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Pioglitazone for type 2 diabetes mellitus (Review)

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[Intervention Review]

Pioglitazone for type 2 diabetes mellitus

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ABSTRACT

Background

Diabetes has long been recognised as a strong, independent risk factor for cardiovascular disease, a problem which accounts for approximately 70% of all mortality in people with diabetes. Prospective studies show that compared to their non-diabetic counterparts, the relative risk of cardiovascular mortality for men with diabetes is two to three and for women with diabetes is three to four. The two biggest trials in type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) and the University Group Diabetes Program (UGDP) study did not reveal a reduction of cardiovascular endpoints through improved metabolic control. Theoretical benefits of the newer peroxisome proliferator activated receptor gamma (PPAR-gamma) activators like pioglitazone on endothelial function and cardiovascular risk factors might result in fewer macrovascular disease events in people with type 2 diabetes mellitus.

Objectives

To assess the effects of pioglitazone in the treatment of type 2 diabetes.

Search methods

Studies were obtained from computerised searches of MEDLINE, EMBASE and *The Cochrane Library*.

Selection criteria

Studies were included if they were randomised controlled trials in adult people with type 2 diabetes mellitus and had a trial duration of at least 24 weeks.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. Pooling of studies by means of random-effects meta-analysis could be performed for adverse events only.

Main results

Twenty-two trials which randomised approximately 6200 people to pioglitazone treatment were identified. Longest duration of therapy was 34.5 months. Published studies of at least 24 weeks pioglitazone treatment in people with type 2 diabetes mellitus did not provide convincing evidence that patient-oriented outcomes like mortality, morbidity, adverse effects, costs and health-related quality of life are positively influenced by this compound. Metabolic control measured by glycosylated haemoglobin A1c (HbA1c) as a surrogate endpoint did not demonstrate clinically relevant differences to other oral antidiabetic drugs. Occurrence of oedema was significantly raised. The results of the single trial with relevant clinical endpoints (Prospective Pioglitazone Clinical Trial In Macrovascular Events - PROactive study) have to be regarded as hypothesis-generating and need confirmation.

Authors' conclusions

Until new evidence becomes available, the benefit-risk ratio of pioglitazone remains unclear. Different therapeutic indications for pioglitazone of the two big U.S. and European drug agencies should be clarified to reduce uncertainties amongst patients and physicians.

PLAIN LANGUAGE SUMMARY

Pioglitazone for type 2 diabetes mellitus

Diseases of the heart and blood vessels account for approximately 70% of all mortality in people with diabetes. Compared to their non-diabetic counterparts the relative risk of mortality caused by disorders of the heart and blood vessels is two to three for men and three to four for women with diabetes. Type 2 diabetes is mainly characterised by a reduced ability of the hormone insulin to stimulate glucose uptake in body fat and muscles (insulin resistance) and affects most people suffering from diabetes. Several medications are on the market to treat diabetes, amongst them pioglitazone as a member of the 'glitazones' reduced risk factors for diseases of the heart and blood vessels. Since the two biggest trials in people with type 2 diabetes showed that improved blood glucose alone is not enough to reduce the risk of the above mentioned diseases we looked for longer-term studies investigating 24 weeks as a minimum of pioglitazone treatment on patient-oriented outcomes. As patient-oriented outcomes we defined mortality, complications of diabetes, side effects of the medication, health-related quality of life, costs and metabolic control (lowering of blood glucose to near normal levels).

Twenty-two trials randomised approximately 6200 people to pioglitazone treatment. The longest duration of pioglitazone therapy was 34.5 months. Unfortunately, the published studies of at least 24 weeks pioglitazone treatment in people with type 2 diabetes mellitus did not provide convincing evidence that patient-oriented outcomes are positively influenced by this compound. The occurrence of oedema was significantly raised. The results of the single trial with relevant endpoints (Prospective Pioglitazone Clinical Trial In Macrovascular Events - PROactive study) have to be confirmed by other independent investigations. Until new evidence becomes available (several large trials are ongoing) the place of pioglitazone in the treatment of type 2 diabetes mellitus remains unclear.

Furthermore, confusion arises due to different labelling of pioglitazone, for example in Europe and the USA. Consumers and physicians need clear guidance and transparent information about which studies exactly are used for the decisions of the relevant drug authorities.

BACKGROUND

Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease is increased. For a detailed overview of diabetes mellitus, please see under 'Additional information' in the information on the Metabolic and Endocrine Disorders Group in *The Cochrane Library* (see 'About', 'Cochrane Review Groups (CRGs)'). For an explanation of methodological terms, see the main glossary in *The Cochrane Library*.

There are two main types of diabetes mellitus, type 1 (formerly termed insulin-dependent diabetes mellitus) and type 2 (formerly termed non-insulin dependent diabetes mellitus):

Type 1 diabetes mellitus

Type 1 diabetes is a chronic disease characterised by hyperglycaemia due to absolute deficiency of insulin secretion which is caused by autoimmune destruction of the pancreatic β-cells. Evidence of autoimmunity is provided by the appearance of autoantibodies prior to the onset of clinical disease. The clinical presentation ranges from mild nonspecific symptoms or no symptoms to coma. Although type 1 diabetes usually develops before 30 years of age, it can occur at any age. At presentation, most patients are thin and have experienced weight loss, polyuria, polydipsia, fatigue, and diabetic ketoacidosis.

Type 2 diabetes mellitus

In type 2 diabetes mellitus, the actions and secretion of insulin are impaired, as opposed to the absolute deficiency of insulin that occurs with type 1 diabetes mellitus. Type 2 diabetes is characterised by two major pathophysiologic defects: (1) insulin resistance, which results in increased hepatic glucose production and decreased peripheral glucose disposal, (2) impaired β-cell secretory function (Kahn 1997). Insulin resistance is an impaired biological response to the effects of exogenous or endogenous insulin. Insulin resistance in the hepatic and peripheral tissues, particularly skeletal muscle, leads to unrestrained hepatic glucose production and diminished insulin-stimulated peripheral glucose uptake and utilization (DeFronzo 1992). Insulin secretion by the pancreatic β-cell is initially sufficient to compensate for insulin resistance, thereby maintaining normal blood glucose levels. Hyperinsulinaemia, which accompanies insulin resistance, can maintain sufficiently normal glucose metabolism as long as pancreatic β-cell function remains normal. However, in patients who may develop type 2 diabetes, insulin secretion eventually fails, leading to hyperglycaemia and clinical diabetes (Warram 1990). Individuals with type 2 diabetes may have few or no classic clinical symptoms (see above) of hyperglycaemia (Ruige 1997). The difficulty in maintaining metabolic control, for example measured by the level of glycosylated haemoglobin A_{1c} (HbA_{1c}) over time may be related to several behavioural factors (for example difficulties with healthy eating, exercise, medication regimens) but primarily reflects the underlying progressive decline in β-cell function (UKPDS-16 1995).

Type 2 diabetes has traditionally been treated in a stepwise manner, starting with lifestyle modifications (Armour 2004; Gimenez-Perez 2001; Moore 2005), exercise (Thomas 2001) and later on pharmacotherapy with oral agents. Several classes of oral agents are available for clinical use. These mainly include insulin secretagogues, drugs that delay the absorption of carbohydrates from the gastrointestinal tract, and insulin sensitisers. Over time, many patients with type 2 diabetes will require insulin therapy (Burt 2005; Misso 2005; Richter 2005; Roberts 2005; Royle 2003; Siebenhofer 2004).

Insulin secretagogues: Currently, the sulphonylureas used are mainly glibenclamide (glyburide), glipizide, chlorpropamide, tolbutamide, and glimepiride. These drugs stimulate pancreatic β-cell insulin secretion by binding to a sulphonylurea receptor (Lindberg 2002). The short-acting non-sulphonylurea insulin secretagogues are repaglinide and nateglinide (Black 2003). These are newer agents that also stimulate insulin secretion by binding to the sulphonylurea receptor.

Alpha-glucosidase inhibitors: Acarbose and miglitol are α-glucosidase inhibitors. These drugs slow the absorption of carbohydrates, reducing especially postprandial elevations in plasma glucose levels. They do not significantly lower fasting plasma glucose levels but cause a modest reduction in HbA_{1c} (Van de Laar 2005).

Insulin sensitisers: Metformin belongs to the biguanides class (Saenz 2005; Salpeter 2003). It might increase insulin sensitivity in the liver by inhibiting hepatic gluconeogenesis and thereby reducing hepatic glucose production. Metformin also seems to increase peripheral insulin sensitivity by enhancing glucose uptake in the muscle. These substances consist of rosiglitazone and pioglitazone. The thiazolidinediones decrease insulin resistance in muscle and adipose tissue by activating the peroxisome proliferator activated receptor γ (PPAR-γ) which increases production of proteins involved in glucose uptake. They also decrease hepatic glucose production by improving hepatic insulin sensitivity (Meriden 2004).

Description of the intervention

Type 2 diabetes mellitus can be treated by non-pharmacological (diet, exercise) and pharmacological means. Insulin, as the natural hormone of the body, might be given as animal (mainly pork or beef) insulin (Richter 2005), genetically constructed 'human' insulin or as insulin-'analogues' with a modified molecular structure compared to human insulin (Roberts 2005; Siebenhofer 2004). Insulin is currently administered by diabetic people in various ways: Subcutaneous injections, insulin pumps (Misso 2005) and maybe in future by inhalation (Burt 2005; Royle 2003). Oral antidiabetic agents are most often used to treat type 2 diabetes mellitus in its initial stages if lifestyle modifications have failed. The thiazolidinediones rosiglitazone and pioglitazone offer new oral treatment options and affect many tissues and parts of the body. In order to evaluate their effects not only on metabolic control in type 2 diabetes mellitus but also on patient-oriented outcomes like cardiovascular disease, longer-term studies of at least 24 weeks continuous intake will be critically appraised in this review.

Adverse effects of the intervention

An increase in bodyweight has been associated with pioglitazone. Oedema, anaemia and congestive heart failure have been reported in patients receiving pioglitazone. There are conflicting reports about liver function abnormalities associated with pioglitazone

use (Farley-Hills 2004; Hisamochi 2003; May 2002; Pinto 2002; Rajagopalan 2005a).

How the intervention might work

Because traditional agents have a limited impact on insulin resistance and β-cell function, thiazolidinediones may be an appropriate choice especially for combination therapy in patients achieving poor glycaemic control with initial monotherapy. By improving insulin sensitivity, thiazolidinediones may exert beneficial effects on cardiovascular risk factors. The excess cardiovascular risk in type 2 diabetes cannot be attributed to classic risk factors alone (mainly hypertension, hypercholesterolaemia and smoking), but if present, these risk factors are at least as important as in patients without diabetes (Stamler 1993). One explanation for the beneficial effects of thiazolidinediones is their unique mechanism of action as selective and potent inhibitors of PPAR-γ. PPAR-γ receptors are present in adipose, hepatic and skeletal muscle tissue and control insulin-responsive genes, which have a wide-ranging influence. Thiazolidinediones appear to improve markers of inflammation and fibrinolysis, exert beneficial effects on vascular reactivity, improve the lipid profile and fat distribution, and decrease pancreatic β-cell injury.

Pioglitazone is a member of the thiazolidinedione group which also encompasses troglitazone (withdrawn due to hepatic toxicity) and rosiglitazone. It increases the sensitivity of skeletal muscle, liver and adipose tissue to insulin without directly stimulating insulin secretion from pancreatic ß-cells. Differences in the side chain on the main thiazolidine-structure in comparison to rosiglitazone are thought to be responsible for the distinct bioavailability, metabolism and antihyperglycaemic potency of pioglitazone. Pioglitazone has several pharmacodynamic properties which could ameliorate the increased risk of cardiovascular disease in type 2 diabetes mellitus. In clinical studies in patients with type 2 diabetes mellitus, pioglitazone has been associated with reductions in the levels of triglycerides and increases in the levels of high density lipoprotein-cholesterol (HDL-C). Some surrogate parameters indicating especially cardiovascular risk were reported to be positively influenced by pioglitazone therapy.

Why it is important to do this review

Diabetes has long been recognised as a strong, independent risk factor for cardiovascular disease, a problem which accounts for approximately 70% of all mortality in people with diabetes (Laakso 1999). Prospective studies show that compared to their non-diabetic counterparts, the relative risk of cardiovascular mortality for men with diabetes is two to three and for women with diabetes is three to four (Manson 1991; Stamler 1993). The increased cardiovascular risk associated with diabetes is reflected in the observation that middle-aged individuals with diabetes have mortality and morbidity risks that are similar to non-diabetic individuals who have already suffered a cardiovascular event (Haffner 1998).

Both epidemiological and prospective data have demonstrated that treatment of hyperglycaemia in type 2 diabetes mellitus is effective in reducing the risk of microvascular disease (for example diabetic retinopathy) but is less potent in reducing that of myocardial infarction, stroke and peripheral vascular disease. Treatment of other cardiovascular risk factors, although by definition less prevalent than hyperglycaemia, appears to be more effective in preventing macrovascular disease than treatment of hyperglycaemia. The University Group Diabetes Program (UGDP) study was the first published long-term investigation of people with type 2 diabetes indicating no reduction of cardiovascular endpoints through improved metabolic control but raised cardiovascular mortality after tolbutamide treatment (UGDP 1982). The study of Ohkubo et al. which included relatively lean Japanese patients with type 2 diabetes, was the first to demonstrate prevention of microvascular complications by intensive glucose control in patients with type 2 diabetes (Ohkubo 1995). This study did not address the question of whether good glycaemic control retards the progression of macrovascular disease. The United Kingdom Prospective Diabetes Study (UKPDS) tested mainly whether intensive glucose control with either a sulphonylurea or insulin influences the risk of micro- and macrovascular complications compared with conventional treatment (UKPDS-33 1998). The 10-year results of the UKPDS evaluated drug treatment in non obese and obese participants with newly diagnosed type 2 diabetes who were referred to hospital clinics. Over 10 years, HbA_{1c} was 7.0% in the intensive group compared with 7.9% in the conventional group. The 0.9% difference in HbA_{1c} between the intensive and conventional groups over 10 years was smaller than the 1.9% difference (9.0% and 7.1%) in HbA_{1c} in the Diabetes Control and Complications Trial (DCCT). The DCCT studied younger patients with type 1 diabetes and assessed the effects of intensive versus conventional insulin therapy on the incidence of microvascular complications of diabetes (retinopathy, nephropathy, neuropathy) over a mean follow-up of 6.5 years (DCCT 1993). The risk of retinopathy, for example, was statistically significant reduced by intensive insulin therapy with a number needed to treat (NNT) to benefit of six (six type 1 diabetic patients need to be treated by intensive in comparison to conventional insulin therapy over 6.5 years to avoid one additional patient to develop diabetic retinopathy). The UKPDS had a factorial design meaning that another study investigating intensive versus regular blood pressure control (HDS 1993; UKPDS-38 1998) was imbedded in the main study. Intensive versus conventional glucose control did not result in a statistically significant difference in diabetes related mortality or macrovascular disease endpoints but reduced the relative risk in the 'any diabetes related aggregate endpoint' (Freemantle 2003). Most of this benefit was due to a reduction in microvascular endpoints including the incidence of retinal photocoagulation, which was assessed by ophthalmologists independent of the study. In the UKPDS, the NNT to prevent one patient developing any of the single endpoints over 10 years was 20 (95% confidence interval (CI) 10 to 500) (UKPDS-33 1998). In contrast to these results, the publication of the UKPDS-34, which focused on obese patients with newly diagnosed type 2 diabetes, described several clinically important differences in macrovascular disease endpoints with 10 years of treatment with metformin (UKPDS-34 1998). In particular, the absolute risk reduction for the aggregate endpoints was more than 10% and for overall mortality was 7%, giving NNTs of 10 and 14, respectively, over 10 years (McCormack 2000).

The UKPDS was criticised on several grounds especially emphasising hidden biases in interpreting the results of this randomised controlled trial (Ewart 2001; McCormack 2000; Nathan 1998). Stratton et al. in their UKPDS-35 publication are often cited, who tried to determine the relation between exposure to glycaemia over time and the risk of macrovascular or microvascular complications in the UKPDS patients (Stratton 2000). This publication is an epidemiological re-interpretation of UKPDS data proclaiming that with each 1% reduction in mean HbA_{1c}, relative reductions in risk of 21% for deaths related to diabetes

and 14% for myocardial infarction could be observed. The RCT itself, though, did not show significant differences in this respect. Moreover, the UKPDS-38, investigating tight versus less tight blood pressure control with the use of an angiotensin converting enzyme inhibitor captopril or a β-blocker atenolol as main treatment, showed relative risk reductions (in the group assigned to tight control compared with that assigned to less tight control) of 24% in diabetes related endpoints, 32% in deaths related to diabetes, 44% in strokes and 37% in microvascular endpoints (UKPDS-38 1998). Due to the factorial design of the UKPDS with two interventions (improvement in metabolic and blood pressure control) aiming at the same outcomes, a fair interpretation of the data needs investigation of the interaction between the two main treatment strategies (McAlister 2003; Montgomery 2003). UKPDS data should be available to the scientific public to evaluate, among other things, the importance of the individual contribution of improved glucose versus blood pressure control in type 2 diabetes mellitus. Unfortunately, until now this has not happened.

Therefore, any new compound in the treatment of type 2 diabetes mellitus, like pioglitazone, should not only be evaluated with regards to surrogate outcomes (for example reductions in fasting plasma glucose or HbA_{1c}) but information is urgently needed about the influence of any antidiabetic agent especially on cardiovascular endpoints, which is the greatest problem in the therapy of type 2 diabetes mellitus. Short-term studies do not provide these facts, consequently we will search for longer-term investigations of at least 24 weeks pioglitazone therapy. Quite a number of health technology assessment reports, (narrative) reviews, systematic reviews and meta-analyses evaluated interventions with pioglitazone in diabetes (Baba 2001; Bloomgarden 2005; Boucher 2002; Boucher 2003; Campbell 2004; Chilcott 2001a; Chilcott 2001b; Chiquette 2004; Czoski-Murray 2004; Gillies 2000; Hanefeld 2001; Natali 2006; NICE 2001; NICE 2003a; NICE 2003b; Qayyum 2006; Waugh 2006). All of them either suffer from methodological problems like inadequate quality assessment of primary studies, focus on surrogate outcomes or are out-of-date. This systematic review tries to collate all available data from RCTs of pioglitazone treatment and evaluates how many studies investigated patient-oriented outcomes like mortality, cardiovascular endpoints, adverse events and health-related quality of life.

OBJECTIVES

To assess the effects of pioglitazone in the treatment of type 2 diabetes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Adult persons (18 years or older) with type 2 diabetes mellitus. To be consistent with changes in classification and diagnostic criteria of type 2 diabetes mellitus through the years, the diagnosis should have been established using the standard criteria valid at the time of the beginning of the trial (ADA 1997; ADA 1999; WHO 1980; WHO 1985; WHO 1998). Ideally, diagnostic criteria should have been described. If necessary, authors' definition of type 2 diabetes mellitus were used.

Types of interventions

Therapy with pioglitazone for a minimum of 24 weeks. The following comparisons were acceptable for evaluation:

- pioglitazone versus placebo;
- pioglitazone versus any other oral antidiabetic medication (for example rosiglitazone, metformin, sulphonylurea compounds like glibenclamide, acarbose);
- pioglitazone in combination with any other oral antidiabetic medication or insulin versus any other combination of oral antidiabetic medication or insulin (insulin agents and treatment schemes had to be identical).

Types of outcome measures

Primary outcomes

- mortality (all-cause mortality; diabetes related mortality (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyper- or hypoglycaemia or sudden death));
- morbidity (all-cause morbidity as well as diabetes and cardiovascular related morbidity, for example angina pectoris, myocardial infarction, stroke, peripheral vascular disease, neuropathy, retinopathy, nephropathy, erectile dysfunction, amputation);
- adverse events (for example hypoglycaemia, congestive heart failure, oedema).

Secondary outcomes

- health-related quality of life (using a validated instrument);
- costs;
- metabolic control as measured by glycosylated haemoglobin A_{1c} (HbA_{1c}).

Covariates, effect modifiers and confounders

- compliance;
- co-morbidities (for example myocardial infarction, stroke);
- co-medication (for example antihypertensive drugs, aspirin);
- age.

Timing of outcome measurement

Outcomes were assessed in the medium (24 weeks to 12 months of treatment) and long term (more than 12 months of treatment).

Search methods for identification of studies

Electronic searches

We used the following sources for the identification of trials:

- *The Cochrane Library* (issue 3, 2006);
- MEDLINE - OVID interface (until August 2006);
- EMBASE - OVID interface (until August 2006).

We also searched databases of ongoing trials: Current Controlled Trials (www.controlled-trials.com - with links to other databases of ongoing trials).

The described search strategy (see Appendix 1 for a detailed search strategy) was used for MEDLINE. For use with EMBASE and *The Cochrane Library* this strategy was slightly adapted.

Additional key words of relevance were not identified during any of the electronic or other searches. If this had been the case, electronic search strategies would have been modified to incorporate these terms. Studies published in any language were included.

Searching other resources

We tried to identify additional studies by searching the reference lists of included trials and (systematic) reviews, meta-analyses and health technology assessment reports identified.

Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two authors (BR in combination with all the other authors) independently scanned the abstract or titles, or both sections of every record retrieved. All potentially relevant articles were investigated as full text. Interrater agreement for study selection was measured using the kappa statistic (Cohen 1960). Where differences in opinion existed, they were resolved by a third party (other authors). If resolving disagreement was not possible, the article would have been added to those 'awaiting assessment' and authors would have been contacted for clarification. An adapted QUOROM (quality of reporting of meta-analyses) flow-chart of study selection was attached (Moher 1999).

Dealing with duplicate publications

In the case of duplicate publications and companion papers of a primary study, we tried to maximise yield of information by simultaneous evaluation of all available data. In cases of doubt, the original publication (usually the oldest version) obtained priority.

Data extraction and management

For studies that fulfilled inclusion criteria, two authors (BR in combination with all the other authors) independently abstracted relevant population and intervention characteristics using standard data extraction templates (for details see Characteristics of included studies and Appendix 2 to Appendix 18) with any disagreements to be resolved by discussion, or if required by a third reviewer. The data extraction form was pilot tested prior to use and modified. Any relevant missing information on the trial would have been sought from the original author(s) of the article, if required.

Assessment of risk of bias in included studies

Two authors (BR in combination with all the other authors) assessed each trial independently. Possible disagreement was resolved by consensus, or with consultation of a third reviewer in case of disagreement. We planned to explore the influence of individual quality criteria in a sensitivity analysis (see under 'sensitivity analyses'). Interrater agreement for key quality indicators was planned to be calculated using the kappa statistic (Cohen 1960). In cases of disagreement, the rest of the group was consulted and a judgement was made based on consensus.

Measures of treatment effect

Dichotomous data

Dichotomous outcomes (for example stroke yes/no) were planned to be expressed as odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CI).

Continuous data

Continuous outcomes (for example metabolic control as measured by glycosylated haemoglobin A_{1c} (HbA_{1c}) were planned to be expressed, if possible, as mean differences with 95% CI.

Time-to-event data

Time-to-event outcomes (for example time until death) were planned to be expressed as hazard ratios (HR) with 95% CI.

Unit of analysis issues

Different units of analysis (for example OR and RR) were planned to be subjected to a sensitivity analysis.

Dealing with missing data

Relevant missing data were obtained from authors. Evaluation of important numerical data such as screened, eligible and randomised patients as well as intention-to-treat and per-protocol population was carefully performed. Drop-outs, misses to follow-up and withdrawn study participants were investigated. Issues of last-observation-carried-forward (LOCF) were critically appraised and compared to specification of primary outcome parameters and power calculation.

Assessment of heterogeneity

In the event of substantial clinical or methodological or statistical heterogeneity, study results were not planned to be combined in a meta-analysis. Heterogeneity was identified by visual inspection of the forest plots, by using a standard χ^2-test and a significance level of $\alpha = 0.1$, in view of the low power of such tests. Quantification of heterogeneity was also examined with I^2, ranging from 0-100% including its 95% confidence interval (Higgins 2002). I^2 demonstrates the percentage of total variation across studies due to heterogeneity and was used to judge the consistency of evidence. I^2 values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003). When heterogeneity was found, we attempted to determine potential reasons for it by examining individual study characteristics and those of subgroups of the main body of evidence.

Assessment of reporting biases

Funnel plots were planned to be used in exploratory data analyses to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to study size, poor methodological design of small studies (Sterne 2001) and publication bias. Thus, this exploratory data tool may be misleading (Tang 2000; Thornton 2000) and we did not place undue emphasis on this tool.

Data synthesis

Data were planned to be summarised statistically if they were available, sufficiently similar and of sufficient quality. Statistical

analysis was planned to be performed according to the statistical guidelines referenced in the newest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2005). Pooled results were planned to be analysed using primarily a random-effects model. Meta-regression was planned to be performed using Stata/SE (version 8, Stata Corporation, Texas U.S.A.) to determine whether various study-level characteristics (for example follow-up interval, duration of the intervention, total attrition, year of publication) affected the between-group change in primary outcomes. We planned to examine interaction terms for all models.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to be only performed if one of the primary outcome parameters demonstrated statistically significant differences between treatment groups. The following subgroup analyses were planned:

- gender (female/male);
- age (depending on data but especially older versus younger patients);
- patients with or without co-morbidities (for example heart attack, stroke, peripheral vascular disease);
- patients with or without co-medication (for example antihypertensive drugs, aspirin).

Subgroup analyses were planned to be mainly used to explore clinical or methodological or statistical heterogeneity.

