A systematic review, meta-analysis, and long-term cost-utility of rosiglitazone and pioglitazone for the treatment of type 2 diabetes mellitus in adults

REPORT

Prepared for the Ontario Ministry of Health and Long-term Care

by

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EXECUTIVE SUMMARY

Introduction

Rosiglitazone and pioglitazone belong to a class of oral anti-diabetic agents, the thiazolidinediones (TZDs), which act to improve insulin sensitivity of peripheral tissues in patients with type 2 diabetes. In Canada, TZDs are approved for use both as monotherapy and in combination with metformin or a sulfonylurea. These new agents are substantially more expensive than established oral antidiabetic medications. As a result, the overall aim of this report is to evaluate the clinical efficacy and incremental cost-effectiveness of pioglitazone and rosiglitazone in the treatment of adults with type 2 diabetes. The use of pioglitazone and rosiglitazone as monotherapy and in combination with metformin, sulfonylurea, or insulin as compared with established treatments are all considered in this report. Separate objectives are:

1. To review the published literature surrounding the clinical efficacy of rosiglitazone and pioglitazone, in terms of glycemic control, in the treatment of patients with type 2 diabetes;
2. To describe and quantify the effect of rosiglitazone and pioglitazone on glycemic control;
3. To estimate the long-term costs and consequences of rosiglitazone and pioglitazone in comparison with conventional therapy using an Ontario-specific decision analytic economic model.

Systematic review and meta-analysis of the efficacy of rosiglitazone and pioglitazone on glycemic control

Methods Electronic databases were searched between 1993 and March 2006. Selection criteria were developed and study selection and data extraction were performed by independent reviewers. The main outcomes were HbA1c and fasting plasma glucose (FPG). Included studies were categorized by drug, dosage, patient type, and comparator. Treatment effects were pooled across studies using a weighted mean difference using random-effects models.

Results The search produced 3,854 unique citations with 26 rosiglitazone and 25 pioglitazone trials met inclusion criteria. Both rosiglitazone and pioglitazone showed

the greatest decreases in HbA1c (up to 1.90%) and FPG (up to 4.55 mmol/L) when they were added to failed monotherapy compared with placebo. Combined results indicated that initiating TZD monotherapy in treatment-naïve patients was associated with a smaller decrease from baseline in HbA1c compared with other regimens. Adding a TZD to failed dual therapy was not as effective at reducing HbA1c (-1.90% vs. -2.30%, respectively) and FPG (-2.90 mmol/L vs. -4.30 mmol/L) as adding insulin to the failed therapy. No study directly compared the addition of a TZD to failed dual therapy with switching patients to insulin.

Summary Overall there were a limited number of studies providing efficacy data for specific populations to determine TZDs best place in therapy. However, the systematic review of available data revealed that both rosiglitazone and pioglitazone were effective in reducing HbA1c and FPG levels in patients with type 2 diabetes, both as monotherapy (versus placebo and active comparator) and in combination with metformin, a sulfonylurea, or insulin when compared with placebo. Adding insulin to failed dual therapy resulted in greater decreases in both HbA1c and FPG compared with the addition of a TZD, however the differences were not statistically significant.

Application of the ODEM to rosiglitazone and Pioglitazone in the treatment of Type 2 Diabetes

Methods

Mean changes from baseline to end of study on five key risk factors (i.e. HbA1c, blood pressure, total cholesterol, HDL cholesterol, smoking status) were abstracted from identified studies where available and combined. Unit costs for each of the drugs used in the treatment scenarios were obtained from the Ontario Drug Benefit Formulary. These data were used as inputs in the ODEM to estimate the cumulative first event rates for 7 DM-related complications, the mean difference in cost, and expected quality-adjusted life-years (QALYs). Incremental cost-effectiveness ratios (ICER) were calculated based on the net cost of healthcare resources associated with the treatment and on effectiveness estimated over a patient's lifetime. In the base case, the ICER was calculated assuming the effect of the intervention continued for 5 years using a discount rate of 3% and a time horizon of 40 years.

Sensitivity analyses were conducted by varying the duration of the program and treatment effect.

Results

In the base case analysis, the strategy of adding rosiglitazone to failed sulfonylurea was dominated by the strategy of adding metformin to failed sulfonylurea. Similarly, adding insulin to failed dual therapy of metformin and sulfonylurea dominated adding rosiglitazone to the same treatment. Adding rosiglitazone to failed insulin monotherapy compared with a 'do nothing' strategy was estimated to be less than $50,000 per QALY. Adding rosiglitazone to failed dual therapy (i.e. sulfonylurea plus metformin) compared with placebo had a $54,001 per QALY and adding rosiglitazone or sulfonylurea to failed metformin produced an incremental cost per QALY of $59,485.

Adding metformin to failed sulfonylurea or adding insulin to failed dual therapy (i.e. sulfonylurea plus metformin) were dominant treatment strategies compared with adding pioglitazone to these failed regimens. Adding pioglitazone to failed metformin resulted in an incremental increase in both costs and QALYs relative to adding sulfonylurea to give an incremental cost-effectiveness ratio of $122,480 per QALY. Pioglitazone add-on to failed insulin was associated with an incremental cost-effectiveness ratio of $55,072 compared with simply continuing insulin monotherapy.

Summary

Half of the pioglitazone treatment scenarios were dominated by other treatment strategies and other regimens were more than $50,000 per QALY. Two of the five rosiglitazone treatments evaluated were dominated, however the strategies that were not dominated were all less than $60,000 per QALY. Adding a TZD to failed insulin compared with continuing on insulin alone had the best ICER and appears to represent reasonable value for money.

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1. INTRODUCTION

1.1. Background

Currently available oral therapies for type 2 diabetes include various agents such as sulfonylureas, non-sulfonylurea insulin secretagogues, metformin, and α-glucosidase inhibitors (such as acarbose). These agents have been used extensively and have been the mainstay of oral treatment for type 2 diabetes and can be used as monotherapy or in combination with other therapies. Another class of oral agents, the thiazolidinediones (TZDs) are also available for use in clinical practice. TZDs are approved for use as monotherapy or in combination with metformin, sulfonylureas, non-sulfonylurea insulin secretagogues or α-glucosidase inhibitors. The two TZDs, or "glitazones", currently available in Canada are rosiglitazone (Avandia®) and pioglitazone (Actos®). Presently, the Ontario Drug Benefit (OBD) Program covers rosiglitazone under special provisions (i.e. Section 8) while pioglitazone is available as an unlimited benefit.

The glitazones may further improve upon long-term outcomes through enhancement of insulin sensitivity of peripheral tissues, and reduction of other metabolic parameters such as blood pressure.(1;2) Glitazones, however, have higher acquisition costs compared with currently available products on the ODB Formulary such as glyburide and metformin, both of which are available in generic formulations. As a result there is a trade-off between the potential for improved health outcomes and higher drug costs. This report summarizes the clinical efficacy of pioglitazone and rosiglitazone and using modeling techniques, quantifies the long-term cost-effectiveness expressed as an incremental cost-effectiveness ratio compared to other oral therapies as well as insulin.

1.2. Objectives

The overall aim of this report is to evaluate the clinical efficacy and incremental cost-effectiveness of pioglitazone and rosiglitazone in the treatment of adults with type 2 diabetes. The use of pioglitazone and rosiglitazone as monotherapy and in combination with metformin, sulfonylurea, or insulin as compared with established treatments are all considered in this report. Separate objectives are:

4. To review the published literature surrounding the clinical efficacy of rosiglitazone and pioglitazone, in terms of glycemic control, in the treatment of patients with type 2 diabetes;
5. To describe and quantify the effect of rosiglitazone and pioglitazone on glycemic control;
6. To estimate the long-term costs and consequences of rosiglitazone and pioglitazone in comparison with conventional therapy using an Ontario-specific decision analytic economic model.

2. SYSTEMATIC REVIEW AND META-ANALYSIS OF THE EFFICACY OF GLITAZONES ON GLYCEMIC CONTROL IN THE TREATMENT OF ADULTS WITH TYPE 2 DIABETES

2.1. Methods

2.1.1. Background

A systematic review was conducted to identify comparative studies that evaluated the clinical efficacy of glitazones. The studies meeting predefined inclusion/exclusion criteria were then used to fulfill two purposes for this section of the health technology assessment report: 1) to qualitatively describe the existing published literature on the efficacy of rosiglitazone and pioglitazone in the treatment of type 2 diabetes mellitus; and 2) to use meta-analytic techniques to quantitatively summarize the efficacy of rosiglitazone and pioglitazone. The latter will also provide estimates of the parameters needed to populate the ODEM in order to evaluate the economic efficiency of these medications.

2.1.2. Search strategy for identification of studies

A preliminary search was undertaken to provide information on available published randomized controlled trials (RCTs) on rosiglitazone and pioglitazone used in the treatment of type 2 diabetes. This search allowed for the determination of the potential size of the literature base and clarified the search terms to be used in the complete search.

A complete search was undertaken by the research teams from the Evidence-based Practice Centre (EPC) and the Program for Assessment of Technology in Health (PATH) for the different electronic databases (MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Reviews). First, a search strategy for type 2 diabetes was created, and then the search terms for the drug interventions were added. To achieve this, a combination of the use of medical subject heading (MeSH) terms, keywords and text strategies were adopted. Specific drug names and manufacturer brands were considered as potential search terms. Appendix A provides a detailed description of the search terms used for each database. The order of the databases outlined in Appendix A also represents the sequence in which the databases were searched.

All databases were searched from 1993 to March 2006 for rosiglitazone and pioglitazone. The results of the searches were imported into a database created in Reference Manager (Version 10) where they were cleansed of duplicates and prepared for screening.

2.1.3. Eligibility Criteria

2.1.3.1. Types of studies

Studies were considered if they were primary randomized controlled trials (RCTs) investigating the efficacy of rosiglitazone or pioglitazone in the treatment of type 2 diabetes in adults (i.e. aged 18 years or older). Review articles were classified into one of two groups: 1) review articles that used robust analytic techniques for pooled data e.g. meta-analysis, or 2) narrative or descriptive reviews. These latter review articles were excluded from the current systematic review; however, relevant reviews that fell into the first class above were used as background/source documents. All non-English articles were excluded. A more detailed description of the inclusion and exclusion criteria used is outlined in Appendix B.

2.1.3.2. Types of participants

The population of interest was adults aged 18 years and older with type 2 diabetes.

2.1.3.3. Interventions

Comparisons of rosiglitazone or pioglitazone, either as monotherapy or as add-on therapy to other anti-diabetic agents for the treatment of type 2 diabetes were selected.

2.1.3.4. Outcome measures

The outcomes of interest were mean changes from baseline to end of study in glycosylated haemoglobin A1c (HbA1C) and fasting plasma glucose (FPG). HbA1c, body mass index (BMI), total cholesterol, HDL cholesterol, and systolic blood pressure were also collected as these were required as inputs for the economic model.

2.1.4. Methods of the review

The title and abstract screening, relevance and quality ratings, and data extraction were done directly on-line, using the web-based systematic review tool Systematic Reviews Systems Version 3.0 by TrialStat. The on-line software permitted raters to see the progress of any article through the process, and after rating, to identify articles in conflict.

Two well-trained and experienced raters from the EPC and PATH independently reviewed titles and abstracts for potential relevance. Articles that were clearly not relevant (as agreed by both raters) were excluded. The included articles were further screened at the second phase of title and abstract using a defined set of criteria (Appendix B). Complete articles for all remaining citations including those determined by either rater as having questionable eligibility, were retrieved. To be included, a study had to meet all inclusion criteria. Disagreements were resolved through discussion and consensus. Expert opinion was used if and when the need for resolving discrepancies arose.

2.1.5. Quality Assessment and Data Abstraction

Quality assessment

Studies were screened to determine quality in the trial design. Specifically, methodological quality of each study was assessed using the Jadad scale for randomized controlled trials (Appendix C).(3) This instrument is composed of three items related directly to the reduction of bias of meta-analytic results. These include randomization, blinding, and study withdrawals and dropouts. A score is given for each of the three items, for a maximum of five points. Each study was evaluated by two reviewers and disagreements were settled in order to reach consensus. No minimum level of quality rating was used to determine eligibility of the study for inclusion. Therefore, this review abstracts detailed data from all studies identified in the literature review regardless of ratings on the quality scale.

In addition, allocation concealment was also considered in the assessment with ratings of adequate, unclear and inadequate. Using the methodology developed

by Hewitt et al,(4) articles were categorized according to whether allocation concealment was adequate (i.e. the person who executed the allocation sequence was different from the person who recruited participants), inadequate (i.e. the person who recruited participates also executed the allocation sequence), or unclear (i.e. the article failed to describe how the researchers concealed the allocation).

Data abstraction

There were 2 levels of data abstraction for each study; the first level dealt with the general characteristics of the study (e.g. year the study was conducted; country(s) study was conducted in, participants, study design, drug dosages)(Appendix B). The second level of data abstraction involved outcome measures and results of analyses. One rater extracted data, and a second checked the accuracy of all data tables. Units expressed in traditional units were converted to the International System of Units (SI) by multiplying the traditional value by the appropriate conversion factor.(5) In cases where data of interest were not reported, the data were computed where possible.

When a study compared two or more doses of a glitazone with one dose of a non-glitazone agent, each group was included in separate meta-analyses according to drug dose in order to avoid duplicating the sample of the control group. Trials that compared more than two interventions groups needed to be treated with care.

All data collected for this review were continuous. Review Manage 4.1 was used for pooling the data. Results from studies using intention-to-treat (ITT) analysis, which aims to include all participants randomized into a trial irrespective of what happened subsequently, were preferred. However, if a large proportion of the studies used Available Case Analyses, which include data only on those whose results are known, they too were included.

The methods outlined in the Cochrane Review Handbook were used to conduct the meta-analyses.(6) When available, the mean change from baseline to endpoint, standard deviations, and the number of participants on whom the

outcome was assessed in each of the treatment groups, were extracted from the publication and entered into Review Manager 4.1. Due to variable reporting however, occasionally it was difficult or impossible to obtain the necessary information from the data summaries presented. Trials varied in the statistics they used to summarize averages (sometimes using medians rather than means) and variation (sometimes using standard errors, confidence intervals, interquartile ranges and ranges rather than standard deviations). When the mean differences from baseline were available, but the measure of variance for the mean difference from baseline was provided in terms of standard errors (SE), the standard error of means was multiplied by the square root of the sample size to estimate the standard deviation (SD):

$$SD = SE \times \sqrt{N}$$

We were careful to ensure when making this transformation that standard errors were standard errors of means calculated from within a treatment group and not standard errors of the difference in means computed between treatment groups.

In the event that standard errors were mislabelled as standard deviations, consultation with a clinical expert and a biostatistician was available. Also, attempts would be made to contact leading authors to rectify the problem.

In cases where the measure of dispersion was not provided, but the level of significance for the mean difference from baseline to endpoint was given in the form of a 95% confidence interval (95% CI), the confidence intervals for means were used to calculate standard deviations via calculation of the standard error of the mean. For 95% confidence intervals with a large sample size (i.e. bigger than 120), the 95% confidence interval was assumed to be 3.92 (2 x 1.96) standard errors wide. The standard deviation for each group was obtained by dividing the length of the confidence interval by 3.92, and then multiplying by the square root of the sample size using the following formula:

$$SD = \sqrt{N} \times (\text{upper limit} - \text{lower limit})/3.92$$

When the level of significance was based on a *P*-value from Student's t-test for the mean difference from baseline, it was possible to calculate standard deviations by first obtaining the corresponding *t*-value from a table of *t*-distribution critical values (noting that the degrees of freedom are $N_E + N_C - 2$, where N_E and N_C are the sample sizes in the two groups, and then transforming the *t*-value into a standard deviation by first computing the standard error of the difference in means (MD) by the *t*-value:

$$\text{Standard error of difference in means} = MD/t$$

Then calculating the standard deviation using the following formula:

$$\text{Standard deviation} = \frac{\text{standard error of difference in means}}{\sqrt{(1/N_E + 1/N_C)}}$$

These methods estimated the average of the standard deviations observed in the two groups, and were entered into Review Manager for both groups. If the sample size was less than 120, SD calculation was based on the "t" score. If the sample size was over 120, SD calculation was based on the "z" score. These scores were standard "t" Distribution and "z" Distribution tables respectively. Tests were assumed to be two-sided.

Some studies calculated a mean percent change from baseline which was a percentage change for each patient, and then the mean of the percentage change was calculated for each treatment group. The absolute value for the mean change was converted by multiplying the mean percent change with the baseline value. In these cases, the level of significance for the mean percent change was provided as a 95% confidence interval, also expressed in percent change. The conversion to the absolute value for the lower and upper boundaries of the 95% CI was obtained by multiplying the percent change associated to each boundary with the baseline value. When the mean difference was not directly available but the *P*-value for the difference between the mean baseline value and the mean endpoint value was provided for an outcome of interest, the mean difference from baseline to endpoint was calculated by subtracting the mean baseline value from the mean endpoint value. The SD

value was calculated from the *P*-value, using the same approach as described previously.

When no measure of variance was provided for the difference from baseline to endpoint but there was a *P*-value based on the Student's t-test, the following formula was used:

$$t=\frac{x-\mu_0}{s/\sqrt{n}}$$

Where changes in BMI were not provided but changes in weight was given with a measure of baseline BMI or height or weight, the missing value was calculated in order to calculate change in BMI from baseline to the end of the study. In cases where weight was provided but height was not, the average height calculated from another study in that meta-analysis was used if the patient population was similar.

In some situations, graphs that were presented in the papers with bars representing the variance (SE or SD) were used to visually estimate the values.

When none of the aforementioned techniques would allow us to calculate the standard deviation of the mean change from baseline for both the experimental and the control groups, the values were imputed by estimating a common correlation (R) from several studies. To impute the standard deviation of a change from baseline when baseline and final standard deviations were known, we used an imputed value R for the correlation coefficient. The value of R was imputed from the weighted average from other studies in the meta-analysis. First, the correlation coefficient for each study was estimated by calculating the correlation coefficient for each group in the study.

$$R = \frac{SD(B)^2 + SD(F)^2 - SD(C)^2}{2 \times SD(B) \times SD(F)}$$

Where B is the baseline, F is final and C is change. Each correlation coefficient was transformed by a z-transform. The weighted z was then transformed to

produce a weighted correlation coefficient. To obtain a standard deviation of the change from baseline, the following formula was used:

$$SD(C) = \sqrt{SD(B) + SD(F) – (2 \times R \times SD(B) \times SD(F))}$$

If there was no method to allow calculation of the standard deviation(s) from the paper then, it was decided to exclude the study from the meta-analysis and risk introducing bias. However, a narrative approach to synthesis was used to include studies in the systematic review, even if they could not be included in the formal meta-analyses.

2.1.6. Statistical Analysis

Pooling of treatment effects were performed with Review Manager 4.1. For all estimates, both a chi square test of statistical heterogeneity and a test for significance were calculated using the random-effects model.

2.2. Results

2.2.1. Description of studies

A total of 3,880 citations were identified by the electronic literature search. From these, 151 were included in full text screening to determine eligibility. One hundred articles were further excluded. A flow diagram depicting the sources of information used, the number of potentially relevant references retrieved, number and reasons for exclusion, and the number of studies ultimately included in the review is provided in Appendix D. The total number of studies meeting our inclusion criteria was 51, 26 measured the efficacy of rosiglitazone and 25 articles measured pioglitazone.

2.2.2. Clinical Efficacy of Rosiglitazone

Of the 26 full publications identified, six studies assessed monotherapy use, three compared rosiglitazone with placebo and three compared rosiglitazone with an active comparator. The remaining studies evaluated rosiglitazone as an add-on therapy regimen; 19 added rosiglitazone to failed monotherapy and two added rosiglitazone to failed dual therapy. One study randomized patients to one of three treatment arms, i.e. two monotherapy arms and one add-on therapy arm.

2.2.2.1. Efficacy of Rosiglitazone as Monotherapy

2.2.2.1.1. Rosiglitazone compared with placebo comparator

Three studies assessed rosiglitazone compared with placebo (Table 1).(7-9) All three studies were dose finding studies and contained at least 3 treatment arms, with two having 5 study arms.(7;8). Both of these studies included patients who were previously treated with oral antidiabetic medications but still had blood glucose levels within normal ranges. The observation periods for the trials varied from 12 weeks to 26 weeks.

