.135 to 0.511)

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Study design Setting	Population Inclusion criteria	Exclusion criteria
Schofl C., 2003	Postmarketing surveillance study.	Age 18 or older, with inadequately controlled DM2 (according to European diabetes guidelines), and required treatment with an oral insulin sensitizer such as PIO, in accordance with the licensed indications.	Contraindications to PIO, as described in the summary of product characteristics; patients with hepatic insufficiency or elevated liver enzymes at baseline (ALT>2.5 times ULN); patients not permitted to receive PIO in combination with insulin.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Age (y) Gender (% male) Race/ethnicity	Intervention	Other medications permitted	Method and timing of AE assessment
Schofl C., 2003	61.0 52.5% male Ethnicity NR	PIO; 28.4% received 15 mg, 70.9% received 30 mg.	55.3% received metformin, 12.5% glimepiride, 3.9% acarbose, 1.4% repaglinide, 1.1% miglitol.	Data documented over 16 weeks; patients underwent 3 examinations during the study: before initiation of PIO therapy, during weeks 4-8, and at the end of 16 weeks. All adverse events reported or observed were documented by the attending physician, even if they were not formally recorded, but were suspected on the basis of patients' stated reasons for withdrawal. Any occurrence of a serious or unknown adverse event was reported to the Drug Safety Department of the sponsor (Takeda Pharmaceutical).

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Adverse events
Schofl C., 2003	Weight decreased by a mean of 1.1 kg, similar trend in BMI. Effect was less pronounced in patietns receiving SU versus other agents. Hepatic function: 9.3% of patients had a 1.5-fold increase in ALT levels, 1.8% had a 2.5 fold increase. Overall, ALT/AST levels decreased by 0.8 U/L. Tolerability: 210/8760 (2.39%) experienced an adverse event. 52 events were categorized as serious. Most common adverse event was weight increase (n=54; 0.6%), followed by edema (n=26, 0.3%), edema in the lower limbs (n=12, 0.1%), nausea (n=13, 0.1%), headaches (n=12, 0.1%), and dizziness (n=11, 0.1%). All other adverse events occurred in <10 patients.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Study design Setting	Population Inclusion criteria	Exclusion criteria
Seino, H., 2003	Time series Japan Single center	Patients with DM2 being treated with an alpha-glucosidase inhibitor (alpha-GI) alone or an alpha-GI and a sulphonylurea (SU). The dosage and method of administration of the alpha-GI alone or the alpha-GI and SU in combination were fixed throughout the period from 8 weeks before the run-in period until the end of the run-in period; A1c was in the range of 7.0% and 12.0% at the start of the run-in and 4 weeks after starting the run-in and the difference between the two measurements was within +/- 1.0%; the fasting plasma glucose 4 weeks after starting the run-in period was 7.8 mmol/l (140 mg/dl) or higher; and age 20 years or older.	Type 1 DM, insulin preparaton, biguanides or insulin sensitizing agent in use within 4 weeks before the start of the run-in period, patients with colon cancer or polyp, or history thereof, or a known family history thereof (parents and siblings); excessive habitual alcohol intake; past history of drug allergy; pregnant, possibly pregnant, and nursing women; serious complications such as those related to the kidneys, liver, heart, pancreas, or blood.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Age (y) Gender (% male) Race/ethnicity	Intervention	Other medications permitted	Method and timing of AE assessment
Seino, H., 2003	Not reported.	Pioglitazone 30 mg.	Dosage and method of administration of alpha-GI, SU, and drugs fro hyperlipidemia in use, as well as exercise and diet therapy, were kept constant throughout the study.	Not reported.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Adverse events
Seino, H., 2003	5/20 patients had adverse drug reactions (25%). Edema in 2 patitns, hypoglycemia in 1 patient, increased CK in 1 patient, herpes viral infectoin associated with increases in Na, Ca, and Cl in 1 patient. All events were mild in severity. Significant decreases from baseline in red blood cells, hemoglobin, hematocrit, AST, ALT, y-GTP, and alkaline phosphatase (p<=0.01; p<=0.05 for only AST), and significant increases in CK and CK isoenzyme MM (p<.0.05); change in lactate dehydrogenase was not significant.

Evidence Table 19. Adverse events in observational studies, ROSI

Author Year Quality score	Study design Country	Population Inclusion criteria	Exclusion criteria	Age (y) Gender (% male) Race/ethnicity	Intervention
Chalasani, N 2005	Cohort with comparison group	Two cohorts identified from medical record system. Cohort 1 were diabetics with elevated baseline liver enzymes who were preseribed rosi and in whom liver enzymes were available within 6m before and 12m after rosi was started. Cohort 2 had normal baseline liver enzymes who were prescribed rosi and LFT were available as for cohort 1.	None reported	Mean age cohort 1: 53, cohort 2 55 Gender: cohort 1, 43%; cohort 2, 32% Ethnicity, % black: cohort 1, 36%; cohort 2, 47%	Mean rosi dosage: Cohort 1, 4.4 mg qd; Cohort 2, 4.4 mg qd

