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Efficacy of Rosiglitazone and Pioglitazone Compared to Other Anti-diabetic Agents: Systematic Review and Budget Impact Analysis

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Efficacy of Rosiglitazone and Pioglitazone Compared to Other Anti-diabetic Agents: Systematic Review and Budget Impact Analysis

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October 2002

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Authorship

Michel Boucher was the principal investigator, and as such was involved in all aspects of the project, including the clinical review and the budget impact analysis. Laura McAuley was the second researcher; she was involved in all aspects of the project related to the review of clinical evidence. Allan Brown was responsible for the budget impact analysis, including its design and the write-up of the budget impact analysis. Erin Keely was the clinical content expert. She provided content information on all aspects of the project and critically reviewed all drafts. Becky Skidmore was responsible for the design and execution of the literature search strategies, for writing the methods section and associated appendix on literature searching, and for verifying and formatting bibliographic references.

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Disclosure of Conflicts of Interest

None reported.

REPORT *IN BRIEF*

October 2002

Efficacy of Rosiglitazone and Pioglitazone Compared to Other Anti-diabetic Agents: Systematic Review and Budget Impact Analysis

Technology Name

Rosiglitazone (Avandia™)
Pioglitazone (Actos™)

Disease/Condition

Diabetes mellitus is a serious disease characterized by an increase in blood glucose. It is estimated that more than one million Canadians over 12 years of age suffer from this condition. Type 2 diabetes is the most common form and affects 90% of persons with diabetes. Serious long-term complications can develop that affect the eyes, kidneys, nerves and blood vessels.

Technology Description

Rosiglitazone and pioglitazone are members of the newest class of oral anti-diabetic drugs called thiazolidinediones. Troglitazone, the first thiazolidinedione derivative developed, was removed from the US market in 2000 because of concerns with liver toxicity.

The Issue

Thiazolidinediones decrease blood glucose levels through a new mechanism of action and appear to address insulin resistance, a key problem in type 2 diabetes. However, they are significantly more costly than existing drugs and patients must be monitored for liver problems. Therefore, there is a need to compare the efficacy and safety of these drugs with other anti-diabetic drugs.

Assessment Objectives

1. To evaluate the evidence that compares rosiglitazone or pioglitazone with other oral anti-diabetic agents (including insulin), either when used alone or when added to a non-thiazolidionedione agent in the treatment of type 2 diabetes.

2. To determine the impact of listing thiazolidinediones on the budget of provincial drug plans in Canada.

Methodology

In this systematic review, only randomized controlled trials comparing the efficacy of rosiglitazone or pioglitazone with other anti-diabetic agents were selected from a broad literature search. Primary outcome measures were fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c). A total of 19 relevant trials were found, 11 rosiglitazone and eight pioglitazone trials. The observation period for most studies was 52 weeks or less.

A budget impact analysis was used to determine the impact of listing rosiglitazone and pioglitazone on the formularies of publicly-funded drug plans in Canada.

Conclusions

- When used alone, both rosiglitazone and pioglitazone have effects similar to comparator drugs on HbA1c and FPG, based on the findings from a small number of comparative trials.
- When added to another anti-diabetic agent, the effect on HbA1c and FPG is significantly greater than continuing therapy with the other anti-diabetic agent alone. This is consistent with the work of others that shows combining two anti-diabetic agents provides a greater effect than using one alone.
- Both drugs were generally well tolerated during the trials reviewed; only a few cases of heart failure and severe hypoglycemia (when added to another agent) were reported. No liver toxicity was observed. Long-term trials are required to evaluate their effect on the development of diabetic complications and long-term safety.
- Based on the budget impact analysis, it is estimated that by 2004, if rosiglitazone and pioglitazone receive formulary listing throughout Canada, the net expenditure for the publicly-funded drug programs would increase nationally between $11.8 and $88.5 million per year, depending upon their utilization and the number of patients treated.

This summary is based on a comprehensive health technology assessment report available from CCOHTA's web site (www.ccohta.ca): Boucher M, McAuley L, Brown A, Keely E, Skidmore B. **Efficacy of rosiglitazone and pioglitazone compared to other anti-diabetic agents: Systematic review and budget impact analysis**.

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EXECUTIVE SUMMARY

Background

Diabetes mellitus is a metabolic disorder characterized by the presence of high blood glucose (hyperglycemia) and is caused by a decrease in the secretion of insulin, a decrease in insulin action, or both. It is associated with significant long-term complications involving the eyes, kidneys, nerves and blood vessels. There are two main types of diabetes mellitus: type 2 diabetes is the more prevalent form, affecting approximately 90% of persons with diabetes. Rosiglitazone and pioglitazone are members of a relatively new class of orally administered drugs for type 2 diabetes called thiazolidinediones.

Objectives

1) To perform a systematic review of the clinical trials that compare rosiglitazone or pioglitazone, either as monotherapy or add-on therapy for the treatment of type 2 diabetes with other oral anti-diabetic agents: alpha-glucosidase inhibitors (acarbose), biguanides (metformin), carbamoyl benzoic acid derivatives (repaglinide) and, sulphonylureas (chlorpropamide, gliclazide, glyburide, tolbutamide). Add-on therapy with insulin was also considered in this review.
2) To perform a budget impact analysis projecting costs associated with the introduction of thiazolidinediones in Canada.

Clinical Efficacy

Methods: MEDLINE®, EMBASE®, HealthSTAR, PASCAL, SciSearch and Toxline® were searched. Retrieval was limited to the publication years 1990 to 2001 with no language restriction. Database alerts/updates were established on several databases. Manufacturers of the two drugs under examination were invited to submit information. Selection criteria were developed and study selection and data extraction were performed in duplicate by independent reviewers. Only randomized controlled trials were considered for inclusion. The main clinical outcomes considered were fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c). A number of secondary outcomes were considered, including cholesterol and triglyceride levels.

Results: A total of 11 rosiglitazone trials and eight pioglitazone trials met selection criteria. Compared to monotherapy with a non-thiazolidinedione agent, there was no statistically significant difference in the reduction of HbA1c with rosiglitazone but there was a statistically significant larger decrease in FPG. When added to another anti-diabetic agent, rosiglitazone caused statistically significant larger decreases from baseline in HbA1c and FPG of 1.3% and 2.8 mmol/l, respectively, compared to continuing monotherapy with a non-thiazolidinedione agent. Also, rosiglitazone produced a statistically significant larger increase from baseline in total-cholesterol, LDL-cholesterol and HDL-cholesterol levels compared to other anti-diabetic agents. There was no statistically significant difference in triglyceride levels.

Compared to monotherapy with another anti-diabetic agent, pioglitazone caused a statistically significant smaller decrease in HbA1c but there was no statistically significant difference in FPG. When added to a non-thiazolidinedione drug, pioglitazone caused statistically significant larger decreases from baseline in HbA1c and FPG of 1.3% and 2.9 mmol/l, respectively, compared to continuing monotherapy with a non-thiazolidinedione agent. Pioglitazone also caused a statistically significant larger increase from baseline in HDL-cholesterol levels, compared to other anti-diabetic agents. No statistically significant differences were observed for total and LDL-cholesterol levels while there was a statistically significant decrease from baseline in triglyceride levels.

Both rosiglitazone and pioglitazone were generally well tolerated during the trials reviewed. No serious liver adverse events were reported. Weight gain, edema, hypoglycemia, and mild decreases in hemoglobin, hematocrit and blood pressure were observed. Only a small number of serious adverse events such as heart failure (HF) and severe hypoglycemia (when added to another agent) were reported. The combination of insulin and a thiazolidinedione was associated with the highest occurrence of edema and hypoglycemia.

Budget Impact Analysis

Methods: The primary focus of the budget impact analysis was to determine the impact on drug expenditures of oral anti-diabetic agents. The perspective taken was that of a provincial drug plan. The analysis was based on a range of estimated proportions of patients with type 2 diabetes requiring optimization of their treatment in a given year (1%, 2.5%, 5%, 7.5%), either by switching from an orally administered non-thiazolidinedione agent to a thiazolidinedione or by adding a thiazolidinedione to another oral anti-diabetic agent. A database in use at the Patented Medicine Prices Review Board (PMPRB) was used in the analysis.

Results: The introduction of rosiglitazone and pioglitazone in Canada is expected to increase drug expenditures for provinces and territories. Assuming rosiglitazone and pioglitazone receive formulary listing in all provinces and territories, it was estimated that provincial drug plan expenditures for Canada as a whole will increase in 2004 by $11.8 million, $29.5 million, $59 million or $88.5 million, based on the four switching-to or adding-on scenarios (1%, 2.5%, 5%, 7.5%).

Conclusions

When used as monotherapy, both rosiglitazone and pioglitazone have an effect on HbA1c and FPG similar to the effect observed with non-thiazolidinedione comparator drugs. These findings are, however, based on a small number of comparative trials. Evidence available about the comparative efficacy of add-on therapy is somewhat more substantial but still limited. It shows that, when rosiglitazone or pioglitazone is added to another anti-diabetic agent in patients with type 2 diabetes not well controlled on a single agent, both thiazolidinediones produce a significantly greater effect on HbA1c and FPG than continuing monotherapy with the other agent. These findings are consistent with the work of others that show combining two anti-diabetic agents provides greater effect than using one alone. However, longer-term studies will be required to evaluate the effect of rosiglitazone and pioglitazone on the development of diabetic complications as well as to assess their long-term safety. Both rosiglitazone and

pioglitazone were generally well tolerated in the trials reviewed and no serious liver adverse events were reported. However, our safety assessment was limited to 4,396 patients and most were followed for less than one year. Recently, both Health Canada and the US FDA released a safety reminder about the risk of using these drugs in patients with HF.

Based on our budget impact analysis, it is estimated that by 2004, if rosiglitazone and pioglitazone receive formulary listing throughout Canada, addition of these drugs would result in a net expenditure increase for the publicly funded drug programs varying between $11.8 and $88.5 million per year, depending on their utilization and the number of patients treated.

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ABBREVIATIONS

ADA:	American Diabetes Association
AGI:	alpha-glucosidase inhibitors
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATC:	Anatomical Therapeutic Chemical
BMI:	body mass index
CBC:	complete blood count
CBA:	carbamoyl benzoic acid
CI:	confidence interval
DBP:	diastolic blood pressure
DDD:	defined daily dose
DIN:	drug identification number
DM:	diabetes mellitus
FDA:	Food and Drug Administration (US)
FPG:	fasting plasma glucose
F/P/T:	federal/provincial/territorial
HbA1c:	glycosylated hemoglobin
HCT:	hematocrit
HDL-C:	high-density-lipoprotein cholesterol
HF:	heart failure
Hgb:	hemoglobin
IN:	insulin
ITT:	intent-to-treat
LDL-C:	low-density-lipoprotein cholesterol
MDD:	mean daily dose
MET:	metformin
MoH:	ministry of health
NHS:	National Health Service
NICE:	National Institute for Clinical Excellence
NIHB:	Non-insurance Health Benefits
NYHA:	New York Heart Association
PAI-1:	plasminogen-activator inhibitor type 1
PIO:	pioglitazone
PLB:	placebo
PMPRB:	Patented Medicine Prices Review Board
PPARγ:	peroxisome proliferator-activated receptor gamma
RBC:	red blood cells
RRR:	relative risk reduction
RSG:	rosiglitazone
SBP:	systolic blood pressure
SD:	standard deviation
SE:	standard error
SU:	sulphonylurea
T-C:	total cholesterol
TG:	triglyceride

TNF-α: tumour necrosis factor
UKPDS: United Kingdom Prospective Diabetes Study
VIT: vitamin
WMD: weighted mean difference

1 INTRODUCTION

1.1 Background

1.1.1 Diabetes mellitus

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia. This hyperglycemia is caused by a decrease in the secretion of insulin, a decrease in insulin action or both. It is associated with significant long-tem complications involving the eyes, kidneys, nerves, and blood vessels.[1,2]

It is currently estimated that between 1.2 and 1.4 million Canadians aged 12 years and over have diabetes, although only 800 000 people have actually been diagnosed.[3] Other estimations suggest that in 2000, there were 2.2 million persons with diabetes in Canada and that by 2010, this number will reach 3 million.[1] In 1996, there were 5,447 deaths for which diabetes was documented as the underlying cause. This ranks diabetes as the seventh leading cause of death in Canada. It has been estimated however that the number of deaths for which diabetes was a contributing factor may be as much as five times higher.[3]

Since 1979, the National Diabetes Data Group has classified diabetes mellitus based on its clinical presentation. Type 1 diabetes was formerly called insulin dependent or juvenile-onset diabetes. Type 2 diabetes is now the accepted term for non-insulin dependent or adult-onset diabetes.[1,4]

Type 1 diabetes: affects about 5 to 10% of the population diagnosed with diabetes.[5] It is primarily due to destruction of pancreatic beta-cells. This usually leads to absolute insulin deficiency.[1]

Type 2 diabetes: is the more prevalent form, affecting approximately 90% of people suffering from diabetes.[5] This condition mainly results from insulin resistance with a relative (rather than absolute) defect in the secretion of insulin.[1,6]

Insulin resistance is a condition in which peripheral tissues show reduced sensitivity to the effects of insulin-stimulated glucose uptake.[7] This leads to hyperglycemia. In response, the pancreas produces more insulin, resulting in a state of hyperinsulinemia. Epidemiological studies suggest that insulin or insulin resistance may have a direct role in the development of atherosclerosis.[7]

1.1.2 Complications

Diabetes is a serious condition and patients with this disease are at risk for greater morbidity and mortality relative to the population without diabetes.[5] Most of the morbidity and mortality associated with type 2 diabetes is attributable to the chronic complications of diabetes.[5,8] There are two major categories of chronic complications, microvascular and macrovascular.[5]

Microvascular: complications are specific to diabetes mellitus and involve the eye (retinopathy), the kidney (nephropathy) and the nervous system (neuropathy). Clinical consequences can be blindness, renal failure and foot problems, with risk of amputation.[8]

Macrovascular: complications are not specific to diabetes, although they occur more frequently in patients affected by this condition. The main large vessels that are involved are those supplying the heart (cardiovascular disease), the brain (cerebrovascular disease) and the legs (peripheral vascular disease). Clinically, these translate into heart attack, stroke and gangrene.[8]

1.1.3 Treatment

There are currently five different classes of oral anti-diabetic agents available in Canada for the treatment of type 2 diabetes mellitus:[9]

- alpha-glucosidase inhibitors (AGI) (e.g. acarbose)
- biguanides (e.g. metformin)
- carbamoyl benzoic acid (CBA) derivatives/meglitinides (e.g. repaglinide)
- sulphonylureas (SU) (e.g. chlorpropamide, gliclazide, glyburide, tolbutamide)
- thiazolidinediones (e.g. pioglitazone, rosiglitazone).

According to the 1998 Canadian clinical guidelines for the management of diabetes,[1] the main goal of therapy is to prevent acute and long-term diabetic complications. For most people with diabetes, improving glycemic control will prevent the onset or delay the progression of long-term microvascular complications. This was confirmed in 1998 by the United Kingdom Prospective Diabetes Study (UKPDS). Over a 10 year period, 3,867 participants who had recently been diagnosed with type 2 diabetes were randomly assigned to intensive therapy with sulphonylurea or insulin versus conventional treatment with diet. Hemoglobin A1c (HbA1c) was 7% in the intensive group compared to 7.9% in the conventional group, which represented an 11% relative risk reduction (RRR) at study endpoint. Compared with the conventional group, intensive therapy was associated with a 12% RRR of any diabetes-related endpoint, a 10% RRR of any diabetes-related death; and a 6% RRR of all-cause mortality. In the intensive therapy group, there was a 25% RRR in microvascular complications and there was no increase in macrovascular complications. However, this group was associated with an increased rate of hypoglycemic episodes and weight gain compared to conventional therapy.[10]

A separate part of the UKPDS study assessed the effect of adding metformin to diet-treated, overweight patients with type 2 diabetes. HbA1c decreased from 8% to 7.4%, compared to conventional treatment (diet alone). Metformin intensive therapy was associated with a 32% RRR of any diabetes-related endpoints, a 42% RRR of diabetes-related death, and a 36% RRR for all cause mortality. There was also a 39% RRR in myocardial infarction. Compared to sulphonylurea or insulin therapy, metformin did not induce weight gain and was associated with fewer hypoglycemic episodes. In a supplementary study, non-overweight and overweight patients on a maximum dose of sulphonylurea were allocated to sulphonylurea monotherapy or addition of metformin. A significant increase in a risk of diabetes-related death and all cause mortality was observed in patients on the combination therapy. However, epidemiological

assessment of the possible association of diabetes-related death in patients on the sulphonylurea/metformin combination did not corroborate these results.[11]

In summary, epidemiological analysis of the data from the UKPDS study showed that there was a 35% reduction in the risk of diabetic microvascular complications for every percentage point reduction in HbA1c.[5]

The Canadian guidelines recommend non-pharmacological therapy such as diet and physical activity as the first step. If targeted serum glucose levels are not achieved within two to four months, then monotherapy with one of the available oral anti-diabetic agents is recommended.[12] Metformin is recommended as initial therapy for obese patients with type 2 diabetes. Other oral agents may be considered as alternatives if the use of metformin is contraindicated.[1,12] Combination therapy is recommended after two to four months of monotherapy, if satisfactory control is not reached. Finally, insulin therapy is introduced as a last step, either in combination with oral anti-diabetic agents or as monotherapy.[1]

1.1.4 Cost

Diabetes is costly. In Canada, the economic burden of this disease, including its complications, is estimated to be over C$13 billion. This estimate incorporates both direct health care costs and indirect costs, including lost productivity due to diabetes-related illness and premature death.[3] In 1997, in the United States (US), the annual per capita health care expenditures for people with diabetes were about 3.8 times those for individuals without diabetes.[5]

1.2 Technology Overview

Thiazolidinediones are the newest class of drugs introduced to clinical practice for the treatment of type 2 diabetes. There are currently two thiazolidinediones available in Canada. Rosiglitazone (Avandia™ – GlaxoSmithKline) is approved for use either as monotherapy or combination therapy with metformin or a sulphonylurea.[13] Pioglitazone (Actos™ – Eli Lilly) is only approved in Canada for monotherapy.[14] Troglitazone, the first thiazolidinedione derivative developed, was never marketed in Canada.[9] This product caused significant hepatotoxicity, leading to death.[15] Pioglitazone and rosiglitazone are thought to be free from this type of toxicity.[15] However, since their introduction in 2000, three cases of possible rosiglitazone-induced hepatotoxicity[16-18] as well as two cases of hepatocellular injury possibly linked to pioglitazone therapy[19,20] have been reported.

The glucose-lowering effect of thiazolidinediones is related to their ability to enhance insulin sensitivity.[15] Although the mechanism of action is not yet fully understood, it is thought that thiazolidinediones reduce insulin resistance by activating the peroxisome proliferator-activated receptor gamma (PPARγ), resulting in increased glucose transport into cells in adipose tissue, but also in muscle, liver and other tissues.[7] The stimulatory effect of thiazolidinediones results in an increase in the number of adipocytes, which explains in part the weight gain and reduction in free-fatty acid levels observed with thiazolidinedione therapy.[15] This stimulatory effect may also contribute to an improvement in insulin sensitivity, along with other peripheral actions such as

increased hepatic glucose disposal, decreased hepatic glucose production and reduction of tumour necrosis factor (TNF)-α.[7] Thiazolidinediones have also been shown to have non-glycemic effects, such as alteration of serum lipid profiles and blood pressure.[7,15] Decreased production of plasminogen-activator inhibitor type 1 (PAI-1), which may increase fibrinolytic activity and potentially have a positive cardiovascular impact, has also been reported with troglitazone. It has been suggested that this same effect could possibly explain the positive effect of metformin on cardiac ischemia.[11] Safety concerns with these drugs include hepatotoxicity,[5,7,15] edema,[5,7,15] weight gain,[7,15] and anemia.[5,15]

Because the pathogenesis of type 2 diabetes involves impaired insulin secretion, decreased muscle glucose uptake and increased hepatic glucose production, all five classes of oral anti-diabetic drugs currently available are effective.[15] They work by one or more of the following four mechanisms of action:

i) increased insulin secretion from the pancreas (SU, CBA derivatives);[15]
ii) improved insulin-mediated glucose uptake by peripheral tissues, therefore reduced insulin resistance (biguanides and thiazolidinediones);[15]
iii) decreased hepatic glucose production (biguanides and thiazolidinediones);[15]
iv) slowed absorption of starch and sucrose in the gut (AGI).[1]

The selection of one particular agent over another one will depend on patient characteristics, the safety profile of the drug as well as cost considerations. For example, metformin is contraindicated in patients with decreased renal or liver function.[1] However, it is the preferred agent in overweight individuals.[12]

Thiazolidinediones are a novel group of compounds that act as insulin sensitizers in peripheral tissues. Their mechanism of action appears to address insulin resistance, a key metabolic problem in type 2 diabetes. However, the higher cost of treatment and the requirement to monitor for liver toxicity should be considered to best define the role of these drugs in the treatment of type 2 diabetes.[21] Accordingly, there is a need to compare the efficacy and safety of thiazolidinediones with other anti-diabetic drugs in the treatment of type 2 diabetes.

2 OBJECTIVES

The purpose of this study is to provide evidence-based information on the comparative efficacy and safety of rosiglitazone and pioglitazone for the treatment of type 2 diabetes mellitus. A class effect for thiazolidinediones was not considered due to possible differences in efficacy and safety between rosiglitazone and pioglitazone.

Specifically, the objectives of this systematic review are:

1. To perform a systematic review of the clinical trials that compare pioglitazone or rosiglitazone, either as monotherapy or as add-on therapy for the treatment of type 2 diabetes with other oral anti-diabetic agent(s):

    - alpha-glucosidase inhibitors (acarbose);
    - biguanides (metformin);
    - carbamoyl benzoic acid derivatives/meglitinides (repaglinide); and
    - sulphonylureas (chlorpropamide, gliclazide, glyburide, tolbutamide).