Table 1. Characteristics of studies included in the analysis of rosiglitazone as monotherapy compared with placebo

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Patel(7) (n=380)	12-week dose-finding, multicentre, double-blind, (24 sites in US)	T2DM with FPG ≥7.8 mmol/L and ≤13.3 mmol/L. Previous antidiabetic medications allowed	PBO or ROSI 0.05mg, 0.25mg, 1mg, or 2mg BID	FPG, HbA1c, fructosamine, C peptide, insulin, lipid levels, and body weight	B/4
Lebovitz(9) (n=493)	26-week placebo controlled multicentre, trial (42 centres in US)	T2DM, Patients were drug naive (27%), prior monotherapy (65%), and prior combination therapy (6%)	PBO or ROSI 2mg BID, or 4mg BID	HbA1c, FPG, fructosamine, endogenous insulin secretion, urinary albumin excretion, serum lipids	B/3
Phillips(8) (n=959)	26-week, double-blind placebo-controlled, multicentre, trial (65 centres in US)	T2DM, FPG 7.8-16.7 mmol/L, fasting C-peptide ≥0.27mmol/L. Patients were drug naïve (24.8%), prior monotherapy (60.0%), and prior combination therapy (15.5%)	PBO or ROSI 4mg OD, 2mg BID, 8mg OD, or 4mg BID	HbA1c, FPG, immuno-reactive insulin, C-peptide, and lipid levels	B/4

Abbreviations: PBO=placebo; ROSI=rosiglitazone, T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

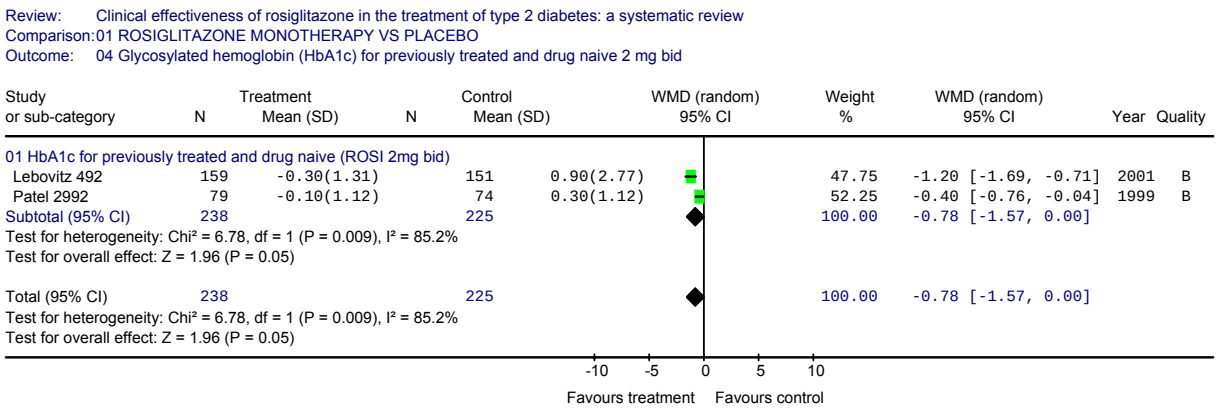
Outcomes

HbA1c

Results from one study were not quantitatively analyzed as standard deviations around the mean changes from baseline were not reported.(8) In this study, patients were randomized to one of five arms: placebo; 4mg OD; 2mg BID; 8mg OD; and 4mg BID. Mean decreases in HbA1c were -0.8%, -0.9%, -1.1%, and -1.5%, respectively by the end of 26 weeks. All rosiglitazone-treated groups had statistically significant decreases in HbA1c compared with the placebo group (*P*<0.0001*)*.

It was possible to pool the HbA1c data for the 2mg BID arms from the remaining two studies.(7;9) Rosiglitazone-treated patients in both studies had larger decreases from baseline in HbA1c compared with the placebo group (WMD: -0.78%, 95% confidence interval (CI): -0.96, -0.39, *P*=0.05)(Figure 1). The study by Lebovitz(9) also analysed the use of rosiglitazone 8 mg/day and the results showed that HbA1c was reduced by 0.60% (SD=1.91) compared with an increase in HbA1c from baseline in the placebo group of 0.90 (SD=2.77) for a weighted mean difference of -1.50% (95% CI: -2.03, -0.97, *P*<0.0001).

Figure 1. Pooled estimate of HbA1c for rosiglitazone 4 mg/day versus placebo in previously treated and drug naïve patients

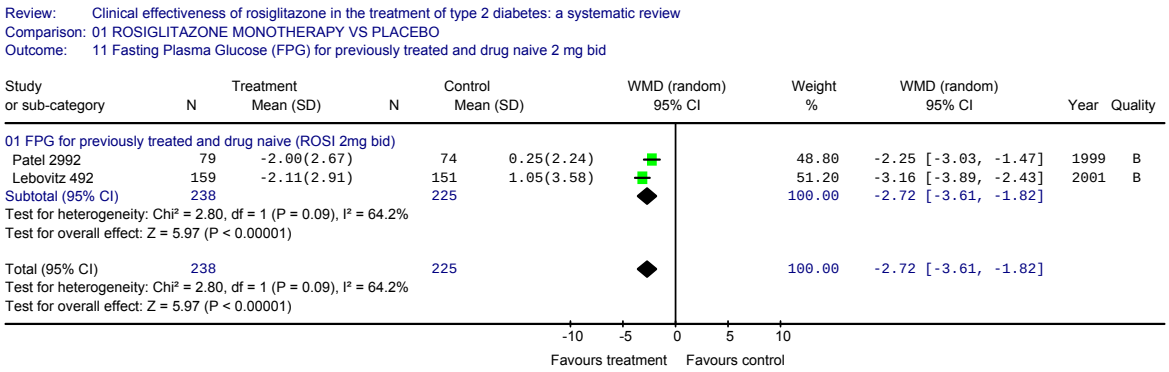


FPG

The paper by Philips et al(8) did not report FPG as an outcome and thus a qualitative description of treatment effect could not be done.

Data from the two remaining studies provided the mean change from baseline and standard deviation (SD) for FPG. Specifically, Patel et al(7) showed that FPG decreased by 2.00 mmol/L (SD=2.67) in patients treated with rosiglitazone 4 mg/day compared with an increase of 0.25 mmol/L (SD=2.24) in the placebo group. These results were combined with the data from the Lebovitz study(9). Rosiglitazone monotherapy provided a statistically significant decrease from baseline in FPG (WMD: -2.72 mmol/L, 95% CI: -3.61, -1.82, *P*<0.001)(Figure 2). The patients randomized to 8 mg/day in the Lebovitz study showed an even greater decrease of FPG (- 3.00 mmol/L).(dose response)

Figure 2 Pooled estimate of FPG for rosiglitazone 4 mg/day versus placebo in previously treated and drug naïve patients



2.2.2.1.2. Rosiglitazone compared with active comparator

Three studies were identified that compared the efficacy of rosiglitazone with an active comparator (Table 2).(10-12): two enrolled treatment naïve patients or patients that were still controlled on monotherapy(10;11) and one recruited patients who were uncontrolled on monotherapy (sulfonylurea or metformin at ≥ 50% of the maximal dose) and the treatment duration was 24 weeks. (12) Neither of the former two studies provided measures of variance around the mean change values from baseline values in HbA1c and FPG, nor did they use the same comparator and thus no pooling was possible. The following sections provide qualitative descriptions of all study findings.

Table 2 Characteristics of studies included in the analysis of rosiglitazone as monotherapy compared with an active comparator

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
St. John Sutton(11) (n=203)	52-week, open-label, multicentre study (19 centres in the US).	T2DM (National Diabetes Data Group definition) patient were treatment naïve or controlled on therapy.	ROSI 4 mg BID or GLB ≤ 20 mg/day OD or BID titrated to optimal glycemic effect.	Change in left ventricular mass index, left ventricular end-diastolic volume and ejection fraction, BP, heart rate, arterial pressure, and pulse pressure; glycemic control and serum lipids.	B/2
DeFronzo (10) (n=145)	12-week, open-label, parallel group, multicentre (40 centres in US)	T2DM (defined by ADA) with suboptimal control on diet and exercise, HbA1c ≥8 ≤11%	Inhaled insulin (INH) vs. PIO 4 mg BID	Percentage of patients achieving HbA1c <8.0%, changes in: HbA1c, FPG, postprandial plasma glucose, body weight, fasting serum lipids	A/3
Raskin(12) (n=252)	24-week, multicentre, three-armed, open-label, parallel-group study (US)	T2DM ≥ 1 year, HbA1c >7.0% ≤12% after monotherapy (SU or MET), ≥50% maximal dose ≥ 3 months, with BMI ≤ 45.	REP vs. ROSI vs. REP/ROSI	Changes in HbA1c and FPG	B/5

Abbreviations: PBO=placebo; REP=repaglinide; ROSI=rosiglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Outcomes

HbA1c

The study comparing rosiglitazone with glyburide in treatment naïve and well-controlled patients concluded that both treatments produced clinically and significant reductions in Hba1c at week 52 compared with baseline values.(11) The actual mean change values were not reported in the paper but the authors noted that the temporal patterns differed between the two treatment groups. Glyburide treatment resulted in an initial rapid reduction in HbA1c from week 0

through week 16, after which glycemic control progressively deteriorated. The progressive reductions in HbA1c were sustained with rosiglitazone such that HbA1c was comparable between treatment groups at week 52.

The second study with a similar study group (i.e. naïve to oral anti-diabetic therapy) randomized patients to12 weeks of treatment with either inhaled insulin (INH) or rosiglitazone 4 mg twice daily. The results showed that HbA1c decrease was greater with INH than with rosiglitazone (-2.3% vs. -1.4%, respectively).(10)

Finally, 252 patients failing sulfonylurea or metformin monotherapy were randomized to one of three treatment arms: repaglinide monotherapy, rosiglitazone monotherapy, and combination therapy (repaglinide plus rosiglitazone) in the last study.(12) The mean reduction in HbA1c in the rosiglitazone monotherapy arm was 0.56% (SD, 1.04) compared with a reduction of 0.17% (SD, 1.08) in the repaglinide monotherapy group.

FPG

The study by St. John Sutton(11) found that both rosiglitazone and glyburide produced clinically and significant reductions in FPG at week 52 compared with baseline values in drug naïve and those still controlled on therapy. Mean FPG levels rosiglitazone-treated patients decreased rapidly from 13.1 to 10.4 mmol/L between weeks 0 and 8, and it continued to decrease through week 52 to 8.9 mmol/L. Among glyburide-treated patients, mean FPG decreased more dramatically than with rosiglitazone between weeks 0 and 8 from 13.6 to 9.5 mmol/L, remained stable from week 8 to 16, and gradually increased through week 52 to 10.5 mmol/L.

Treatment with INH or rosiglitazone produced similar changes from baseline in FPG (-3.56 vs. - 3.11 mmol/L, respectively) after 12 weeks in patients naïve to treatment(10).

In the study that compared rosiglitazone to repaglinide in patients failing monotherapy, the mean reductions in FPG values relative to baseline were -3.70 mmol/L (SD, 2.77) for rosiglitazone and -3.00 mmol/L (SD, 2.79) for repaglinide.(12)

2.2.2.2. Efficacy of Rosiglitazone as Add-on to Monotherapy

2.2.2.2.1. Rosiglitazone compared with placebo comparator for patients not failed on current treatment

One study evaluated the efficacy of adding rosiglitazone to pre-existing metformin and/or sulfonylurea therapy in Korean type 2 diabetes patients.(13) The characteristics of this study are outlined in Table 3. In short, patients were randomized to 4 mg/day of rosiglitazone treatment or control for 12 weeks.

Table 3 Characteristics of studies included in the analysis of rosiglitazone as add-on therapy compared with pre-existing treatment

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Kim(13) (n=125)	12-week, open-labelled, controlled study (1 centre in Korea)	T2DM with FPG ≥7mmol/L, HbA1c ≥7%, and a fasting C-peptide level >1.1 mg/mL and on MET and/or SU therapy ≥ 3 months.	ROSI 4mg/day added to existing MET and/or SU vs. existing MET and/or SU	Changes in FPG, HbA1c, plasma insulin, C-peptide, HOMA-IR, HOMA (beta-cell function), QUICKI, and serum lipids.	B/2

Abbreviations: PBO=placebo; REP=repaglinide; ROSI=rosiglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Outcomes

HbA1c

Kim and colleagues(13) found that after 12 weeks of rosiglitazone being added to current therapy, HbA1c was reduced by 1.2% (P<0.001) compared with a 0.1% reduction in patients continuing on previous oral therapy.

FPG

Fasting plasma glucose decreased significantly compared to baseline in both the rosiglitazone treatment arm (-3.4 mmol/L, P<0.001) as well as in the control arm (-1.2 mmol/L, P<0.05).(13)

2.2.2.2.2. Rosiglitazone add-on therapy compared with placebo comparator for patients failing monotherapy

The efficacy of adding rosiglitazone to failed monotherapy was evaluated in eight different studies (Table 4).(12;14-20) Four studies measured the effect of adding rosiglitazone to failed sulfonylurea; (14-16)}(20) three studies looked at the addition of rosiglitazone to the failure of metformin(17-19); and 1 study assessed the impact of adding rosiglitazone to repaglinide in patients where repaglinide failed to control blood glucose.(12) The next few sections will describe the results of each of the 3 comparisons for both of the outcomes of interest.

Table 4 Characteristics of studies included in the analysis of rosiglitazone as add-on therapy to failed monotherapy compared with placebo

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Barnett(20) (n=177)	26-week, double-blind, placebo-controlled, parallel group, multicentre study (31 centres in UK)	Indo-Asian with T2DM with FPG ≥7 and ≤15 mmol/L and HbA1c ≥7.5% and on SU ≥ 4 months	ROSI 8 mg/day +SU vs. PBO + SU	HbA1c, plasma insulin, C-peptide, insulin sensitivity and B-cell function, and serum lipids.	B/3
Vongthavaravat(15) (n=348)	Multicentre, open-label, 26-week study (India, Brazil, The Philippines, Thailand, Argentina and Tunisia)	T2DM receiving SU therapy for at least 6 months with FPG ≥ 7 ≤15 mmol/L	ROSI 2mg BID + SU vs. SU alone	HbA1c and FPG	A/2
Wolffenbuttel(14) (n=574)	26-week, multicentre, double-blind, placebo-controlled, parallel-group study (60 centres Italy, UK, France, Spain, Holland and Switzerland)	T2DM, treated with SU and BMI 22-38, FPG ≤15.0 mmol/L, HbA1c ≥7.5%.	ROSI 2 mg + SU vs. ROSI 4 mg + SU vs. SU + PBO	HbA1c, FPG, fructosamine, insulin levels, C-peptide, albumin excretion rate and lipid measures.	B/3
Zhu(16) (n=530)	24-week, multicentre,	T2DM, exposure to	ROSI 2mg BID + SU vs.	FPG, HbA1c, and proportion	A/5

	double-blind, placebo-controlled, parallel group study (3 centres in China)	hepatitis B and C, BMI 19-38. FPG 7.5-12.9 mmol/L and HbA1c ≥7.5% and received SU ≥ 6 months	ROSI 4mg BID + SU vs. SU + PBO	of patients with clinically significant responses.	
Fonseca(17) (n=348)	26-week, double-blind, placebo-controlled, multicentre (36 sites in the US) trial	T2DM previously treated but inadequately controlled with MET	PBO + MET vs. ROSI 4mg OD + MET vs. ROSI 8 mg OD +MET	HbA1c	A/5
Gomez-Perez(18) (n=116)	26-week, double-blind, placebo-controlled, open-labelled study (4 centres in Mexico).	T2DM inadequately controlled with MET monotherapy	PBO + MET 2.5 g/day or ROSI 2mg BID + MET 2.5 g/day or ROSI 4mg BID + MET 2.5 g/day	HbA1c	B/4
Negro(19) (n=38)	52-week, double-blind, study at one centre (Italy)	T2DM on 2,550 mg/day of MET with a nocturnal decline in BP less than 10%	ROSI 8 mg/day + MET vs. PBO + MET	BP, FPG, insulin, HbA1c, total cholesterol and TRGs	A/3
Raskin(12) (n=252)	24-week, multicentre, three-armed, open-label, parallel-group study (US)	T2DM ≥ 1 year, HbA1c >7.0 ≤12% after previous monotherapy (SU or MET), ≥50% maximal dose ≥ 3 months, with BMI ≤ 45.	REP vs. ROSI vs. REP/ROSI	HbA1c and FPG	B/5

Abbreviations: PBO=placebo; REP=repaglinide; ROSI=rosiglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Outcomes

HbA1c

Sulfonylurea failure

All four studies comparing the addition of rosiglitazone to failed sulfonylurea monotherapy showed a greater improvement in HbA1c in the treatment arm compared with the control arm.(14-16;20) Three of the four studies that used a rosiglitazone dose of 4 mg daily provided adequate information to allow for a pooling of the mean changes from baseline in HbA1c values using meta-analytic techniques (Figure 3).(14-16) The weighted mean difference was a decrease of 1.10% (95% CI, -1.25, -0.95, P<0.001) greater in the rosiglitazone group than in the control group. Barnett (20) and Zhu(16) also evaluated the addition of rosiglitazone 8 mg/day to failed sulfonylurea and found that HbA1c was reduced by 1.16 and 1.9 respectively, compared with an increase of 0.26% in the Zhu trial and a reduction of 0.4% in the Barnett trial in the control groups. These results could not be pooled using meta-analytic techniques but the results are outlined in Table 5 to illustrate the dose-response effect.

Figure 3. Pooled estimate of HbA1c for rosiglitazone 4 mg/day added-on to failure of monotherapy versus placebo

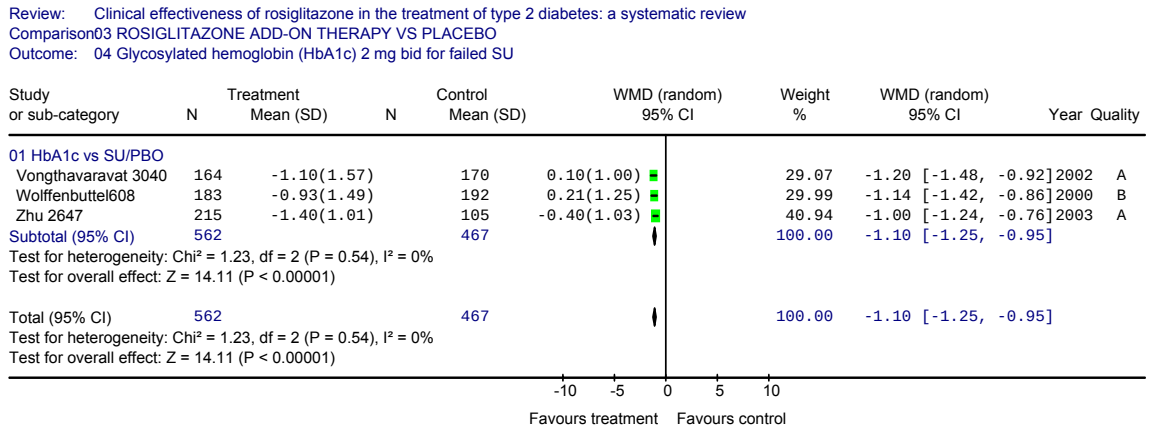


Table 5 Mean change in HbA1c compared to baseline for add-on rosiglitazone 8 mg/day therapy to failed sulfonylurea monotherapy versus placebo

Author	TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Zhu(16)	8mg/d	210	-1.9% (1.00)	105	-0.4% (1.03)	-1.50% (-1.74, -1.26)
Barnett(20)	8mg/d	84	-1.16% (NR)	87	0.26% (NR)	-1.86% (NR)

Abbreviations: NR=not reported, TDD=total daily dose

Metformin failure

As mentioned previously, the addition of rosiglitazone to failed metformin therapy was evaluated in 3 studies.(17-19) Two studies measured the impact of adding rosiglitazone 4 mg/day(17;18), while all three reported the results of adding 8 mg/day of rosiglitazone to failed metformin compared with metformin plus placebo. Despite the number of papers addressing this treatment regimen, only one study provided a measure of variance for the change values for the intervention and the control groups and thus pooling of the data was not possible. Both studies using rosiglitazone 4 mg/day showed a decrease in the treatment group and an increase in the control group with respect to changes in HbA1c from baseline to end of study (Table 6). Similar trends were found when the dose of rosiglitazone was increased to 8 mg/day but with a greater reduction in the 8 mg/day groups (Table 7).

