Comparative Clinical and Budget Evaluations of Rosiglitazone and Pioglitazone with other Anti-diabetic Agents

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Technology Name
Rosiglitazone (Avandia™)
Pioglitazone (Actos™)

Methods
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.

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-thiazolidinedione 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.

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.

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/meglitinides (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, resulting in 405 unique records. Retrieval was limited to the publication years 1990 to 2001 with no language restriction. Database alerts were established on several databases. These were run throughout the duration of the project. 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 inclusion 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 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 heart failure.

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.
1. **Introduction**

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia 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.\(^1,2\) 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.\(^3\)

There are two main types of diabetes. Type 1 affects 5 to 10% of the population diagnosed with diabetes.\(^4\) It is primarily due to destruction of pancreatic beta-cells and usually leads to absolute insulin deficiency.\(^1\) Type 2 is the more prevalent form, affecting approximately 90% of patients with diabetes.\(^4\) It results mainly from insulin resistance with a relative (rather than absolute) defect in the secretion of insulin.\(^1,5\) Insulin resistance is a condition in which peripheral tissues show a reduced sensitivity to the effects of glucose uptake stimulated by insulin.\(^6\) Diabetes is a serious condition and patients with this disease are at risk for greater morbidity and mortality, relative to the population without diabetes.\(^4\) Most of the morbidity and mortality associated with type 2 diabetes can be attributed to the chronic complications of the disease.\(^4,7\)

There are currently five different classes of oral anti-diabetic agents available in Canada\(^8\) for the treatment of type 2 diabetes mellitus:

i) alpha-glucoSIDase inhibitors (AGI) (e.g. acarbose)
ii) biguanides (e.g. metformin)
iii) carbamoyl benzoic acid (CBA) derivatives/meglitinides (e.g. repaglinide)
iv) sulphonylureas (SU) (e.g. chlorpropamide, gliclazide, glyburide, tolbutamide) and
v) thiazolinediones

Thiazolinediones constitute the newest class of drugs introduced to clinical practice. There are currently two representatives of this class available in Canada. Rosiglitazone (Avandia\(^{\text{TM}}\) – GlaxoSmithKline) is approved for use either as monotherapy or combination therapy with metformin or a sulphonylurea.\(^9\) Pioglitazone (Actos\(^{\text{TM}}\) – Eli Lilly) is only approved in Canada for monotherapy.\(^10\)

The glucose-lowering effect of thiazolinediones is related to their ability to enhance insulin sensitivity.\(^11\) Although their mechanism of action is not yet fully understood, it is thought that thiazolinediones reduce insulin resistance by activating the peroxisome proliferator-activated receptor gamma (PPAR\(\gamma\)), resulting in increased glucose transport into cells in adipose tissue, but also in muscle, liver and other tissues.\(^6\) This mechanism of action appears to address insulin resistance, a key metabolic problem in type 2 diabetes.

Given their higher cost and some safety concerns with these drugs, which include hepatotoxicity,\(^4,6,11\) edema,\(^4,6,11\) weight gain\(^6,11\) and anemia,\(^11\) there is a need to compare the efficacy and safety of thiazolinediones to other anti-diabetic drugs in the treatment of type 2 diabetes. There is also a need to evaluate the potential impact on provincial drug plan costs that the listing of these agents could cause.
2. **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/meglitinides (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.

3. **Clinical Review**

**Methods**

Published literature was obtained by searching DIALOG® databases MEDLINE®, EMBASE®, HealthSTAR®, PASCAL, SciSearch® and Toxline® on May 16, 2001, resulting in 405 unique records. Retrieval was limited to the publication years 1990 to 2001 with no language restrictions. Database alerts were established on several DIALOG® databases. These were run throughout the duration of the project. Searches were performed and updated on the CD ROM versions of The Cochrane Library. Web sites of regulatory agencies, health technology assessment and related agencies were also searched, as were specialized databases, such as those of the University of York NHS Centre for Reviews and Dissemination. In addition, manufacturers of the two thiazolidinediones available in Canada [Eli Lilly – Actos™ (pioglitazone) and GlaxoSmithKline – Avandia™ (rosiglitazone)] were invited to submit information.

