Title: Evidence for Cardiovascular Risks with Rosiglitazone Use

Date: 11 March 2008

Context and policy issues:

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia (elevated blood glucose levels). DM results from a defect in insulin secretion, insulin action or both.\(^1,2\) It can result in severe complications, including limb amputation, blindness, kidney failure, heart disease, stroke and premature death.\(^1,2\) Over 2.25 million Canadians are estimated to have DM.\(^1\) Of all the diagnosed cases, 90% are type 2 DM and 10% are type 1 DM. If the present trends continue, the prevalence of type 2 DM will increase because of the aging population and rising rates of obesity.

Treatment of DM includes six classes of anti-diabetic drugs: sulfonylureas, biguanides, alpha-glucoside inhibitors, meglinitides, thiazolidones, and insulin and insulin analogues.\(^2\) Rosiglitazone (RSG), a member of the thiazolidone (TZD) class of antidiabetic agents, improves glycemic control by improving insulin sensitivity. It is used in the management of type 2 DM. Recently, due to cardiac safety concerns, new restrictions were issued on the use of RSG.\(^3-5\) Cardiovascular concerns with RSG have been emerging and there are some controversies surrounding RSG and cardiovascular events.

Research question:

What is the evidence that rosiglitazone is associated with an increased risk of acute myocardial infarction, congestive heart failure or death in type 2 diabetic patients?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a...
focused Internet search. Results include articles published between 2003 and the February 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and observational studies.

**Summary of findings:**

Four systematic reviews, three randomized controlled trials (RCTs) and two observational studies reporting on cardiovascular effects of rosiglitazone (RSG) on type 2 DM patients were identified.

**Systematic Reviews and Meta-Analyses**

A Cochrane systematic review published in 2007 concluded that the published randomized controlled trials (RCTs) of at least 24 weeks duration did not provide evidence that patient-oriented outcomes (mortality, morbidity, adverse effects, costs and health-related quality of life) are positively influenced by RSG. This review included 18 RCTs which had 3888 people randomized to RSG. The majority of the included RCTs did not investigate cardiovascular outcomes. One large RCT (ADOPT- A Diabetes Outcomes Progression Trial) comparing RSG versus metformin versus glyburide, indicated increased cardiovascular risk with RSG. Rate of cardiovascular disease [expressed as percentage of patients with event(s)] was 4.3%, 4.0% and 2.8% for RSG, metformin and glyburide groups respectively, for all cardiovascular events and 3.4%, 3.2% and 1.8% for RSG, metformin and glyburide groups respectively, for serious cardiovascular events.

A systematic review by Singh et al. published in 2007 evaluated long-term cardiovascular events with rosiglitazone treatment in patients with impaired glucose tolerance or type 2 DM. This review included four RCTs with a total of 14,291 patients (6421 receiving RSG and 7870 receiving control therapy). They showed that compared to control, RSG significantly increased the risk of myocardial infarction (MI) [relative risk (RR) = 1.42 and 95% confidence interval (CI) = 1.06, 1.91; p = 0.02] and heart failure (HF) [RR (95% CI) = 2.09 (1.52, 2.88); p <0.001] without a significant increase in risk of cardiovascular mortality [RR (95% CI) = 0.90 (0.63, 1.26); p = 0.53]. There were variations in the number needed to harm (NNH) with RSG depending on the baseline risk of cardiovascular events (Table 1). Of the four RCTs, three [Dargie et al., Home et al. (RECORD – Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes), and Kahn et al. (ADOPT)] were in patients with type 2 DM and are detailed in Appendix 1. The remaining one RCT was in patients with impaired glucose tolerance and not type 2 DM, the population of interest for this report. This RCT (Gerstein et al., 2006) had a total of 5269 patients and the RR (95% CI) for RSG compared to control (placebo) was 1.78 (0.79, 4.01) for MI, 7.00 (1.59, 30.76) for HF, and 1.20 (0.52, 2.77) for cardiovascular mortality. The small RCT by Dargie et al. showed there were no significant differences between the RSG group and the control (placebo) group with respect to MI, HF or cardiovascular mortality. The results of the RECORD trial presented here, were those from an interim analysis. The investigators of the RECORD trial decided to publish their interim findings because in their absence, concerns raised by a recent meta-analysis could well compromise the study’s integrity through an increase in the dropout rate and potential biases in reporting events. Their interim results showed that there were no significant differences between the RSG group [RSG + (metformin or sulfonylurea)] and the control group (metformin + sulfonylurea) regarding MI or cardiovascular death, but there was a significant increase in risk of HF in the RSG group. The ADOPT trial showed that there were no significant differences between the RSG group and the control (metformin or glyburide) group with respect to MI, CHF or cardiovascular death. The risk
of CHF was significantly higher for the RSG group as compared with the glyburide group [hazard ratio (HR) (95% CI) = 2.20 (1.01, 4.79)]. This review concluded that among patients with impaired glucose tolerance or type 2 DM, RSG use for at least 12 months was associated with a significantly increased risk of MI or HF, without a significantly increased risk of cardiovascular mortality.