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- repeating the analysis excluding unpublished studies;
- repeating the analysis taking account of study quality, as specified above;
- repeating the analysis excluding any very long or large studies to establish how much they dominate the results;
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

The robustness of the results was also planned be tested by repeating the analysis using different measures of effects size (risk difference, odds ratio etc.) and different statistical models (fixed and random effects models).

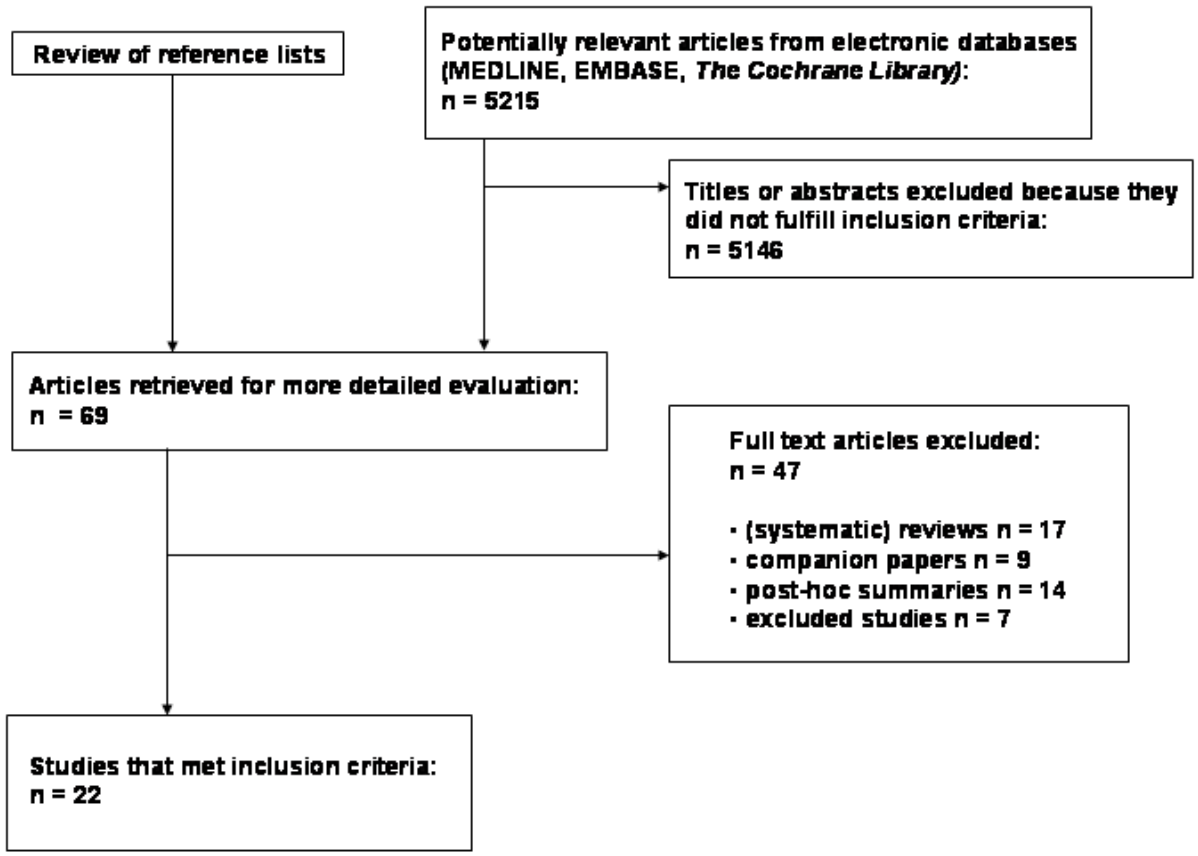
RESULTS

Description of studies

Results of the search

The initial search identified 5215 records, from these, 69 full papers were identified for further examination. The other studies were excluded on the basis of their abstracts because they were not relevant to the question under study (see Figure 1 for details of the amended QUOROM (quality of reporting of meta-analyses) statement). After screening the full text of the selected papers, 22 studies finally met the inclusion criteria.

Figure 1. QUOROM (quality of reporting of meta-analyses) flow-chart of study selection



Most studies of at least 24 weeks pioglitazone treatment were published in the years 2004 and 2005 (eight trials), with the first trial being published in 2000.

Assessment of publication bias inter-rater agreement

Inter-rater agreement for study selection, that is qualifying a study as 'included' or 'potentially' relevant was 100%.

Missing data

We contacted one author (Dormandy 2005) for clarification of the validity of a composite secondary endpoint and received valuable additional information (see discussion).

Included studies

Interventions

Comparisons

Sixteen of the 22 included publications investigated pioglitazone monotherapy versus another monotherapy, six publications evaluated the combination of pioglitazone with another glucose-lowering intervention versus a comparable combination.

Monotherapy

Four studies compared pioglitazone to placebo (study four, see below)

- pioglitazone (7.5 mg/day; 15 mg/day; 30 mg/day; 45 mg/day) versus placebo;
- pioglitazone (30 mg/day) versus placebo;
- pioglitazone (30 mg/day; 45 mg/day) versus placebo.

The majority of trials (nine) investigated the comparison of pioglitazone to insulin secretagogues (studies eight and nine, see below).

- pioglitazone (30 mg/day) vs glibenclamide (2.5 mg/day) vs placebo;
- pioglitazone (30-45 mg/day) vs glibenclamide (1.75-10.5 mg/day);
- pioglitazone (mean 17 mg/day) vs glibenclamide (1.25-2.5 mg/day);
- pioglitazone (up to 45 mg/day) vs gliclazide (up to 320 mg/day);
- pioglitazone (up to 45 mg/day) vs glimepiride (up to 8 mg/day);
- pioglitazone (45 mg/day) vs glimepiride (1-6 mg/day);
- pioglitazone (30 mg/day) vs repaglinide (median 6.0 mg/day) vs pioglitazone (30 mg/day) + repaglinide (median 10.0 mg/day).

One study reported a comparison of acarbose versus pioglitazone.

- pioglitazone (45 mg/day) vs acarbose (50-300 mg/day).

One study was a head-to-head comparison of pioglitazone versus rosiglitazone.

- pioglitazone (30-45 mg/day) vs rosiglitazone (4-8 mg/day).

Four studies contrasted metformin administration to pioglitazone.

- pioglitazone (up to 45 mg/day) vs metformin (up to 2550 mg/day);
- pioglitazone (up to 45 mg/day vs metformin(up to 2550 mg/day);
- pioglitazone (up to 45 mg/day) vs metformin (up to 3000 mg/day) vs gliclazide (up to 360 mg/day);
- pioglitazone (30-45 mg/day) vs metformin (750 mg/day) vs glimepiride (1.0-2.0 mg/day).

Combination therapy

Seven studies investigated pioglitazone combination therapy, mainly with metformin, versus a similar combination with another compound (study seven, see above).

- pioglitazone (up to 45 mg/day) + metformin (pre-study dose) vs gliclazide (up to 320 mg/day) + metformin (pre-study dose);
- pioglitazone (up to 45 mg/day) + sulphonylurea (pre-study dose) vs metformin (up to 2550 mg/day) + sulphonylurea (pre-study dose);
- pioglitazone (15-45 mg/day) + other glucose-lowering drugs vs placebo + other glucose-lowering drugs;
- pioglitazone (30 mg/day) + insulin vs placebo + insulin;
- pioglitazone (15 mg/day) + glimepiride (4 mg /day) vs rosiglitazone (4 mg/day) + glimepiride (4 mg/day);
- pioglitazone (15 mg/day) + metformin (up to 3000 mg/day) vs rosiglitazone (4 mg/day) + metformin (up to 3000 mg/day);

Two trials compared the thiazolidinediones pio- and rosiglitazone with each other, in combination with metformin or glimepiride.

Number of study centres

Five studies had one study centre only, one publication did not provide information and the majority of trials had a multicentre design ranging from three to 321 centres. Four studies involved 100 centres or more (Charbonnel 2005a; Dormandy 2005; Goldberg 2005; Schernthaner 2004).

Country and location

Most studies were performed in European countries, six in the U.S.A. and Canada, four in Latin America, two in Japan and one in Australia, Israel, Russia and South Africa, respectively.

Setting

Only one study (Dormandy 2005) presented details about the study setting, like recruitment of participants from the community and hospitals.

Treatment before study

If stated, most studies specified that sulphonylureas, metformin or both were used by participants before entering the study.

Methods

Duration of the intervention

Most studies had a treatment duration of approximately six months, nine lasted 12 months and the longest trial had a mean duration of 34.5 months (Dormandy 2005).

Duration of follow-up

Treatment duration and follow-up were identical in all studies, no post-intervention follow-up was reported.

Run-in period

Eleven studies described run-in periods, mostly between two and four weeks where usually previous antidiabetic medication was stopped, titration of new medication started or a placebo intervention initiated.

Language of publication

All included studies were published in English.

Participants

Who participated

Study participants were mainly white individuals with type 2 diabetes mellitus, only a few studies were performed in pharmaco-naive (that is, people treated with diet only) patients.

Inclusion criteria

Investigators specified various inclusion criteria, such as diet non-responders or certain glycosylated haemoglobin A_{1c} (HbA_{1c}) levels. One publication requested participants to be inadequately controlled with metformin alone, at equal or greater than 50% of the maximal recommended dose or maximal tolerated dose for equal or greater than three months (Matthews 2005).

Exclusion criteria

Investigators specified various exclusion criteria. Eight of 22 included studies stipulated specific criteria for the severity of congestive heart failure (NYHA (New York Heart Association) classification): Five studies mentioned NYHA class III or IV as an exclusion criterion and one study NYHA II or above, I-IV or II-IV, respectively.

Diagnostic criteria

Eight studies provided some details of diagnostic criteria for inclusion of patients with type 2 diabetes mellitus.

Co-morbidities

Only three studies indicated data on co-morbidities (Dormandy 2005; Goldberg 2005; Lawrence 2004).

Co-medications

Fifteen of the 22 included studies reported co-medications, either glucose-lowering drugs or medication for other disorders, or both.

Outcomes

Primary outcomes

Most studies investigated HbA_{1c} and lipid parameters (such as total cholesterol, high-density and low-density lipoprotein cholesterol, triglycerides) as primary endpoints.

Secondary outcomes

Most studies evaluated lipid parameters, fasting and non-fasting plasma glucose, adverse events, insulin, HbA_{1c}, C-peptide and indicators for insulin resistance as secondary outcomes.

Excluded studies

Seven studies had to be excluded after careful evaluation of the full publication. Main reasons for exclusion were trial duration of less than 24 weeks or non-randomised design (for details see Characteristics of excluded studies).

Risk of bias in included studies

For details of study quality see Appendix 14, Appendix 15, Appendix 16, Appendix 17 and Appendix 18.

Overview

All included trials were of a parallel study design. No crossover studies or factorial trials fulfilling the inclusion criteria were detected. Six or seven of the 22 included studies had a non-inferiority or equivalence design (Charbonnel 2005a; Goldberg 2005; Matthews 2005; Pavo 2003; Scherbaum 2002 (?); Schernthaner 2004; Smith 2005) with three trials specifying a 95% confidence interval of equivalence. The other studies investigated superiority or inferiority of pioglitazone compared to comparator compounds.
Interrater agreement for the key quality indicators randomisation, concealment of allocation and blinding was 100%.

Allocation

All included studies were randomised controlled clinical trials of parallel design and randomised individuals. The method of randomisation was somewhat specified in ten studies, statements that randomisation was stratified for centres were given in three publications and two studies specified a randomisation ratio, that is randomisation was not equal between pioglitazone and comparator drugs.
Six studies particularized concealment of allocation (Derosa 2004; Derosa 2006; Dormandy 2005; Mattoo 2005; Schernthaner 2004; Tan 2004a).

Blinding

Fifteen studies had a double-blind, four studies an open-label design and three publications did not lay down information on blinding. The actual versus stated blinding was detectable in one study only (Dormandy 2005). No publication reported checking of blinding conditions.

Incomplete outcome data

Screened and randomised patients

Nine studies reported numbers of screened patients (Charbonnel 2005a; Dormandy 2005; Goke 2002; Goldberg 2005; Langenfeld 2005; Pavo 2003; Scherbaum 2002; Schernthaner 2004; Tan 2004a).
Altogether approximately 6200 participants were randomised to pioglitazone treatment (range nine to 2605, median 89 individuals). Forty per cent of randomised individuals were contributed by a single study (Dormandy 2005).Discontinuing participants and attrition ratesNineteen studies described discontinuing participants and provided some details about the reasons for terminating the trial. Discontinuation rates in the pioglitazone arms varied between four and 58 per cent, with six studies reporting high drop-out rates above 20% (Aronoff 2000; Dormandy 2005; Jovanovic 2004; Scherbaum 2002; Tan 2004a; Tan 2004b). Discontinuation rates between intervention and control groups were dissimilar in nine studies (Aronoff 2000; Goke 2002; Hanefeld 2004; Jovanovic 2004; Langenfeld 2005; Lawrence 2004; Pavo 2003; Scherbaum 2002; Watanabe 2005). Three studies did not report details on attrition rates.Intention-to-treat, per-protocol analyses and missing dataNine studies reported an intention-to-treat analysis, six trials a per-protocol evaluation. Intention-to-treat was clearly defined in five studies, only.
Nine studies used the last-observation-carried-forward (LOCF) imputation method for missing data. For example, a study of 12 months duration could extrapolate missing HbA_{1c} values for randomised patients and declare these as endpoints, if the first post-randomisation HbA_{1c} value (for example after three months) was available. Two studies used other methods for imputation. A clear definition of the LOCF population was provided by three studies, only.

Other potential sources of bias

Compliance measurements

Eight of 22 included studies tried to investigate patients' compliance with the recommended treatments.

Definition of primary endpoint, secondary endpoints

Thirteen studies clearly defined primary endpoints, mostly one parameter, with four studies presenting more than one parameter as a primary outcome.
The number of secondary endpoints varied between five and 12. The total number of detailed endpoints in the included studies ranged from seven to 24. Only five studies adjusted for multiple outcomes, repeated measurements, or both.Power calculationEleven studies showed details of power calculation, the number of participants per group ranged from 14 to 2500.FundingSixteen studies reported commercial funding, seven publications did not indicate possible funding sources (Derosa 2004; Derosa 2006; Jovanovic 2004; Pavo 2003; Schernthaner 2004; Watanabe 2005; Yamanouchi 2005).Publication statusAll studies were published in peer review journals, none was circulated as a journal supplement.

Effects of interventions

Baseline characteristics

For details of baseline characteristics see Appendix 2; Appendix 3; Appendix 4; Appendix 5 and Appendix 6.

Six studies demonstrated clinically relevant differences between intervention and control groups, for example gender ratio (Lawrence 2004; Pavo 2003; Scherbaum 2002; Tan 2004a; Tan 2004b; Yamanouchi 2005). More men then women participated in the studies, in the pioglitazone arms women's involvement ranged between 15% and 59%.

The mean age of patients randomised to pioglitazone treatment encompassed 53 to 63 years, diabetes duration ranged between three to 14 years.
The main ethnic group participating in the trials consisted of white people, a few studies included a Hispanic population as well.
Pharmaco-naive patients usually constituted a minor part of the study participants, but three studies exclusively investigated this group (Pavo 2003; Schernthaner 2004; Yamanouchi 2005).
Most study participants with type 2 diabetes mellitus were also obese, the mean body mass indices (BMI) in patients randomised to pioglitazone therapy ranged between 24.4 and 33.7 kg/m^2, two Japanese studies showed a mean BMI of 24.4 and 25.8.
Metabolic control as measured by mean HbA_{1c} varied in the pioglitazone arms between 7.4% and 10.3%, most participants ranged between 8% and 9%.

Primary outcomes

For details of primary outcomes see Appendix 12.

Mortality

With the exception of one study no trial explored mortality as an endpoint. The study by Dormandy et al was a double-blind RCT with matching placebo in patients with type 2 diabetes mellitus who had evidence of macrovascular disease (Dormandy 2005). Placebo or pioglitazone titrated up to 45 mg/day (89% to 93% of participants) were taken in addition to the participants' glucose-lowering drugs and other medications. The average time of observation was 34.5 months. The overall mean age was 62 years with a median time of diabetes duration of eight years. At randomisation, 62% of participants were taking metformin or sulphonylureas, respectively, either as monotherapy or in combination. More than 30% of patients were on insulin.
The primary composite endpoint (time from randomisation to all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle) did not show statistically significant differences between the pioglitazone and placebo group: The hazard ratio (HR) was 0.90 (95% CI 0.80 to 1.02, P=0.095).
Of all secondary endpoints only the so-called "main" secondary endpoint (time to the first event of the composite endpoint of death from any cause, myocardial infarction (excluding silent myocardial infarction) and stroke) indicated a statistical significant difference between pioglitazone and placebo (HR 0.84 (95% CI 0.72 to 0.98, P=0.027)). The individual components of the primary composite endpoint did not disclose statistically significant differences between intervention and control groups.
HbA_{1c} decreased significantly by 0.8% in the pioglitazone and 0.3% in the placebo group and levels of high-density lipoprotein cholesterol increased significantly by 19% and 10%, respectively. The median change in blood pressure was 3 mm Hg versus 0 mm Hg for pioglitazone compared to placebo (P = 0.03).
Significantly more patients developed oedema and heart failure, including heart failure needing hospital admission, following administration of pioglitazone (6% versus 4% on placebo).

Morbidity

Apart from one study by Dormandy et al not a single included trial looked into morbidity (for example diabetes and cardiovascular related morbidity like myocardial infarction, stroke, peripheral vascular disease, neuropathy, retinopathy or nephropathy). For details about the study by Dormandy et al see under 'Mortality'.

Adverse events

For details of adverse events see Appendix 7, Appendix 8, Appendix 9, Appendix 10 and Appendix 11.

Seven studies made some statement about the number of participants who died during the course of the trial, only one study was powered to detect differences between groups in the primary composite endpoint (time from randomisation to all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle - Dormandy 2005).
The percentage of overall and serious adverse events was comparable between intervention and control groups. We noted a somewhat higher discontinuation rate following pioglitazone administration especially in comparison to monotherapy with other oral antidiabetic drugs. However, true numbers are difficult to evaluate due to study protocols defining withdrawals because of lack of efficacy as a serious adverse event.
Six studies reported a more pronounced (sometimes dose-related) decrease of haemoglobin after pioglitazone intake in comparison to other active compounds or placebo. Haemoglobin reductions ranged between 0.5 and 0.75 g/dl.
Fifteen studies evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment, seven studies described a rise in body mass index up to 1.5 kg/m^2.
Eleven of the 22 included studies showed data on hypoglycaemic episodes: Compared to active monotherapy control pioglitazone treatment resulted in somewhat lower rates of hypoglycaemia. If pioglitazone was combined with insulin more hypoglycaemic incidents happened. The biggest trial which compared pioglitazone versus placebo in combination with a variety of other glucose-lowering drugs reported hypoglycaemia rates of 27.9% after pioglitazone and 20.1% after placebo combinations (Dormandy 2005). Severe hypoglycaemic events were rarely reported.
The specific adverse event "oedema" was evaluated in 18 of 22 studies. Overall, 11.565 participants provided data on the occurrence of oedema. The total number of events was 842 in the pioglitazone and 430 in the control groups. Pooling of the 18 studies by means of random-effects meta-analysis revealed a relative risk of 2.86 (95% confidence interval (CI) 2.14 to 3.18, P < 0.00001). The test for heterogeneity indicated an I^2-value of 45.8%. The use of a fixed-effect model resulted in a risk ratio of 1.98 (95% CI 1.78 to 2.20). The robustness of this result was also tested by repeating the analysis using the odds ratio as a different measure of effect size, demonstrating an odds ratio of 3.15 (95% CI 2.34 to 4.23) and 2.22 (95% CI 1.96 to 2.52) for a random-effects and fixed-effect model, respectively. Since oedema event rates in many studies exceeded 10%, application of the risk ratio appeared to be the more valid parameter.
We repeated the analysis excluding the large study by Dormandy et al in order to establish how much it dominated the results. The relative risk in the random-effects model did not change substantially and was 2.85 (95% CI 2.27 to 3.59), but heterogeneity decreased to an I^2 of 0%. Moreover, selection of the four studies with combination therapies only did not significantly alter these results (data not shown).

Secondary outcomes

For details of secondary outcomes see Appendix 13.

Health-related quality of life

No study investigated health-related quality of life.

Costs

No study reported data on costs of pioglitazone therapy compared to other glucose-lowering medications or placebo.

Metabolic control as measured by glycosylated haemoglobin A_{1c} (HbA_{1c})

Active glucose-lowering compounds like metformin, glibenclamide, gliclazide or glimepiride resulted in similar reductions of Hb_{A1c} compared to pioglitazone treatment.

Heterogeneity

Only adverse events (oedema) as one of our primary outcomes could be subjected to meta-analysis. Heterogeneity as indicated by I^2 was not substantial but could be significantly reduced after elimination of the biggest trial by Dormandy et al which included a great variety of participants from more than 300 study centres in 19 European countries who were treated with various glucose-lowering combination therapies

Subgroup analyses

Not performed due to lack of data.

Sensitivity analyses

Various sensitivity analyses did not change significantly the risk estimates for development of oedema after pioglitazone treatment.

Assessment of publication bias

Not performed due to insufficient amounts of data.

DISCUSSION

Summary of main results

This systematic review shows that published studies of at least 24 weeks pioglitazone treatment in people with type 2 diabetes mellitus did not provide convincing evidence that patient-oriented outcomes like mortality, morbidity, adverse effects and health-related quality of life are positively influenced by this compound. Metabolic control measured by glycosylated haemoglobin A_{1c} (HbA_{1c}) as a surrogate endpoint did not demonstrate clinically significant differences to other oral antidiabetic drugs. No study investigated economic costs of pioglitazone therapy. Occurrence of oedema was significantly raised.

Twenty-one of the 22 included studies reported only surrogate outcomes, the results of the single trial with relevant clinical endpoints have to be seen as hypothesis-generating and need confirmation. We know of five ongoing studies (ACCORD; BARI-2D; CHICAGO; PERISCOPE; PPAR, see also Hanefeld 2005) which eventually could contribute valuable information about the role of pioglitazone treatment in type 2 diabetes mellitus (for details see 'Characteristics of ongoing studies'). Until new results are available the benefit-risk ratio for pioglitazone ambiguous.

Therapeutic indication

According to the European Medicines Agency (EMEA) "pioglitazone is indicated as oral monotherapy in type 2 diabetes mellitus patients, particularly overweight patients, inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance (www.emea.eu.int). Pioglitazone is also indicated for oral combination treatment in type 2 diabetes mellitus patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or sulphonylurea:

- in combination with metformin only in obese patients;
- in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated."

In the Food and Drug Administration (FDA) 'INDICATIONS AND USAGE label' (www.fda.gov) pioglitazone (ACTOS) "is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM). ACTOS is indicated for monotherapy. ACTOS is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control."

Patients and physicians alike need to know why the two biggest drug agencies in the world established different criteria for the therapeutic indication of pioglitazone usage. Supposedly, both received very similar data from the manufacturer of pioglitazone. Moreover, taking into account our in- and exclusion criteria, only a single trial of at least 24 weeks duration of pioglitazone treatment explicitly provided data fulfilling the criteria by the EMEA (Matthews 2005).

PROactive (Prospective Pioglitazone Clinical Trial In Macrovascular Events) study

The PROactive study was a much anticipated trial because it was the first large-scale study to be reported that was designed to determine whether the theoretical benefits of pioglitazone on endothelial function and cardiovascular risk factors might result in fewer macrovascular disease events in people with type 2 diabetes mellitus. Much debate centred around issues of interpretation (Skyler 2005; Skyler 2006).

In the Lancet publication (Dormandy 2005) a "main" secondary endpoint, consisting of the time to the first event of the composite endpoint of death from any cause, myocardial infarction (excluding silent myocardial infarction), and stroke showed significant statistical differences in favour of pioglitazone The other mentioned secondary endpoints cardiovascular death and time to individual components of the primary composite endpoint did not reveal statistical significant differences.

In the Diabetes Care publication of the study design and baseline characteristics (see under included studies Dormandy 2005, additional non-primary studies) individual components of the primary endpoint and cardiovascular mortality were specified as secondary outcomes.

Databases of ongoing trials (www.clinicaltrials.gov published with identifier NCT00174993) stated: "Primary Outcomes: Time to death, non-fatal myocardial infarction, acute coronary syndrome, cardiac intervention (PCI/CABG), stroke, leg amputation, revascularization

in the leg. Minimum 30 months follow up. Secondary Outcomes: Adverse events".
In a recent letter to the editor published in the Lancet, the PROactive study executive committee and data and safety monitoring committee in response to the criticism stated (PROactive 2006): "It has come to our attention that there is a belief in some quarters that this endpoint was not prespecified and that the finding was obtained through a post-hoc analysis ... this belief is based, in part, on an earlier publication of the PROactive study design, which listed the primary and secondary endpoints, but did not mention this specific composite ... during the latter part of 2004 and early 2005, a working party representing members of the Study Executive Committee and the sponsor prepared a formal statistical analysis plan for the study. At this time, it was recognised that the clinically important composite of death, myocardial infarction, and stroke was not currently part of the intended analysis. This was added to the plan in a draft circulated in March, 2005, and the final version of the plan clearly identifies this endpoint as the intended main secondary endpoint. The final version was signed and released on May 13, 2005. A copy of the plan was registered as received by the US Food and Drug Administration on May 17. The study database was formally locked on May 25, and statistical analysis of unblinded data started only after that date."
The main investigator kindly provided us with the statistical analysis plan (Version 1.3 (FINAL) / 12 May 2005 AD-4833 / Pioglitazone) which states on page nine: "The study protocol identifies the following as secondary endpoints:

- The individual components of the primary endpoint
- Cardiovascular mortality

In addition, at the time of preparation of this plan, it was decided to add one further composite endpoint to the list of secondary endpoints, namely, all-cause mortality, acute myocardial infarction (excluding silent MI) and stroke. The reason for this addition is so that the analysis can report the extent of treatment effects with respect to an endpoint which is also used commonly in large cardiovascular outcome studies."