All relevant studies eligible for inclusion were independently reviewed by two investigators (MB, LM) and assigned a quality rating using the Jadad scale. Only randomized controlled trials in adult patients with type 2 diabetes mellitus were considered for inclusion in the review. Data abstraction was performed by the same two investigators working independently.

The primary outcomes of interest were fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c). Secondary outcomes included:

i) serum lipid profile (total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density-lipoprotein (LDL) cholesterol, triglycerides)

ii) hematological parameters [hemoglobin (Hgb), hematocrit (Hct)]

iii) liver function tests [alamine aminotransferase (ALT), aspartate aminotransferase (AST)]

iv) hypoglycemia and

v) other relevant parameters: weight, blood pressure (diastolic, systolic), edema.

Quantitative evaluation was performed with Review Manager 4.1.1. For all pooled estimates a chi square test of statistical heterogeneity was performed. Statistical heterogeneity was defined at a significance level of 10%. Because statistical heterogeneity was detected in some of the
pooled estimates, the random effects model was used for all endpoints. When there were no measurements of variance, a qualitative evaluation was conducted.

**Results**

**Rosiglitazone**

A total of 11 relevant studies were included; three full publications and eight unpublished trials. Results were presented several times under different formats, either abstracts and/or posters, for a number of unpublished trials. Quality scores varied between 1 and 4 out of a possible score of 5 (Table 1). Two studies assessed monotherapy and eight evaluated add-on therapy. One study had three comparison arms, i.e. two monotherapy arms and one add-on therapy arm. The analytic horizon varied from 12 to 52 weeks, with one 148-week open-label study.

**Table 1: Characteristics of studies comparing rosiglitazone to other anti-diabetic agents**

<table>
<thead>
<tr>
<th>Study</th>
<th>Qty Score</th>
<th>Publication Type</th>
<th>Study Length (wks)</th>
<th>Active Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charbonnel et al.16-20</td>
<td>2</td>
<td>Abstract/Posters</td>
<td>52</td>
<td>RSG</td>
<td>GLY</td>
</tr>
<tr>
<td>Fonseca et al.21</td>
<td>4</td>
<td>Journal article</td>
<td>26</td>
<td>RSG+MET</td>
<td>PLB+MET</td>
</tr>
<tr>
<td>Gomez-Perez et al.22</td>
<td>1</td>
<td>Abstract</td>
<td>26</td>
<td>RSG+MET</td>
<td>PLB+MET</td>
</tr>
<tr>
<td>Hallé et al.23-26</td>
<td>2</td>
<td>Posters</td>
<td>26</td>
<td>RSG+GLY</td>
<td>PLB+GLY</td>
</tr>
<tr>
<td>James et al.27,28</td>
<td>2</td>
<td>Abstract/Poster</td>
<td>26</td>
<td>RSG+GLI</td>
<td>GLI</td>
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<tr>
<td>Jovanovic et al.14,15</td>
<td>2</td>
<td>Abstract/Poster</td>
<td>24</td>
<td>RSG+REP</td>
<td>REP</td>
</tr>
<tr>
<td>Jovanovic et al.14,15</td>
<td>2</td>
<td>Abstract/Poster</td>
<td>24</td>
<td>REP</td>
<td>RSG</td>
</tr>
<tr>
<td>Mattin et al.29</td>
<td>1</td>
<td>Abstract</td>
<td>12</td>
<td>RSG+SU</td>
<td>SU</td>
</tr>
<tr>
<td>Raskin et al.30</td>
<td>4</td>
<td>Journal article</td>
<td>26</td>
<td>RSG+IN</td>
<td>PLB+IN</td>
</tr>
<tr>
<td>St-John Sutton et al.31-37</td>
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<td>Abstract/Posters</td>
<td>148</td>
<td>RSG</td>
<td>GLY</td>
</tr>
<tr>
<td>Wolfenbuttel et al.38</td>
<td>2</td>
<td>Journal article</td>
<td>26</td>
<td>RSG+SU</td>
<td>PLB+SU</td>
</tr>
<tr>
<td>Xixing et al.39,41</td>
<td>2</td>
<td>Abstracts/Poster</td>
<td>24</td>
<td>RSG+SU</td>
<td>PLB+SU</td>
</tr>
</tbody>
</table>