    Add-on therapy with insulin was also considered for this review, since insulin has been used in combination with oral anti-diabetic agents for the treatment of type 2 diabetes.[9]

    The term "add-on" therapy is preferred to "combination therapy" in the context of this review as most combination therapy trials compared non-thiazolidinedione-based monotherapy with non-thiazolidinedione agent + "add-on" thiazolidinedione combination therapy.

2. To perform a budget impact analysis for the introduction of thiazolidinediones in Canada. The perspective taken was that of a provincial drug plan.

3 CLINICAL EFFICACY

3.1 Methods

3.1.1 Literature search

Published literature was obtained by searching a number of databases (Appendix 1). On the DIALOG® system, MEDLINE®, EMBASE®, HealthSTAR, PASCAL, SciSearch and Toxline® were searched, limiting retrieval to the publication years 1990 to 2001 with no language restrictions. Database alerts/updates were established on Adis LMS Drug Alerts, Current Contents Search®, EMBASE® Alert, MEDLINE®, PASCAL, Pharmaceutical News Index (PNI®), and SciSearch; the Current Contents Search® and SciSearch alerts were discontinued August 2001. Searches were performed and updated on the CD ROM versions of The Cochrane Library. Web sites of regulatory agencies, health technology assessment and near-technology assessment agencies were also searched, as were specialized databases, such as the University of York NHS Centre for Reviews and Dissemination. The Google™ search engine was used to search for a variety of information on the Internet. The bibliographies of selected papers were searched. In addition, manufacturers of the two thiazolidinediones available in Canada [Eli Lilly – Actos™ (pioglitazone) and GlaxoSmithKline – Avandia™ (rosiglitazone)] were contacted to obtain copies of each product monograph. Manufacturers were also invited to submit any relevant information (published or unpublished).

3.1.2 Data retrieval

Two researchers (MB and LM) independently reviewed the results of the database literature search. References that could potentially be used in the review were ordered for more detailed evaluation. These were identified based on the title and the abstract. Studies that met the inclusion criteria for the review were set aside for data abstraction. Recent review articles on thiazolidinediones and/or type 2 diabetes were ordered for hand searching of their bibliographies. This was done independently by two reviewers (MB and LM). Information received from the manufacturers was reviewed by the principal investigator (MB) in order to identify any references that could potentially be used in the current review. These were then photocopied and independently reviewed by the two reviewers (MB and LM) to identify potentially relevant studies. Finally, database alerts were scanned by a single reviewer (MB) to identify potentially relevant studies or review articles. These were then ordered for independent assessment by the two reviewers (MB and LM).

3.1.3 Study inclusion criteria

Types of participants: Adult patients (i.e. > 18 years of age) with type 2 diabetes mellitus requiring drug therapy.

Types of interventions: Rosiglitazone or pioglitazone, either used as monotherapy or add-on therapy to a non-thiazolidinedione drug, with other anti-diabetic agents (as defined in 2.1).

Outcomes of interest:

Primary outcomes:
i) fasting plasma glucose (FPG);
ii) glycosylated hemoglobin (HgA1c)

Secondary outcomes:
i) iserum lipid profiles: total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density-lipoprotein (LDL)-cholesterol, triglyceride;
ii) hematological parameters: hemoglobin (Hgb), hematocrit (Hct);
iii) liver function tests: alamine aminotransferase (ALT), aspartate aminotransferase (AST);
iv) hypoglycemia (severity of symptoms and withdrawals); and
v) other relevant parameters: weight, blood pressure (diastolic, systolic), edema

Types of studies: Randomized controlled trials (RCTs) investigating the efficacy of rosiglitazone or pioglitazone in type 2 diabetes were considered for this systematic review. Because we were aware *a priori* of the availability of a number of RTCs, it was not necessary to consider the inclusion of non-randomized studies.

3.1.4 Data abstraction and quality assessment

A data abstraction form was developed by the two clinical reviewers (MB and LM) with input from the clinical co-author (EK) (Appendix 2). The two clinical reviewers (MB and LM) independently completed the data abstraction form for each study. Once the initial data abstraction was completed, the two reviewers met and went through each study to ensure agreement. Units for all outcomes not expressed in SI units were converted to SI units using standard equations.[22] When mean changes in weight were expressed in terms of body mass index (BMI), conversion to weight values was done using the standard equation for BMI,[23] assuming an average adult height of 1.7 meters. In cases where data of interest were not reported, the data were computed where possible, or requests for the information were sent to the authors of the publications.

When a study compared two different doses of a thiazolidinedione treatment against one dose of a non-thiazolidinedione treatment, the higher thiazolidinedione dose was selected in order to avoid duplicating the sample size of the control group. It should be noted that by pooling the higher dose, this may have resulted in a larger effect size for the thiazolidinedione group. This issue is addressed in the interpretation of the results.

In addition to the data extraction form, each study was independently rated for quality using the Jadad scale (Appendix 3). This instrument is composed of three items related directly to the reduction of bias (randomization, double blinding, and study withdrawals and dropouts). A score is given for each of the three items, for a maximum of five points. Allocation concealment is also considered in the assessment with ratings of adequate, unclear and inadequate.[24] Prior to initiating the assessment of quality, the two clinical reviewers (MB and LM) underwent a training exercise, independently rating five studies unrelated to the current review. This was done to ensure that both reviewers had a common understanding of the scale.

3.1.5 Statistical analysis

All data extracted for this review were continuous. Review Manager 4.1 was used for pooling the data. The intent-to-treat (ITT) results were used for the analysis. If these data were not available, only the results for evaluable subjects were used. If the publication did not specify whether the statistical analysis was by ITT, this was assumed to be the case. When the mean difference from baseline to endpoint was directly available, along with the standard deviation (SD), it was directly extracted from the publication and entered into Review Manager 4.1. When the mean difference from baseline was available, but the measure of dispersion for the mean difference from baseline was provided in terms of standard error (SE), the SD was calculated using the standard equation for the SE.[25] When 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 SD was calculated using the standard equation for the 95% CI.[25] When the level of significance was based on a p value for the mean difference from baseline, the SD was calculated from the standard equation for the p value.[25] 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 extracted from standard "t" Distribution and "z" Distribution tables.[25] Tests were assumed to be two-sided.

When the mean difference from baseline was expressed in terms of percent change from baseline, 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% CI, also expressed in percent change. The conversion to the absolute value for the lower and higher 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.

A limited number of mean difference values were expressed as median difference, specifically for the lipid profile. Because the majority of the studies reviewed reported serum lipid parameters in terms of mean values, it was assumed that the "lipid parameter population" had a normal distribution, in which case the mean and the median values should be relatively close to one another. Therefore, the use of the median value, instead of the mean value, was assumed to be a preference of the authors of the study, rather than a methodological requirement. Consequently, we planned to substitute the median value for the mean value for the purpose of pooling the data. However because most of the parameters expressed as median change from baseline did not have an associated measure of dispersion, such parameters were only pooled from one trial and these were limited to LDL-cholesterol levels.[26]

For each outcome of interest for which data were pooled, Review Manager 4.1 performed a Chi – square test for assessing the level of statistical heterogeneity between the different studies combined. As per current recommendations, statistical heterogeneity was defined as a significance level of 10% to account for the low power of the tests,[27] although the more

traditional significant level of 5% has also been suggested.[28] Because statistical heterogeneity was detected in some of the pooled estimates, the random effect model was used for all endpoints, irrespective of the result of the Chi-square test of heterogeneity.

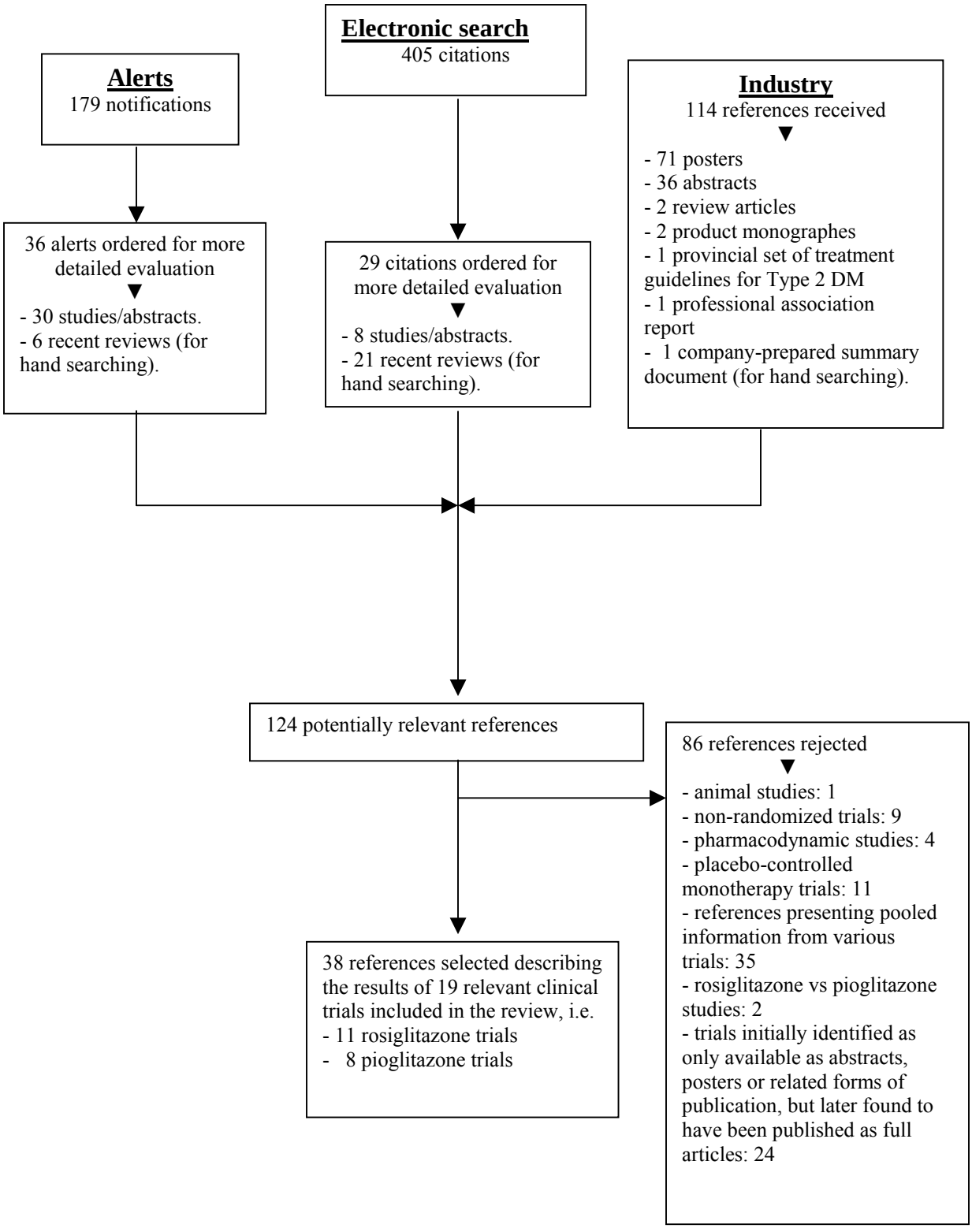
3.2 Results

3.2.1 Quantity and quality of research available

A total of 405 citations were identified by the electronic literature search. From these, 29 citations were ordered for more detailed evaluation, i.e. 21 review articles and eight trials. The bibliographies of the review articles were screened for potentially relevant studies. This lead to ordering 12 additional review articles, nine trials, three abstracts, three case reports, two letters and one editorial. In addition, a total of 71 posters, 36 abstracts, two review articles, two product monographs, one professional association report, one company-prepared summary document and, one provincial set of guidelines for the treatment of type 2 diabetes mellitus were received from the two drug manufacturers. As of January 1, 2002, a total of 179 alert notifications were received. Of these, 36 were ordered for more detailed evaluation, i.e. 30 trials and abstracts and six recent review articles for hand searching, including the full supplement issue of Diabetes[29] containing the proceedings of the 61st Scientific Sessions of the American Diabetes Association (ADA).

Only trials were considered as potentially relevant studies. The other references were either rejected or used in the discussion section. Reasons for not considering electronic search citations and other preliminary sources of information as potentially relevant references included: animal studies, non-randomized studies, non-rosiglitazone/pioglitazone comparative studies, pediatric studies, pharmacodynamic studies (unless relevant clinical outcomes as endpoints), pharmacokinetic studies, placebo-controlled monotherapy studies, toxicology studies.

SUMMARY OF LITERATURE SEARCH RESULTS



Similar to the approach recommended in the QUOROM statement,[30] the flow chart above depicts the sources of information used, the number of potentially relevant references retrieved, the number of excluded references, the reasons for exclusion, and the number of references ultimately included in the review. A total of 124 potentially relevant references were identified through the search process. Of these, 86 were excluded because they did not meet the pre-determined inclusion criteria described previously in Section 3.1.3. These references are listed in Appendix 4. Thirty eight references describing the results of 19 trials were selected for the systematic review, i.e. 11 for rosiglitazone and eight for pioglitazone. This indicates that, for some trials, results were presented several times under different formats. This appears to have been the case especially for trials not yet published. Reviewers spent a lot of time carefully assessing each relevant reference to match each to a specific trial. There was no disagreement between the two reviewers deciding which potentially relevant studies met the inclusion criteria to be included as relevant studies for data abstraction. There was also no disagreement regarding the quality score assigned to each of the included trials.

Two Japanese studies met our inclusion criteria.[31,32] One of them, Kaneko and colleagues[31] was published in Japanese. A Japanese collaborator, Professor Akinori Hisashige, MD, PhD (University of Tokushima, Japan) performed data abstraction and quality assessment for this study. Three other potentially relevant studies were also assessed for inclusion in the review by the same collaborator as all were written exclusively in Japanese[33-35] but none met our inclusion criteria.

Since some studies did not provide sufficient information to allow a quantitative comparison to be performed for a number of outcomes, eight clarification letters were sent to study authors. At the time of preparation of this report, only two responses had been received. Requests for clarification were mainly based on the following situations:

i) the mean difference from baseline for the primary outcomes was not available;
ii) the mean difference from baseline for the primary outcomes was available but was not associated with any measure of dispersion;
iii) the mean difference from baseline for the primary outcomes was available but it was not clear whether the measure of dispersion or p value provided was associated with the mean difference from baseline or with the mean difference compared with the control group; or
iv) an important piece of information was missing, for example the units used for the outcome of interest were not specified, e.g. conventional or SI units.

3.2.2 Assessment of clinical efficacy – rosiglitazone

Eleven relevant studies were identified for the rosiglitazone clinical review (three full publications and eight in the form of abstracts and posters) (Table 1).

Table 1: Characteristics of studies included in the analysis rosiglitazone versus other anti-diabetic drugs

Study	Quality Score	Publication Type	Study Length (weeks)	Active Group			Control Group		
				Drug(s)	Dose	N	Drug(s)	Dose	N
Charbonnel et al.*	2/5	Abstracts/ posters	52	RSG	8 mg/d	195	SU[§]	2.5 – 15 mg/d	203
Fonseca et al.[36]	4/5	Journal articles	26	RSG + MET	8 mg/d+ 2.5g/d	113	PLB + MET	2.5 g/d	116
Gomez-Perez et al.[37]	1/5	Abstract	26	RSG+ MET	8 mg/d+ 2.5g/d	36	PLB + MET	2.5 g/d	34
Hallé et al.**	2/5	Abstracts	26	RSG + SU [§]	8 mg/d+ 20 mg/d	56	PLB + SU [§]	20 mg/d	53
James et al.***	2/5	Abstract/ poster	26	RSG + SU[o]	8 mg/d + 160 mg/d	189	SU[o]	320 mg/d	171
Jovanovic et al.****	2/5	poster	24	RSG+ CBA[¥]	4-8 mg/d +1.5-12mg/d	127	CBA [¥]	1.5-12 mg/d	63
Jovanovic et al.****	2/5	Poster	24	CBA[¥]	1.5-12 mg/d	63	RSG	4-8 mg/d	62
Matfin et al.[38]	1/5	Abstract	12	RSG + SU	4 mg/d + usual dose	60[€]	SU	Usual dose	60[€]
Raskin et al.[26]	4/5	Journal article	26	RSG + IN	8 mg/d+ titrate	103	PLB+ IN	Titrate	104
St. John***** Sutton et al.	1/5	Posters	148	RSG	8 mg/d	104	SU[§]	Mean of 10.5 mg/d	99
Wolffenbuttel et al.[39]	2/5	Journal article	26	RSG + SU [†]	4 mg/d+ usual dose	183	PLB + SU [†]	Usual dose	192
Xixing et al.******	2/5	Abstract/ poster	24	RSG+ SU[¶]	8 mg/d+ usual dose	210	PLB+ SU[¶]	Usual dose	105

* five posters and one abstract were identified for the same study[40-44]
** four posters were identified for the same study [45-48]
*** one poster and one abstract were identified for the same study [49,50]
**** one poster was identified for the final results, one abstract for the interim results, the two treatment groups belong to the same study [51,52]
***** six posters and one oral presentation abstract were identified for the same study [53-59]
****** one abstract on efficacy data, one abstract on safety data and one poster were identified for the same study. [60-62]
[§] glyburide [o] gliclazide [¥] repaglinide
[€] initial total sample size N=120 (randomly assigned), intent-to-treat sample size N=119
[†] gliclazide (MDD:185 mg), glibenclamide (MDD:12.6 mg), glipizide (MDD:17 mg)
[¶] 34% on glyburide (MDD:7.5 mg), 25% on gliclazide (MDD:160 mg), others: glipizide, chlorpropamide, tolbutamide and, gliquidone

Two studies assessed monotherapy use, while eight evaluated add-on therapy regimens. One study had three comparison arms, i.e. two monotherapy arms and one combination therapy arm.[51,52] The observation periods for the trials selected varied from 12 to 52 weeks, with the exception of one 148-week open-label trial. In general, the quality of the full publications was rated higher than the quality of the abstracts and the posters. Most participants in these trials did not have satisfactory glycemic control on non-thiazolidinedione monotherapy prior to enrollment.

Primary outcomes

Although 11 studies met the inclusion criteria for the review, not all provided quantitative information to allow an estimate of an effect size. Figure 1 and Figure 2 summarize the quantitative assessment of HbA1c and FPG for the studies for which such an evaluation was possible. When quantitative information was not available, a qualitative evaluation was done.

Monotherapy

Although three studies compared rosiglitazone monotherapy with other anti-diabetic monotherapy regimens, the effect size could only be derived from two studies, as the mean change from baseline ∀ SD was not available for the study undertaken by St. John Sutton and colleagues.[53] This was an open-label 148-week, multicentre, parallel, randomized, active comparison cardiac safety study where rosiglitazone (8 mg/day administered as 4 mg po BID) was compared with glyburide (mean dose: 10.5 mg/day). The secondary outcomes included HbA1c and FPG. From baseline to 52 weeks, rosiglitazone-treated patients showed a statistically significantly greater reduction in FPG compared to glyburide (-3.61 mmol/l vs. -3.11 mmol/l, $p<0.006$). There was however no difference in the reduction of HbA1c (-0.9 ∀ 1.4% in both groups).[59] Interim results at 100 weeks showed that rosiglitazone produced a gradual, sustained reduction in HbA1c from a mean baseline of 9.1% to 7.9%. In comparison, glyburide produced an initial rapid decrease in HbA1c during the first 12 weeks from a mean baseline level of 9.5% to 8.2% and then fluctuated between 8.1% and 8.5% until week 100. Concerning FPG, rosiglitazone and glyburide were reported to have similar temporal responses during the 100 week observation period. At 100 weeks, FPG was lower in the rosiglitazone group, compared to the glyburide group (8.8 mmol/l vs. 9.7 mmol/l).[54]

It was possible to pool the results from two monotherapy studies.[40,51] The first study by Charbonnel and colleagues[40] was a 52-week, randomized, double-blind study of 587 type 2 diabetes patients comparing two different doses of rosiglitazone (4 mg/day and 8 mg/day, in two divided doses) with glyburide (optimal dose titration). Only the 8 mg/day group data was considered in order to avoid duplicating the number of patients in the control group. Glyburide-treated patients had a larger decrease from baseline in HbA1c (-0.72% ∀ 1) compared with the rosiglitazone-treated group (-0.53% ∀ 1.31), although the difference was not statistically significant. The results were reversed for FPG as glyburide produced a smaller decrease from baseline (-1.67 mmol/l ∀ 2.5) compared with the rosiglitazone-treated group (-2.28 mmol/l ∀ 2.6, $p = 0.033$).

The second study was a 24-week, randomized, multicentre, three armed, parallel-group, open-label clinical trial in which 240 participants were recruited.[51,52] Participants were persons with type 2 diabetes with inadequate glycemic control on either sulphonylurea or metformin monotherapy prior to randomization to repaglinide or rosiglitazone-based regimens. Results for the two monotherapy arms comparing rosiglitazone to repaglinide were available for 125 evaluable subjects. Dosage varied from 0.5 to 4 mg per meal (not to exceed 16 mg/day) for repaglinide and from 4 to 8 mg/day for rosiglitazone (Clifford C. Hall, PhD, Novo Nordisk Pharmaceuticals, Princeton, NJ: personal communication, 2002 Jan 15). In this study, HbA1c was reduced more from baseline in the rosiglitazone-treated monotherapy group than in the repaglinide-treated monotherapy group (-0.56% ∀ 1.1 vs. -0.17% ∀ 1.11). The advantage for rosiglitazone was maintained for FPG, although it was somewhat reduced (-3.66 mmol/l∀ 2.93 vs. -3 mmol/l∀ 2.95).