It might be correct, as the PROactive executive committee formulates, that it is legitimate for the endpoints of a study to be amended as the study progresses, but the fact that in the statistical analysis plan the new endpoint was not clearly defined as the intended main secondary endpoint still casts doubts on the scientific rigour of the interpretation of the PROactive study. Moreover, as explained above, these results have to be seen as hypothesis-generating and need confirmation. Single components of the composite endpoints should not be extracted and declared as being significant, even if the composite endpoint itself revealed statically significant differences, unless proven by appropriate statistical methods.

Potential biases in the review process

We focused on a minimum duration of 24 weeks pioglitazone therapy in order to have a chance to detect clinically meaningful differences in patient-oriented parameters. Theoretically, studies of a shorter duration could demonstrate a significant impact on these outcomes but this is highly unlikely, even with regards to important adverse events.
Moreover, it was difficult to separate primary studies from companion papers because the latter quite often did not identify themselves as an additional publication of a parent study (for details see 'References of included studies', primary studies are marked by an asterisk).

Furthermore, many publications were found which consisted of a post-hoc analyses of a varying number of published and unpublished studies. Data on file hopefully can be evaluated in future updates of this review. The following publications were additional papers summarising two or more primary studies on the efficacy of pioglitazone:

- post-hoc analysis of three studies - no references mentioned (Belcher 2004);
- post-hoc analysis of four studies - Charbonnel 2005; Hanefeld 2004; Matthews 2005; Schernthaner 2004 mentioned (Belcher 2005);
- post-hoc analysis of two studies - Hanefeld 2004; Matthews 2005 mentioned (Betteridge 2005)
- post-hoc analysis of four studies - Charbonnel 2005; Hanefeld 2004; Matthews 2005; Schernthaner 2004 mentioned (Ceriello 2005);
- post-hoc analysis of two studies - Charbonnel 2005; Matthews 2005 mentioned (Charbonnel 2005b);
- post-hoc analysis of two studies - Hanefeld 2004; Matthews 2005 mentioned (Charbonnel 2005c);
- post-hoc analysis of four studies - Hanefeld 2004; Matthews 2005 and data on file studies (Takeda) mentioned (Khan 2004);
- post-hoc analysis of four studies - Hanefeld 2004; Matthews 2005 mentioned (Lester 2005);
- post-hoc analysis of two studies - no references mentioned (Perez 2004);
- post-hoc analysis of five studies - Rosenblatt 2001 and four data on file studies (Takeda) mentioned (Rajagopalan 2004);
- post-hoc analysis of four studies - Hanefeld 2004; Matthews 2005 and two data on file studies (Takeda) mentioned (Rajagopalan 2005b);
- post-hoc analysis of two studies - Hanefeld 2004; Lenton 2003 (abstract) mentioned (Roden 2005)
- post-hoc analysis of three studies - Aronoff 2000; Einhorn 2000; Kipnes 2001 mentioned (Tan 2004c);
- post-hoc analysis of four studies - Einhorn 2000; Kipnes 2001; Rosenstock 2002 mentioned (Tan 2004d).

Paper journals should ask authors for proof of thorough search of the literature because these post-hoc analyses could undermine the idea of systematic reviews by selective reporting of studies which may introduce bias in the reported results.

AUTHORS' CONCLUSIONS

Implications for practice

We showed that published studies of at least 24 weeks pioglitazone treatment in people with type 2 diabetes mellitus did not provide convincing evidence that patient-oriented outcomes like mortality, morbidity, adverse effects and health-related quality of life are positively influenced by this compound. On the other hand, occurrence of oedema was significantly raised. In the largest pioglitazone endpoint trial of clinical relevance significantly more patients developed heart failure, including heart failure needing hospital admission. Until new evidence becomes available, the benefit-risk ratio of pioglitazone remains unclear.

Implications for research

Five ongoing studies (ACCORD; BARI-2D; CHICAGO; PERISCOPE; PPAR) may contribute important information about the role of pioglitazone treatment in type 2 diabetes mellitus. The hypothesis-generating positive findings of secondary endpoints with regard to cardiovascular outcomes of the PROactive study (Prospective Pioglitazone Clinical Trial In Macrovascular Events) need confirmation. Future trials should avoid confusion about outcomes by clear a-priori definition and statistical justification of anticipated endpoints.

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Action to Control Cardiovascular Risk in Diabetes (ACCORD). Ongoing study Recruitment occurred in two non-contiguous periods: an initial period that began in January 2001 for the Vanguard Phase of the trial (during which 1174 participants were randomized) and then a subsequent period beginning in January 2003 and ending in October 2005.Follow-up is scheduled to end in June 2009, with the primary results announced in early 2010..

BARI-2D *{published data only}*

Bypass Angioplasty Revascularization Investigation in Type 2 Diabetics (BARI 2D). Ongoing study Study start: September 2000;
Study completion: June 2007.

CHICAGO *{published data only}*

A Study of Pioglitazone HCl Versus Glimepiride in Subjects With Type 2 Diabetes Measuring the Progression of Atherosclerosis (CHICAGO). Ongoing study Study start: August 2003;
Study completion: October 2006
Last follow-up: April 2006;
Data entry closure: July 2006.

PERISCOPE *{published data only}*

Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE). Ongoing study Study start: August 2003;
Expected completion: March 2008
Last follow-up: August 2007;
Data entry closure: November 2007.

PPAR *{published data only}*

Pioglitazone Protects DM Patients Against Re-Infarction (PPAR Study). Ongoing study Study start: April 2005; Expected completion: April 2009
Last follow-up: April 2009;
Data entry closure: April 2009.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aronoff 2000

Methods	DURATION OF INTERVENTION: 26 weeks DURATION OF FOLLOW-UP: 26 weeks RUN-IN PERIOD: - 6 -8 weeks single-blind washout period, including 2 weeks for baseline measurements. - patients who had never received pharmacological antidiabetic therapy were enrolled in the study and entered a 6-week single-blind run-in period LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: 78% white patients with type 2 diabetes mellitus INCLUSION CRITERIA: type 2 diabetes; HbA1c >= 7.0%, FPG >=140 mg/dl; fasting C-peptide >1 ng/ml EXCLUSION CRITERIA: chronic insulin use; history of ketoacidosis; unstable or progressive diabetic retinopathy, nephropathy, neuropathy; impaired liver function; impaired kidney function; anaemia; within 6 months of the study: myocardial infarction, coronary angioplasty or bypass graft, unstable angina, transient ischaemic attacks, documented cerebrovascular accident DIAGNOSTIC CRITERIA: HbA1c >= 7.0%, FPG >=140 mg/dl; fasting C-peptide >1 ng/ml CO-MORBIDITIES: not stated CO-MEDICATIONS: not stated
Interventions	NUMBER OF STUDY CENTRES: 35 COUNTRY/ LOCATION: all regions of the USA SETTING: unclear; investigators consisted of board-certified endocrinologists and primary care physicians in academic and nonacademic sites INTERVENTION (DOSE/DAY): pioglitazone 7.5, 15, 30, 45 mg/day (four groups) CONTROL (DOSE/DAY): placebo TREATMENT BEFORE STUDY: - most commonly sulphonylureas (glyburide and gliclazide), 13% had received 2 or more antidiabetic medications. - discontinuation of prior antidiabetic medication at the beginning of the washout period (i.e. 8 weeks before receiving double-blind treatment). no required modifications of current dietary regimens during the study
Outcomes	PRIMARY OUTCOMES: not stated (HbA1c) SECONDARY OUTCOMES: lipid parameters, FPG, safety assessment and adverse effects
Notes	AIM OF STUDY: to assess the metabolic effects of 4 doses of pioglitazone monotherapy in the treatment of patients with type 2 diabetes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Charbonnel 2005a

Methods	DURATION OF INTERVENTION: 52 weeks DURATION OF FOLLOW-UP: 52 weeks RUN-IN PERIOD: not stated LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: drug-naive patients with type 2 diabetes mellitus INCLUSION CRITERIA: 35-75 years, type 2 diabetes inadequately controlled with diet alone, HbA1c 7.5-11% with stable or worsening glycaemic control over a period of at least 3 months; if antihypertensive treatment was indicated during the study, patients were treated with ACE inhibitors or Ca antagonists EXCLUSION CRITERIA: previous glucose-lowering medication, specific contraindications to either drug; long-term treatment with corticosteroids, start of beta-blockers not permitted during study or within 4 weeks prior to screening DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: not stated CO-MEDICATIONS: if antihypertensive treatment was indicated during the study, patients were treated with ACE inhibitors or Ca antagonists. 14% of patients in each group were receiving treatment with beta-blockers at baseline
Interventions	NUMBER OF STUDY CENTRES: 219 COUNTRY/ LOCATION: 14 European countries, Canada, South Africa and Israel SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; up to 45 mg/day (reached by 80.7%, mean dose 42 mg/day) CONTROL (DOSE/DAY): glicliazide; up to 320 mg/day (reached by 27.9%, mean dose 198 mg/day) TREATMENT BEFORE STUDY: - patients treated with diet alone prior to intervention. dietary advice was given at baseline with the target of body weight normalization. - 14% in each group taking beta-blockers at baseline (exclusion criterion!) Both groups: dietary advice given at baseline with target of body weight normalisation; if body weight increased more than 5% during treatment or HbA1c increased to greater than 9% after completed dose titration, patients were given further intensive dietary advice TITRATION: 16-week forced-titration period to a maximum dose and a 36-week maintenance period at the maximum tolerated dose of drug
Outcomes	PRIMARY OUTCOMES: HbA1c (change from baseline to last available post-treatment value) SECONDARY OUTCOMES: FPG, insulin, plasma lipids, C-peptide, pro-insulin, adverse effects
Notes	AIM OF STUDY:

Charbonnel 2005a *(Continued)*

	to compare the effects of of pioglitazone and gliclazide on metabolic control in drug-naive patients with type 2 diabetes mellitus

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Derosa 2004

Methods	DURATION OF INTERVENTION: 12 months DURATION OF FOLLOW-UP: 12 months RUN-IN PERIOD: none LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: white patients with type 2 diabetes mellitus and metabolic syndrome INCLUSION CRITERIA: white patients of either sex and ages >=18 years; type 2 diabetes according to ADA criteria (duration >=6 months); poor glycaemic control (HbA1c >=7.5% or >=1 adverse effect with diet and oral hypoglycaemic agents (e.g. SU or metformin) given up to the maximum tolerated dose; all patients also diagnosed with metabolic syndrome (National Cholesterol Education Program Adult Treatment Panel III classification; triglyceridaemia (TG >=150 mg/dl) and hypertension (WHO criteria BP >=130/>=85 mmHg); fasting C-peptide level >1.0 ng/ml EXCLUSION CRITERIA: receiving glimepiride, history of ketoacidosis, unstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy; impaired hepatic function, impaired renal function, severe anaemia; severe cardiovascular disease (e.g. NYHA class III or IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before enrolment; women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions DIAGNOSTIC CRITERIA: ADA 2001 CO-MORBIDITIES: not stated CO-MEDICATIONS: 40.2% receiving antihypertensive drugs. no patient was receiving lipid-lowering or antiaggregant drugs
Interventions	NUMBER OF STUDY CENTRES: three COUNTRY/ LOCATION: Italy SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; 15 mg once daily; + fixed oral dose of glimepiride (4 mg/day divided into 2 doses) CONTROL (DOSE/DAY): rosiglitazone; 4 mg once daily; +fixed oral dose of glimepiride (4 mg/day divided into 2 doses) TREATMENT BEFORE STUDY: 52.9% poor glycaemic control with metformin; 31% with SUs; 16.1% with glyburide; 14.9% with gliclazide

Derosa 2004 *(Continued)*

Outcomes	PRIMARY OUTCOMES: changes in BMI, HbA1c, lipid profile, and lipoprotein variables were the primary efficacy variables SECONDARY OUTCOMES: fasting and postprandial plasma glucose, insulin levels, insulin resistance (HOMA); blood pressure; adverse events
Notes	AIM OF STUDY: to assess the differential effect on glucose and lipid variables of the combination of glimepiride plus pioglitazone or rosiglitazone in patients with type 2 diabetes and the metabolic syndrome

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Derosa 2006

Methods	DURATION OF INTERVENTION: 12 months DURATION OF FOLLOW-UP: 12 months RUN-IN PERIOD: none LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: white patients with type 2 diabetes mellitus and metabolic syndrome INCLUSION CRITERIA: white patients of either sex and ages >=18 years; type 2 diabetes according to ADA criteria (duration >=6 months); poor glycaemic control (HbA1c >=7.5% or adverse effects with diet and metformin given up to the maximum tolerated dose; all patients also diagnosed with metabolic syndrome (National Cholesterol Education Program Adult Treatment Panel III classification; triglyceridaemia (TG >=150 mg/dl) and hypertension (WHO criteria BP >=130/>=85 mmHg); fasting C-peptide level >1.0 ng/ml; overweight (BMI 25.0-28.1 kg/m2) EXCLUSION CRITERIA: history of ketoacidosis, unstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy; impaired hepatic function, impaired renal function, severe anaemia; severe cardiovascular disease (e.g. NYHA class I to IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before enrolment; women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions DIAGNOSTIC CRITERIA: ADA 2001 CO-MORBIDITIES: not stated CO-MEDICATIONS: not stated - at baseline, patients began a controlled-energy diet (600 kcal daily deficit), based on ADA recommendations; - every 2 weeks dietitians and/or specialists provided instructions on dietary intake which was part of a behaviour-modification programme; - during the study, behaviour-modification sessions on weight-loss strategies were given to individual patients at baseline and at 6 months, and as a group at 3, 6, 9 and 12 months;

Derosa 2006 *(Continued)*

	- individuals were also encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20–30 min, three to five times a week.
Interventions	NUMBER OF STUDY CENTRES: three COUNTRY/ LOCATION: Italy SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; 15 mg once daily; + metformin up to 3000 mg/day CONTROL (DOSE/DAY): rosiglitazone; 4 mg once daily; +metformin up to 3000 mg/day METFORMIN DOSE (both groups): mean dosage 2250 mg +- 750 mg/day TREATMENT BEFORE STUDY: not stated
Outcomes	PRIMARY OUTCOMES: changes in lipoprotein a and homocystein levels from baseline to the end of 12 months SECONDARY OUTCOMES: HbA1c; fasting and postprandial plasma glucose, insulin levels, insulin resistance (HOMA); lipid profile; BMI; adverse events
Notes	AIM OF STUDY: to evaluate the differential effect on homocysteine and lipoprotein a plasma levels of the two combinations, metformin plus pioglitazone and metformin plus rosiglitazone, in patients with type 2 diabetes - patients were required to have poor glycaemic control with diet, or experienced adverse effects with diet and metformin, administered up to the maximum tolerated dose (comment: if individuals experienced side effects of metformin treatment, how could they be randomised to metformin plus additional pioglitazone or rosiglitazone treatment?)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Dormandy 2005

Methods	DURATION OF INTERVENTION: 34.5 months (mean) DURATION OF FOLLOW-UP: 34.5 months (mean) RUN-IN PERIOD: none LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: patients with type 2 diabetes mellitus who had evidence of macrovascular disease INCLUSION CRITERIA: patients with type 2 diabetes aged 35–75 years; HBA1c greater than the local laboratory equivalent of 6·5% for a Diabetes Control and Complications Trial-traceable assay (DCCT), despite existing treatment

Dormandy 2005 *(Continued)*

	with diet alone or with oral glucose-lowering agents with or without insulin. evidence of macrovascular disease before recruitment, defined by one or more of the following criteria: myocardial infarction or stroke at least 6 months before entry to the trial, percutaneous coronary intervention or coronary artery bypass surgery at least 6 months before recruitment, acute coronary syndrome at least 3 months before recruitment, or objective evidence of coronary artery disease or obstructive arterial disease in the leg. Objective evidence of coronary artery disease was defined as a positive exercise test, angiography showing at least one stenosis of more than 50%, or positive scintigraphy. obstructive arterial disease of the leg was defined as a previous major amputation or intermittent claudication with an ankle or toe brachial pressure index of less than 0·9 EXCLUSION CRITERIA: type 1 diabetes; taking only insulin; planned coronary or peripheral revascularisation; NYHA II class II heart failure or above; ischaemic ulcers, gangrene, or rest pain in the leg; haemodialysis; greater than 2·5 times the upper limit of ALAT. DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: Intervention vs control: - history of hypertension 75% vs 76%; - current smoker 13% vs 14%; - past smoker 46% vs 44%; - microvascular disease (retinopathy, nephropathy, neuropathy) 43% vs 41%. - previous myocardial infarction 47% vs 46%; - previous stroke 19% vs 19%; - previous percutaneous intervention or coronary artery bypass graft 31% vs 31%; - previous acute coronary syndrome 14% vs 14%; - objective evidence of coronary artery disease 48% vs 48%; - symptomatic peripheral arterial obstructive disease 19% vs 20%; - two or more macrovascular disease criteria 47% vs 49%. CO-MEDICATIONS: Intervention vs control: - beta-blockers 55% vs 54%; - ACE inhibitors 63% vs 63%; - AT II antagonists 7% vs7% - Ca-channel blockers 34% vs 37%; - nitrates 39% vs 40%; - thiazide diuretics 15% vs 16%; - loop diuretics 14% vs 14%; - antiplatelet medications 85% vs 83%; - aspirin 75% vs 72%; - statins 43% vs 43%; - fibrates 10% vs 11%.
Interventions	NUMBER OF STUDY CENTRES: 321 COUNTRY/ LOCATION: 19 European countries SETTING: recruitment from community (1681 patients) and hospitals (3557 patients) INTERVENTION (DOSE/DAY): pioglitazone titrated from 15 mg to 45 mg in addition to other glucose-lowering drugs and other medications CONTROL (DOSE/DAY): matching placebo in addition to other glucose-lowering drugs and other medications TREATMENT BEFORE STUDY: Blood glucose lowering treatment - intervention vs control: - metformin only 10% vs 10%; - sulphonylureas only 20% vs 19%; - metformin + sulphonylureas 25% vs 25%; - insulin only <1% vs <1% - insulin + metformin 18% vs 18%; - insulin + sulphonylureas 8% vs 8%;

Dormandy 2005 *(Continued)*

	- insulin + metformin + sulphonylureas 4% vs 4%; - other combinations 12% vs 12%; - diet only 4% vs 4%. TITRATION: - pioglitazone 15 mg for the first month, 30 mg for the second month, and 45 mg thereafter to achieve the maximum tolerated dose, according to the licensed dose range for pioglitazone (89% of patients reached the 45 mg dose at the 2-month visit compared with 91% of matching placebo); - throughout the study, investigators were required to increase all therapy to an optimum, according to the International Diabetes Federation European Region 1999 guidelines.
Outcomes	PRIMARY OUTCOMES: composite endpoint - time from randomisation to all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle SECONDARY OUTCOMES: LANCET publication: - time to the first event of the composite endpoint of death from any cause, myocardial infarction (excluding silent myocardial infarction), and stroke (so-called "main secondary endpoint" in the Lancet publication); - cardiovascular death; - time to individual components of the primary composite endpoint.; DIABETES CARE publication (study design & baseline characteristics): - individual components of the primary endpoint and cardiovascular mortality. STATISTICAL ANALYSIS PLAN Version 1.3 (FINAL) / 12 May 2005 AD-4833 / Pioglitazone: "The study protocol identifies the following as secondary endpoints: - The individual components of the primary endpoint - Cardiovascular mortality In addition, at the time of preparation of this plan, it was decided to add one further composite endpoint to the list of secondary endpoints, namely, all-cause mortality, acute myocardial infarction (excluding silent MI) and stroke. The reason for this addition is so that the analysis can report the extent of treatment effects with respect to an endpoint which is also used commonly in large cardiovascular outcome studies" WWW.CLINICALTRIALS.GOV (published with identifier NCT00174993): "Primary Outcomes: Time to death, non-fatal myocardial infarction, acute coronary syndrome, cardiac intervention (PCI/CABG), stroke, leg amputation, revascularisation in the leg. Minimum 30 months follow up Secondary Outcomes: Adverse events"
Notes	AIM OF STUDY: to ascertain whether pioglitazone reduces cardiovascular morbidity and mortality in in high-risk patients with type 2 diabetes, and to assess the safety and tolerability of such treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ebeling 2001

Methods	DURATION OF INTERVENTION: 6 months DURATION OF FOLLOW-UP: 6 months RUN-IN PERIOD: not stated

Ebeling 2001 *(Continued)*

	LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: patients with type 2 diabetes mellitus from Helsinki University Hospital who took part in a phase III study INCLUSION CRITERIA: type 2 diabetes treated with diet and oral medication or diet alone; BMI >=25 kg/m2, age 35-75 years; HbA1c >=7.5%, fasting serum glucose >=7.8mmol/L EXCLUSION CRITERIA: not stated DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: not stated CO-MEDICATIONS: mainly antihypertensives (same before and after the study)
Interventions	NUMBER OF STUDY CENTRES: one COUNTRY/ LOCATION: Finland SETTING: outpatient clinics INTERVENTION 1 (DOSE/DAY): pioglitazone; 30 mg/day Control 1 (DOSE/DAY): glibenclamide; 2.5 mg/day CONTROL 2 (DOSE/DAY): placebo TREATMENT BEFORE STUDY: not stated TITRATION: clinics visited at 2-6 week intervals for safety measurements; if the reduction in HbA1c at week 9 was not greater than or equal to 0.3%, antidiabetic medication was doubled in glibenclamide group (0 patients) and increased to 45 mg/day in the pioglitazone group (4 of 9 patients)
Outcomes	PRIMARY OUTCOMES: not stated (inflammatory markers) SECONDARY OUTCOMES: HbA1c, C-peptide, serum insulin, lipids, free fatty acids, fasting serum glucose, adverse events
Notes	AIM OF STUDY: study of inflammatory factors in type 2 diabetes: 1.are inflammatory factors and activation of the complement system related? 2.how does improvement of glycaemic control by pioglitazone or glibenclamide affect concentrations of acute phase seroproteins? 3.is improved metabolic control related to changes in complement activation?