§ Four posters and one abstract were identified for the same study
∞ Four posters were identified for the same study
† One poster and one abstract were identified for the same study
* One poster was identified for the final results and one abstract for the interim results (the two treatment groups belong to the same study)
‡ Six posters and one oral presentation abstract were identified for the same study
¶ One abstract on efficacy data, one abstract on safety data and one poster were identified for the same study
** Initial total sample size N=120 (randomly assigned), intent-to-treat sample size N=119

Abbreviations: GLI= gliclazide, GLY= glyburide, IN= insulin, MET= metformin, PLB= placebo, REP= repaglinide, RSG= rosiglitazone, SU= unspecified sulphonylureas
a) **Primary Outcomes**

**Monotherapy:** Three studies compared rosiglitazone monotherapy with non-thiazolidinedione monotherapy. Results from one study were not quantitatively analyzed as the mean change from baseline +/- standard deviation (SD) was not available. In this study comparing rosiglitazone with glyburide, rosiglitazone-treated patients showed a statistically significantly greater reduction from baseline to 52 weeks in FPG (-3.61 mmol/l vs -3.11 mmol/l, p=0.006). Mean change from baseline in HbA1c was similar for both groups (-0.9 +/- 1.4%).

It was possible to pool the results from two monotherapy studies (Figures 1 and 2). With data pooling, rosiglitazone monotherapy provided a small and statistically significant decrease from baseline in FPG [weighted mean difference (WMD) with 95% confidence interval (CI): -0.62 mmol/l (-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 (chi-square = 6.34, df= 1, p= 0.012), our pooled estimate for HbA1c should be interpreted with caution, especially since the results of only two trials were combined.

**Figure 1:** Pooled estimate of HbA1c from rosiglitazone trials

<table>
<thead>
<tr>
<th>Comparison: 01 Glycemic control</th>
<th>Outcomes: 01 Glycocontrolled hemoglobin (HbA1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Treatment</strong></td>
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<tr>
<td>Rosiglitazone (Rosig)</td>
<td>Monotherapy</td>
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<td>Rosiglitazone (Rosig)</td>
<td>Monotherapy</td>
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<tr>
<td>Suiseki (Rosig)</td>
<td>Monotherapy</td>
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</tbody>
</table>

Test for heterogeneity chi-square = 3.34, df = 1, p = 0.07
Test for overall effect z = 0.27, p = 0.8

<table>
<thead>
<tr>
<th>Comparison: 02 Combination therapy</th>
<th>Outcomes: 02 Glycocontrolled hemoglobin (HbA1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Treatment</strong></td>
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<tr>
<td>Rosiglitazone (Rosig)</td>
<td>Monotherapy</td>
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<td>Rosiglitazone (Rosig)</td>
<td>Monotherapy</td>
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</table>

Test for heterogeneity chi-square = 4.54, df = 1, p = 0.08
Test for overall effect z = 0.57, p = 0.993
Add-on combination therapy: A total of nine add-on therapy studies were included in the analysis, although quantitative estimates of the effect size for HbA1c and FPG were based on eight and seven studies, respectively (Figures 1 and 2). With data pooling, 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 other anti-diabetic agents. The latter pooled estimate was, however, associated with borderline statistical heterogeneity (chi-square= 10.81, df= 6, p= 0.094).

Data on FPG from one study could not be included in the pooled estimate as there was no measure of variance for the control group. In this study, patients were to either continue their usual sulphonylurea monotherapy or to add rosiglitazone to their regimen. Add-on therapy provided a statistically significant decrease from baseline in mean FPG (-2.62 mmol/l, p<0.0001) while an increase was observed (+ 0.31 mmol/l; no p value) in the group that continued their usual regimen.29

b) Secondary Outcomes

Serum lipid profile: For total cholesterol levels, combined results of three studies21,30,38 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). For HDL cholesterol, quantitative evaluation was possible for two trials.21,30 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). Quantitative evaluation was possible for the same trials21,30 in the case of LDL cholesterol. Rosiglitazone was associated with a statistically significant WMD (increase
from baseline) of 0.39 mmol/l (95% CI: 0.30; 0.48). Finally, for triglyceride levels, there was no statistically significant difference between rosiglitazone and non-thiazolidinedione-based approaches [WMD: -0.09 mmol/l (95% CI: -0.40; 0.23)], when quantitative studies\textsuperscript{21,30,38} were combined. In summary, rosiglitazone caused a statistically significant larger increase from baseline in total, LDL, and HDL cholesterol levels, compared to other anti-diabetic agents. There was no statistically significant difference in triglyceride levels.