**Table 1: Variation in NNH**

<table>
<thead>
<tr>
<th>Event</th>
<th>Population</th>
<th>Baseline Risk of Event per Year (%)</th>
<th>NNH* (95% CI) per Year with RSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>Trial participants with recently diagnosed type 2 DM: mean age 57 years with no history of unstable or severe angina(^7)</td>
<td>0.29</td>
<td>822 (379, 5748)</td>
</tr>
<tr>
<td></td>
<td>Cohort of US community based patients with type 2 DM: aged 45 to 67 years with no prior history of MI(^7)</td>
<td>1.08</td>
<td>221 (102, 1544)</td>
</tr>
<tr>
<td></td>
<td>Cohort of US community based patients with type 2 DM: aged 45 to 67 years with prior history of MI(^7)</td>
<td>3.22</td>
<td>74 (35, 518)</td>
</tr>
<tr>
<td>HF</td>
<td>Trial participants with recently diagnosed type 2 DM: mean age 57 years with no history of CHF(^7)</td>
<td>0.24</td>
<td>383 (222, 802)</td>
</tr>
<tr>
<td></td>
<td>Cohort of US community based patients with type 2 DM: mean age 63 years with no history of HF(^14)</td>
<td>3.09</td>
<td>30 (18, 63)</td>
</tr>
</tbody>
</table>

* Calculated using RR (95% CI) = 1.42 (1.06, 1.91) for MI and 2.09 (1.52, 2.88) for HF (values obtained from the meta-analysis). CHF = congestive heart failure, HF = heart failure, MI = myocardial infarction, NNH = number needed to harm (i.e. the number of patients that would need to be treated with the drug to cause harm in one patient)

A systematic review by Lago et al. published in 2007 evaluated CHF and cardiovascular death in patients with pre-diabetes and type 2 DM.\(^{15}\) They compared TZD [RSG or pioglitazone (PIO)] with control treatment and reported results separately for RSG and PIO. This review included five RCTs with a total of 14,491 participants (6523 receiving RSG and 7968 receiving control therapy). They showed that RSG significantly increased the risk of CHF [RR (95% CI) = 2.18 (1.44, 3.32); p = 0.0003] without a significant increase in cardiovascular death [RR (95% CI) = 0.91 (0.63, 1.32); p = 0.63]. Of the five RCTs, three (Dargie et al.,\(^9\) Home et al.,\(^10\) and Kahn et al.(ADOPT)\(^7\)) were with type 2 DM and are detailed in Appendix 1. The remaining two RCTs were with pre-diabetic patients not type 2 DM, the population of interest for this report.\(^{11,16}\) One RCT (Gerstein et al., 2006)\(^11\) was also included in the systematic review by Singh et al.\(^8\) and is described above. The other RCT (Bhatt et al., 2007) compared RSG with placebo in 200 patients with metabolic syndrome (i.e. with hypertension, dyslipidemia, or glucose intolerance) undergoing percutaneous coronary intervention.\(^{16}\) This RCT showed no significant change in risk of CHF [RR (95% CI) = 2.88 (0.12, 69.94)] or cardiovascular death [RR (95% CI) = 0.48 (0.04, 5.21)] with RSG as compared to placebo. This review demonstrated that compared with control treatment, RSG treatment significantly increased the risk of CHF, without significantly increasing the risk of cardiovascular death.
A meta-analyses by Nissen and Wolski published in 2007 evaluated the effect of RSG on the risk of MI and cardiovascular death. They included 42 RCTs with 15,560 patients in the RSG group and 12,283 patients in the control group. The RSG group received either RSG alone or in combination with one or more anti-diabetic drugs and the control group received either placebo or one or more anti-diabetic drugs. In the included trials, the number of patients ranged between 39 and 2635 and the trial duration was greater than 24 weeks. Of the 42 trials included in this meta-analysis, five were trials that had been submitted to the FDA for the March 1999 advisory board hearing that recommended approval of RSG, 35 were trials identified in the GlaxoSmithKline clinical-trial registry, and two were the recently published large trials (DREAM and ADOPT). They computed the pooled odds ratio (OR) and showed that in the RSG group, as compared to the control group, OR (95% CI) was 1.43 (1.03, 1.98) (p = 0.03) for MI and 1.64 (0.98, 2.74) (p = 0.06) for cardiovascular death. They concluded that RSG was associated with a significant increase in the risk of MI and with an increase in the risk of cardiovascular death that had borderline significance. The authors mentioned a number of limitations in their meta-analyses. The trials pooled were not originally intended to investigate cardiovascular outcomes. Most trials did not centrally adjudicate cardiovascular outcomes, and the definitions of MI were not available. Many of the trials were small and short-term, resulting in few adverse cardiovascular events or death. The authors mentioned the urgent need for comprehensive evaluations to clarify the cardiovascular risks of RSG. They suggested a robust assessment would be possible if the source data from completed trials was made available by the manufacturer.