Evidence Table 19. Adverse events in observational studies, ROSI

Author Year Quality score	Other medications permitted	Method and timing of AE assessment	Adverse events
Chalasani, N 2005	% new statin prescriptions during follow-up: cohort 1, 11; cohort 2, 14 Otherwise NR	Mean duration of therapy (days): cohort 1, 357; cohort 2, 423	cohort 1 vs cohort 2: Incidence of mild to moderate or severe elevations of transaminases at 12m: p=0.2 Frequency of discontinuation of rosi: p=1.0 Cohort 1 with AST or ALR>2.5 times upper limit normal at baseline: none developed mild, moderate or severe elevatnsion by 12m Conclusion: persons wtih elevate liver enzymes to not have a higher risk of hepatotoxicity from rosi than those with baseline normal liver function

Evidence Table 19. Adverse events in observational studies, ROSI

Author Year Quality score	Study design Country	Population Inclusion criteria	Exclusion criteria	Age (y) Gender (% male) Race/ethnicity	Intervention
Freed MI 2002	RCT	DM2 Patients with DM2, aged 35 to 80y, FPG <=160 mg/dl if previously treated with diet and exercise only, or <=220 mg/dl if treated with a SU; TG<=500 mg/dl; LDL <=160 mg/dl; acceptable glycemic control	LDL <100 mg/dl in the absence of a lipid-lowering agent at screening; renal or hepatic disease; jaundice; severe hypertriglyceridemia; New York Heart Association class III/IV congestive heart failure; angina or coronary insufficiency; anemia; SBP>180 mm Hg; DBP>110 mm Hg; history of drug or alcohol abuse; taking anorectic agents; taking any medication affecting cytochrome P450 3A enzyme system	60(10) NR NR	Addition of atorvastatin or placebo to rosiglitazone
Kiayias 2002	Cohort with comparison Greece	DM2	NR	Mean Age: 58.6 Male (52.6%) Ethnicity: 100% Greek	Rosiglitazone 4 or 8mg daily, added to metformin and SU

Evidence Table 19. Adverse events in observational studies, ROSI

Author Year Quality score	Other medications permitted	Method and timing of AE assessment	Adverse events
Freed MI 2002	SU	Method NR AEs assessed during 8-w open-label run-in period and at 24w	During 8-w run-in period (on ROSI), 56% experienced AE: - hypoglycemia: 11% (most on SU) - URTI: 7% - edema: 5% - hematocrit: change -5.3% - weight: change 1.4-1.7kg Double-blind 16-w treatment phase (on ROSI and atorvastatin): - similar AEs to 8-w phase - weight: change 2.0-2.5kg - no hepatic AES, no change LFT - no apparent musculoskeletal toxicity
Kiayias 2002	NR	Method NR AE's, A1c, FPG, liver function assessed at 20 weeks	Cohort with comparison, at 20 weeks of treatment with ROSI with SU and metformin: - Hypoglycemia (18.6% at 4 mg/day, 4.6% at 8 mg/day) - Mean body weight increase (4.2 kg at 4mg/day and 4.6 kg at 8mg/day) - No signs found of liver disease/dysfunction

Evidence Table 19. Adverse events in observational studies, ROSI

Author Year Quality score	Study design Country	Population Inclusion criteria	Exclusion criteria	Age (y) Gender (% male) Race/ethnicity	Intervention
Marceille, J 2004	Retrospective cohort USA	DM2 prescribed ROSI before 10/01, prescribed insulin, over 18 years of age, followed at Hines Veterans Affairs Hospital or outpatient clinic	Patients not receiving insulin before start of ROSI, or received ROSI after care at Hines, refill records/chart documentation showing non-compliance wth ROSI or insulin	Age Range: 18-up Male: (98.5%) Caucasian: 69.7% African-American: 21.5% Asian: 1.4% Other: 7.1%	ROSI (doses varied/NR) with insulin
Miyazaki, Y 2005	Before-After Study USA	DM2, aged 30-70 years, BMI < 37kg/m, stable body weight for 3 months before entry, FPG between 140-260 mg/dL	Patients with previous use of insulin, metformin or another TZD, cardiac, hepatic, renal or other chronic diseases as determined by history or current tests, participation in heavy exercise, use of medications known to effect glucose metabolism, other than SUs	Mean Age: 54 Male: (48.6%) White: 29.7% Mexican-American: 70.2%	ROSI 8mg/day, 13 subjects also receiving SU, 24 subjects treated with diet/no SU

