Drug Class Review
on
Thiazolidinediones

Final Report Update 1
Evidence Tables

August 2008

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

Original Report Date: May 2006
A literature scan of this topic is done periodically

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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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Prior version of this report can be accessed at the DERP website.

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Shading indicates new evidence added to Update 1.

Evidence Table 1. Systematic reviews of TZDs

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Berlie 2007	To obtain a precise estimate of the odds for developing TZD-induced edema and to compare rates between pio and rosi and with various combinations of oral agents	Medline (1966-5/2006), CINHAL (1982-5/2006), Cochrane Control Trials Register (to 1st quarter 2006), EMBASE (1996-2005) "manual search for review articles and original manuscript" (no details) Abstracts; ADA, AHA, ACC (2003-present) Takeda and GlaxoSmithKline were contacted for studies in their new Drug Applications	Prospective, RCTS, active- or placebo-controlled; monotherapy or combined therapy; data on edema	26 RCTs 15,332 subjects with DM2

Evidence Table 1. Systematic reviews of TZDs

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Bolen 2007 (and AHRQ 2007 Review)	To summarize the literature on the beneftis and harms of oral agents in the treatment of adutls with type 2 diabetes	Medline, EMBASE, Cochrane Contral Register of Controlled Trials (inception to 1/2006); industry data and FDA web-site; heand search 15 journals, reviewed reference lists	English-language, assessed benefits and/or harms of oral diabetes drugs (excluding 1st generation SU) compared to other oral agents (not insulin)	RCTs: 216 Systematic reviews: 2

Evidence Table 1. Systematic reviews of TZDs

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
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

Evidence Table 1. Systematic reviews of TZDs

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
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

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Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
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

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Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
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
Eurich 2007	To review literature on the association between antidiabetic agents and morbidity and mortality in people with heart failure and diabetes	Medline, Health-STAR, EMBASE, CINAHL, international Pharmaceutical Abstracts, Allied and Complementary Medicine, cochrane Controlled Trials Registerm date of inception to 7/07 Manual search reference lists; contacted experts	Contemporaneous comparison group; examined association between antidiabetic agents and hospital admission or mortality	4 TZD trials 22,476 patients

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Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
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
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)

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Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Lago 2007	To examine the risk of heart failure and of cardiac death in patients given TZDs	Medline, Database of Abstracts of Reviews of Effects, Cochrane Library; up to 3/2007; start date NR; databases of European Society of Cardiology, AHA, ACC, ADA by hand; reference lists	RCTs, double-blind studies with risk estimates or frequency data for congestive heart failure and cardiovascular death	7 trials 20191 patients
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

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Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Noble J 2005	"we review the evidence supporting use of TZD(s)… for the treatment of DM2"	NR	NR	NR

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Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Phatak, 2006	To examine factors affecting the size of A1c response to TZDs	PubMed, EBSCO, Sci-lit; dates NR GlaxoSmithKline public web-site	RCTs, English-language, placebo- and active-controlled	42 8322 subjects

Evidence Table 1. Systematic reviews of TZDs

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Riche, 2007	To evaluate the impact of TZDs on repeat TVR after PCI	Medline, EMBASE, CINAHL, Cochrane database; through 7/2006 (start date NR); English only; abstrafts from AHA, ACC, ADA searched 2001 - 2006	RCTS evaluating TZDs vs standards of care; ≥ 6m follow-up; data provided on repeat TVR with number of patients receiving repeat TVR reported	7 608 subjects

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Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Richter, 2006 (Pio cochrane)	To assess the effects of pio in the treatment of type 2 diabetes	Medline, EMBASE, Cochrane database; last search 8/2006; reference lists searched	RCTs in adults with type 2 diabetes; study duration ≥ 24w	22 6200
Richter, 2007 (Rosi cochrane)	To assess the effects of rosi in the treatment of type 2 diabetes	Medline, EMBASE, Cochrane database; last search 8/2006; reference lists searched	RCTs in adults with type 2 diabetes; study duration ≥ 24w	18 3888

Evidence Table 1. Systematic reviews of TZDs

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Rosmarakis, 2007	To review RCT evidence on the effect of TZDs on in-stent restenosis after PCI	PubMed, last searcy 6/2006; reference lists reviewed	RCTs examining TZDs vs various comparators and effect on in-stent restenosis after coronary stent implantation; in English	5 235 (text states 259)
Singh 2007 (Diabetes Care)	To evaluate the risk of CHF in type 2 diabetes and to classify this AE under the dose-time-susceptibility system	RCTS: existing reviews; PubMed (1/2003 to 9/2006); manufacturer's web-site Controlled observational studies and case reports: PubMed (to 9/2006, start date NR); Web of Knolwedge Cited References and PubMed related articles Case reports also: EMBASE, Google Scholar (to 9/2006, start date NR)	Controlled observational studies with data to calculate OR of new onset CHF in patients receiving TZDs vs other oral agents Case reports with CHF and TZD	RCTs: 3 10,731 Observational studies: 4 67,382 Case reports: 162 case subjects
Singh 2007 (Jama)	To review the long-term cardiovascular risks of rosi	Medline, GlaxoSmithKline clinical trials register, FDA web-site; product information sheets; last search 5/2007	RCTs in DM2 or IGT and trial duration ≥ 12m; provided numerical data on all Aes and monitored CVD Aes	4 14,291 Also 3 systematic reviews

Evidence Table 1. Systematic reviews of TZDs

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients
Stolar 2003 Review of Aes only	"provides an overview of the cardiovascular risk profile of patients with type 2 diabetes and discusses the	1966-4/2003	NR	NR; total number of studies NR
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

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Berlie 2007	7/26 were open label trials	All subjects with DM2 Average age range across studies: 53.7 to 61.9y Average duration diabetes across studies: 5.6m to 13.6y Mean baseline A1c across studies 7.5 to 10.2% with pio and 7.9 to 9.1% with rosi	Total daily dosage (mg) Monotherapy-placebo trials: pio 7.5-45, rosi 4-8 Combination trials: pio 15-30; rosi 4-8

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Bolen 2007 (and AHRQ 2007 Review)	Intermediate outcomes: 135 RCTs and 1 systematic review Final health outcomes: Adverse events: 167 studies, 1/3 of which were RCTs; 2 systematic reviews	Adults with type 2 diabetes	Various dosages and combinations

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Boucher M 2002, 2003 COHTA Report	RCTs only Primary outcomes A1c and FPG	Discussed for each study in narrative	Treatment duration PIO: 12-268w ROSI: 12-148w

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Chilcott J 2001 overlaps with HTA report; examines Pio only	RCTs 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

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Chiquette E 2004	RCTs only Median duration of treatment: PIO 16w, ROSI 26w Minority of trials reported weight maintenance strategy	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

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Czoski-Murray 2004 HTA report	RCTs only	Described Table 7 for PIO, reported for 1 ROSI study	ROSI: dosage 4 to 8 mg qd PIO: dosage 15-30 mg qd
Eurich 2007	Unclear from review; reviewing primary studies, 1 RCT and 3 chort with comparison	Patients with diabetes and heart failure	TZD vs a variety of comparators and placeob

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Henry RR 2003	NR	NR	NR; no information on dosages, duration, cointerventions
Inzucchi SE 2002	RCTs ROSI: 2 placebo-controlled studies PIO: 1 placebo-controlled study	NR	NR; no information on dosages, duration, cointerventions

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Lago 2007	RCTs only	Diabetes and prediabetes	TZD vs a variety of comparators and placebo
Meriden T 2003	Reported in narrative for individual studies	Reported in narrative for individual studies	Reported in narrative for individual studies

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Noble J 2005	NR	Discussed for each study in narrative	Discussed for individual studies; no summary data

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Phatak, 2006	RCTs only	Diabetes; mean age 57.5y; 42.3% female subjects; basleine A1c 8.9% (SD 0.8)	TZDs vs a variety of comparators and placebo; 50% of studies were monotherapy; mean baseline A1c 9.1%(SD 1.0)

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Riche, 2007	RCTs only; all placebo-controlled with comparator standard drug therapy	1/7 studies non-diabetic; 1/7 metabolic syndrome; 5/7 type 2 diabetes	Pio or rosi given at various dosages either 1-day pre-operatively or 1-2 weeks post-operatively

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Richter, 2006 (Pio cochrane)	RCTs only; various comparators	Type 2 diabetes, largely Caucasian populations; mostly persons on other oral hypoglycemic agents; mean age patients 53 - 63y; diabetes duration 3 - 14y; baseline A1c 7.4 - 10.3%	Pio mono- or combined therapy at various dosages
Richter, 2007 (Rosi cochrane)	RCTs only; various comparators	Type 2 diabetes, largely Caucasian populations; mostly persons on other oral hypoglycemic agents; mean age patients 47 - 61y; diabetes duration 4 - 9y; baseline A1c 6.8 - 9.5%, mean 8.8%	Rosi mono- or combined therapy at various dosages

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Rosmarakis, 2007	RCTs only; various comparators	4/5 studies diabetes; 1/5 nondiabetes	Pio or rosi; dosages and use of other oral agents NR; first dose of TZD given between 1d prior to procedure up to 2w after; 3/5 studies compared pio to standard treatment; 2/5 studies compared pio to rosi; all studies 6-m duration
Singh 2007 (Diabetes Care)	RCTs, observational studies, case reports	Prediabetes or diabetes	TZD vs placebo at various dosages
Singh 2007 (Jama)	RCTs, systematic reviews, meta-analyses; rosi vs placebo or active oral agent	Prediabetes or type 2 diabetes	Rosi vs active drug or placebo

Evidence Table 1. Systematic reviews of TZDs

Author Year	Characteristics of identified articles: study designs	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Stolar 2003 Review of Aes only	NR	Reported only for selected individual studies	Reported only for selected individual studies
van Wijk JPH 2003	RCTs ROSI: 11 studies PIO: 8 studies	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

Evidence Table 1. Systematic reviews of TZDs

Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Berlie 2007	A1c mean reduction; 0.56 - 2.3%	None	Weight gain (kg): pio -0.59 3.86; rosi 1.2 to 5.0 Pooled OR: All included studies (pio and rosi, all comparators): 2.26(95% CI, 2.02 - 2.53), p<0.000001 Placebo-controlled pio vs rosi, indirect comparisons: 3.03(95% CI, 2.15 - 3.91) TZD montherapy placebo-controlled studies: 2.35 (95% CI, 1.40 - 3.91) TZD combination therapy placebo- or no-treatment control: 2.14 (95% CI, 1.88 - 2.43)

Evidence Table 1. Systematic reviews of TZDs

Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Bolen 2007 (and AHRQ 2007 Review)	A1c: decreased 1% which was similar to SU and metformin HDL: pio increased more than rosi (1-2 mg/dl); pio increased vs metformin or SU (3-5 mg/dl) LDL: rosi increased LDL more than pio (10-15 mg/dl) Triglycerides: pio decreased (15-52 mg/dl) vs rosi (increase 6-13 mg/dl); pio decreased more than metformin		Mortality: ?insufficient data CV D mortality: ?insufficient data CHF: risk is increased with TZDs vs other oral agents Microvascular outcomes: ?insufficient data Weight: TZDs increased weight similar to SU (3kg) as monotherapy or in combination with other oral agents; TZDs increased weight compared with metformin, acarbose, and repeglinide Hypoglycemia: less frequent with TZDs than SU (risk difference 4-9%) Edema: TZDs higher risk than SU (absolute risk difference 2 to 21%) CHF: TZDs higher risk than with metformin or SU, absolute risks 0.8 to 3.6%; abolute risk difference 0.7 to 2.2%) Mild anemia: TZDs higher risk than other drugs (absolute risk difference 1 to 5%) Elevated ALT: low rates (<1%) with TZDs

Evidence Table 1. Systematic reviews of TZDs

Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Boucher M 2002, 2003 COHTA Report	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)	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

Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Chilcott J 2001 overlaps with HTA report; examines Pio only	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;	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

Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Chiquette E 2004	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	None	NR

Evidence Table 1. Systematic reviews of TZDs

Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Czoski-Murray 2004 HTA report	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	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
Eurich 2007	NR	NR	Pooled OR for TZDs vs other treatments for all cause mortality: 0.83 (95% CI, 0.71 - 0.97) Pooled OR for TZDs vs other treatments on hospital admissions for heart failure 1.13 (95% CI, 0.1.04 - 1.22)

Evidence Table 1. Systematic reviews of TZDs

Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Henry RR 2003	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	None	NR
Inzucchi SE 2002	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)	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

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Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Lago 2007	NR	NR	Risk of CHF compared to controls (placebo- and active-controlled trials): RR 1.72 (95% CI, 1.21 - 2.42), p=0.002; placebo-controlled trials only: RR 1.97 (95% CI, 0.94 - 4.13); pio only: RR 1.32 (95% CI, 1.04 - 1.68); rosi only: RR 2.18 (95% CI, 1.44 - 3.32), p=0.0003 Risk of cardiovascular death compared to controls: RR 0.93 (95% CI, 0.67 - 1.29), p=0.68; placebo-controlled trials only: RR 1.08 (95% CI, 0.66 - 1.76): pio only: RR 1.01 (95% CI, 0.51 - 2.09); rosi only: RR 0.91 (95% CI, 0.63 - 1.3)
Meriden T 2003	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	None	NR