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Goke 2002

Methods	DURATION OF INTERVENTION: 26 weeks +- 5 days DURATION OF FOLLOW-UP: 26 weeks +- 5 days RUN-IN PERIOD: - one week with disease- and bodyweight-oriented dietary regimen; patients were asked to continue with recommended diet throughout the study - for acarbose, titration phase 3 weeks starting at 50 mg once daily up to 300 mg daily administered in 3 doses LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: patients were either newly diagnosed with type 2 diabetes mellitus or had previous treatment with oral antihyperglycaemic drugs INCLUSION CRITERIA: type 2 diabetes, newly diagnosed or previous treatment with oral antidiabetic drugs; diabetes not well controlled with HbA1c 7.5-11.5%, FPG >=140 mg/dl, BMI 25-43 kg/m2 EXCLUSION CRITERIA: insulin dependent diabetes, required other specific antidiabetic drugs, history of ketoacidosis, disease causing malabsorption or digestive problems, history of heart disease, haematological disease or HIV infection, evidence of liver, kidney or bone marrow impairment patients were discontinued if HbA1c levels were >11.5% or FPG >250 mg/dl for more than 3 months, if clinical complications of diabetes occurred or if adverse events occurred DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: not stated CO-MEDICATIONS: not stated
Interventions	NUMBER OF STUDY CENTRES: 47 COUNTRY/ LOCATION: Germany SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; 45 mg/day CONTROL (DOSE/DAY): acarbose; starting at 50 mg once daily up to 300 mg daily administered in 3 doses TREATMENT BEFORE STUDY: - 27.9% on metformin, 24.9% on sulphonylureas; - patients previously on oral antidiabetics (intervention 46.5%, control 47.8%) had to discontinue those 2 months prior to starting the study.
Outcomes	PRIMARY OUTCOMES: not stated (HbA1c) SECONDARY OUTCOMES: FPG, fasting insulin, C-peptide, HOMA: insulin resistance, triglycerides, total cholesterol, HDL-, LDL-, VLDL-cholesterol, adverse events
Notes	AIM OF STUDY: - to examine the efficacy of of pioglitazone compared with acarbose treatment in patients with type 2 diabetes mellitus, either newly diagnosed or previously treated but not well controlled; effects on glycaemic parameters, lipid profiles and safety;

Goke 2002 *(Continued)*

	- at the end of the 26 weeks of study, patients receiving pioglitazone could continue with the same treatment and those receiving acarbose could start taking pioglitazone in addition to the acarbose, for a further 38-week extension period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Goldberg 2005

Methods	DURATION OF INTERVENTION: 24 weeks DURATION OF FOLLOW-UP: 24 weeks RUN-IN PERIOD: oral placebo; single-blind; 4 weeks LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: patients with type 2 diabetes mellitus who were treated with diet alone or oral monotherapy INCLUSION CRITERIA: men or women >= 35 years of age with a diagnosis of type 2 diabetes (WHO) with fasting triglyceride levels >= 150 mg/dl and< 600 mg/dl and fasting LDL cholesterol levels < 130 mg/dl; fasting serum C-peptide levels >= 1 ng/ml and HbA1c values >= 7 and <= 11% if naive to previous oral antihyperglycemic therapy or HbA1c values >= 7 and <= 9.5% if previously treated with oral antihyperglycemic monotherapy. EXCLUSION CRITERIA: treatment within 60 days of screening with insulin, systemic glucocorticoid therapy; combination oral antihyperglycemic therapy, any lipid-lowering agent, or any weight loss agent; known allergy to any thiazolidinedione; serum creatinine >= 176.8 µmol/dl (>= 2.0 mg/dl) or 2+ dipstick proteinuria at screening; ALT or AST >= 1.5 times the upper limit of normal or significant clinical liver disease; hemoglobin < 10.5 g/dl (females) or < 11.5 g/dl (males) at screening; abnormal thyrotropin; functional NYHA class III or IV, history of CVD, or heart surgery within 6 months of screening; receiving renal dialysis or having renal transplant; current therapy for malignancy other than basal cell or squamous cell skin cancer; known history of HIV infection; signs or symptoms of drug or alcohol abuse; any condition or situation precluding adherence to and completion of the protocol. For female subjects, appropriate birth control was required, and pregnancy, breast-feeding, or the intent to become pregnant during the study period prohibited participation. DIAGNOSTIC CRITERIA: WHO CO-MORBIDITIES: intervention 1 vs control 1: - pre-existing CVD or previous myocardial infarction 8.4% vs 6.6% CO-MEDICATIONS: intervention 1 vs control 1: - metformin 45.8% vs 44.7%; - insulin secretagogues (including - repaglinide and nateglinide) 45.8% vs 46.1%; - thiazolidinediones 8.5% vs 9.2%.
Interventions	NUMBER OF STUDY CENTRES: 100 (USA 78) COUNTRY/ LOCATION: USA, Puerto Rico, Mexico, Colombia SETTING: unclear

Goldberg 2005 *(Continued)*

	INTERVENTION 1(DOSE/DAY): pioglitazone; 30 mg daily for 12 weeks; thereafter 45 mg once daily for 12 weeks CONTROL 1 (DOSE/DAY): rosiglitazone; 4 mg daily for 12 weeks; thereafter 4 mg twice daily (8 mg/day) for 12 weeks TREATMENT BEFORE STUDY: participants discontinued any current oral antihyperglycaemic treatment TITRATION: - pioglitazone; 30 mg daily for 12 weeks; thereafter 45 mg once daily for 12 weeks - rosiglitazone; 4 mg daily for 12 weeks; thereafter 4 mg twice daily (8 mg/day) for 12 weeks
Outcomes	PRIMARY OUTCOMES: triglycerides change from baseline to the last observed value SECONDARY OUTCOMES: total cholesterol; plasma glucose; free fatty acids; apolipoprotein B; total insulin; C-peptide; highly sensitive C-reactive protein; plasminogen activator inhibitor-1 (PAI-1); HDL-C; LDL-C particle size and concentration; surrogates of insulin resistance and beta-cell function (HOMA); safety assessments including adverse events, body weight, pedal oedema and hypoglycaemic episodes
Notes	AIM OF STUDY: to test the hypothesis that pioglitazone has greater triglyceride-lowering effects than rosiglitazone - comparison of maximally effective monotherapy doses of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia receiving no concomitant glucose-lowering or lipid-lowering therapies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hanefeld 2004

Methods	DURATION OF INTERVENTION: 52 weeks DURATION OF FOLLOW-UP: 52 weeks RUN-IN PERIOD: none LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: mainly white patients with type 2 diabetes mellitus INCLUSION CRITERIA: age 35-75 years, type 2 diabetes inadequately managed on sulphonylureas alone (at >=50% maximal recommended dosage or at maximal tolerated dose for >=3 months) and with stable or worsening glycaemic control for >=3 months; HbA1c 7.5-11.0%, fasting C-peptide >=1.5 ng/ml at screening; female patients post-menopausal, sterilised or using adequate contraception EXCLUSION CRITERIA: type 1 diabetes or ketoacidosis; history of myocardial infarction, transient ischaemic attacks, or stroke in previous 6 months; symptomatic heart failure; malabsorption or pancreatitis; familial polyposis coli; malignant disease in previous 10 years; history of states associated with lactic acidosis or hypoxaemia; substance abuse; pregnant or breast-feeding women; previous treatment with metformin, pioglitazone or other TZDs not permitted DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES:

Hanefeld 2004 *(Continued)*

	not stated CO-MEDICATIONS: thiazides allowed to treat oedema; if antihypertensive treatment indicated, ACE inhibitors, angiotensin II receptor antagonists or Ca antagonists used
Interventions	NUMBER OF STUDY CENTRES: multi, not stated COUNTRY/ LOCATION: various European countries, Canada SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; up to 45 mg/day + sulphonylurea at pre-study dose CONTROL (DOSE/DAY): metformin; 850 mg up to 3x/day (up to 2550 mg/day) + sulphonylurea at pre-study dose TREATMENT BEFORE STUDY: - sulphonylurea at pre-study level, no dose increases permitted; SU dose could only be downtitrated in case of symptomatic hypoglyceamia; - most commonly used SUs in both groups: glibenclamide (42%); gliclazide (31%); glimepiride (19%) SU use from baseline to 52 weeks remained similar in both groups and there were very few cases of dose reduction. TITRATION: 12 weeks forced titration: - intervention 1: pioglitazone up to 45 mg/day with metformin placebo; starting with pioglitazone 15 mg/day; dose levels increased at weeks 4, 8, and 12 (maximal dose reached by 62%); - control: metformin 850 mg with pioglitazone placebo up to three times a day (2550 mg/day); starting with metformin 850 mg/day; dose levels increased at weeks 4, 8, and 12 (55% reached maximal dose); - cessation or down-titration only allowed on basis of tolerability issues, including actual hypoglycaemia or increased risk of hypoglycaemia. Maximum tolerated dose established at week 12 maintained throughout remainder of study.
Outcomes	PRIMARY OUTCOMES: change in HbA1c from baseline to week 52 SECONDARY OUTCOMES: FPG, insulin, C-peptide, lipids, 32,33 split pro-insulin, urinary albumine and creatinine, safety parameters, adverse events
Notes	AIM OF STUDY: to assess the 1 year efficacy and safety of the addition of pioglitazone or metformin to existing sulphonylurea therapy in patients with inadequately controlled type 2 diabetes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jovanovic 2004

Methods	DURATION OF INTERVENTION: 24 weeks DURATION OF FOLLOW-UP: 24 weeks RUN-IN PERIOD: two week wash-out period (with cessation of previous antidiabetic medication) LANGUAGE OF PUBLICATION:

Jovanovic 2004 *(Continued)*

	English
Participants	WHO PARTCIPATED: mainly white patients with type 2 diabetes mellitus INCLUSION CRITERIA: participants >=18 years, BMI <45 kg/m2, had type 2 diabetes for at least 12 months, with HbA1c >7% and <12%; previously treated with sulphonylurea or metformin (at 50% or more of max recommended dose) for at least 3 months EXCLUSION CRITERIA: patients treated within the previous 3 months with: insulin, repaglinide, TZDs, alpha-glucosidase inhibitors, combination therapy with antidiabetic medications. treatment discontinued for unacceptable hyperglycaemia (FPG above 270 mg/dl on 2 or more consecutive occasions in spite of dose escalations to the maximum allowed dosages), in absence of treatable intercurrent illness DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: not stated CO-MEDICATIONS: not stated
Interventions	NUMBER OF STUDY CENTRES: multi, not stated COUNTRY/ LOCATION: USA SETTING: unclear INTERVENTION 1 (DOSE/DAY): pioglitazone; 30 mg/day CONTROL 1 (DOSE/DAY): repaglinide; dosage adjusted up to max of 4 mg/meal (target FPG values of 80-120 mg/dl), median final dose 6.0 mg/day CONTROL 2 (DOSE/DAY): repaglinide+pioglitazone; pioglitazone 30 mg/day, repaglinide adjusted as above, median final dose 10.0 mg/day TREATMENT BEFORE STUDY: sulphonylurea or metformin TITRATION: - for repaglinide: 12 weeks of dose optimisation - repaglinide monotherapy initiated at 0.5 mg/meal if HbA1c was at 8% or below, or at 1mg per meal for all other patients; - in repaglinide/pioglitazone combination therapy, repaglinide as above, plus 30 mg q.d. pioglitazone; patients receiving repaglinide had dosage adjusted to achieve FPG values of 80-120 mg/dl.
Outcomes	PRIMARY OUTCOMES: changes in HbA1c values from baseline to the end of study treatment SECONDARY OUTCOMES: FPG, lipids, adverse events, hypoglycaemia
Notes	AIM OF STUDY: to assess the efficacy, safety and tolerability of the repaglinide+pioglitazone combination therapy in comparison to monotherapy with either agent after unsatisfactory response to sulphonylurea or metformin monotherapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Langenfeld 2005

Methods	DURATION OF INTERVENTION: 24 weeks +- 4 weeks DURATION OF FOLLOW-UP: 24 weeks RUN-IN PERIOD: none LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: patients with type 2 diabetes mellitus INCLUSION CRITERIA: type 2 diabetes, treated with oral antidiabetic agents, but never received TZDs; age 40-75 years; HbA1c >=6.6% and <=9.9% EXCLUSION CRITERIA: significant hepatic or renal disease; congestive heart failure (NYHA class II to IV), smoking at time of randomisation and during previous 6 months; carotid artery stenosis DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: not stated CO-MEDICATIONS: - intervention: statins 20.2% at start, 32.8% at end; renin-angiotensin inhibiting substances 58.4% at start, 60.7% at end; antiplatelet therapy 28.1% at start, 39.3% at end; - control: statins 15.5% at start, 15.5% at end; renin-angiotensin inhibiting substances 48.8% at start, 51.2% at end; antiplatelet therapy 31.0% at start, 40.5% at end; - other additional antidiabetic medication, including SU but not metformin was allowed in the pioglitazone group; in the glimepiride group all kinds of other antidiabetic medication except TZDs were allowed.
Interventions	NUMBER OF STUDY CENTRES: one COUNTRY/ LOCATION: Germany SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone 45 mg/day CONTROL (DOSE/DAY): glimepiride 1 to 6 mg/day, average dose 2.7+-1.6 mg TREATMENT BEFORE STUDY: - intervention: 65.2% monotherapy, 34.8% combination therapy; -control: 63.1% monotherapy, 36.9% combination therapy. TITRATION: glimepiride titrated from 1 mg to 6 mg/day for optimal glycaemic control; duration of titration period not stated
Outcomes	PRIMARY OUTCOMES: not stated (carotid intima media thickness) SECONDARY OUTCOMES: HbA1c, fasting serum glucose, fasting serum insulin, HOMA: insulin resistance, BMI, blood pressure, lipid parameters, highly-sensitive C-reactive protein; von Willebrand factor
Notes	AIM OF STUDY:

Langenfeld 2005 *(Continued)*

	to investigate whether pioglitazone therapy decreases carotid intima media thickness in patients with type 2 diabetes (glimepirid-based comparison group used to compensate for concomitant effects of metabolic control)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lawrence 2004

Methods	DURATION OF INTERVENTION: 6 months DURATION OF FOLLOW-UP: 6 months RUN-IN PERIOD: 3 months with dietary treatment only, at visit 6 weeks pre-randomisation any patient having developed symptoms of uncontrolled diabetes or who had fasting plasma glucose of >13 mmol/L was withdrawn and commenced or recommenced on oral antihyperglycaemic agents LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: overweight, diet-controlled patients with type 2 diabetes mellitus INCLUSION CRITERIA: type 2 diabetes, 45-80 years; diet-treated with an HbA1c <7.0% or low-dose oral hypoglycaemic therapy with HbA1c <7.5%; BMI >27kg/m2; women of childbearing age had to be sterilised or use a reliable contraceptive EXCLUSION CRITERIA: diet-treated with an HbA1c >10%; currently taking lipid-lowering therapy; previously intolerant of any study medications; study medications would be contraindicated (alanine transaminase more than three times the upper limit of normal, serum creatinine >150 µmol/L, history of heart failure); recent myocardial infarction (<3 months); uncontrolled angina; uncontrolled hypertension DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: treated hypertension: - intervention 40%; - control 1 60%; - control 2 65%; - one current smoker in each group. CO-MEDICATIONS: treated with aspirin: - intervention 15%; - control 1 30%; - control 2 20%.
Interventions	NUMBER OF STUDY CENTRES: one COUNTRY/ LOCATION: UK SETTING: unclear INTERVENTION 1 (DOSE/DAY): pioglitazone; 30 mg once a day (up to 45 mg o.d.) CONTROL 1 (DOSE/DAY): metformin; 500 mg twice a day (up to 1g t.i.d)

Lawrence 2004 *(Continued)*

	CONTROL 2 (DOSE/DAY): gliclazide; 80 mg once a day (up to 160 mg b.d.) TREATMENT BEFORE STUDY: 12-15 in each group previously on oral antihyperglycaemic agents; 8-12 in each group treated hypertension; 3-6 in each group treated with aspirin TITRATION: if fasting blood glucose remained >7 mmol/L treatment was uptitrated to a maximum of metformin 1g t.i.d., pioglitazone 45 mg o.d., or gliclazide 160 mg b.d. (for three months, then kept fixed for a further three months)
Outcomes	PRIMARY OUTCOMES: lipoprotein subfractions; sample size calculation based on triglycerides SECONDARY OUTCOMES: HbA1c, renal function, liver function, glucose, full blood count
Notes	AIM OF STUDY: to compare the effects of metformin, pioglitazone, and gliclazide on lipoprotein subfractions in overweight, diet-controlled type 2 diabetic patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Matthews 2005

Methods	DURATION OF INTERVENTION: 52 weeks DURATION OF FOLLOW-UP: 52 weeks RUN-IN PERIOD: none, but dietary advice given with the aim of body weight normalisation LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: patients with type 2 diabetes mellitus inadequately controlled with metformin alone INCLUSION CRITERIA: type 2 diabetes inadequately managed with metformin alone (at >=50% of max recommended dose or at max tolerated dose for >=3 months); age 35 and 75 years; HbA1c >=7.5% or <=11.0%; fasting C-peptide of >=1.5 ng/ml, stable or worsening glycaemic control for >=3 months prior to screening EXCLUSION CRITERIA: type 1 diabetes, ketoacidosis, myocardial infarction, transient ischaemic attacks or stroke in previous 6 months, symptomatic heart failure, acute malabsorption or chronic pancreatitis, familial polyposis coli, malignant disease in the previous 10 years or substance abuse; female patients had to be postmenopausal, sterilised or using adequate contraception; pregnant or breastfeeding excluded; previous treatment with insulin, gliclazide, pioglitazone or other sulphonylureas or TZDs not permitted DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: not stated CO-MEDICATIONS: during study, thiazides permitted to treat oedema; if antihypertensive treatment was indicated, ACE inhibitors, angiotensin II receptor antagonists or calcium antagonists were given
Interventions	NUMBER OF STUDY CENTRES:

Matthews 2005 *(Continued)*

	75 COUNTRY/ LOCATION: nine European countries, Australia SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; 15 mg once a day, up to 45 mg once a day (70% of patients up to maximum dose, mean daily dose 39 mg); plus metformin at pre-study dose CONTROL (DOSE/DAY): gliclazide; 80 mg once a day, up to 160 mg twice a day (33% of patients up to maximum dose, mean daily dose 212 mg); plus metformin at pre-study dose TREATMENT BEFORE STUDY: - intervention: mean metformin dose 1726 mg/day (500-3000 mg/day); - control: mean metformin dose 1705 mg/day (500-3000 mg/day). TITRATION: 16 weeks forced dose titration, pioglitazone titrated from 15 mg once daily to 30 and 45 mg; gliclazide from 80 mg once daily to 160 mg, 240 mg (160 and 80 mg), and 320 mg (160 mg twice a day); cessation of titration only permitted on the basis of tolerability issues, including actual hypoglycaemia or risk of hypoglycaemia; dose achieved at week 16 was maintained for remaining 36 weeks
Outcomes	PRIMARY OUTCOMES: change in HbA1c from baseline to week 52 SECONDARY OUTCOMES: FPG, insulin, lipids, C-peptide, 32,33 split pro-insulin, urinary albumin and creatinine, adverse events, laboratory tests, clinical examination
Notes	AIM OF STUDY: to assess the long-term efficacy, safety and tolerability of add-on therapy of pioglitazone, compared with addition of sulphonylurea (gliclazide), to continued metformin in patients with type 2 diabetes inadequately controlled with metformin alone.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mattoo 2005

Methods	DURATION OF INTERVENTION: 6 months DURATION OF FOLLOW-UP: 6 months RUN-IN PERIOD: up to 14 days: patients remained on their prescribed insulin therapy regimen (insulin monotherapy or insulin plus oral antidiabetic medication) LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: patients with type 2 diabetes mellitus on insulin therapy INCLUSION CRITERIA: type 2 diabetes according to WHO criteria; used insulin therapy (with or without an oral antihyperglycaemic medication) for >= 3 months; had an HbA1c value >= 7.5% at screening and were >= 30 years old at the time of diabetes diagnosis EXCLUSION CRITERIA:

Mattoo 2005 *(Continued)*

	type 1 diabetes; clinical signs or symptoms of any chronic systemic condition (liver disease, diminished cardiac function, renal impairment, transplantation or dialysis, HIV infection), or sign or symptoms of drug or alcohol abuse; previous thizolidinedione use, systemic glucocorticoid therapy, nicotinic acid at a dose > 500 mg/d, or therapy for malignancy other than basal cell or squamous cell skin cancer; women who were breastfeeding or pregnant, as well as women of childbearing potential who were not actively practicing birth control DIAGNOSTIC CRITERIA: WHO 1999 CO-MORBIDITIES: not stated CO-MEDICATIONS: patients were allowed to use any concomitant medication required, except another oral antidiabetic medication, systemic glucocorticoid therapy, or nicotinic acid (> 500 mg/d)
Interventions	NUMBER OF STUDY CENTRES: multi, not stated COUNTRY/ LOCATION: not stated, multinational SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; 30 mg/day + insulin CONTROL (DOSE/DAY): placebo + insulin TREATMENT BEFORE STUDY: - all patients received diabetes education, including dietary and exercise guidelines, and were instructed to maintain their individual diet and exercise regimens throughout the study; - patients were instructed on self-monitoring of blood glucose; - if the patients were using insulin plus oral antidiabetic medication combination therapy, the oral antidiabetic medication was taken unchanged until the day before visit 2 (insulin intensification period of three months between visit 2 and visit 6, see below), at which point it was stopped. TITRATION: - all patients went through a 3-month insulin intensification period; - the intent of this intensification was to exclude patients, who could obtain glycaemic control (i.e. attain an HbA1c value < 7.0%) with insulin alone; - patients with HbA1c values >= 7.0% after insulin intensification were randomised.
Outcomes	PRIMARY OUTCOMES: change in HbA1c from baseline (sample size calculation) SECONDARY OUTCOMES: adverse events including hypoglycaemic episodes, safety parameters, body weight, FPG, serum lipids, free fatty acids, highly sensitive CRP, plasminogen activator inhibitor-1 (PAI-1)
Notes	AIM OF STUDY: to test the hypothesis that adding pioglitazone 30 mg (compared to placebo) would further improve the glycaemic control of patients on insulin therapy who still had an HbA1c value > 7%. The effect of pioglitazone plus insulin on the serum lipid profile and selected cardiovascular risk factors in these patients was also studied

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Pavo 2003

Methods	DURATION OF INTERVENTION: 32 weeks DURATION OF FOLLOW-UP: 32 weeks RUN-IN PERIOD: single-blind run-in phase (3-5 weeks), one placebo tablet and three placebo capsules LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: pharmaco-naive patients with type 2 diabetes mellitus INCLUSION CRITERIA: patients with recently diagnosed type 2 diabetes (<12 months), defined by WHO criteria, HbA1c 7.5-11.0%; >=40 years EXCLUSION CRITERIA: history of lactic acidosis, liver disease, NYHA cardiac status class III or IV congestive heart failure, HIV infection, renal transplant, impaired kidney function, impaired liver function (defined), BMI below 20 kg/m2 or above 40 kg/m2, breastfeeding, pregnant, or of childbearing potential, participation in any clinical trial that included any drugs; undergoing therapy with nicotinic acid, renal dialysis or cancer therapy; anaemia; systemic glucocorticoid therapy or use of OAM, ACE inhibitors, or angiotensin II receptor agonists within 30 days; known allergy to metformin or any TZD drug DIAGNOSTIC CRITERIA: WHO 1999 CO-MORBIDITIES: not stated CO-MEDICATIONS: not stated
Interventions	NUMBER OF STUDY CENTRES: 19 COUNTRY/ LOCATION: Russia (4 sites), Hungary (15 sites) SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; 30 mg/day, titrated to max of 45 mg/day, mean dose 41.5 mg/day CONTROL (DOSE/DAY): metformin; 850 mg/day, titrated to max of 2550 mg/day, mean dose 2292 mg/day TREATMENT BEFORE STUDY: patients received diabetes education and individualised dietary and physical activity instructions (run-in) TITRATION: - intervention: after randomisation, one 30 mg pioglitazone capsule and 3 placebo tablets daily, after 8 weeks, if FGP >= 7mmol/L, pioglitazone increased to 45mg capsule (+3 placebo tablets) (77% of group); - control: after randomisation, one placebo capsule, one 850mg metformin tablet, 2 placebo tablets identical to metformin tablet daily; then 2 weeks post-randomisation dose increased to two 850mg tablets (1700mg) +1 placebo tablet +1 placebo capsule; after 8 weeks, if FGP >=7mmol/L, metformin increased to three 850mg tablets (2550mg) +1 placebo capsule (73% of group).
Outcomes	PRIMARY OUTCOMES: change in HbA1c SECONDARY OUTCOMES: insulin sensitivity (HOMA-S), lipoproteins, safety (BP, heart rate, weight, routine blood laboratory parameters, adverse events
Notes	AIM OF STUDY: to compare the efficacy and tolerability of monotherapy with pioglitazone to metformin in recently diagnosed type 2 diabetes patients (naive to oral antihyperglycaemic medication).

Pavo 2003 *(Continued)*

	the primary objective was to compare the effect of each treatment on glycaemic control (change in HbA1c)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Scherbaum 2002

Methods	DURATION OF INTERVENTION: 26 weeks DURATION OF FOLLOW-UP: 26 weeks RUN-IN PERIOD: 10 week placebo washout period (at the end, HbA1c had to remain between 7.5 and 12% and FPG between 140 and 250 mg/dl) - discontinuationof previous oral antidiabetic therapy LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: patients with type 2 diabetes mellitus, phase II study INCLUSION CRITERIA: type 2 diabetes, 35 to 70 years, BMI 25-35 kg/m2 at screening, HbA1c 7.5-12%, FPG 140-300 mg/dl (=250 mg/dl at end of washout period); female participants had to be postmenopausal, surgically sterilised, or using appropriate contraception EXCLUSION CRITERIA: type 1 diabetes, secondary failure to treatment with sulphonylureas, 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, myocardial infarction, hypertension (defined), stroke, hypothyroidism, history of transient ischaemic attack or stroke, significant anaemia of any aetiology, clinically relevant haematological or malignant disease in the last 10 years, HIV infection, alcohol or drug abuse, participation in clinical trial in 3 months prior to study DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: not stated CO-MEDICATIONS: not stated
Interventions	NUMBER OF STUDY CENTRES: 59 COUNTRY/ LOCATION: Germany SETTING: unclear INTERVENTION 1 (DOSE/DAY): pioglitazone; 15 mg/day (once daily) INTERVENTION 2 (DOSE/DAY): pioglitazone; 30 mg/day (once daily) CONTROL (DOSE/DAY): matching placebo TREATMENT BEFORE STUDY: 61% previous antidiabetic treatment, most commonly (13%) acarbose and (17%) glibenclamide

Scherbaum 2002 *(Continued)*

Outcomes	PRIMARY OUTCOMES: change in HbA1c from baseline to final visit SECONDARY OUTCOMES: blood glucose, C-peptide, blood pressure, plama lipids, body weight, adverse events (incl. hypoglycaemia)
Notes	AIM OF STUDY: to compare the efficacy and tolerability of pioglitazone 15 mg/day and 30 mg/day monotherapy to placebo in European patients with type 2 diabetes (in addition to dietary control) phase II study

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Schernthaner 2004

Methods	DURATION OF INTERVENTION: 52 weeks DURATION OF FOLLOW-UP: 52 weeks RUN-IN PERIOD: none LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: pharmaco-naive patients with type 2 diabetes mellitus INCLUSION CRITERIA: 35-75 years, type 2 diabetes inadequately treated with diet alone, HbA1c 7.5-11% with stable or worsening glycaemia for at least 3 months; corticosteroids and beta-blockers permitted if treatment commenced at least 4 weeks before screening; antihypertensive agents - except thiazides - allowed dependent on clinical need; lipid-lowering agents also permitted EXCLUSION CRITERIA: prior use of glucose-lowering pharmacotherapy, specific contraindications to either drug DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: not stated CO-MEDICATIONS: - Intervention: ACE inhibitors 31%, 11% lipid lowering therapy; - control: ACE inhibitors 29%, 10% lipid lowering therapy.
Interventions	NUMBER OF STUDY CENTRES: 167 COUNTRY/ LOCATION: 12 European countries SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; up to 45 mg/day (14.1% on 30 mg/day, 85.9% on 45 mg/day; mean dose 43 mg/day) CONTROL (DOSE/DAY): metformin; up to 850 mg three times daily (2550 mg/day) (11.8% on 850 mg/day, 26.5% on 1700 mg/day, 61.6% on 2550 mg/day; mean dose 2124 mg/day) TREATMENT BEFORE STUDY: both groups: instructed to adhere to disease- and weight-oriented diet throughout the study; dietary advice given at baseline with aim of body weight normalisation; if body weight increased any more than 5% at any stage or HbA1c increased to greater than 9% after completed dose titration, patients were given additional intensive dietary counselling TITRATION:

Schernthaner 2004 *(Continued)*

	12 week forced dose titration: - intervention: starting on 30mg/day of pioglitazone, up to 45 mg/day (with metformin placebo); - control: starting on 850mg of metformin once daily, up to three times daily (2550 mg/day) (with pioglitazone placebo); - dose levels increased, maintained or decreased at weeks 4, 8 and 12 according to tolerability; dose reached at week 12 fixed for remainder of study.
Outcomes	PRIMARY OUTCOMES: HbA1c SECONDARY OUTCOMES: FPG, insulin, lipid profiles, adverse events, laboratory tests, at selected centres: C-peptide and proinsulin and standard oral glucose tolerance test
Notes	AIM OF STUDY: to compare the effects of pioglitazone with metformin on metabolic variables in type 2 diabetes patients naive to oral hypoglycaemic therapy; to determine any additional benefits on lipid profiles, hyperinsulinaemia, and glucose disposal during oral glucose tolerance tests

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Smith 2005

Methods	DURATION OF INTERVENTION: 24 weeks DURATION OF FOLLOW-UP: 24 weeks RUN-IN PERIOD: none LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: mainly white patients with type 2 diabetes mellitus INCLUSION CRITERIA: 35 to 75 years, type 2 diabetes (defined as FPG of 126 mg/dl or higher at entry or FPG of more than 115 mg/dl and a 2h oral glucose tolerance test of 200 mg/dl or higher); FPG at entry had to be 200 mg/dl or less; for women adequate contraceptive control required (defined); patients could be treated with diet, metformin or sulphonylurea (continued as necessary throughout the study) EXCLUSION CRITERIA: significant renal, cardiac, liver, lung or neurological disease; controlled hypertension 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 abusers, or unwilling to abstain from caffeine for 48 hours and alcohol for 24 hours prior to metabolic rate measurements; metal objects that would interfere with measurement of visceral fat with CT (e.g. implanted rods, surgical clips) prevented people from participating; also excluded: patients taking drugs known to affect lipid metabolism, energy metabolism or body weight, e.g. orlistat, sibutramine, ephedrine, phenylpropanolamine, corticosteroids DIAGNOSTIC CRITERIA: FPG of 126 mg/dl or higher at entry or FPG of more than 115 mg/dl and a 2h oral glucose tolerance test of 200 mg/dl or higher CO-MORBIDITIES: not stated CO-MEDICATIONS: some took sulphonylureas (placebo group 9/21, pioglitazone 11/21), some metformin
Interventions	NUMBER OF STUDY CENTRES:

Smith 2005 *(Continued)*

	one COUNTRY/ LOCATION: USA SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; 30 mg/day CONTROL (DOSE/DAY): placebo TREATMENT BEFORE STUDY: sulphonylurea or metformin continued as necessary (if taken before). instructions on a healthy diet for diabetic patients by a dietitian. TITRATION: HbA1c target was 7.0% or less; if after 8 weeks, the HbA1c level was 7% or greater or FPG was 100 mg/dl or greater, dosage of pioglitazone (or matching placebo) increased to 45 mg/day (all but one patient); patients on sulphonylureas or metformin experiencing hypoglycaemia had the dose of these medications reduced or the medication discontinued
Outcomes	PRIMARY OUTCOMES: not stated (visceral, subcutaneous and total body fat) SECONDARY OUTCOMES: HbA1c, insulin, glucose, insulin resistance (QUICKI), triglycerides, HDL, LDL and total cholesterol, weight, BMI, subjective measures for hunger and fullness (visual analogue scale), resting metabolic rate, change of metabolic rate after a meal; body composition
Notes	AIM OF STUDY: primary aim to evaluate the effect of TZDs on visceral, subcutaneous and total body fat; secondary aims to determine effects of pioglitazone on a) energy expenditure, b) hunger and satiety, c) blood lipids, d) the role of insulin/sulphonylurea usage on weight gain in patients with type 2 diabetes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tan 2004a

Methods	DURATION OF INTERVENTION: 52 weeks DURATION OF FOLLOW-UP: 52 weeks RUN-IN PERIOD: 1-3 weeks, patients received diaries for recording self-monitored blood glucose and hypoglycaemic events; diabetes education and diet and exercise instructions; patients currently on anthyperglycaemic monotherapy continued this until day 1 of titration period LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: Mexican patients with type 2 diabetes mellitus INCLUSION CRITERIA: type 2 diabetes, HbA1c >7.5 to <=11% in patients not receiving oral antihyperglycaemic agent monotherapy, and >7.5 to <=9.5% in patients receiving oral antihyperglycaemic agent monotherapy; eligible patients must have undergone an adequate trial of dietary and lifestyle interventions before enrollment EXCLUSION CRITERIA:

Tan 2004a *(Continued)*

	treatment with TZD or insulin within previous 3 months; current prescription of maximum dose of oral antihyperglycaemic agent or for combination therapy; treatment with systemic glucocorticoids (incl. topical and inhaled) within previous 30 days; cardiac disease with substantial limitation of functional capacity (NYHA class III or IV); serum triglycerides >400mg/dl, serum creatinine >2.0mg/dl, renal transplantation or current renal dialysis; ALT or AST >2.5 times upper limit of normal; clinical signs or symptoms of liver disease; haemoglobin <105 g/L for women or <115 g/L for men; previous HIV infection, signs and symptoms of substance abuse DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: not stated CO-MEDICATIONS: - intervention: antilipidaemic agents (fibrates, statins, or both) 12.4%; - control: antilipidaemic agents (fibrates, statins, or both) 11.4%.
Interventions	NUMBER OF STUDY CENTRES: 19 COUNTRY/ LOCATION: Mexico SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; 15 mg up to 45 mg q.d.; mean final dose 37 mg q.d. CONTROL (DOSE/DAY): glimepiride; 2 mg up to 8 mg q.d., mean final dose 6 mg q.d. TREATMENT BEFORE STUDY: - intervention: 76% receiving oral antihyperglycaemic agent (52.1% secretagogues, 22.3% metformin), antilipidaemic agents (fibrates, statins, or both) 12.4%; - control: 77.2% receiving oral antihyperglycaemic agent (57.7% secretagogues, 19.5% metformin), antilipidaemic agents (fibrates, statins, or both) 11.4%; - all patients received diabetes education and diet and exercise instructions. TITRATION: 12 weeks, initial dose pioglitazone 15 mg q.d. and glimepiride 2 mg q.d.; goal of titration to achieve FPG <=7 mmol/l and 1h postprandial blood glucose <=10 mmol/l; if FPG or post-prandial blood glucose concentrations were consistently higher than glycaemic target, dose adjustments were made at 4 week intervals (through week 12 of titration period); pioglitazone: 15mg increments up to max of 45 mg q.d.; glimepiride 2mg increments up to max of 8 mg q.d.; investigators encouraged to keep doses constant thereafter
Outcomes	PRIMARY OUTCOMES: insulin sensitivity (HOMA, QUICKI, fasting insulin concentrations) SECONDARY OUTCOMES: HbA1c; lipids, lipoproteins, adverse events
Notes	AIM OF STUDY: to compare the effectiveness of 52 weeks treatment with pioglitazone and glimepiride in providing long term glycaemic control and increasing insulin sensitivity in Mexican patients with type 2 diabetes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Tan 2004b

Methods	DURATION OF INTERVENTION:

Tan 2004b *(Continued)*

	52 weeks DURATION OF FOLLOW-UP: 52 weeks RUN-IN PERIOD: 1-3 week washout period (OAD); instructions to maintain current diet and exercise regimen throughout study; diaries for recording self-monitored blood glucose measurements and hypoglycaemic events LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: Scandinavian patients with type 2 diabetes mellitus INCLUSION CRITERIA: type 2 diabetes, naive to oral antidiabetics or monotherapy; HbA1c >7.5% to <=11% for patients not receiving oral antidiabetics or >7.5% and <=9.5% for patients receiving monotherapy; fasting C-peptide of 0.333 pmol/L (1 ng/ml) at screening; had received adequate trial of dietary or lifestyle intervention EXCLUSION CRITERIA: insulin treatment within 30 days prior to screening; glucocorticoid therapy (excluding topical or inhaled preparations) within 4 weeks of screening; currently on maximum dose of one oral antihyperglycaemic or on combination therapy; cardiac disease with substantial limitation of functional capacity (NYHA class III or IV cardiac status); serum creatinine >177 µmol/L; renal transplant or current renal dialysis; ALT or AST >2.5 times the upper limit of normal; clinical signs or symptoms of liver disease, haemoglobin or haematocrit below the lower limit of normal DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: not stated CO-MEDICATIONS: lipoprotein-altering medication at screening: - control: 26%; - intervention: 32%. antihypertensives at sceening: - control: 43%; - intervention: 50%.
Interventions	NUMBER OF STUDY CENTRES: 22 COUNTRY/ LOCATION: Denmark, Finland, Norway, Sweden SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone; from 30 mg/day to 45 mg/day CONTROL (DOSE/DAY): micronized glibenclamide; from 1.75 mg/day to max 10.5 mg/day TREATMENT BEFORE STUDY: - control: 69% oral antidiabetics at screening (55% SU, 44% metformin, one patient repaglinide); - intervention: 70% oral antidiabetics at screening (58% SU, 42% metformin); - during the washout period patients received instructions to maintain current diet and exercise regimen throughout the study. TITRATION: 12 week titration period; glibenclamide initial dose 1.75 mg, pioglitazone initial dose 30 mg; titration goal to achieve FBG of <=7mmol/L and 1h postprandial glucose of <=10 mmol/L; dose of medication adjusted if FBG or postprandial glucose consistently higher than the titration goal; for pioglitazone, dose increased to 45 mg/day, for glibenclamide increased to 3.5 mg/day at week 4, to 7.0 mg/day at week 8, and to 10.5 mg at week 12; dose adjustments for optimal control allowed during maintenance period intervention: 75% received maximal dose allowed (45 mg); control: 62% received maximal dose allowed (10.5 mg)
Outcomes	PRIMARY OUTCOMES: HOMA insulin sensitivity (used for power calculation)

Tan 2004b *(Continued)*

	SECONDARY OUTCOMES: HbA1c, FPG, fasting serum insulin, lipids, safety assessments incl. adverse event recording
Notes	AIM OF STUDY: to compare the effect of 52 weeks' treatment with micronized glibenclamide and pioglitazone on indicators of insulin sensitivity, glycaemic control, serum lipids and safety or tolerability in type 2 diabetic patients who were either naïve to oral antihyperglycaemic medication or had previously received oral monotherapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Watanabe 2005

Methods	DURATION OF INTERVENTION: 6 months DURATION OF FOLLOW-UP: 6 months RUN-IN PERIOD: none LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: untreated Japanese patients with type 2 diabetes mellitus INCLUSION CRITERIA: untreated type 2 diabetes patients according to criteria of the Japanese Diabetes Society (FPG > 126 mg/dl), HbA1c 6.5-8.0% EXCLUSION CRITERIA: kidney disease DIAGNOSTIC CRITERIA: criteria of the Japanese Diabetes Society (FPG > 126 mg/dl), HbA1c 6.5-8.0% CO-MORBIDITIES: not stated CO-MEDICATIONS: - patients were forbidden to change dosing schedule of drugs they were receiving in addition to study drugs; - intervention (individuals): Ca antagonist 8, ACE inhibitor 8, statins 13, beta-blocker 3; - control (individuals): Ca antagonist 10, ACE inhibitor 11, statins 14, beta-blocker 3.
Interventions	NUMBER OF STUDY CENTRES: one COUNTRY/ LOCATION: Japan SETTING: unclear INTERVENTION (DOSE/DAY): pioglitazone, started at 15 mg/day, mean dose 17.3 mg/day CONTROL (DOSE/DAY): glibenclamide, 1.25-2.5 mg/day (mean dose 1.56 mg/day) TREATMENT BEFORE STUDY: not stated
Outcomes	PRIMARY OUTCOMES:

Watanabe 2005 *(Continued)*

	not stated (pulse wave velocity) SECONDARY OUTCOMES: BMI, blood pressure, HbA1c, brachial ankle pulse wave velocity, FPG, fasting immunoreactive insulin, HOMA: insulin resistance, lipid parameters
Notes	AIM OF STUDY: to investigate the anti-arteriosclerotic effects of pioglitazone in patients with diabetes mellitus using pulse wave velocity as an index of efficacy

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Yamanouchi 2005

Methods	DURATION OF INTERVENTION: 12 months DURATION OF FOLLOW-UP: 12 months RUN-IN PERIOD: one month for baseline measurements LANGUAGE OF PUBLICATION: English
Participants	WHO PARTCIPATED: drug-naive Japanese patients with a short duration of type 2 diabetes mellitus INCLUSION CRITERIA: patients continued in the study if they met the inclusion criteria of HbA1c >= 7.0% and FPG >= 7.78 mmol/ l, at the end of the 1-month observation period; all patients had a body mass index (BMI) between 22 and 35 kg/m2 (mean 25.9 kg/m2); the criteria for obesity in Japanese people are BMI = 25 kg/m2 EXCLUSION CRITERIA: patients who had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy; patients with liver dysfunction (AST, ALT > 1.5× upper limit of normal); impaired kidney function (serum creatinine > 133µmol/l), or anaemia; patients with a myocardial infarction, angina, congestive heart failure, or a documented cerebrovascular accident DIAGNOSTIC CRITERIA: not stated CO-MORBIDITIES: not stated CO-MEDICATIONS: - antihypertensive drugs or other concurrent treatments, including dietary regimens, remained unchanged throughout the study; - the number of patients taking antihypertensive medications were 16 (42%), 18 (46%) and 18 (49%) (for the pioglitazone, metformin and glimepiride groups, respectively); - none of the participants was on lipid-lowering therapy.
Interventions	NUMBER OF STUDY CENTRES: not stated COUNTRY/ LOCATION: Japan SETTING: unclear INTERVENTION 1 (DOSE/DAY): pioglitazone; 30-45 mg/day

Yamanouchi 2005 *(Continued)*

	CONTROL 1 (DOSE/DAY): metformin; 750 mg/day CONTROL 2 (DOSE/DAY): glimepiride; 1.0-2.0 mg/day TREATMENT BEFORE STUDY: - 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, including the 1 month for baseline measurements before the study (observation period).
Outcomes	PRIMARY OUTCOMES: HbA1c SECONDARY OUTCOMES: FPG, 1,5-anhydroglucitol, plasma insulin, haematology, biochemistry, adverse events, BMI, blood pressure, lipids, free fatt acids
Notes	AIM OF STUDY: to compare changes in major metabolites for 12 months when TZD, biguanide, or glimepiride were used in drug-naive Japanese patients with type 2 diabetes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ACE = ; ADA = American Diabetes Association; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATII or AT2 = ; b.d. = bis in die, twice daily; BMI = body mass index (kg(m2); BP = blood pressure; CRP = C-reactive protein; CVD = cardiovascular disease; FPG = fasting plasma glucose; HbA1c = glycosylated haemoglobin A1c; HOMA = homeostasis model assessment (of insulin sensitvity); NYHA = New York Heart Association; OAM = oral antidiabetic medication; o.d. = once daily; PPAR = peroxisome proliferator activated receptor; q.d. = quaque die, once a day; QUICKI = quantitative insulin sensitivity check index; SU = sulfonylureas; t.i.d. = ter in die, three times daily; TZD = thiazolidinediones ("glitazones"); WHO = World Health Organisation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Koshiyama 2001	not a randomised controlled clinical trial
Nagashima 2005	treatment duration less than 24 weeks
Nishio 2006	randomised controlled trial, but no placebo or other intervention in the control group
Roberts 2005b	glimepiride versus "thiazolidinediones", no data on pioglitazone available
Schofl 2005	treatment duration less than 24 weeks, observational study
Takagi 2005	conventional anti-diabetic treatment versus "thiazolidinedione treatment", no data on pioglitazone available
Tseng 2005	treatment duration less than 24 weeks

Characteristics of ongoing studies *[ordered by study ID]*

ACCORD

Trial name or title	Action to Control Cardiovascular Risk in Diabetes (ACCORD)
Methods	
Participants	All 10,251 participants will be in the overarching glycemia trial. In addition, one 2 X 2 trial will also address the lipid question in 5,518 of the participants and the other 2 X 2 trial will address the blood pressure question in 4,733 of the participants. The three specific primary ACCORD hypotheses are as follow. In middle-aged or older people with type 2 diabetes who are at high risk for having a cardiovascular disease (CVD) event because of existing clinical or subclinical CVD or CVD risk factors: 1. does a therapeutic strategy that targets a HbA1c of < 6.0% reduce the rate of CVD events more than a strategy that targets a HbA1c of 7.0% to 7.9% (with the expectation of achieving a median level of 7.5%)? 2. in the context of good glycemic control, does a therapeutic strategy that uses a fibrate to raise HDL-C/lower triglyceride levels and uses a statin for treatment of LDL-C reduce the rate of CVD events compared to a strategy that only uses a statin for treatment of LDL-C? 3. In the context of good glycemic control, does a therapeutic strategy that targets a systolic blood pressure (SBP) of < 120 mm Hg reduce the rate of CVD events compared to a strategy that targets a SBP of < 140 mm Hg? The 10,251 participants will be treated and followed for about 4 to 8 years (approximate mean of 5.6 years) at 77 Clinical Sites administratively located within 7 Clinical Center Networks in the United States and Canada.
Interventions	The design is a randomized, multicenter, double 2 X 2 factorial design in 10,251 patients with type 2 diabetes mellitus. The trial is designed to test the effects on major CVD events of intensive glycemia control, of treatment to increase HDL-cholesterol and lower triglycerides (in the context of good LDL-C and glycemia control), and of intensive blood pressure control (in the context of good glycemia control).
Outcomes	The primary outcome measure for the trial is the first occurrence of a major cardiovascular disease event, specifically nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. The ACCORD study is designed to have: * 89% power to detect a 15% treatment effect of intensive glycemic control compared with standard glycemic control, * 87% power to detect a 20% treatment effect of lipid control through LDL-C treatment and fibrates compared with lipid control using LDL-C treatment alone, * 94% power to detect a 20% treatment effect of intensive blood pressure control compared with standard blood pressure control. Secondary hypotheses include treatment differences in other cardiovascular outcomes, total mortality, microvascular outcomes, health-related quality of life, and cost-effectiveness.
Starting date	Recruitment occurred in two non-contiguous periods: an initial period that began in January 2001 for the Vanguard Phase of the trial (during which 1174 participants were randomized) and then a subsequent period beginning in January 2003 and ending in October 2005. Follow-up is scheduled to end in June 2009, with the primary results announced in early 2010.
Contact information	ACCORD is sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The NHLBI Project Office is responsible for the administration and monitoring of the trial.
Notes	Despite the importance of this health problem in the North American population, there is a lack of definitive data on the effects of intensive control of glycemia and other CVD risk factors on CVD event rates in diabetic patients. The overall goal of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is to address this challenge by testing three complementary medical treatment strategies for type 2 dia-

ACCORD *(Continued)*

	betes to enhance the options for reducing the still very high rate of major CVD morbidity and mortality in this disease.

BARI-2D

Trial name or title	Bypass Angioplasty Revascularization Investigation in Type 2 Diabetics (BARI 2D)
Methods	
Participants	Eligibility - Genders Eligible for Study: Both Criteria Inclusion Criteria for BARI 2D 1. Diagnosis of Type 2 diabetes mellitus. 2. Coronary arteriogram showing one or more vessels amenable to revascularization (=50% stenosis). 3. Objective documentation of ischemia OR subjectively documented typical angina with =70% stenosis in at least one artery. 4. Suitability for coronary revascularization by at least one of the available methods (does not require the ability to achieve complete revascularization). 5. Ability to perform all tasks related to glycemic control and risk factor management. 6. Age 25 or older. 7. Informed written consent. Exclusion Criteria for BARI 2D 1. Definite need for invasive intervention as determined by the attending cardiologist. 2. Prior bypass surgery (CABG) or prior catheter-based intervention within the past 12 months. 3. Planned intervention for disease in bypass graft(s) if the patient is randomized to a strategy of initial revascularization. 4. Class III or IV CHF. 5. Creatinine > 2.0 mg/dl. 6. HbA1c > 13%. 7. Need for major vascular surgery concomitant with revascularization (e.g., carotid endarterectomy). 8. Left main stenosis > 50%. 9. Non-cardiac illness expected to limit survival. 10. Hepatic disease (ALT> 2 times the ULN). 11. Fasting triglycerides > 1000 mg/dl in the presence of moderate glycemic control (HbA1c <9.0%). 12. Current alcohol abuse. 13. Chronic steroid use judged to interfere with the control of diabetes, exceeding 10 mg. of Prednisone per day or the equivalent. 14. Pregnancy, known, suspected, or planned in next 5 years. 15. Geographically inaccessible or unable to return for follow-up. 16. Enrolled in a competing randomized trial or clinical study. 17. Unable to understand or cooperate with protocol requirements. Patients with Type 2 diabetes mellitus and CAD documented by coronary arteriography will be eligible for the trial if revascularization is not required for prompt control of severe or unstable angina. Diabetic patients who are being treated with insulin or oral hypoglycemic drugs will be eligible as well as diabetic patients treated with diet and exercise alone provided that a diagnosis of diabetes can be confirmed by record review or that a fasting plasma glucose (FPG)>125/mg/dl (7.0 mmol/l) can be obtained. The determination of suitability for BARI 2D will be made by a physician-investigator at each participating institution on clinical grounds at the time of coronary angiography. Significant CAD will be defined as at least one stenosis >50%. Angina and ischemia will be assessed by use of patient self-report, physician examination, and appropriate diagnostic measures including exercise myocardial perfusion imaging, exercise echocardiography, and IV dipyridamole or

BARI-2D *(Continued)*

	adenosine myocardial perfusion imaging or invasively by doppler or pressure wire. Objective documentation of myocardial ischemia includes any of the following: 1. Exercise or pharmacologically-induced: 1. =1 mm of horizontal or downsloping ST depression or elevation for =60-80 milliseconds after the end of the QRS complex; 2. myocardial perfusion defect; 3. myocardial wall motion abnormality. 2. Stabilized, prior acute coronary syndrome with CK-MB or troponin elevation or with new, =0.5 mm ST depression or elevation, or T wave inversion of =3 mm in 2 contiguous ECG leads. 3. Doppler or pressure wire showing coronary flow reserve (CFR) <2.0 or fractional flow reserve (FFR) <0.75. Among patients without documented ischemia, only patients with stenosis = 70% presenting with classic anginal symptoms will be eligible for randomization.
Interventions	Study Type: Interventional Study Design: Treatment, Randomized, Factorial Assignment A. Primary Aim The primary aim of the BARI 2D trial is to test the following two hypotheses of treatment efficacy in 2800 patients with Type 2 diabetes mellitus and documented stable CAD, in the setting of uniform glycemic control and intensive management of all other risk factors including dyslipidemia, hypertension, smoking, and obesity: 1. Coronary Revascularization Hypothesis: a strategy of initial elective revascularization of choice (surgical or catheter-based) combined with aggressive medical therapy results in lower 5-year mortality compared to a strategy of aggressive medical therapy alone; 2. Method of Glycemic Control Hypothesis: with a target HbA1c level of <7.0%, a strategy of hyperglycemia management directed at insulin sensitization results in lower 5-year mortality compared to a strategy of insulin provision. B. Secondary Aims The secondary aims of the BARI 2D trial include: a) comparing the death, myocardial infarction or stroke combined endpoint event rate between the revascularization versus medical therapy groups and between the insulin sensitization versus insulin provision groups; b) comparing rates of myocardial infarction, other ischemic events, angina and quality of life associated with each revascularization and hyperglycemia management strategy; c) evaluating the relative economic costs associated with the trial treatment strategies, d) exploring the effect of glycemic control strategy on the progression and mechanism of vasculopathy including changes in PAI-1 gene expression.
Outcomes	The primary aim of the BARI 2D trial is to test the following two hypotheses of treatment efficacy in 2800 patients with Type 2 diabetes mellitus and documented stable CAD, in the setting of uniform glycemic control and intensive management of all other risk factors including dyslipidemia, hypertension, smoking, and obesity: 1. Coronary Revascularization Hypothesis: a strategy of initial elective revascularization of choice (surgical or catheter-based) combined with aggressive medical therapy results in lower 5-year mortality compared to a strategy of aggressive medical therapy alone; 2. Method of Glycemic Control Hypothesis: with a target HbA1c level of <7.0%, a strategy of hyperglycemia management directed at insulin sensitization results in lower 5-year mortality compared to a strategy of insulin provision.
Starting date	Study start: September 2000; Study completion: June 2007
Contact information	http://www.bari2d.org/public/contactus.html
Notes	The BARI 2D trial is a multicenter study that uses a 2x2 factorial design, with 2800 patients being assigned at random to initial elective revascularization with aggressive medical therapy or aggressive medical therapy alone with equal probability, and simultaneously being assigned at random to an

BARI-2D *(Continued)*

	insulin providing or insulin sensitizing strategy of glycemic control (with a target value for HbA1c of <7.0% for all patients).