Evidence Table 19. Adverse events in observational studies, ROSI

Author Year Quality score	Other medications permitted	Method and timing of AE assessment	Adverse events
Marceille, J 2004	NR	Method NR, assessments taken at baseline and 12 months	Retrospective cohort study of ROSI and insulin, at 12 months (p-value from baseline): - shortness of breath: 14%; p=0.07 - dyspnea on exertion: 9.4%; p=0.75 - paroxysmal nocturnal dyspnea: 3.6%; p=0.16 - lower extremity edema: 36%; p<0.0001 - cough: 1.4%; p=0.16 - pulmonary edema: 0; p=0.32 - jugular venous distention: 2.9%; p=0.53 - hepatomegaly: 2.2%; p=0.08 rales: 4.3%; p=0.68
Miyazaki, Y 2005	NR	75g oral glucose test and determination of body fat, before and after 12 weeks FPG (glucose oxidase method) and body weight assessed every 2 weeks, A1c (affinity chromatography) and fasting plasma lipids (enzymatically) assessed twice between baseline and 12 weeks, At 10 weeks, blood drawn following at 10-12 hour fast	Before-after study of ROSI with and diet or SU, at 12 weeks: - increase noted in body weight, BMI, fat percentage, plasma total cholestrol, LDL-cholestrol, dn HDL-cholestrol

Evidence Table 19. Adverse events in observational studies, ROSI

Author Year Quality score	Study design Country	Population Inclusion criteria	Exclusion criteria	Age (y) Gender (% male) Race/ethnicity	Intervention
Orbay, E 2004	Cohort Study Turkey	Insufficiently controlled DM2 receiving glimepiride and metformin therapy for at least 12 months, constant doses for at least 2 months before entry, aged 40-70 years, FPG between 126-270 mg/dl, A1c levels between 7.0-8.0% at screening	Patients with significant renal or hepatic impairment, hypertension, anemia, cardiac insufficiency, symptomatic diabetic neuropathy, pregnancy, significant abnormalities in exam at screening, previous participation in any ROSI study or investigational drug within 30 days of screening	Mean Age: 56.83 Male: (56.6%) Ethnicity NR	ROSI 4mg daily with 3 mg glimepiride twice daily and 850 mg metformin twice daily
Osei, K 2004	Cohort with comparison USA	DM2 or IGT First-degree relatives of African-Americans with DM2 (n=12), compared with relatives with normal glucose tolerance (n=19)	Patients with symptoms of hyperglycemia, taking medications known to influence glucose and insulin metabolism, with liver, heart, lung and kidney diseases, established diabetes on antidiabetic medications, participation in endurance exercise or regular competitive sports	Mean Age:49.7 Gender: NR Ethnicity: 100% African-American	Patients with DM2/IGT received ROSI at 4mg/day for first 4 weeks, then increased to 8 mg/day (single dose) from 4-12 weeks

Evidence Table 19. Adverse events in observational studies, ROSI

Author Year Quality score	Other medications permitted	Method and timing of AE assessment	Adverse events
Orbay, E 2004	NR	Physical exams, vital signs measurement, weight measurement, electocardiogram, adverse event query, lab tests	Open-label study of ROSI added to SU and metformin, at 26 weeks: - elevations in aminotransferase and aspartate aminotransferase not found - Patients reported of hypoglycemia, not considered serious
Osei, K 2004	NR	Blood tests, liver and renal tests, A1c levels assessed at baseline and 12 weeks	Cohort with comparison, at 12 weeks of treatment with ROSI 8mg/day: - No significant weight gain found - No discernable clinical pitting edema found

Evidence Table 19. Adverse events in observational studies, ROSI

Author Year Quality score	Study design Country	Population Inclusion criteria	Exclusion criteria	Age (y) Gender (% male) Race/ethnicity	Intervention
Pietruck, F 2005	Before-After Study Germany	NODM after renal transplantation	NR	Mean Age: 55 Male: (50%) Ethnicity NR	ROSI 4mg/day starting, 8mg/day maximum
Roy, R 2004	Cohort Study USA	DM2	NR	Mean Age: 51.0 Male (35.4%) Latino: 83.3% African-American: 14.5% East Indian: 2%	Rosiglitazone 8mg daily, added to metformin and SU
Sarafidis, P 2004	Cohort Study Greece	DM2 poorly glycemic control, poorly controlled/newly diagnosed hypertension	NR	Mean Age: 63.8 Male (45%) Ethnicity NR	Rosiglitazone 4mg daily, added to SU

Evidence Table 19. Adverse events in observational studies, ROSI

Author Year Quality score	Other medications permitted	Method and timing of AE assessment	Adverse events
Pietruck, F 2005	Predisone, tacrolimus, cyclosporine,	Method/timing of assessments NR	Before-after study of ROSI, - one patient discontinued/excluded after 5 days due to edema and weight gain of 4 kg - one patient received additional antidiabetic after 14 months
Roy, R 2004	NR	Method NR AE's, A1c assessed at 12 months	Observational, at 12 months of treatment of ROSI, with metformin and SU: - edema in 2 patients (4.1%)
Sarafidis, P 2004	Anti-hypertensive medications	Clinic visits ever 2 months for 26 weeks: physical exams, rountine lab tests, insulin sensitivity assessed with clamp	Observational, at 26-weeks of treatment of ROSI added to SU: - No elevation of liver function tests above normal - No complaints of leg edema or heart failure symptoms - No laboratory/clinical finding of anemia or renal function deterioration