**Liver function parameters:** The vast majority of subjects in the trials that were reviewed, maintained liver enzyme levels within the normal range and no serious liver adverse events were reported.\textsuperscript{16,17,19-21,23,29,30,32,38,40}

**Hematological parameters:** From a qualitative point of view, changes in Hgb and Hct levels varied from -3.9 g/l\textsuperscript{38} to -12 g/l\textsuperscript{23} and from -1.52\textsuperscript{38} to -3.5\textsuperscript{23} respectively. Quantitative analysis was only possible with one study.\textsuperscript{27} In this study, rosiglitazone add-on therapy 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 Hgb and -2.52\% (95% CI: -3.37; -1.67) for Hct, compared to the glyburide monotherapy. Overall, decreases in hematological parameters in the included studies rarely led to clinical anemia. In one trial, two patients treated with rosiglitazone withdrew due to anemia.\textsuperscript{21}

**Hypoglycemia:** The majority of hypoglycemic events reported were mild to moderate in nature. The occurrence of hypoglycemia was relatively infrequent with rosiglitazone monotherapy, ranging between 0.5\% and 1\%.\textsuperscript{17} In comparison, hypoglycemia was observed in 1.8\%\textsuperscript{21} to 12.1\%\textsuperscript{17} of control group subjects and 38\% of patients on insulin monotherapy.\textsuperscript{30} However, the occurrence increased when rosiglitazone was used in combination with another oral anti-diabetic drug, varying from 2.6\%\textsuperscript{21} to 6.1\%.\textsuperscript{28} Hypoglycemia was particularly high when rosiglitazone was combined with insulin, ranging between 53\% and 67\%.\textsuperscript{30} Overall, four patients withdrew due to hypoglycemia: one in a control (insulin) group\textsuperscript{30} and three in active treatment groups (one using a gliclazide/ rosiglitazone\textsuperscript{27} combination and two using an insulin/rosiglitazone combination\textsuperscript{30}).

**Weight:** Rosiglitazone therapy was associated with an increase in body weight. Qualitative evaluation showed that the mean increase from baseline varied from 0.7 kg\textsuperscript{21} to 5.3 kg.\textsuperscript{30} The larger mean increase was observed with add-on therapy with insulin.\textsuperscript{30} In comparison, reported changes in mean body weight for the control varied from a 1.2 kg decrease with metformin monotherapy\textsuperscript{21} to an increase of 0.9 kg with insulin monotherapy.\textsuperscript{30} A quantitative evaluation was only possible with one study.\textsuperscript{27} Rosiglitazone add-on therapy was associated with a statistically significant WMD (increase from baseline) of 3.3 kg (95% CI: 2.08; 4.52) compared with glyburide monotherapy.

**Blood pressure:** The use of rosiglitazone was associated with a small, but sometimes statistically significant, decrease in blood pressure. When combined with another anti-diabetic drug, the reduction in diastolic blood pressure (DBP) varied from 1.4 mmHg\textsuperscript{29} to 2.6 mmHg.\textsuperscript{30} In comparison, changes in DBP in the control groups varied from no change\textsuperscript{30} to a 0.9 mmHg decrease.\textsuperscript{29} Quantitative evaluation was limited to one trial.\textsuperscript{31,36,37} Compared to glyburide, rosiglitazone was associated with statistically significant WMDs (decrease from baseline) of -3.1
mmHg (95% CI: -4.95; -1.25), and -3.90 mmHg (95% CI: -6.66; -1.14) in DBP and systolic blood pressure (SBP), respectively.

**Edema:** Edema was observed in 2.5 to 3.5% of patients on rosiglitazone monotherapy and in 10.8% of subjects on both rosiglitazone and gliclazide. Severe edema was reported in 0.9% of rosiglitazone/gliclazide-treated patients while it was not observed in gliclazide monotherapy patients. The highest occurrence was in combination with insulin, varying from 13.1 to 16.2%. In comparison, edema was observed in 0.9% to 2.9% of patients on other oral anti-diabetic agents and in 4.7% of subjects on insulin monotherapy. Heart failure was reported in four patients treated with both insulin and rosiglitazone while one patient treated with insulin developed this condition.