Table 6 Mean change in HbA1c compared to baseline for add-on rosiglitazone 4 mg/day therapy to failed metformin monotherapy versus placebo

Author	TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Fonseca(17)	4 mg/d	116	-0.56% (1.39)	113	0.45% (1.29)	-1.01% (-1.36, -0.66)
Gomez-Perez(18)	4 mg/d	35	-0.7% (NR)	34	0.3% (NR)	-1.0% (NR)

Abbreviations: NR=not reported, TDD=total daily dose

Table 7 Mean change in HbA1c compared to baseline for add-on rosiglitazone 8 mg/day therapy to failed metformin monotherapy versus placebo

Author	TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Fonseca(17)	8 mg/d	110	-0.78% (2.18)	113	0.45% (1.29)	-1.23% (-1.70, -0.76)
Gomez-Perez(18)	8 mg/d	36	-1.2% (NR)	34	0.3% (NR)	-1.5% (NR)
Negro(19)	8 mg/d	19	-1.1% (NR)	19	0.2% (NR)	-1.3% (NR)

Abbreviations: NR=not reported, TDD=total daily dose

Repaglinide switch following failure of sulfonylurea or metformin

One randomized controlled trial compared the addition of rosiglitazone to repaglinide with repaglinide alone in patients demonstrating unsatisfactory responses to sulfonylurea or metformin monotherapy.(12) Mean HbA1c values showed a decline over 24 weeks for the combination therapy regimen (-1.43%), while the response to repaglinide monotherapy in these chronically treated patients was small (- 0.17%).

FPG

Sulfonylurea failure

Results from the three studies that added rosiglitazone 4 mg/day to failed sulfonylurea showed a greater improvement in fasting plasma glucose compared with continuing current treatment.(14-16) The decrease in FPG from baseline varied from -1.20 to -2.13% with the addition of rosiglitazone compared with -0.32% to +0.40%.(Table 8) Only one study provided adequate data for meta-analysis(15) so pooling of the data for this category was not possible.

The two studies that measured the efficacy of adding 8 mg/day of rosiglitazone to failed sulfonylurea found that there was a greater reduction in FPG compared with the rosiglitazone 4 mg/day group as well as the control group (Table 9).

Table 8 Mean change in FPG compared to baseline for add-on rosiglitazone 4 mg/day therapy to failed sulfonylurea monotherapy versus placebo

Author	TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Wolffenbuttel(14)	4 mg/d	183	-2.09 mmol/L (NR)	192	-0.32 mmol/L (NR)	-1.77 mmol/L (NR)
Vongthavaravat(15)	4 mg/d	164	-2.13 mmol/L (5.00)	110	0.29 mmol/L (2.63)	-2.42 mmol/L (-3.33, -1.51)
Zhu(16)	4 mg/d	215	-1.2 mmol/L (NR)	105	0.4 mmol/L (NR)	-1.3 mmol/L (NR)

Abbreviations: NR=not reported, TDD=total daily dose

Table 9 Mean change in FPG compared to baseline for add-on rosiglitazone 8 mg/day therapy to failed sulfonylurea monotherapy versus placebo

Author	TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Zhu(16)	8mg/d	210	-2.0 mmol/L (NR)	105	0.4 mmol/L (NR)	-2.4 mmol/L (NR)
Barnett(20)	8mg/d	84	-2.5 mmol/L (NR)	87	0.2 mmol/L (NR)	-2.7 mmol/L (NR)

Abbreviations: NR=not reported, TDD=total daily dose

Metformin failure

As was the case with HbA1c for this group of studies, quantitative evaluation of FPG was not possible. In the studies that evaluated the addition of rosiglitazone, mean FPG levels decreased significantly from baseline in a dose-dependent fashion in both the 4 mg/day and 8 mg/day rosiglitazone groups. The control groups however, experienced increases in HbA1c (Tables 10 & 11).

Table 10 Mean change in FPG compared to baseline for add-on rosiglitazone 4 mg/day therapy to failed metformin monotherapy versus placebo

Author	TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Fonseca(17)	4 mg/d	116	-1.83 mmol/L (2.81)	113	0.33 mmol/L (3.61)	-2.16 mmol/L (-3.00, -1.32)
Gomez-Perez(18)	4 mg/d	35	-2.50 mmol/L (NR)	34	0.21 mmol/L (NR)	-2.71 mmol/L (NR)

Abbreviations: NR=not reported, TDD=total daily dose

Table 11 Mean change in FPG compared to baseline for add-on rosiglitazone 8 mg/day therapy to failed metformin monotherapy versus placebo

Author	TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Fonseca(17)	8 mg/d	110	-2.69 mmol/L (3.45)	113	0.33 mmol/L (3.61)	-3.02 mmol/L (-3.95, -2.09)
Gomez-Perez(18)	8 mg/d	36	-3.50 mmol/L (NR)	34	0.21 (NR) mmol/L	-3.71 mmol/L (NR)
Negro(19)	8 mg/d	19	-1.35 mmol/L (NR)	19	0.11 mmol/L (NR)	-1.46 mmol/L (NR)

Abbreviations: NR=not reported, TDD=total daily dose

Repaglinide switch following failure of sulfonylurea or metformin

For patients treated with a combination of repaglinide and rosiglitazone therapy, the mean changes in FPG relative to baseline were greater than for those treated with repaglinide monotherapy (-5.2 mmol/L vs. -3.0 mmol/L, $P \leq 0.001$, respectively).

Summary of studies evaluating the effect of rosiglitazone added to failure of monotherapy compared with placebo

In summary, all of the results showed that add-on therapy with rosiglitazone resulted in statistically significant reductions from baseline values for both HbA1c and FPG, compared with continuing monotherapy on one of the traditional oral agents. There was also a trend towards further reductions in these outcomes as the dose of rosiglitazone was increased to 8 mg/day.

2.2.2.2.3. Rosiglitazone add-on therapy compared with placebo comparator for patients failing insulin monotherapy

Two US randomized controlled trials were identified that assessed the impact of rosiglitazone added to insulin in the treatment of patients inadequately controlled on insulin monotherapy.(21;22). Both studies were approximately 24 weeks in duration and enrolled similar patients (Table 12).

Table 12 Characteristics of studies included in the analysis of rosiglitazone as add-on therapy to failed insulin monotherapy compared with placebo

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Raskin(21) (n=319)	26-week, double-blind PBO-controlled, multicentre study (38 centres in the US)	T2DM inadequately controlled on insulin (≥30 U insulin per day, and HbA1c ≥7.5%).	ROSI 2 mg BID + insulin vs. 4 mg BID + insulin vs. Insulin + PBO	HbA1c, FPG, lipids, and total daily insulin dose.	A/5
Reynolds (22) (n=21)	6-month controlled trial (1 centre in the US)	T2DM inadequately controlled in insulin (HbA1c >7%) and BMI >27.	ROSI 4 mg + insulin vs. PBO + insulin	Body weight, waist circumference, blood pressure, HbA1c and serum lipids.	B/1

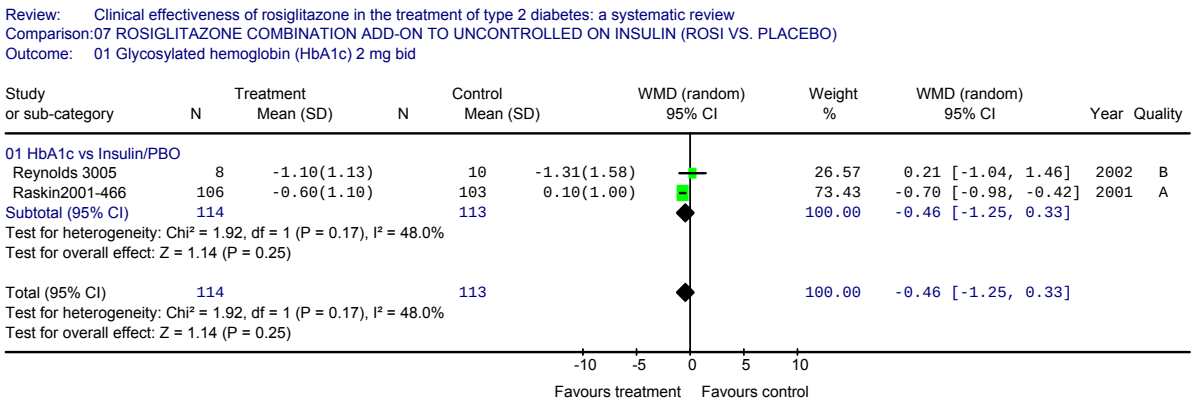
Abbreviations: PBO=placebo; REP=repaglinide; ROSI=rosiglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Outcomes

HbA1c

Add-on rosiglitazone 4 mg/day to failed insulin resulted in decreases in HbA1c by the end of both studies compared with baseline.(21;22) Data pooling resulted in a reduction in HbA1c (WMD: -0.46% (95% CI: -1.25, -0.33; *P*=0.25), however this was not statistically significant.(Figure 4) Increasing the rosiglitazone dose to 8 mg/day caused a statistically significant decrease in HbA1c values at study end compared with baseline (-1.20%, *P*< 0.001) and with control (-1.30, *P*< 0.001).(21)

Figure 4. Pooled estimate of HbA1c for rosiglitazone 4 mg/day added-on to failure of insulin monotherapy versus placebo



FPG

One of the two articles(21) reported the impact of adding rosiglitazone to failed insulin monotherapy on FPG. This study found that there were significant differences in change from baseline in mean FPG in both rosiglitazone groups (i.e. 4 mg/day and 8 mg/day). The reduction in the in the 4 mg/day group was 2.30 mmol/L (*P*<0.001) and 2.50 mmol/L (*P*<0.001) in the 8 mg/day group compared with a slight increase in the placebo group (+0.60 mmol/L).

2.2.2.2.4. Rosiglitazone add-on therapy compared with upward titration of current therapy for patients on half-maximum monotherapy

A total of four studies tested the effect of aggressive earlier introduction of combination therapy compared with the upward titration of existing therapy.(23-26)(Table 13). This challenges the conventional paradigm of dose escalation of

monotherapy by comparing the addition of rosiglitazone to sub-maximal monotherapy. Three of the studies evaluated the up-titration of sulfonylurea(23;24;26) and the fourth study evaluated the upward titration of metformin.(25)

Table 13 Characteristics of studies included in the analysis of rosiglitazone as add-on therapy to failed sub-maximal monotherapy compared with upward titration of existing monotherapy

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Rosenstock(26) (n=227)	2-year, multicentre, prospective, double-blind, parallel group study (48 North American centres)	T2DM aged ≥60 years with previous SU (glipizide) monotherapy 1/4 to 1/2 max dose ≥ 3 months with FPG ≥7.0 ≤13.9 mmol/L	ROSI 4mg OD + SU 10mg BID vs. PBO + SU (uptitrated)	Time to FPG ≥10 mmol/L; time to titration of maximum SU dose and changes in FPG, HbA1c and free fatty acids.	B/3
Kerenyi(23) (n=340)	26-week, multicentre, double-blind, placebo-controlled, parallel group study (15 countries	T2DM, FPG 7-15 mmol/L on half-maximal dose (7.5 mg/day) of SU (glibenclamide)	ROSI 4 mg BID + SU 7.5 mg vs. SU alone titrated up to a maximum dose of 15 mg/day.	Change in HbA1c, FPG, insulin, and C-peptide, insulin sensitivity, B-cell function, and lipids.	B/1
Baksi(24) (n=471)	26-week, double-blind, placebo-controlled, parallel group study (7 European countries)	T2DM inadequately controlled on 160 mg/day of SU (gliclazide), FPG ≥7.0 ≤5.0 mmol/L.	ROSI 4 mg BID + 160 mg/day SU vs. SU uptitrated to a max 320 mg/day + PBO	Change in HbA1c, FPG, insulin , C-peptide and lipid levels	B/1
Bailey(25) (n=569)	24-week, multicentre (90 centres in 14 European countries), double-blind, parallel-group study	T2DM treated with MET 1 to 2 g/day, alone or in combination with oral insulin secretagogue or acarbose, with FPG ≥7 ≤12 mmol/L	ROSI + MET vs. up titrated MET	Change in HbA1c, FPG, plasma insulin and lipids, proportion achieving HbA1c and FPG targets.	A/4

Abbreviations: PBO=placebo; REP=repaglinide; ROSI=rosiglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

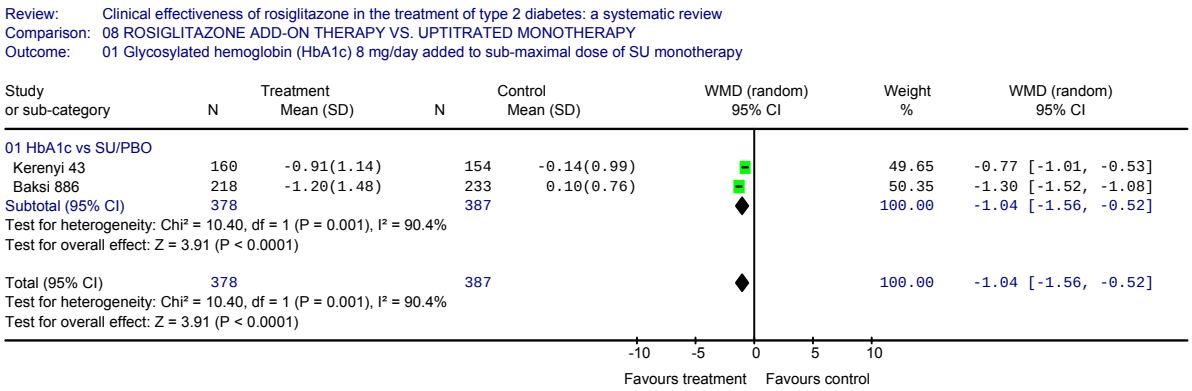
Outcomes

HbA1c

Uptitrated sulfonylurea

All of the studies that measured the addition of a sub-maximal dose sulfonylurea compared with the upward titration of sulfonylurea showed significant decreases in HbA1c from baseline as well as compared to the uptitrated group at endpoint. (23;24;26). Data from two of the studies could be combined for meta-analysis and it was determined that adding rosiglitazone 8 mg/day resulted in a statistically significant reduction from baseline in HbA1c (WMD: -1.04% (95% CI: -1.56, -0.52; *P*<0.001) (Figure 5). This pooled estimated was however associated with statistically significant heterogeneity (Chi-square: 10.40, df=1, *P*=0.001).

Figure 5. Pooled estimate of HbA1c for rosiglitazone added-on to failed sub-maximal dose of sulfonylurea monotherapy versus upward titration of existing sulfonylurea monotherapy



Uptitrated metformin

One study evaluated the efficacy of adding rosiglitazone to sub-maximal doses of metformin compared with increasing the dose of metformin.(25) At week 24, there was a reduction in mean HbA1c in the rosiglitazone/metformin group of 0.33% (from 7.4% to 7.1%), compared with a reduction of 0.13% from 7.5% to 7.4%) with uptitrated metformin (treatment difference -.22%; *P*=0.001).

FPG

Uptitrated sulfonylurea

All studies showed a statistically significant decrease in mean FPG compared with the uptitrated sulfonylurea groups (Table 14). The differences in mean changes from baseline between treatment and control groups varied from -2.1 mmol/L to -2.92 mmol/L. Only one study provided sufficient data to allow meta-analysis(23) so no pooling was undertaken.

Table 14 Mean change in FPG compared with baseline for add-on rosiglitazone therapy to failed sub-maximal dose of sulfonylurea monotherapy versus upward titration of existing sulfonylurea

Author	TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Kerenyi, (23)	8 mg/d	165	-2.14 (2.06)	170	0.15 (2.48)	-2.29 (-2.78, -1.80)
Baksi(24)	8 mg/d	225	-2.37 (NR)	241	0.55 (NR)	-2.92 (NR)
Rosenstock(26)	4 mg/d	115	-1.32 (NR)	110	0.78 (NR)	-2.1 (NR)

Abbreviations: PBO=placebo; REP=repaglinide; ROSI=rosiglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Up-titrated metformin

Add-on rosiglitazone therapy to sub-maximal doses of metformin provided a greater decrease from baseline in mean FPG (-1.22 mmol/L) compared with patients that titrated their metformin dose upwards (-0.28 mmol/L) for a treatment difference of -0.94 mmol/L ($P < 0.001$).(25)

2.2.2.2.5. Rosiglitazone add-on to failed monotherapy compared with add-on active comparator to failed monotherapy

Four studies measured the effectiveness of adding rosiglitazone to failed monotherapy compared with adding a different oral antidiabetic agent (i.e. sulfonylurea or metformin).(27-30)(Table 15) Half of the clinical trials evaluated the efficacy of combining rosiglitazone or metformin in patients who were inadequately controlled with sulfonylurea alone.(27;28) The other two studies

compared the effects of adding rosiglitazone or sulfonylurea to failed metformin monotherapy.(29;30)

Table 15 Characteristics of studies included in the analysis of rosiglitazone as add-on therapy to failed monotherapy compared with the add-on of an active comparator

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Yang(27) (n=211)	12-week, multicentre, double-blind, parallel, placebo-controlled clinical trial	Chinese T2DM patients inadequately controlled on SU	SU + MET 0.5g BID vs. SU + ROSI 4mg OD	HbA1c, FPG, lipids	B/2
Jung(28) (n=30)	6-month, unblinded trial, at one centre in Korea	T2DM Korean patients inadequately controlled on SU (HbA1c >8%)	ROSI 4mg/d + SU vs. MET + SU	Plasma concentrations of resistin, anthro-pometric, FPG, HbA1c, lipids, and adiponectin concentration	B/2
Derosa (30) (n=99)	52-week, double-blind, multicentre (2 centres in Italy), controlled trial	T2DM uncontrolled SU or MET (HbA1c >7% &/or FPG >120mg/dL), overweight, hypertensive and hypertri-glyceridemic	MET 1,500 mg/day + glimipiride 2 mg/day vs. MET 1,500 mg/day + ROSI 4 mg/day	BMI, HbA1c, PAI-1, fibrinogen, t-PA, lipid profile and lipoprotein parameters, BP	A/5
Garber(29) (n=318)	24-week double-blind, multicentre (76 US sites)	T2DM uncontrolled on MET (≥1,500mg/d for ≥8 weeks, HbA1c >7.0 ≤12.0% and BMI ≥23 ≤45	MET + SU combination tablets vs. MET + ROSI 4mg/d titrated to achieve target.	HbA1c, weight, fructosamine, FPG, plasma glucose and fasting insulin levels.	B/3

Abbreviations: PBO=placebo; REP=repaglinide; ROSI=rosiglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

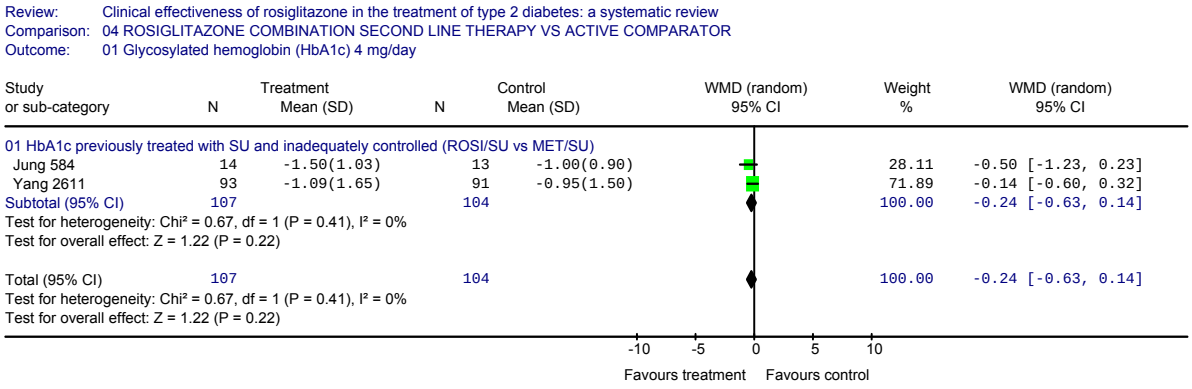
Outcomes

HbA1c

Rosiglitazone add-on to failure of sulfonylurea monotherapy compared with add-on of metformin

After three months of combination therapy of rosiglitazone plus sulfonylurea, it was found that HbA1c decreased by 1.09% compared with a decrease of 0.95% in the metformin plus sulfonylurea group in Chinese patients.(27) Both reductions from baseline were statistically significant however, they were not statistically significantly different from each other. The second study found similar effects in Korean patients with type 2 diabetes.(28) This paper measured a significant reduction in HbA1c from baseline in both groups (-1.05% vs. -1.0% in the rosiglitazone and metformin groups respectively) but no difference compared with each other. Pooled results show that the addition of rosiglitazone 4 mg once daily to failed sulfonylurea treatment resulted in a non-significant decrease in HbA1c from baseline (WMD: -0.24% (95% CI: -0.63, 0.14; *P*=0.22)) compared to adding metformin to failed sulfonylurea (Figure 6).