CHICAGO

Trial name or title	A Study of Pioglitazone HCl Versus Glimepiride in Subjects With Type 2 Diabetes Measuring the Progression of Atherosclerosis (CHICAGO)
Methods	
Participants	Study subjects will be treated with either pioglitazone or glimepiride for approximately 72 weeks (18 months). Subjects will make 12 or 13 visits to the study center, 4 visits to the center conducting the carotid ultrasound, and 2 visits to the center conducting the electron beam tomography scan. During visits to the study center, subjects will have blood drawn at each visit, have urine collected at 5 visits, have their vital signs and abdominal and hip girth measured at each visit, have 3 physical exams over the course of the study, and have an ECG at the beginning and end of the study. At each visit, information will be collected regarding adverse events the subject may have experienced and any medications the subject is taking. Eligibility: Ages Eligible for Study: 45 Years - 85 Years, Genders Eligible for Study: Both Inclusion Criteria: - Subjects aged 45 to 85 years, inclusive. - Subjects with type 2 diabetes. - Subjects with HbA1c >6.0% and <9% if taking antidiabetic medications, or HbA1c >6.5% and <10% if not taking antidiabetic medication. Exclusion Criteria: - Subjects with type 1 diabetes, symptomatic CAD, cerebrovascular disease or peripheral vascular disease. - Subjects taking more than two antidiabetic therapies. - Subjects taking thiazolidinediones (TZDs) currently or in the past 12 weeks - Subjects with New York Heart Association Class III or IV cardiac failure or left ventricular dysfunction (left ventricular ejection fraction <40%)
Interventions	Study Design: Treatment, Randomized, Double-Blind, Active Control, Parallel Assignment, Efficacy Study Study subjects will be treated with either pioglitazone or glimepiride for approximately 72 weeks (18 months).
Outcomes	Primary Outcomes: Absolute change in carotid intima-media thickness (CIMT) from baseline to final visit (18 months).
Starting date	Study start: August 2003; Study completion: October 2006 Last follow-up: April 2006; Data entry closure: July 2006
Contact information	Takeda Global Research & Development Center, Inc ClinicalTrials.gov Identifier: NCT00225264
Notes	The primary purpose of this study is to compare the effects of pioglitazone HCl versus glimepiride on the amount of thickening of the carotid artery, a large vessel in the neck. The carotid artery is measured using a noninvasive procedure called an ultrasound. It is believed that the amount of

CHICAGO *(Continued)*

	thickness of the carotid artery can be an indication of the amount of atherosclerosis or heart disease that a person has.

PERISCOPE

Trial name or title	Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE)
Methods	
Participants	Subjects with type 2 diabetes requiring angiography will have the IVUS procedure performed at baseline and again following 18 months of treatment. Subjects who meet eligibility criteria will be titrated up to a maximum of 45 mg/day pioglitazone HCl or 4 mg/day glimepiride. Subjects will make 11 visits to the study center. During study visits, subjects will have weight, and vital signs assessed as well as abdominal and hip girth. Physical exams will be done at baseline, 12 months, and 18 months. ECG will be done at baseline and 18 months. Lab assessments will be done at each visit. Completed blood count, chemistries, urinalysis and markers of atherosclerosis will be drawn at baseline, and months 6, 12 and 18. At each visit, information will be collected regarding adverse events the subject may have experienced and any medications the subject is taking. Compliance with study medication will also be assessed at each visit.
Interventions	Study Type: Interventional Study Design: Treatment, Randomized, Double-Blind, Active Control, Parallel Assignment, Efficacy Study Subjects who meet eligibility criteria will be titrated up to a maximum of 45 mg/day pioglitazone HCl or 4 mg/day glimepiride.
Outcomes	Primary Outcomes: Effect of treatment on the nominal change in percent atheroma volume of the identified target coronary artery segment from baseline after 18 months of treatment as measured by intravascular ultrasound (IVUS) imaging of the coronary arteries. Expected Total Enrollment: 440
Starting date	Study start: August 2003; Expected completion: March 2008 Last follow-up: August 2007; Data entry closure: November 2007
Contact information	Brigit Isaacson, MT, MBA 847-383-3237 bisaacson@tgrd.com ClinicalTrials.gov Identifier: NCT00225277
Notes	The primary purpose of this study is to compare the effect of pioglitazone HCl versus glimepiride on the coronary atheroma volume using IVUS of the coronary arteries after up to 18 months of treatment.

PPAR

Trial name or title	Pioglitazone Protects DM Patients Against Re-Infarction (PPAR Study)
Methods	
Participants	Type 2 diabetes mellitus is a well-established risk factor for coronary heart disease and atherosclerotic change in coronary artery. So we designed a prospective randomized multi-center trial named the pioglitazone could reduce the recurrence of myocardial infarction in patients with DM and my-

PPAR *(Continued)*

	ocardial infarction(PPAR study) to evaluate whether pioglitazone could reduce the recurrence of myocardial infarction in patients with DM(HbA1c<6.5%) and myocardial infarction. 100 hospitals will participate in the PPAR study. Patients with DM who have history of prior myocardial infarction are randomly allocated to receive pioglitazone or (1)instructs weight reduction, appropriate diet, regular exercise and/or (2)prescribes sulfonylurea agents. The number of patients to be recruited is 3000 and this study will continue at least 2 years. The primary end-points are (1) cardiovascular mortality and (2) hospitalization for cardiovascular events. Effects in suppression of new diabetes development also will be evaluated. We should recognize DM as important therapeutic target to decrease recurrence of cardiovascular events. PPAR study, a large scale multi-center trial in Japan, will provide us new evidence how to treat DM patients with prior myocardial infarction. Eligibility: Ages Eligible for Study: 20 Years and above, Genders Eligible for Study: Both Inclusion Criteria: 1. diabetes mellitus (HbA1c < 6.5%) 2. History of myocardial infarction Exclusion Criteria: 1. Symptomatic CHF 2. Type I diabetes 3. History of coronary artery bypass graft 4. Severe liver and/or kidney dysfunction 5. History of allergic response to drugs 6. arteriosclerosis obliterans
Interventions	Study Type: Interventional Study Design: Prevention, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study Patients with DM who have history of prior myocardial infarction are randomly allocated to receive pioglitazone or (1)instructs weight reduction, appropriate diet, regular exercise and/or (2)prescribes sulfonylurea agents.
Outcomes	Primary Outcomes: 1.Cardiovascular mortality; 2.Hospitalization due to cardiovascular events Secondary Outcomes: (1) All cause mortality; (2) Hospitalization due to coronary artery disease; (3) Progression of IGT to diabetes; (4) Development or deterioration of either hypertension or hyperlipidemia; (5) Deterioraion of renal function; (6) Hospitalization due to cerebrovascular disease; (7) Hospitalization due to heart failure Expected Total Enrollment: 3000
Starting date	Study start: April 2005; Expected completion: April 2009 Last follow-up: April 2009; Data entry closure: April 2009
Contact information	Masafumi Kitakaze, MD, PhD 81-6-6833-5012 Ext. 2225 kitakaze@zf6.so-net.ne.jp Jiyoong Kim, MD 81-6-6833-5012 Ext. 8212 jikim@attglobal.net Japan, OSAKA National Cardiovascular Center, Suita, OSAKA, 565-8565, Japan; Recruiting Masafumi Kitakaze, MD, PhD 81-6-6833-5012 Ext. 2225 kitakaze@zf6.so-net.ne.jp Study chairs or principal investigators Masafumi Kitakaze, MD, PhD, Study Chair, National Cardiovascular Center ClinicalTrials.gov Identifier: NCT00212004

PPAR *(Continued)*

Notes	To evaluate whether the pioglitazone could reduce the recurrence of myocardial infarction in patients with DM and old myocardial infarction

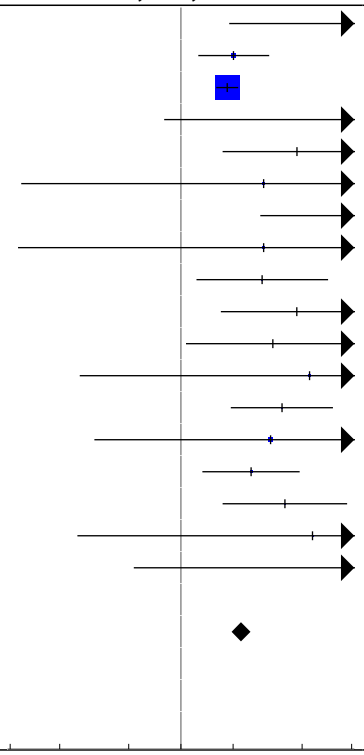
DATA AND ANALYSES

Comparison 1. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. of patients experiencing oedema	18	11565	Odds Ratio (M-H, Fixed, 95% CI)	2.22 [1.96, 2.52]

Analysis 1.1. Comparison 1 Adverse events, Outcome 1 No. of patients experiencing oedema.

Study or subgroup	Pioglitazone n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Aronoff 2000	12/329	0/408		0.12%	32.17[1.9,545.33]
Charbonnel 2005a	54/635	28/635		7.43%	2.01[1.26,3.23]
Dormandy 2005	562/2605	341/2633		77.19%	1.85[1.6,2.14]
Goke 2002	6/129	0/136		0.13%	14.37[0.8,257.69]
Hanefeld 2004	22/319	5/320		1.35%	4.67[1.74,12.48]
Jovanovic 2004	1/62	0/61		0.14%	3[0.12,75.09]
Langenfeld 2005	21/89	2/84		0.46%	12.66[2.87,55.93]
Lawrence 2004	1/21	0/20		0.14%	3[0.12,78.04]
Matthews 2005	20/317	7/313		1.92%	2.94[1.23,7.06]
Mattoo 2005	20/142	5/147		1.23%	4.66[1.7,12.78]
Pavo 2003	13/105	4/100		1.04%	3.39[1.07,10.78]
Scherbaum 2002	2/78	0/84		0.14%	5.52[0.26,116.86]
Schernthaner 2004	40/597	11/597		2.98%	3.83[1.94,7.53]
Smith 2005	3/24	1/24		0.25%	3.29[0.32,34.08]
Tan 2004a	35/121	17/123		3.48%	2.54[1.33,4.84]
Tan 2004b	24/91	9/109		1.75%	3.98[1.74,9.09]
Watanabe 2005	2/15	0/15		0.12%	5.74[0.25,130.37]
Yamanouchi 2005	4/38	0/39		0.13%	10.3[0.54,198.3]
Total (95% CI)	**5717**	**5848**		**100%**	**2.22[1.96,2.52]**
Total events: 842 (Pioglitazone), 430 (Control)					
Heterogeneity: Tau^2=0; Chi^2=28.07, df=17(P=0.04); I^2=39.43%					
Test for overall effect: Z=12.53(P<0.0001)					



APPENDICES

Appendix 1. Search strategy

Search terms

Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign ($) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent.

1. exp THIAZOLIDINEDIONES/
2. (pioglitazon$ or thiazolidinedion$).tw.

3. 1 or 2

4. randomized controlled trial.pt.
5. controlled clinical trial.pt.
6. randomized controlled trials.sh.
7. random allocation.sh.
8. double-blind method.sh.
9. single-blind method.sh.
10. ((singl$ or doubl$ or tripl$ or trebl$) adj6 (mask$ or blind$)).tw.
11. (random$ adj25 (trial$ or stud$ or investigat$ or cross over or crossover)).tw.

12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

13. exp meta-analysis/
14. exp Review Literature/
15. meta-analysis.pt.
16. systematic review$.tw.
17. search$.tw.
18. medline.tw.
19. cochrane database of systematic reviews.jn.

20. 13 or 14 or 15 or 16 or 17 or 18 or 19

21. letter.pt.
22. comment.pt.
23. editorial.pt.
24. historical-article.pt.

25. 21 or 22 or 23 or 24
26. 20 not 25

27. exp Technology Assessment, Biomedical/
28. HTA.tw.
29. (health technology adj6 assessment$).tw.
30. (biomedical adj6 technology assessment$).tw.

31. 27 or 28 or 29 or 30

32. exp diabetes mellitus/
33. diabet$.tw.
34. IDDM.tw.
35. NIDDM.tw.
36. MODY.tw.
37. (late onset adj diabet$).tw.
38. (maturity onset adj diabet$).tw.
39. (non insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).tw.

(Continued)

40. ((typ$ 1 or typ$ 2) adj6 diabet$).tw.
41. ((typ$ I or typ$ II) adj6 diabet$).tw.
42. (insulin$ depend$ or insulin?depend$).tw.
43. (T1DM or T2DM).tw.

44. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43

45. 3 and 12 and 44
46. 3 and 26 and 44
47. 3 and 31 and 44

48. 45 or 46 or 47

Appendix 2. Baseline characteristics (I)

Characteristic	Aronoff 2000	Charbonnel 2005a	Derosa 2004	Derosa2006	Dormandy 2005	Ebeling 2001
	I1: pioglitazone 7.5 mg; 15 mg; 30 mg; 45 mg C1: placebo	I1: pioglitazone C1: gliclazide	I1: pioglitazone + glimepiride C1: rosiglitazone + glimepiride	I1: pioglitazone + metformin C1: rosiglitazone + metformin	I1: pioglitazone + other glucose-lowering drugs C1: placebo + other glucose-lowering drugs	I1: pioglitazone C1: glibenclamide C2: placebo
Sex [%]	Total: female 42; male 58	?	I1: female 53; male 47 C1: female 48; male 52	I1: female 50 ; male 50 C1: female 48 ; male 52	I1: female 33; male 67 C1: female 34; male 66	Total: female 28; male 72
Age [years], mean (SD)	Total: 54	?	I1: 53 (6) C1: 54 (5)	I1: 55 (5) C1: 56 (4)	I1: 62 (8) C1: 62 (8)	Total: 55 (2)
Ethnic groups [%]	caucasian: 78 hispanic: 12 african-american: 8 asian: 2%; other: 1		?	?	I1: white 98 C1: white 99	
Duration of disease [years], mean (SD)	?	?	I1: 5 (2) C1: 6 (3)	I1: 6 (4) C1: 5 (4)	I1: 8 (median) C1: 8 (median)	Total: 5.9 (1.3)
Body mass index [kg/m2], mean (SD)	?	?	I1: 24.4 (0.8) C1: 24.3 (0.7)	I1: 26.9 (1.2) C1: 26.4 (1.4)	I1: 30.7 (4.7) C1: 31.0 (4.8)	Total: 30.9 (0.8)
Pharmaco-naive patients [%]	Total: 31	?	?	?	I1: 4 C1: 4	?
HbA1c [%], mean (SD)	I1: 10.0 (1.8); 10.2 (1.8); 10.2 (1.9); 10.3 (1.9)	I1: 8.7 C1: 8.7	I1: 8.2 (0.7) C1: 8.0 (0.8)	I1: 8.2 (0.8) C1: 8.1 (0.9)	I1: 7.8 C1: 7.9	I1: 9.1 (0.9) C1: 8.9 (0.9)

(Continued)

	C1: 10.4 (2.0)					C2: 8.6 (0.6)
Co-morbidities [%]	?	?	?	?	macrovascular morbidity = entry criterion (see 'characteristics of included studies') current smoker; microvascular disease I1: 13; 43 C1: 14; 41	?
Notes	no table with baseline characteristics; SDs calculated	no table with baseline characteristics	none	none	none	SDs calculated

Symbols & abbreviations: ? = unclear;
I = intervention;
C = control
SD = standard deviation; SE = standard error

Appendix 3. Baseline characteristics (II)

Characteristic	Goke 2002	Goldberg 2005	Hanefeld 2004	Jovanovic 2004	Langenfeld 2005
	I1: pioglitazone C1: acarbose	I1: pioglitazone C1: rosiglitazone	I1: pioglitazone + sulfonylureas C1: metformin + sulfonylureas	I1: pioglitazone C1: repaglinide C2: repaglinide + pioglitazone	I1: pioglitazone C1: glimepiride
Sex [%]	I1: female 47; male 53 C1: female 46; male 54	I1: female 46; male 54 C1: female 45; male 55	I1: female 46; male 54 C1: female 45; male 55	I1: female 50; male 50 C1: female 41; male 59 C2: female32; male 68	I1: female 38; male 62 C1: female 38; male 62
Age [years], mean (SD)	I1: 59 (9) C1: 59 (9)	I1: 56 (11) C1: 56 (11)	I1: 60 (9) C1: 60 (8)	I1: 56 (12) C1: 58 (13) C2: 59 (11)	I1: 62 (8) C1: 63 (7)

(Continued)

Ethnic groups [%]	?	I1: white 65; hispanic 29; asian 3; african 2; other 2 C1: white 60; hispanic 32; asian 3; african 3; other 2	I1: caucasian 99; african-american 1 C1: caucasian 99; african-american 1	I1: caucasian 82; hispanic 11; black 3; other 3 C1: caucasian 75; hispanic 11; black 5; other 8 C2: caucasian 82; hispanic 15; black 1; other 2	I1: white 99; other 1 C1: white 96; other 4
Duration of disease [years], mean (SD)	[months] I1: 57 (55) C1: 59 (50)	I1: 4 (4) C1: 4 (5)	I1: 7 (6) C1: 7 (6)	I1: 6 (4) C1: 7 (6) C2: 7 (6)	I1: 7 (8) C1: 7 (7)
Body mass index [kg/m2], mean (SD)	I1: 30.9 (5.3) C1: 30.8 (4.4)	I1: 33.7 (12.9) C1: 32.6 (6.6)	I1: 30.2 (4.4) C1: 30.0 (4.6)	I1: 32.1 (5.3) C1: 31.2 (5.3) C2: 32.3 (5.1)	I1: 31.7 (5.0) C1: 31.8 (4.3)
Pharmaco-naive patients [%]	I1: 54 C1: 52	I1: 24 C1: 25	?	I1: 0 C1: 0 C2: 0	?
HbA1c [%], mean (SD)	I1: 9.0 (1.2) C1: 9.0 (1.3)	I1: 7.6 (1.2) C1: 7.5 (1.2)	I1: 8.8 (1.0) C1: 8.8 (1.0)	I1: 9.4 C1: 9.0 C2: 9.3	I1: 7.5 (0.9) C1: 7.4 (0.9)
Co-morbidities [%]	?	Preexisting CVD or previous MI [%] I1: 9 C1: 7	?	?	?
Notes	Smokers [%] - I1: 17 C1: 19	none	none	none	none

Symbols & abbreviations: ? = unclear; I = intervention; C = control
SD = standard deviation; SE = standard error
CVD = vardiovascular disease; MI = myocardial infarction

Appendix 4. Baseline characteristics (III)

Characteristic	Lawrence 2004	Matthews 2005	Mattoo 2005	Pavo 2003	Scherbaum 2002
	I1: pioglitazone C1: metformin C2: gliclazide	I1: pioglitazone + metformin C1: gliclazide + metformin	I1: pioglitazone + insulin C1: placebo + insulin	I1: pioglitazone C1: metformin	I1: pioglitazone 15mg I2: pioglitazone 30mg C1: placebo
Sex [%]	I1: female 30; male 70 C1: female 40; male 60 C2: female 35; male 65	I1: female 49; male 51 C1: female 51; male 49	I1: female 56; male 44 C1: female 57; male 43	I1: female 56; male 44 C1: female 44; male 56	I1: female 37; male 63 C1: female 59; male 41 C2: female 44; male 56
Age [years], mean (SD)	I1: 60 (8) C1: 60 (9) C2: 64 (11)	I1: 56 (9) C1: 57 (9)	I1: 59 (7) C1: 59 (7)	I1: 54 (9) C1: 56 (8)	I1: 58 C1: 60 C2: 59
Ethnic groups [%]	?	I1: caucasian 99; oriental 1 C1: caucasian 100	I1: white 97; other 4 C1: white 97; other 3	I1: C1:	?
Duration of disease [years], mean (SD)	?	I1: 6 (5) C1: 6 (5)	months - I1: 163 (81) C1: 161 (74)	months - I1: 6 (4) C1: 6 (4)	I1: 5 C1: 5 C2: 6
Body mass index [kg/m2], mean (SD)	I1: C1:	I1: 32.6 (5.0) C1: 32.6 (5.8)	I1: 32.5 (4.8) C1: 31.8 (5.0)	I1: 31.3 (4.2) C1: 31.1 (4.4)	I1: 29.9 C1: 29.3 C2:29.9
Pharmaco-naive patients [%]	I1: 60 C1: 70 C2: 75	I1: 0 C1: 0	I1: 0 I2: 0	I1: 100 C1: 100	?
HbA1c [%], mean (SD)	I1: 7.4 (0.9) C1: 8.0 (0.9) C2: 7.9 (0.9)	I1: 8.7 (1.0) C1: 8.5 (0.9)	I1: 8.9 (1.3) C1: 8.8 (1.2)	I1: 8.6 C1: 8.6	I1: 9.3 (1.2) C1: 9.1 (1.2) C2: 8.8 (1.1)
Co-morbidities [%]	Treated hypertension [%] - I1: 40;C1: 60; C2: 65 Current smoker [%] - I1: 5; C1: 5; C2: 5	?	?	?	?
Notes	none	none	SDs calculated	none	none

Symbols & abbreviations: ? = unclear; I = intervention; C = control

(Continued)

SD = standard deviation; SE = standard error

Appendix 5. Baseline characteristics (IV)

Characteristic	Schernthaner 2004	Smith 2005	Tan 2004a	Tan 2004b	Watanabe 2005
	I1: pioglitazone C1: metformin	I1: pioglitazone C1: placebo	I1: pioglitazone C1: glimepiride	I1: pioglitazone C1: glibenclamide	I1: pioglitazone C1: glibenclamide
Sex [%]	I1: female 47; male 53 C1: female 42; male 58	I1: female 57; male 23 C1: female 52; male 48	I1: female 55; male 45 C1: female 47; male 53	I1: female 38; male 62 C1: female 27; male 73	I1: female 15; male 85 C1: female 14; male 76
Age [years], mean (SD)	I1: 57 (9) C1: 56 (9)	I1: 56 (10) C1: 53 (9)	I1: 55 (8) C1: 56 (9)	I1: 60 (9) C1: 58 (9)	I1: 63 (10) C1: 65 (8)
Ethnic groups [%]	?	I1: white 71; non-white 29 C1: white 76; non-white 24	I1: hispanic 100 C1: hispanic 99; white 1	I1: caucasian 99; other 1 C1:caucasian 100	?:
Duration of disease [years], mean (SD)	I1: 3 (4) C1: 3 (4)	?	months - I1: 78 (79) C1: 81 (83)	[months] - I1: 57 (57) C1: 63 (56)	?:
Body mass index [kg/m2], mean (SD)	I1: 31.2 (4.9) C1: 31.4 (5.2)	I1: 32.1 (5.6) C1: 31.9 (5.0)	I1: 29.3 (3.3) C1: 28.8 (3.2)	I1: 30.2 (5.6) C1: 29.6 (4.8)	I1: 24.4 (4.4) C1: 24.7 (3.7)
Pharmaco-naive patients [%]	I1: 100 C1: 100	?	I1: 24 C1: 23	I1: 30 C1: 31	?
HbA1c [%], mean (SD)	I1: 8.7 (1.0) C1: 8.7 (1.0)	I1: 6.9 (1,4) C1: 6.5 (0.7)	I1: 8.5 (0.9) C1: 8.5 (1.0)	I1: 8.4 (0.7) C1: 8.5 (0.8)	I1: 6.9 (0.2) C1: 7.2 (0.5)
Co-morbidities [%]	?	?	?	?	smokers [%] - I1: 39 C1: 29

(Continued)

Notes	none	none	none	none	SDs for HbA1c correct?
Symbols & abbreviations: ? = unclear; I = intervention; C = control SD = standard deviation; SE = standard error					

Appendix 6. Baseline characteristics (V)

Characteristic	Yamanouchi 2005
	I1: pioglitazone C1: metformin C2: glimepiride
Sex [%]	I1: female 53; male 47 C1: female 49; male 51 C2: female 49; male 51
Age [years], mean (SD)	I1: 55 (9) C1: 55 (10) C2: 56 (9)
Ethnic groups [%]	?
Duration of disease [years], mean (SD)	I1: 3 (2) C1: 3 (3) C2: 3 (3)
Body mass index [kg/m2], mean (SD)	I1: 25.8 (4.2) C1: 26.2 (3.8) C2: 25.6 (3.5)
Pharmaco-naive patients [%]	I1: 100 C1: 100 C2: 100
HbA1c [%], mean (SD)	I1: 10.2 (0.8) C1: 9.9 (0.7) C2: 9.8 (0.7)
Co-morbidities [%]	?

(Continued)

Notes	none

Symbols & abbreviations: ? = unclear;
I = intervention; C = control
SD = standard deviation; SE = standard error

Appendix 7. Adverse events (I)

Characteristic	Aronoff 2000	Charbonnel 2005a	Derosa 2004	Derosa 2004	Dormandy 2005	Ebeling 2001
	I1: pioglitazone 7.5 mg; 15 mg; 30 mg; 45 mg C1: placebo	I1: pioglitazone C1: gliclazide	I1: pioglitazone + glimepiride C1: rosiglitazone + glimepiride	I1: pioglitazone + metformin C1: rosiglitazone + metformin	I1: pioglitazone + other glucose-lowering drugs C1: placebo + other glucose-lowering drugs	I1: pioglitazone C1: glibenclamide C2: placebo
[n] of participants who died	no statement	no statement	no statement	no statement	I1: 177 (6.8%) C1: 186 (7.1%)	no statement
[%] adverse events	I1: 76% C1: 85%	I1: 75% C1: 71%	I1: 6.7% (3/45) C1: 11.9% (5/42)	I1: 8.3% (4/48) C1: 10.4% (5/48)	?	I1: ? C1: ? C2: ?
[%] serious adverse events	I1: ? C1: ?	I1: ? C1: ?	I1: 0% C1: 0%	I1: ? C1: ?	I1: 46.2% (1204/2605) C1: 48.4% (1275/2633)	I1: ? C1: ? C2: ?
[%] drop-outs due to adverse events	I1: 2% (7.5 mg); 4% (15 mg); 5% (30 mg); 5% (45 mg) C1: 3%	I1: ? C1: ?	I1: 0% C1: 0%	I1: ? C1: ?	I1: 9.0% (235/2605) C1: 7.7% (202/2633)	I1: ? C1: ? C2: ?
[%] oedema	I1: 3.6% (12/329) C1: 0%	I1: 8.7% (54/?) C1: 4.5% (28/?)	I1: ? C1: ?	I1: ? C1: ?	oedema without heart failure - I1: 21.6% (562/2605) C1: 13.0% (341/2633)	I1: ? C1: ? C2: ?