**Pioglitazone**

A total of eight relevant studies were included: five full publications, two abstracts and one poster (Table 2). Quality scores were generally low, 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. The duration of the studies included in the pioglitazone review varied from 12 to 28 weeks.

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality Score</th>
<th>Publication Type</th>
<th>Study Length (wks)</th>
<th>Active Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebeling et al.</td>
<td>2</td>
<td>Journal article</td>
<td>26</td>
<td>PIO 30-45 mg/d</td>
<td>GLY 2.5-5 mg/d</td>
</tr>
<tr>
<td>Einhorn et al.</td>
<td>2</td>
<td>Journal article</td>
<td>16</td>
<td>PIO+MET 30 mg/d+</td>
<td>PLB+MET Titrated</td>
</tr>
<tr>
<td>Scherbaum and Göke</td>
<td>1</td>
<td>Abstracts</td>
<td>16-28</td>
<td>PIO 45 mg/d</td>
<td>Acarbose 900 mg/d</td>
</tr>
<tr>
<td>Jovanovic et al.</td>
<td>2</td>
<td>Poster</td>
<td>24</td>
<td>PIO+REP 30 mg/d</td>
<td>REP 1.5-12 mg/d</td>
</tr>
<tr>
<td>Jovanovic et al.</td>
<td>2</td>
<td>Poster</td>
<td>24</td>
<td>REP 1.5-12 mg/d</td>
<td>PIO 30 mg/d</td>
</tr>
<tr>
<td>Kaneko et al.</td>
<td>3</td>
<td>Journal article</td>
<td>12</td>
<td>PIO+SU 30 mg/d</td>
<td>PLB+SU N/A</td>
</tr>
<tr>
<td>Kipnes et al.</td>
<td>2</td>
<td>Journal article</td>
<td>16</td>
<td>PIO+GLY 30 mg/d</td>
<td>PLB+GLY Usual dose</td>
</tr>
<tr>
<td>Miyazaki et al.</td>
<td>2</td>
<td>Journal article</td>
<td>16</td>
<td>PIO+SU 45 mg/d</td>
<td>SU Usual dose</td>
</tr>
<tr>
<td>Rubin et al.</td>
<td>2</td>
<td>Abstract</td>
<td>16</td>
<td>PIO+IN 30 mg/d</td>
<td>PLB+IN &gt;30 U/d</td>
</tr>
</tbody>
</table>

痍 German Pioglitazone Study Group. Interim results published in abstract in 2000 and final results published in three abstracts in 2001, i.e. two on safety and one on efficacy.

.Glide The two treatment groups belong to the same study.

Abbreviations: GLI = gliclazide, GLY = glyburide, IN = insulin, MET = metformin, N/A = not available, PIO = pioglitazone, PLB = placebo, REP = repaglinide, SU = unspecified sulphonylureas.
c) Primary Outcomes

**Monotherapy**: Three monotherapy studies were identified but only two\(^{15,42}\) (Figures 7 and 8) could be pooled for quantitative comparison of HbA1c, as there were no measures of variance or level of significance provided in the third study.\(^{46}\) This study compared pioglitazone with acarbose. The median decrease in HbA1c and FPG was larger in the pioglitazone group (HbA1c: -1.20%, FPG: -2.7 mmol/l) than in the control group (HbA1c: -0.20%, FPG: -0.7 mmol/l).\(^{46}\) Meta-analysis of the two monotherapy trials revealed 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 the comparator drugs glyburide and repaglinide (Figure 7). Only one study had quantitative information on FPG.\(^{15}\) In this study, pioglitazone monotherapy was associated with a smaller, but not statistically significant, decrease from baseline in FPG [WMD: 0.89 mmol/l (95% CI: -0.26; 2.04)], compared with repaglinide monotherapy (Figure 8).