Figure 6. Pooled estimate of HbA1c for rosiglitazone added-on to failed sulfonylurea monotherapy versus add-on of metformin



Rosiglitazone add-on to failure of metformin monotherapy compared with add-on of sulfonylurea

Data on HbA1c could not be included in a pooled estimate as there was no measure of variance for any of the study groups. After 24 weeks of treatment, the mean HbA1c decrease in the metformin-glibenclamide treatment group was significantly greater (-1.5%) than in the metformin plus rosiglitazone group

(-1.1%) (difference -0.4%, *P*<0.001).(29) However, after 12 months of treatment, there was a greater decrease in HbA1c in the rosiglitazone plus metformin group (-1.2%, *P*<0.01) than in the glimepiride plus metformin group (-0.9%, P< 0.05) (Table 16).(30)

Table 16 Mean change in HbA1c compared to baseline for add-on rosiglitazone therapy to failed metformin monotherapy versus add-on of sulfonylurea

Author	TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Derosa(30)	4 mg/d	48	-1.2% (NR)	47	-0.9% (NR)	-0.3% (NR)
Garber(29)	7.1 mg/d	150	-1.1% (NR)	152	-1.5% (NR)	0.4% (NR)

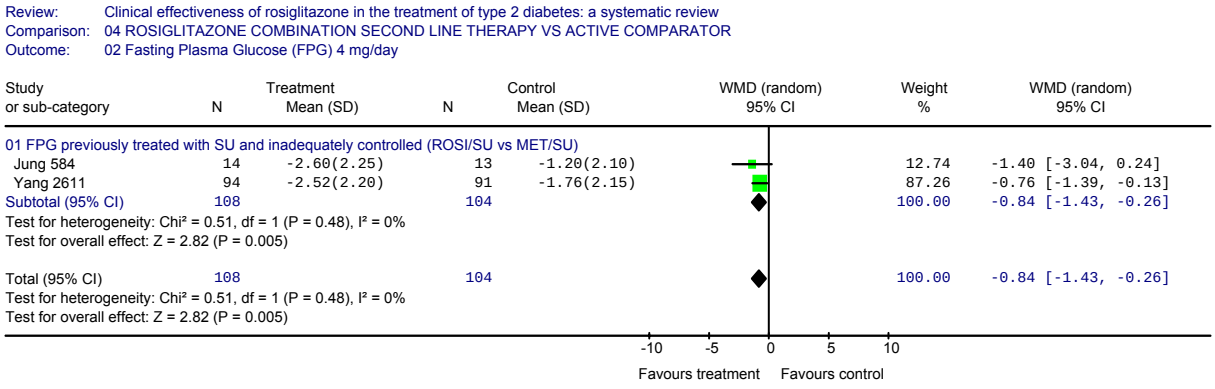
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

FPG

Rosiglitazone add-on to failure of sulfonylurea monotherapy compared with add-on of metformin

Both studies found a significant decrease in FPG in the two treatment groups compared with baseline. Yang et al(27) noted that the reduction in patients treated with rosiglitazone was significantly greater than those treated with metformin. When the results of both studies were combined, the overall effect was statistically significant (WMD: -0.84 mmol/L (95% CI: -1.43, -0.26, *P*=0.005) (Figure 7).

Figure 7. Pooled estimate of FPG for rosiglitazone added-on to failed sulfonylurea monotherapy versus add-on of metformin



Rosiglitazone add-on to failure of metformin monotherapy compared with add-on of sulfonylurea

Similar to the results of the changes in HbA1c, patients treated with sulfonylurea-metformin tablets experienced a greater reduction in FPG than those receiving rosiglitazone plus metformin after 24 weeks (-2.26 mmol/L vs. -2 mmol/L, respectively; *P*<0.03).(29) Conversely, the 1-year study demonstrated a greater decrease in FPG in the rosiglitazone plus metformin group (-1.61 mmol/L, P<0.01) than in the sulfonylurea plus metformin group (-1.11 mmol/L, *P*<0.05)(Table 17).(30)

Table 17 Mean change in HbA1c compared to baseline for add-on rosiglitazone therapy to failed metformin monotherapy versus add-on of sulfonylurea

Author	TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Derosa(30)	4 mg/d	48	-1.61 mmol/L (NR)	47	-1.11 mmol/L	-0.5 mmol/L
Garber(29)	7.1 mg/d	150	-2.0 mmol/L (NR)	152	-2.6 mmol/L (NR)	+0.6 mmol/L (NR)

Abbreviations: NR=not reported, TDD=total daily dose

2.2.2.3. Efficacy of rosiglitazone as add-on to dual therapy

2.2.2.3.1. Rosiglitazone add-on therapy to failed dual therapy compared with placebo add-on to failed dual therapy

Only one study assessed the efficacy of adding rosiglitazone to an established regimen of sulfonylurea (glyburide) plus metformin in patients with who had not achieved adequate glycemic control (HbA1c >7.0% and ≤10.0%).(31) Patients were randomized to receive 4 mg/day of rosiglitazone, which could be titrated to a maximum of 8 mg/day, or placebo for 24 weeks (Table 18).

Table 18 Characteristics of the study included in the analysis of rosiglitazone as add-on therapy to failed dual therapy compared with placebo add-on to failed dual therapy

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Dailey(31) (n=365)	24-week, double-blind, PBO-controlled, multicentre study (61 centres in the US)	T2DM inadequately controlled (HbA1c >7.0% and <=10.0%) on stable regimen of MET/SU	ROSI 4 mg OD (titration) + MET/SU tablets vs. PBO + MET/SU tablets	HbA1c, FPG, insulin, lipid values	B/4

Abbreviations: PBO=placebo; REP=repaglinide; ROSI=rosiglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Outcomes

HbA1c

After 24 weeks, patients administered glyburide/metformin tablets plus rosiglitazone achieved greater reductions in HbA1c levels compared with those who received glyburide/metformin plus placebo (-0.9% vs. +0.1%), a statistically significant difference (-1.0%, *P*<0.001).(31)

FPG

Compared with baseline, FPG levels at the end of the study decreased by 2.28 mmol/L in the group receiving rosiglitazone but increased by 0.39 mmol/L in the placebo group. The between-group difference of -2.67 mmol/L was statistically significant (*P*<0.001).

2.2.2.3.2. Rosiglitazone add-on therapy to failed dual therapy compared with insulin add-on to failed dual therapy

Rosenstock and colleagues(32) enrolled insulin-naïve patients inadequately controlled on dual oral therapy with sulfonylurea and metformin, to evaluate the efficacy of add-on insulin glargine versus rosiglitazone (Table 19).

Table 19 Characteristics of studies included in the analysis of rosiglitazone as add-on therapy to failed dual therapy compared with insulin add-on to failed dual therapy

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Rosenstock(32) (n=217)	24-week, open-label, parallel, multicentre trial (42 US centres)	T2DM insulin naive patients uncontrolled on dual therapy (i.e. SU + MET). and BMI of >25 kg/m^2	ROSI 4mg/d. + SU + MET vs. Insulin glargine 10 units/day + SU + MET Titration was permitted	HbA1c, hypoglycemia profile; FPG, body weight, and serum lipids; proportion of patients achieving HbA1c ≤7%	B/2

Abbreviations: PBO=placebo; REP=repaglinide; ROSI=rosiglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Outcomes

HbA1c

After 24 weeks of therapy, patients receiving insulin glargine in addition to failed metformin plus sulfonylurea experienced a reduction in HbA1c of 1.66% compared with a decrease of 1.51% in the rosiglitazone group. However, the difference between groups was not statistically significant (*P*=0.1446).(32)

FPG

Fasting plasma glucose decreased significantly from baseline to 24-weeks in both groups; however, greater reductions occurred in the insulin glargine group than in the rosiglitazone group (-3.60 mmol/L vs. -2.57 mmol/L, *P*= 0.001). This difference was observed as early as week 2 of treatment and continued throughout the 24-week study period.

2.2.3. Clinical Efficacy of Pioglitazone

Of the 25 full publications identified in the literature search, fourteen studies assessed pioglitazone as monotherapy: 4 compared pioglitazone with placebo, and 10 compared pioglitazone with an active comparator. The remaining 11 studies evaluated add-on therapy regimens: 10 added pioglitazone to failed monotherapy, and 1 added pioglitazone to failed dual therapy treatment. Some of the studies had more than two treatment arms and thus were included in more than one analysis; this explains any discrepancy in the total number of studies in all of the analyses.

2.2.3.1. Efficacy of Pioglitazone as Monotherapy

2.2.3.1.1. Pioglitazone compared with placebo comparator

Four studies assessed pioglitazone compared with placebo (Table 20). Three of the papers included previously treated as well as drug naïve patients in their study populations.(33-35) The last study recruited only drug naïve patients,(36) however given that the previously treated patients in the other 3 studies were still controlled on treatment, results were combined where possible. The treatment periods for these trials varied from 16 to 26 weeks.

Table 20. Characteristics of studies included in the analysis of pioglitazone as monotherapy compared with placebo

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment/ Jadad
Aronoff(35) (n=408)	26-week, double-blind placebo-controlled, multicentre (35 centres in US) trial. treatment.	T2DM with HbA1c ≥7.0%, Patients were previously treated and treatment naïve	PIO 7.5 mg vs. PIO 15 mg vs. PIO 30 mg vs. PIO 45 mg vs. PBO	HbA1c, FPG, lipids	B/3
Herz(36) (n=297)	16-week, double-blind, placebo-controlled, parallel-group, multicentre (41 centres in Canada and Spain) study	Recently diagnosed, drug naive with suboptimal glycemic control (HbA1c ≥6.5% ≤9.8%) and mild dyslipidemia	PIO 30 mg vs. PIO 45 mg vs. PBO	HbA1c, insulin sensitivity, and lipid profiles	B/3
Rosenblatt (34) (n=197)	16-week, double-blind, placebo-controlled multicentre (27 sites in the US), trial.	T2DM, HbA1c ≥8%. Patients previously treated and treatment naïve.	PIO 30 mg vs. PBO	HbA1c; FPG, fasting serum insulin, C-peptide and lipids	A/4
Scherbaum(33) (n=252)	26-week double-blind, placebo-controlled, parallel-group multicentre (59 centres in Germany) study.	T2DM, HbA1c ≥ 7.5% ≤12%. Patients previously treated and treatment naïve.	PIO 15 mg vs. PIO 30 mg vs. PBO	HbA1c, FPG, C-peptide levels, blood pressure, plasma lipids, and weight	B/3

Abbreviations: PBO=placebo; REP=repaglinide; PIO=pioglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Outcomes

HbA1c

Aronoff(35) et al randomized patients to one of 5 arms: placebo, pioglitazone 7.5, 15, 30 or 45 mg/day. HbA1c increased in both the pioglitazone 7.5 mg/day (+0.20%) and in the placebo (+0.70) groups and then decreased as the dose of

pioglitazone was increased in the 15, 30 and 45 mg/day by 0.30%, 0.30% and 0.90%, respectively. The results from the 15, 30 and 45 mg/day were combined with the findings from other studies where possible.

The pooled estimate for initiating patients on 15 mg/day of pioglitazone monotherapy was associated with a statistically significant decrease from baseline in HbA1c, compared with no treatment.(33;35) The overall effect size was a weighted mean difference of -0.77% (95% CI: -1.18, -0.36; *P*<0.001) (Figure 8). A dose-related response was evident as the results were pooled for the 30 and 45 mg/day. HbA1c values decreased by a greater amount in the treatment arms compared with no treatment. The overall effect size was a statistically significant weighted mean difference in HbA1c of -0.87% (95% CI:-1.19, -0.55; *P*<0.001) in the 30 mg/day arm(33-36) and -1.12% (95% CI: -2.00, -0.24; *P*=0.01) in the 45 mg/day group(35;36) (Figures 9 and 10, respectively).

Figure 8. Pooled estimate of HbA1c for pioglitazone 15 mg/day monotherapy compared with placebo in patients naïve to treatment and those still controlled on monotherapy

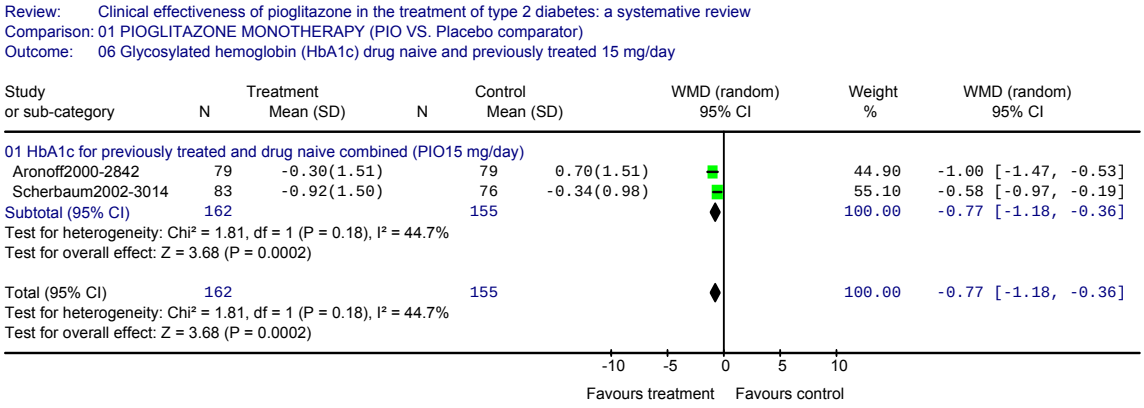


Figure 9. Pooled estimate of HbA1c for pioglitazone 30 mg/day monotherapy compared with placebo in patients naïve to treatment and those still controlled on monotherapy

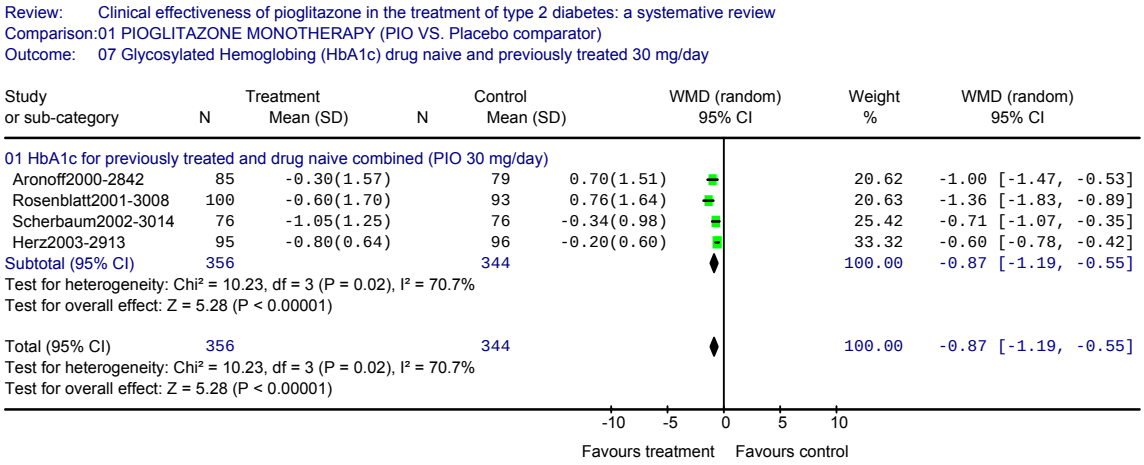
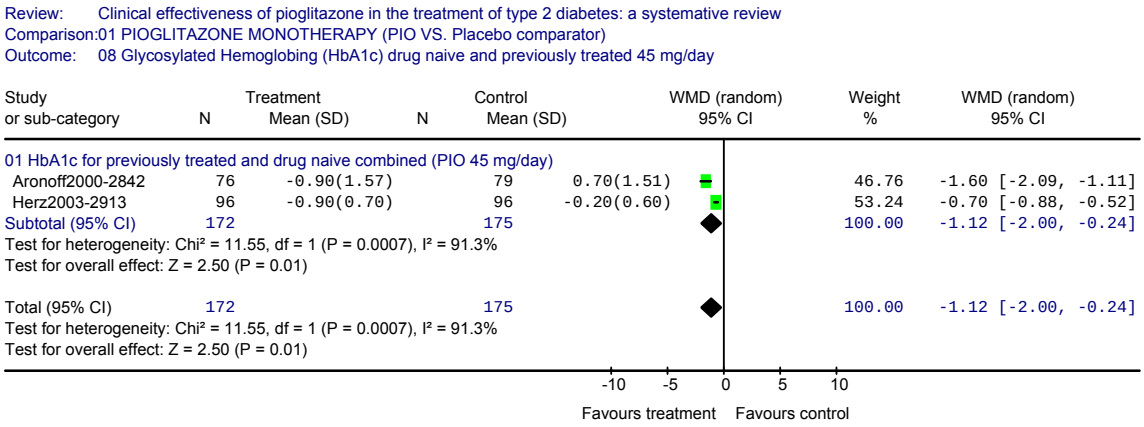


Figure 10. Pooled estimate of HbA1c for pioglitazone 45 mg/day monotherapy compared with placebo in patients naïve to treatment and those still controlled on monotherapy



FPG

One study reported that pioglitazone 7.5 mg/day decreased fasting plasma glucose by 1.00 mmol/L while placebo increased FPG by 0.52 mmol/L.(35) Combined results from two studies(33;35) suggested that FPG decreased by a greater amount in the pioglitazone 15 mg/day group than in the placebo group (WMD: -2.08 mmol/L, 95% CI: -2.73, -1.43 mmol/L; *P*<0.001) (Figure 11). The weighted mean difference for initiating 30 mg/day of pioglitazone was -2.51 mmol/L (95% CI: -3.15, -1.97; *P*<0.001) (Figure 12).(33-35) Herz et al(36) reported that FPG was reduced by 1.4 and 1.6 mmol/L in the pioglitazone 30 and

45 mg/day, respectively compared with a decrease of 0.1 mg/day in the placebo group. These values could not be combined with other results because no measure of variation around the point estimate was provided by the authors. Pioglitazone 45 mg/day was associated with a reduction of 3.10 mmol/L in the clinical trial conducted by Aronoff.(35)

Figure 11. Pooled estimate of FPG for pioglitazone 15 mg/day monotherapy compared with placebo in patients naïve to treatment and those still controlled on monotherapy

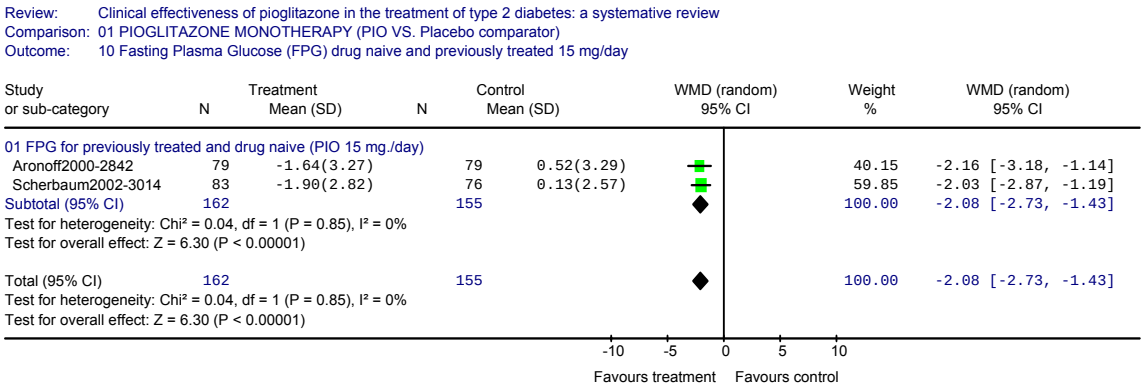
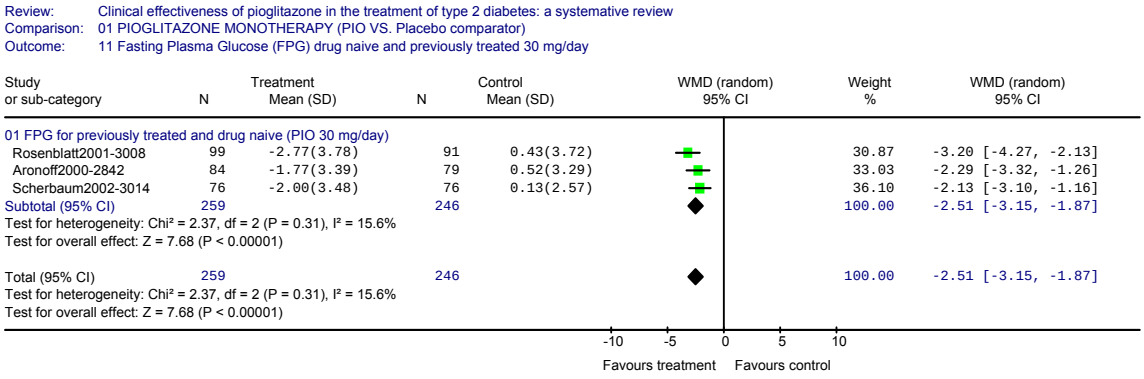


Figure 12. Pooled estimate of FPG for pioglitazone 30 mg/day monotherapy compared with placebo in patients naïve to treatment and those still controlled on monotherapy



2.2.3.1.2. Pioglitazone compared with active comparator

The majority of literature evaluating the efficacy of pioglitazone as monotherapy compared the new treatment with an active comparator. Of the ten papers in this category, 6 articles had data that compared pioglitazone with sulfonylurea(37-42); 4 with metformin(38;42-44);1 with repaglinide(45); and 1 with acarbose.(46) Some articles had more than one treatment arm and thus data could be used in

more than one analysis. All of the randomized controlled trials enrolled patients who were either treatment naïve or had previous oral anti-diabetic agent treatment but were still controlled.