Figure 1

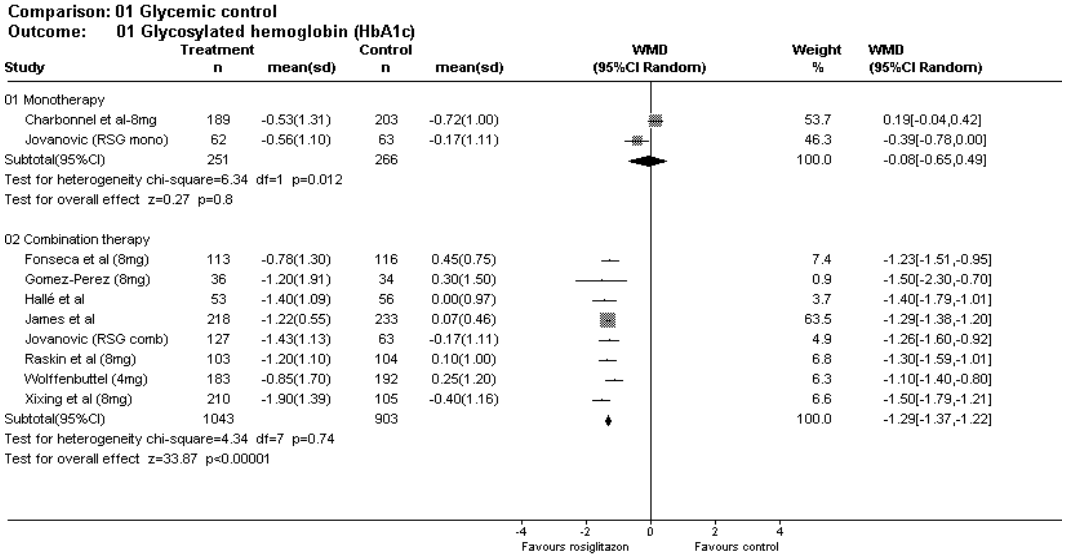
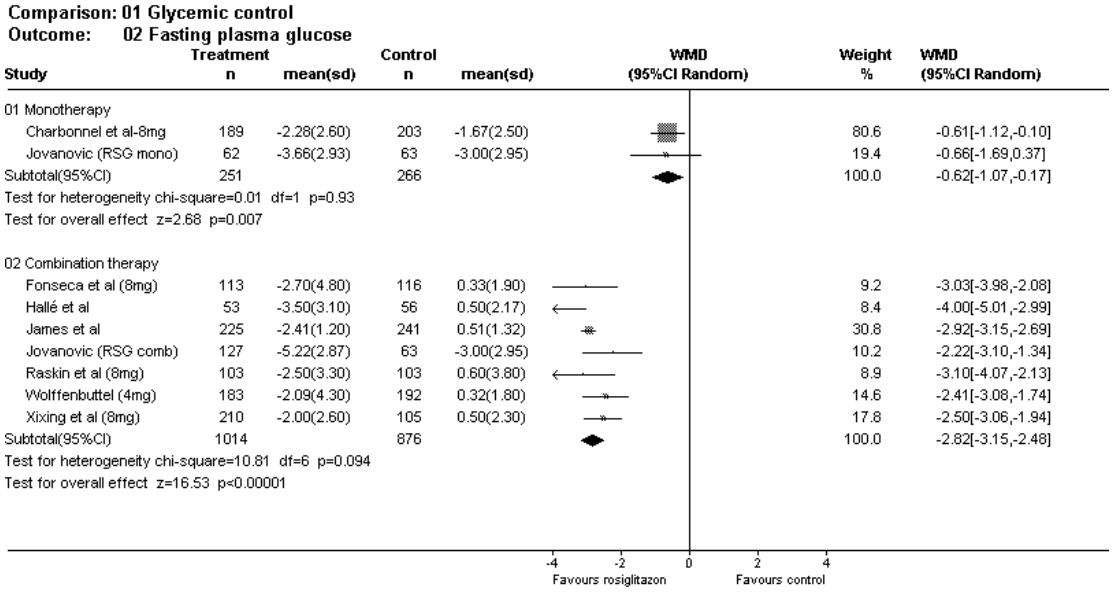


Figure 2



In summary, rosiglitazone monotherapy provided a small and statistically significant decrease from baseline in FPG [WMD: -0.62 mmol/l (95%CI: -1.07, -0.17)] (Figure 2) but a non-statistically significant decrease in HbA1c [WMD: -0.08% (95%CI: -0.65, 0.49)] (Figure 1), compared with monotherapy with either glyburide or repaglinide. Because there was evidence of statistical heterogeneity for the pooled estimate of HbA1c for the monotherapy regimen comparison (Chi-square: 6.34, df: 1, p: 0.012), this value should be interpretated with caution, especially as the results of only two trials were pooled.

Add-on therapy

A total of nine combination therapy studies were included in the analysis, although the estimates of the effect sizes for HbA1c and FPG were based on eight and seven studies, respectively. In all cases, the add-on regimen with rosiglitazone provided better glycemic control than continuing non-thiazolidinedione monotherapy (see Figure 1 and Figure 2).

The study from Fonseca and colleagues was a 26-week randomized, double-blind, placebo-controlled trial comparing subjects with suboptimal glycemic control despite use of metformin 2.5 g/day monotherapy with subjects who used rosiglitazone, in addition to metformin 2.5 g/day.[36] A total of 348 persons with type 2 diabetes were randomized. Two doses of rosiglitazone were tested, 4 mg/day and 8 mg/day. Both add-on regimens provided better glycemic control (mean change from baseline: FPG: -1.8mmol/l ∀ 3.4, -2.7 mmol/l ∀ 4.8 and HbA1c: -0.56% ∀ 1, -0.78% ∀ 1.3 for the 4 mg and 8 mg regimens respectively) than continuing monotherapy with metformin. The 8 mg regimen was associated with a small increase from baseline in glycemic endpoints (FPG: +0.33 mmol/l ∀ 1.9 and HbA1c: +0.45% ∀ 0.75). Statistical analysis was based on the ITT population.

The second study was a recent abstract presented at ADA scientific sessions by Gomez-Perez and colleagues.[37] The design was similar to the study described above, and focused on persons with type 2 diabetes in Mexico. Only HbA1c outcomes were reported and the statistical analysis was based on ITT. Both rosiglitazone dosing regimens (mean change from baseline -0.7% ∀ 1.45, -1.2% ∀ 1.91 for the 4 mg and 8 mg regimens respectively) provided better glycemic control than continuing metformin monotherapy (+0.3% ∀ 1.5).

The third study was a 26-week randomized, double-blind trial comparing a group of patients not adequately controlled with the maximal dose of glyburide monotherapy (20 mg/day) with another group of patients using rosiglitazone 8 mg/day in addition to continuing glyburide 20 mg/day.[45] This North American trial recruited 114 patients with type 2 diabetes from both the US and Canada. To be eligible, participants had to be treated for more than two months prior to study entry with more than half the maximal dose of a sulphonylurea agent. In this study, add-on therapy provided better glycemic control (HbA1c: -1.4% ∀ 1.09, FPG: -3.5 mmol/l ∀ 3.1) than continuing glyburide monotherapy (HbA1c: -0.0% ∀ 0.97, FPG: +0.5 mmol/l ∀ 2.17).

The next study compared the effect of adding rosiglitazone 8 mg/day to gliclazide 160 mg/day (half the usual maximum dose), titrating the dose of gliclazide up to the usual maximum recommended daily dose of 320 mg in patients with type 2 diabetes.[49,50] This was a 26-week, multicentre, double-blind, European study in which 473 patients were randomized; only 367 completed the observation period. There was a significant reduction in mean HbA1c compared to both baseline (-1.2%, $p<0.0001$) and gliclazide monotherapy (-1.3%, $p = 0.0001$). A significant reduction in mean FPG was also observed compared with baseline (-2.4 mmol/l, $p<0.0001$) and gliclazide monotherapy (-3 mmol/l, $p = 0.0001$).

In the only study comparing a CBA derivative to rosiglitazone, Jovanovic and colleagues included a combination therapy arm.[51,52] In this study, results were available for 63 evaluable subjects on repaglinide monotherapy (dose titration range: 0.5 mg to 4 mg/meal – not to exceed

16 mg/day) and 127 evaluable subjects on repaglinide/rosiglitazone combination treatment (dose titration range: repaglinide 0.5 mg to 4 mg/meal – not to exceed 16 mg/day, rosiglitazone: 4 to 8 mg/day) (Clifford C. Hall, PhD, Novo Nordisk Pharmaceuticals, Princeton, NJ: personal communication, 2002 Jan 15). Glycemic control was improved with the combination therapy (HbA1c: -1.43% ∀ 1.13; FPG: - 5.22 mmol/l ∀ 2.87) compared with repaglinide monotherapy (HbA1c: -0.17% ∀ 1.11; FPG: -3 mmol/l ∀ 2.95).

Matfin and colleagues reported the results of a 12-week, multicentre, randomized, open-label study where a total of 120 patients with type 2 diabetes were recruited in India (ITT population = 119).[38] Patients were to either continue their usual sulphonylurea monotherapy or to add rosiglitazone 4 mg/day to their regimen. The add-on combination therapy provided a statistically significant decrease from baseline in mean FPG (-2.62 mmol/l, $p<0.0001$), compared with an increase in the sulphonylurea monotherapy group (+0.31 mmol/l; no p value).

Raskin and colleagues published a 26-week, randomized, double-blind study comparing insulin monotherapy to add-on therapy of insulin + rosiglitazone (4 mg/day and 8 mg/day).[26] This trial was conducted in the US and 319 patients with type 2 diabetes who did not have adequate glycemic control on twice-daily insulin therapy (total daily dose > or = 30 units) were recruited. Statistical analysis was done on an ITT basis. Although only the results from the 8 mg/day add-on therapy group were pooled in the meta-analysis, both combination therapy groups offered improved glycemic control (mean change from baseline: FPG: -2.3 mmol/l ∀ 3.9, -2.5 mmol/l ∀ 3.3; HbA1c: -0.6% ∀ 1.1, -1.2% ∀ 1.1 for the 4 mg and 8 mg regimens respectively) compared to continuing monotherapy with insulin (FPG: +0.6 mmol/l ∀ 3.8; HbA1c: +0.1% ∀ 1).

Wolffenbuttel and colleagues evaluated the addition of two different doses of rosiglitazone (2 mg/day and 4 mg/day) to existing sulphonylurea treatment (47.6% of patients on gliclazide, 41.8% on glibenclamide, 9.4% on glipizide and 0.3% on carbutamide or glimepiride).[39] This was a phase III, European, multicentre, double-blind, parallel-group study in which 574 patients with type 2 diabetes were recruited. Statistical analysis was based on ITT. Again, only the results from the higher rosiglitazone group (4 mg/day) were incorporated in our meta-analysis. However, in both add-on therapy groups, glycemic control was improved (mean change from baseline: FPG: -2.09 mmol/l ∀ 4.3, -0.95 mmol/l ∀ 2.02; HbA1c: -0.85% ∀ 1.7, -0.5% ∀ 1.07 for the 4 mg and 2 mg regimens respectively) over continuing sulphonylurea monotherapy (FPG: +0.32 mmol/l ∀ 1.8; HbA1c: +0.25% ∀ 1.2).

Finally, Xixing and colleagues compared the addition of two different doses of rosiglitazone (4 mg/day and 8 mg/day) to sulphonylurea therapy (glyburide, glipizide, gliclazide, chlorpropamide, gliquidone, or tolbutamide) for patients with type 2 diabetes whose glycemia was inadequately controlled.[61,62] This was a 24-week, double-blind, placebo-controlled, parallel-group trial involving 554 participants in China. Glycemic control was superior in the add-on therapy groups (mean change from baseline: FPG: -2 mmol/l ∀ 2.6, -1.2 mmol/l ∀ 2.44; HbA1c: -1.9% ∀ 1.39, -1.4% ∀ 1,21 for the 8 mg and 4 mg regimens respectively) as compared with sulphonylurea monotherapy (FPG: +0.5 mmol/l ∀ 2.3; HbA1c: -0.4% ∀ 1.16).

In summary, add-on therapy with rosiglitazone resulted in a statistically significant reduction from baseline in both HbA1c [WMD: -1.29% (95%CI: -1.37, -1.22)] (Figure 1) and FPG [WMD: -2.82 mmol/l (95%CI: -3.15, -2.48)] (Figure 2), compared to continuing monotherapy with one of the traditional agents. The latter pooled estimate was however associated with borderline statistical heterogeneity (Chi-square: 10.81, df: 6, p: 0.094). Therefore, interpretation should be done with caution.

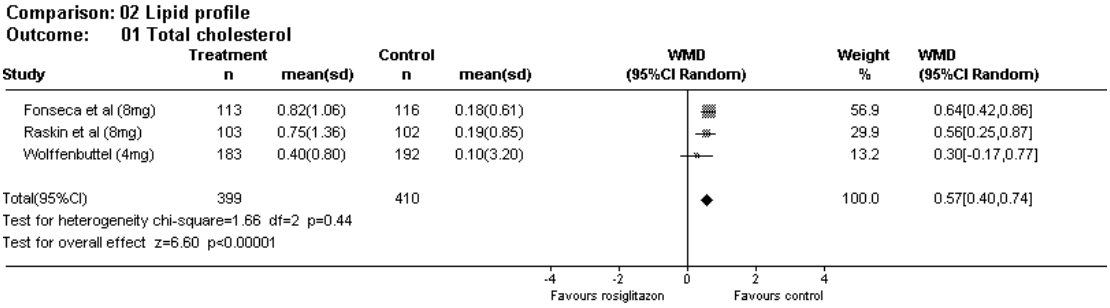
Secondary outcomes

Results for secondary outcomes were not reported in all studies and when they were, the mean difference from baseline was not always available. Accordingly, the pooling of secondary outcomes was only possible for a subset of the studies included in the current review. When a quantitative evaluation was not possible, a qualitative assessment was carried out.

Serum lipid profile

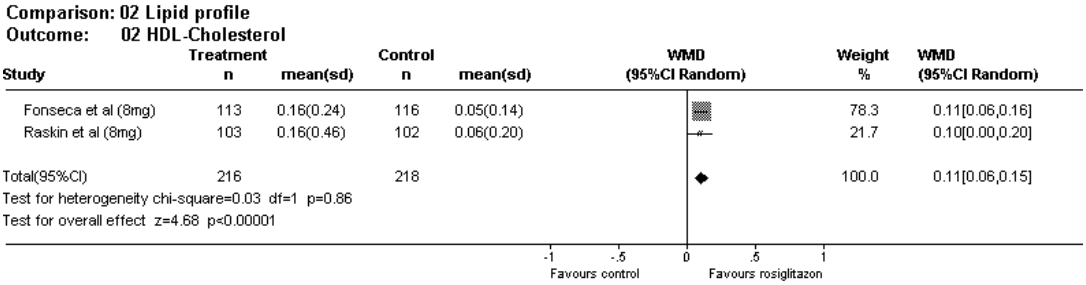
Total cholesterol: Although total cholesterol tended to increase in both the active and control groups, the increase was larger in the rosiglitazone-treated subjects. Combined results of three studies (Figure 3) showed that rosiglitazone was associated with a statistically significant WMD (increase from baseline) in total cholesterol of 0.57 mmol/l (95%CI: 0.40, 0.74), compared to other anti-diabetic agents (insulin, metformin and sulphonylureas).

Figure 3



HDL-cholesterol: A slight increase in HDL-cholesterol levels was observed in subjects treated with metformin or insulin, while a pronounced increase occurred in the rosiglitazone-treated groups. Overall, treatment with rosiglitazone was associated with a statistically significant WMD (increase from baseline) in HDL-cholesterol of 0.11 mmol/l (95%CI: 0.06, 0.15) (Figure 4), compared to control groups.

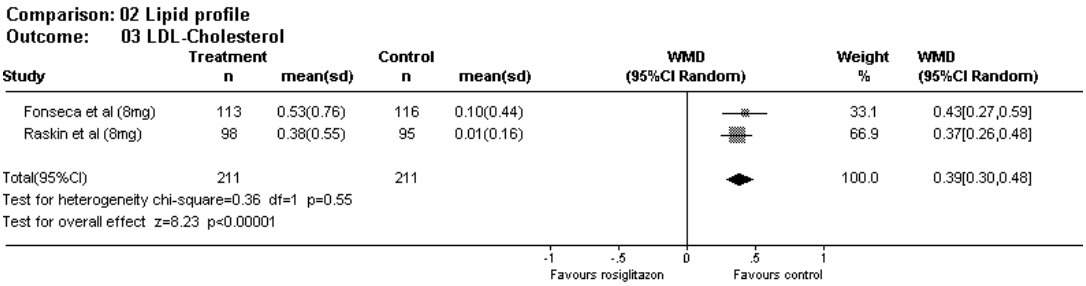
Figure 4



From a qualitative perspective, Charbonnel and colleagues reported an estimated increase from baseline in HDL-cholesterol levels of about 0.15 mmol/l between week 1 and week 52.[41] Wolffenbuttel and colleagues reported a small but statistically significant increase from baseline of 0.1 mmol/l in serum HDL-cholesterol levels for both rosiglitazone-treated groups (2 mg/day and 4 mg/day), while no increase was observed in the sulphonylurea-treated group.[39] In a 148-week, open-label, randomized study comparing patients on rosiglitazone 8 mg/day with patients optimally treated with a glyburide regimen, interim results showed a median increase from baseline in HDL-cholesterol levels of 0.17 mmol/l at week 52 and 0.24 mmol/l at week 100. In comparison, glyburide was associated with an increase from baseline of 0.14 mmol/l at week 100.[57]

LDL-cholesterol: LDL-cholesterol levels increased in both control and active treatment groups. However, where only a slight increase was observed for the metformin or insulin-treated subjects, a larger increase was reported for the rosiglitazone groups. Overall, the use of rosiglitazone was associated with a statistically significant WMD (increase from baseline) of 0.39 mmol/l (95% CI: 0.30, 0.48), compared to the control groups (Figure 5).

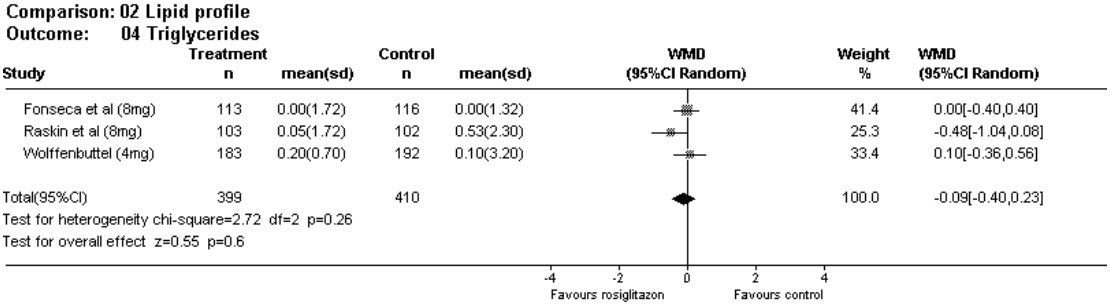
Figure 5



An initial increase from baseline of 0.4 mmol/l at week 52, followed by a slight decrease of 0.04 mmol/l in mean serum LDL-cholesterol levels was reported by Matfin and colleagues.[57] These investigators were part of the study by St. John Sutton and colleagues (Table 1). Wolffenbuttel and colleagues reported no increase in LDL-cholesterol levels for the sulphonylurea group, while an increase from baseline of 0.1 mmol/l and 0.2 mmol/l was reported for the rosiglitazone 2 mg/day group and rosiglitazone 4 mg/day group, respectively.[39]

Triglycerides: The effect of rosiglitazone on triglyceride levels varied from study to study. In general, a small increase from baseline was observed for both rosiglitazone and other anti-diabetic drugs (insulin, metformin, sulphonylureas) (Figure 6). When the three quantitative studies were combined, there was no statistically meaningful difference between the two approaches, although there was a tendency toward a smaller increase from baseline in triglyceride levels with rosiglitazone [WMD: -0.09 mmol/l (95%CI: -0.40, 0.23)], compared to traditional agents.

Figure 6



From a qualitative point of view, minimal changes in triglyceride levels were reported by Rosenstock and colleagues as well as by Freed and colleagues.[45,46] These authors were involved in the same study as Hallé and colleagues (Table 1). Gomez-Perez and colleagues reported a 5.6% reduction in serum triglyceride levels in the combined rosiglitazone + metformin groups.[37] An initial mean increase from baseline of 0.14 mmol/l at week 52, followed by a decrease of 0.14 mmol/l was reported by investigators who were part of the study by St. John Sutton and colleagues. Pooled data from patients completing 24 months of rosiglitazone therapy (4 and 8 mg/day) indicated that the drug increases triglyceride levels in patients with initial low to moderate serum triglyceride levels while a decrease was observed in patients with initial high triglyceride levels.[57] However, Fonseca and colleagues also performed a sub-group analysis of patients with initial low (< 2.26 mmol/l) and high (> or = 2.26 mmol/l) triglyceride levels and reported a small increase in triglyceride levels in the rosiglitazone-treated patients belonging to both sub-groups.[36]

In summary, for the effects on serum lipid profiles, rosiglitazone produced a statistically significant larger increase from baseline in total-cholesterol, LDL-cholesterol and HDL-cholesterol levels compared to other anti-diabetic agents. There was no statistically significant difference in triglyceride levels.