**Figure 7**: Pooled estimate of HbA1c from pioglitazone trials

<table>
<thead>
<tr>
<th>Comparison: 01 Glycemic control</th>
<th>Outcome: 03 Glycosylated hemoglobin (HbA1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Treatment</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Monotherapy</td>
<td></td>
</tr>
<tr>
<td>Sheehan et al.</td>
<td>9</td>
</tr>
<tr>
<td>Jovanovik (no mon)</td>
<td>62</td>
</tr>
<tr>
<td>Subtotal (95%CI)</td>
<td>70</td>
</tr>
<tr>
<td>Test for heterogeneity chi-square</td>
<td>0.28</td>
</tr>
<tr>
<td>Test for overall effect z=2.00</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Combination Therapy</td>
<td></td>
</tr>
<tr>
<td>Enforn et al.</td>
<td>120</td>
</tr>
<tr>
<td>Jovanovik ( PIO comb)</td>
<td>141</td>
</tr>
<tr>
<td>Kornel et al.</td>
<td>75</td>
</tr>
<tr>
<td>Kipnes et al. (pre)</td>
<td>182</td>
</tr>
<tr>
<td>Vassili et al.</td>
<td>12</td>
</tr>
<tr>
<td>Ruben et al. (post)</td>
<td>198</td>
</tr>
<tr>
<td>Subtotal (95%CI)</td>
<td>749</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=4.48 df=5 p=0.1002
Test for overall effect z=3.34 p=0.00001
Figure 8: Pooled estimate of FPG from pioglitazone trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Weight</th>
<th>VMD (95%CI Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add-on therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licon et al (90 mon)</td>
<td>62</td>
<td>-1.48 (3.25)</td>
<td>61</td>
<td>-1.89 (3.25)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>125</td>
<td>-2.20 (2.50)</td>
<td>121</td>
<td>-1.85 (2.50)</td>
</tr>
<tr>
<td>Test for heterogeneity chi-square= 0.00, df= 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment effect= 0.00, p= 0.0005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Secondary Outcomes

**Add-on therapy**: A total of six add-on combination therapy trials were included in the analysis, although quantitative estimates of the effect size for FPG were only based on five studies (Figures 7 and 8). When the results of the six add-on therapy studies were combined, add-on therapy with pioglitazone was associated with a statistically significant WMD (decrease from baseline) in HbA1c of -1.29% (95% CI: -1.60; -0.99), compared to simply continuing non-thiazolidinedione monotherapy. The five studies combined for the evaluation of FPG also revealed a statistically significant WMD (decrease from baseline) of -2.87 mmol/l (95% CI: -3.59; -2.15), compared to continuing 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 interpreted cautiously until further confirmation is available.

**Serum lipid profile**: Based on the results of four studies, the effect of pioglitazone on total cholesterol levels was similar to the effect associated with comparator drugs (metformin and sulphonylureas) [WMD: -0.01 mmol/l (95% CI: -0.19; 0.17)]. This result was, however, associated with evidence of statistical heterogeneity (chi-square= 9.21, df= 3, p= 0.027). Quantitative information could only be derived from three studies for HDL cholesterol levels. A WMD (increase from baseline) of 0.10 mmol/l (95% CI: -3.59; -2.15) was computed, in favor of pioglitazone. Again, statistical heterogeneity was detected with this pooled estimate (chi-square= 8.18, df= 2, p= 0.017). The same three studies were combined for LDL cholesterol levels. Pioglitazone was associated with a relatively neutral effect, leading to a non-statistically significant WMD of -0.03 mmol/l (95% CI: -0.12; 0.05), in favor of pioglitazone. Finally, for triglyceride levels, pooling of quantitative studies showed a statistically significant WMD (decrease from baseline) of -0.57 mmol/l (95% CI: -0.84; -0.29) in favor of pioglitazone. However, this result was also associated with evidence of statistical...
heterogeneity (chi-square= 8.51, df= 2, p= 0.014). In summary, compared to other anti-diabetic agents, pioglitazone caused a statistically significant larger increase from baseline in HDL cholesterol levels and a statistically significant decrease from baseline in triglyceride levels. No statistically significant differences were observed for total and LDL cholesterol levels. However, three of the pooled estimates were associated with evidence of statistical heterogeneity.