(Continued)

haemoglobin [g/dl]	I1: -0.74 (45 mg) a dose-related decrease was noted) C1: -0.2	I1: -0.7 C1: ?	I1: ? C1: ?	I1: ? C1: ?	?	I1: ? C1: ? C2: ?
body weight [kg]	I1: -0.59 (7.5 mg); +1.30 (15 mg); +1.29 (30 mg); +2.82 (40 mg) C1: -1.28	I1: +2.8 kg C1: + 1.9 kg	I1: ? C1: ?	I1: ? C1: ?	I1: +3.6 C1: -0.4	I1: ? C1: ? C2: ?
body mass index (BMI) [kg/m2]	I1: ? C1: ?	I1: ? C1: ?	I1: + 1.2 C1: +1.5	I1: -0.3 C1: -0.4	?	I1: +0.9 C1: +0.8 C2: -0.6
[%] hypoglycaemic episodes	I1: 1.2% (4/329) C1: 0%	I1: 3.5% (22/?) C1: 10.1% (63/?)	I1: ? C1: ?	I1: ? C1: ?	I1: 27.9% (726/2605) C1: 20.1% (528/2633)	I1: ? C1: ? C2: ?
[%] severe hypoglycaemic episodes	I1: 0% C1: 0%	I1: ? C1: ?	I1: ? C1: ?	I1: ? C1: ?	hypoglycaemia resulting in hospital admission I1: 0.7% (19/2605) C1: 0.4% (11/2633)	I1: ? C1: ? C2: ?
Notes					(1) [n] of patients with most common events (excluding endpoints - for 2605 pioglitazone and 2633 placebo treated participants) - angina pectoris; hospital admission; hospital admission for diabetes control; accident; atrial fibrillation; pneumonia; transient ischaemic attack; neoplasms (malignant, colon/rectal, lung, bladder, haematological, breast, other): I1: 89; 1145; 55; 51; 42; 53; 34; 112 (97, 16, 15, 14, 6, 3, 47) C1: 122; 1217; 91; 49; 51; 35; 39; 113 (99, 15,12, 6, 10, 11, 46) (2) reports of heart failure in [n] of patients - for 2605 pioglitazone and 2633 placebo treated participants) - any report of heart failure; heart failure not needing hospital admission; heart failure needing hospital admission; fatal heart failure I1: 281; 132; 149; 25 C1: 302; 117; 153; 22	
Symbols & abbreviations: ? = unclear; I = intervention; C = control						

Appendix 8. Adverse events (II)

Characteristic	Goke 2002	Goldberg 2005	Hanefeld 2004	Jovanovic 2004	Langenfeld 2005
	I1: pioglitazone C1: acarbose	I1: pioglitazone C1: rosiglitazone	I1: pioglitazone + sulfonylureas C1: metformin + sulfonylureas	I1: pioglitazone C1: repaglinide C2: repaglinide + pioglitazone	I1: pioglitazone C1: glimepiride
[n] of participants who died	not stated	I1: 0.3% (1/369) C1: 0.5% (2/366)	I1: 0.3% (1/319) C1: 0.6% (2/320)	not stated	none
[%] adverse events	I1: 10.1% (13/129) C1: 39.7% (54/136)	I1: ? C1: ?	I1: 59.9% (191/319) C1: 61.9% (198/320)	I1: ? C1: ? C2: ?	I1: ? C1: ?
[%] serious adverse events	I1: 0% C1: 0%	I1: ? C1: ?	I1: 6.6% (21/319) C1: 9.7% (31/320)	I1: ? C1: ? C2: ?	I1: ? C1: ?
[%] drop-outs due to adverse events	I1: 0.8% (1/129) C1: 3.7% (5/136)	I1: 2.7% (10/369) C1: 2.7% (10/366)	I1: 6.3% C1: 5.9%	I1: 1.6% (1/62) C1: 4.9% (3/61) C2: 4.1% (5/123)	I1: 1.1% (1/89) C1: 0%
[%] oedema	I1: 4.7% (6/129) C1: 0%	I1: ? C1: ?	I1: 6.9% (22/319) C1: 1.6% (5/320)	I1: 2% (1/62) C1: 0% C2: 6% (7/123)	I1: 23.6% (21/89) C1: 2.4% (2/84)
haemoglobin [g/dl]	I1: ? C1: ?	I1: ? C1: ?	I1: -0.6 C1: ?	I1: -0.5 C1: -0.1 C2: -0.6	I1: ? C1: ?
body weight [kg]	I1: +1.2 C1: -2.1	I1: +2.0 C1: +1.6	I1: +2.8 C1: -1.0	I1: +2.0 C1: +0.3 C2: +5.5	I1: ? C1: ?
body mass index (BMI) [kg/m2]	I1: ? C1: ?	I1: ? C1: ?	I1: ? C1: ?	I1: ? C1: ? C2: ?	I1: +1.4 C1: 0
[%] hypoglycaemic episodes	I1: ? C1: ?	I1: ? C1: ?	I1: 10.7% (34/319) C1: 14.1% (45/320)	I1: 7% (4/62) C1: 13% (8/61) C2: 24% (30/123)	I1: 16.6% (17/89) C1: 20.2% (17/84)
[%] severe hypoglycaemic episodes	I1: ? C1: ?	I1: ? C1: ?	I1: 0% C1: 0%	I1: 0% C1: 0% C2: 0%	I1: 0% C1: 0%
Notes					cardiac failure: I1: 2.2% (2/89)

(Continued)

Symbols & abbreviations: ? = unclear; I = intervention; C = control

Appendix 9. Adverse events (III)

Characteristic	Lawrence 2004	Matthews 2005	Mattoo 2005	Pavo 2003	Scherbaum 2002
	I1: pioglitazone C1: metformin C2: gliclazide	I1: pioglitazone + metformin C1: gliclazide + metformin	I1: pioglitazone + insulin C1: placebo + insulin	I1: pioglitazone C1: metformin	I1: pioglitazone 15mg I2: pioglitazone 30mg C1: placebo
[n] of participants who died	I1: 0% C1: 4.(% (1/21) C2: 0%	I1: 0% C1: 0.6% (2/313)	I1: 0% C1: 0.7% (1/147)	no statement	no statement
[%] adverse events	I1: ? C1: ? C2: ?	I1: 55.5% (176/317) C1: 58.1% (182/313)	I1: 76.8% (109/142) C1: 66.7% (98/147)	I1: 51.4% C1: 47.0%	I1: ? I2: ? C1: ?
[%] serious adverse events	I1: ? C1: ? C2: ?	I1: 4.7% (15/317) C1: 6.4% (20/313)	I1: ? C1: ?	I1: ? C1: ?	I1: 1.2% (1/89) I2: 0% C1: 4.8% (4/84)
[%] drop-outs due to adverse events	I1: 4.8% (1/21) C1: 4.8% (1/21) C2: 9.1% (2/22)	I1: 4.1% (13/317) C1: 4.5% (14/313)	I1: 4.9% (7/142) C1: 2.0% (3/147)	I1: 1.9% (2/105) C1: 0%	I1: 2.2% (2/89) I2: 0% (0/78) C1: 2.4% (2/84)
[%] oedema	I1: 4.8% (1/21) C1: 0% C2: 0%	I1: 6.3% (20/317) C1: 2.2% (7/313)	I1: 14.1% (20/142) C1: 3.4% (5/147)	I1: 12.4% (13/105) C1: 4% (4/100)	I1: 0% I2: 2.6% (2/78) C1: 0%
haemoglobin [g/dl]	I1: ? C1: ? C2: ?	I1: -0.6 C1: -0.3	I1: ? C1: ?	I1: ? C1: ?	I1: ? I2: ? C1: ?
body weight [kg]	I1: ? C1: ? C2: ?	I1: +1.5 C1: +1.4	I1: +4.1 C1: +0.2	I1: +0.7 C1: -2.4	I1: +0.3 I2: +0.8 C1: -1.1
body mass index (BMI) [kg/m2]	I1: +1.5 C1: -0.6 C2: +1.9	I1: ? C1: ?	I1: ? C1: ?	I1: ? C1: ?	I1: ? I2: ? C1: ?
[%] hypoglycaemic episodes	I1: ? C1: ? C2:	I1: 1.3% (4/317) C1: 11.2% (35/313)	I1: 63.4% C1: 51%	I1: ? C1: ?	I1: ? I2: ? C1: ?
[%] severe hypoglycaemic episodes	I1: ? C1: ?	I1: 0% C1: 0%	I1: ? C1: ?	I1: ? C1: ?	I1: ? I2: ?

(Continued)

	C2: ?		C1: ?
Notes		I1: 2/313 pulmonary oedema	
Symbols & abbreviations: ? = unclear; I = intervention; C = control			

Appendix 10. Adverse events (IV)

Characteristic	Schernthaner 2004	Smith 2005	Tan 2004a	Tan 2004b	Watanabe 2005
	I1: pioglitazone C1: metformin	I1: pioglitazone C1: placebo	I1: pioglitazone C1: glimepiride	I1: pioglitazone C1: glibenclamide	I1: pioglitazone C1: glibenclamide
[n] of participants who died	I1: 0.5% (3/597) C1: 0.3% (2/597)	no statement	no statement	no statement	no statement
[%] adverse events	I1: 52.9% (316/597) C1: 58.0% (346/597)	I1: ? C1: ?	I1: 86.8% (105/121) C1: 76.4%(94/123)	I1: 76.9% (70/91) C1: 83.5% (91/109)	I1: ? C1: ?
[%] serious adverse events	I1: 4.9% (29/597) C1: 7.4% (44/597)	I1: ? C1: ?	I1: 6.6% (8/121) C1: 4.1% (5/123)	I1: 7.7% (7/91) C1: 7.3% (8/109)	I1: ? C1: ?
[%] drop-outs due to adverse events	I1: 7.0% (42/597) C1: 6.5% (39/597)	I1: ? C1: ?	I1: 4.1% (5/121) C1: 2.4% (3/123)	I1: 6.6% (6/91) C1: 9.2% (10/109)	I1: 13.3% (2/15) C1: 6.7% (1/15)
[%] oedema	I1: 6.7% (40/597) C1: 1.8% (11/597)	I1: 12.5% (3/24) C1: 4.2% (1/24)	I1: 28.9% (35/121) C1: 13.8% (17/123)	I1: 26.4% (24/91) C1: 8.2% (9/109)	I1: 13.3% (2/15) C1: ?
haemoglobin [g/dl]	I1: -0.59 C1: -0.44	I1: ? C1: ?	I1: ? C1: ?	I1: ? C1: ?	I1: ? C1: ?
body weight [kg]	I1: +1.9 C1: -2.5	I1: +3.9 C1: -0.8	I1: +1.5 C1: +0.8	I1: +3.0 C1: +1.1	I1: ? C1: ?
body mass index (BMI) [kg/m2]	I1: ? C1: ?	I1: ? C1: ?	I1: ? C1: ?	I1: ? C1: ?	I1: +0.1 C1: -0.6
[%] hypoglycaemic episodes	I1: ? C1: ?	I1: ? C1: ?	I1: 15.7% (19/121) C1: 30.9% (38/123)	I1: 4.3% (4/91) C1: 29.4% (32/109)	I1: ? C1: ?
[%] severe hypoglycaemic episodes	I1: ? C1: ?	I1: ? C1: ?	I1: ? C1: ?	I1: ? C1: ?	I1: ? C1: 6.7% (1/15)?

(Continued)

Notes	hepatotoxicity - I1: 2/597 C1: 1/597	pulmonary oedema - I1: 1/24

Symbols & abbreviations: ? = unclear I = intervention; C = control

Appendix 11. Adverse events (V)

Characteristic	Yamanouchi 2005
	I1: pioglitazone C1: metformin C2: glimepiride
[n] of participants who died	no statement
[%] adverse events	I1: ? C1: ? C2: ?
[%] serious adverse events	I1: ? C1: ? C2: ?
[%] drop-outs due to adverse events	I1: 5.3% (2/38) C1: 0% (0/39) C2: 0% (0/37)
[%] oedema	I1: 10.5% (4/38) C1: ? C2: ?
haemoglobin [g/dl]	I1: ? C1: ? C2: ?
body weight [kg]	I1: ? C1: ? C2: ?
body mass index (BMI) [kg/m2]	I1: +0.9 C1: -0.7 C2: -0.2
[%] hypoglycaemic episodes	I1: ? C1: ? C2: 2.6% (1/38)
[%] severe hypoglycaemic episodes	I1: ? C1: ? C2: ?
Notes	

(Continued)

Symbols & abbreviations: ? = unclear;
I = intervention; C = control

Appendix 12. Primary outcomes

Characteristic	Mortality	Morbidity	Adverse events	Notes
Aronoff 2000: I1: pioglitazone 7.5 mg; 15 mg; 30 mg; 45 mg C1: placebo	not investigated	not investigated	see table 'Adverse events'	
Charbonnel 2005a: I1: pioglitazone C1: gliclazide	not investigated	not investigated	see table 'Adverse events'	
Derosa 2004: I1: pioglitazone + glimepiride C1: rosiglitazone + glimepiride	not investigated	not investigated	see table 'Adverse events'	
Derosa 2006: I1: pioglitazone + metformin C1: rosiglitazone + metformin	not investigated	not investigated	see table 'Adverse events'	
Dormandy 2005: I1: pioglitazone + other glucose-lowering drugs C1: placebo + other glucose-lowering drugs	Primary composite endpoint - I1: 19.7% (514/2605) C1: 21.7% (572/2633) HR 0.90 (95% CI 0.80 to 1.02, p=0.095) "Main" secondary endpoint - I1: 11.6% (301/2605) C1: 13.6% (358/2633) HR 0.84 (95% CI 0.72 to 0.98, p=0.027) [n] of first occurence of the individual components of the primary composite endpoint: death - I1: 177, C1: 186 - HR 0.96 (95% CI 0.78 to 1.18); non-fatal myocardial infarction (including silent myocardial infarction) - I1: 119, C1: 144 - HR 0.83 (95% CI 0.65 to 1.06); stroke - I1: 86; C1: 107 - HR 0.81 (95% CI 0.61 to 1.07); major leg amputation - I1: 26, C1: 26 - HR 1.01 (95% CI 0.58 to 1.73);	see composite primary and secondary endpoints for mortality	see table 'Adverse events'	

(Continued)

	acute coronary syndrome - I1: 56, C1: 72 - HR 0.78 (95% CI 0.55 to 1.11); coronary revascularisation - I1: 169, C1: 193 - HR 0.88 (95% CI 0.72 to 1.08); leg revascularisation - I1: 80, C1: 65 - HR 1.25 (95% CI 0.90 to 1.73); total - I1: 803 events, C1: 900 events.		
Ebeling 2001: I1: pioglitazone C1: glibenclamide C2: placebo	not investigated	not investigated	see table 'Adverse events'
Goke 2002: I1: pioglitazone C1: acarbose	not investigated	not investigated	see table 'Adverse events'
Goldberg 2005: I1: pioglitazone C1: rosiglitazone	not investigated	not investigated	see table 'Adverse events'
Hanefeld 2004: I1: pioglitazone + sulfonylureas C1: metformin + sulfonylureas	not investigated	not investigated	see table 'Adverse events'
Jovanovic 2004: I1: pioglitazone C1: repaglinide C2: repaglinide + pioglitazone	not investigated	not investigated	see table 'Adverse events'
Langenfeld 2005: I1: pioglitazone C1: glimepiride	not investigated	not investigated	see table 'Adverse events'
Lawrence 2004: I1: pioglitazone C1: metformin C2: gliclazide	not investigated	not investigated	see table 'Adverse events'
Matthews 2005: I1: pioglitazone + metformin C1: gliclazide + metformin	not investigated	not investigated	see table 'Adverse events'
Mattoo 2005: I1: pioglitazone + insulin C1: placebo + insulin	not investigated	not investigated	see table 'Adverse events'

(Continued)

Pavo 2003: I1: pioglitazone C1: metformin	not investigated	not investigated	see table 'Adverse events'
Scherbaum 2002: I1: pioglitazone 15mg I2: pioglitazone 30mg C1: placebo	not investigated	not investigated	see table 'Adverse events'
Schernthaner 2004: I1: pioglitazone C1: metformin	not investigated	not investigated	see table 'Adverse events'
Smith 2005: I1: pioglitazone C1: placebo	not investigated	not investigated	see table 'Adverse events'
Tan 2004a: I1: pioglitazone C1: glimepiride	not investigated	not investigated	see table 'Adverse events'
Tan 2004b: I1: pioglitazone C1: glibenclamide	not investigated	not investigated	see table 'Adverse events'
Watanabe 2005: I1: pioglitazone C1: glibenclamide	not investigated	not investigated	see table 'Adverse events'
Yamanouchi 2005: I1: pioglitazone C1: metformin C2: glimepiride	not investigated	not investigated	see table 'Adverse events'

Symbols & abbreviations: ? = unclear;
I = intervention; C = control;
HR = hazard ratio; CI = confidence intervall

Appendix 13. Secondary outcomes

Characteristic	Quality of life	Costs	HbA1c [%] (SD)	Notes
Aronoff 2000:	not investigated	not investigated	I1:	SDs calculated

(Continued)

I1: pioglitazone 7.5 mg; 15 mg; 30 mg; 45 mg C1: placebo			end of study data: 7.5 mg 10.2 (2.24); 15 mg 9.9 (2.40); 30 mg 9.9 (2.67); 45 mg 9.4 (2.53) change data: 7.5 mg 0.2 (1.52); 15 mg -0.3 (1.51); 30 mg -0.3 (1.57); 45 mg -0.9 (1.57) C1: end of study data: 11.1 (2.31) change data: 0.7 (1.51)	
Charbonnel 2005a: I1: pioglitazone C1: gliclazide	not investigated	not investigated	I1: end of study data: 7.2 change data: -1.4 C1: end of study data: 7.3 change data: -1.4	
Derosa 2004: I1: pioglitazone + glimepiride C1: rosiglitazone + glimepiride	not investigated	not investigated	I1: end of study data: 6.8 (0.8) change data: C1: end of study data: 6.7 (0.9) change data:	
Derosa 2006: I1: pioglitazone + metformin C1: rosiglitazone + metformin	not investigated	not investigated	I1: end of study data: 6.8 (0.3) change data: C1: end of study data: 6.8 (0.5) change data:	
Dormandy 2005: I1: pioglitazone + other glucose-lowering drugs C1: placebo + other glucose-lowering drugs	not investigated	not investigated	I1: end of study data: -0.8 change data: C1: end of study data: -0.3 change data:	
Ebeling 2001: I1: pioglitazone C1: glibenclamide C2: placebo	not investigated	not investigated	I1: end of study data: 8.0 (1.5) change data: C1: end of study data: 7.7 (0.63) change data: C2: end of study data: 8.4 (0.95) change data:	SDs calculated
Goke 2002: I1: pioglitazone C1: acarbose	not investigated	not investigated	I1: end of study data: 7.82 (1.95) change data: C1: end of study data: 8.55 (1.96) change data:	
Goldberg 2005: I1: pioglitazone C1: rosiglitazone	not investigated	not investigated	I1: end of study data: change data: -0.7 (1.91) C1: end of study data:	SDs calculated

(Continued)

			change data: -0.6 (1.89)	
Hanefeld 2004: I1: pioglitazone + sulfonylureas C1: metformin + sulfonylureas	not investigated	not investigated	I1: end of study data: 7.61 (1.07) change data: -1.20 C1: end of study data: 7.45 (1.07) change data: -1.36	SDs calculated
Jovanovic 2004: I1: pioglitazone C1: repaglinide C2: repaglinide + pioglitazone	not investigated	not investigated	I1: end of study data: 9.5 change data: 0.32 (1.26) C1: end of study data: 8.9 change data: -0.18 (1.33) C2: end of study data: 7.5 change data: -1.76 (1,22)	SDs calculated
Langenfeld 2005: I1: pioglitazone C1: glimepiride	not investigated	not investigated	I1: end of study data: 6.71 (0.89) change data: -0.8 (0.9) C1: end of study data: 6.83 (0.85) change data: -0.6 (0.8)	
Lawrence 2004: I1: pioglitazone C1: metformin C2: gliclazide	not investigated	not investigated	I1: end of study data: 6.62 (0.5) change data: -0.81 (0.63) C1: end of study data: 6.9 (0.5) change data: -1.12 (0.84) C2: end of study data: 6.64 (0.5) change data: -1.21 (0.82)	
Matthews 2005: I1: pioglitazone + metformin C1: gliclazide + metformin	not investigated	not investigated	I1: end of study data: change data: -0.99 C1: end of study data: change data: -1.01	
Mattoo 2005: I1: pioglitazone + insulin C1: placebo + insulin	not investigated	not investigated	I1: end of study data: 8.11 (1.07) change data: -0.69 (1.07) C1: end of study data: 8.66 (0.97) change data: ?	SDs calculated
Pavo 2003: I1: pioglitazone C1: metformin	not investigated	not investigated	I1: end of study data: change data: -1.3 C1: end of study data: change data: -1.5	
Scherbaum 2002: I1: pioglitazone 15mg	not investigated	not investigated	I1: end of study data: 7.99 (0.95) change data: -0.92 (1.50)	

(Continued)

I2: pioglitazone 30mg C1: placebo			C1: end of study data: 7.78 (1.18) change data: -1.05 (1.25) C2: end of study data: 8.29 (1.05) change data: -0.34 (0.98)	
Schernthaner 2004: I1: pioglitazone C1: metformin	not investigated	not investigated	I1: end of study data: 7.28 change data: -1.41 C1: end of study data: 7.18 change data: -1.50	
Smith 2005: I1: pioglitazone C1: placebo	not investigated	not investigated	I1: end of study data: change data: -0.96 (1.11) C1: end of study data: -0.11 (0.79) change data:	
Tan 2004a: I1: pioglitazone C1: glimepiride	not investigated	not investigated	I1: end of study data: change data: -0.78 (1.78) C1: end of study data: change data: -0.68 (1.87)	SDs calculated
Tan 2004b: I1: pioglitazone C1: glibenclamide	not investigated	not investigated	I1: end of study data: change data: -0.4 C1: end of study data: change data: -0.5	
Watanabe 2005: I1: pioglitazone C1: glibenclamide	not investigated	not investigated	I1: end of study data: 6.1 (0.33) change data: C1: end of study data: 6.3 (0.40) change data:	
Yamanouchi 2005: I1: pioglitazone C1: metformin C2: glimepiride	not investigated	not investigated	I1: end of study data: 7.9 (1.0) change data: C1: end of study data: 7.8 (1.0) change data: C2: end of study data: 7.7 (0.9) change data:	
Symbols & abbreviations: ? = unclear; HbA1c = glycosylated haemoglobin A1c; I = intervention; C = control SD = standard deviation				

Appendix 14. Risk of bias (I)

Characteristic	Aronoff 2000	Charbonnel 2005a	Derosa 2004	Derosa 2006	Dormandy 2005	Ebeling 2001
	I1: pioglitazone 7.5 mg; 15 mg; 30 mg; 45 mg C1: placebo	I1: pioglitazone C1: gliclazide	I1: pioglitazone + glimepiride C1: rosiglitazone + glimepiride	I1: pioglitazone + metformin C1: rosiglitazone + metformin	I1: pioglitazone + other glucose-lowering drugs C1: placebo + other glucose-lowering drugs	I1: pioglitazone C1: glibenclamide C2: placebo
Randomised controlled clinical trial (RCT)	Y	Y	Y	Y	Y	Y
Non-inferiority / equivalence trial	N	Y	N	N	N	N
Controlled clinical trial	N	N	N	N	N	N
Design: parallel, crossover, factorial RCT	parallel	parallel	parallel	parallel	parallel	parallel
Design: crossover study	N	N	N	N	N	N
Design: factorial study	N	N	N	N	N	N
Crossover study: wash-out phase	NA	NA	NA	NA	NA	NA
Crossover study: carryover effect tested	NA	NA	NA	NA	NA	NA
Crossover study: period effect tested	NA	NA	NA	NA	NA	NA
Method of randomisation	?	?	envelopes containing randomisation codes prepared by a statistician	envelopes containing randomisation codes prepared by a statistician	method of randomised permuted blocks within centre; central randomisation service	?
Unit of randomisation (individuals, cluster - specify)	individuals	individuals	individuals	individuals	individuals	individuals
Randomisation stratified for centres	?	?	?	?	Y	NA
Randomisation ratio	(I1) 4 : (C1) 1	NA	NA	NA	NA	NA
Concealment of allocation	?	?	envelopes; a copy of the randomisation code was provided	envelopes; a copy of the randomisation code was provided	central interactive voice response system	?