Liver function parameters

No serious adverse effects with respect to liver function were reported. In the study by Charbonnel and colleagues, no patients had clinically significant increases in liver transaminase levels.[40-42,44] Matfin and colleagues also reported no adverse effects on ALT levels.[38] Most studies reported that no patients had an increase in ALT and AST values greater than 2.5 times[26]

or three times the upper limit of the reference range.[39,45] Fonseca and colleagues observed a slight decrease in the mean ALT level for all groups (-1.9 U/L in the control group and the rosiglitazone 4 mg/day group, -3.4 U/L in the rosiglitazone 8 mg/day group). Similar results were reported for the mean AST level (-3.5 U/L, control; -12 U/L, 4 mg/day rosiglitazone; -14.7 U/L, 8 mg/day rosiglitazone). Two patients in the metformin monotherapy group were noted to have more than three times the upper limit of the reference range for transaminase values during the study.[36] Also, no rosiglitazone-treated patients had ALT values above three times the upper limit of the reference range over 100 weeks of treatment in an open label study.[54] Finally, Xixing and colleagues reported that the serology status for hepatitis B or hepatitis C did not influence the ALT response in patients with type 2 diabetes using the rosiglitazone/ sulphonylurea combination in China. All patients had ALT levels less than 2.5 times the upper limit of the normal range. Small decreases in ALT were noted in rosiglitazone/sulphonylurea-treated subjects, while an increase was seen in the sulphonylurea monotherapy group.[61]

In summary, the vast majority of subjects in the trials maintained liver enzyme levels within the normal range and no serious liver adverse events were reported.

Hematological parameters

Small decreases in haemoglobin and hematocrit levels were generally associated with the use of rosiglitazone. Quantitative analysis was only possible using data from the study by James and colleagues.[50] In this study, the rosiglitazone-treated group was associated with a statistically significant WMD (decrease from baseline) of -0.89 g/dl (-8.9 g/l) (95% CI: -1.17, -0.61) for haemoglobin and -2.52% (95% CI: -3.37, -1.67) for hematocrit, compared to the glyburide-treated group.

Regarding the other studies, Charbonnel and colleagues qualitatively reported clinically insignificant decreases in haemoglobin and hematocrit in the rosiglitazone group.[41,44] Fonseca and colleagues reported a significant reduction from baseline in the two rosiglitazone-treated groups for haemoglobin (-5 g/l and -8 g/l for the 4 mg and 8 mg groups respectively, $p < 0.0001$ for both) and hematocrit (-1.8% and - 2.5% for the 4 mg and 8 mg group respectively, $p < 0.0001$ for both). In comparison, there were no significant changes in these parameters in the control group. One patient in each rosiglitazone group withdrew because of anemia.[36] Rosenstock and colleagues, who were part of the Hallé and colleagues study group, reported a small decrease in hemaglobin (-1.2 g/l) and hematocrit (-3.5%) in the rosiglitazone/glyburide group.[45] Raskin and colleagues observed small but statistically significant decreases in hemoglobin (-0.5 g/dl with insulin/rosiglitazone 4 mg/day and -1 g/dl with insulin/rosiglitazone 8 mg/day vs. 0.0 g/dl with insulin monotherapy) and in hematocrit (-1.9% with insulin/rosiglitazone 4 mg/day and -3% with insulin/rosiglitazone 8 mg/day vs. -0.3% with insulin monotherapy) levels during the rosiglitazone treatment.[26] Over a 100-week observation period, a higher frequency of anemia was reported in rosiglitazone-treated patients, with a mean decrease in haemoglobin from 15.1 g/ml at baseline to 13.9 g/ml at week 100.[54,58] Finally, Wolffenbuttel and colleagues reported statistically significant small decreases in both hemoglobin levels (-3.9 g/l, 2 mg/day; -6.6 g/l, 4 mg/day) and hematocrit levels (-1.52%, 2 mg/day; -2.34%, 4 mg/day). Since no information was available for the control group, no comparison was done.[39]

In summary, the use of rosiglitazone was associated with small decreases in haemoglobin (varying from - 3.9 g/l to –12 g/l) and in hematocrit (varying from -1.52% to - 3.5%). However, this rarely led to clinical anemia. Two patients treated with rosiglitazone withdrew due to anemia.

Hypoglycemia

Charbonnel and colleagues observed a higher rate of hypoglycemia symptoms in the glyburide group (12.1%), compared with the rosiglitazone 4 mg/day (0.5%) and 8 mg/day (1%) groups.[41,42,44] Fonseca and colleagues indicated that no patients withdrew from their study because of hypoglycemia. However, mild to moderate reactions were observed in 1.8% of patients on metformin monotherapy, 2.6% on metformin/rosiglitazone 4 mg/day and 4.5% on metformin/rosiglitazone 8 mg/day.[36] Hypoglycemia occurred more frequently in the rosiglitazone/glyburide group, compared with glyburide monotherapy patients in the study by Hallé and colleagues.[45-48] Hypoglycemia was reported in 6.1% of patients on the gliclazide/rosiglitazone combination, compared with 2.1% of patients on gliclazide monotherapy studied by James and colleagues.[49,50] The majority of these events were mild to moderate in severity. One patient on the combination regimen withdrew from the study due to hypoglycemia.[50] Raskin and colleagues reported relatively high levels of hypoglycemia, i.e. 38% in the insulin monotherapy group, 53% in the insulin/rosiglitazone 4 mg/day group and, 67% in the insulin/rosiglitazone 8 mg/day group. Except for four subjects, reactions were of mild or moderate severity. Three participants withdrew from the study because of hypoglycemia, one in the insulin monotherapy group and two in the insulin/rosiglitazone 8 mg/day group.[26] Compared to the rosiglitazone 8 mg/day group, hypoglycemia was more frequent in the glyburide group studied by St. John Sutton and colleagues.[54,58] In the study by Wolffenbuttel and colleagues, hypoglycemia occurred in 2%, 3.4%, and 5.3% of patients on sulphonylurea monotherapy, sulphonylurea/rosiglitazone 2 mg/day and sulphonylurea/ rosiglitazone 4 mg/day.[39] Finally, Xixing and colleagues reported a higher incidence of hypoglycemia in patients treated with a combination of rosiglitazone and sulphonylurea, compared to sulphonylurea monotherapy.[62]

In summary, the majority of hypoglycemic events reported in the trials reviewed were mild to moderate in nature. Occurrence of hypoglycemia was relatively infrequent when rosiglitazone was used alone, ranging between 0.5% and 1%, depending on the dose. However, occurrence increased when it was used in combination with another oral anti-diabetic drug, varying from 2.6% to 6.1% of patients, depending on the dose and the combination used. Hypoglycemia was particularly common when rosiglitazone was combined with insulin, ranging between 53% and 67%, depending on the dose used. Only a minority of patients required dosing adjustments to manage symptomatic hypoglycemic events. In total, four patients were reported to have withdrawn because of hypoglycemia: one in a control group and three in active groups (one using a gliclazide/rosiglitazone combination and two using an insulin/rosiglitazone combination).

Other relevant parameters

Weight: Rosiglitazone therapy was generally associated with an increase in weight. A quantitative evaluation of weight change was only possible for the study by James and colleagues.[50] In this study, which ran over a 26-week period, the rosiglitazone-treated group was associated with a statistically significant WMD (increase from baseline) of 3.3 kg (95% CI: 2.08 to 4.52) compared with the glyburide-treated group.

For the other studies, Charbonnel and colleagues observed no weight gain in the glyburide and rosiglitazone 4 mg/day groups but did in five participants (2.6%) in the rosiglitazone 8 mg/day group.[41,42,44] Fonseca and colleagues reported a mean decrease from baseline in body mass of 1.2 kg (no p value was reported) for the metformin monotherapy group while rosiglitazone groups experienced a mean increase from baseline of 0.7 kg (4 mg/day) and 1.9 kg (8 mg/day) (p value = 0.0001 for both groups).[36] In the study by Hallé and colleagues, an increase in the mean weight in the rosiglitazone/glyburide group (5.2 kg) compared to weight loss (-0.8 kg) in the glyburide monotherapy group was observed after 26 weeks of therapy.[45,47] Body weight significantly increased in all groups studied by Raskin and colleagues (0.9, 4.0, and 5.3 kg in the insulin monotherapy, insulin/rosiglitazone 4 mg/day and, insulin/rosiglitazone 8 mg/day groups, respectively).[26] Five percent of patients treated for 100 weeks in an open-label study reported weight increase.[54,58] In the study by Wolffenbuttel and colleagues, small but statistically significant increases from baseline in mean body weight were observed in the rosiglitazone treatment groups (2 mg/day: 0.8 kg, p=0.002 and 4 mg/day: 1.8 kg, p< 0.0001). Since no information was available for the control group, comparison was not possible.[39] Finally, Xixing reported a higher incidence of weight increase in the rosiglitazone/sulphonylurea group than in the sulphonylurea monotherapy subjects.[62]

Blood pressure: The use of rosiglitazone was associated with a small, but sometimes statistically significant decrease in blood pressure. Quantitative evaluation was based on the results at week 52 in the study by St. John Sutton and colleagues.[53,55,56] The rosiglitazone-treated group was associated with statistically significant WMDs (decrease from baseline) of -3.1 mm Hg (95% CI: -4.95 to -1.25), and -3.90 mm Hg (95% CI: -6.66 to -1.14) in diastolic and systolic blood pressure, respectively, compared to the glyburide-treated group. The same group also reported that rosiglitazone 8 mg/day was associated with a mean reduction from baseline of 2.7 mm Hg in diastolic blood pressure at week 100, while rosiglitazone had a relatively neutral effect on systolic blood pressure (1.0 mm Hg) (no p value given).[57]

Hallé and colleagues only reported small decreases in mean systolic and diastolic blood pressure in both the rosiglitazone/glyburide group and the glyburide monotherapy group without specifying the magnitude.[45-48] Matfin and colleagues reported that diastolic blood pressure fell by 1.4 mm Hg on rosiglitazone/sulphonylurea therapy, which was a non-statistically significant difference, compared to sulphonylurea monotherapy (-0.9 mm Hg).[38] Finally, Raskin and colleagues reported a decrease of 2.6 mm Hg in diastolic blood pressure in the insulin/rosiglitazone 8 mg/day group (p<0.005), while no changes were observed in the control group and the insulin/rosiglitazone 4 mg/day group.[26]

Edema: In their study, Fonseca and colleagues observed edema in 0.9% of patients in the control group, 2.5% in the rosiglitazone 4 mg/day group and 3.5 % in the rosiglitazone 8 mg/day group. No patients withdrew from the study because of edema.[36] Hallé and colleagues reported an increased rate of adverse effects related to edema in the rosiglitazone/glyburide group, compared to the glyburide monotherapy group. No values were provided however.[45-48] James and colleagues reported that 10.8% of patients on rosiglitazone/gliclazide combination had edema, compared to only 2.9% for the gliclazide monotherapy group.[50] Severe edema was reported in 0.9% of rosiglitazone/gliclazide-treated patients while it was not observed in gliclazide monotherapy patients.[49] More patients in the insulin/rosiglitazone groups reported edema (13.1% with insulin/rosiglitazone 4 mg/day, 16.2% with insulin/rosiglitazone 8 mg/day), compared to insulin monotherapy (4.7%). Investigators classified these events as mild to moderate. None were considered serious. Congestive HF was reported in two patients in each insulin/rosiglitazone group and in one patient on insulin monotherapy.[26] Finally, Xixing and colleagues observed a higher incidence of leg edema in rosiglitazone-treated patients, but did not provide any values.[62]

In summary, weight gain was associated with the use of rosiglitazone. The magnitude of the increase varied between 0.7 kg and 5.3 kg, depending on the dose and the combination regimen used. The higher increases were reported with the insulin combinations. A mild hypotensive effect was also reported with rosiglitazone, with decreases of about 3 mm Hg in diastolic blood pressure and 4 mm Hg in systolic blood pressure. Edema was observed in 2.5 to 3.5 % of patients on rosiglitazone monotherapy. The occurrence increased to 10.8% when rosiglitazone was combined with gliclazide. The highest occurrence was associated with the combined use of rosiglitazone and insulin, where edema was observed in 13.1 to 16.2% of patients, depending on the dose used.

3.2.3 Assessment of clinical efficacy – pioglitazone

A total of eight relevant studies were identified for the pioglitazone clinical review, i.e. five full publications, two abstracts and one poster (Table 2). The majority of these studies received a low quality assessment score, with only one study reaching a score of 3/5 on the Jadad scale. Two studies compared monotherapy regimens and five examined add-on therapy. An additional study (Jovanovic and colleagues) included three comparison arms, i.e. two monotherapy arms and one add-on therapy arm.[51,52] The duration of the studies included in the pioglitazone review varied from 12 to 28 weeks.

Table 2: Characteristics of studies included in the analysis pioglitazone versus other anti-diabetic drugs

Study	Quality Score	Publication Type	Study Length (weeks)	Active Group			Control Group		
				Drug(s)	Dose	n	Drugs	Dose	n
Ebeling et al.[63]	2/5	Journal article	26	PIO	30 - 45 mg/d	9	SU §	2.5 – 5 mg/d	10
Einhorn et al.[64]	2/5	Journal article	16	PIO+ MET	30 mg/d + titrate	168	PLB+ MET	Titrate	160
Scherbaumand Göke*	1/5	Abstract	16 - 28	PIO	45 mg/d	59	Acarbose	900 mg/d	59
Jovanovic et al.**	2/5	Poster	24	PIO+ CBA¥	30 mg/d +1.5-12 mg/d	123	CBA ¥	1.5-12 mg/d	61
Javanovic et al.**	2/5	Poster	24	CBA¥	1.5-12 mg/d	61	PIO	30 mg/d	62
Kaneko et al.[31]	3/5	Journal article	12	PIO + SU	30 mg/d	76	PLB+ SU	N/A	73
Kipnes et al.[65]	2/5	Journal article	16	PIO+ SU ¶	30 mg/d+ usual dose	189	PLB+ SU ¶	Usual dose	187
Miyazaki et al.[32]	2/5	Journal article	16	PIO + SU	45 mg/d + usual dose	12	SU	Usual dose	11
Rubin et al.[66]	2/5	Abstract	16	PIO+IN	30 mg/d+ >30 U/d	188	PLB+ IN	>30 U/d	187

* German Pioglitazone Study Group; interim results published in abstract in 2000 and final results published in three abstracts in 2001, two on safety and one on efficacy.[67-70]
** the two treatment groups belong to the same study[52]
§ glyburide ¥ repaglinide
¶ glyburide and glipizide (70% on at least half the maximum daily dose)

Primary outcomes

Figure 7 and Figure 8 provide a summary of the quantitative evaluation of the effect of pioglitazone on HbA1c and FPG. These were based on seven and six studies, respectively. When a quantitative evaluation was not possible, a qualitative assessment was carried out.

Monotherapy

Although three relevant monotherapy studies were identified, only two could be pooled for quantitative comparison of HbA1c, as there were no measures of dispersion around the mean and no levels of significance provided in the study by Sherbaum and Göke.[67]

Ebeling and colleagues reported the results of a subgroup of 29 patients who were part of a larger Phase III randomized, double-blind Finnish study comparing pioglitazone, glyburide and placebo.[63] They were interested in studying the relationship between markers of the inflammatory process and glycemic control in this subgroup. The full results of this study could not be obtained. As shown in Figure 7, the reduction in HbA1c was slightly larger in the glyburide population than in the pioglitazone population (-1.20% ∀ 1.7 vs. -1.10% ∀ 1.3). There was no information on FPG in the Ebeling study. The second study was the study by Jovanovic and colleagues.[52] This trial compared repaglinide monotherapy to pioglitazone monotherapy. There was also a third arm, combination therapy with pioglitazone and repaglinide. The dose in this study was 0.5 to 4 mg per meal (not to exceed 16 mg/day) for repaglinide and 30 mg/day for pioglitazone (Clifford C. Hall, PhD, Novo Nordisk Pharmaceuticals, Princeton, NJ: personal communication, 2002 Jan 15). This study had the same design as the companion

rosiglitazone/repaglinide study discussed in Section 3.2.2. Compared to repaglinide, which caused a decrease from baseline in HbA1c of -0.18% ∀ 1.33, pioglitazone use was associated with some deterioration in glycemic control, i.e. HbA1c increased from baseline by +0.32% ∀ 1.26. FPG was reduced in both monotherapy groups, although the decrease from baseline was larger in the repaglinide group (-1.89 mmol/l ∀ 3.25), compared with a decrease of 1 mmol/l ∀ 3.23 for pioglitazone.

Figure 7

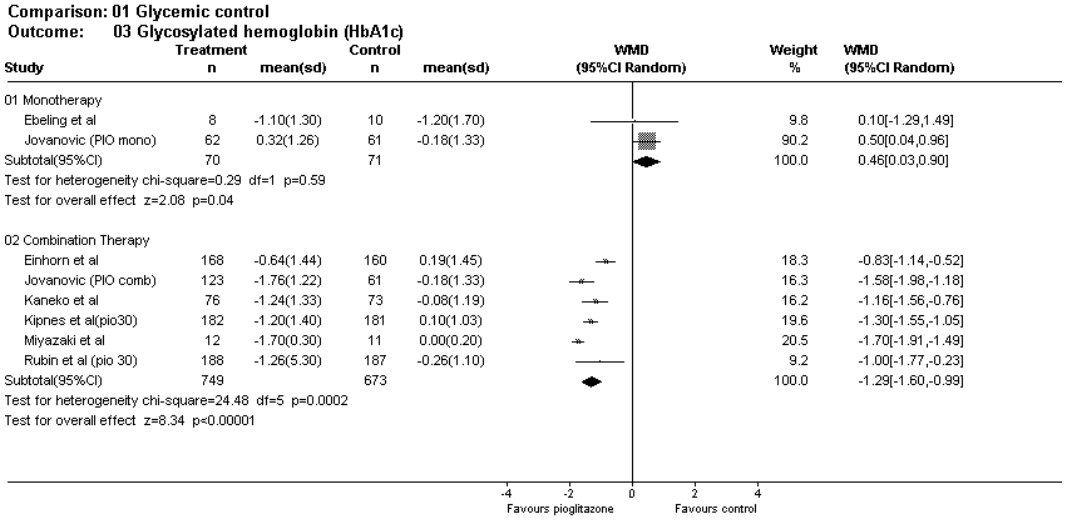
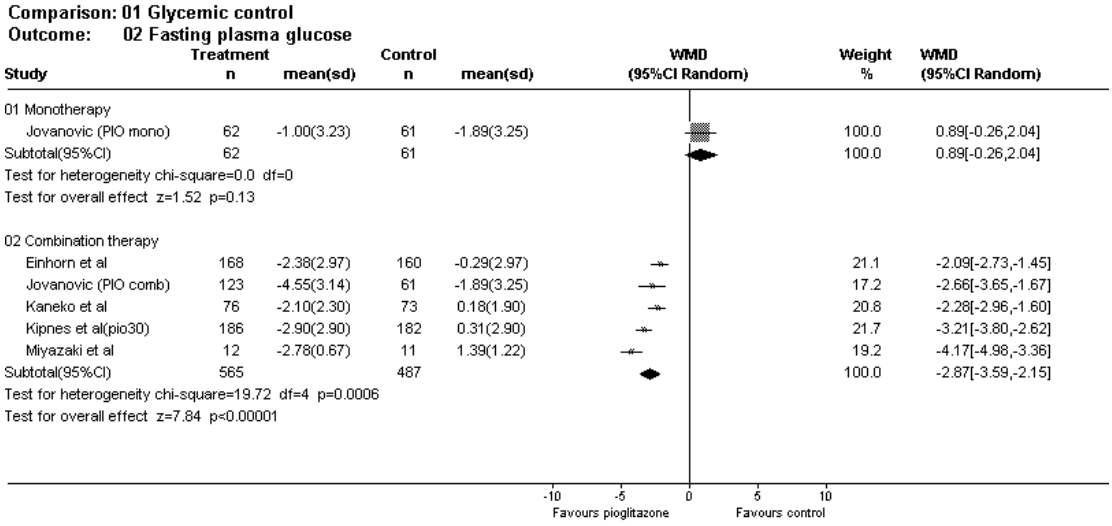


Figure 8



The study by Scherbaum and Göke was a multicentre, parallel-group, randomized study. It compared pioglitazone 45 mg/day with acarbose 900 mg/day in 271 type 2 diabetes subjects who did not have satisfactory glycemic control prior to study recruitment. Of these, 143 were newly diagnosed and 128 were using unspecified anti-diabetic drugs. These were discontinued eight weeks before randomization. The median decrease in HbA1c and FPG was larger in

pioglitazone-treated patients (HbA1c: -1.20%, FPG: -2.7 mmol/l) than in patients on acarbose (HbA1c: -0.20%, FPG: -0.7 mmol/l).[67]

In summary, combined results indicate that monotherapy with pioglitazone was associated with a statistically significant smaller decrease from baseline in HbA1c [WMD: 0.46% (95% CI: 0.03, 0.90)], compared with two non-thiazolidinedione regimens, i.e. glyburide and repaglinide (Figure 7). Quantitative evaluation of the effect of pioglitazone monotherapy on FPG was only based on one study. Pioglitazone was associated with a smaller but not statistically significant decrease from baseline in FPG [WMD: 0.89 mmo/l (95% CI: -0.26, 2.04)], compared with repaglinide monotherapy (Figure 8).

Add-on therapy

Six studies were included in this analysis. All add-on regimens provided better glycemic control, compared to continuing monotherapy regimens.

Einhorn and colleagues reported results from a randomized, double-blind trial, comparing metformin monotherapy with metformin/pioglitazone add-on therapy over 16 weeks.[64] Patients used their usual pre-trial dose of metformin. A total of 328 American adults on metformin with poorly controlled type 2 diabetes were randomized. The study was completed by 249 participants. An ITT approach was used for data analysis. Add-on therapy provided an improvement in HbA1c (-0.64% ∀ 1.44) and FPG (-2.38 mmol/l ∀ 2.97) compared with continuing metformin monotherapy (+ 0.19% ∀ 1.45 for HbA1c, -0.29 mmol/l ∀ 2.97 for FPG).

The study by Jovanonic and colleagues included a third arm comparing the repaglinide/pioglitazone combination to monotherapy.[51,52] Combination treatment with repaglinide and pioglitazone provided a greater improvement in glycemic control for both HbA1c (-1.76% ∀ 1.22) and FPG (-4.55 mmol/l ∀ 3.14), compared with repaglinide monotherapy (HbA1c: -0.18% ∀ 1.33, FPG:-1.89 mmol/l ∀ 3.25).