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Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Noble J 2005	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	None	NR

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Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Phatak, 2006	Weighted between-group change in A1c (all comparators) TZDs: -0.82% (SD 0.13) Pio: -1.04% (SD 0.07) Rosi: -0.67% (SD 0.10) Weighted between-group change in A1c for placebo-controlled trials: Pio: -1.03 (SD 0.19) Rosi: -0.98 (SD 0.18) Change in A1c greater with higher baseline A1c (>9.0%) (no statistics) Duration of study treatment correlated with decrease in A1c (p=0.003)	Study duration, age, sex duration therapy examined with meta-regression	NR

Evidence Table 1. Systematic reviews of TZDs

Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Riche, 2007	Repeat TVR RR Overall: range 0.13 to 0.67; pooled estimate 0.35 (95% CI, 0.22 - 0.57) Pio: 0.24 (95% CI, 0.11 - 0.51) Rosi: 0.45 (95% CI, 0.25 - 0.83) Diabetes: 0.34 (95% CI, 0.19 - 0.63) No diabetes: 0.37 (95% CI, 0.18 - 0.77)	Pio, rosi, diabetes, no diabetes	NR

Evidence Table 1. Systematic reviews of TZDs

Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Richter, 2006 (Pio cochrane)	Mortality: only reported by 1 study (Proactive) as part of a composite endpoint (mortality, stroke, nonfatal MI, surgical vascular intervention: placebo-controlled, HR 0.90 (95% CI, 0.80 - 1.02) A1c: reductions similar to other oral agents	NR	7/22 trials reported AEs Overall and serious AEs comparable between intervention groups Hb: decrease noted in 6 studies examining this outcome: range 0.5 - 0.75 g/dl Weight: increased in 15 studies examining this outcome: up to 3.9kg Edema: RR 2.86 (95% CI, 1.14 - 3.18) Hypoglycemia episodes: Pio rates < SU rates; pio + insulin increased rates No pooled data and no statistics
Richter, 2007 (Rosi cochrane)	Mortality: only reported by 1 study (ADOPT): 2.3% with rosi, 2.1% metformin, 2.2% glyburide A1c: similar reductions with rosi as metformin, glibenclamide, or glimepiride	NR	Edema: OR rosi vs comparators, random effects model: 4.62 (95% CI, 2.28 - 9.38) Severe hypoglycemic episodes: somewhat lower with rosi than active monotherapy, particularly SU; no pooled data and no statistics From ADOPT trial only: CVD events: % serious/% total events: rosi 3.4/4.3; metformin 3.2/4.0; glyburide 1.8/ 2.8 CHF, total events (%): rosi 1.5, metformin 1.3, glyburide 0.6 Fracture rates: higher with rosi than; no statistics reported

Evidence Table 1. Systematic reviews of TZDs

Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Rosmarakis, 2007	Restenosis rate measured with quantitative coronary angiography at 6m: pio or rosi vs standard therapy: OR 0.29 (95% CI, 0.15 - 0.56)	NR	Mortality: 2/259: 1 in control arm; 1 with TZD "No drug-related side effects"
Singh 2007 (Diabetes Care)	NR	NR	New onset CHF: RCTs: (3): OR 2.1 (95% CI, 1.08 - 4.08) Observational studies: (4): OR 1.55 (95% CI, 1.33 - 1.80) Case reports: 162 case subjects with 99 analyzable cases; median duration of onset of CHF 24w; CHF occurred in subjects <60y (26% of cases) and with low and high dosage
Singh 2007 (Jama)	NR	NR	Relative risk (95% CI) rosi vs comparator: MI: 1.42 (1.06 - 1.91) Heart failure: 2.09 (1.52 - 2.88) CV mortality: 0.90 (0.63 - 1.26) Number needed to harm: MI: 822 per year with rosi if baseline risk 0.29% (low risk, ADOPT)

Evidence Table 1. Systematic reviews of TZDs

Author Year	Efficacy and effectiveness results	Subgroups	Adverse events
Stolar 2003 Review of Aes only	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	NR	Peripheral edema occurs in approximately 2 to 5% of patients receiving ROSI or PIO
van Wijk JPH 2003	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	Monotherapy: PIO trials showed greater benefit on all lipid levels vs ROSI ($p<0.05$)	NR

Evidence Table 2. Quality assessment of systematic reviews of TZDS

Author Year	Clear review question?	Comprehensive sources?	Literature search strategy specified?	Important studies missing?	Explicit eligibility criteria?	Adequate detail about primary studies?	Standard method of appriasal of studies?
Berlie 2007	Yes	Yes	Yes	No	Yes	Yes	Quality not assessed
Bolen 2007 (AHRQ Review)	Yes	Yes	Yes (in AHRQ report)	No	Yes	Yes	Yes
Boucheer M 2002, 2003 COHTA Report	Yes	Yes (MEDLINE, EMBASE, Cochrane, and others; grey literature, bibliographies	Yes	No	Yes	Yes	QA (Jadad scale)
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	QA performed, but no studies excluded on this basis as couldn't evaluate 5 incomplete reports; Jadad score used

Evidence Table 2. Quality assessment of systematic reviews of TZDS

Author Year	Clear review question?	Comprehensive sources?	Literature search strategy specified?	Important studies missing?	Explicit eligibility criteria?	Adequate detail about primary studies?	Standard method of appriasal of studies?
Chiquette E 2004	Yes	Yes (MEDLINE, EMBASE, Cochrane, and others; grey literature, bibliographies	Yes (HTA search strategy)	No	Yes	Yes	QA performed; no details on appriach; no studies excluded on this basis
Czoski-Murray 2004 HTA report	Yes	Yes (MEDLINE, EMBASE, Cochrane, and others; grey literature, bibliographies	Yes	No	Yes	Yes	Jadad used for RCTs
Eurich 2007	Yes	Yes	Yes	No	Yes	No (study design NR)	Yes

Evidence Table 2. Quality assessment of systematic reviews of TZDS

Author Year	Clear review question?	Comprehensive sources?	Literature search strategy specified?	Important studies missing?	Explicit eligibility criteria?	Adequate detail about primary studies?	Standard method of appriasal of 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	No quality assessment
Inzucchi SE 2002	Yes	MEDLINE plus bibliographies	No	No	Yes	No	No quality assessment
Lago 2007	Yes	Yes	Yes	No	Yes	Yes	Yes
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	No quality assessment

Evidence Table 2. Quality assessment of systematic reviews of TZDS

Author Year	Clear review question?	Comprehensive sources?	Literature search strategy specified?	Important studies missing?	Explicit eligibility criteria?	Adequate detail about primary studies?	Standard method of appriasal of studies?
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	No quality assessment
Padwal, 2005	Yes	Yes	Yes	No	Yes	Yes	No
Phatak	Yes	Yes	Yes	No	Yes	Yes	No
Riche, 2007 (pio, cochrane)	Yes	Yes	Yes	No	Yes	Yes	Unclear; states performed by results NR
Richter 2006 (Pio Cochrane review)	Yes	Yes	Yes	No	Yes	Yes	Yes
Richter, 2007 (rosi, Cochrane)	Yes	Yes	Yes	No	Yes	Yes	Yes
Rosmarakis, 2007	Yes	No (PubMed only with reference lists checked)	Yes	No	Yes	No (other diabetes drugs NR)	Yes

Evidence Table 2. Quality assessment of systematic reviews of TZDS

Author Year	Clear review question?	Comprehensive sources?	Literature search strategy specified?	Important studies missing?	Explicit eligibility criteria?	Adequate detail about primary studies?	Standard method of appriasal of studies?
Singh 2007 (Diabetes Care)	Yes	No (relied on 2 prior reviews)	Yes	No	Yes	Yes	No
Singh 2007 (Jama)	Yes	Yes	Yes	No	Yes	Yes	No
Stolar 2003 Review of Aes only	Yes	MEDLINE plus bibliographies	Yes	No	No	No, selected studies described in narrative fashion	No quality assessment
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	No quality assessment

Evidence Table 2. Quality assessment of systematic reviews of TZDS

Author Year	Exclusion criteria	Quality	Funder	Comments
Berlie 2007	None (at review level)	Fair	NR	Unclear how reporting of individual study arms accounted for weighting of comparator arm; studies pooled across all comparators and mono/combined therapies
Bolen 2007 (AHRQ Review)	Studies < 40 subjects; <3m follow-up	Good	AHRQ	
Boucheer M 2002, 2003 COHTA Report	Encompassed by inclusion criteria	Good	Addresses efficacy and Aes	Canadian Coordinating Orrice for health Technology Assessment, Ottawa, ON Canada
Chilcott J 2001 PIO review	Encompassed by inclusion criteria	Good	Addresses efficacy and Aes	UK National Health Service Research and Development Health Technology Assessment Programme

Evidence Table 2. Quality assessment of systematic reviews of TZDS

Author Year	Exclusion criteria	Quality	Funder	Comments
Chiquette E 2004	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	Encompassed by inclusion criteria	Good	Addresses efficacy and Aes	UK National Health Service Research and Development Health Technology Assessment Programme
Eurich 2007	None (at review level)	Fair	Canadian Institutes for Health Research, alberta heritage Foundation for Medical Research	Pooled estimates included observational studies and RCTs

Evidence Table 2. Quality assessment of systematic reviews of TZDS

Author Year	Exclusion criteria	Quality	Funder	Comments
Henry RR 2003	None reported	Poor No quality assessment, only MEDLINE, no duplicate abstraction	Addresses effects on insulin resistance only	NR
Inzucchi SE 2002	Follow-up <3m, study groups <10 subjects	Poor No quality assessment, no duplicate abstraction	Addresses efficacy and Aes	NR
Lago 2007	None (at review level)	Good	No funding source	
Meriden T 2003	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.

Evidence Table 2. Quality assessment of systematic reviews of TZDS

Author Year	Exclusion criteria	Quality	Funder	Comments
Noble J 2005	None reported	Poor No quality assessment; no details on abstraction	Addresses efficacy and Aes	NR
Padwal, 2005	Studies with n<50; preexisting diabetes; abstracts	Fair	NR	
Phatak	Troglitazone; no baseline or post-intervention A1c values for each study group	Fair	NR: second author is Merck employee	
Riche, 2007 (pio, cochrane)	None (at review level)	Fair	NR	
Richter 2006 (Pio Cochrane review)	None (at review level)	Good	None	
Richter, 2007 (rosi, Cochrane)	None (at review level)	Good	None	
Rosmarakis, 2007	None (at review level)	Fair-poor	NR	

Evidence Table 2. Quality assessment of systematic reviews of TZDS

Author Year	Exclusion criteria	Quality	Funder	Comments
Singh 2007 (Diabetes Care)	Studies reporting only edema were excluded	Fair	NR	
Singh 2007 (Jama)	None (at review level)	Fair	NR	
Stolar 2003 Review of Aes only	NR	Poor	Addresses efficacy and Aes	NR
van Wijk JPH 2003	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 trials of pioglitazone vs rosiglitazone (New for Update #1)

Author, year	Inclusion Criteria	Exclusion Criteria	Baseline Demographics	Baseline Characteristics	Other Medications at Baseline
Chappuis, 2007	Patients with T2DM for a duration of at least 6 mos ad under stable metabolic control (HbA1c 6.5-9%).They had to be on a maximum of 2 oral anti diabetic agents.	Patients treated with insulin or glitazones, or exhibiting symptoms of heart failure (NYHA class III or IV), active neoplasia, unstable cardio vascular disease, or severely impaired liver or kidney function	Mean age:NR; Male: 58.82%; Female: 41.18%; White: %; Black:	A1c:7.6; Weight:NR; BMI:29.3; Duration of diabetes: .	Antihypertensives:NR% Lipid lowering:NR% Insulin:NR% Metformin:96% Sulfonylureas:71%% Acarbose: % Or
Derosa (J Int Med Research) 2006, 2006, 2007, 2007, 2006a	Caucasians >=18 yrs with T2DM according to ADA criteria with a duration >=6 mos and who had poor glycemic control (HbA1c>7.5%) or had experienced adverse effects with diet and metformin given at up to the maximum tolerated dose. Pts had metabolic syndrome according to National Cholesterol Education Program Adult Tx Panel III classification, and presented with Triglyceridemia and hypertension according to the WHO criteria, fasting C-peptide level>1.0ng/ml and were overweight (BMI 25.0-28.1 kg/m2).	Hx of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy, impaired hepatic function, impaired renal function or severe anemia. Pts with serious cardiovascular disease or cerebrovascular conditions within 6 mos before study enrolment were also excluded.	Mean age: ; Male: .%; Female: .%; White: %; Black:	A1c: ; Weight: ; BMI: ; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin: % Metformin: % Sulfonylureas: % Acarbose: % Oral hyp