Outcomes

HbA1c

Sulfonylurea comparator

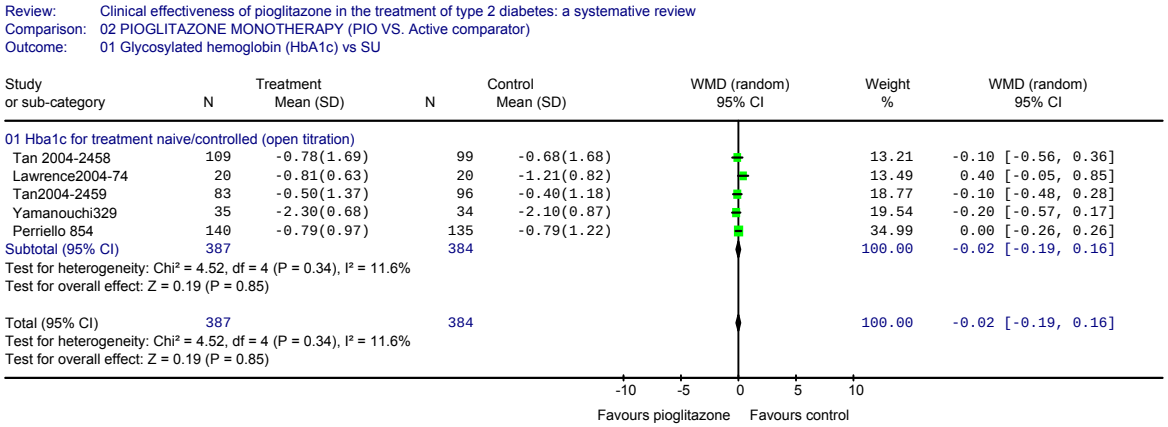
Four of the six trials measuring the efficacy of pioglitazone compared with sulfonylurea as first line therapy (i.e. patients either naïve to drug treatment or controlled on sub-maximal doses of an oral anti-diabetic agent) had a 1-year treatment period, (37-39;41) while the remaining 2 studies lasted 24(42) and 40 weeks(40) respectively (Table 21). Unfortunately, there were no measures of variance around the mean baseline and final HbA1c values in the Charbonnel study(39) and as a result the data from this paper could not be combined with others. The authors of this study did report however, that the reduction in the pioglitazone arm was similar to that in the sulfonylurea arm (-1.5% vs. -1.4%, respectively). Data on the remaining 5 studies could be extracted and combined to calculate a weighted mean difference of the change in HbA1c from baseline to end of study (Figure 13). Combined results indicate that initiating pioglitazone monotherapy in patients naïve to treatment or still controlled on current monotherapy was associated with a slightly larger decrease from baseline in HbA1c (WMD: -0.02% (95% CI: -0.19, 0.16) compared with sulfonylurea but this difference was not statistically significant (*P*=0.85).

Table 21. Characteristics of studies included in the analysis of pioglitazone as monotherapy compared with sulfonylurea

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Perriello (37) (n=283)	52-week, double-blind, multicentre (33 centres in Italy), parallel group trial	T2DM treated with diet or one glucose-lowering drug and HbA1c <7.5%.	PIO 30-45 mg/day vs. SU (gliclazide 80-320 mg/day)	HbA1c, FPG, insulin, and homeostasisassessment of insulin resistance	B/4
Yamanouchi(38) (n=114)	52-week, Japanese, controlled trial	Newly diagnosed T2DM, HbA1c ≥7.0% and FPG ≥7.78 mmol/L	PIO 30-45 mg/day vs. MET 750 mg/day vs. SU (Glimepiride 1.0-2.0 mg/day)	HbA1c, FPG, lipids, fasting plasma insulin and body weight	A/3
Tan(40) (n=200)	40-week, multicentre (22 centres in Denmark, Finland, Norway and Sweden)	T2DM drug naive or receiving monotherapy (not failed)	PIO up to 45 mg/day vs. SU (glibenclamide) up to 10.5 mg/day	Insulin sensitivity, glycemic control, and lipids	B/1
Tan(41) (n=244)	52-week, double-blind, parallel-group, multicentre (19 Mexican centres), trial	T2DM both drug naive and previously treated	SU (glimepiride) 2 mg/day up to 8 mg/day vs. PIO 15 mg/day up to 45 mg/day	Glycemic control and insulin sensitivity	A/4
Charbonnel (39) (n=1,270)	52-week, double-blind, parallel-group, multicentre (Europe, Australia, Canada, South Africa and Israel)	Uncontrolled T2DM (HbA1c 7.5-11%)	PIO up to 45 mg/day vs. SU (gliclazide) up to 320 mg/day	HbA1c, FPG, fasting plasma insulin, and plasma lipids	D/2
Lawrence (42) (n=60)	6-month, open-label, parallel-group study.	T2DM, BMI>27, low dose oral agents HbA1c <7.5%; and diet treated >7%	MET vs. PIO vs. SU (gliclazide) uptitrated to optimize glycaemia	Change in proportion of LDL as LDL3	B/2

Abbreviations: PBO=placebo; REP=repaglinide; PIO=pioglitazone, SMBG=self-monitoring blood glucose, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Figure 13. Pooled estimate of HbA1c for pioglitazone monotherapy compared with sulfonylurea in patients naïve to treatment and those still controlled on monotherapy



Metformin comparator

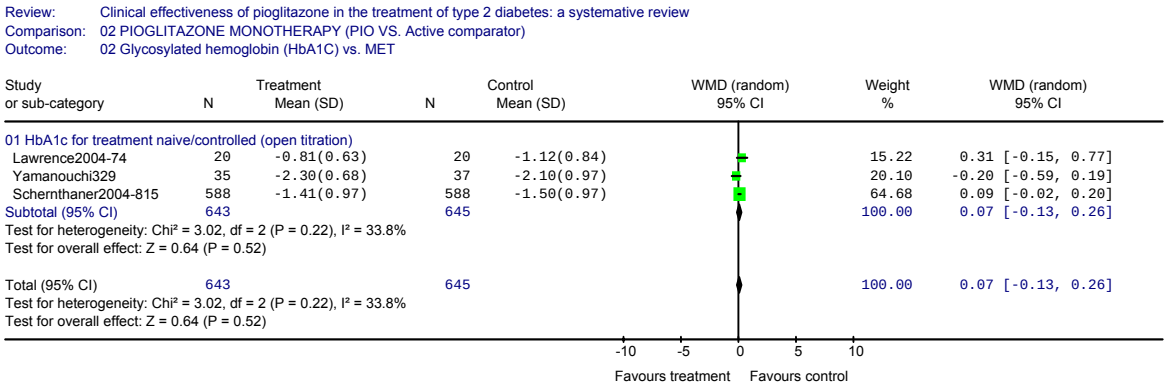
Two of the studies identified above had 3 treatment arms: pioglitazone, metformin, and sulfonylurea.(38;42) As a result, the results from the metformin-treated groups were also combined with the other two studies measuring the efficacy of pioglitazone relative to metformin.(43) (44) The characteristics for all four studies are outlined in Table 22. All but one of the papers favoured metformin over pioglitazone in treatment-naïve patients with respect to decreasing HbA1c levels. Yamanouchi(38) found that pioglitazone reduced HbA1c by 0.20% more than pioglitazone in this patient population. The pooling of the data from studies in this grouping revealed that initiating pioglitazone monotherapy in treatment naïve patients was associated with a smaller, but not statistically significant, decrease from baseline in HbA1c (WMD: +0.07% (95% CI: -0.13, 0.26; *P*=0.52)) compared with metformin (Figure 14). The data from the study by Pavo et al(43) could not be incorporated into a pooled estimate but the results support the overall findings from the other studies that metformin reduces HbA1c more than pioglitazone (-1.5% vs. -1.30% respectively).

Table 22. Characteristics of studies included in the analysis of pioglitazone as monotherapy compared with metformin

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment/ Jadad
Yamanouchi(38) (n=114)	52-week, Japanese, controlled trial	Newly diagnosed T2DM, HbA1c ≥7.0% and FPG ≥7.78 mmol/L	PIO 30-45 mg/day vs. MET 750 mg/day vs. SU (Glimepiride 1.0-2.0 mg/day)	HbA1c, FPG, lipids, free fatty acids, fasting plasma insulin levels and body weight	A/3
Lawrence(42) (n=60)	6-month, open-label, parallel-group study.	T2DM, BMI>27, low dose oral agents with HbA1c <7.5% and diet treated >7%	MET vs. PIO vs. SU (gliclazide) uptitrated for 3 months to optimize glycaemia and kept fixed for further 3 months	Change in proportion of LDL as LDL3	B/2
Pavo, (43) (n=205)	32-week, double blind, multicentre (4 centres in Russia 15 centres in Hungary) clinical trial	Recently diagnosed T2DM (WHO definition) diabetes, drug naive patients	Upward titration to PIO 45 mg vs. MET 2,550 mg	HbA1c, FPG, insulin sensitivity	B/4
Scherntha ner(44) (n=1,199)	40-week, parallel-group, double-blind, multicentre (167 centres in 12 European countries) study	T2DM inadequately treated with diet alone (HbA1c ≥7.5% ≤11%	PIO up to 45 mg/day vs. MET 850 mg up to 3 times per day	HbA1c, FPG, lipid profiles, and adverse events	A/4

Abbreviations: PBO=placebo; REP=repaglinide; PIO=pioglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Figure 14. Pooled estimate of HbA1c for pioglitazone monotherapy compared with metformin in patients naïve to treatment and those still controlled on monotherapy



Other comparators

Two articles used active comparators other than sulfonylurea and metformin. One clinical trial compared the efficacy of combination therapy (repaglinide plus pioglitazone) with repaglinide or pioglitazone monotherapy in patients inadequately controlled on sulfonylurea or metformin monotherapy.(45) The other study, conducted in Germany, was designed to examine the efficacy of pioglitazone compared with acarbose treatment in patients either newly diagnosed or previously treated but not well controlled.(46) Both studies were 6 months in duration (Table 23).

Table 23. Characteristics of studies included in the analysis of pioglitazone as monotherapy compared with other oral anti-diabetic agents

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Jovanovic (45) (n=246)	36-week, open-label, parallel-group, multicentre (US centres), study	T2DM inadequately controlled on SU or MET monotherapy (HbA1c >7%)	REP 0.5 or 1.0 mg, REP + PIO 0.5 or 1.0mg REP (up to max of 4 mg/meal) + 30 mg/day PIO vs. PIO 30mg/day	HbA1c and FPG	B/2
Goke(46) (n=271)	36-week, open-label, parallel-group, multicentre (47 centres in Germany) study	Newly diagnosed or previously treated and uncontrolled, (HbA1c ≥ 7.5% ≤ 11.5%, FPG ≥140mg/dL), and BMI ≥ 25 ≤ 43 kg/m^2	PIO 45 mg/day vs. acarbose 50 mg/day up to 300 mg/day	HbA1c, insulin resistance and lipids	A/3

Abbreviations: PBO=placebo; REP=repaglinide; PIO=pioglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Treatment with repaglinide for patients who had previously failed oral antidiabetic monotherapy improved HbA1c values by 0.18% compared with an increased in HbA1c of 0.32% with 30 mg/day of pioglitazone. Conversely, pioglitazone treatment improved mean serum HbA1c levels to a significantly greater extent than acarbose treatment (Table 24).

Table 24 Mean change in HbA1c compared to baseline for pioglitazone monotherapy compared with other oral anti-diabetic agents

Author	PIO TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Jovanovic,(45) PIO vs. Repaglinide	30 mg/d	57	+0.32% (1.21)	54	-0.18% (1.25)	+0.50% (0.04, 0.96)
Goke(46) PIO vs. Acarbose	45 mg/d	129	-1.16% (NR)	136	-0.48% (NR)	-0.68% (NR)

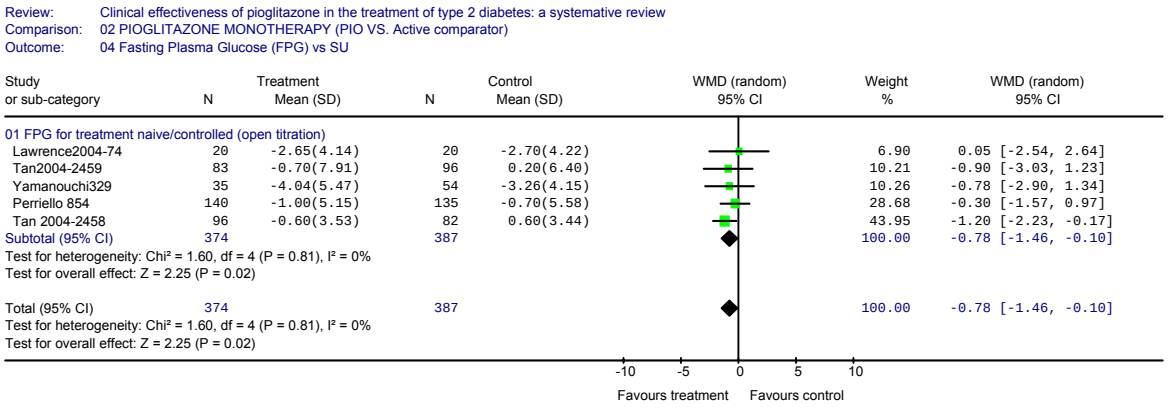
PIO=pioglitazone, TDD=total daily dose, NR=not reported

FPG

Sulfonylurea comparator

Five of the six studies in this category had useable data that could be pooled.(37;38;40-42) The results suggest that pioglitazone was associated with a statistically significantly larger decrease in FPG compared with sulfonylurea with a weighted mean difference of -0.78 mmol/L (95% CI: -1.46, -0.10; *P*=0.02) (Figure 15). The results from the Charbonnel paper could not be included but the data also indicated that FPG was reduced by 0.4 mmol/L more in the pioglitazone-treated patients compared with the sulfonylurea-treated patients.(39)

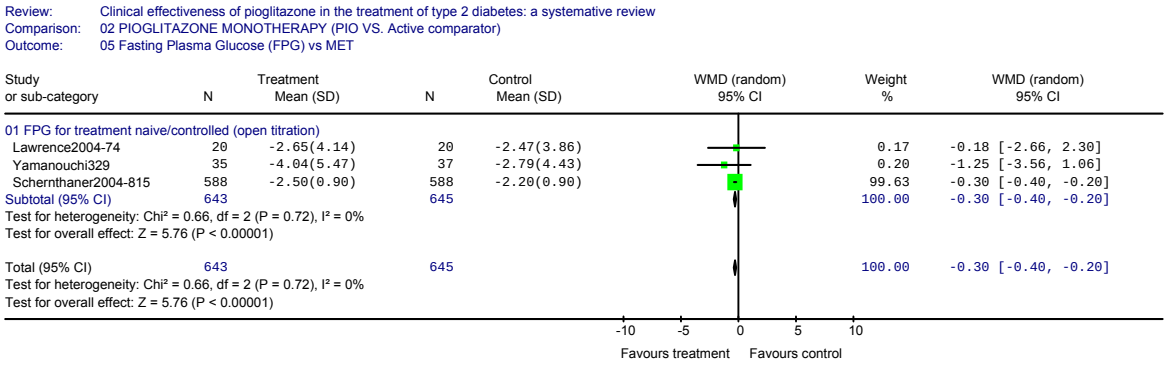
Figure 15. Pooled estimate of FPG for pioglitazone monotherapy compared with sulfonylurea in patients naïve to treatment and those still controlled on monotherapy



Metformin comparator

All of the studies found a greater reduction in FPG in the pioglitazone-treated patients relative to those treated with metformin. Again, the results from the Pavo article (43) could not be included in the pooled analysis due to insufficient data. The results that could be combined from the remaining three studies illustrate that the weighted mean difference in FPG from baseline to endpoint was -0.30 mmol/L (95%CI: -0.40, -0.20; *P*<0.001) in favour of pioglitazone (Figure 16).

Figure 16. Pooled estimate of FPG for pioglitazone monotherapy compared with metformin in patients naïve to treatment and those still controlled on monotherapy



Other comparators

As was seen with the HbA1c results, mean fasting plasma glucose values had indicated a greater efficacy response for repaglinide monotherapy than for pioglitazone monotherapy (-1.88 mmol/L vs. -1.03 mmol/L, respectively).(45) Conversely, Goke et al(46) found that fasting plasma glucose was decreased from baseline in both treatment groups at the study endpoint, but the decrease was significantly greater with pioglitazone than with acarbose (Table 25).

Table 25 Mean change in FPG compared to baseline for pioglitazone monotherapy compared with other oral anti-diabetic agents

Author	PIO TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Jovanovic,(45) PIO vs. Repaglinide	30 mg/d	56	-1.03 mmol/L (3.07)	54	-1.88 mmol/L (3.08)	+0.85 mmol/L (-0.30, 2.00)
Goke(46) PIO vs. Acarbose	45 mg/d	129	-3.13 mmol/L (4.09)	136	-1.25 mmol/L (3.66)	-1.88 mmol/L (-2.82, -0.94)

PIO=pioglitazone; TDD=total daily dose, NR=not reported

2.2.3.2. Efficacy of Pioglitazone as Add-on to Failed Monotherapy

2.2.3.2.1. Pioglitazone add-on therapy compared with placebo comparator for patients failing monotherapy

Adding pioglitazone to failed sulfonylurea or metformin monotherapy in type 2 diabetic patients was evaluated in two studies(47;48) and one study(49),

respectively. Another group of researchers measured the impact of switching patients from failed monotherapy with sulfonylurea or metformin to repaglinide monotherapy or repaglinide plus pioglitazone combination therapy.(45) (Table 26)

Table 26. Characteristics of studies included in the analysis of pioglitazone added to failed monotherapy compared with placebo

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Kipnes(47) (n=560)	16-week, double-blind, placebo-controlled, multicentre (54 centres in US) study	T2DM on stable regimen of a SU for ≥ 30 days and HbA1c ≥ 8.0%	PIO 15 mg/day + SU vs. PIO 30 mg/day + SU vs. PBO + SU	HbA1c, FPG, insulin, C-peptide, and lipids	B/3
Tseng(48) (n=48)	12-week, double-blind, placebo controlled trial conducted in Taiwan	Taiwanese patients with T2DM on existing SU	PIO 30 mg/day + SU vs. PBO + SU	Glycemic control and lipids	B/2
Einhorn(49) (n=328)	16-week, multicentre, US, double-blind study	T2DM uncontrolled on MET (HbA1c ≥8.0%, fasting C-peptide >1.0 mg/mL)	PIO 30 mg/day + MET vs. PBO + MET	HbA1c, plasma glucose, insulin, C-peptide, and lipids	B/3
Jovanovic(45) (n=246)	36-week, open-label, parallel-group, multicentre (all US centres), study	T2DM inadequately controlled on SU or MET monotherapy (HbA1c >7%)	REP 0.5 or 1.0 mg, REP + PIO at 0.5 or 1.0 mg REP (up to max of 4 mg/meal) + 30 mg/day PIO vs. PIO 30 mg/day	HbA1c and FPG	B/2

Abbreviations: PBO=placebo; REP=repaglinide; PIO=pioglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Outcomes

HbA1c

Sulfonylurea failure

The small-scale study conducted by Tseng(48) found that, HbA1c levels decreased significantly from baseline to end of study with pioglitazone 30 mg/day (P<0.05) compared with a percentage increase in HbA1c levels of 2.6% in the placebo group (actual values not provided). Kipnes et al(47) randomized patients to receive once daily pioglitazone 15 mg, pioglitazone 30 mg, or placebo plus sulfonylurea. The study revealed there were dose-dependent decreases in the HbA1c levels in both pioglitazone plus sulfonylurea groups, which were statistically significant compared with placebo and with baseline (Table 27).