The study by Kaneko and colleagues was a 12-week randomized, double-blind trial comparing sulphonylurea monotherapy (dose not specified) to the combination of pioglitazone (30 mg/day) + sulphonylurea (dose not specified).[31] A total of 149 adults with type 2 diabetes on sulphonylurea treatment were recruited, although the diagnosis was not confirmed at study entry. The add-on pioglitazone/sulphonylurea regimen provided a decrease from baseline in both primary outcomes, i.e. HbA1c: -1.24% ∀ 1.33, FPG: -2.1 mmol/l ∀ 2.3, compared with continuing sulphonylurea monotherapy, which was associated with a small decrease from baseline in HbA1c (-0.08% ∀ 1.19), and a small increase from baseline in FPG (+0.18 mmol/l ∀ 1.9).

Kipnes and colleagues also compared the efficacy and safety of pioglitazone add-on therapy with continuing sulphonylurea monotherapy.[65] This was a 16-week, double-blind trial. Subjects were randomized after a single-blind period during which they continued their usual dose of sulphonylurea treatment but discontinued other anti-diabetic drugs. In total, 560 adults with type 2 diabetes with sub-optimal glycemic control were randomized to receive, in combination with their usual dose of sulphonylurea treatment, either placebo or pioglitazone 15 or 30 mg/day.

Patients receiving pioglitazone add-on therapy had a decrease from baseline in HbA1c (pioglitazone 15 mg/day: -0.8% ∀ 1.4, pioglitazone 30 mg/day: -1.2% ∀ 1.4) and FPG (pioglitazone 15 mg/day: -1.9 mmol/l ∀ 2.9, pioglitazone 30 mg/day: -2.9 mmol/l ∀ 2.9) while patients continuing sulphonylurea monotherapy had a small increase from baseline for both endpoints (HbA1c: +0.1% ∀ 1.03, FPG: +0.31 mmol/l ∀ 2.9).

In a pharmacodynamic study, Miyazaki and colleagues assessed the effect on glucose and lipid metabolism of the addition of pioglitazone to sulphonylurea-treated patients with type 2 diabetes.[32] This study was a randomized, double-blind study in which 23 patients were recruited. All patients were on a special diet and received a 75g oral glucose tolerance test as part of the procedure for measuring insulin sensitivity. HbA1c and FPG, along with other parameters, were measured before and after 16 weeks of pioglitazone treatment, and maintained their usual sulphonylurea regimens. Insulin sensitivity was assessed with a euglycemic insulin clamp. Pioglitazone add-on regimen was associated with an improvement in glycemia for both HbA1c (-1.7% ∀ 0.3) and FPG (-2.78 mmol/l ∀ 0.67), compared to continuing sulphonylurea monotherapy (HbA1c: 0% ∀ 0.2, FPG: +1.39 mmol/l ∀ 1.22).

Rubin and colleagues compared insulin monotherapy to insulin + pioglitazone add-on therapy. This double-blind Phase III study randomized 566 patients with type 2 diabetes who were experiencing unsatisfactory glycemic control with insulin therapy.[66] After six weeks of stable dose insulin monotherapy, subjects were randomized to receive either placebo, pioglitazone 15 mg/day or pioglitzone 30 mg/day in addition to their usual insulin regimen. Both insulin + pioglitazone 15 mg/day and insulin + pioglitazone 30 mg/day add-on regimens were associated with a statistically significant decrease from baseline in HbA1c (-0.99%, $p< 0.05$ and -1.26%, $p<0.05$, respectively) and FPG (-1.91 mmol/l, $p<0.05$ and -2.7 mmol/l, $p<0.05$). In comparison, continuing insulin monotherapy was associated with a statistically significant smaller decrease from baseline in HbA1c (-0.26%, $p<0.05$) and a non-significant increase in FPG (+0.03 mmol/l).

In summary, pioglitazone add-on regimens were all associated with a statistically significant WMD (decrease from baseline) in HbA1c, compared with simply continuing non-thiazolidinedione monotherapy. When the results of the six add-on therapy studies were combined together, the overall effect size was a statistically significant WMD (decrease from baseline) in HbA1c of -1.29% (95% CI: -1.60, -0.99) in favor of the pioglitazone add-on therapy. The five studies combined for the evaluation of FPG all individually had a statistically significant WMD (decrease from baseline) in FPG in favor of add-on therapy with pioglitazone. This led to an overall WMD (decrease from baseline) of -2.87 mmol/l (95% CI: -3.59 to -2.15), compared to monotherapy with another agent. It should be noted however that pooled estimates for the two add-on therapy endpoints are both associated with strong evidence of statistical heterogeneity (Chi-square: 24.48, df: 5, p: 0.0002 for HbA1c and Chi-square: 19.72, df: 4 and p: 0.0006 for FPG).

For this reason, these findings should be interpretated tentatively until further confirmation is available.

Secondary outcomes

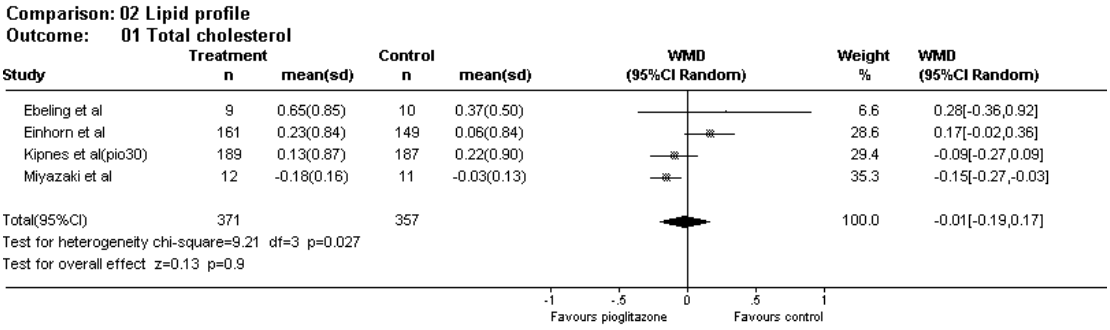
Results for secondary outcomes were not reported in all studies, and when they were, a quantitative evaluation was not always possible. A qualitative assessment was carried out when quantitative comparisons were not possible.

Serum lipid profile

Total cholesterol: Quantitative evaluation was possible using four studies (Figure 9). Total cholesterol levels increased for both pioglitazone and comparator groups in three studies.[63-65] The increase was larger for the pioglitazone group in two studies,[63,64] and smaller in one.[65] There was no statistical difference in the WMD for these studies. Miyazaki and colleagues reported a decrease in total cholesterol levels for both the pioglitazone/sulphonylurea and the sulphonylurea monotherapy regimens.[32] The decrease was however larger in the pioglitazone group, with a statistically significant WMD in favor of pioglitazone. When the results of all four studies were pooled together, the pioglitazone effect on total cholesterol was similar to the effect associated with the use of traditional anti-diabetic agents (metformin and sulphonylureas) [WMD: -0.01 mmol/l (95% CI: -0.19, 0.17)] (Figure 9). However, this pooled result was associated with evidence of statistical heterogeneity (Chi-square: 9.21, df: 3, p: 0.027).

Qualitative results were available from two other studies. In the study by Scherbaum and Göke, total cholesterol did not change in the pioglitazone group, while a small decrease of 0.04 mmol/l was observed for acarbose.[69] Kaneko and colleagues reported an increase in both the pioglitazone/sulphonylurea combination therapy and sulphonylurea monotherapy groups, although the increase was slightly larger in the pioglitazone-treated subjects (+0.17 mmol/l) than in the comparator group (+0.14 mmol/l).[31]

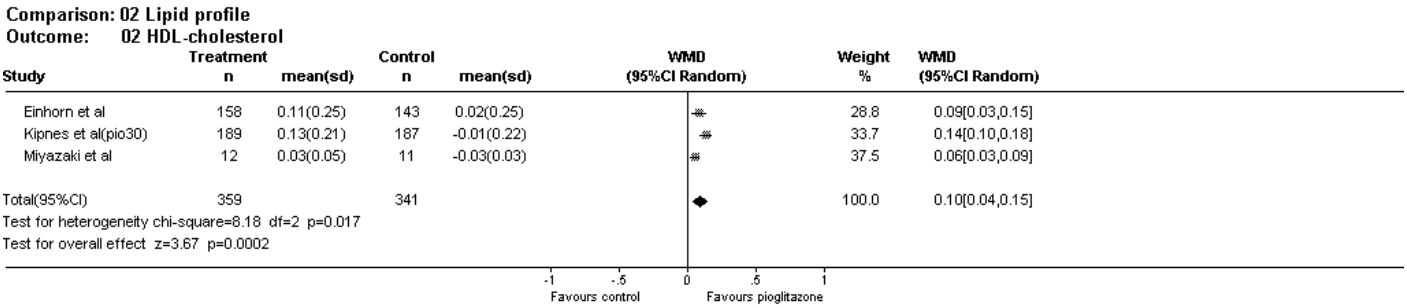
Figure 9



Overall, pioglitazone and non-thiazolidinedione agents were found to have a similar effects on serum total cholesterol levels.

HDL-cholesterol: Quantitative information could be derived from three studies (Figure 10). In all cases, pioglitazone-containing arms were associated with statistically significant increases in HDL-cholesterol levels, compared to non-thiazolidinedione-containing regimens (metformin and sulphonylureas). A WMD (increase from baseline) of 0.10 mmol/l (95% CI: 0.04, 0.15) was computed, in favor of pioglitazone. Again, because statistical heterogeneity was detected with the pooled estimate (Chi-square: 8.18, df: 2, p: 0.017), interpretation should be cautious.

Figure 10

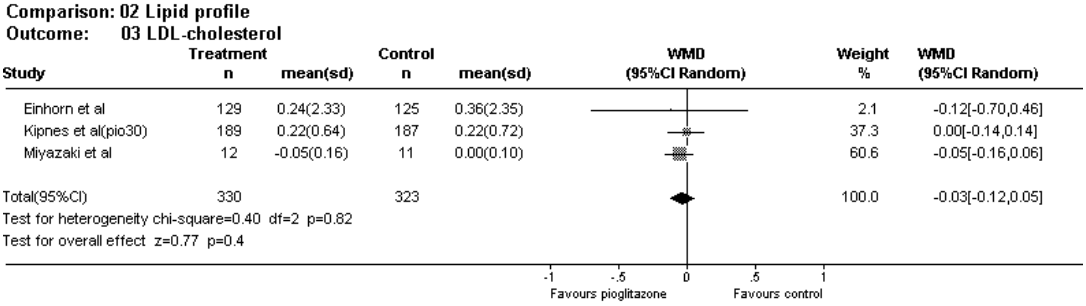


Qualitative results were available for three other studies. Ebeling and colleagues observed an increase from baseline of 0.22 mmol/l with pioglitazone and a decrease of 0.02 mmol/l with glyburide.[63] In the German study, pioglitazone monotherapy was associated with a median increase from baseline of 0.18 mmol/l, while no changes were observed with acarbose.[69] Finally, a larger increase from baseline was associated with pioglitazone/sulphonylurea therapy (+0.19 mmol/l) in a Japanese study, compared to sulphonylurea monotherapy (+0.10 mmol/l).[31]

Overall, HDL-cholesterol levels were elevated more in pioglitazone-containing regimens, compared with non-thiazolidinedione regimens.

LDL-cholesterol: In the three studies combined, pioglitazone was shown to either result in a smaller increase from baseline in LDL-cholesterol levels or a small decrease, compared to traditional agents (metformin or sulphonylurea). Overall, pioglitazone was associated with a relatively neutral effect, leading to a non-statistically significant WMD of -0.03mmol/l (95% CI: -0.12, 0.05), in favor of pioglitazone. (Figure 11)

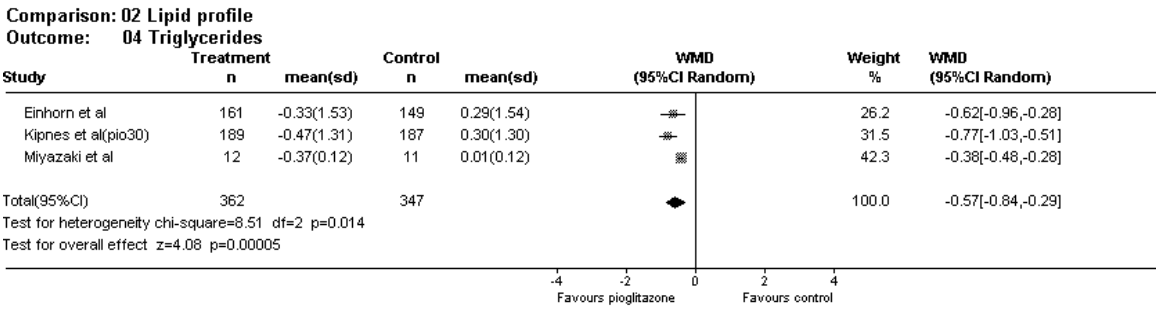
Figure 11



A similar result was reported by the German Pioglitazone Study Group which observed no change in serum LDL-cholesterol levels for pioglitazone monotherapy, while a small increase of 0.03 mmol/l was observed for acarbose monotherapy.[69]

Triglyceride: All three studies showed a statistically significant decrease from baseline in serum triglyceride levels, compared with non-thiazolidinedione regimens (metformin or sulphonylureas). Overall, a WMD (decrease from baseline) of -0.57 mmol/l (95% CI: -0.84, -0.29) was calculated in favor of pioglitazone (Figure 12). However, this result was also associated with evidence of statistical heterogeneity (Chi-square: 8.51, df: 2, p: 0.014).

Figure 12



Ebeling and colleagues also observed a decrease from baseline in serum triglyceride levels with pioglitazone monotherapy (-0.37 mmol/l), while an increase was reported with glyburide (+0.24 mmol/l).[63] The German Pioglitazone Study Group reported a larger decrease (median change from baseline: -0.46 mmol/l) with pioglitazone monotherapy than with acarbose monotherapy (median change from baseline:-0.08 mmol/l).[69] Results from Kaneko and colleagues showed a decrease from baseline of -0.36 mmol/l with the pioglitazone + sulphonylurea regimen. No changes in serum triglyceride levels were observed with sulphonylurea monotherapy.[31]

Overall, the use of pioglitazone was associated with a decrease in serum triglyceride levels, compared to non-thiazolidinedione agents.

In summary, with respect to effect on serum lipid parameters, pioglitazone caused a statistically significant larger increase from baseline in HDL-cholesterol levels, compared to other anti-diabetic agents. No statistically significant differences were observed for total and LDL-cholesterol levels while there was a statistically significant decrease from baseline in triglyceride levels.

Liver function parameters

Both Einhorn and colleagues as well as Kipnes and colleagues reported that no patient had ALT values that increased to more than three times the upper limit of the normal range in their studies. There were no cases of drug-induced hepatotoxicity.[64,65] In their interim analysis, Scherbaum and Göke reported that hepatotoxicity was not encountered in either the pioglitazone or acarbose groups.[68] No liver function results were available in their final analysis.[67,69] Finally, Rubin and colleagues reported no differences concerning liver function test measurements between patients on insulin monotherapy and patients on the pioglitazone/insulin regimen.[66]

In summary, the majority of subjects maintained liver function tests within the normal range and no serious hepatic adverse events were reported in the trials included in the review.

Hematological parameters

Hematological results were reported in two studies. Kipnes and colleagues observed significant dose-related decreases from baseline in hemoglobin and hematocrit levels in all groups. Mean values remained in the normal range. No patient withdrew because of anemia. The decrease in haemoglobin was - 0.5 ∀ 0.9 g/dl in the pioglitazone 30 mg/day + sulphonylurea group, compared to - 0.02 ∀ 0.8 g/dl for the sulphonylurea monotherapy group.[65] A statistically significant WMD (decrease from baseline) of -0.48 g/dl (- 4.8 g/l) (95% CI: -0.65, -0.31) was computed in favour of sulphonylurea monotherapy. Einhorn and colleagues reported small mean decreases from baseline in haemoglobin and hematocrit with pioglitazone plus metformin. Values stabilized within 10 to 12 weeks and remained within normal limits. No patient withdrew due to anemia.[64]

Overall, the use of pioglitazone was associated with small decreases in both haemoglobin and hematocrit indices. No patients withdrew from the studies due to anemia.

Hypoglycemia

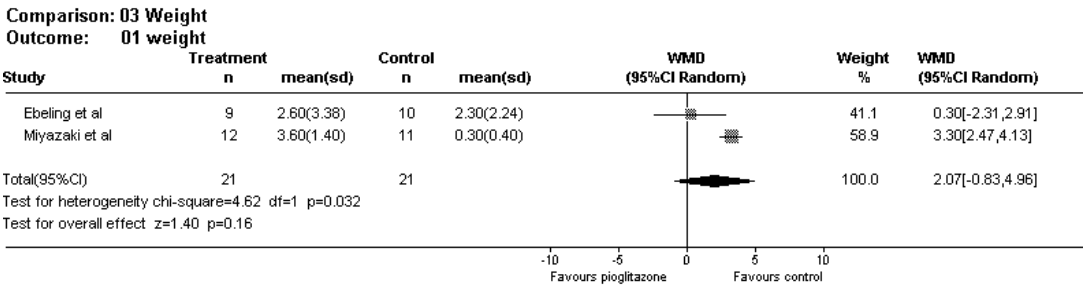
Einhorn and colleagues reported that one patient in each treatment group (metformin vs. metformin+pioglitazone) had hypoglycemic episodes.[64] Kipnes and colleagues observed that seven patients (3.7%) in the pioglitazone 30 mg/day+sulphonylurea group, 1 patient (0.5%) in the sulphonylurea monotherapy group and none in the pioglitazone 15 mg/day+sulphonylurea group had hypoglycemic episodes. No patients withdrew from the study due to hypoglycemia.[65] Finally, the incidence of hypoglycemia was 7% higher in the combined pioglitazone/insulin groups, compared to insulin monotherapy in the study by Rubin and colleagues.[66]

In summary, hypoglycemia was not common with pioglitazone monotherapy. Occurrence however increased when pioglitazone was used in combination with another anti-diabetic agent, especially with insulin. Hypoglycemia was generally described as mild in nature. Only a minority of subjects required an intervention to manage symptomatic hypoglycemic episodes and these interventions were limited to a reduction in drug dosage. No patients were reported to have withdrawn because of hypoglycemia.

Other relevant parameters

Weight: Quantitative evaluation was possible for two studies (Figure 13). Ebeling and colleagues[63] reported a statistically significant increase from baseline in weight in both treatment groups. Although the increase was larger in the pioglitazone/metformin group, it was associated with a non-statistically significant WMD of 0.3 kg (95% CI: -2.31, 2.91), compared to metformin monotherapy. Miyazaki and colleagues also reported weight increase from baseline in both treatment groups, although the increase in the sulphonylurea monotherapy group was small (0.3 kg ∀ 0.4).[32] A statistically significant WMD (increase from baseline) of 3.3 kg (95% CI: 2.47, 4.13) was associated with the pioglitazone/sulphonylurea regimen, compared to the sulphonylurea monotherapy group. When the results from both studies were combined, the overall effect size was a non-statistically significant WMD (increase from baseline) of 2.07 kg (95% CI: -0.83, 4.96) for the pioglitazone-treated patients. However, statistical heterogeneity (Chi-square: 4.62, df: 1, p: 0.032) was identified, which indicates that this quantitave pooled estimate needs to be interpretated with some caution.

Figure 13



Similar results are available from the other studies. Einhorn and colleagues reported a mean decrease in weight from baseline of 1.36 kg in patients on metformin monotherapy while a mean increase of 0.95 kg was observed in the pioglitazone + metformin group.[64] Kenako and colleagues also observed an increase in weight, from baseline, in the pioglitazone + sulphonylurea group (+1.4 kg), compared to a slight decrease in the sulphonylurea monotherapy group (-0.1 kg).[31] In the study by Kipnes and colleagues, there was a mean decrease of 0.8 kg in weight for patients treated with sulphonylurea monotherapy, compared to mean increases of 1.9 kg and 2.9 kg for the pioglitazone 15 mg/day and pioglitazone 30 mg/day add-on therapy groups, respectively.[65] Finally, Rubin and colleagues reported a 5% higher incidence of weight gain in patients on pioglitazone+insulin regimen, compared to insulin monotherapy.[66]

Blood pressure: Scherbaum and Göke reported a small decrease from baseline of 5 mm Hg in systolic blood pressure for patients on pioglitazone but no changes for diastolic blood pressure. An increase from baseline of 1 mm Hg in systolic blood pressure and no changes in diastolic blood pressure were observed for patients on acarbose. When blood pressure was assessed in the subgroup of hypertensive patients, pioglitazone was associated with a decrease from baseline of 10 mm Hg and 2 mm Hg in systolic and diastolic blood pressures, respectively. Patients on acarbose had a decrease from baseline of 1.5 and 2 mm Hg in systolic and diastolic blood

pressures, respectively.[70] In the trial conducted by Miyazaki and colleagues, no significant changes in blood pressure were observed in either the pioglitazone/sulphonylurea group or the sulphonylurea monotherapy group.[32]

Edema: Einhorn and colleagues reported that 5.9% of subjects in the pioglitazone/metformin group, compared to 2.5% in the metformin monotherapy group, had edema. No patient withdrew from the study due to edema or HF.[64] Kipnes and colleagues reported an incidence of edema of 7% in the combined pioglitazone + sulphonylurea groups, compared with 2% in the sulphonylurea monotherapy group. Events were considered to be mild to moderate in nature but one patient in the pioglitazone 15 mg/day combination group was withdrawn from the study because of edema.[65] Finally, the incidence of edema reported by Rubin and colleagues was 8% higher in the pioglitazone/insulin groups, compared to insulin monotherapy.[66]

In summary, pioglitazone use was associated with weight gains varying from 0.95 to 3.6 kg, a small decrease from baseline in systolic blood pressure and a higher occurrence of edema. The magnitude of the weight gain may have been related to the dose and the regimen used. Preliminary information would suggest that the decrease in blood pressure observed is more important in patients with type 2 diabetes and hypertension. Highest occurrence of edema was observed when pioglitazone was combined with insulin.