Evidence Table 3. Head-to-head trials of pioglitazone vs rosiglitazone (New for Update #1)

Author, year	Intervention	Total Daily Dose	Sample Size	Outcome Measure	Results
Chappuis, 2007	Pioglitazone monotherapy	30 mg for 4 wks	17	BMI at 12 weeks	Change in BMI from baseline: +0.5 (SD 0.6), p=0.15 , vs Rosi
		45 mg for 8 wks	17	HbA1c at 12 weeks	% Change in HbA1c from baseline: -0.3 (SD 0.6), p=0.43 vs. Rosi
	Rosiglitazone monotherapy	4 mg for 4 wks	17	BMI at 12 weeks	change in BMI from baseline: +0.3 (SD 0.5)
		8 mg for 8 wks	17	HbA1c at 12 weeks	% change in HbA1c from baseline - 0.5(SD 0.6)
Derosa (J Int Med Research) 2006, 2006, 2007, 2007, 2006a	Pioglitazone combination therapy	15 mg	103	BMI at 12 months	final: 26.6 (SD 1.1). Change from baseline: -0.3, p>0.05 (from J. of clinical Ther)
			48	AST & ALT at 12 months	25(SD 8), 26 (SD9), p>0.05, change from baseline: -3, -2
				HCT at 12 months	Final: 8.6(SD3.8), p<0.05 vs baseline, change from baseline: -2.3
				HbA1c at 12 months	Final: 6.8 (SD 0.3), p<0.01 vs. baseline, change from baseline: -1.4
					Improvements in plasma level of HbA1c at 12 mos: 17.1%, p<0.01 vs. basline, p=NS between Pio and Rosi
	Rosiglitazone combination therapy	4mg	48	AST & ALT at 12 months	final: 25(SD 9), 27(SD 10), p>0.05, change from baseline: -2, -2
				HCT at 12 months	Final: 8.0(SD 3.4), p<0.05 vs baseline, change from baseline: -2.4
				HbA1c at 12 months	Improvements in plasma level of HbA1c at 12 mos: 16.0%, p<0.01 vs baseline
			48	BMI at 12 months	final 6.8 (SD 0.5), change from baseline: -1.3, p<0.001
					Final: 26.0 (SD 1.2), change from baseline: -0.4

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Year	Randomization method adequate/	Allocation concealment adequate?	Groups similar at baseline?	Comment	Inclusion criteria specified?	Exclusion criteria specified?
Agarwal	2005	Method not described	Yes	Yes		Yes	Yes
Bakris	2006	Method not described	Method not described	Yes		Yes	Yes
Basu	2006	Method not described	Method not described	Yes		Yes	Yes
Belfort	2006	Yes	Yes	Yes		Yes	Yes
Bhatt	2007	Method not described	Method not described	Yes		Yes	Yes

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Year	Randomization method adequate/	Allocation concealment adequate?	Groups similar at baseline?	Comment	Inclusion criteria specified?	Exclusion criteria specified?
Cao	2006	Method not described	Method not described	Yes	Only completers examined; more LAD in rosi group and more circumflex and RA lesions in control group	Yes	Yes
Chappuis	2007	Method not described	Method not described	Yes		Yes	Yes
DREAM Trial Investigators	2006	Yes	Yes	Yes		Yes	Yes
Dailey	2004	Method not described	Method not described	Yes		Yes	Yes
Dargie	2007	Yes	Method not described	No	Higher rate of NYHA class II and prior MI in rosi group	Yes	Yes

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Year	Randomization method adequate/	Allocation concealment adequate?	Groups similar at baseline?	Comment	Inclusion criteria specified?	Exclusion criteria specified?
DeRosa (Pharmacotherapy), 2006 (Diab, Obes, Metab)	2005	Yes	Yes	Yes		Yes	Yes
Derosa (J Int Med Research) 2006, 2006, 2007, 2007	2006a	Yes	Yes	Yes		Yes	Yes
Garber	2006	Method not described	Method not described	Yes		Yes	Yes
Gastialdelli	2007	Method not described	Method not described	Yes		Yes	Yes
Goldstein	2006	Method not described	Method not described			Yes	Yes
Hanefeld	2007	Method not described	Method not described	Yes		Yes	Yes
Hanefield, Betteridge 2005	2004	Method not described	Method not described	Yes		Yes	Yes

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Year	Randomization method adequate/	Allocation concealment adequate?	Groups similar at baseline?	Comment	Inclusion criteria specified?	Exclusion criteria specified?
Heliovaara	2007	Method not described	Method not described	Yes	HOMA and HDL cholesterol differed	Yes	Yes
Home, Home 2005	2007	Yes	Yes	No	Background met stratum had lower age, higher BMI, and shorter duration since diagnosis than background SU stratum	Yes	Yes
Jain	2006	Method not described	Method not described	Yes		Yes	Yes
Kahn	2006	Method not described	Method not described	Yes		Yes	Yes
Kulenovic	2006	Method not described	Method not described	No	Older in Gliben group	Yes	Yes

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Year	Randomization method adequate/	Allocation concealment adequate?	Groups similar at baseline?	Comment	Inclusion criteria specified?	Exclusion criteria specified?
Lautamaki	2005	Method not described	Method not described	NR	Reported for analyzed patients only (54/62)	Yes	Yes
Mazzone	2006	Method not described	Method not described	No	More hx MI in glimep than pio	Yes	Yes
Negro	2005	Method not described	Method not described	Yes		Yes	Yes
Nishio	2006	Method not described	Method not described	Yes		Yes	Yes
Osman	2004	Method not described	Method not described	Yes		Yes	Yes
Perriello	2006	Method not described	Method not described	Yes		Yes	No
Pfutzner	2006	Method not described	Method not described	Yes		Yes	Yes
Pfutzner, Forst 2005, Forst 2005	2005	Method not described	Method not described	NR	Reported for per-protocol population only (173/192 enrolled)	Yes	Yes

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Year	Randomization method adequate/	Allocation concealment adequate?	Groups similar at baseline?	Comment	Inclusion criteria specified?	Exclusion criteria specified?
Raskin	2004	Method not described	Method not described	Yes		Yes	Yes
Roden (Trial 1)	2005	Method not described	Method not described	Yes		Yes	Yes
Roden (Trial 2)	2005	Method not described	Method not described	Yes		Yes	Yes
Rosenstock	2006	Method not described	Method not described	Yes		Yes	Yes
Sharma	2006	Yes	Yes	Yes		Yes	Yes
Sourij	2006	Method not described	Method not described	Yes		Yes	Yes
Stocker	2007	Yes	Method not described	Yes		Yes	Yes

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Year	Randomization method adequate/	Allocation concealment adequate?	Groups similar at baseline?	Comment	Inclusion criteria specified?	Exclusion criteria specified?
Teramoto	2007	Method not described	Method not described	Yes		Yes	Yes
Tseng	2005	Method not described	Method not described	Yes		No	No
Umpierrez	2006	Method not described	Method not described	No		Yes	Yes
Yamanouchi	2005	Yes	Yes	Yes		Yes	Yes

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Withdrawal Rate differential or high?	Comment	Loss to followup differential or high?	Comment
Agarwal	Unable to determine	No	No	Yes	No	1/22 (4.5%) pio vs 3/22 (13.6%) glipizide	No	
Bakris	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	71/389 (18.3%) overall; 19.6% rosi vs 16.8% gly	No	
Basu	NR	NR	NR	Yes	No		No	
Belfort	NR	Yes	NR	Yes	No		No	
Bhatt	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	No	Unable to determine	85 of 200 did not have CIMT data, but # withdrawn not clear for other outcomes.	Unable to determine	

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Withdrawal Rate differential or high?	Comment	Loss to followup differential or high?	Comment
Cao	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	63/360 (17.5%) did not complete followup.	Unable to determine	
Chappuis	NR	NR	NR	No	Unable to determine		Unable to determine	
DREAM Trial Investigators	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	713+612 stopped drug or withdrew out of 5269 (23%); no differential	No	
Dailey	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	36/181 (19.9%) in rosi group vs 68/184 (37.0%) placebo	No	
Dargie	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes		No	

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Withdrawal Rate differential or high?	Comment	Loss to followup differential or high?	Comment
DeRosa (Pharmacotherapy), 2006 (Diab, Obes, Metab)	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	No		No	
Derosa (J Int Med Research) 2006, 2006, 2007, 2007	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	No		No	
Garber	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	Yes		No	
Gastialdelli	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Unable to determine		Unable to determine	
Goldstein	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Unable to determine		Unable to determine	
Hanefeld	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	Yes	114/598 (19.1%); higher for rosi 4 mg (23.5%)	No	
Hanefield, Betteridge 2005	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	Yes			

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Withdrawal Rate differential or high?	Comment	Loss to followup differential or high?	Comment
Heliovaara	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	No	Unable to determine		Unable to determine	
Home, Home 2005	Yes	No	No	Yes	Yes		Yes	10%
Jain	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	Yes	240/502 (52.1%)	Yes	43/502 (8.6%)
Kahn	Yes	Unclear, reported as double blind	Yes	Yes	Yes	1733/4360 withdrew (39.7%)	Yes	234/4360 (5.4%)
Kulenovic	NR	NR	NR	No	Unable to determine		Unable to determine	

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Withdrawal Rate differential or high?	Comment	Loss to followup differential or high?	Comment
Lautamaki	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	No		No	
Mazzone		Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes		No	
Negro	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	No	Unable to determine		Unable to determine	
Nishio	No	NR	NR	No	Unable to determine		Unable to determine	
Osman	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Unable to determine	Unclear for A1c, 11/16 did not consent to f/u angio for CIMT	Unable to determine	
Perriello	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	No		No	
Pfutzner	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	No	Unable to determine		Unable to determine	
Pfutzner, Forst 2005, Forst 2005	No	No	No	Yes	No	90.5% completed	Unable to determine	

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Withdrawal Rate differential or high?	Comment	Loss to followup differential or high?	Comment
Raskin	No	No	No	Yes	Yes	71/252 (28.2%). Lower d/c rate for combination vs montx groups; 40% in monotx groups	Unable to determine	
Roden (Trial 1)	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	No	Unable to determine		Unable to determine	
Roden (Trial 2)	NR	NR	NR	No	Unable to determine		Unable to determine	
Rosenstock	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	Completers: Intervention 90/116 (78%), placebo 57/111 (51%)	No	
Sharma	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes	No		Yes	8.6% overall; 1/18 (5.5%) met vs 2/17 pio (11.8%)
Sourij	Unclear, reported as double blind	Unclear, reported as double blind	Yes	No	Unable to determine		Unable to determine	
Stocker	No	No	No	Yes	Yes		No	

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Withdrawal Rate differential or high?	Comment	Loss to followup differential or high?	Comment
Teramoto	No	No	No	Yes	No		Unable to determine	Exact loss to F/U NR
Tseng	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	No	Unable to determine		Unable to determine	
Umpierrez	No	No	No	Yes	No	29/210 (13.8%)	Yes	4/101 glimepiride (4%) vs 15/109 pio (13.8%)
Yamanouchi	NR	NR	NR	Yes	No	8/114 (7%)	No	3/114 (2.6%)

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	ITT analysis?	Comment	Post-randomization exclusions?	Comment	Funding	Other
Agarwal	Unable to determine	number analyzed not clear: 40/44?	Yes	2/44 discontinued from the study drug for unclear reason; 1 discontinued by physician	Takeda	End point was blinded to personnel performing the technical and data analysis
Bakris	Yes	374/389 (96.1%) analyzed	Yes	12/389 excluded for protocol deviation; 20/389 excluded for "other"	GlaxoSmithKline	
Basu	No	2/21 subjects (9.5%) withdrew and were not analyzed	No		Takeda	
Belfort	No	47/55 analyzed (85.5%)	Yes	2 withdrawan for CAD		
Bhatt	Unable to determine	all results have same sample size as baseline group; unclear if no attrition or if only completers analyzed	Unable to determine		GlaxoSmithKline	

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	ITT analysis?	Comment	Post-randomization exclusions?	Comment	Funding	Other
Cao	No		Unable to determine		Not reported	
Chappuis	Unable to determine		Unable to determine		Swiss Diabetes Foundation	
DREAM Trial Investigators	Yes		No			
Dailey	Yes	LOCF, but high loss to followup	Yes	5 in placebo group withdrawn for reason 'other'	Bristol-Myers Squibb	
Dargie	Yes	ITT population for placebo 110/114; rosi 108/110	Unable to determine		GlaxoSmithKline	