Table 27 Mean change in HbA1c compared with baseline for pioglitazone added to failed sulfonylurea versus placebo

Author	PIO TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Kipnes(47)	15 mg/d	157	-0.80% (1.28)	159	+0.10% (1.51)	-0.90% (-1.21, -0.59)
Kipnes(47)	30 mg/d	161	-1.20% (2.29)	159	+0.10% (1.51)	-1.30 (-1.61, -0.99)

TDD=total daily dose, NR=not reported

Metformin failure

One study randomized patients poorly controlled on metformin monotherapy to receive once-daily pioglitazone 30 mg plus metformin or placebo plus metformin.(49) The mean change in HbA1c from baseline in the placebo plus metformin group showed a statistically significant increase (+0.19%, P<0.05) compared with a significant mean decrease in the pioglitazone plus metformin group (-0.64%, P<0.05).

Metformin or Sulfonylurea failure and switch to repaglinide

One study compared the efficacy of combination therapy (pioglitazone plus repaglinide) with repaglinide or pioglitazone over a 24-week treatment period in patients showing inadequate response to previous sulfonylurea or metformin monotherapy.(45) Mean HbA1c values showed only small reductions over the

course of treatment with repaglinide monotherapy (-0.18%), while changes in HbA1c values were much greater in the repaglinide/pioglitazone combination group (-1.76%; *P*<0.01 compare with monotherapy).

FPG

Sulfonylurea failure

No data pooling could be done for this outcome as the study conducted in Taiwan did not provide appropriate data. The authors of this paper reported that pioglitazone plus sulfonylurea significantly decreased fasting plasma glucose by 19.5% after 12 weeks of treatment in Taiwanese type 2 diabetic patients.(48) The larger, US study(47) found that the placebo plus sulfonylurea group showed mean increases from baseline in fasting plasma glucose levels compared with mean decreases from baseline for both pioglitazone plus sulfonylurea groups and these differences were statistically significant (Table 28).

Table 28 Mean change in FPG compared with baseline for pioglitazone added to failed sulfonylurea compared to placebo

Author	PIO TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Kipnes(47)	15 mg/d	157	-1.88 mmol/L (2.68)	159	+0.31 mmol/L (2.68)	-2.19 mmol/L (-2.78, -1.60)
Kipnes(47)	30 mg/d	161	-2.90 (2.66)	159	+0.31 mmol/L (2.68)	-3.21 mmol/L (-3.80, -2.62)

TDD=total daily dose, NR=not reported

Metformin failure

Einhorn et al.(49) found that the placebo plus metformin group showed small mean decreases in fasting plasma glucose from baseline (-0.23 mmol/L), compared with statistically significant mean decreases from baseline with pioglitazone plus metformin combination therapy (-2.34 mmol/L, $P \leq 0.05$).

Metformin or sulfonylurea failure and switch to repaglinide

Mean fasting plasma glucose values indicated a much greater efficacy response for combination therapy (pioglitazone plus repaglinide) compared with repaglinide

monotherapy by the end of the treatment period in patients failing monotherapy with other oral agents (i.e. metformin and sulfonylurea).(45) Mean reductions in fasting plasma glucose values relative to baseline were -4.55 mmol/L for repaglinide plus pioglitazone, significantly greater than the effects of repaglinide monotherapy (-1.03 mmol/L).

2.2.3.2.2. Pioglitazone add-on to insulin therapy compared with insulin monotherapy for patients failing current treatment and switching to insulin

One study assessed the value of switching patients with inadequate glycemic control on sulfonylurea monotherapy or sulfonylurea therapy in combination with other oral antidiabetic agents to insulin alone or to insulin plus pioglitazone.(50) This 18-week, multinational, multicentre, randomized, trial involved 190 patients and by the end of the study, HbA1c levels were lower in the combination group than in the insulin monotherapy group. HbA1c was reduced by 1.2% in the insulin plus pioglitazone group and 0.5% in the insulin monotherapy group. These reductions however, were not significant.

Similarly, FPG levels were lower in the insulin plus pioglitazone group compared with the group switched to insulin monotherapy (-1.72 mmol/L vs. -0.89 mmol/L, respectively). These differences however, did not reach statistical significance.

2.2.3.2.3. Pioglitazone add-on therapy compared with placebo comparator for patients failing insulin treatment

Two studies were identified that measured the impact of adding pioglitazone to patients poorly controlled on insulin therapy (Table 29).(51;52) Rosenstock(51) randomized patients to one of three treatment arms: pioglitazone 15 mg/day plus insulin, pioglitazone 30 mg/day plus insulin or insulin plus placebo for 16 weeks. Mattoo(52) assigned patients to pioglitazone 30 mg/day plus insulin or insulin plus placebo. Results were combined for the pioglitazone 30 mg/day treatment arms using meta-analytic techniques.

Table 29. Characteristics of studies included in the analysis of pioglitazone as monotherapy compared with placebo

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Rosenstock(51) (n=566)	16-week, double-blind, placebo-controlled, multicentre (79 centres in US) study	T2DM using insulin (with or without an oral antihyperglycemic medication) for ≥ 30 days with HbA1c ≥ 8.0%	Insulin + PIO 15 mg/day vs. Insulin + PIO 30 mg/day vs. Insulin + PBO	HbA1c, FPG, C-peptide, lipids	B/3
Mattoo(52) (n=289)	6-month, double-blind, multicentre, multinational, placebo-controlled, parallel group study	T2DM using insulin (with or without an oral antihyperglycemic medication) for ≥ 3 months with HbA1c ≥7.5%	Insulin + PIO 30mg vs. Insulin + PBO	HbA1c, FPG, lipids	A/5

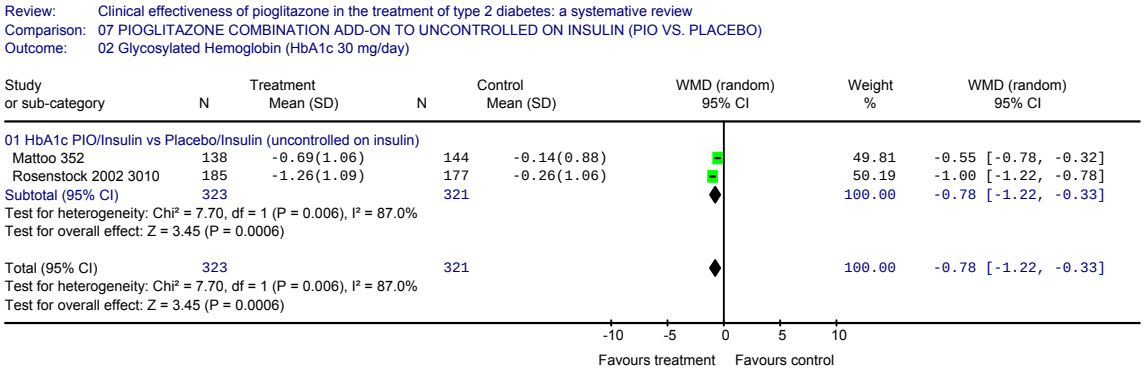
Abbreviations: PBO=placebo; REP=repaglinide; PIO=pioglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Outcomes

HbA1c

Pooling the results from the pioglitazone 30 mg/day treatment arms in both studies(51;52) revealed that adding pioglitazone to failed insulin was associated with a statistically significant weighted mean difference in HbA1c, compared with simply continuing on insulin monotherapy. The overall effect size was a statistically significant weighted mean difference of -0.78% (95% CI: -1.22, -0.33; *P*=0.0006) (Figure 17). It should be noted, however, that pooled estimates for this endpoint is associated with strong evidence of statistical heterogeneity (chi-square=7.70, df=1, P=0.006). For this reason, these findings should be interpreted cautiously.

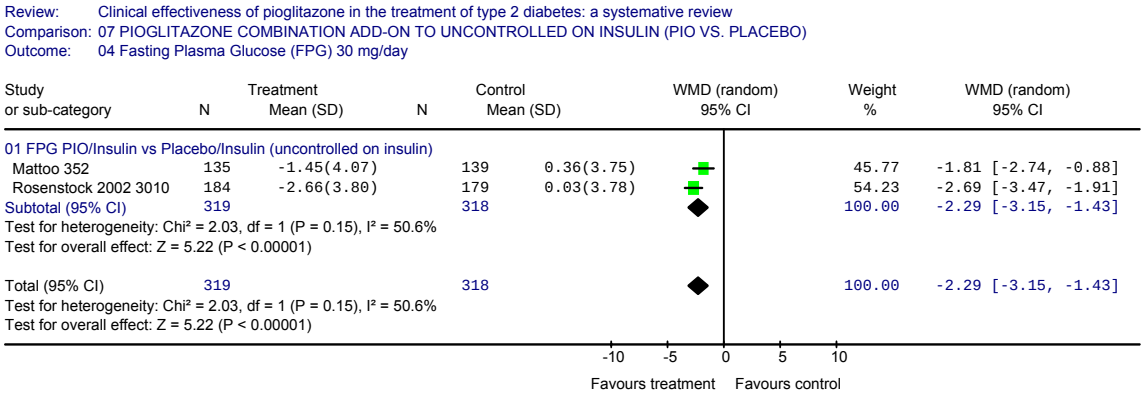
Figure 17. Pooled estimate of HbA1c for pioglitazone 30 mg/day added to insulin compared with placebo in patients inadequately controlled on insulin alone



FPG

Pioglitazone added to failed insulin was associated with a statistically significant weighted mean difference in FPG, compared with simply continuing insulin monotherapy. The overall effect size was -2.29 mmol/L (95% CI: -3.15, -1.43; P<0.001)(Figure 18).(51;52)

Figure 18. Pooled estimate of FPG for pioglitazone 30 mg/day added to insulin compared with placebo in patients inadequately controlled on insulin alone



2.2.3.2.4. Pioglitazone add-on therapy compared with active comparator for patients failing monotherapy

A total of three studies evaluated the addition of pioglitazone to failed monotherapy compared with adding another oral anti-diabetic agent. Two of the articles added pioglitazone or metformin to failed sulfonylurea(53;54) and the

third paper measured the influence of adding sulfonylurea to failed metformin monotherapy.(55)(Table 30)

Table 30. Characteristics of studies included in the analysis of pioglitazone as monotherapy compared with placebo

Author	Methods	Participants	Interventions	Outcomes	Allocation concealment /Jadad
Hanefeld(53) (n=639)	52-week, multicentre, multinational (Europe and Canada), double-blind, parallel group study	T2DM patients inadequately controlled on SU alone	PIO 15 mg (up to 45 mg/day) + SU vs. MET 850 mg (up to 3 times daily, 2,550 mg) + SU	HbA1c, FPG, insulin, lipids, C-peptide, 32, 33 split pro-insulin, and urinary albumin and creatinine	B/4
Nagasaka (54) (n=78)	16-week trial conducted in Japan	T2DM poorly controlled with moderate doses of SU	PIO 15 mg/day for women (n=40), PIO 30 mg/day for men (n=38) + SU vs. MET 750 mg/day + SU	HbA1c, FPG, insulin, lipids	B/1
Matthews(55) (n=630)	52-week, double-blind, multicentre (75 centres in 9 European countries and Australia) study	T2DM uncontrolled (HbA1c ≥7.5 ≤11.0%) on MET alone (at ≥50% of the max dose or at max tolerated dose for ≥3 months)	PIO 15 mg OD (up to 45 mg) + MET vs. SU (gliclazide) 80 mg OD (up to 320 mg) + MET	HbA1c, FPG, insulin, lipids, C-peptide, 32, 33 split pro-insulin, and urinary albumin and creatinine	B/3

Abbreviations: PBO=placebo; REP=repaglinide; PIO=pioglitazone, SU=sulfonylurea; T2DM=type 2 diabetes mellitus
Allocation Concealment: A=adequate; B=unclear; C=inadequate; D=not used

Outcomes

HbA1c

Sulfonylurea failure

Data on HbA1c could not be pooled as neither study provided measures of variance around the mean changes from baseline in HbA1c for any group. In the 1-year study(53), the investigators found that there was a mean reduction of 1.20% in HbA1c in the sulfonylurea plus pioglitazone group, which was similar to the reduction of 1.36% observed in the sulfonylurea plus metformin group.

Likewise, the study involving Japanese patients found that the overall decrease in HbA1c levels was similar for the pioglitazone (-1.2%) and metformin (-1.3%) groups.(54) Both studies revealed that HbA1c was reduced to a greater degree in the metformin group compared with the pioglitazone treatment group however; these differences were not statistically significant (Table 31).

Table 31 Mean change in HbA1c compared with baseline for pioglitazone added to failed sulfonylurea compared with metformin

Author	PIO TDD	N	Mean change (SD) (Treatment)	N	Mean change (SD) (Control)	Difference of means (95% CI)
Hanefeld(53)	30-45 mg/d	315	-1.21% NR	313	-1.36% NR	+0.15% NR
Nagasaka S(54)	15-30 mg/day	35	-1.2% NR	36	-1.3% NR	+0.1% NR

TDD=total daily dose, NR=not reported

Metformin failure

There was only one study that assessed the efficacy of add-on therapy of pioglitazone, compared with addition of sulfonylurea, to continued metformin in patients with type 2 diabetes inadequately controlled with metformin alone.(55) At the end of 52 weeks of treatment, there was a comparable mean reduction in HbA1c (0.99% in the metformin plus pioglitazone group and 1.01% in the metformin plus sulfonylurea group) and there was no statistically significant between-group difference (95% CI: -0.15%, 0.19%; *P*=0.837).

FPG

Sulfonylurea failure

As was the case with HbA1c, Hanefeld et al(53) found that FPG was reduced in both the pioglitazone group as well as the metformin group but to a slightly greater degree in metformin-treated patients after 52 weeks of treatment (-2.1 mmol/L vs. -2.4 mmol/L, respectively). Nagasaka(54) did not report changes in fasting plasma glucose in their study.

Metformin failure

Adding pioglitazone to failed metformin reduced fasting plasma glucose by a comparable amount to those patients treated with sulfonylurea added to failed metformin. Decreases of 2.1 mmol/L were seen in the metformin plus pioglitazone group and 1.6 mmol/L in the metformin plus sulfonylurea group.(55)

2.2.3.2.5. Pioglitazone add-on therapy to existing failed oral treatment compared with switching to insulin monotherapy

The study by Raz et al(50) discussed in section 2.2.3.2.2, contained three treatment arms. Patients failing sulfonylurea therapy, either as monotherapy or in combination with other oral anti-diabetic agents, could also have been randomized to add pioglitazone to the failed sulfonylurea. The efficacy of this treatment regimen was compared with those who were switched to insulin monotherapy.

After the 18-week treatment period, HbA1c levels achieved by patients treated with insulin monotherapy were similar to those achieved in the sulfonylurea plus pioglitazone group. HbA1c values decreased by 0.5% in the insulin group and by 0.4% in the sulfonylurea plus pioglitazone combination group from baseline to end of trial.

Mean fasting blood glucose levels were reduced by 0.89 mmol/L in the insulin monotherapy and by 0.11 mmol/L in the sulfonylurea plus pioglitazone group, these differences however, did not reach statistical significance.

2.2.3.3. Efficacy of Pioglitazone as Add-on to Dual Therapy

2.2.3.3.1. Pioglitazone add-on therapy to failed dual therapy compared with switching to insulin

One published study evaluated the addition of pioglitazone or bedtime NPH insulin to patients inadequately controlled on maximal doses of metformin and sulfonylurea combination therapy.(56) This Canadian, 16-week, non-blinded, open-label, randomized controlled trial involved 62 patients with type 2 diabetes with HbA1c levels >8.0%.

By the end of the study, both the pioglitazone-treated patients and the insulin-treated patients had similar improvements in HbA1c levels (-1.9% and -2.3%, respectively). Likewise, the reduction in fasting plasma glucose was greater in the insulin group compared with the pioglitazone group (-4.3 mmol/L vs. -2.9 mmol/L, respectively), however the difference did not reach statistical significance.

2.3. Summary

In this systematic review, glitazones were shown to be effective in reducing HbA1c and FPG levels in patients with type 2 diabetes, both as monotherapy (versus placebo and active comparator) and in combination with metformin, a sulfonylurea, or insulin when compared with placebo. These agents were comparable with other oral antidiabetic agents as monotherapy in reducing blood glucose levels. When sulfonylurea was added to failed metformin monotherapy for 24 weeks, HbA1c and FPG decreased to a greater extent than when rosiglitazone was added to failed metformin monotherapy. However, when the treatment duration was extended to 52 weeks, rosiglitazone plus metformin had a more favourable effect on both outcomes. Pioglitazone added to failed monotherapy (i.e. sulfonylurea or metformin) produced similar reductions in clinical outcomes as those compared with other antidiabetic agents in such combinations. The addition of insulin to patients failing dual therapy with metformin and sulfonylurea experienced greater reductions in both HbA1c and FPG than when a glitazone was added to failed dual therapy.

2. LONG-TERM COSTS AND EFFECTS OF ROSIGLITAZONE AND PIOGLITAZONE IN THE TREATMENT OF TYPE 2 DIABETES

3.1. Background

In chronic diseases such as type 2 diabetes, establishing the cost-effectiveness of new therapies is essential. In spite of this, long-term outcome studies that measure the disease outcomes associated with glitazone treatment are not currently available. Therefore, the only way to estimate the cost-effectiveness in terms of final health outcomes is by the use of long-term modelling of disease progression and complications to extrapolate surrogate outcome randomized controlled trial data. Comparing treatments in terms of final health outcomes is important for decision makers because it allows them to assess the relative value of a wide range of therapies currently available using a consistent and important endpoint (i.e. quality-adjusted life-year (QALY)).

The objective of this component of the study was to assess the incremental cost-effectiveness of pioglitazone and rosiglitazone in the treatment of patients with type 2 diabetes. We used secondary data on surrogate outcomes from published randomized controlled trials, coupled with estimates modelled from the Ontario Diabetes Economic Model (ODEM) on the long-term quality of life effects and cost implications of microvascular and macrovascular diabetes-related complications. This permitted us to estimate the lifetime costs and effects of these interventions in terms of the cost per QALY gained.(57) The use of pioglitazone and rosiglitazone as monotherapy and in combination with metformin, sulfonylurea, or insulin as compared with established treatments were all considered.

3.2. Methods

The UKPDS Outcomes Model and its Adaptation for Ontario

The recently developed computer simulation model, the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model, uses a system of equations to predict the occurrence and timing of seven diabetes-related complications (i.e. fatal or non-fatal myocardial infarction [MI], other ischaemic heart disease, stroke, heart failure, amputation, renal failure and blindness) and

death, and thereby calculates life expectancy and quality-adjusted life expectancy for patients with Type 2 diabetes.(58) To account for event-related dependencies, the model makes use of time varying risk factors (e.g. blood pressure, HbA1c) which also facilitates its application to patient groups at different stages of the disease.

The UKPDS Outcomes Model is based on data on over 5,000 patients with over 53,000 years of patient follow-up however, the model needed to be adapted if it is to be used in another geographic area such as Ontario. Differences in the incidence and prevalence of diabetes, differences in baseline demographic and diabetes risk factors, in overall mortality or mortality from diabetes-related complications, in costs (e.g. treatment and management of complications), and differences in cost and effects of treatment programs exist across countries. As a result, the UKPDS Outcomes Model was populated with Ontario-specific data for use in this region.