4 BUDGET IMPACT ANALYSIS

4.1 Background

An important consideration for any treatment modality is its cost. The purpose of this budget impact analysis was to examine the potential impact of the introduction of pioglitazone and rosiglitazone on costs at a macro level. The perspective taken for this analysis was that of Canadian provincial drug plans. It should be noted that this was not a full economic evaluation, in which both costs and consequences would have been analyzed for an assessment of "value-for-money". Instead, our budget impact analysis examined only the cost side at a macro level: specifically, the potential impact on provincial drug plan costs that the listing of rosiglitazone and pioglitazone could cause for the year 2004.

Rosiglitazone and pioglitazone received Health Canada approval in 2000.[71] Table 3 shows their formulary status as of 2002.

Table 3: Formulary status of Rosiglitazone and Pioglitazone*

Jurisdiction	Rosiglitazone	Pioglitazone
BC	D	U
AB	S	S
SK	S	S
MB	S	N
ON	N	N
QC	S	S
NB	S	S
NS	N	N
PEI	N	N
NF	S	S
NIHB¶	S	S

*As of 2002
Source: Compliance and Enforcement Section, PMPRB
Legend:
D – Declined
S – On formulary with "special access" requirements
U – Currently under review
N – Not listed on formulary
¶ – Non-insured health benefits program of Health Canada

Our intention in this budget impact analysis was not to provide an accurate prediction of what the provincial drug plan expenditure on rosiglitazone and pioglitazone will actually be in 2004. That will depend on the formulary status the provinces choose to award, among other factors. Instead, we provided an estimate of the cost impact for the provincial drug plans "as if" rosiglitazone and pioglitazone had been listed in provincial formularies for use without restriction, under a range

of plausible scenarios. The intention was to provide input to decision makers for consideration in their budget planning. For the main analysis (base results analysis), we postulated that the listing of pioglitazone and rosiglitazone could have two effects on drug utilization: i) they could replace some utilization of non-thiazolidinedione oral anti-diabetic agents for type 2 diabetes mellitus, and ii) they could be added to monotherapy with a non-thiazolidinedione oral anti-diabetic agents (add-on therapy). In economic terms, they could be used as substitutes, or compliments, or both. In addition, as a secondary analysis, we followed a similar approach for the effect of thiazolidinedione listing on type 2 diabetes mellitus patients who are being treated with insulin.

The budget impact was calculated with 1999 usage levels as the base case. That was the latest year for which the PMPRB database we used had data on oral anti-diabetic agents. Since rosiglitazone and pioglitazone were not on the Canadian market then (they were approved by Health Canada in 2000), this gives a clear picture of utilization patterns prior to their introduction. The impact was projected to 2004. The base results analysis included three scenarios: a 1%, 2.5%, and 5% expenditure impact. For example, the 1% scenario supposes that 1% of 1999 expenditure on oral anti-diabetics is replaced by rosiglitazone and pioglitazone, and 1% of 1999 expenditure is used in combination with rosiglitazone and pioglitazone. The 2.5% and 5% scenarios were analyzed in a similar fashion. A 7.5% scenario was added to the base results as an upper bound sensitivity analysis.

4.2 Methods

4.2.1 Rationale

Published estimates for "switch rates" and "add-on rates" for new uses of drugs would be useful, but, as in this case, they are rarely available in the literature. Therefore, the following rationale was used to arrive at plausible rates. Because type 2 diabetes is a progressive disease, a certain proportion of patients will require adjustment to their drug therapy over time. Observations from the UKPDS study indicate that after three years of monotherapy, only 50% of patients with type 2 diabetes were adequately controlled.[72] Accordingly, we have estimated that about 10% to 20% of patients with this condition will require some form of intensification of therapy every year.

The question then was: what proportion of this population would use thiazolidinediones? Since there is currently long term complication data available from the UKPDS study for traditional agents such as metformin and sulphonylureas and since similar long-term data are not available for the thiazolidinediones, it would be anticipated that thiazolidinediones would mainly be prescribed as second-line agents, for patients not responding to traditional agents. For non-responders to current treatment, clinicians may "switch" an agent for another one or may add an agent to current treatment. We assumed that one "non-responder" in four will switch to a thiazolidinedione, i.e. 2.5% to 5% of the population with type 2 diabetes. Similarly, it was assumed one in four will "add-on" a thiazolidinedione. The 1% scenario was a lower bound analysis. As mentioned above, a 7.5% scenario was added as a sensitivity analysis.

4.2.2 Data sources

The PMPRB provided the data used in the budget impact analysis. The data includes program expenditure and quantity information, for the period 1995 to 1999, based on six provincial drug programs: British Columbia (BC), Alberta (AB), Saskatchewan (SK), Manitoba (MB), Ontario (ON) and Nova Scotia (NS). The provincial information was provided to the PMPRB to allow it to fulfill its mandate to conduct analysis as part of the Federal Provincial Territorial (F/P/T) Working Group on Drug Prices.

The manufacturers' list prices for pioglitazone and rosiglitazone were extracted from the PPS Pharma Publication (2001 edition) and Lifecycle databases. These sources represent publicly available manufacturers' list price information for these drugs. It should be noted that because rosiglitazone and pioglitazone are new patented drug products recently introduced in Canada, their prices were under review at PMPRB at the time our analysis was conducted.

To translate quantities into days of treatment, the PMPRB constructed a file based on defined daily dose (DDD) information produced by the World Health Organization (WHO).[73] The file includes DDD information for most drugs sold in tablet or capsule form.

4.2.3 Methodology

Table 4 lists oral anti-diabetic agents used for type 2 diabetes. This group of drugs has the code A10B in the Anatomical Therapeutic Chemical (ATC) Classification System for Human Medicines. Table 4 shows that in 1999, for the six provinces covered in this database, expenditure on the A10B drugs was about $27 million. Expanding that to a figure for Canada, based on population, gives a figure of about $37 million. The total Canadian figure should be interpreted realizing that the contribution from the provinces and territories not included in the PMPRB database (Newfoundland (NF), Prince Edward Island (PEI), New Brunswick (NB), Québec (QC), Yukon, North West Territories (NWT), Nunavut (NVT)) was a projection based on their proportion of the total Canadian population and not on regional patterns of utilization of oral anti-diabetic agents.

Table 4: Oral anti-diabetic agents

ATC Code	DIN	Brand Name	Chemical Ingredient	Defined Daily Dose (MG)	Total 1999 Expenditure	Share (%)
A10BA02	2045710	NOVO-METFORMIN TAB 500MG	METFORMIN HYDROCHLORIDE	2000	2,319,871	8.6
A10BA02	2099233	GLUCOPHAGE - TAB 500MG	METFORMIN HYDROCHLORIDE	2000	5,539,034	20.6
A10BA02	2148765	GEN-METFORMIN - TAB 500MG	METFORMIN HYDROCHLORIDE	2000	157,564	0.6
A10BA02	2162822	NU-METFORMIN - TAB 500MG	METFORMIN HYDROCHLORIDE	2000	6,545,814	24.3
A10BA02	2167786	APO-METFORMIN - TAB 500MG	METFORMIN HYDROCHLORIDE	2000	873,402	3.2
A10BB01	720933	EUGLUCON (**)	GLYBURIDE	10	15,063	0.1
A10BB01	720941	EUGLUCON (**)	GLYBURIDE	10	210,986	0.8
A10BB01	808733	GEN GLYBE TAB 2.5MG	GLYBURIDE	10	274,081	1.0
A10BB01	808741	GEN GLYBE TAB 5MG	GLYBURIDE	10	2,988,084	11.1
A10BB01	1900927	ALBERT GLYBURIDE TAB 2.5MG	GLYBURIDE	10	5,960	0.0
A10BB01	1900935	ALBERT GLYBURIDE TAB 5MG	GLYBURIDE	10	98,682	0.4
A10BB01	1913654	APO GLYBURIDE TAB 2.5MG	GLYBURIDE	10	6,692	0.0
A10BB01	1913662	APO GLYBURIDE TAB 5MG	GLYBURIDE	10	533	0.0
A10BB01	1913670	NOVO-GLYBURIDE TAB 2.5MG	GLYBURIDE	10	9,618	0.0
A10BB01	1913689	NOVO-GLYBURIDE TAB 5MG	GLYBURIDE	10	133,832	0.5
A10BB01	1987534	DIABETA TABLETS 2.5MG	GLYBURIDE	10	230,773	0.9
A10BB01	1987836	DIABETA TAB 5MG	GLYBURIDE	10	2,765,774	10.3
A10BB01	2020734	NU-GLYBURIDE TAB 2.5MG	GLYBURIDE	10	178,905	0.7
A10BB01	2020742	NU-GLYBURIDE TAB 5MG	GLYBURIDE	10	2,099,423	7.8
A10BB01	2224550	DIABETA - TAB 2.5MG	GLYBURIDE	10	14,024	0.1
A10BB01	2224569	DIABETA - TAB 5MG	GLYBURIDE	10	317,291	1.2
A10BB01	2236734	PMS-GLYBURIDE (**)	GLYBURIDE	10	36,704	0.1
A10BB02	21350	NOVO-PROPAMIDE 250MG	CHLORPROPAMIDE	380	12,595	0.0
A10BB02	24708	DIABINESE TAB 100MG	CHLORPROPAMIDE	380	61,200	0.2
A10BB02	312711	APO CHLORPROPAMIDE TAB 250MG	CHLORPROPAMIDE	380	1,524	0.0
A10BB02	399302	APO CHLORPROPAMIDE TAB 100MG	CHLORPROPAMIDE	380	31,644	0.1
A10BB03	21849	NOVO-BUTAMIDE 500MG	TOLBUTAMIDE	1500	14,874	0.1
A10BB03	312762	APO TOLBUTAMIDE TAB 500MG	TOLBUTAMIDE	1500	11,345	0.0
A10BB09	765996	DIAMICRON TAB 80MG	GLICLAZIDE	160	239,521	0.9
A10BB31	15598	DIMELOR TABLET 1843 500MG	ACETOHEXAMIDE	500	507	0.0
A10BF01	2190885	PRANDASE - TAB 50MG	ACARBOSE	300	274,841	1.0
A10BF01	2190893	PRANDASE - TAB 100MG	ACARBOSE	300	1,439,871	5.4
					26,910,030	**100.0**

* Source: **ATC index with DDDs**[73]

**Euglucon and PMS-Glyburide were not included in the impact calculations because the PMPRB database does not include dosage information for these products. The excluded products account for about one percent of expenditures.

For each brand name listed in Table 4, expenditures were aggregated across patients by drug identification number (DIN). The appropriate proportion of this sum (1%, 2.5%, or 5%) was then taken for each province. When a patient is switched to a thiazolidinedione, there is a savings in expenditure on non-thiazolidinedine drugs that are not used. We have called this expenditure saving due to switching "displaced expenditure". In terms of the 1999 base year, the estimated potential saved expenditures on non-thiazolidinedine drugs A10B drugs are given below in Table 5.

Table 5: Estimated displaced expenditures (1999 base year)

Scenario	AB	NS	ON	MB	SK	BC
1%	$30,828	$4,237	$156,058	$21,148	$12,631	$44,198
2.5%	$77,069	$10,593	$390,146	$52,869	$31,579	$110,495
5%	$154,138	$21,187	$780,291	$105,738	$63,157	$220,990

To calculate the additional expenditures that could be generated if 1%, 2.5%, or 5% of patients were switched to one of the thiazolidinediones, the approach was as follows:

1) The "defined daily dose" file was used to translate A10B quantities at DIN level into patient days of treatment, and summed across DINs; 1%, 2.5%, or 5% of this sum was taken to obtain the three scenarios for each province.
2) The prices for pioglitazone (45 mg tablet: $4.15 per tablet) and rosiglitazone (8 mg tablet: $2.75 per tablet) were obtained from the PPS Pharma Publication and Lifecycle databases. An average price of $3.31 for rosiglitazone and pioglitazone was obtained based on utilization (using a 60%/40% market share split).
3) "Days of treatment" obtained in step (1) was multiplied by the average price obtained in step (2).

The additional potential expenditures from switching for 1999 are reported in Table 6.

Table 6: Estimated new expenditures (1999 base year)

Scenario	AB	NS	ON	MB	SK	BC
1%	$325,449	$56,590	$2,043,707	$293,434	$208,398	$523,017
2.5%	$813,623	$141,475	$5,109,268	$733,585	$520,996	$1,307,542
5%	$1,627,246	$282,951	$10,218,536	$1,467,170	$1,041,992	$2,615,084

To obtain estimated displaced expenditures and new expenditures from switching projected to 2004, a constant annual five percent growth in drug use was assumed for the base results analysis. This assumption was based on analysis contained in the section on Oral Anti-diabetics in Pharmacast & Beyond.[74] This assumption raised the 1999 expenditures by 27.6 percent (five percent growth over five years). These results are presented in Tables 7 and 8.

Table 7: Estimated displaced expenditures at 2004 projection

Scenario	AB	NS	ON	MB	SK	BC
1%	$39,345	$5,408	$199,174	$26,990	$16,121	$56,409
2.5%	$98,362	$13,520	$497,936	$67,476	$40,303	$141,023
5%	$196,724	$27,040	$995,872	$134,951	$80,606	$282,045

Table 8: Estimated new expenditures at 2004 projection

Scenario	AB	NS	ON	MB	SK	BC
1%	$415,365	$72,225	$2,608,346	$374,504	$265,975	$667,517
2.5%	$1,038,412	$180,562	$6,520,864	$936,261	$664,937	$1,668,792
5%	$2,076,823	$361,125	$13,041,729	$1,872,522	$1,329,875	$3,337,583

In order to get the net budget impact, we note that our rationale (section 4.2.1) includes an equal amount of "switching-to" and "adding-on" of rosiglitazone and pioglitazone. So, for the 1999 base case for example, we would need to double the new expenditure effect (Table 6) and subtract from that the savings from displaced expenditures (Table 5). Those results are presented below in Table 9 for the 1999 base year and in Table 10 for the 2004 projection.

4.3 Results

Tables 9 and 10 below present estimates of the increase to provincial drug plan expenditures resulting from the introduction of pioglitazone and rosiglitazone. As in the methods section, we present results for low (1%) medium (2.5%) and high penetration scenarios (5%). It is clear that cost savings from displaced expenditures on other anti-diabetic drugs are far outweighed by increased expenditures from switching-to or adding-on pioglitazone and rosiglitazone.

Table 9: Estimated increase to provincial drug plans (1999 base year)

Scenario	AB	NS	ON	MB	SK	BC
1%	$620,070	$108,943	$3,931,356	$565,720	$404,165	$1,001,836
2.5%	$1,550,177	$272,357	$9,828,390	$1,414,301	$1,010,413	$2,504,589
5%	$3,100,354	$544,715	$19,656,781	$2,828,602	$2,020,827	$5,009,178
Population	2,959,429	939,222	11,517,304	1,142,562	1,025,720	4,028,132
Canada Total Population 1999[75]: 30,493,433						

Table 10: Estimated increase to provincial drug plans (2004 projection)

Scenario	AB	NS	ON	MB	SK	BC
1%	$791,385	$139,042	$5,017,518	$722,018	$515,829	$1,278,625
2.5%	$1,978,462	$347,604	$12,543,792	$1,805,046	$1,289,571	$3,196,561
5%	$3,956,922	$695,210	$25,087,586	$3,610,093	$2,579,144	$6,393,121
Population	3,117,172	948,334	12,248,592	1,156,388	1,026,982	4,285,911
Canada Total Population 2004:[75] 31,756,242						

For ease of reference, the 1999 and 2004 (projected) populations for the provinces and territories not included in the PMPRB database are reported below in Table 11. By using Table 11 and Table 12 the reader could calculate estimated cost increases for the non-included provinces.

Table 11: Population statistics for non-included provinces and territories

Year	NF	PEI	NB	QC	YK	NWT	NVT
1999	540,775	137,639	754,348	7,349,103	31,084	41,113	27,002
2004	531,963	141,006	758,857	7,437,551	30,721	43,002	29,763

Table 12 shows estimated impacts on Canada for the 1999 base year and 2004 projection. They are based on drug plan utilization data for the included provinces (AB, NS, ON, MB, SK, BC), which are then expanded based on population proportion to get the total figure for Canada.

Table 12: Total estimated cost increase to drug plans

Year	Scenario	Total Impact for Included Provinces	Total Estimated Impact for Canada	Estimated Impact per Canadian*
1999	1%	$6,632,090	$9,357,382	$0.31
	2.5%	$16,580,227	$23,393,458	$0.77
	5%	$33,160,457	$46,786,920	$1.53
		Population included in provinces: 21,612,369	Population in Canada: 30,493,433	
2004	1%	$8,464,417	$11,797,990	$0.37
	2.5%	$21,161,036	$29,494,966	$0.93
	5%	$42,322,076	$58,989,937	$1.86
		Population included in provinces: 22,783,379	Population in Canada: 31,756,242	

*Calculated as the total estimated cost impact for Canada divided by the total Canadian population.

4.4 Sensitivity Analysis

The results thus far will be referred to as the "base results". In addition, sensitivity analyses were carried out varying the assumptions on prices, market growth rate* (adding 2.5% and 7.5% growth scenarios to the 5% growth base results analysis), and percent of patients switching to or adding-on thiazolidinediones (adding a 7.5% scenario). The detailed sensitivity analysis results are presented in Appendix 6, in Tables 13-21.

As for the base results analysis, for each of the appendix tables for the sensitivity analysis the estimates for the included provinces are based on actual regional 1999 utilization patterns of non-thiazolidinedione oral anti-diabetic agents in the provincial drug plans. The "total Canada" estimate, however, is calculated by scaling up the total included province figure based on proportion of population.

* The assumptions underlying the market growth rate scenarios are based on analysis contained in the section on Oral Antidiabetics in **Pharmacast & Beyond: Canada**[74]

In Table 13, an additional element is added to the base results – a scenario where 7.5% of patients require optimization of their treatment regime. The details for the included provinces are contained in the table. The effect is to boost the 2004 estimate for increased expenditures relative to the 5% switching-to or adding-on scenario for the included provinces and for Canada as a whole: $63.5 million versus $42.3 million, and $88.5 million versus $59 million respectively.

Table 14 shows a low price lower bound scenario, where rosiglitazone predominates and its price of $2.75 per tablet is given full weight in the aggregate price. The reader is referred to the appendix tables for the details. As an example, the base result for the 5% switching-to and adding-on scenario for the Canadian estimate can be compared to the corresponding low price result in Table 14. An expenditure increase of $59 million for the base result compares to $48.6 million for the low price assumption.

Several other price sensitivity analyses were carried out, and they are all summarized in Table 22 using the total Canada estimate as an example. Again, the reader is referred to the various appendix tables for details.

Table 22: Other pricing sensitivity results

Appendix Table	Difference from Base Result Assumptions	Sensitivity Analysis Results for Increased Canadian Expenditures (5% Optimization)	Base Result for Increased Canadian Expenditures (5% Optimization)
14	Low price scenario $2.75 aggregate price	$48.6 million	$59 million
15	High price scenario $4.15 aggregate price	$74.6 million	$59 million
18	75%/25% split for rosiglitazone and pioglitazone, (vs. 60%/40%) $3.10 aggregate price	$55.1 million	$59 million
19	Rosiglitazone at $3.86 and pioglitazone at $4.15 for a $3.976 aggregate price	$71.3 million	$59 million
20	$3.22 aggregate price	$57.3 million	$59 million

Sensitivity analysis was also carried out on the base result assumption of a 5% annual growth for drug utilization. Table 16 presents detailed results for a low growth rate assumption of 2.5% and Table 17 shows results for a high growth rate of 7.5%. At 2.5% growth rate and assuming a 5% rate for switching-to or adding-on a thiazolidinedione, the estimated expenditure increase for Canada was $52.3 million. At 7.5% it was $66.3 million. This compares with the base result analysis (which assumes 5% growth rate) of $59 million.

4.5 Insulin Analysis

To assess the possible influence of thiazolidinedione listing on costs for patients using insulin, we used a similar methodology to that used in our base results analysis for oral anti-diabetic agents. Again, our perspective was that of the provincial drug plans.

We assumed that 50% of all insulin claims to provincial drug plans are for patients with type 2 diabetes, based on the following reasoning. To estimate the proportion of insulin claims for patients with type 2 diabetes, it was assumed that about 10% of them will progress to insulin therapy. Since about 90% of diabetes patients have type 2 diabetes, approximately 9% of the entire population with diabetes will be patients with type 2 diabetes on insulin. Also, all patients with type 1 diabetes (10% of all patients with diabetes) will require insulin. Since the proportion of patients on insulin is similar between type 1 and type 2 (each with 9% or 10% of the entire diabetic population), we assume that 50% of all insulin claims will be for patients with type 1 diabetes, and 50% will be for patients with type 2 diabetes.