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	ITT analysis?	Comment	Post-randomization exclusions?	Comment	Funding	Other
DeRosa (Pharmacotherapy), 2006 (Diab, Obes, Metab)	Yes	95/99 analyzed (96%)	Yes	Withdrawal for protocol violation (1 or 2 patients only)	Not reported	
Derosa (J Int Med Research) 2006, 2006, 2007, 2007	No		Yes	Some exclusions for protocol violations	Not reported	
Garber	Yes		Yes	11 patients withdrawn for reason "other"	Bristol-Myers Squibb	
Gastialdelli	Unable to determine		Unable to determine			
Goldstein			Unable to determine		GlaxoSmithKline	
Hanefeld	Yes	587/598 analyzed (98.2%) LOCF	No		SmithKline Beecham	
Hanefield, Betteridge 2005	Yes				SmithKline Beecham	

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	ITT analysis?	Comment	Post-randomization exclusions?	Comment	Funding	Other
Heliovaara	Unable to determine		Unable to determine		Eli Lilly	No information on attrition, number analyzed not explicit.
Home, Home 2005	Yes		Yes		GlaxoSmithKline	
Jain	Yes	Used LOCF but very high withdrawal rate	Yes	61 excluded for patient noncompliance, protocol violaton, or investigator discretion	Not reported	
Kahn	Yes	4127/4360 analyzed (95%)	Yes		GlaxoSmithKline	
Kulenovic	Unable to determine	States ITT	Unable to determine		Not reported	

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	ITT analysis?	Comment	Post-randomization exclusions?	Comment	Funding	Other
Lautamaki	No	Completers only analyzed (54/62)	Yes	3 excluded due to protocol violation, 1 due to unstable angina	Foundations and GlaxoSmithKline	
Mazzone	Yes	458/462 analyzed (99.1%)	Yes	1 protocol violation, 3 investigator decision	Takeda	
Negro	Unable to determine		Unable to determine		Not reported	
Nishio	Yes	Number analyzed equals total N	Unable to determine		Not reported	
Osman	No		Unable to determine		NIH	
Perriello	Yes	275/283 analyzed (97.2%)	Yes	275/283 analyzed (97.2%)	Not reported	
Pfutzner	Unable to determine		Unable to determine			
Pfutzner, Forst 2005, Forst 2005	Yes	173/179 (96.6%) analyzed	Unable to determine		Takeda	

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	ITT analysis?	Comment	Post-randomization exclusions?	Comment	Funding	Other
Raskin	Yes		Yes	8 excluded for non-compliance	Novo Nordisk	
Roden (Trial 1)	No	1098/1194 analyzed (92%)	Unable to determine		Eli Lilly and Takeda	
Roden (Trial 2)	Yes	606/639 analyzed (94.8%)	Unable to determine		Eli Lilly and Takeda	
Rosenstock	Yes		Yes	11/227 for protocol violation	GlaxoSmithKline	
Sharma	No	30/35 analyzed (85.7%)	No			
Sourij	Unable to determine		Unable to determine		Takeda Austria	Unable to determine number analyzed
Stocker	No	75/92 analyzed (81.5%)	No		GlaxoSmithKline	

Evidence Table 4. Quality assessment of randomized controlled trials (New for Update 1)

Author	ITT analysis?	Comment	Post-randomization exclusions?	Comment	Funding	Other
Teramoto	Yes	91/92 analyzed (98.9%)	Unable to determine		Japan Pioglitazone Study Group (Type unclear)	
Tseng	Unable to determine	Results reported for 48/48 randomized; unclear if any withdrawals	Unable to determine		Not reported	
Umpierrez	Yes	203/210 analyzed (96.7%)	Yes		Sanofi-Aventis	
Yamanouchi	No	only completers analyzed=93%	No		Not reported	

Evidence Table 5. Placebo-controlled trials of pioglitazone (new for Update #1)

Author, year	Inclusion Criteria	Exclusion Criteria	Baseline Demographics	Baseline Characteristics
Belfort, 2006	the diagnosis of nonalcoholic steatohepatitis and impaired glucose tolerance or type 2 diabetes	normal results on the oral glucose tolerance test;abnormal findings on laboratory tests; levels of plasma aspartate aminotransferase andalanine aminotransferase were 2.5 times or morethe upper limit of the normal range; history of heavy alcohol use (>12 to 15 g of alcohol per day, or >12 oz of beer, 5 oz of wine, or 1.5 oz of distilled spirits); fasting glucose level of 240 mg per deciliter (13.3 mmol per liter) or greater; type 1 diabetes, heart disease, hepatic disease (other than nonalcoholic steatohepatitis), or renal disease; receivingmetformin, thiazolidinediones, or insulin.	Mean age:51; Male: 44.68%; Female: 55.32%; White: %; Black:	A1c: ; Weight:92.1; BMI: ; Duration of diabetes: .
Gastaldelli, 2007	Healthy diabetic subjects. Not taking any medication other than sulfonylureas known to affect glucose or lipid metabolism. Body weight stable for >or= 3 months of the study and no subject participated in a heavy exercise program prior to the study. Subjects were asked to consume a weight maintaining diet containing 50% cardohydrate, 30% fat and 20% protein for 3 days prior to the study.	NR	Mean age:53; Male: .%; Female: .%; White: %; Black:	A1c:8.2; Weight: ; BMI:29.4; Duration of diabetes: .

Evidence Table 5. Placebo-controlled trials of pioglitazone (new for Update #1)

Author, year	Inclusion Criteria	Exclusion Criteria	Baseline Demographics	Baseline Characteristics
Nishio, 2006	Acute coronary syndrome and type 2 diabetes who had received coronary stenting were eligible for the study if their homeostasis model assessment of insulin resistance (HOMA-IR) was >2.0	Spastic angina pectoris, congestive heart failure, hepatic dysfunction, chronic renal disease, recent stroke, impaired glucose tolerance, insulin-dependent diabetes, familial hypercholesterolemia, thyroid dysfunction, adrenal dysfunction, or an intolerance of aspirin, ticlopidine, heparin,	Mean age:66.9; Male: 72.2%; Female: 27.8%; White: %; Black:	A1c:7.3; Weight: ; BMI:24.6; Duration of diabetes: .
Sourij, 2006	stable CAD and recently detected type 2 diabetes	diabetes by history or fasting blood glucose >6.1 mmol/l, acute coronary syndrome or cerebrovascular event within the previous 8 weeks, heart failure according to NYHA III	Mean age:60.25; Male: 92.86%; Female: 7.14%; White: %; Black:	A1c:6.1; Weight: ; BMI:28.2; Duration of diabetes: .
Tseng, 2005	Type 2 diabetics in Taiwan	NR	Mean age:56.19; Male: 35.42%; Female: 64.58%; White: %; Black:	A1c: ; Weight:61.97; BMI: ; Duration of diabetes: .

Evidence Table 5. Placebo-controlled trials of pioglitazone (new for Update #1)

Author, year	Intervention	Total Daily Dose	Sample Size	Outcome Measure	Results
Belfort, 2006	Placebo		21	at	
				BMI change at 26 weeks	change -0.2, p=0.62 vs baseline
				Weight at 26 weeks	change -0.5, p=0.53 vs baseline
	Pioglitazone monotherapy	30 mg	26	BMI at 26 weeks	change 1.1,
				HbA1c at 26 weeks	change -0.7, p<0.001 vs baseline
				Weight at 26 weeks	change 2.5 (weight gain) , p<0.001 vs baseline
	Placebo		47	HbA1c at 26 weeks	change -0.1, p=0.73 vs baseline
Gastaldelli, 2007			.	BMI at 4 months	BMI at 4 mos(Kg/m2) : 28.4 (SE 1.2), p<0.01 pre vs. post
				HbA1c at 4 months	% HbA1C at 4 mos: 6.6 (SE 0.4), p<0.01 pre vs. post
	Pioglitazone+SU	45mg	10	BMI at 4 months	BMI at 4 mos (Kg/m2): 30.0 (SE 1.4), change +1.1 p< 0.01 pre vs. post
				HbA1c at 4 months	% HbA1c at 4 mos: 7.3 (SE 0.6), change -2.0 p< 0.01 pre vs. post, p<0.001 vs. placebo
	Placebo+SU			BMI at	BMI at 4 mos (kg/m2):29.8 (SE 1.4), , change -0.1 p-value=NS
				HbA1c at 4 months	% HbA1c at 4 mos: 9.2 (SE 0.5), change +0.9
	Placebo		12	BMI at 4 months	BMI at 4 mos (Kg/m2): 30.0 (SE 1.2), change +0.2, P-value>0.05

Evidence Table 5. Placebo-controlled trials of pioglitazone (new for Update #1)

Author, year	Intervention	Total Daily Dose	Sample Size	Outcome Measure	Results
				HbA1c at 4 months	% HbA1c at 4 mos: 8.7 (SE 0.5), change +0.6
				at	This group was not studied.
Nishio, 2006	Pioglitazone monotherapy	30 mg	26	BMI at 26 weeks	change +0.1between group p=0.818
				HbA1c at 26 weeks	change -1.7, between group p=0.263
	No treatment		28	BMI at 26 weeks	change -0.1
	No treatment		54	HbA1c at 26 weeks	change -0.4
Sourij, 2006	Pioglitazone monotherapy	30 mg	21	HbA1c at 12 weeks	6.1 (0.6), change 0%
	Placebo		42	HbA1c at 12 weeks	5.9 (0.4), change -0.2, between group p>0.05
Tseng, 2005	Pioglitazone+various SU	30 mg	23	Weight at 12 weeks	change 1.2
	Placebo+existing SU		25	HbA1c at 12 weeks	percent change at endpoint 2.6
				Weight at 12 weeks	no change
	Pioglitazone+various SU	30 mg	48	HbA1c at 12 weeks	percent change at endpoint -8.7

Evidence Table 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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: 0% 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 5. 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 6. Placebo-controlled trials of rosiglitazone (New for Update 1)

Author, year	Inclusion Criteria	Exclusion Criteria	Baseline Demographics	Baseline Characteristics
Dailey, 2004	inadequately controlled type 2 diabetes (glycosylated hemoglobin [HbA1C] levels 7.0% and 10.0%) were enrolled if they were between 20 and 78 years of age and had a body mass index 23 and 40 kg/m2	uncontrolled diabetes (HbA1C levels more than 10%); polyuria and polydipsia with >10% weight loss; use of hypoglycemic agents other thanstable daily doses of metformin, sulfonylureas, or thiazolidinediones within 8 weeks ; renal dysfunction(serum creatinine level >/=1.5 mg/dL [men] or1.4 mg/dL [women]); abnormal liver function (serumalanine aminotransferase, aspartate aminotransferase, or total bilirubin levels >/=twice the upper limit of normal);anemia; clinically substantial cardiac or psychiatric disease; and long-term insulin therapy. unable or unwilling to perform selfmonitoring of blood glucose levels.	Mean age:57; Male: 59.45%; Female: 40.55%; White:74%; Black:8	A1c:8.1; Weight:93; BMI:32; Duration of diabetes: .
Dargie, 2007	inadequate glycemic control; any antidiabetes treatment except for a thiazolidinedione,insulin, or combination therapy with an insulinsecretagogue and acarbose. Only stable patients in NYHA functional class I to II CHF;	body mass index more than 35 kg/m2,creatinine clearance less than 40 ml/min; significant hepatic disease, or laboratory-confirmed anemia;	Mean age:64; Male: 81.65%; Female: 18.35%; White:99.1%; Black:	A1c:7.8; Weight:84.6; BMI: ; Duration of diabetes: .
Gastaldelli, 2007	Healthy diabetic subjects. Not taking any medication other than sulfonylureas known to affect glucose or lipid metabolism. Body weight stable for >or= 3 months of the study and no subject participated in a heavy exercise program prior to the study. Subjects were asked to consume a weight maintaining diet containing 50% cardohydrate, 30% fat and 20% protein for 3 days prior to the study.	NR	Mean age:53; Male: .%; Female: .%; White: %; Black:	A1c:8.2; Weight: ; BMI:29.4; Duration of diabetes: .

Evidence Table 6. Placebo-controlled trials of rosiglitazone (New for Update 1)

Author, year	Inclusion Criteria	Exclusion Criteria	Baseline Demographics	Baseline Characteristics
Lautamaki, 2005	Past or current angina pectoris symptoms under stress, type 2 diabetes treated with diet or withmetformin and/or sulfonylurea, and good or moderate glycemic control(HbA1c [A1C]<8.5%)	Unstable angina pectoris, symptomatic tachy- or bradyarrhythmias, history of percutaneous transluminal coronary angioplasty during the preceding 6 months, asthma, chronic useof insulin, or the clinical signs of the heart	Mean age:64; Male: 70.37%; Female: 29.63%; White: %; Black:	A1c: ; Weight: ; BMI: ; Duration of diabetes: .
Negro, 2005	Type 2 diabetic ambulatory patients; not known hypertensives and were not on any antihypertensive medication; with a nocturnal decline in BPless than 10% (nondippers)	History of pancreatitis, gastrointestinal and/or malabsorption conditions, heart disease or insufficiency, malignant disease, renal or hepatic impairment, drug or alcohol abuse and pregnancy/lactation; micro–macroalbuminuria and retinopathy	Mean age:60; Male: 57.89%; Female: 42.11%; White:100%; Black:	A1c:8.3; Weight: ; BMI: ; Duration of diabetes: .
Osman, 2004	Type 2 diabetics undergoing coronaryangiography	already on a TZD, abnormal baseline liver function studies or chronic liver disease, ejection fraction<30% or heart failure, serum creatinine<2.5mg/dL, life expectancy of <12 months, ostial orbifurcation lesions, total occlusions, or lesions with reference vessel diameter <2.5 cm.	Mean age:55.4; Male: 37.5%; Female: 62.5%; White: %; Black:	A1c:9.5; Weight: ; BMI: ; Duration of diabetes: .
			Mean age:55.4; Male: 37.5%; Female: 62.5%; White: %; Black:	A1c:9.5; Weight: ; BMI: ; Duration of diabetes: .
Pfutzner, 2006	Not reported		Mean age:62.8; Male: 52.94%; Female: 47.06%; White: %; Black:	A1c:8.1; Weight: ; BMI:28.7; Duration of diabetes: .