The adaptation of the model to the Ontario setting has been described in detail elsewhere.(59) In brief, more than 734,000 patients with diabetes were identified in the Ontario Diabetes Database (ODD)(60) and followed for up to 10 years. Various administrative databases were linked to this population in order to measure the prevalence and incidence of complications, healthcare resource utilization (i.e. inpatient and outpatient hospitalizations, outpatient visits, prescription drugs, emergency room visits, and home care), and death. Unit costs were collected and assigned to each of the different healthcare sectors. Complication-specific costs were divided into two time periods: 1) *immediate costs* that accrue within the year in which a complication first occurs; and 2) *long-term costs* that reflect the ongoing costs in subsequent years associated with the ongoing management of the complication (including subsequent events of the same type). Hospital inpatient and non-inpatient event and state costs were estimated for each of the seven complications. The perspective taken for estimating costs was that of the Ontario Ministry of Health and Long-term Care. All healthcare costs used it the model were based on direct costs as it was not

possible to measure productivity costs or other patient costs from the data available. All calculated costs are in 2006 Canadian dollars.

Efficacy Data

Some of the results of the systematic review reported in section 2 of this report were used for the cost-effectiveness analyses. Only relevant comparisons that attempted to address the issue of where the glitazones fit in therapy were evaluated for cost-effectiveness.

Mean changes from baseline to endpoint for the following outcomes were abstracted where available from each article: HbA1c, systolic blood pressure (SBP), body mass index (BMI), total cholesterol, and HDL cholesterol. The means for each outcome of interest within a group of similar studies were combined using a weighted average based on the number of patients enrolled in the study. The differences of means for each comparison were then calculated by subtracting the intervention value from the control value for use as input parameters for the ODEM.

Economic model assumptions

In situations where efficacy data on a required risk factor were not available, it was assumed that there was no change in this variable from baseline to endpoint. The treatment duration and efficacy was assumed to be 5 years for the base case analysis. The time horizon for the model was 40 years with a discount rate of 3%. The drug dosages in each of the evaluations reflect what was used in the identified randomized clinical trials. Drug unit costs were obtained from the Ontario Drug Benefit Formulary/Comparative Drug Index No. 39(61) and are outlined in Table 32. In addition, we included a 10% pharmacy mark-up for each prescription plus a pharmacy dispensing fee of $6.11. After consultation with clinical experts, it was assumed that patients receiving sulfonylurea used two test strips per day, while patients receiving a glitazone or metformin used 1 strip per week at a unit cost of $0.729 (Bernard Zinman, Mount Sinai Hospital and University of Toronto, Toronto; Stewart Harris, Centre for Studies in Family Medicine, University of Western Ontario, London; Hertzel Gerstein, Diabetes

Care and Research Progra, Hamilton Health Sciences, Hamilton: personal personal communication, 2007 February 6). Patients receiving insulin were assumed to use 3 strips and 3 needles per day at a unit cost of $0.26.

Table 32 Summary of drug unit costs included in the model

Drug dose	Unit Cost ($CDN)
Acarbose 50mg	0.3123
Acarbose 100mg	0.2259
Glyburide 2.5mg	0.0393
Glyburide 5mg	0.0683
Metformin 500mg	0.1216
Pioglitazone 15mg	2.1463
Pioglitazone 30mg	3.0070
Pioglitazone 45mg	4.5213
Rosiglitazone 2mg	1.2853
Rosiglitazone 4mg	2.0169
Rosiglitazone 8mg	2.8842
Insulin--Novolin ge NPH (per unit)	0.0214

Cost-utility analyses

The primary outcome measure for the economic evaluation was the QALY. First, it was determined whether certain strategies were dominated by other strategies, which had both higher costs and lower therapeutic benefits. Second, among non-dominated alternatives, incremental cost-utility ratios were calculated using the ratio of the difference in costs to the difference in outcomes between the two alternatives. In order to use the patient-level model to estimate the cost-utility of each glitazone, we used a cohort of diabetes patients from Ontario and applied the differences of means calculated from the pooled estimates of the changes in risk factors to the entire group. These results were compared to the model results when baseline values of the cohort were used so as to represent the control group.

Sensitivity analyses

Simple sensitivity analyses were conducted by varying both the program and treatment effect duration simultaneously in order to estimate the incremental cost-effectiveness. Treatment and efficacy durations were altered by 1, 3, and 10 years.

3.3. Results

3.3.1. Clinical efficacy of rosiglitazone

Four treatment strategies involving the introduction of rosiglitazone were identified that were relevant for our purposes. The strategies evaluated were: 1) add-on of rosiglitazone to failed monotherapy; 2) add-on to failed dual therapy compared with continuing on failed dual therapy; 3) add-on to failed dual therapy compared with adding insulin to failed dual therapy; and 4) add-on to failed insulin compared with continuing on insulin (Table 33).

Table 33 Relevant comparisons for economic evaluation: Rosiglitazone

Treatment Scenario	# of Studies
Add-on to failed monotherapy	
ROSI + SU vs. MET + SU	2
ROSI + MET vs. SU + MET	2
Add-on to failed dual therapy vs. PBO	
ROSI + MET/SU vs. PBO + MET/SU	1
Add-on to failed dual therapy vs. Insulin	
ROSI + MET/SU vs. Insulin + MET/SU	1
Add-on to failed insulin	
ROSI + Insulin vs. PBO + Insulin	2
Total	**8**

Abbreviations: MET=metformin, PBO=placebo, ROSI-rosiglitazone, SU=sulfonylurea

3.3.1.1. Add-on to failed monotherapy

Failed sulfonylurea

The combined data from the two studies that measured the impact of adding rosiglitazone or metformin to failed sulfonylurea(27;28) established that rosiglitazone reduced HbA1c to a greater degree and had a more favourable impact on HDL cholesterol. On the other hand, this treatment combination caused an increase in BMI as well as total cholesterol. The influence on systolic blood pressure was not measured in either of the two studies (Table 34).

Failed metformin

The effects of two combination regimens, sulfonylurea plus metformin versus rosiglitazone plus metformin in patients inadequately controlled on metformin monotherapy, were compared in two studies.(29;30) The pooled results showed that the addition of sulfonylurea had a greater overall effect on HbA1c and HDL cholesterol than rosiglitazone. However, there was a greater decrease in systolic blood pressure and BMI in the rosiglitazone group (Table 34).

3.3.1.2. Add-on to failed dual therapy compared with placebo

Dailey et al(31) assessed the efficacy of adding rosiglitazone to an established regimen of glyburide/metformin in patients who had not achieved adequate glycemic control levels. After 24 weeks, therapy with glyburide/metformin plus rosiglitazone resulted in a greater reduction in HbA1c levels compared with combination therapy that included placebo. This treatment also increased HDL cholesterol to a greater degree (Table 34).

3.3.1.3. Add-on to failed dual therapy compared with insulin

One group of researchers evaluated the efficacy of add-on insulin glargine versus rosiglitazone in insulin-naïve patients inadequately controlled on dual oral therapy with sulfonylurea plus metformin.(32) The addition of insulin was more effective in reducing HbA1c and total-to-HDL cholesterol levels relative to the addition of rosiglitazone in these patients (Table 34). Unfortunately, other variables that drive the ODEM were not reported in the paper.

3.3.1.4. Add-on to failed insulin

Adding rosiglitazone to insulin in patients inadequately controlled on insulin monotherapy was evaluated in two different studies.(21;22) Table 34 illustrates that this treatment regimen had favourable effects on HbA1c, BMI and HDL cholesterol while increasing systolic blood pressure and total:HDL ratio.

Table 34 Efficacy of rosiglitazone from pooled estimates (difference of means)

Comparison	HbA1c (%)	SBP (mmHg)	BMI (kg/m^2)	Total: HDL	Total chol. (mmol/L)	HDL (mmo/L)
ROSI + SU vs. MET + SU	-0.24	--	1.0	--	0.38	0.05
ROSI + MET vs. SU + MET	0.23	-2.2	-0.5	--	0.59	0.16
ROSI + MET + SU vs. PBO + MET + SU	-1.04	--	--	--	0.39	0.11
ROSI + MET + SU vs. Insulin + MET + SU	0.15	--	--	--	0.75	--
ROSI + Insulin vs. PBO + Insulin	-0.63	1.89	-1.50	--	0.31	0.08

Abbreviations: BMI=body mass index; chol.=cholesterol; HDL=high-density lipoprotein; MET=metformin; PBO=placebo; ROSI=rosiglitazone; SBP=systolic blood pressure; SU=sulfonylurea

3.3.2. Clinical efficacy of pioglitazone

Three treatment scenarios were identified for use in the ODEM to model the long-term consequences of pioglitazone therapy: 1) add-on to failed monotherapy; 2) add-on to failed dual therapy compared with initiation of insulin; and 3) add-on to failed insulin therapy compared with placebo. Only one treatment regimen included data from more than one study to determine the long-term cost-effectiveness of pioglitazone (Table 35).

Table 35 Relevant comparisons for economic evaluation: Pioglitazone

Treatment Scenario	# of Studies
Add-on to failed monotherapy	
PIO + SU vs. MET + SU	2
PIO + MET vs. SU + MET	1
Add-on to failed dual therapy	
PIO + MET/SU vs. Insulin + MET/SU	1
Add-on to failed insulin	
PIO + Insulin vs. PBO + Insulin	2
Total	**6**

Abbreviations: MET=metformin, PBO=placebo, PIO-pioglitazone, SU=sulfonylurea

3.3.2.1. Add-on to failed monotherapy

Failed sulfonylurea

Pooled data from the two studies that measured the impact of adding pioglitazone or metformin to failed sulfonylurea(53;54) demonstrated that metformin reduced HbA1c by a greater amount and resulted in less weight gain. Pioglitazone, however, was shown to decrease systolic blood pressure and increase HDL cholesterol to a greater degree than metformin. There was no difference in the changes in total-to-HDL cholesterol ratio between the two treatments (Table 36).

Failed metformin

One study evaluated the impact of adding sulfonylurea to failed metformin compared with adding pioglitazone to failed metformin.(55) The results revealed that adding sulfonylurea reduced HbA1c by a greater amount than the addition of pioglitazone to people uncontrolled on metformin monotherapy (-1.01% compared with -0.99%, respectively). Also, patients receiving combination pioglitazone therapy had a greater increase in BMI than those patients receiving sulfonylurea combination therapy. On the other hand, there were favourable results in terms of lipid profiles with pioglitazone treatment (i.e. greater increase in HDL and greater reduction in total-to-HDL cholesterol ratio) compared with sulfonylurea treatment (Table 36).

3.3.2.2. Add-on to failed dual therapy

A small (n=62), non-blinded, open-label study randomized patients to receive the addition of pioglitazone or bedtime isophane (NPH) insulin to maximal doses of metformin and sulfonylurea in patients with poor glucose control.(56) Adding pioglitazone in this case resulted in a greater increase in BMI and total cholesterol, as well as a lesser decrease in HbA1c when compared with adding insulin. At the same time, adding pioglitazone increased HDL cholesterol and decreased systolic blood pressure to a greater degree than adding insulin (Table 36).

3.3.2.3. Add-on to failed insulin

The metabolic effects of pioglitazone in combination with insulin in patients whose diabetes was not adequately controlled with insulin therapy was evaluated in two studies.(51;52) The introduction of pioglitazone was associated with a more favourable impact on HbA1c, total-to-HDL cholesterol, and HDL cholesterol than continuing on insulin alone. This treatment regimen, however, caused an increase in BMI (Table 36).

Table 36 Efficacy of pioglitazone from pooled estimates (difference of means)

Comparison	HbA1c (%)	SBP (mmHg)	BMI (kg/m^2)	Total: HDL	Total chol. (mmol/L)	HDL (mmo/L)
PIO + SU vs. MET + SU	0.14	-1	1.08	--	--	--
PIO + MET vs. SU + MET	0.02	--	0.04	-0.34	--	--
PIO + MET + SU vs. Insulin + MET + SU	0.40	-2	0.08	--	0.52	0.1
PIO + Insulin vs. PBO + Insulin	-0.80	--	1.29	-0.38	0.06	0.11

Abbreviations: BMI=body mass index; chol.=cholesterol; HDL=high-density lipoprotein; MET=metformin; PBO=placebo; PIO=pioglitazone; SBP=systolic blood pressure; SU=sulfonylurea

3.3.3. Cost-utility analyses

3.3.3.1. Rosiglitazone

The incremental costs, effects and cost-utility results for various rosiglitazone treatment strategies are presented in Table 37. The incremental results show the extra lifetime costs of one strategy relative to another divided by the extra benefits gained by that strategy relative to the other strategy. In the base case analysis, the strategy of adding rosiglitazone to failed sulfonylurea was dominated by the strategy of adding metformin to failed sulfonylurea. Similarly, adding insulin to failed dual therapy of metformin and sulfonylurea dominated adding rosiglitazone to the same treatment. Adding rosiglitazone to failed insulin monotherapy compared with a 'do nothing' strategy was estimated to cost $37,802 per QALY gained. Adding rosiglitazone to failed dual therapy (i.e. sulfonylurea plus metformin) compared with placebo resulted in a cost-utility of

$54,001 per QALY and adding rosiglitazone or sulfonylurea to failed metformin produced an incremental cost per QALY gained of $59,485.

Table 37 Estimated incremental cost, QALY and cost-utility results for rosiglitazone (base case analysis)

Treatment strategy	Incremental Cost	Incremental QALY	Incremental cost per QALY (CDN$)
ROSI + SU vs. MET + SU	$1,940	-0.0088	Dominated
ROSI + MET vs. SU + MET	$2,069	0.0348	$59,485
ROSI + MET + SU vs. MET + SU + PBO	$5,774	0.1069	$54,001
ROSI + MET + SU vs. Insulin + MET + SU	$1,818	-0.0114	Dominated
ROSI + Insulin vs. Insulin + PBO	$2,928	0.0775	$37,802

Abbreviations: MET=metformin; PBO=placebo; ROSI=rosiglitazone; SU=sulfonylurea

3.3.3.2. Pioglitazone

The incremental costs, QALYs and incremental cost per QALY results for pioglitazone strategies are presented in table 38. Of the four strategies using pioglitazone as an add-on therapy, two of them were more costly and less effective (i.e. dominated) than the other treatment regimens. Adding pioglitazone to failed metformin resulted in an incremental increase in both costs and QALYs relative to adding sulfonylurea. Pioglitazone add-on to failed insulin was associated with an incremental cost-effectiveness ratio of $55,072 compared with simply continuing insulin monotherapy. However, adding pioglitazone to failed metformin monotherapy resulted in a cost-utility of $122,480.

Table 38 Estimated incremental cost, QALY and cost-utility results for pioglitazone (base case analysis)

Treatment strategy	Incremental cost	Incremental QALY	Incremental cost per QALY (CDN$)
PIO + SU vs. MET + SU	$4,307	-0.018	Dominated
PIO + MET vs. SU + MET	$3,970	0.0324	$122,480
PIO + MET + SU vs. Insulin + MET + SU	$3,967	-0.0195	Dominated
PIO + Insulin vs. Insulin + PBO	$4,956	0.0900	$55,072

Abbreviations: MET=metformin; PBO=placebo; PIO=pioglitazone; SU=sulfonylurea

3.3.4. Sensitivity analyses

3.3.4.1. Rosiglitazone

The results from altering the treatment and efficacy duration for each of the different comparisons using rosiglitazone are shown in Tables 39, 40, and 41. Each comparison is discussed separately below.

Rosiglitazone or sulfonylurea add-on to failed metformin

Increasing the treatment and efficacy duration of rosiglitazone plus failed metformin compared with adding sulfonylurea to failed metformin resulted in an incremental increase in QALYs over time but also increase in cost. The resulting impact on cost per QALY ranged from $27,244 (1-year) to $106,545 (10-year) (Table 39).

Table 39. Incremental cost-utility analysis results for rosiglitazone added to failed metformin compared with addition of sulfonylurea added to failed metformin: sensitivity analyses surrounding treatment and efficacy duration

Treatment effect & duration	Incremental cost	Incremental QALY	Incremental cost per QALY (CDN$)
1 year	$489	0.0180	$27,244
3 year	$1,188	0.0237	$50,154
5 years (base case)	$2,069	0.0348	$59,485
10 years	$5,031	0.0472	$106,545

Abbreviations: ICER=incremental cost-effectiveness ratio; QALY(s)=quality-adjusted life-years(s)

Rosiglitazone add-on to failed metformin plus sulfonylurea dual therapy

Extending the duration of triple therapy with rosiglitazone plus metformin plus sulfonylurea past 1-year resulted in little change in cost per QALY for 3- to 10-year assumptions. However, with only 1-year treatment effect and duration, the cost per QALY increased substantially to $162,970 (Table 40).

Table 40 Incremental cost-utility analysis results for rosiglitazone added to failed metformin plus sulfonylurea dual therapy compared with continuing on dual therapy: sensitivity analyses surrounding treatment duration

Treatment effect & duration	Incremental cost	Incremental QALY	Incremental cost per QALY (CDN$)
1 year	$1,143	0.0070	$162,970
3 year	$3,676	0.0660	$55,667
5 years (base case)	$5,774	0.1069	$54,001
10 years	$9,676	0.1752	$55,222

Abbreviations: ICER=incremental cost-effectiveness ratio; QALY(s)=quality-adjusted life-years(s)

Rosiglitazone add-on to failed insulin

The impact of combining rosiglitazone with failed insulin on cost-effectiveness ranged from $12,904 per QALY (1 year) to $87,374 per QALY (Table 41).

Table 41 Incremental cost-utility analysis results for rosiglitazone added to failed insulin compared with continuing on insulin monotherapy: sensitivity analyses surrounding treatment duration

Treatment effect & duration	Incremental cost	Incremental QALY	Incremental cost per QALY (CDN$)
1 year	$494	0.0383	$12,904
3 year	$1,733	0.0533	$32,520
5 years (base case)	$2,928	0.0775	$37,802
10 years	$10,080	0.1154	$87,374

Abbreviations: ICER=incremental cost-effectiveness ratio; QALY(s)=quality-adjusted life-years(s)

3.3.4.2. Pioglitazone

Pioglitazone or sulfonylurea add-on to failed metformin

Pioglitazone combined with failed metformin therapy for 5-year or 10-year duration resulted in similar incremental cost-effectiveness ratios ($122, 480 and $122,821 respectively) relative to adding sulfonylurea to failed metformin for the

same time periods. However, as the duration of treatment was shortened, the cost-effectiveness ratios increased and were as high as $220,245 for 1-year of treatment (Table 42).

Table 42 Incremental cost-utility analysis results for pioglitazone added to failed metformin compared with addition of sulfonylurea added to failed metformin: sensitivity analyses surrounding treatment duration

Treatment effect & duration	Incremental cost	Incremental QALY	Incremental cost per QALY (CDN$)
1 year	$900	0.0041	$220,245
3 year	$2,592	0.0187	$138,474
5 years (base case)	$3,970	0.0324	$122,480
10 years	$6,658	0.0542	$122,821

Abbreviations: ICER=incremental cost-effectiveness ratio; QALY(s)=quality-adjusted life-years(s)

Pioglitazone add-on to failed insulin

The incremental cost-effectiveness ratios for adding pioglitazone to failed insulin compared with continuing on insulin therapy were similar for the 3-year ($53,359), 5-year ($55,072) and 10-year ($52,298) treatment durations. On the other hand when the treatment duration was on for 1 year, the ratio was $216,562 (Table 43).

Table 43 Incremental cost-utility analysis results for pioglitazone added to failed insulin compared with continuing on insulin monotherapy: sensitivity analyses surrounding treatment duration

Treatment effect & duration	Incremental cost	Incremental QALY	Incremental cost per QALY (CDN$)
1 year	$1.258	0.0058	$216,562
3 year	$3,299	0.0618	$53,359
5 years (base case)	$4,956	0.0900	$55,072
10 years	$8,311	0.1589	$52,298

Abbreviations: ICER=incremental cost-effectiveness ratio; QALY(s)=quality-adjusted life-years(s)

3.4. Summary

The results of the ODEM indicated that adding rosiglitazone to failed dual therapy (i.e. sulfonylurea + metformin) was associated with the highest quality-adjusted life-expectancy (8.4 years) relative to all other comparisons. Extending this

treatment regimen past the base case of 5 years resulted in even more gains in QALYs over time. However, two of the rosiglitazone combination treatment scenarios produced fewer quality-adjusted life-years than their comparators (rosiglitazone + sulfonylurea versus metformin + sulfonylurea, and rosiglitazone + metformin + sulfonylurea versus insulin + metformin + sulfonylurea) and were more costly and thus were dominated strategies. In the base case, the lowest incremental cost-effectiveness ratio was seen when rosiglitazone was added to failed insulin compared to continuing on insulin alone (i.e. $37,802 per QALY).