(Continued)

			only to the statistician	only to the statistician		
Stated blinding (open; single, double, triple blind)	dou-ble-blind	dou-ble-blind	dou-ble-blind	dou-ble-blind	double-blind	dou-ble-blind
Actual blinding: participant	?	?	?	?	Y	?
Actual blinding: caregiver / treatment administrator	?	?	?	?	Y	?
Actual blinding: outcome assessor	?	?	?	?	?	?
Actual blinding: others	?	?	?	?	?	?
Blinding checked: participant	?	?	?	?	?	?
Blinding checked: caregiver / treatment administrator	?	?	?	?	?	?
Primary endpoint defined	N	Y	N	N	Y	N
[n] of primary endpoint(s)	1?	1	8	2	1	7?
[n] of secondary endpoints	8	11	5	12	8	10?
Total [n] of endpoints	9	12	13	14	9	17?
Prior publication of study design	N	N	N	N	Y	N
Outcomes of prior / current publication identical	NA	NA	NA	NA	N	NA
Power calculation	N	Y	N	N	Y	N
[n] participants per group calculated	NA	450	NA	NA	2500; with 760 patients expe-riencing one first endpoint event or more	?
Non-inferiority trial: interval for equiva-lence specified	NA	Y	NA	NA	NA	NA
Intention-to-treat analysis (ITT)	Y	Y	Y	Y	Y	?
Per-protocol-analysis	Y	N	N	N	N	?
ITT defined	N	Y	?	?	Y	NA
Missing data: last-observation-car-ried-forward (LOCF)	Y	N	?	?	?	N
Missing data: other methods	N	NA	NA	NA	?	NA
LOCF defined	N	NA	?	?	?	NA

(Continued)

Analysis stratified for centres	?	?	?	?	?	NA
[n] of screened patients	?	I1: ? C1: ? Total: 2412	?	?	5602	?
[n] of randomised participants	I1: 7.5 mg - 81; 15 mg - 81; 30 mg - 87; 45 mg - 80 C1: 79 Total: 408	I1: ? C1: ? Total: 1270	I1: ? C1: ? Total: 91	I1: ? C1: ? Total: 103	I1: 2605 C1: 2633 Total: 5238	I1: 9 C1: 10 C2: 10 Total: 29
[n] of participants finishing the study	I1: 44-58% C1: 33%	over 80%	I1: 45 C1: 42 Total: 87	I1: 48 C1: 48 Total: 96	I1: 2427 C1: 2446 Total: 4873	I1: 9 C1: 10 C2: 10 Total: 29
[n] of patients analysed for primary end-point	HbA1c: I1: 7.5 mg - 80; 15 mg - 79; 30 mg - 85; 45 mg - 76 C1: 79; total: 399	?	I1: 45 C1: 42 Total: 87	I1: 48 C1: 48 Total: 96	I1: 2605 C1: 2633 Total: 5238	I1: 9 C1: 10 C2: 10 Total: 29
Description of discontinuing participants	Y	N	Y	Y	Y	N
Drop-outs (reasons explained)	Y	N	Y	?	Y	N
Withdrawals (reasons explained)	Y	N	Y	?	Y	N
Losses-to-follow-up (reasons explained)	N	N	Y	?	Y	N
[n] of participants who discontinued	?	?	I1: 2 C2: 2 Total: 4	I1: ? C1: ? Total: 7	I1: 855 C1: 877 Total: 1732	?
[%] discontinuation rate	I1: 42-56% C1: 67%	?	I1: 4.4% C1: 4.8% Total: 4.6%	I1: ? C1: ? Total: 6.8%	I1: 32.8% C1: 33.3% Total: 33.1%	?
Discontinuation rate similar between groups	N	?	Y	?	Y	?
[%] crossover between groups	?	?	?	?	?	?
Differences [n] calculated to analysed patients	NA	?	NA	NA	N	NA
Adjustment for multiple outcomes / repeated measurements	N	N	Y	Y	?	N
Baseline characteristics: clinically relevant differences	?	?	N	N	N	N

(Continued)

Treatment identical (apart from intervention)	Y	Y	Y	Y	Y	Y
Compliance measured	N	N	Y	Y	Y	N
Other important covariates measured (specify)	N	N	N	N	Y	N
Co-morbidities measured	N	N	N	N	Y	N
Co-medications measured	N	Y	N	N	Y	Y
Specific doubts about study quality	N	N	N	N	N	sparse data
Funding: commercial	Y	Y	?	?	Y	Y
Funding: non-commercial	N	N	?	?	N	N
Publication status: peer review journal	Y	Y	Y	Y	Y	Y
Publication status: journal supplement	N	N	N	N	N	N
Publication status: abstract	N	N	N	N	N	N
Publication status: other	NA	NA	NA	NA	NA	NA
Notes	one companion publication	one companion publication; the Oxford Centre for Diabetes Endocrinology and Metabolism is in a partnership, formed initially between the NHS, University of Oxford ND Novo Nordisk, and has been extended to include Servier Laboratories Limited and Takeda Chemical Industries Limited	co-medication not specified for intervention vs control; two companion publications	drop-outs per group not specified	the protocol was amended in May 2003, to specify that the trial should continue until the last patient recruited had been followed-up for 30 months and at least 760 patients had had one or more endpoint events; 25 prespecified sets of subgroups	phase III study; part of another study?

(Continued)

Symbols & abbreviations: Y = yes; N = no; ? = unclear I = intervention; C = control

Appendix 15. Risk of bias (II)

Characteristic	Goke 2002	Goldberg 2005	Hanefeld 2004	Jovanovic 2004	Langenfeld 2005
	I1: pioglitazone C1: acarbose	I1: pioglitazone C1: rosiglitazone	I1: pioglitazone + sulfonylureas C1: metformin + sulfonylureas	I1: pioglitazone C1: repaglinide C2: repaglinide + pioglitazone	I1: pioglitazone C1: glimepiride
Randomised controlled clinical trial (RCT)	Y	Y	Y	Y	Y
Non-inferiority / equivalence trial	N	Y	N	N	N
Controlled clinical trial	N	N	N	N	N
Design: parallel, crossover, factorial RCT	parallel	parallel	parallel	parallel	parallel
Design: crossover study	N	N	N	N	N
Design: factorial study	N	N	N	N	N
Crossover study: wash-out phase	NA	NA	NA	NA	NA
Crossover study: carryover effect tested	NA	NA	NA	NA	NA
Crossover study: period effect tested	NA	NA	NA	NA	NA
Method of randomisation	computerized, telephone randomisation - stratified for gender, 2 BMI classes and study centers in blocks of 4	stratified for being previously treated with oral antidiabetic drugs and sex	?	?	?
Unit of randomisation (individuals, cluster - specify)	individuals	individuals	individuals	individuals	individuals
Randomisation stratified for centres	Y	?	?	?	NA
Randomisation ratio	NA	NA	NA	1:1:2	NA

(Continued)

Concealment of allocation	?	?	?	?	?
Stated blinding (open; single, double, triple blind)	open-label	double-blind	double-blind	open-label	open-label
Actual blinding: participant	NA	?	?	NA	NA
Actual blinding: caregiver / treatment administrator	NA	?	?	NA	NA
Actual blinding: outcome assessor	?	?	?	?	Y
Actual blinding: others	NA	?	?	NA	NA
Blinding checked: participant	NA	?	?	NA	NA
Blinding checked: caregiver / treatment administrator	NA	?	?	NA	NA
Primary endpoint defined	N	Y	Y	Y	N
[n] of primary endpoint(s)	1?	1	1	1	1
[n] of secondary endpoints	9	16	11	6	12
Total [n] of endpoints	10	17	12	7	13
Prior publication of study design	N	N	N	N	N
Outcomes of prior / current publication identical	NA	NA	NA	NA	NA
Power calculation	N	N	N	Y	N
[n] participants per group calculated	NA	NA	NA	?	NA
Non-inferiority trial: interval for equivalence specified	NA	NA	NA	NA	NA
Intention-to-treat analysis (ITT)	Y	?	Y	?	?
Per-protocol-analysis	Y (HbA1c)	?	?	?	Y
ITT defined	N	?	Y	NA	NA
Missing data: last-observation-carried-forward (LOCF)	Y	Y	Y	N	N
Missing data: other methods	N	Y	N	imputed data by means of the incremental mean imputation (IMI) method	N
LOCF defined	N	N	Y	NA	NA

(Continued)

Analysis stratified for centres	?	Y	?	?	NA
[n] of screened patients	381	4410	?	?	Total: 192
[n] of randomised participants	I1: 129 C1: 136 Total: 265	I1: 369 C1: 366 Total: 735	I1: 319 C1: 320 Total: 639	I1: 62 C1: 61 C2: 123 Total: 246	I1: 89 C1: 84 Total: 173
[n] of participants finishing the study	I1: 110 C1: 97 Total: 207	I1: 299 C1: 286 Total: 585	I1: 81.5% C1: 87.2% Total: >80%	I1: 26 C1: 36 C: 105 Total: 167	I1: 81 C1: 81 Total: 162
[n] of patients analysed for primary end-point	I1: 129 C1: 136 Total: 265	I1: 363 C1: 356 Total: 719	I1: 319 C1: 320 Total: 639	I1: 57 C1: 54 C2: 123 Total: 234	I1: 89 C1: 84 Total: 173
Description of discontinuing participants	Y	Y	Y	Y	Y
Drop-outs (reasons explained)	Y	Y	Y	Y	Y
Withdrawals (reasons explained)	Y	Y	Y	Y	Y
Losses-to-follow-up (reasons explained)	Y	Y	?	?	?
[n] of participants who discontinued	I1: 19 C1: 39 Total: 58	I1: 70 C1: 80 Total: 150	I1: 62 C1: 41 Total: 103	I1: 36 C1: 25 C2: 18 Total: 79	I1: 8 C1: 3 Total: 11
[%] discontinuation rate	I1: 14.7% C1: 28.7% Total: 21.9%	I1: 19.0% C1: 21.9% Total: 20.4%	I1: 19.5% C1: 12.8% Total: 16.1%	I1: 58.1% C1: 41.0% C2: 14.6%	I1: 9.9% C1: 3.6% Total: 6.8%
Discontinuation rate similar between groups	N	Y	N	N	N
[%] crossover between groups	C1 to I1: n=24 (24.7%)	?	?	?	?
Differences [n] calculated to analysed patients	NA	NA	NA	?	NA
Adjustment for multiple outcomes / repeated measurements	N	N	N	N	N
Baseline characteristics: clinically relevant differences	N	N	N	N	N
Treatment identical (apart from intervention)	Y	Y	Y	Y	Y
Compliance measured	Y	N	N	N	Y
Other important covariates measured (specify)	N	N	N	N	N

(Continued)

Co-morbidities measured	N	Y	N	N	N
Co-medications measured	N	N	Y	N	Y
Specific doubts about study quality	Y	N	N	?	N
Funding: commercial	Y	Y	Y	?	Y
Funding: non-commercial	N	N	N	?	N
Publication status: peer review journal	Y	Y	Y	Y	Y
Publication status: journal supplement	N	N	N	N	N
Publication status: abstract	N	N	N	N	N
Publication status: other	NA	NA	NA	NA	NA
Notes	one-sided statistical tests with alpha set at 2.5%; one companion publication	no quantitative data on adverse events	none	randomisation ratio not mentioned (data in table of baseline characteristics only)	unclear whether imputation methods were used for missing data; two companion publications

Symbols & abbreviations: Y = yes; N = no; ? = unclear I = intervention; C = control

Appendix 16. Risk of bias (III)

Characteristic	Lawrence 2004	Matthews 2005	Mattoo 2005	Pavo 2003	Scherbaum 2002
	I1: pioglitazone C1: metformin C2: gliclazide	I1: pioglitazone + metformin C1: gliclazide + metformin	I1: pioglitazone + insulin C1: placebo + insulin	I1: pioglitazone C1: metformin	I1: pioglitazone 15mg I2: pioglitazone 30mg C1: placebo
Randomised controlled clinical trial (RCT)	Y	Y	Y	Y	Y
Non-inferiority / equivalence trial	N	Y	N	Y	Y?
Controlled clinical trial	N	N	N	N	N
Design: parallel, crossover, factorial RCT	parallel	parallel	parallel	parallel	parallel
Design: crossover study	N	N	N	N	N

(Continued)

Design: factorial study	N	N	N	N	N
Crossover study: wash-out phase	NA	NA	NA	NA	NA
Crossover study: carryover effect tested	NA	NA	NA	NA	NA
Crossover study: period effect tested	NA	NA	NA	NA	NA
Method of randomisation	?	?	central randomisation table; stratification between non- and intensified insulin regimens	?	?
Unit of randomisation (individuals, cluster - specify)	individuals	individuals	individuals	individuals	individuals
Randomisation stratified for centres	NA	?	?	?	?
Randomisation ratio	NA	NA	NA	NA	NA
Concealment of allocation	?	?	Y (automated interactive voice response system - Clinical Trial Study Management System)	?	?
Stated blinding (open; single, double, triple blind)	open-label	double-blind	double-blind	double-blind	double-blind
Actual blinding: participant	NA	?	?	?	?
Actual blinding: caregiver / treatment administrator	NA	?	?	?	?
Actual blinding: outcome assessor	?	?	?	?	?
Actual blinding: others	NA	?	?	?	?
Blinding checked: participant	NA	?	?	?	?
Blinding checked: caregiver / treatment administrator	NA	?	?	?	?
Primary endpoint defined	Y	?	Y	Y	Y
[n] of primary endpoint(s)	1	1	1	1	1
[n] of secondary endpoints	21	11	9	10	10
Total [n] of endpoints	22	12	10	11	11

(Continued)

Prior publication of study design	N	N	N	N	N
Outcomes of prior / current publication identical	NA	NA	NA	NA	NA
Power calculation	Y	Y (calculated for patients completing at least 24 weeks of the study)	Y	Y	Y
[n] participants per group calculated	14	225	125	100	80 (53 suitable for evaluation)
Non-inferiority trial: interval for equivalence specified	NA	NA	NA	Y	N
Intention-to-treat analysis (ITT)	?	Y	Y	?	Y
Per-protocol-analysis	?	?	?	?	Y
ITT defined	NA	Y	Y	NA	N
Missing data: last-observation-carried-forward (LOCF)	?	?	Y	Y	?
Missing data: other methods	?	?	N	N	?
LOCF defined	NA	NA	Y	Y	NA
Analysis stratified for centres	NA	?	?	Y	?
[n] of screened patients	?	?	?	321	509
[n] of randomised participants	I1: 21 C1: 21 C2: 22 Total: 64	I1: 317 C1: 313 Total: 630	I1: 142 C1: 147 Total: 289	I1: 105 C1: 100 Total: 205	I1: 89 I2: 78 C2: 84 Total: 251
[n] of participants finishing the study	I1: 20 C1: 20 C2: 20 Total: 60	I1: 261 C1: 271 Total: 532	I1: 128 C1: 135 Total: 263	I1: 100 C1: 91 Total 191	I1: 61 I2: 64 C2: 59 Total: 184
[n] of patients analysed for primary endpoint	I1: 20 C1: 20 C2: 20 Total: 60	I1: ? C1: ? Total: 620	I1: 142 C1: 147 Total: 289	I1: ? C1: ? Total; ?	I1: 83? I2: 72? C2: 78? Total: 225
Description of discontinuing participants	Y	Y	Y	Y	Y
Drop-outs (reasons explained)	Y	?	Y	Y	Y
Withdrawals (reasons explained)	Y	?	Y	Y	Y
Losses-to-follow-up (reasons explained)	NA	?	Y	Y	?

(Continued)

[n] of participants who discontinued	I1: 1 C1: 1 C2: 2 Total: 5	I1: 56 C1: 42 Total: 98	I1: 14 C1: 12 Total: 26	I1: 5 C1: 9 Total: 14	I1: 22 I2: 8 C2: 22 Total: 52
[%] discontinuation rate	I1: 4.8% C1: 4.8% C2: 9.1% Total: 7.8%	I1: 17.7% C1: 13.4% Total: 15.6%	I1: 9.9% C1: 8.2% Total: 9.0%	I1: 4.8% C1: 9.0% Total: 6.8%	I1: 24.7% I2: 10.3% C2: 26.2% Total: 20.7%
Discontinuation rate similar between groups	N	Y	Y	N	N
[%] crossover between groups	?	?	?	?	?
Differences [n] calculated to analysed patients	N	N	N	N	N
Adjustment for multiple outcomes / repeated measurements	Y (primary analysis only)	N	N	N	N
Baseline characteristics: clinically relevant differences	Y	N	N	Y	Y
Treatment identical (apart from intervention)	N	Y	Y	Y	Y
Compliance measured	N	N	Y	Y	Y
Other important covariates measured (specify)	N	N	N	N	N
Co-morbidities measured	Y	N	N	N	N
Co-medications measured	Y	N	N	N	N
Specific doubts about study quality	N	N	N	N	N
Funding: commercial	Y	Y	Y	Y (but not stated)	Y
Funding: non-commercial	N	N	N	N	N
Publication status: peer review journal	Y	Y	Y	Y	Y
Publication status: journal supplement	N	N	N	N	N
Publication status: abstract	N	N	N	N	N
Publication status: other	NA	NA	NA	NA	NA
Notes	no quantitative data on adverse events	none	none	no funding described, but authors from pharmaceutical companies	phase II study

(Continued)

Symbols & abbreviations: Y = yes; N = no; ? = unclear I = intervention; C = control

Appendix 17. Risk of bias (IV)

Characteristic	Schernthaner 2004	Smith 2005	Tan 2004a	Tan 2004b	Watanabe 2005
	I1: pioglitazone C1: metformin	I1: pioglitazone C1: placebo	I1: pioglitazone C1: glimepiride	I1: pioglitazone C1: glibenclamide	I1: pioglitazone C1: glibenclamide
Randomised controlled clinical trial (RCT)	Y	Y	Y	Y	Y
Non-inferiority / equivalence trial	Y	Y	N	N	N
Controlled clinical trial	N	N	N	N	N
Design: parallel, crossover, factorial RCT	parallel	parallel	parallel	parallel	parallel
Design: crossover study	N	N	N	N	N
Design: factorial study	N	N	N	N	N
Crossover study: wash-out phase	NA	NA	NA	NA	NA
Crossover study: carryover effect tested	NA	NA	NA	NA	NA
Crossover study: period effect tested	NA	NA	NA	NA	NA
Method of randomisation	central block randomisation using a computer-generated list	?	central randomisation table; equal proportions; blocked within investigative site; stratification: oral antidiabetic drug-naive and -experienced patients	?	envelope method
Unit of randomisation (individuals, cluster - specify)	individuals	individuals	individuals	individuals	individuals
Randomisation stratified for centres	?	NA	Y	?	NA
Randomisation ratio	NA	NA	NA	NA	NA
Concealment of allocation	list was administered	?	randomisation table ad-	?	?

(Continued)

	centrally via telephone randomisation and re-supply service		ministered by an automated interactive voice-reponse system		
Stated blinding (open; single, double, triple blind)	double-blind	double-blind	double-blind	?	?
Actual blinding: participant	?	?	?	?	?
Actual blinding: caregiver / treatment administrator	?	?	?	?	?
Actual blinding: outcome assessor	?	?	?	?	?
Actual blinding: others	?	?	?	?	?
Blinding checked: participant	?	?	?	?	?
Blinding checked: caregiver / treatment administrator	?	?	?	?	?
Primary endpoint defined	Y	?	Y	Y	N
[n] of primary endpoint(s)	1	?	3	1	1?
[n] of secondary endpoints	9 (12)	?	9	10	12
Total [n] of endpoints	10 (13)	24	12	11	13
Prior publication of study design	N	N	N	N	N
Outcomes of prior / current publication identical	NA	NA	NA	NA	NA
Power calculation	Y	N	N	Y	N
[n] participants per group calculated	450	NA	NA	100	NA
Non-inferiority trial: interval for equivalence specified	Y	NA	NA	NA	NA
Intention-to-treat analysis (ITT)	Y	Y	Y	Y	?
Per-protocol-analysis	?	?	Y	Y	?
ITT defined	N	N	N	N	?
Missing data: last-observation-carried-forward (LOCF)	Y	?	Y	Y	?
Missing data: other methods	N	?	N	N	?
LOCF defined	N	NA	N	N	?
Analysis stratified for centres	?	NA	Y	Y	NA

(Continued)

[n] of screened patients	2145	?	584	?	?
[n] of randomised participants	I1: 597 C1: 597 Total: 1194	I1: 24 C1: 24 Total: 48	I1: 121 C1: 123 Total: 244	I1: 91 C1: 109 Total: 200	I1: 15 C1: 15 Total: 30
[n] of participants finishing the study	I1: 499 C1: 501 Total: 1000	I1: 21 C1: 21 Total: 42	I1: 87 C1: 89 Total: 176	I1: 55 C1: 68 Total: 123	I1: 13 C1: 14 Total: 27
[n] of patients analysed for primary end-point	I1: ? C1: ? Total: ?	I1: 21 C1: 21 Total: 42	I1: 83 C1: 73 Total: 156	I1: ? C1: ? Total: ?	I1: 13 C1: 14 Total: 27
Description of discontinuing participants	Y	N	Y	Y	Y
Drop-outs (reasons explained)	Y	?	Y	Y	Y
Withdrawals (reasons explained)	Y	?	Y	?	Y
Losses-to-follow-up (reasons explained)	Y	?	Y	?	NA
[n] of participants who discontinued	I1: 98 C1: 96 Total: 194	I1: 3 C1: 3 Total: 6	I1: 34 C1: 34 Total: 68	I1: 36 C1: 41 Total: 77	I1: 2 C1: 1 Total: 3
[%] discontinuation rate	I1: 16.4% C1: 16.1% Total: 16.2%	I1: 12.5% C1: 12.5% Total: 12.5%	I1: 28.1% C1: 27.6% Total: 27.9%	I1: 39.6% C1: 37.6% Total: 38.5%	I1: 13.3% C1: 6.7% Total: 10%
Discontinuation rate similar between groups	Y	Y	Y	Y	N
[%] crossover between groups	?	?	?	?	?
Differences [n] calculated to analysed patients	N	NA	NA	160 planned vs 113 completed; due to lower variability (SD 50% instead of 70%) power was adequate	NA
Adjustment for multiple outcomes / repeated measurements	N	Y	N	N	N
Baseline characteristics: clinically relevant differences	N	N	Y	Y	N
Treatment identical (apart from intervention)	Y	Y	Y	Y	Y
Compliance measured	?	N	N	N	N
Other important covariates measured (specify)	N	N	N	N	N

(Continued)

Co-morbidities measured	N	N	N	N	N
Co-medications measured	Y	N	Y	Y	Y
Specific doubts about study quality	N	many parameters, few patients	N	N	N
Funding: commercial	?	Y	Y	Y	?
Funding: non-commercial	?	N	N	N	?
Publication status: peer review journal	Y	Y	Y	Y	Y
Publication status: journal supplement	N	N	N	N	N
Publication status: abstract	N	N	N	N	N
Publication status: other	NA	NA	NA	NA	NA
Notes	none	sparse data on adverse events	primary endpoint described in abstract only; publication relates to Eli Lilly and Company protocol H6E-MC-GLAD	2-year head-to-head comparison of treatment failure rates of pioglitazone and gliclazide mentioned in discussion	none

Symbols & abbreviations: Y = yes; N = no; ? = unclear I = intervention; C = control

Appendix 18. Risk of bias (V)

Characteristic	Yamanouchi 2005
	I1: pioglitazone C1: metformin C2: glimepiride
Randomised controlled clinical trial (RCT)	Y
Non-inferiority / equivalence trial	N
Controlled clinical trial	N
Design: parallel, crossover, factorial RCT	parallel
Design: crossover study	N

(Continued)

Design: factorial study	N
Crossover study: wash-out phase	NA
Crossover study: carryover effect tested	NA
Crossover study: period effect tested	NA
Method of randomisation	sealed sequentially numbered envelopes
Unit of randomisation (individuals, cluster - specify)	individuals
Randomisation stratified for centres	?
Randomisation ratio	NA
Concealment of allocation	?
Stated blinding (open; single, double, triple blind)	?
Actual blinding: participant	?
Actual blinding: caregiver / treatment administrator	?
Actual blinding: outcome assessor	?
Actual blinding: others	?
Blinding checked: participant	?
Blinding checked: caregiver / treatment administrator	?
Primary endpoint defined	Y
[n] of primary endpoint(s)	1
[n] of secondary endpoints	11
Total [n] of endpoints	12
Prior publication of study design	N
Outcomes of prior / current publication identical	NA
Power calculation	Y
[n] participants per group calculated	30
Non-inferiority trial: interval for equivalence specified	NA
Intention-to-treat analysis (ITT)	?
Per-protocol-analysis	?
ITT defined	?

(Continued)

Missing data: last-observation-carried-forward (LOCF)	?
Missing data: other methods	?
LOCF defined	?
Analysis stratified for centres	?
[n] of screened patients	?
[n] of randomised participants	I1: 38 C1: 39 C2: 37 Total: 114
[n] of participants finishing the study	I1: 35 C1: 37 C2: 34 Total: 106
[n] of patients analysed for primary endpoint	I1: C1: C2: Total:
Description of discontinuing participants	Y
Drop-outs (reasons explained)	Y
Withdrawals (reasons explained)	Y
Losses-to-follow-up (reasons explained)	Y
[n] of participants who discontinued	I1: 3 C1: 2 C2: 3 Total: 8
[%] discontinuation rate	I1: 7.9% C1: 5.1% C2: 8.1% Total: 7.0%
Discontinuation rate similar between groups	Y
[%] crossover between groups	?
Differences [n] calculated to analysed patients	N
Adjustment for multiple outcomes / repeated measurements	N
Baseline characteristics: clinically relevant differences	Y
Treatment identical (apart from intervention)	Y
Compliance measured	N

(Continued)

Other important covariates measured (specify)	N
Co-morbidities measured	N
Co-medications measured	Y
Specific doubts about study quality	N
Funding: commercial	?
Funding: non-commercial	?
Publication status: peer review journal	Y
Publication status: journal supplement	N
Publication status: abstract	N
Publication status: other	NA
Notes	pre-trial calculation performed for pioglitazone vs diet-alone treated participants; "maximum dose of metformin in Japan is limited to 750 mg/day"

Symbols & abbreviations: Y = yes; N = no; ? = unclear I = intervention; C = control

WHAT'S NEW

Date	Event	Description
6 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

BERND RICHTER: Protocol and review development, selection of studies, quality assessment, data extraction, data analysis.

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DECLARATIONS OF INTEREST

None known.

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INDEX TERMS

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Diabetes Mellitus, Type 2 [*drug therapy]; Hypoglycemic Agents [*therapeutic use]; Pioglitazone; Randomized Controlled Trials as Topic; Thiazolidinediones [*therapeutic use]

MeSH check words

Humans