Evidence Table 6. Placebo-controlled trials of rosiglitazone (New for Update 1)

Author, year	Inclusion Criteria	Exclusion Criteria	Baseline Demographics	Baseline Characteristics
Rosenstock, 2006	Male and female; aged =60 years, with documented T2DM, treated with submaximal SU monotherapy for =3 months; been on one-quarter to one-half of the maximum-labelled SU dose for =2 months prior with fasting plasma glucose (FPG) =7.0 and =13.9 mmol/l .	Severe or unstable angina, coronary insufficiency or congestive heart failure (NYHA class III/IV)	Mean age:73.6; Male: 73.57%; Female: 26.43%; White: %; Black:	A1c:7.7; Weight: ; BMI:30.3; Duration of diabetes: .

Evidence Table 6. Placebo-controlled trials of rosiglitazone (New for Update 1)

Author, year	Intervention	Total Daily Dose	Sample Size	Outcome Measure	Results
Dailey, 2004	Rosiglitazone combination therapy	4-8 mg	181	Weight at 24	weight increase 3 kg
	Placebo		184	HbA1c at 24 weeks	change from baseline +0.1%
				Weight at 24 weeks	weight increase 0.03 kg
	Rosiglitazone combination therapy	4-8 mg	365	HbA1c at 24 weeks	change from baseline -.9%
Dargie, 2007	Rosiglitazone monotherapy	4 mg	108	at	
				Weight at 52 weeks	1.3 (SD 4.8)
	Placebo		110	HbA1c at 52 weeks	adjusted between group diff -0.65% (95% CI -0.94to -0.37), p<0.0001
			218	Weight at 52 weeks	change -0.3(SD 3.2)
Gastaldelli, 2007	Placebo+SU			BMI at	BMI at 4 mos (kg/m2):29.8 (SE 1.4), , change -0.1 p-value=NS
				HbA1c at 4 months	% HbA1c at 4 mos: 9.2 (SE 0.5), change +0.9
	Placebo		12	BMI at 4 months	BMI at 4 mos (Kg/m2): 30.0 (SE 1.2), change +0.2, P-value>0.05

Evidence Table 6. Placebo-controlled trials of rosiglitazone (New for Update 1)

Author, year	Intervention	Total Daily Dose	Sample Size	Outcome Measure	Results
				HbA1c at 4 months	% HbA1c at 4 mos: 8.7 (SE 0.5), change +0.6
	Rosiglitazone monotherapy	8 mg		BMI at 4 months	BMI at 4 mos(kg/m2): 30.6 (SE 1.2),change +1.4, p<0.01 pre vs. post.
				HbA1c at 4 months	% HbA1c at 4 mos: 7.3 (SE 0.3), p<0.01, change -1.4 pre vs. post, p<0.001 vs. placebo
			64	at	This group was not studied.
Lautamaki, 2005	Placebo		27	HbA1c at 16 weeks	change +0.2
	Rosiglitazone monotherapy	8-Apr		HbA1c at 16 weeks	change -0.4 p< 0.0001 vs placebo
				Weight at 16 weeks	from 85.3 (17.4) to 87.2 (17.7) P = 0.03
	Placebo		54	Weight at 16 weeks	No change
Negro, 2005	Placebo+metformin		19	Weight at 12 months	83.9 (4.5), change +0.3
	Rosiglitazone monotherapy	8 mg		HbA1c at 12 months	7.3 (0,7), change -1.1
				Weight at 12 months	86.8 (4.6) change 0.9
	Placebo+metformin		38	HbA1c at 12 months	8.3 (0.5), change +0.2
Osman, 2004	Placebo		8	HbA1c at 24 weeks	change from baseline -1.1
	Rosiglitazone monotherapy	8 mg	16	HbA1c at 26 weeks	change from baseline -24.1
Pfutzner, 2006	Placebo+glimepiride		30	BMI at 16 weeks	29.8 (3.4), change -0.2
	Rosiglitazone combination	4 mg	31	BMI at 16 weeks	27.7 (4.1), change 0.0
				HbA1c at 16 weeks	7.1 (1.7) change = -1.2
	Rosiglitazone	3 mg	41	BMI at 16 weeks	29.5 (4.8) change +0.2

Evidence Table 6. Placebo-controlled trials of rosiglitazone (New for Update 1)

Author, year	Intervention	Total Daily Dose	Sample Size	Outcome Measure	Results
	combination	8 mg		HbA1c at 16 weeks	6.7 (1.0) change -1.3
	Placebo+glimepiride		102	HbA1c at 16 weeks	7.7 (1.5) change = 0
Rosenstock, 2006	Placebo+Glipizide	10 mg	111	QOL at	DTSQ satisfaction score change from baseline -1.61, p<0.01
				Weight at 104 weeks	mean change -1.2 kg
	Rosiglitazone+Glipizide	10 mg	116	QOL at	DTSQ satisfaction score change from baseline +1.15, p<0.05
				Weight at 104 weeks	mean change +4.3 kg
		4-8 mg		HbA1c at 104 weeks	change -0.65%; between group change -0.79%, p<0.0001
	Placebo+Glipizide		227	HbA1c at 104 weeks	change +0.13% p=0.187

Evidence Table 6. 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): 9.3 (NR) years

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 6. 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): NR (NR) years

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 6. 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): 7.3 (5.7) years

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 6. 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 6. 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): 10.3 (NR) years

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 6. 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 6. 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):

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 6. 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): NR (NR) years

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 6. 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 6. 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): 11.0 (6.4) 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
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 6. 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 6. 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): 4.93 (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
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 6. 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 6. 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): 5 (NR) years

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 6. 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 6. 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): 5.47 (6.26) years

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 6. 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): 5.2 (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
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
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
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 6. 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): 5.9 (6.14) 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	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 6. 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 6. 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): 5.3 (NR) years

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 6. 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):

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 6. 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 6. 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: % Female

Type 2 diabetes duration (SD):

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 6. 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): NR (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
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 6. 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): NR (NR) years

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 6. 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): NR (NR) years

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 6. 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): 7.3 (range 0-34) years

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 6. 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 6. 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): NR (NR) years

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 6. 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 6. 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): NR (NR) years

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 7. Active control trials of pioglitazone (New for Update 1)

Author, year	Inclusion Criteria	Exclusion Criteria	Baseline Demographics	Baseline Characteristics	Other Medications at Baseline
Agarwal, 2005	Patients with type 2 diabetes requiring treatment with oral hypoglycemic drugs or insulin	Presence of liver disease, New York Heart Association (NYHA) class III or IV heart failure,	Mean age:65.55; Male: 100%; Female: 0%;	A1c:7.7; Weight: ; BMI: ; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin:63.3%
Basu, 2006	type 2 diabetes between the ages of30 and 75 years were enrolled (7 werepreviously treated with dietary and	Not reported but none had a history of edema, cardiac, hepatic, or renal problems	Mean age:57; Male: 63.16%; Female: 36.84%; White: %; Black:	A1c:6.7; Weight:89; BMI:31; Duration of diabetes:	Antihypertensives: % Lipid lowering: % Insulin: % Metformin:57%
Heliovaara, 2007	Type 2 diabetes treated with diet and one oral medicine or diet alone, age over 40 yr, glycosylated hemoglobin	systemic inflammation (e.g. a flu) or local inflammation requiring antibiotic treatment	Mean age:57.3; Male: 66.1%; Female: 33.9%; White: %; Black:	A1c:8.27; Weight: ; BMI: ; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin: % Metformin: % Sulfonylureas: %
Jain, 2006	Treatment-naïve men and nonpregnant,nonlactating women 18–80 years of age, from theUnited States or Puerto	Any patient whose treatment had previouslyfailed due to lack of efficacy or signs of intolerance,or who had recently	Mean age:52.1; Male: 54.58%; Female: 45.42%;	A1c:9.2; Weight:94.1; BMI:32.7; Duration of	Antihypertensives: % Lipid lowering: % Insulin:0% Metformin:0%

Evidence Table 7. Active control trials of pioglitazone (New for Update 1)

Author, year	Inclusion Criteria	Exclusion Criteria	Baseline Demographics	Baseline Characteristics	Other Medications at Baseline
Mazzone, 2006	men and women; ages of 45 and 85 years with type 2 DM who were newly diagnosed with type2 DM that was diet-controlled or treated with sulfonylurea or metformin monotherapy, sulfonylurea/ metformin combination therapy, orany of these plus insulin. Individuals taking medication for glycemia were included if they had HbA1c value of 6.5% or greater and less than 9%; those not taking medication for glycemia were included if they had HbA1c values of greater than 6.5% and less than 10%.	symptomatic coronary artery disease, cerebrovascular disease, or peripheral artery disease; functional NYHA class III or IV heart failure;left ventricular dysfunction measured as left ventricular ejection fraction < 40%; current use ofdiuretics or angiotensin-converting enzymeinhibitors for the treatment of heart failure; or significant cardiac valvular disease; treated with athiazolidinedione within 12 weeks ; did not respondto or were intolerant of sulfonylurea or thiazolidinedione treatment; required more than 2 oral agents for glycemic control; had unexplained microscopic hematuria, a triglycerides level > 500 mg/dL (5.7 mmol/L), elevated serum creatinine level, decreased hemoglobin level, an alanine transaminase level of 2.5 or more times the upper limit of normal; had active liver disease or jaundice; or weighed > 135 kg or had a BMI > 45.	Mean age:60; Male: 63.1%; Female: 36.9%; White:62%; Black:29	A1c:7.4; Weight: ; BMI:32; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin:13% Metformin:64% Sulfonylureas:49% Acarbose: % Oral
Perriello, 2006	Type 2 diabetes who were treated with diet or oneglucose-lowering drug and had HbA1c > 7.5%	NR	Mean age:58; Male: 65.37%; Female: 34.63%; White: %; Black:	A1c:8.8; Weight:80.8; BMI:29; Duration of diabetes:	Antihypertensives: % Lipid lowering: % Insulin: % Metformin: % Sulfonylureas: %
Pfutzner, Forst	type 2 diabetes but without prior thiazolidinedione treatment; age	type 1 diabetes, drug or alcohol addiction, pregnancy, breast-	Mean age:63; Male: 61.85%; Female:	A1c:7.48; Weight: ; BMI:31.7;	Antihypertensives: % Lipid lowering: %

Evidence Table 7. Active control trials of pioglitazone (New for Update 1)

Author, year	Inclusion Criteria	Exclusion Criteria	Baseline Demographics	Baseline Characteristics	Other Medications at Baseline
Sharma, 2006	Duration of diabetes = 6 m, apparently healthy and treatment naïve, diagnosis of T2DM based on ADA criteria,	Diabetes secondary to another cause, presence of ketonuria, severe concurrent infectious illness; impaired renal function	Mean age: ; Male: .%; Female: .%; White: %; Black:	A1c: ; Weight: ; BMI: ; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin: % Metformin: % Sulfonylureas: %
Teramoto, 2007	Japanese T2DM patients between 20-79y, received dietary and exercise instructions, without anti-diabetic	Patients taking any medication known to affect glucose metabolism; history of ketoacidosis, or with an unstable	Mean age: ; Male: .%; Female: .%; White: %; Black:	A1c: ; Weight: ; BMI: ; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin: % Metformin: % Sulfonylureas: %
Umpierrez, 2006	aged 18–79 years with type 2 diabetes for at least 6 months;	insulin, thiazolidinediones, or sulfonylurea within 3 months	Mean age:53.8; Male: 53.2%;	A1c:8.35; Weight: ; BMI:34.16;	Antihypertensives: % Lipid lowering: %
Yamanouchi, 2005	Short duration of Type 2 diabetes; no patient had ever received an oral hypoglycaemic agent or a lipid drug. All patients were treated with diet and exercise alone for at least 3 months	Unstable or rapidly progressive diabetic retinopathy,nephropathy, or neuropathy; liver dysfunction [aspartate aminotransferase (AST), alanineaminotransferase (ALT) > 1.5 × upper limit of	Mean age:55.2; Male: 58.77%; Female: 41.23%; White: %; Black:	A1c:10.6; Weight: ; BMI:25.9; Duration of diabetes: .	Antihypertensives:45.6 % Lipid lowering: % Insulin:0% Metformin:0% Sulfonylureas:0% Acarbose: % Oral