Randomized Controlled Trials

The three RCTs identified in our search were included in the systematic reviews described above. Details of the RCTs are provided in Appendix 1.

Observational Studies

A retrospective cohort study, comparing pioglitazone (PIO) with RSG, was conducted by Gerrits et al. in type 2 DM patients. They used data from 2003 to 2006 from a large health care insurer in the US. A total of 29,911 eligible patients were identified in the database. There were 14,807 and 15,104 patients in the PIO and RSG groups respectively. Baseline demographics, medical history and dispensed medications were generally well balanced. The median age was 56 years in both groups. In the earlier years of the study, patients were more frequently initiated on RSG whereas in the later years of the study, patients were more frequently initiated on PIO. The average follow up time was 1.2 years in the PIO group and 1.3 years in the RSG group. Among the patients on PIO, 161 (1.1%) were hospitalized for acute myocardial infarction (AMI) while in the RSG group the corresponding numbers were 214 (1.4%). Using multivariate Cox's proportional hazards analysis, the investigators estimated the HR of incident hospitalization for AMI with PIO as compared to RSG. The unadjusted HR (95% CI) for hospitalization for AMI was 0.82 (0.67, 1.01). After adjustment for baseline covariates the HR (95% CI) was 0.78 (0.63, 0.96). They concluded there was a 22% relative risk reduction of hospitalization for AMI with PIO as compared to RSG. The investigators mentioned some limitations of their study. Despite general similarity of baseline characteristics between the PIO and RSG groups, there were small differences in baseline metformin and lipid-altering drug use. On one hand the claims databases have been shown to provide comprehensive and reliable data on drug exposure but on the other hand, in these databases there can be general concern regarding the accuracy of recorded inpatient and outpatient diagnoses.
Lipscombe et al. performed a nested case-control analysis of a retrospective cohort study using health care databases in Ontario. They examined cardiovascular outcomes with thiazolidones (PIO and RSG) as compared to other oral hypoglycemic agents (OHA). They included patients, aged 66 years or older with DM, treated with at least one oral hypoglycemic agent between April 1, 2002 and March 31, 2005 and followed them until March 31, 2006. Because patients receiving insulin tend to have either more advanced DM or type I DM they excluded patients who received insulin in the year preceding cohort entry. However, patients who started receiving insulin during follow-up were retained in the study. The study population included 159,026 patients with a mean age of 74.7 years and a median follow-up of 3.8 years. The adjusted rate ratios for CHF, MI and all cause mortality with RSG as compared to other OHA are shown in Table 2. All rate ratios were adjusted for exposure to other hypoglycemic drugs, past TZD use, and potential confounders. This population-based study showed that RSG treatment was associated with an increase in risk of CHF, AMI and mortality when compared with other combination oral hypoglycemic agents. The increase in risk of CHF and all-cause mortality was significant for all three RSG treatment groups (Table 2). The increase in risk for AMI was significant for the current RSG monotherapy group but not significant for the current RSG combination therapy group and the past treatment with RSG group (Table 2). The investigators mentioned some limitations of their study. The use of administrative data has a potential for misclassification of some exposures, covariates and outcomes. This was however minimized by using validated end points of CHF and AMI hospital visits as outcomes. Though the cases and controls were matched for important risk factors and adjusted for confounders, selection bias cannot be completely ruled out. The population studied may represent an older and more select population of patients with more advanced diabetes because under the Ontario Drug Benefit reimbursement criteria, most of these patients will have failed or had a contraindication to other drugs.