Table 23: Insulin products commonly used in type 2 diabetes mellitus*

Insulin Preparations	Brand Name	DIN	Price per Container	Price/day
Short-acting insulin preparations	Humulin R 3 ml cartridge	01959220	$3.64	$0.15
	Humulin R 10 ml vial	00586714	$3.40	$0.04
	Novolin GE Toronto 10 ml vial	02024233	$3.05	$0.04
	Novolin GE Toronto 3 ml cartridge	02024284	$3.62	$0.14
Intermediate-acting Insulin preparations	Humulin N 3 ml cartridge	01959239	$3.31	$0.26
	Humulin N 10 ml vial	00587737	$3.50	$0.08
	Novolin GE NPH 10 ml vial	02024225	$3.07	$0.07
	Novolin GE NPH 3 ml cartridge	02024268	$3.61	$0.29
Pre-mixed Insulin preparations	Humulin 30/70 3 ml cartridge	01959212	$3.40	$0.41
	Humulin 30/70 10 ml vial	00795879	$3.87	$0.14
	Novolin GE 30/70 10 ml vial	02024217	$5.22	$0.19
	Novolin GE 30/70 3 ml cartridge	02025248	$4.00	$0.48

* Source: PMPRB

Table 23 lists the insulin products we assumed most patients with type 2 diabetes are using. These are a subset of the code A10A group of drugs in the ATC Classification System for Human Medicines. These products were used for the calculation of "displaced expenditures" when patients not well controlled on traditional oral agents can possibly delay the initiation of insulin treatment by using a thiazolidinedione. For each brand name listed in Table 14, expenditures were aggregated across patients by DIN for 1999. It should be noted that the price per day was calculated based on an average dose of 0.5 unit/kilogram/day for an adult of 70 kilograms. The usual treatment options are pre-mixed insulin, or a combination of short and intermediate-acting insulin. For patients using the short and intermediate-acting insulin preparations it was assumed that one third of the daily dose was in the form of short-acting insulin and two-thirds in the form of intermediate-acting insulin. The pre-mixed 30/70 preparations contain both short and intermediate-acting insulin pre-mixed in a 30% and 70% ratio. The appropriate proportion of the sum (1%, 2.5%, 5%, or 7.5%) was then taken for each

province, and that amount was projected to 2004 using a 5% annual growth rate for drug use. The results are presented in Table 24.

Table 24: Estimated displaced expenditures at 2004 projection – insulin analysis

Scenario	AB	NS	ON	MB	SK	BC
1%	$17,324	$2,445	$56,911	$12,352	$15,492	$27,740
2.5%	$43,311	$6,113	$142,278	$30,880	$38,729	$69,349
5%	$86,622	$12,225	$284,556	$61,760	$77,459	$138,698
7.5%	$129,933	$18,338	$426,833	$92,640	$116,188	$208,048

It should be noted that there might be additional cost savings in delaying the initiation of insulin that are not taken into account in our analysis. Use of ancillary equipment necessary for insulin treatment such as syringes, needles, alcohol swabs and blood glucose test strips may be reduced or eliminated for the period of time patients will not require insulin. However, the cost for these is not covered by all provincial drug plans. Also, glucose monitoring costs were not considered in our base results analysis. Glucose monitoring is required for patients on oral anti-diabetic agents, although at somewhat less frequent intervals than for patients on insulin therapy. Accordingly, these ancillary costs were not considered in the insulin analysis.

"New expenditures" for switching-to or adding-on thiazolidinediones were calculated using a method analogous to that for the oral anti-diabetics base results. As short and intermediate-acting preparations are generally used in combination, only the intermediate-acting and pre-mixed preparations were used for the new expenditure calculation. Including the short-acting preparations would have resulted in double counting in terms of thiazolidinedione utilization. The new expenditure projections for 2004 are presented in Table 25. As in the case of the oral anti-diabetic agents, the new expenditure effect is much larger than the savings from displaced expenditures, and an increase in provincial drug plan expenditures for insulin users would be expected from listing of the thiazolidinediones.

Table 25: Estimated new expenditures at 2004 projection – insulin analysis

Scenario	AB	NS	ON	MB	SK	BC
1%	$688,323	$86,012	$301,163	$474,608	$66,040	$847,808
2.5%	$1,720,809	$215,029	$752,908	$1,186,521	$165,100	$2,119,520
5%	$3,441,617	$430,059	$1,505,816	$2,373,042	$330,200	$4,239,040
7.5%	$5,162,426	$645,088	$2,258,724	$3,559,563	$495,300	$6,358,560

Details of the net cost impact to drug plans, with the individual included province estimates, are reported in Appendix 6, Table 21. As was done in the oral anti-diabetic agents analysis, the net impact is calculated as twice the new expenditures, less the displaced expenditures. Table 26 below shows the results for the six included provinces (which are based on regional insulin utilization patterns) and for Canada (scaled up based on proportion of population).

Table 26: Estimated cost impact to drug plans in 2004 – insulin analysis

Scenario	Total Estimated Impact for Included Provinces	Total Estimated Impact for Canada
1 %	$4,795,646	$6,684,333
2.5 %	$11,989,114	$16,710,831
5 %	$23,978,228	$33,421,663
7.5 %	$35,967,342	$50,132,494

5 DISCUSSION

5.1 Clinical Efficacy and Safety

Our review demonstrates that both rosiglitazone and pioglitazone are effective in reducing HbA1c and FPG in adults with type 2 diabetes. The decrease in glycemia was significant when either agent was used as add-on therapy with another agent. When monotherapy was studied however, these agents did not produce an effect significantly different from that of the other oral anti-diabetic agents.

Efficacy: Combined clinical data indicate that rosiglitazone monotherapy caused a slightly larger decrease from baseline in both HbA1c and FPG, while pioglitazone monotherapy caused a slightly smaller decrease from baseline in these endpoints, compared to other anti-diabetic agents. Because monotherapy findings for the two thiazolidinediones were based on only two small trials which we assigned relatively low quality scores, our results are likely not definitive. Pooled estimates of all add-on regimens for both drugs showed a statistically significant reduction in HbA1c and FPG, compared to simply continuing monotherapy with non-thiazolidinedione agents. The reductions in glycemic parameters for add-on regimens, even if relatively small in absolute numbers, are clinically significant. It has been shown that there is a 35% reduction in the risk of diabetic microvascular complications for every percentage point reduction in HbA1c.[5]

These results are comparable to the findings reported in clinical trials evaluating combination therapy with two traditional agents such as metformin and sulphonylureas. For example, Hermann and colleagues[76] reported that monotherapy with metformin led to glycemic control comparable to the control observed with glyburide monotherapy. Adding one of these agents to the other, particularly when prescribed in the higher dosage range in patients who had not achieved good glycemic control with monotherapy, led to a significant reduction in glycemia.[76] Recently, Inzucchi and colleagues reviewed several anti-diabetic combination (add-on) regimen studies and reported that, with few exceptions, the addition of one oral agent to an oral agent of another class led to a statistically significant additive reduction in HbA1c.[72]

Our findings do not provide information on the long-term effects of rosiglitazone and pioglitazone on the progression of diabetic complications. Additional studies, similar to the UKPDS study that provided evidence of morbidity and mortality benefits with traditional anti-diabetic agents such as insulin, sulphonylureas and metformin, will be required to determine the long-term value of rosiglitazone and pioglitazone in patients with type 2 diabetes.

Safety: From a safety perspective, thiazolidinediones were generally well tolerated. Both agents had favorable effects on HDL-cholesterol, but rosiglitazone was associated with a larger increase in both total cholesterol and LDL-cholesterol, compared to other anti-diabetic agents. It has been suggested that this increase in LDL-cholesterol levels could be predominantly explained by a shift from small and dense to large and buoyant LDL-cholesterol particles, which may be less atherogenic. However, these observations on changes in LDL-cholesterol composition originated from troglitazone studies and have not been confirmed with rosiglitazone or pioglitazone.[72,77]

A possible limitation of the pooled estimate for LDL-cholesterol levels is that median changes from baseline, as opposed to mean changes, were used for one of the pooled trials. As indicated in section 3.1.5, this was based on the assumption that for lipid parameters, mean and median values are similar. The pioglitazone effect on both total cholesterol and LDL-cholesterol was not different from the one observed for other oral anti-diabetic agents. Rosiglitazone was associated with a mild increase from baseline in triglyceride levels, but this increase appeared smaller than that observed with other anti-diabetic agents. However, pioglitazone was associated with a decrease from baseline in triglyceride levels when evaluated against comparative regimens. The effect of thiazolidinediones on serum lipid parameters may be an important clinical consideration, as dyslipidemia plays an important part in the development of atherosclerosis and diabetes mellitus is an important risk factor for the development of atherosclerotic disease.[78]

There were no liver-related serious adverse events reported in the trials reviewed. However, troglitazone, the first thiazolidinedione approved by the FDA in 1997, was withdrawn from the US market in 2000, following 61 reports of fatal hepatotoxicity possibly or probably associated with the drug and seven cases requiring liver transplant.[79] The cause of troglitazone hepatotoxicity has not yet been identified, therefore it is not yet clear whether this undesired reaction is actually a class effect that all thiazolidinediones share, or whether it is specific to troglitazone. Despite sharing the same thiazolidine-2-4-dione chemical structure, it appears that troglitazone, rosiglitazone and pioglitazone do not share the same metabolic pathway. The hepatotoxicity observed with troglitazone might be related to its α-tocopherol side chain, although this is still controversial.[79] Also, troglitazone was associated with a higher occurrence of elevated liver enzymes, compared to placebo, in all placebo-controlled clinical trials, while for rosiglitazone and pioglitazone the incidence was equal to placebo.[79] It has therefore been suggested that hepatotoxicity is not a thiazolidinedione class effect.[79]

Nonetheless, three possible cases of rosiglitazone-induced hepatotoxicity were reported in 2000.[16-18] A direct cause-effect relationship could not be established and other factors might have explained the patients' symptoms, at least in two of the reported cases.[80,81] Health Canada recently reported one death in a patient using rosiglitazone, along with other medications. Liver enzymes were elevated. Ten cases of possible hepato-biliary problems were also reported, although there was insufficient information to link these to rosiglitazone.[82] Recently, two cases of hepatocellular injury possibly associated with pioglitazone were reported.[19,20] Manufacturers of the drugs have listed a contraindication to use of their respective thiazolidinedione in patients with serious hepatic impairment. Monitoring of liver enzymes is also recommended prior to initiation of the drug, and periodically thereafter.[13,14]

Relatively mild anemia was reported for both rosiglitazone and pioglitazone patients in the trials reviewed. This generally did not lead to participant withdrawal, except for two rosiglitazone users in the study by Fonseca et al.[36]

A limited number of trials reported a reduction in blood pressure for patients using either rosiglitazone or pioglitazone. Although this reduction was small, it carries the potential for a therapeutic benefit, considering that hypertension has been linked to insulin resistance.[6] Also, weight gain and edema were more frequent in the rosiglitazone and pioglitazone-treated subjects, compared to control groups. One subject treated with a pioglitazone/sulphonylurea combination

regimen was withdrawn from the study by Kipnes and colleagues because of edema.[65] The percentage of patients with edema was highest in the studies assessing the concurrent use of a thiazolidinedione and insulin. Raskin and colleagues reported HF in four patients on the insulin plus rosiglitazone regimens and one patient on the insulin monothrapy.[26] There is concern that edema could potentially exacerbate HF in some patients. Pioglitazone is contraindicated in patients with New York Heart Association (NYHA) Class II, III or IV cardiac status.[14] Rosiglitazone is contraindicated in patients with NYHA Class III or IV cardiac status.[13] In addition, both Health Canada[83] and the FDA[84] recently released a safety reminder for patients not to use these drugs if they develop signs and symptoms of HF.

Hypoglycemic symptoms were infrequent when rosiglitazone or pioglitazone were used as monotherapy. They were more common when thiazolidinediones were used in combination with another oral anti-diabetic agent. Combination use of insulin and a thiazolidinedione was associated with the highest rate of hypoglycemia. It should be noted that none of the thiazolidinediones are currently approved for use in combination with insulin in Canada.[13,14]

Limitations: Interpretation of our results should be made in light of a number of limiting factors. For the review of clinical evidence, the studies included were generally rated by us to be of low to intermediate quality. It is possible that this was a consequence of the reporting format of several studies (abstracts, posters), which did not allow reporting of many details.

The two primary outcomes, FPG and HbA1c, were assessed over a mix of different observation periods varying from 12 to 52 weeks. These observation periods should allow proper assessment of the effect of thiazolididiones on glycemic control as the minimal time required to measure the effect is 12 weeks, based on the temporal response for both glyburide and rosiglitazone.[53] However, they do not allow assessment of the long-term effects of the drugs on morbidity and mortality. We are aware that a number of these trials have been extended into open-label studies. However, even if the observation period was extended to 148 weeks as was done by investigators who were part of the study by St. John Sutton and colleagues,[54,58] it would still not allow measurement of the long-term clinical benefit (or harm) of thiazolidinediones on diabetic complication-related morbidity and mortality.

Our review was limited to monotherapy and add-on therapy regimens with two anti-diabetic agents. Triple therapy consisting of adding a thiazolidinedione to regimens for patients with type 2 diabetes inadequately controlled on maximum doses of sulphonylureas and metformin is now emerging.[85-87]

Heterogeneity was observed for a number of combined results, particularly for pioglitazone. This means the variation between the results of these trials may not be explained solely on the play of chance.[88] Instead, such statistical heterogeneity may be partially explained by the underlying clinical heterogeneity across the trials included.[88] As examples, trials included in the current review have been conducted in many areas of the world, including North America (Canada, US, Mexico), Western Europe and Asia (India, China, Japan). Also, although the majority of the participants in these trials did not have satisfactory control of their glycemia prior to study entry, only one trial included newly diagnosed patients.[67,68] In another study, subjects were on a special diet and counselled by a dietician.[32]

Clinical heterogeneity may not have been the only source of statistical heterogeneity. Indeed, the quality of the methodology used in the included studies may have been another important factor.[88] For instance, although all trials reviewed randomized participants, some used an unblinded design,[37,38,52,56] which led to a lower quality assessment score. Although most trials had a run-in period prior to randomization, participants had to discontinue their regular regimen prior to randomization in a number of trials.[36,44,52,56,63-67] This carries the potential for inadequate glycemic control in the comparator groups as subjects may have been reasonably stabilized on a specific regimen prior to study entry. This approach has been criticized as subjects in the control groups might have lost glucose control, resulting in a difference between the active and control groups owing more to worsening control in the latter group than to benefit in the treated group.[89] These factors, and possibly others, may explain the significant statistical heterogeneity reported for some of the pooled estimates.

A limited sensitivity analysis was conducted for pioglitazone add-on studies for which quantitative HbA1c information was available, since statistical heterogeneity was detected when these were pooled. Various scenarios were tested, based on the above discussion (Appendix 5). Statistical heterogeneity remained despite pooling only the studies conducted in the US (scenario # 1), only pooling double-blind studies (scenario # 2) and pooling a mix of 15 mg daily regimen and 30 mg daily regimen studies (scenario # 3). However, statistical heterogeneity improved when only sulphonylurea trials were pooled (scenario # 5) and heterogeneity disappeared when only the two studies with pioglitazone 15 mg/day regimens were combined (scenario # 4). Of interest, it may be observed that the WMD for each of these scenarios is comparable to the main analysis (Figure 7), except for scenario # 4 for which only 15 mg add-on regimens were pooled. This observation, although limited, suggests our analysis is robust. Furthermore, the fact that the WMD for scenario # 4 is smaller is consistent with the lower dosing regimens used, i.e. 15 mg/day instead of 30 mg/day.

5.2 Budget Impact Analysis

Our budget impact analysis asked a hypothetical question based on the premise that pioglitazone and rosiglitazone were listed for reimbursement under the F/P/T drug plans: what would be the expected impact on costs for the drug plans in 2004? We recognize that the formulary status of rosiglitazone and pioglitazone will most likely vary from one jurisdiction to another in 2004. Table 3 in section 4.1 shows how formulary status varied among jurisdictions at the time the analysis was conducted. However, we analyzed the hypothetical case of uniform formulary listing across all provinces and territories as a "what if" exercise of potential assistance to decision makers for budget planning purposes.

The non-thiazolidinedione oral anti-diabetic drugs covered by the F/P/T drug plans, although heavily used, are relatively inexpensive, of the order of 10 cents per dosage form. By contrast the 45 mg pioglitazone tablet is $4.15 and the 8 mg rosiglitazone tablet is $2.75. Given that, it is not surprising to find that the expected impact of listing rosiglitazone and pioglitazone will be to increase expenditures. For example, for the 2.5% scenario for switching-to and adding-on, the 2004 impact on provinces included in the PMPRB database is ($millions): AB 2.0, NS 0.3, ON 12.5, MB 1.6, SK 1.3, and BC 3.2. For the non-included provinces and territories, a rough

calculation can be made using our estimated impact per Canadian, from Table 12 section 4.3, and the 2004 population estimates from Table 10. For example, for Quebec under the 2.5% scenario this gives an estimated impact of about $6.9 million for 2004. It should be noted that estimates for the included provinces were based on actual 1999 utilization patterns for the provinces included in the PMPRB database. To arrive at a total estimate for Canada, the included province total was scaled up based on population proportions. The non-included portion results were not based on regional utilization patterns (these data are not available), and should be interpreted in that light.

Some external validation of our approach is available from Alberta data. Rosiglitazone and pioglitazone became available via special authorization for the seniors' drug coverage by Alberta Health and Wellness in December 2000. Expenditures on them were $1.01 million in the period December 2000 to June 2001.[90] An annualized expenditure would therefore be approximately $2 million, which would be in line with the estimated increase in expenditures in 1999 under the 2.5% and 5% penetration scenarios for Alberta (see Table 9).

The focus of our analysis was on the impact of thiazolidinedione listing on non-thiazolidinedione oral anti-diabetic agents. When we explicitly considered the impact on insulin use, we found a similar effect in that the estimated costs saved from switching from insulin to rosiglitazone and pioglitazone were more than offset by the additional costs of switching-to or adding these drugs on. If the possible impact on insulin use is also taken into account, we estimated additional Canadian expenditure increases for the provincial drug plans across the four optimization scenarios (1%, 2.5%, 5%, and 7.5%) of $6.7 million, $16.7 million, $33.4 million, and $50.1 million respectively. However, ancillary insulin therapy equipment such as glucometers, needles and alcohol swabs were not considered in our analysis, as many of these are not covered by F/P/T drug plans. If these costs were considered, they could offset, to some degree, our estimated increased expenditures.

Our base results analysis gives an estimated expenditure increase in 2004 for F/P/T drug plans ranging from $11.8 million to $88.5 million across the 1% to 7.5% scenarios. We estimated about $37 million was spent in Canada on non-thiazolidinedione anti-diabetic drugs in 1999 (section 4.2.3). In 2004 nominal dollars, that extrapolates roughly to $41.5 million.[*] So, the magnitude of expenditures for the non-thiazolidinedione oral anti-diabetic agents as a group is comparable to the estimated impact of listing rosiglitazone and pioglitazone.

As with any exercise in modeling, there are limitations to our approach. For example, the perspective is that of the provincial drug plans, so impacts in other areas of the health care system and societal level impacts were not considered. Other possible limitations are discussed below.

The analysis on displaced expenditures includes some costs incurred by the claimants, e.g. co-payments, premiums, etc. The extent of these costs may vary by jurisdiction, reflecting differences in reimbursement rules across programs. As a result, the inclusion of claimant costs

[*] This assumes the following inflation rates for Consumer Price Index (CPI): 2.7% in 2000, 2.5% in 2001, 2.0% in 2002, 2.3% in 2003, and 2.1% in 2004. Source: The Conference Board of Canada. **WebLinx – Economic Intelligence**. Available: http://www.conferenceboard.ca/weblinx/

may cause estimates of displaced expenditures to be overstated. In addition, the estimates of displaced expenditures assume that the various F/P/T programs incur the full cost of the two new medicines for all claimants. This may not be the case because deductibles, co-payments, and other limitations differ across programs. These considerations suggest that the estimates of displaced expenditures provided reflect upper bounds.

The displaced expenditure calculations were done in terms of DDDs as used by the WHO. However the new expenditure calculations for the thiazolidinediones were carried out using their usual maximum dose tablet strengths; it is difficult to arrive at a DDD for relatively new products like rosiglitazone and pioglitazone. Accordingly, the method for calculating cost savings and new expenditures are somewhat different and may lead to more conservative estimates for displaced expenditures relative to new expenditures. Nevertheless, we have included a sensitivity analysis on prices that covers a range of possible price and dose combinations.

When estimating the impact on Canada as a whole (Table 12), the results for the included provinces (AB, NS, ON, MB, SK, and BC) were scaled up based on the proportion of total population contributed by the non-included regions. Therefore, the non-included component of the total Canada cost estimates was not based on past regional patterns of oral anti-diabetic utilization. So, for provinces and territories not in the PMPRB database (NF, PEI, NB, QC, YK, NWT, and NVT) the results should be interpreted with caution, as utilization patterns will vary from region to region based on demographic, prescribing and other factors.

Finally, published estimated rates for switching-to and adding-on of the thiazolidinediones were not available in the literature, so a plausible rationale had to be developed to obtain our estimated budget impact. This is a common feature of the budget impact analysis process in general.

6 CONCLUSION

Clinical efficacy: When used as monotherapy, both rosiglitazone and pioglitazone have an effect on HbA1c and FPG similar to the effect observed with non-thiazolidinedione comparator drugs. These findings are however based on a small number of comparative trials. Evidence available on the comparative efficacy of add-on therapy is somewhat more substantial but still limited. It shows that, when added to another anti-diabetic agent in patients with type 2 diabetes not well controlled on a single agent, both thiazolidinediones produce a significantly greater effect on HbA1c and FPG than continuing monotherapy with the other agent. These findings are consistent with the work of others that show combining two anti-diabetic agents provides greater effect than use of one agent alone. However, longer-term studies will be required to evaluate the effect of rosiglitazone and pioglitazone on the development of diabetic complications as well as to assess their long-term safety. Both rosiglitazone and pioglitazone were generally well tolerated in the trials reviewed and no serious liver adverse events were reported. However, our safety assessment was limited to 4,396 patients and most were followed for less than one year. Recently, both Health Canada and the FDA have released safety reminders about the risk of using these drugs in patients with HF.

Budget impact analysis: Based on our budget impact analysis, it is estimated that by 2004, if rosiglitazone and pioglitazone receive formulary listing throughout Canada, this listing would result in a net expenditure increase for the publicly funded drug programs varying between $11.8 and $88.5 million per year, depending on their utilization and the number of patients treated.