Evidence Table 7. Active control trials of pioglitazone (New for Update 1)

Author, year	Intervention	TotalDailyDose	Sample Size	Outcome Measure	Results
Agarwal, 2005	Glipizide	mean 16(8)	22	HbA1c at 16 weeks	change from baseline -0.4(1.8)
	Pioglitazone monotherapy	15-45 mg	44	HbA1c at 16 weeks	change -0.1(1.2), between group difference 0.3(95% CI, -0.67 -1.31) p=0.52
Basu, 2006	Glipizide monotherapy	10 mg (median dosage)	11	HbA1c at 12 weeks	6.9 (0.3) change +0.4
				Weight at 12 weeks	87.9 (5) change +0.5
	Pioglitazone monotherapy	45 mg	8	Weight at 12 weeks	95.2 (9) change 3.1
			19	HbA1c at 12 weeks	7.5 (0.8) change +0.4
Heliovaara, 2007	Glibenclamide	1.75-10.5 mg	20	BMI at 52 weeks	change from baseline+0.2 (SE NR)
			59	HbA1c at 52 weeks	change from baseline -0.6(SE NR)
	Pioglitazone	30-45 mg	29	BMI at 52 weeks	change from baseline 0.5(SE NR)
				HbA1c at 52 weeks	change from baseline -0.6(SE NR)
Jain, 2006	Glyburide	5-15 mg	251	Weight at 56 weeks	change from baseline 1.95
			502	HbA1c at 56 weeks	change from baseline -2.02
	Pioglitazone	15-45 mg	251	HbA1c at 56 weeks	change from baseline -2.07%
				Weight at 56 weeks	change from baseline 3.66

Evidence Table 7. Active control trials of pioglitazone (New for Update 1)

Author, year	Intervention	TotalDailyDose	Sample Size	Outcome Measure	Results
Mazzone, 2006	Control	1-4 mg	228	HbA1c at 72 weeks	Treatment-group difference (pioglitazone-glimepiride) at final visit, -0.32% (95% confidence interval, -0.52% to -0.12%; P=.002).
				Weight at 72 weeks	weight gain 1.0 kg
	Pioglitazone monotherapy	15-45 mg	230	HbA1c at 72 weeks	Treatment-group difference (pioglitazone-glimepiride) at final visit, -0.32% (95% confidence interval, -0.52% to -0.12%; P=.002).
			458	Weight at 72 weeks	weight gain 3.2 kg
Perriello, 2006	Gliclazide	184 mg (mean dose)	137	HbA1c at 1 years	change -0.79
	Pioglitazone monotherapy	40 mg (mean dose)	283	HbA1c at 1 years	change -0.79
Pfutzner, Forst	Glimepiride	2.7 mg (mean)	84	HbA1c at 26 weeks	change -0.6 (0.75), p<0.001
	Pioglitazone	45 mg	173	HbA1c at 26 weeks	change -0.78 (0.86), p<0.001

Evidence Table 7. Active control trials of pioglitazone (New for Update 1)

Author, year	Intervention	TotalDailyDose	Sample Size	Outcome Measure	Results
Sharma, 2006	Metformin	1291 mg(mean)	15	HbA1c at 12 weeks	final: 7.56(0.8), p=0.14 vs baseline, change from baseline -0.47
	Pioglitazone	21.9(mean)	35	HbA1c at 12 weeks	final: 7.30 (0.8), p=0.34 vs baseline, p=0.43 vs metformin, change from baseline: -0.42
Teramoto, 2007	Glibenclamide	1.25-2.5mg	46	HbA1c at	Change from baseline: -1.43(1.09) p<0.05 vs baseline
	Pioglitazone monotherapy	15-30mg	92	HbA1c at 24 weeks	Change from baseline: -0.80 (1.14)) , p<0.05 vs baseline and p>0.05 vs. glibenclamide
Umpierrez, 2006	Glimepiride	45 mg	203	HbA1c at 26 weeks	change -1.30 (0.077)
	Pioglitazone	2-8 mg	107	HbA1c at 26 weeks	change-1.23 (0.073)
Yamanouchi, 2005	Glimepiride	1-2 mg	37	BMI at 52 weeks	25.4 (4.0), p>0.05 from baseline
				HbA1c at 52 weeks	7.7 (0.9), p<0.005 from baseline
	Metformin	750 mg	39	BMI at 52 weeks	25.5 (4.2), p>0.05 from baseline
				HbA1c at 52 weeks	7.8(1.0), p<0.005 from baseline
	Pioglitazone	30-45 mg	38	BMI at 52 weeks	26.7 (3.9), p>0.05 from baseline
			114	HbA1c at 52 weeks	7.9 (1.0), p<0.005 from baseline, NSD among groups

Evidence Table 7. 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

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:** years **Ethnicity:** NR
Gender: 0% Female
Type 2 diabetes duration (SD):

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 7. 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: 0% Female
Type 2 diabetes duration (SD):

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 7. 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 7. 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
Intervention: Pio up to 45mg qd + metformin placebo qd; or Pio placebo + metformin 850 mg, both together up to tid
Patients started with Pio 15mg od or metformin 850 mg od, dose increased at weeks 4,8,12
After week 12, dosages remained unchanged
Treatment duration 12 months; mean duration 11 months both groups
104-week outcomes reported in Charbonnel 2005
Dosages increased until investigator felt that increase could cause hypoglycemia, if patient had symptomatic hypoglycemia, or if AE reported
Drugs permitted to be taken; ACE inhibitors, angiotensin II receptor antagonists, calcium antagonists, thiazid diuretics, antihypertensives
Attrition 18.5% in Pio group, 12.8% in metformin+Su group, =100 total. In addition, 11 patients were withdrawn as no post baseline data. 319+320 patients were analyzed, whch includes the 100 patients who dropped out
Primary efficacy endpoint: A1c from baseline to week 52
Secondary endpoints: changes in FPG, insulin, lipids, C-peptide, 32,33 split proinsulin, urinary albumen and creatinine
Efficacy analysis reported as "ITT": LOCF, all patients who had received 1+dose of study medication and A1c at baseline and at least 1 follow-up measure
Safety analysis: included all patients who had received 1+ dose of study medication

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)
Comments on DB
"other HYPERglycemic"
Intervention has population characteristics
Where put multiple countries?
Where indicate 1' vs 2' endpoints?
What does relevance yes/no mean?
Treatment and study duration

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): 7.1 (5.6) years

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: %		

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

Hanefeld, M 2004		Quality rating: Fair
	-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
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	

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

Hanefeld, M 2004		Quality rating: Fair
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 7. 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): 5.7 (NR) years

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 7. 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 7. 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): NR (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 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 7. 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 7. 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	Number Withdrawn/	Lost to follow-up/	Analyzed
	2145/	NR/	1199	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): 3.3 (NR) years

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 7. 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 7. 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): 6.7 (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	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 7. 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, 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: 0% Female

Type 2 diabetes duration (SD): 2.8 (NR) years

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 8. Active control trials of rosiglitazone (New for Update #1)

Author, Year	Inclusion Criteria	Exclusion Criteria	Baseline demographics	Baseline Characteristics	Other Medications at Baseline
Bakris, 2006	male and female; aged 40–80 years with T2DM]; MA, defined by urine albumin : creatinine ratio (UACR) > 30 and < 300 mg albumin/g creatinine, where patients had the average of two prebaseline UACR measurements (taken at prescreening and screening) in this range; previously treated with diet and exercise alone, a single oral antidiabeticagent, or combination oral antidiabetic therapy; capillary FPG levels > 6.6 mmol/l at visit 3; able to tolerate MET at a minimum dose of 1 g/day.	use of any TZD in the 3 months prior to screening; use of insulin for > 6 months; clinically significant hepatic disease; anemia; severe angina; systolic BP > 159 mmHg and/or diastolic BP > 99 mmHg (patients could receive antihypertensives to optimize BP, although these could not be adjusted or introduced after baseline); and body mass index (BMI) < 22 kg/m.	Mean age:60; Male: 68.45%; Female: 31.55%; White:77%; Black:	A1c:8.4; Weight:90; BMI:31.7; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin: % Metformin:100% Sulfonylureas: % Acarbose: % Oral h
DeRosa, 2006	type 2 diabetes mellitus for at least 6 months; fasting C-peptide level above 1.0 ng/ml; inadequateglycemic control (defined as hemoglobin A1c[A1C] > 7% and/or fasting plasma glucose [FPG]consistently > 120 mg/dl, and postprandialglucose [PPG] consistently > 160 mg/dl) with dietand oral hypoglycemic agents such assulfonylureas or metformin, both to theirmaximum tolerated dosage; and diagnosis ofmetabolic syndrome according to the National Cholesterol Educational Program panelclassification (Adult Treatment Panel III).	history of ketoacidosis or those with unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; impaired liver function, impaired kidney function, or anemia; unstable cardiovascular conditions (e.g., New York Heart Association class III or IV heart failure or a history ofmyocardial infarction or stroke) or cerebrovasculardisorders within 6 months of study enrollment;women who were pregnant, lactating, or of childbearing potential while not taking adequatecontraceptive	Mean age:53; Male: 50.53%; Female: 49.47%; White: %; Black:	A1c:8.0; Weight: ; BMI:26.7; Duration of diabetes: .	Antihypertensives:42% Lipid lowering: % Insulin: % Metformin: % Sulfonylureas:33.7 % Acarbose: % Oral

Evidence Table 8. Active control trials of rosiglitazone (New for Update #1)

Author, Year	Inclusion Criteria	Exclusion Criteria	Baseline demographics	Baseline Characteristics	Other Medications at Baseline
		precautions; and consumption ofglimepiride or thiazolidinediones, or previousintolerance to these drugs			
Garber, 2006	Age 20–78 years; established type 2 diabetesrequiring oral therapy; stable dosage of metformin at least1500 mg/day for at least 8 weeks, glycosylated haemoglobin (HbA1C) levels >7.0and <12.0% and body mass index >23 and <45 kg/m2; acceptable methods of birth control and to have negative pregnancy test resultswithin 72 h of study treatment.	marked polyuria and polydipsia with >10% weight loss, the use of any hypoglycaemic agent other than metformin within 8 weeks before screening, anaemia [haemoglobin level: <12.5 g/dl (men) and <11.0 g/dl (women)] and significantly abnormal renal, cardiac or hepatic dysfunction or disease; Pregnant or nursing women and patients with known sensitivity to any study medications	Mean age:56; Male: 60.38%; Female: 39.62%; White:80%; Black:5	A1c:8.5; Weight:93; BMI:32; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin: % Metformin:100% Sulfonylureas: % Acarbose: % Oral h
Goldstein, 2006	male and female subjects aged 18–75 years with T2DM, HbA1c of 6.5–8.5% for subjectshaving received prior combination treatment and7–10% for drug-naive or prior monotherapy subjects,FPG of 126–270 mg/dL (screening and randomization), and a body mass index (BMI) at least 27 kg/m2 at randomization.	uncontrolled hypertension,congestive heart failure requiring treatment, severeangina, clinically significant renal or hepatic disease, and active or chronic metabolic acidosis. suffered anemia or severe edema associated with thiazolidinedione therapy. Subjects non-compliant with metformin uptitration during the study run-in period; insulin in the 3-months prior to study entry.	Mean age:55.2; Male: 56.56%; Female: 43.44%; White:69.7%; Black:6.6	A1c: ; Weight: ; BMI:33.9; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin: % Metformin: % Sulfonylureas: % Acarbose: % Oral hyp
Hanefeld, 2007	aged 40 to 80 years with type 2 diabetes (fasting plasma glucose [FPG]= 7.0 to 15.0 mmol/l; C-peptide >/= 0.27 nmol/l;body mass	Insulin therapy or those with diabetic complications requiring treatment, heart failure NYHA III/IV, or serious renal, hepatic	Mean age:60; Male: 48.55%; Female: 51.45%; White:98.3%; Black:	A1c:8.2; Weight: ; BMI: ; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin:0% Metformin: %

Evidence Table 8. Active control trials of rosiglitazone (New for Update #1)