Using randomized clinical trial data on surrogate outcomes from pioglitazone studies, the economic model estimated that the highest gain in quality-adjusted life years resulted when pioglitazone was added to failed insulin (8.3 years) compared to all other treatments. This therapy was associated with an incremental cost-effectiveness ratio of $55,072 relative to continuing insulin monotherapy. The only other non-dominated strategy - adding pioglitazone to failed metformin versus sulfonylurea plus failed metformin - resulted in an ICER of $122,480 per QALY gained. In the univariate sensitivity analyses, adding pioglitazone to failed insulin compared with continuing on insulin therapy revealed a decrease in incremental cost-effectiveness ratios over time. These ratios began to approach the threshold of $50,000 per QALY, a commonly quoted ratio suggested as moderate evidence for adoption of a new technology or treatment.

4. DISCUSSION

Based on a systematic review of the published literature, it was shown that the glitazones are effective as both monotherapy and combination therapy at reducing blood glucose levels. Adding a glitazone to patients not adequately controlled on their current therapy was also shown to be an effective treatment strategy compared to simply continuing on previous therapy.

Using the ODEM, it was estimated that some combination therapy regimens with rosiglitazone and pioglitazone reduced the risk of severe complications and increased life expectancy and quality adjusted life expectancy in patients with type 2 diabetes at acceptable costs. The incremental cost-effectiveness ratios of combination therapy with rosiglitazone for three of the treatment strategies were found to be within recognized ranges of acceptability for cost-effectiveness. Half of the treatment regimens for pioglitazone combination therapy were dominated and only one strategy represented a reasonably attractive strategy (i.e. addition of pioglitazone to failed insulin therapy). These findings should be re-evaluated as soon as additional evidence becomes available.

We have used the patient-level computer simulation model to estimate the long-term impact of health interventions for people with type 2 diabetes. The model uses a wide variety of input data, including knowledge of previous events for individuals, and has the ability to take into account changes in some risk factor values over time. In particular, it estimates changes in outcomes such as life expectancy and quality adjusted life expectancy, when risk factors such as blood glucose level, blood pressure, lipid levels and smoking status are changed. The use of the algorithm in the ODEM meant that we were restricted in which clinical efficacy parameters of the clinical trials that could be used to predict long-term outcomes.

A key aspect of the ODEM is that it is designed to capture the association between different types of complications at an individual patient level. The long-term modelling of a chronic multifactorial disease such as diabetes requires a number of assumptions to be made, which extrapolate beyond the existing

evidence. The clinical efficacy of rosiglitazone and pioglitazone used in this particular application of the ODEM was based on the mean estimates of the key risk factors reported in the published literature. Changes in these risk factor values at the end of each study were combined and applied uniformly to each patient in a population of patients with diabetes to represent a 'treatment' group. In instances where information on the key factors was not available, it was assumed that that there were no changes in these variables in the model. This may lead to misleading results. For example, lipid profiles have a large impact on downstream cardiovascular complications, so when these data were not available the cost-effectiveness results may not reflect the true treatment effects.

At the same time, when lipid data were available, it was not possible to control for concomitant use of cholesterol-lowering medications alongside the study drug and thus lipid improvement may be due to this therapy and not to the glitazone. It should also be recognized that statin therapy will add to the cost of treatment and therefore should be assessed in a cost-effectiveness framework similar to the model presented here. This would be possible with appropriate clinical trial data comparing combination therapy with statins and pioglitazone or rosiglitazone.

As is the case with all model-based cost-effectiveness analyses, ours has several limitations because of the restricted availability of clinical data. Depicting complex and multifaceted disease such as type 2 diabetes in a computer model that simulates lifetime heath and cost outcomes is especially controversial. The potential for bias is further added by the fact that the study results of pioglitazone and rosiglitazone are based on clinical trials with a highly selected population that may differ from the 'real' type 2 diabetes with respect to comorbidities, use of concomitant medications, and ethnicity. However, modelling is justified while the uncertainty remains and relevant information is not available, which is the main reason for this procedure.(62)

As demonstrated in this review, only short-term clinical data exist for glitazones at this point in time. Therefore a type 2 diabetes model was used to estimate

expected long-term clinical and economic outcomes. The ODEM enabled the simulation of the longer term evaluation of clinical data with respect to final health outcomes (i.e. quality of life and mortality) and costs, thus providing a generalizable assessment of the relative costs-effectiveness of pioglitazone and rosiglitazone.(63) The use of an economic model of type 2 diabetes progression combined with Canadian-specific healthcare cost data strengthens the present economic analysis.

In summary, there were relatively little data that provided guidance as to where the glitazones fit in current practice and thus little evidence to direct reimbursement policy decisions from the public payer perspective. More research is required that evaluates the addition of a glitazone to failed dual therapy compared with switching patients to insulin.

APPENDICES

APPENDIX A Rosiglitazone and Pioglitazone Search Strategies

Database: Ovid MEDLINE(R) Search Strategy:

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1 exp diabetes mellitus/ (175728)
2 exp diabetes mellitus, type II/ (33201)
3 (("type 2 diabet:" or "type 2 DM" or diabet:) adj2 "type 2").af. (14855)
4 (("type II diabet:" or "type II DM" or diabet:) adj2 "type II").af. (34545)
5 NIDDM.af. (6419)
6 "non insulin dependent diabet:".af. (9180)
7 "adult onset diabet:".af. (342)
8 3 or 4 or 5 or 6 or 7 (40467)
9 1 and 8 (36812)
10 2 or 9 (36812)
11 exp pioglitazone/ (0)
12 exp rosiglitazone/ or exp metformin plus rosiglitazone/ (0)
13 2,4 thiazolidinedione derivative/ (0)
14 pioglitazon$.af. (725)
15 rosiglitazon$.af. (995)
16 exp troglitazone/ (0)
17 troglitazon$.mp. (1448)
18 exp thiazolidinedione/ (2739)
19 thiazolidinedion$.af. (3240)
20 actos.af. (24)
21 avandia.af. (20)
22 1101025-46-8.rn. (0)
23 "peroxisome profilerator activated receptor gamma agonist$".af. (0)
24 "ppar gamma agonist$".af. (215)
25 ad-4833.af. (16)
26 u-72107.af. (2)
27 122320-73-4.rn. (782)
28 brl-49653.af. (81)
29 97322-87-7.rn. (1156)
30 thiazole$.af. (14153)
31 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (15398)
32 9 and 31 (1125)
33 10 and 31 (1125)
34 limit 33 to (human and english language and yr=1993 - 2005) (811)
35 from 34 keep 1-811 (811)

APPENDIX A (cont'd)

Database: EMBASE Search Strategy:

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1 exp diabetes mellitus/ (154212)
2 exp diabetes mellitus, type II/ (31221)
3 (("type 2 diabet:" or "type 2 DM" or diabet:) adj2 "type 2").af. (14528)
4 (("type II diabet:" or "type II DM" or diabet:) adj2 "type II").af. (4096)
5 NIDDM.af. (6002)
6 "non insulin dependent diabet:".af. (33079)
7 "adult onset diabet:".af. (232)
8 3 or 4 or 5 or 6 or 7 (36769)
9 1 and 8 (35007)
10 2 or 9 (35007)
11 exp pioglitazone/ (1792)
12 exp rosiglitazone/ or exp metformin plus rosiglitazone/ (2247)
13 2,4 thiazolidinedione derivative/ (1548)
14 pioglitazon$.af. (1821)
15 rosiglitazon$.af. (2278)
16 exp troglitazone/ (2718)
17 troglitazon$.mp. (2766)
18 exp thiazolidinedione/ (1548)
19 thiazolidinedion$.af. (2508)
20 actos.af. (295)
21 avandia.af. (380)
22 1101025-46-8.rn. (0)
23 "peroxisome profilerator activated receptor gamma agonist$".af. (0)
24 "ppar gamma agonist$".af. (155)
25 ad-4833.af. (28)
26 u-72107.af. (9)
27 122320-73-4.rn. (2288)
28 brl-49653.af. (202)
29 97322-87-7.rn. (2728)
30 thiazole$.af. (3003)
31 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (8624)
32 9 and 31 (2315)
33 10 and 31 (2315)
34 limit 33 to (human and english language and yr=1993 - 2005) (1745)
35 from 34 keep 1-1000 (1000)

APPENDIX A (cont'd)

Database: CDSR, ACP Journal Club, DARE, CCTR
Search Strategy:

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1 exp diabetes mellitus/ (3011)
2 exp diabetes mellitus, type II/ (0)
3 (("type 2 diabet:" or "type 2 DM" or diabet:) adj2 "type 2").af. (1897)
4 (("type II diabet:" or "type II DM" or diabet:) adj2 "type II").af. (3100)
5 NIDDM.af. (971)
6 "non insulin dependent diabet:".af. (1538)
7 "adult onset diabet:".af. (60)
8 3 or 4 or 5 or 6 or 7 (4188)
9 1 and 8 (837)
10 2 or 9 (837)
11 exp pioglitazone/ (0)
12 exp rosiglitazone/ or exp metformin plus rosiglitazone/ (0)
13 2,4 thiazolidinedione derivative/ (0)
14 pioglitazon$.af. (58)
15 rosiglitazon$.af. (92)
16 exp troglitazone/ (0)
17 troglitazon$.mp. (138)
18 exp thiazolidinedione/ (0)
19 thiazolidinedion$.af. (225)
20 actos.af. (3)
21 avandia.af. (5)
22 1101025-46-8.rn. (0)
23 "peroxisome profilerator activated receptor gamma agonist$".af. (0)
24 "ppar gamma agonist$".af. (6)
25 ad-4833.af. (10)
26 u-72107.af. (0)
27 122320-73-4.rn. (0)
28 brl-49653.af. (0)
29 97322-87-7.rn. (0)
30 thiazole$.af. (620)
31 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (742)
32 9 and 31 (30)
33 10 and 31 (30)
34 10 not 8 (0)
35 8 and 31 (230)
36 limit 35 to yr=1993 - 2004 [Limit not valid in: DARE; records were retained] (228)
from 36 keep 1-228 (228)

APPENDIX A (cont'd)

Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature
Search Strategy:

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1 exp diabetes mellitus/ (16178)
2 exp diabetes mellitus, type II/ (0)
3 (("type 2 diabet:" or "type 2 DM" or diabet:) adj2 "type 2").af. (3630)
4 (("type II diabet:" or "type II DM" or diabet:) adj2 "type II").af. (855)
5 NIDDM.af. (1220)
6 "non insulin dependent diabet:".af. (5027)
7 "adult onset diabet:".af. (79)
8 3 or 4 or 5 or 6 or 7 (6917)
9 1 and 8 (5312)
10 2 or 9 (5312)
11 exp pioglitazone/ (0)
12 exp rosiglitazone/ or exp metformin plus rosiglitazone/ (0)
13 2,4 thiazolidinedione derivative/ (0)
14 pioglitazon$.af. (70)
15 rosiglitazon$.af. (103)
16 exp troglitazone/ (57)
17 troglitazon$.mp. (79)
18 exp thiazolidinedione/ (0)
19 thiazolidinedion$.af. (111)
20 actos.af. (19)
21 avandia.af. (28)
22 1101025-46-8.rn. (0)
23 "peroxisome profilerator activated receptor gamma agonist$".af. (0)
24 "ppar gamma agonist$".af. (6)
25 ad-4833.af. (0)
26 u-72107.af. (0)
27 122320-73-4.rn. (0)
28 brl-49653.af. (2)
29 97322-87-7.rn. (0)
30 thiazole$.af. (4)
31 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (279)
32 9 and 31 (175)
33 10 and 31 (175)
34 limit 33 to (english and yr=1993 - 2005) (175)
35 from 34 keep 1-175 (175)

APPENDIX B Glitazones Systematic Literature Review: Stage 1: Title and Abstract screening

1. Does this article have an ABSTRACT?
Yes
No

2. Is this article in ENGLISH?
Yes (inclusion)
No (exclusion)
Can't tell (inclusion)

3. HUMAN subjects or study participants?
Yes (inclusion)
No (exclusion)
Can't tell (inclusion)

4. Is it a CELL/TISSUE/GENETIC RESEARCH involving diabetes?
Yes (exclusion)
No (inclusion)
Can't tell (inclusion)

5. TYPE OF STUDY used in this article:
Primary (inclusion)
Reviews - analytical e.g. systematic reviews (exclusion)
Reviews - narrative or descriptive (exclusion)
Others, e.g. letters, theses, case reports, editorials, comments, conference reports/proceedings (exclusion)
Can't tell (inclusion)

6. What is the FOCUS OF STUDY in this article?
Mainly Type II Diabetes (inclusion)
Type II and Type I Diabtes (inclusion)
Type II Diabetes and other diseases (inclusion)
Other types of Diabetes e.g. gestational diabetes (exclusion)
Not Type II Diabetes (exclusion)
Can't tell (inclusion)

7. Does the article deal with any of the following in people with Type II Diabetes? Intervention related to these risk factors and complications:
HbA1c (Glycemic Control), Blood Pressure (Hypertension), Total:HDL (cholesterol ratio) Hyperlipidemia/Dyslipidemia, Smoking Status, Cardiovascular Disease, Wound & Foot care, Amputation (Neuropathy), Stroke (Cerebrovascular Disease), Diet & Nutrition (Obesity), Renal Impairment/Failure (Nephropathy), Ischemic Heart Disease (Angina), Myocardial Infarction (Heart Attack), Blindness (Retinopathy), and Congestive Heart Failure (CHF)

Drugs and Non-drugs interventions e.g. Insulin, Educational Programmes, Fitness programmes, etc. (inclusion)
Disease progression - longitudinal/cohort study (inclusion)
Cost (inclusion)
Quality of life (inclusion)
None of the above (exclusion)
Can't tell (inclusion)

8. AGES of subjects or study participants:
Adults i.e. 18 years and over (inclusion)
Children/ Adolescents (exclusion)
Can't tell (inclusion)

APPENDIX B (cont'd) Glitazones Systematic Literature Review: Stage 2: Title and Abstract screening

1. Does the article mention the use of thiazolidinediones (TZDs) (rosiglitzones or pioglitazones), as an intervention? (Note: We are not interested in articles that deal with troglitazones)
Pioglitazones (inclusion)
Rosiglitazones (inclusion)
Glitazones,Thiazolidinediones (TZDs) (inclusion)
Can't tell (inclusion)
None of the above (exclusion)

2. Is there a comparison group mentioned in the study?
Placebo group (inclusion)
Treatment Group(s) (inclusion)
Can't tell (inclusion)
None of the above (exclusion)

3. Study Design:
Randomized controlled trial (inclusion)
Systematic review (inclusion)
Economic evaluation (inclusion)
None of the above (exclusion)
Can't tell (inclusion)

4. Highly specific study population (i.e. patients with renal or coronary artery disease)?
Yes (exclusion)
No (inclusion)
Can't tell (inclusion)

5. Do you think this article should be retrieved?
Yes (inclusion)
No (exclusion)
Can't tell (inclusion)

APPENDIX B (cont'd) Glitazones Systematic Literature Review:
Stage 3: Full text screening

1. Do all the patient's enrolled in the study HAVE type 2 diabetes (i.e. not IGT)?
Yes (inclusion)
No (exclusion)
Can't tell (inclusion)

2. Does the article mention the use of one of the following
Pioglitazones (inclusion)
Rosiglitazones (inclusion)
Neither of the above (exclusion)
Can't tell (inclusion)

3. Is this paper the primary report of the clinical trial data?
Yes (inclusion)
No (exclusion)
Can't tell (inclusion)

4. Is there a comparison group mentioned in the study?
Placebo group (inclusion)
Treatment Group(s) (inclusion)
Neither of the above (exclusion)
Can't tell (inclusion)

5. Are patients truly randomized to treatment groups?
Yes (inclusion)
No (exclusion)
Can't tell (exclusion)

6. Is there a highly specific study population (i.e. renal or coronary artery disease)?
Yes (exclusion)
No (inclusion)
Can't tell (inclusion)

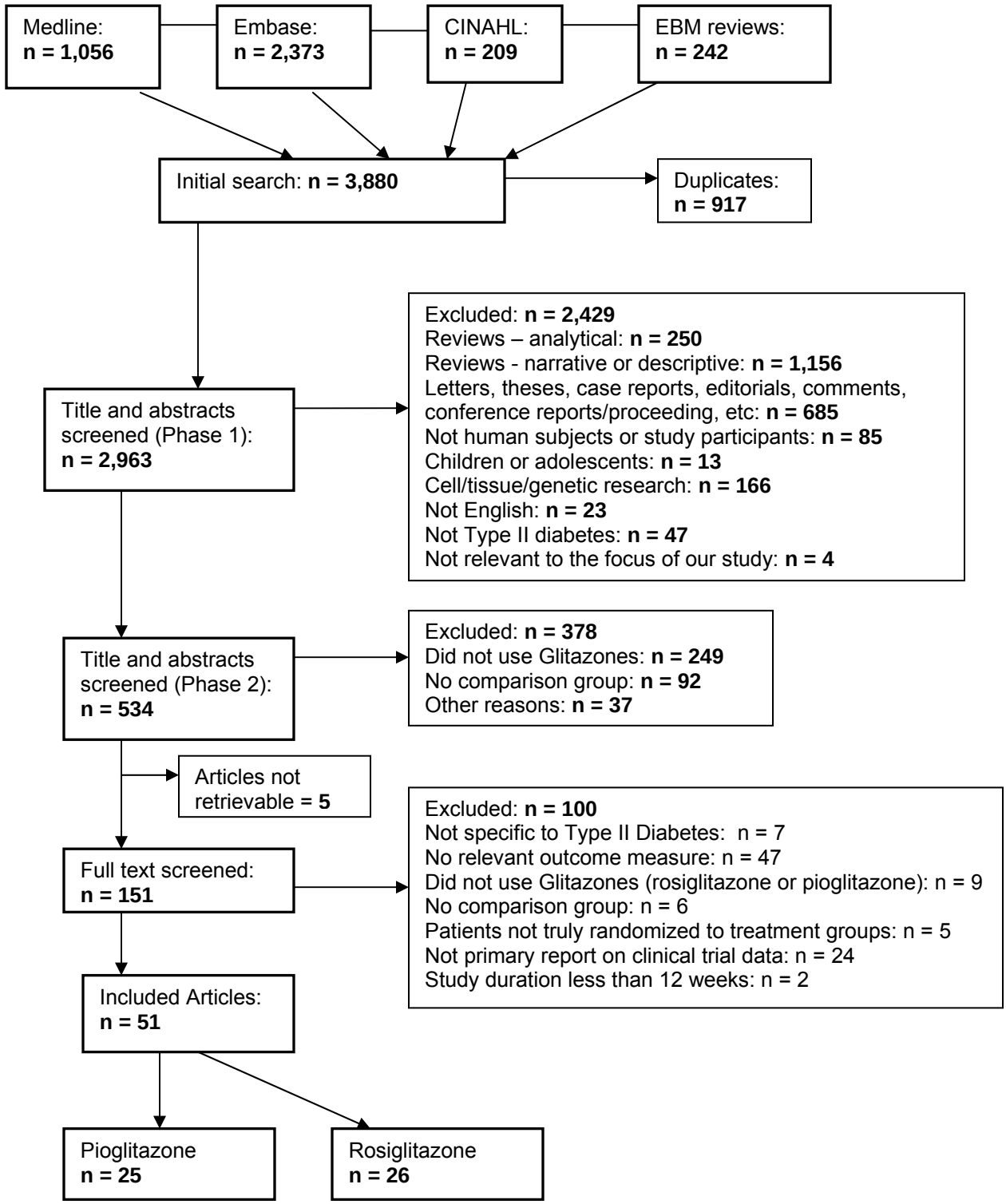
7. What was the duration of the study?
< 12 weeks (exclusion)
>= 12 weeks (inclusion)
Can't tell (inclusion)

8. Is the primary OUTCOME MEASURE at least one of the following?
Glycemic control (HbA1c) - (inclusion)
Blood pressure - (inclusion)
Lipids (cholesterol) - (inclusion)
None of the above - (exclusion)
Can't tell - (inclusion)

APPENDIX C Quality Score for Jadad Scale

CRITERIA	RESULT	SCORING	SCORE
Reported as randomized	☐ YES ☐ NO	1 point for YES	
Randomization is appropriate	☐ YES ☐ NO ☐ NOT DESCRIBED	1 point for YES -1 point for NO	
Double blinding is reported	☐ YES ☐ NO	1 point for YES	
Double blinding is appropriate	☐ YES ☐ NO ☐ NOT DESCRIBED	1 point for YES -1 point for NO	
Withdrawals are reported by number and reason per arm	☐ YES ☐ NO	1 point for YES	
JADAD SCORE			_____ /5

APPENDIX D Flow Diagram of RCTS of Glitazones



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