Note: After the completion of this report, we became aware that the results of two clinical trials included in this review as abstracts had just been published as full articles. These are:

1) *We cited*: Gómez-Perez FJ, Fanghänel-Salmón G, Berry RA, Warsi G, Gould EM. Rosiglitazone-metformin combination therapy improves glycemic control in Mexican patients with type 2 diabetes [abstract]. **Diabetes** 2001;50 Suppl 2:A436.

   The full article was published as: Gómez-Perez FJ, Fanghänel-Salmón G, Barbosa JA, Montes-Villarreal J, Berry RA, Warsi G, et al. Efficacy and safety of rosiglitazone plus metformin in Mexicans with type 2 diabetes. **Diabetes Metab Res Rev** 2002;18(2):27-34.

2) *We cited*: Rubin C, Egan J, Schneider R. Combination therapy with pioglitazone and insulin in patients with type 2 diabetes [abstract]. **Diabetes** 1999;48 Suppl 1:A110.

   The full article was published as: Rosenstock J, Einhorn D, Hershon K, Glazer NB, Pioglitazone 014 Study Group. Efficacy and safety of pioglitazone in type 2 diabetes: a randomised, placebo-controlled study in patients receiving stable insulin therapy. **Int J Clin Pract** 2002;56(4):251-7.

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APPENDIX 1: Literature Search Strategy

Search Legend

!	Explode (i.e., concept plus all sub-hierarchies)
*	Truncation symbol, any number of characters
?	Truncation symbol, single character
n	Near/next (i.e., terms are near/next to one another, any order)
" "	Phrase
l	Link (i.e., to subheading)
ti	Title
ab	Abstract
de	Descriptor
dt	Publication type
tn	Trade name
mn	Manufacturer name
nd	Device name
md	Device manufacturer
rn	Registry number (i.e., CAS)
tw	Text word

DATABASES	LIMITS	KEYWORDS/DESCRIPTORS
DIALOG® MEDLINE® EMBASE® HealthSTAR PASCAL SciSearch Toxline®	1990- Human	diabetes mellitus, non-insulin-dependent/de OR non insulin dependent diabetes mellitus/de OR "type 2 diabet*" OR "type 2 DM" OR diabet*(2n)"type 2" OR "type II diabet*" OR "type II DM" OR diabet*(2n)"type II" OR "non insulin dependent diabet*" OR NIDDM/ti,ab OR "adult onset diabet*" OR "maturity onset diabet*" OR MODY/ti,ab *AND* pioglitazone/de OR rosiglitazone/de OR thiazolidinedione* OR glitazone* OR "peroxisome proliferator activating receptor gamma agonist*" OR "PPAR gamma agonist*" OR "BRL 49653" OR BRL49653 OR pioglitazone OR rosiglitazone OR Actos OR Avandia OR Glustin OR Nyracta OR Venvia OR tn=Actos OR tn=Avandia OR tn=Glustin OR tn=Nyracta OR tn=Venvia OR rn=111025-46-8 OR rn=122320-73-4 *AND* comparative study/de OR evaluation studies/de OR clinical trials, phase II/de OR clinical trials, phase III/de OR clinical trials, phase IV/de OR controlled clinical trials/de OR multicenter studies/de OR randomized controlled trials/de OR epidemiologic research design!/de OR dt=review OR dt=meta-analysis OR dt=multicenter study OR dt=randomized controlled trial OR dt=controlled clinical trial OR dt=clinical trial, phase II OR dt=clinical trial, phase III OR dt=clinical trial, phase IV OR comparative study!/de OR controlled study!/de OR major clinical study/de OR multicenter study/de OR phase 2 clinical trial/de OR phase 3 clinical trial/de OR phase 4 clinical trial/de OR evidence based medicine!/de OR dt=review OR dt=short survey OR random* OR "double blind*" OR "double dumm*" OR "double mask*" OR "triple blind*" OR "triple dumm*" OR "triple mask*" OR "trebleblind*" OR "treble dumm*" OR "treble mask*" OR placebo* OR prospective* OR "meta analys*" OR metaanaly* OR "quantitative review*" OR "quantitative overview*" OR "systematic review*" OR "systematic overview*" OR "methodologic* review*" OR "methodologic* overview*" OR "collaborative review*" OR "collaborative overview*" OR

		"integrative research review*" OR "multicent* stud*" OR "multi-cent* stud*" OR "multicent* trial*" OR "multi-cent* trial*" OR "control* stud*" OR "control* trial*" OR RCT? OR "control* clinical trial*" OR "control* clinical stud*" OR "evaluat* stud*" OR "compar* stud*" *AND* human OR people or person? OR wom?n OR man OR men OR adult OR elderly OR aged Performed 16 May 2001 405 unique records EMBASE® - 229 records MEDLINE® - 145 records HealthSTAR - 3 records PASCAL - 23 records SciSearch - 4 records Toxline® - 3 records
The Cochrane Collaboration & Update Software Ltd. The Cochrane Library, Issue 3, 2002		diabetes mellitus, non-insulin-dependent*/de OR "non insulin dependent diabet*" OR NIDDM OR "adult onset diabet*" OR "maturity onset diabet*" OR MODY *AND* thiazolidinedione* OR glitazone* OR "peroxisome proliferator activating receptor gamma agonist*" OR "PPAR gamma agonist*" OR "BRL 49653" OR BRL49653 OR pioglitazone OR rosiglitazone OR actos OR avandia OR glustin OR nyracta OR venvia OR 111025-46-8 OR 122320-73-4 The Cochrane Database of Systematic Reviews = 1 complete review, 4 protocols; Database of Reviews of Effectiveness = 1 reference; The Cochrane Controlled Trials Register = 32 references; 1 abstract by INAHTA and other healthcare agencies
DIALOG® Alerts: ADIS LMS Drug Alerts Current Contents Search® EMBASE® Alert MEDLINE® PASCAL Pharmaceutical News	Human *(MEDLINE® only)*	*Same descriptors and keywords as per MEDLINE®, etc. Current Contents Search® and SciSearch alerts discontinued 17 Aug 2001*

Index (PNI®) SciSearch		
Websites of health technology assessment (HTA) and near-HTA assessment agencies; regulatory agencies; trial registries; other databases		e.g. NZHTA; AHRQ; Health Canada Therapeutic Products Directorate; US Center for Drug Evaluation and Research; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD databases

APPENDIX 2: Data Extraction Form

Reference number	
Study Title	

Is the diagnosis of type 2 diabetes confirmed: _____ Yes _____ No
How:_____
Is the study sponsored by a drug company: _____ Yes _____ No

Study Arms*	1		2		3	
Number of patients						
Recruited						
Dropped out						
Evaluable						
Sex						
Age (years)						
Obesity (>120% IBW)						
Drug(s)						
Dose & frequency						
Duration of tx (weeks)						
Outcomes (units**)	Baseline	End-point	Baseline	End-point	Baseline	End-point
FPG (mmol/L or mg/dL)						
HgA1c (%)						
Triglyc (mmol/Lor mg/dL)						
Total-C (mmol/L or mg/L)						
LDL-C (mmol/L or mg/L)						
HDL-C (mmol/L or mg/L)						
ALT (U/L)						
AST (U/L)						
Weight (Lb or Kg)						
CBC (/L or /mm^3)						
Hgb (g/L or g/dL)						
RBC indices (/L or /mm^3)						
Hct (%)						
Vit B12 (pmol/L or pg/mL)						
Creat (umol/L or mg/dL)						
BP (mm Hg)						
Other (Units:)						

* See protocol for definitions ** (Circle SI or conventional units)
IBW = ideal body weight

APPENDIX 3: Quality Assessment of RCTs

Jadad Scale			**Score**
1. Was the study described as randomized?	❑ yes	❑ no	
Was the method of randomization described?	❑ yes	❑ no	
If the method of randomization was explained was it appropriate?	❑ yes	❑ no	
***Randomization score*:**			/2
2. Was the study described as double-blind?	❑ yes	❑ no	
Was the method of double blinding described?	❑ yes	❑ no	
If the method of blinding was explained was it appropriate?	❑ yes	❑ no	
Double blind score:			/2
3. Was there a description of withdrawals and dropouts?	❑ yes	❑ no	/1
***Total Score*:**			/5

Scoring of the Jadad Scale:

A) Give a score of 1 point for each 'yes' or 0 points for each 'no'. There are no in-between marks.

B) Give 1 additional point if:

For question 1, the method to generate the sequence of randomization was described and it was **appropriate** (table of random numbers, computer generated, coin tossing, etc...)

and / or

If on question 2 the method of double-blinding was described and it was **appropriate** (identical placebo, active placebo, dummy, etc.)

Deduct 1 point if:

For question 1, the method to generate the sequence of randomization was described and it was **inappropriate** (patients were allocated alternately, or according to date of birth, hospital number, etc.)

and / or

For question 2, the study was described as double-blind but the method of blinding was **inappropriate** (e.g. comparison of tablet vs. injection with no double dummy).

Other Quality assessment item

Was the adequacy of allocation concealment described?

Adequate / inadequate / unclear

APPENDIX 4: Excluded Studies

A) Animal studies

1. Buchanan TA, Meehan WP, Jeng YY, Yang D, Chan TM, Nadler JL, et al. Blood pressure lowering by pioglitazone. Evidence for a direct vascular effect. **J Clin Invest** 1995;96(1):354-60.

B) References presenting the results of placebo-controlled monotherapy studies initially identified in the form of an abstract, a poster or a presentation but later found to have been published as a full article.

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APPENDIX 5: Sensitivity Analysis for Statistical Heterogenity

Comparison: 01 Glycemic control
Outcome: 01 Sensitivity analysis HbA1c

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 Sensitivity analysis (HbA1c - combo) - US studies only							
Einhorn et al	168	-0.64(1.44)	160	0.19(1.45)		17.8	-0.83[-1.14,-0.52]
Jovanovic (PIO comb)	123	-1.76(1.22)	61	-0.18(1.33)		11.1	-1.58[-1.98,-1.18]
Kipnes et al(pio30)	182	-1.20(1.40)	181	0.10(1.03)		27.3	-1.30[-1.55,-1.05]
Miyazaki et al	12	-1.70(0.30)	11	0.00(0.20)		40.8	-1.70[-1.91,-1.49]
Rubin et al (pio 30)	188	-1.26(5.30)	187	-0.26(1.10)		2.9	-1.00[-1.77,-0.23]
Subtotal(95%CI)	673		600			100.0	-1.40[-1.53,-1.27]
Test for heterogeneity chi-square=23.25 df=4 p=0.0001							
Test for overall effect z=20.79 p<0.00001							
02 Sensitivity analysis (HbA1c - combo) - blinded studies only							
Einhorn et al	168	-0.64(1.44)	160	0.19(1.45)		17.9	-0.83[-1.14,-0.52]
Kaneko et al	76	-1.24(1.33)	73	-0.08(1.19)		10.7	-1.16[-1.56,-0.76]
Kipnes et al(pio30)	182	-1.20(1.40)	181	0.10(1.03)		27.5	-1.30[-1.55,-1.05]
Miyazaki et al	12	-1.70(0.30)	11	0.00(0.20)		41.0	-1.70[-1.91,-1.49]
Rubin et al (pio 30)	188	-1.26(5.30)	187	-0.26(1.10)		2.9	-1.00[-1.77,-0.23]
Subtotal(95%CI)	626		612			100.0	-1.36[-1.49,-1.22]
Test for heterogeneity chi-square=23.38 df=4 p=0.0001							
Test for overall effect z=20.07 p<0.00001							
03 Sensitivity analysis (HbA1c-combo) - using lower dose of pio + other pio studies							
Einhorn et al	168	-0.64(1.44)	160	0.19(1.45)		15.8	-0.83[-1.14,-0.52]
Jovanovic (PIO comb)	123	-1.76(1.22)	61	-0.18(1.33)		9.8	-1.58[-1.98,-1.18]
Kaneko et al	76	-1.24(1.33)	73	-0.08(1.19)		9.5	-1.16[-1.56,-0.76]
Kipnes et al(pio 15)	176	-0.80(1.40)	181	0.10(1.03)		23.7	-0.90[-1.16,-0.64]
Miyazaki et al	12	-1.70(0.30)	11	0.00(0.20)		36.2	-1.70[-1.91,-1.49]
Rubin et al (pio 15)	191	-0.99(3.80)	187	-0.26(1.10)		4.9	-0.73[-1.29,-0.17]
Subtotal(95%CI)	746		673			100.0	-1.26[-1.39,-1.14]
Test for heterogeneity chi-square=38.41 df=5 p<0.00001							
Test for overall effect z=19.86 p<0.00001							
04 Sensitivity analysis - only pooling the pio studies with lower dose groups							
Kipnes et al(pio 15)	176	-0.80(1.40)	181	0.10(1.03)		82.8	-0.90[-1.16,-0.64]
Rubin et al (pio 15)	191	-0.99(3.80)	187	-0.26(1.10)		17.2	-0.73[-1.29,-0.17]
Subtotal(95%CI)	367		368			100.0	-0.87[-1.10,-0.64]
Test for heterogeneity chi-square=0.29 df=1 p=0.59							
Test for overall effect z=7.34 p<0.00001							
05 Sensitivity analysis (HbA1c - combo) only sulphonylureas anti-diabetic agents							
Kaneko et al	76	-1.24(1.33)	73	-0.08(1.19)		13.5	-1.16[-1.56,-0.76]
Kipnes et al(pio30)	182	-1.20(1.40)	181	0.10(1.03)		34.7	-1.30[-1.55,-1.05]
Miyazaki et al	12	-1.70(0.30)	11	0.00(0.20)		51.8	-1.70[-1.91,-1.49]
Subtotal(95%CI)	270		265			100.0	-1.49[-1.64,-1.34]
Test for heterogeneity chi-square=8.68 df=2 p=0.013							
Test for overall effect z=19.60 p<0.00001							

-10 -5 0 5 10
Favours pioglitazone Favours control

APPENDIX 6: Sensitivity Analysis for Budget Impact Section

Table 13: Base results with 7.5% optimization scenario added

	Price	Weight	Aggregate Price
Rosiglitazone (8 mg/ tab)	$2.75	0.6	$3.31
Pioglitazone (45 mg/ tab)	$4.15	0.4	

Growth Rate: 5.00%

Estimated increase to provincial drug plans (2004 Projection) $C

Scenario	AB	NS	ON	MB	SK	BC	Total Included Provincial	Total Estimated for Canada
1%	791,385	139,042	5,017,518	722,018	515,829	1,278,625	8,464,417	11,797,990
2.5%	1,978,462	347,604	12,543,792	1,805,046	1,289,571	3,196,561	21,161,036	29,494,966
5%	3,956,922	695,210	25,087,586	3,610,093	2,579,144	6,393,121	42,322,076	58,989,937
7.5%	5,935,385	1,042,814	37,631,379	5,415,138	3,868,715	9,589,681	63,483,112	88,484,903

Table 14: Low price

	Price	Weight	Aggregate Price
Rosiglitazone (8 mg/ tab)	$2.75	1	$2.75
Pioglitazone (45 mg/ tab)	$4.15	0	

Growth Rate: 5.00%

Estimated increase to provincial drug plans (2004 projection) $C

Scenario	AB	NS	ON	MB	SK	BC	Total Included Provincial	Total Estimated for Canada
1%	650,838	114,603	4,134,935	595,298	425,831	1,052,758	6,974,263	9,720,963
2.5%	1,627,096	286,508	10,337,337	1,488,245	1,064,578	2,631,894	17,435,657	24,302,407
5%	3,254,191	573,016	20,674,675	2,976,490	2,129,155	5,263,788	34,871,315	48,604,815
7.5%	4,881,287	859,524	31,012,012	4,464,734	3,193,733	7,895,681	52,306,972	72,907,222

Table 15: High price

	Price	Weight	Aggregate Price
Rosiglitazone (8 mg/ tab)	$2.75	0	$4.15
Pioglitazone (45 mg/ tab)	$4.15	1	

Growth Rate: 5.00%

Estimated increase to provincial drug plans (2004 Projection) $C

Scenario	AB	NS	ON	MB	SK	BC	Total Included Provincial	Total Estimated for Canada
1%	1,002,204	175,700	6,341,391	912,099	650,825	1,617,424	10,699,643	14,913,523
2.5%	2,505,511	439,249	15,853,477	2,280,248	1,627,062	4,043,560	26,749,107	37,283,808
5%	5,011,021	878,499	31,706,953	4,560,496	3,254,125	8,087,121	53,498,215	74,567,616
7.5%	7,516,532	1,317,748	47,560,430	6,840,744	4,881,187	12,130,681	80,247,322	111,851,424

Table 16: Low growth

	Price	Weight	Aggregate Price
Rosiglitazone (8 mg/ tab)	$2.75	0.6	$3.31
Pioglitazone (45 mg/ tab)	$4.15	0.4	

Growth Rate: 2.50%

Estimated increase to provincial drug plans (2004 Projection) $C

Scenario	AB	NS	ON	MB	SK	BC	Total Included Provincial	Total Estimated for Canada
1%	701,553	123,259	4,447,969	640,061	457,276	1,133,485	7,503,602	10,458,773
2.5%	1,753,882	308,147	11,119,921	1,600,152	1,143,190	2,833,712	18,759,004	26,146,933
5%	3,507,765	616,294	22,239,843	3,200,303	2,286,379	5,667,425	37,518,009	52,293,866
7.5%	5,261,647	924,442	33,359,764	4,800,455	3,429,569	8,501,137	56,277,013	78,440,799

Table 17: High growth

	Price	Weight	Aggregate Price
Rosiglitazone (8 mg/ tab)	$2.75	0.6	$3.31
Pioglitazone (45 mg/ tab)	$4.15	0.4	

Growth Rate: 7.50%

Estimated increase to provincial drug plans (2004 projection) $C

Scenario	AB	NS	ON	MB	SK	BC	Total Included Provincial	Total Estimated for Canada
1%	890,192	156,402	5,643,970	812,165	580,231	1,438,264	9,521,224	13,271,003
2.5%	2,225,479	391,004	14,109,925	2,030,412	1,450,579	3,595,661	23,803,059	33,177,507
5%	4,450,958	782,008	28,219,850	4,060,824	2,901,157	7,191,322	47,606,119	66,355,014
7.5%	6,676,436	1,173,012	42,329,775	6,091,235	4,351,736	10,786,983	71,409,178	99,532,521

Table 18: 75/25 split

	Price	Weight	Aggregate Price
Rosiglitazone (8 mg/ tab)	$2.75	0.75	$3.10
Pioglitazone (45 mg/ tab)	$4.15	0.25	

Growth Rate: 5.00%

Estimated increase to provincial drug plans (2004 Projection) $C

Scenario	AB	NS	ON	MB	SK	BC	Total Included Provincial	Total Estimated for Canada
1%	738,680	129,877	4,686,549	674,498	482,080	1,193,924	7,905,608	11,019,103
2.5%	1,846,699	324,693	11,716,372	1,686,246	1,205,199	2,984,810	19,764,020	27,547,757
5%	3,693,399	649,387	23,432,744	3,372,491	2,410,398	5,969,621	39,528,040	55,095,515
7.5%	5,540,098	974,080	35,149,117	5,058,737	3,615,596	8,954,431	59,292,060	82,643,272

Table 19: Rosiglitazone at $3.86

	Price	Weight	Aggregate Price
Rosiglitazone	$3.86	0.6	$3.976
Pioglitazone (45 mg/ tab)	$4.15	0.4	

Growth Rate: 5.00%

Estimated increase to provincial drug plans (2004 Projection) $C

Scenario	AB	NS	ON	MB	SK	BC	Total Included Provincial	Total Estimated for Canada
1%	958,534	168,106	6,067,160	872,725	622,861	1,547,244	10,236,631	14,268,162
2.5%	2,396,336	420,266	15,167,899	2,181,813	1,557,154	3,868,110	25,591,579	35,670,405
5%	4,792,672	840,532	30,335,799	4,363,627	3,114,307	7,736,221	51,183,157	71,340,811
7.5%	7,189,008	1,260,798	45,503,698	6,545,440	4,671,461	11,604,331	76,774,736	107,011,216

Table 20: Aggregate price at $3.22

	Aggregate Price
Rosiglitazone (8 mg/ tab)	Assumption of $3.22
Pioglitazone (45 mg/ tab)	

Growth Rate: 5.00%

Estimated increase to provincial drug plans (2004 Projection) $C

Scenario	AB	NS	ON	MB	SK	BC	Total Included Provincial	Total Estimated for Canada
1%	768,797	135,114	4,875,674	701,653	501,365	1,242,324	8,224,926	11,464,180
2.5%	1,921,992	337,785	12,189,184	1,754,132	1,253,412	3,105,810	20,562,316	28,660,449
5%	3,843,984	675,571	24,378,368	3,508,263	2,506,824	6,211,621	41,124,631	57,320,898
7.5%	5,765,976	1,013,356	36,567,552	5,262,395	3,760,235	9,317,431	61,686,947	85,981,347

Table 21: Insulin net impact results

	Price	Weight	Aggregate Price
Rosiglitazone (8 mg/ tab)	$2.75	0.6	$3.31
Pioglitazone (45 mg/ tab)	$4.15	0.4	

Growth Rate: 5.00%

Estimated increase to provincial drug plans (2004 Projection) $C

Scenario	AB	NS	ON	MB	SK	BC	Total Included Provincial	Total Estimated for Canada
1%	1,359,322	169,578	545,415	936,865	116,588	1,667,876	4,795,646	6,684,333
2.5%	3,398,306	423,946	1,363,538	2,342,162	291,471	4,169,691	11,989,114	16,710,831
5%	6,796,612	847,892	2,727,077	4,684,324	582,941	8,339,381	23,978,228	33,421,663
7.5%	10,194,918	1,271,839	4,090,615	7,026,486	874,412	12,509,072	35,967,342	50,132,494