Author, Year	Inclusion Criteria	Exclusion Criteria	Baseline demographics	Baseline Characteristics	Other Medications at Baseline
	index [BMI] = 22 to 38 kg/m2)	(liver function tests > 2.5 times the upper limit of normal) or haematologic impairment and women of childbearing potential.			Sulfonylureas: % Acarbose: % Oral hyp
Kahn, 2006	ages of 30 and 75 years, with fasting plasma glucose levels ranging from 126 to 180 mg per deciliter (7.0 to 10.0 mmol per liter) while their only treatment was lifestyle management	clinically significant hepatic disease, renalimpairment, a history of lactic acidosis, unstableor severe angina, known congestive heart failure(CHF, New York Heart Association class I, II, III,or IV), or uncontrolled hypertension	Mean age:57; Male: 58%; Female: 42%; White:88.4%; Black:4.0	A1c:7.36; Weight:91.7; BMI:32.2; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin: % Metformin: % Sulfonylureas: % Acarbose: % Oral hyp
Kulenovic, 2006	patients with Type 2 diabetes who had not achieving sufficient control on diet	Liver diseases, other endocrine disorders, manifested renal complications and those treated for hypertension	Mean age:48.6; Male: .%; Female: .%; White: %; Black:	A1c:7.75; Weight: ; BMI:26.3; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin: % Metformin: % Sulfonylureas: % Acarbose: % Oral hyp
Raskin, 2004	(= 18 years of age, body mass index (BMI) = 45 kg/m2) who had Type 2 diabetes for at least 12 months, with HbA1c values > 7.0% and = 12%	treated within the previous 3 months with any of thefollowing agents: insulin, repaglinide, thiazolidinediones, a-glucosidase	Mean age:58; Male: 54.37%; Female: 45.63%; White: %; Black:	A1c:9.1; Weight: ; BMI:32; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin: % Metformin:40%

Evidence Table 8. Active control trials of rosiglitazone (New for Update #1)

Author, Year	Inclusion Criteria	Exclusion Criteria	Baseline demographics	Baseline Characteristics	Other Medications at Baseline
	during previous monotherapy with sulphonylurea ormetformin (at 50% or more of the maximal recommended dosages) for at least 3 months.	inhibitors, or combination therapy with antidiabetic medications.			Sulfonylureas:60% Acarbose: % Oral h
Stocker, 2007	21 and 80 years of age, with a glycosylated hemoglobin level above 7.0% during treatmentwith either diet modification or sulfonylurea monotherapy	known inflammatory diseases (includinginflammatory bowel disease, vasculitis, and rheumatologic disease), insulin use, corticosteroid use, an infection within 1 month of enrollment, glomerular filtration rate b60 mL/min, pregnancy, known history of myocardial infarction or congestive heart failure, secondary diabetes (including Cushing's syndrome and acromegaly), hypersensitivity to metformin or rosiglitazone, or a history of carotid endarterectomy	Mean age:65; Male: 61.96%; Female: 38.04%; White: %; Black:	A1c:8.48; Weight:84.5; BMI:29.58; Duration of diabetes: .	Antihypertensives: % Lipid lowering: % Insulin: % Metformin:0% Sulfonylureas:74% Acarbose: % Oral hy

Evidence Table 8. Active control trials of rosiglitazone (New for Update #1)

Author, Year	Intervention	Total Daily Dose	Sample Size	Outcome Measure	Results
Bakris, 2006	Glyburide	mean 13.7mg	180	HbA1c at 32 weeks	change -0.92 (SEM 0.08)
				Weight at 32 weeks	change 1.5 (SEM 3.53)
	Rosiglitazone combination therapy	mean dose 7.2 mg	194	Weight at 32 weeks	change 1.94 (4.63)
			374	HbA1c at 32 weeks	change - 0.72 (SE 0.10)
DeRosa, 2006	Glimepiride	2 mg	95	BMI at 12 months	25.2 (1.4), change from baseline -1.3, p<0.05
	Rosiglitazone	1500 mg	48	HbA1c at 12 months	6.8 (0.6), change from baseline -0.6, p<0.05

Evidence Table 8. Active control trials of rosiglitazone (New for Update #1)

Author, Year	Intervention	Total Daily Dose	Sample Size	Outcome Measure	Results
		4 mg	48	BMI at 12 months	24.5 (1.1), change from baseline -1.4, p<0.05
Garber, 2006	Glibenclamide	7.6 mg (mean)	160	HbA1c at 24 weeks	change -1.5%
	Rosiglitazone	7.1 mg (mean)	318	HbA1c at 24 weeks	change -1.1% (between group p<0.001)
Goldstein, 2006	No additional treatment	1500 -2000mg	51	HbA1c at 24 weeks	change from baseline -0.65 (95%CI 1.18)
	Rosiglitazone combination therapy	1000 mg	71	HbA1c at 24 weeks	change from baseline-0.61 (95 % CI 1.16)
		4 mg	122	HbA1c at 24 weeks	change from baseline-0.61 (95 % CI 1.16)
Hanefeld, 2007	Control	2.5-15 mg	203	HbA1c at 52 weeks	baseline 8.2% mean change -0.7%
				Weight at 52 weeks	weight gain 1.90

Evidence Table 8. Active control trials of rosiglitazone (New for Update #1)

Author, Year	Intervention	Total Daily Dose	Sample Size	Outcome Measure	Results
	Rosiglitazone monotherapy	4 mg	195	Weight at 52 weeks	weight gain 1.75
			587	HbA1c at 52 weeks	baseline 8.1% mean change -0.3%
		8 mg	189	HbA1c at 52 weeks	baseline 8.2%- 0.5% mean change
				Weight at 52 weeks	weight gain 2.95
Kahn, 2006	Glyburide	5-15 mg	1441	HbA1c at 4 years	< 7% 26%
				Weight at 5 years	change 1.6
	Metformin	500-2000 mg	1454	HbA1c at 4 years	< 7% 36%
				Weight at 5 years	-2.9
	Rosiglitazone monotherapy	4-8 mg	1456	Weight at 5 years	change 4.8
			4351	HbA1c at 4 years	< 7%40%
Kulenovic, 2006	Glibenclamide	3.5-10.5 mg	10	BMI at 12 weeks	27.1 (1.7)
				HbA1c at 12 weeks	6.5 (1.0)
	Rosiglitazone monotherapy	4-8 mg	10	BMI at 12 weeks	26.3 (1.7)
			20	HbA1c at 12 weeks	6.6 (0.8)
Raskin, 2004	Control	12	63	HbA1c at 24 weeks	mean change from baseline -0.17 SE 0.14
				Weight at 24 weeks	weight gain 1.6

Evidence Table 8. Active control trials of rosiglitazone (New for Update #1)

Author, Year	Intervention	Total Daily Dose	Sample Size	Outcome Measure	Results
	Rosiglitazone combination therapy	6.0/4.0	127	Weight at 24 we	weight gain 4.4
			252	HbA1c at 24 weeks	change from baseline -1.43 SE 0.10
	Rosiglitazone monotherapy	8	62	HbA1c at 24 weeks	mean change from baseline -0.56 SE 0.14
				Weight at 24 weeks	weight gain 2.3
Stocker, 2007	Metformin	1700 mg	47	HbA1c at 24 weeks	change-1.19 (0.13)
	Rosiglitazone	4 mg	92	HbA1c at 24 weeks	change -1.08 (0.14)p-value>0.05, between groups

Evidence Table 8. 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 8. 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

P value NR if not specified.

Evidence Table 8. 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 8. 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 8. 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 8. Efficacy - Selected active-controlled trials type 2 diabetes, rosiglitazone

Vongthavaravat V 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 8. Efficacy - Selected active-controlled trials type 2 diabetes, rosiglitazone

Vongthavaravat V 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 9. 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)		

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 9. 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 9. 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 9. 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	
LDL, change from baseline to 8 weeks: mg/dl (SD)		
	+20(NR)	-5.0(NR)
p vs placebo	0.025	

Evidence Table 9. Efficacy - Placebo-controlled trials in prediabetes or metabolic syndrome, rosiglitazone

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

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 10. 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: 0% 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 10. 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 10. 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: 0% 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 10. 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 11. 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 11. 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 11. 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 11. 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 12. Adverse events reported in placebo-controlled trials of pioglitazone (New for Update 1)

Author, year	Intervention	Dose	Sample Size	Type of Adverse Event	Adverse Event	% with AE	Comments
Mazzone, 2006	Control	1-4 mg	228	Cardiovascular	Myocardial Infarction	0.44	
					New onset heart failure	0	
					Stroke	0.44	
				Other	Death	0	
	Pioglitazone monotherapy	15-45 mg	230	Cardiovascular	Myocardial Infarction	0	
					New onset heart failure	0.43	
				Other	Death	0.43	
			458	Cardiovascular	Stroke	0	
Nishio, 2006	No treatment		28	Other	Restenosis	57.1	between goup p 0.005
			54	Other	Restenosis	57.1	between goup p 0.005
	Pioglitazone monotherapy	30	26	Other	Restenosis	7.7	
Sharma, 2006	Metformin	1291 mg(mean)	15	Gastrointestinal			most commonly reported in met group.
			15	Metabolic	Weight gain	20	median 1.5(1-6)kg
	Pioglitazone	21.9(mean)	15	Gastrointestinal	increased liver enzymes	6.67	mild increase<3 fold
				Metabolic	Hypoglycemia	20	Symptoms suggestive of hypoglycemia verbally communicated by 3 patients on follow-up visit. However none of these could be documented.
				Other	Edema	20	mild and lower limb edema
			35	Metabolic	Weight gain	53.33	median 4.25 (2-7)kg
Tseng, 2005	Pioglitazone+various SU	30 mg	23	Pulmonary	Cough	11.5	
			48	Pulmonary	Cough	11.5	
	Placebo+existing SU		25	Pulmonary	Cough	8%	

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.

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
Neoplasms: %		
	4	4
NSD		

Comments: P value NR if not specified.

Evidence Table 12. Adverse events efficacy trials, pioglitazone

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.
rates reported for Pio 15 mg and 30 mg groups combined

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.

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.

Evidence Table 12. Adverse events efficacy trials, pioglitazone

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.
placebo: severe angina, Pio: mild ECG abnormality

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.

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.

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.
Reasons for withdrawal in PIO and metformin: GI 1.5%, 2.5%; general disorders 1.5%, 0.3%; headache, dizziness 1.7%, 0.3%

Evidence Table 13. Adverse events reported in trials of rosiglitazone (New for Update 1)

Author, year	Intervention	Dose	Sample Size	Type of Adverse Event	Adverse Event	% with AE	Comments
Bakris, 2006	Glyburide	mean 13.7mg	180				
	Rosiglitazone combination therapy	mean dose 7.2 mg	194	Cardiovascular			
			374	Cardiovascular			
Dailey, 2004	Placebo		184	Metabolic	Hypoglycemia	24.46	
				Other	Edema	2.17	
	Rosiglitazone combination therapy	4-8 mg	181				
				Other	Edema	7.73	
			365	Metabolic	Hypoglycemia	52.49	
Dargie, 2007	Placebo		110	Other	Cardiovascular hospitalization	13.16	between group p=0.465
					Dyspnea	16.67	New or worsening dyspnea, between group p=0.197
					Edema	8.77	new or worsening edema, between group p=0.005
			218	Cardiovascular	Chronic heart failure	3.51	definite worsening of CHF, between group p=0.465
	Rosiglitazone monotherapy	4 mg	108	Cardiovascular	Chronic heart failure	19.09	definite worsening of CHF
				Other	Cardiovascular hospitalization	19.09	
					Dyspnea	26.36	new or worsening dyspnea
					Edema	25.45	new or worsening edema

Evidence Table 13. Adverse events reported in trials of rosiglitazone (New for Update 1)

Author, year	Intervention	Dose	Sample Size	Type of Adverse Event	Adverse Event	% with AE	Comments
Hanefeld, 2007	Control	2.5-15 mg	203	Metabolic	Hypoglycemia	12.08	
				Other	Edema	1.93	
	Rosiglitazone monotherapy	4 mg	195				
				Other	Edema	3.5	
			587	Metabolic	Hypoglycemia	0.5	
		8 mg	189	Metabolic	Hypoglycemia	1.57	
				Other	Edema	8.9	
Raskin, 2004	Control		63	Metabolic	Hypoglycemia	6.35	
					Weight gain	1.59	
				Other	Edema	0	
	Rosiglitazone combination therapy	6.0/4.0	127	Metabolic	Weight gain	6.3	
				Other	Edema	3.94	
			252	Metabolic	Hypoglycemia	8.66	
	Rosiglitazone monotherapy	8 mg	62				
				Metabolic	Hypoglycemia	1.61	
					Weight gain	1.61	
				Other	Edema	3.23	
Rosenstock, 2006	Placebo+Glipizide	10 mg	227	Other	Death	1.8	
			111	Cardiovascular	congestive heart failure	2.7	
				Metabolic	Hypoglycemia	27.03	symptomatic hypoglycemia
				Other			event rate per 1000 patient days ER visits 1.5, between group p<0.0001
					Edema	9.01	
					Hospitalization		event rate per 1000 patient days hospitalizations 0.75, between group p<0.05

Evidence Table 13. Adverse events reported in trials of rosiglitazone (New for Update 1)

Author, year	Intervention	Dose	Sample Size	Type of Adverse Event	Adverse Event	% with AE	Comments
	Rosiglitazone+Glipizide	10 mg	116	Cardiovascular	congestive heart failure	3.45	
				Other			Event rate per 1000 patient days ER visits 0.6
					Edema	23.28	
					Hospitalization		event rate per 1000 patient days hospitalizations 0.35
		4-8 mg	116	Metabolic	Hypoglycemia	31.9	symptomatic hypoglycemia

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Barnett, A 2003

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

Comments: 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	

Comments: 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		

Comments: 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

Comments: P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

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				

Comments: P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

Vongthavaravat V 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)

Comments: P value NR if not specified.