Liver function parameters: Overall, for the majority of subjects the results of liver function tests were within the normal range and no serious hepatic adverse events were reported in the included trials.43,44,46,47,49,51

Hematological parameters: Hematological results were reported in two studies. In the first, qualitative analysis showed small mean decreases from baseline in both Hgb and Hct levels associated with a pioglitazone plus metformin regimen. Values stabilized within 10 to 12 weeks and remained within normal limits.43 In the second study,49 pioglitazone add-on therapy was associated with a statistically significant WMD (decrease from baseline) of -0.48 g/dl (-4.8 g/l) (95% CI: -0.65; -0.31), compared to sulphonylurea monotherapy. No patients withdrew from either trial due to anemia.43,49

Hypoglycemia: The occurrence of hypoglycemia with pioglitazone add-on therapy varied from 0 to 3.7%,49 while 0.6% of subjects on metformin monotherapy43 and 0.5% of subjects on sulphonylurea monotherapy49 reported hypoglycemia. The incidence of hypoglycemia was 7% higher in the combined pioglitazone/insulin groups, compared to insulin monotherapy.51 Hypoglycemia was generally described as mild in nature. A minority of subjects required dosing adjustments to manage symptomatic hypoglycemic episodes. No patients were withdrawn due to hypoglycemia.

Weight: Pioglitazone was generally associated with an increase in body weight. In add-on therapy studies, this increase varied from 0.95 kg43 to 2.9 kg.49 Comparatively, the body weight of patients in control groups decreased between 0.1 kg48 to 1.36 kg.43 The occurrence of weight gain was 5% higher in patients on the pioglitazone/insulin regimen, compared to insulin monotherapy.51 Quantitative evaluation was possible for two small studies (total of 42 patients)42,50 and resulted in a non-statistically significant WMD (increase from baseline) of 2.07 kg (95% CI: -0.83; 4.96) for the pioglitazone-treated patients, compared to the sulphonylurea monotherapy group. However, statistical heterogeneity (chi-square= 4.62, df= 1, p= 0.032) was identified.

Blood pressure: For SBP, a 5 mmHg decrease from baseline was reported with pioglitazone monotherapy in one study.45 No significant changes were reported with pioglitazone/sulphonylurea add-on therapy in another trial.50 For DBP, no significant changes were reported.45,50 In comparison, acarbose was associated with a 1 mmHg increase in SBP but no changes in DBP.45 No significant changes in blood pressure were reported with sulphphonylurea monotherapy.50

Edema: Edema was reported in 5.9%43 to 7%49 of patients on pioglitazone add-on regimens while this outcome was observed in 2%49 to 2.5%43 of control group subjects. One patient in a pioglitazone add-on therapy group was withdrawn due to edema.49 The incidence of edema was 8% higher in the pioglitazone/insulin groups, compared to the insulin monotherapy group.51
4. **Budget Impact Analysis**

The purpose of the budget impact analysis (BIA) was to examine the potential impact on provincial drug plan costs that could result from unrestricted listing of rosiglitazone and pioglitazone in the year 2004. The perspective taken was that of a provincial drug plan. It should be noted that this is not a full economic evaluation, in which both costs and consequences would be analyzed for an assessment of “value-for-money”.

For this 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 agent (add-on therapy). In economic terms, they could be used as substitutes, or complements, or both.

The base results analysis included three scenarios: a 1%, 2.5% and 5% expenditure impact. A 7.5% expenditure impact was also included as an upper bound scenario. These scenarios were based on disease characteristics and clinical management. For example, the 5% scenario supposes that for the base-year of 1999, 5% of drug expenditure on non-thiazolidinedione oral anti-diabetic agents is replaced by a thiazolidinedione and that 5% is combined with a thiazolidinedione.

The Patented Medicine Prices Review Board (PMPRB) provided the data used in the BIA. The data includes program expenditure and quantity information for six provincial drug programs: British Columbia (BC), Alberta (AB), Saskatchewan (SK), Manitoba (MB), Ontario (ON) and Nova Scotia (NS). The budget impact was first calculated for these six provinces and then extrapolated based on the projected total population in Canada in 2004. 52

Based on our BIA, it is estimated that by 2004, if rosiglitazone and pioglitazone receive formulary listing throughout Canada, the 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 (Table 3).