Evidence Table 13. Adverse events efficacy trials, rosiglitazone

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		

Comments: 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)

Comments: P value NR if not specified.

Evidence Table 14. 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
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.

Evidence Table 14. 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
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

Evidence Table 14. 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)
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)		

Evidence Table 14. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Liver Function	Hypoglycemia
Boyle P., 2002		
Delea T., 2003		
Gegick C., 2004	No patient had an ALT value >=3 times the ULN, none above the ULN.	

Evidence Table 14. 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
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
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")

Evidence Table 14. 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
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
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

Evidence Table 14. 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
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)	
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	

Evidence Table 14. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Liver Function	Hypoglycemia
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
King A, 2000		

Evidence Table 14. 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 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
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

Evidence Table 14. 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 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
Lebovitz H., 2002	Not reported	8 to 12 weeks	Data not reported: most participants were white, age <65, gender NR

Evidence Table 14. 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 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	
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			

Evidence Table 14. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Liver Function	Hypoglycemia
King K., 2004		
LaCivita K., 2002	No clinically significant changes in tests of liver function	
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	

Evidence Table 14. 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
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
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 14. 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
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
Tang W., 2003	NR	12 months	55 68% male Ethnicity NR

Evidence Table 14. 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
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)		
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 14. Adverse events in comparative observational studies of pioglitazone vs rosiglitazone

Author Year Quality score	Liver Function	Hypoglycemia
Olansky L., 2003		
Tang W., 2003		

Evidence Table 15. Quality assessment of comparative observational studies of adverse events (pio vs rosi)

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
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
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
King K., 2004	Retrospective cohort	Yes	Chart review, no details	Blinding not reported	No	Duration of followup not clear	Fair
LaCivita K., 2002	Retrospective cohort	Yes (weight), other AEs no	No	Methods not described	No	Yes (at least 2 months; mean 6 months)	Fair-Poor
Lebovitz H., 2002	Retrospective analysis of prospectively collected data from RCTs	Yes	Yes	Not clear if blinded	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
Tang W., 2003	Retrospective cohort	Yes	Yes	No- unblinded	No	Yes (12 months)	Fair

Evidence Table 16. Adverse events in comparative observational studies of TZDs vs other agents

Author, year (Quality rating)	Study design	Comparison	Study objective	Time period covered	Data source	Sample size
Hanefeld 2006 (POOR)	Prospective cohort	pioglitazone vs glibenclamide	To compare efficacy of add-on therapy with pioglitazone vs add-on therapy with glibenclamide	Not reported	75 primary care sites in Germany	**500** 250 pio, 250 glibenclamide
Hartung 2005	Case-control	TZDs vs SU vs metformin vs metformin + SU vs insulin vs insulin + TZD vs alpha-glucosidase inhibitor			Oregon Medicaid claims data	**1940**
Johannes 2007 (GOOD)	Retrospective cohort	TZDs vs metformin plus sulfonylurea	To evaluate whether the risk of coronary heart disease differs among adult diabetic patients treated with TZDs and similar patients treated with combined oral metformin and SU therapy	January 1, 1999 to June 30, 2002	US health care claims database, from 17 states	**25,140** 12,570 metformin + SU initiators, matched to 12,570 TZD initiators

Evidence Table 16. Adverse events in comparative observational studies of TZDs vs other agents

Author, year (Quality rating)	Population; baseline characteristics	Outcome measures	Statistical methods	Results
Hanefeld 2006 (POOR)	Patients with type 2 diabetes insufficiently controlled with metformin alone in primary care practices	Progression to insulin therapy	Log-rank test	Progression to insulin: Pio: 55/250 (22%) Glibenclamide: 138/250 (55%) p<0.001 Mean annual progression rates: Pio: 6.6% Glibenclamide: 16.4% p<0.001
Hartung 2005		Hospital admission for heart failure		Adjusted odds ratio (95% CI) TZDs: 1.37 (0.98, 1.92) SU: 0.95 (0.73, 1.24) Metformin: 0.97 (0.72, 1.30) Metformin + SU: 0.90 (0.60, 1.34) Insulin: 1.25 (0.92, 1.69) Insulin + TZDs: 1.35 (0.84, 2.18) Alpha-glucosidase inhibitor: 0.82 (0.28, 2.18)
Johannes 2007 (GOOD)		Incidence of acute MI, coronary revascularization, sudden death	Cox Proportional Hazards regression, adjusted for age at study drug initiation, gender, year of cohort entry, insulin use, any oral antidiabetic medication use, claims indicators of smoking, and claims evidence of MI, angina, atherosclerosis, CR, congestive heart failure, hypertension, hyperlipidemia, and obesity	Adjusted hazard ratio (95% CI) TZDs: 1.02 (0.87, 1.20) Metformin + SU (reference): 1.00

Evidence Table 16. Adverse events in comparative observational studies of TZDs vs other agents

Author, year (Quality rating)	Study design	Comparison	Study objective	Time period covered	Data source	Sample size
Kahler 2007 (FAIR)	Retrospective cohort	SU monotherapy vs metformin monotherapy vs metformin + SU vs TZD use vs no drugs	To evaluate the impact of several classes of oral antihyperglycemic therapy relative to SU monotherapy on all-cause mortality among a cohort of patietns with diabetes.	October 1, 1998 to September 30, 2000	Veterans Health Administration data from the Diabetes Epidemiology Cohort.	**39,721** 19,053 SU monotherapy, 2,988 metformin monotherapy, 13,820 metformin + SU, 673 TZD users (alone or in combination with other oral agents), 3,185 no drugs
Karter 2005 (FAIR)	Retrospective cohort	Pioglitazone vs SU vs metformin vs insulin	To determine if short-term use of pioglitazone is associated with increased risk of admission to hospital because of heart failure	October 1999 to November 2001	Kaiser Permanente Northern California Diabetes Registry	**23,440** 3556 pio, 5921 SU, 11,937 metformin, 2026 insulin
Koro 2007 (FAIR)	Nested case-control	TZDs vs other anti-diabetic agents	To evaluate the risk of breast, colon, and prostate cancers developing in patients exposed to TZDs compared with other anti-diabetic agents	January 1, 1997 to December 31, 2004	US Integrated Healthcare Information Services database	**126,971** 513 breast cancer cases, matched to 2557 controls 408 colon cancer cases, matched to 2027 controls 643 prostate cancer cases, matched to 3176 controls

Evidence Table 16. Adverse events in comparative observational studies of TZDs vs other agents

Author, year (Quality rating)	Population; baseline characteristics	Outcome measures	Statistical methods	Results
Kahler 2007 (FAIR)		All-cause mortality		Adjusted odds ratio (95% CI) SU (reference): 1.00 TZDs: 1.04 (0.75, 1.46) Metformin: 0.87 (0.68, 1.10) Metformin + SU: 0.92 (0.82, 1.05) No drugs: 0.90 (0.74, 1.09)
Karter 2005 (FAIR)		Hospital admission for heart failure		Adjusted hazard ratio (95% CI) Pioglitazone: 1.28 (0.85, 1.92) Insulin: 1.56 (1.00, 2.45) Metformin: 0.70 (0.49, 0.99) SU (reference): 1.00
Koro 2007 (FAIR)		Incidence of breast, colon, and prostate cancers	Conditional logistic regression. Adjusted odds ratio. Matching to control for age, sex,calendar time and years of recorded history in the database before the index date	Adjusted odds ratio (95% CI) TZD use (mono- or combination therapy) compared to other anti-diabetic agents Breast cancer: 0.89 (0.68, 1.15) Colon cancer: 1.03 (0.84, 1.32) Prostate cancer: 1.04 (0.83, 1.31)

Evidence Table 16. Adverse events in comparative observational studies of TZDs vs other agents

Author, year (Quality rating)	Study design	Comparison	Study objective	Time period covered	Data source	Sample size
Masoudi 2005 (GOOD)	Retrospective cohort	TZDs vs metformin vs no insulin sensitizer	To provide information about the balance of risks and benefits relevant to recommendations for use of TZDs and metformin	April 1998 to March 1999, and July 2000 to June 2001	Medicare	**16,417** 2,226 TZD, 1,861 metformin, 12,069 no insulin sensitizer
McAfee 2007 (GOOD)	Retrospective cohort	rosiglitazone vs metformin vs sulfonylurea	To compare risk of MI and coronary revascularization in type 2 diabetic patients treated with rosiglitazone, metformin, or sulfonylurea	July 1, 2000 through December 31, 2004	Health insurance claim data from a managed care organization (Ingenix Research Database)	**26,931** (8977 rosiglitazone, 8977 metformin, 8977 sulfonylurea)

Evidence Table 16. Adverse events in comparative observational studies of TZDs vs other agents

Author, year (Quality rating)	Population; baseline characteristics	Outcome measures	Statistical methods	Results
Masoudi 2005 (GOOD)	Older patients with diabetes and heart failure	Primary: time to death due to all causes	Adjusted for patient, provider, and hospital characteristics, sampling time frame, and differences in other medical treatment at discharge	Adjusted hazard ratio (95% CI) for all cause mortality: TZD use: 0.87 (0.80, 0.94) Metformin use: 0.86 (0.78, 0.97) SU use: 0.99 (0.91, 1.08) Insulin use: 0.96 (0.88, 1.05) TZD + Metformin: 0.76 (0.58, 0.99)
McAfee 2007 (GOOD)	Patients with type 2 diabetes	First occurrence of MI, coronary revascularization (CR), and composite of hospitalization for MI or CR	Kaplan Meier curves, Incidence rates and 95% CI. Adjusted for baseline covariates (age, sex, total cost, hyperlipidemia, and nitrate use)	Adjusted hazard ratio (95% CI) for composite outcome: rosglitazone monotherapy vs metformin monotherapy: 1.07 (0.85, 1.34) rosiglitazone monotherapy vs SU monotherapy: 0.82 (0.67, 1.02) rosiglitazone combined with insulin vs other oral antidiabetics combined with insulin: 0.88 (0.59, 1.32) Rosiglitazone therapy vs all other non-rosiglitazone therapies: 0.93 (0.80, 1.10) No increased risk of MI or coronary revascularization for rosiglitazone therapy vs other oral hypoglycemic therapies

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
Comparative observational studies							
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
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
King K., 2004	Retrospective cohort	Yes	Chart review, no details	Blinding not reported	No	Duration of followup not clear	Fair
LaCivita K., 2002	Retrospective cohort	Yes (weight), other AEs no	No	Methods not described	No	Yes (at least 2 months; mean 6 months)	Fair-Poor
Lebovitz H., 2002	Retrospective analysis of prospectively collected data from RCTs	Yes	Yes	Not clear if blinded	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

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
Tang W., 2003	Retrospective cohort	Yes	Yes	No- unblinded	No	Yes (12 months)	Fair
Safety-only studies, PIO							
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
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
Jung W., 2005	Prospective cohort with comparison	Yes (hypoglycemic episodes)	Yes	Blinding not reported	No	Yes for hypoglycemic episodes (72 hours)	Fair
King A., 2002	Retrospective cohort	Liver function only	Yes (for liver function)	No	No	Fair (2 months or longer)	Fair to Poor
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
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

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
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
Rajagopalan R., 2005	Before-after Japan Multicenter	Yes	Yes	Blinding not reported	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

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							
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 Germany	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
Safety-only trial			
Jun J., 2003	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.
Observational studies			
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.

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	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
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

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Study design Setting	Population Inclusion criteria	Exclusion criteria
King A., 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.
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.
Ono M., 2005	Prospective cohort with comparison Germany Single center	Patients with type 2 DM with A1c<=7%.	Not reported.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Study design Setting	Population Inclusion criteria	Exclusion criteria
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.
Rajagopalan R., 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.

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
Safety-only trial				
Jun J., 2003	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.
Observational studi				
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

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	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
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.

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
King A., 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.
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.
Ono M., 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.

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
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.
Rajagopalan R., 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)

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
Safety-only trial	
Jun J., 2003	No patients developed hepatic dysfunction after treatment with pioglitazone. Edema was noted in 3 patients who received pioglitazone (mild, and treatment could be continued).
Observational studi	
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.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Adverse events
Jung W., 2005	8 patients (5.6%) withdrew secondary to significant peripheral edema; 1 patient had exacerbation of congestive heart failure, 1 reported myalgias.
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.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Adverse events
King A., 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.
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).
Ono M., 2005	ALT levels significantly decreased during treatment.

Evidence Table 18. Adverse events in observational studies and excluded trials, PIO

Author Year Quality score	Adverse events
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)
Rajagopalan R., 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)

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 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
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

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
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

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
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
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