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

Efficacy: Our study demonstrates that both rosiglitazone and pioglitazone are effective in reducing HbA1c and FPG in adults with type 2 diabetes. Combined results from monotherapy trials indicate these agents have an effect on short-term glycemic control similar to other oral anti-diabetic agents. However, our findings are not definitive because monotherapy data were based on a small number of trials. The amount of evidence available for add-on therapy is somewhat more substantial, although still limited. For patients not well controlled on non-thiazolidinedione monotherapy, pooled estimates of all add-on regimens for both drugs show a statistically significant reduction in HbA1c and FPG, compared to simply continuing monotherapy with another agent. These findings are consistent with previous research showing that the addition of an oral anti-diabetic agent to that of another class results in a statistically significant additive reduction in HbA1c.\(^{55}\) Compared to non-thiazolidinediones, both rosiglitazone and pioglitazone had a favorable effect on HDL cholesterol levels. However, difference exists for the other lipid parameters.

Safety: From a safety perspective, there were no liver-related serious adverse events reported in the trials reviewed. However, three cases of hepatotoxicity possibly related to rosiglitazone\(^{54-56}\) and two others possibly related to pioglitazone\(^{57,58}\) have recently been reported, although a direct cause-effect relationship could not be established in at least two of the reported cases for rosiglitazone.\(^{59,60}\) (Troglitazone, the first thiazolidinedione approved by the FDA in 1997, was withdrawn from the US market in 2000, because of hepatotoxicity.\(^{61}\))

Also, there is a concern that thiazolidinediones could exacerbate heart failure in some patients. Pioglitazone is currently contraindicated in patients with New York Heart Association (NYHA) Class II, III or IV cardiac status\(^{10}\) and rosiglitazone is contraindicated in patients with NYHA Class III or IV cardiac status.\(^9\) Both Health Canada\(^{62}\) and the FDA\(^{63}\) recently released a safety reminder for patients not to use these drugs if they develop signs and symptoms of heart failure.

Finally, although infrequent when rosiglitazone or pioglitazone were used as monotherapy, hypoglycemia was more common when these agents were used in combination with another agent, particularly insulin. None of the thiazolidinediones are currently approved in Canada for use in combination with insulin.\(^9,10\) Since most of the trials included have an analytic horizon of less than one year, additional studies assessing the effect of rosiglitazone and pioglitazone on diabetes-related morbidity and mortality will be required to determine their long-term benefit and safety.

Limitations: Interpretation of our results should be cautious as limitations exist. In particular, the evidence available for the clinical review was limited in volume, studies included were generally rated to be of low to intermediate quality, no studies assessed long-term effects and significant statistical heterogeneity was identified for some of the pooled estimates.
Our BIA asked a hypothetical question: what would the expected impact on costs be for the drug plans in 2004 should thiazolidinediones be listed? Our base results analysis gives an estimated expenditure increase for the provincial drug plans ranging from $11.8 million to $88.5 million across 1 to 7.5% uptake scenarios. As with any exercise in modeling, there are limitations to our approach due to assumptions made. For example, published estimated rates for utilization patterns of the thiazolidinediones were not available in the literature, so a plausible rationale had to be developed. (This is a common feature of the BIA process). Some external validation of our approach is available in the case of Alberta. Rosiglitazone and pioglitazone became available via special authorization for the seniors’ drug coverage of Alberta Health and Wellness in December 2000. Expenditures for these drugs were $1.01 million in the period December 2000 to June 2001. An annualized expenditure would therefore be approximately $2 million, which would be in line with our estimated increase in expenditures in 1999 under the 2.5% ($1.6 million) and 5% ($3.1 million) penetration scenarios for Alberta.

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 heart failure.

Budget impact analysis: Based on our BIA, it is estimated that by 2004, if rosiglitazone and pioglitazone receive unrestricted formulary listing throughout Canada, addition of these drugs would result in a net expenditure increase for the publicly funded drug programs varying between $29.5 and $59 million per year, based on our most likely scenarios of 2.5% and 5.0% penetration rates. The lower (1%) and upper (7.5%) boundaries of the sensitivity analysis give an impact of $11.8 and $88.5 million per year.
7. References


34. Murphy K, Salzman A. Rosiglitazone is superior to glyburide in establishing long-term glycemic control in patients with type 2 diabetes [poster]. 2000. Poster no 450.