### Table 2: Rate Ratios with RSG as compared to other OHA therapies

<table>
<thead>
<tr>
<th>Event</th>
<th>Pattern of use</th>
<th>Number of Cases</th>
<th>Number of Controls</th>
<th>Adjusted Rate Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>Current other OHA combination therapy</td>
<td>3695</td>
<td>18351</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current RSG monotherapy†</td>
<td>53</td>
<td>147</td>
<td>1.76 (1.27, 2.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Current RSG combination therapy†</td>
<td>282</td>
<td>1404</td>
<td>1.00 (0.87, 1.16)</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>Past treatment with RSG§</td>
<td>95</td>
<td>424</td>
<td>1.06 (0.84, 1.34)</td>
<td>0.65</td>
</tr>
<tr>
<td>CHF</td>
<td>Current other OHA combination therapy</td>
<td>3478</td>
<td>18045</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current RSG monotherapy†</td>
<td>62</td>
<td>151</td>
<td>1.98 (1.44, 2.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Current RSG combination therapy†</td>
<td>364</td>
<td>1330</td>
<td>1.43 (1.25, 1.63)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Event Pattern of use | Number of Cases | Number of Controls | Adjusted Rate Ratio (95% CI) | p-value |
---|---|---|---|---|
**Past treatment with RSG§** | 136 | 385 | 1.75 (1.41, 2.16) | <0.001 |
**Current other OHA combination therapy** | 5529 | 18835 | | |
**Current RSG monotherapy†** | 76 | 255 | 1.47 (1.12, 1.93) | 0.005 |
**Current RSG combination therapy†** | 358 | 1027 | 1.26 (1.10, 1.44) | <0.001 |
**Past treatment with RSG§** | 314 | 576 | 1.98 (1.70, 2.31) | <0.001 |

Other than TZDs; more than 97% were receiving metformin + sulfonylurea; †Current users are those who were dispensed the drug with the days supplied overlapping the index date by 14 days or more; §Past users are those who were dispensed the drug with the days supplied ending between 15 and 365 days before the index date. AMI = acute myocardial infarction, CHF = congestive heart failure, OHA = oral hypoglycemic agent, RSG = rosiglitazone.

**Limitations**

The patient population included in three of the systematic reviews was not specifically type 2 DM patients. Two systematic reviews pooled RCTs with type 2 DM patients as well as pre-diabetic patients. The third systematic review derived summary estimates pooling a large number of RCTs (42), but many were of small sample size and also there were variations in the patient population. Of the 42 RCTs, one large RCT (DREAM) was in patients with impaired glucose tolerance or impaired fasting glucose, two RCTs were in chronic psoriasis patients, and one RCT was in patients with Alzheimer’s disease.

Observational studies provide results from a real-world setting but have potential limitations which need to be taken into consideration in interpreting results. Since the treatment is not allocated through randomization, there is a possibility of confounding due to imbalances in unmeasured and unmeasurable risk factors. However, this is less of an issue for the two observational studies included here, as they were large studies.

**Conclusions and implications for decision or policy making:**

One meta-analysis showed that RSG significantly increased the risk of MI and HF without a significant increase in risk of cardiovascular mortality. A second meta-analysis showed that RSG significantly increased the risk of CHF without a significant increase in cardiovascular death. A third meta-analysis showed that RSG was associated with a significant increase in the risk of MI and with an increase in the risk of cardiovascular death that had borderline significance. The interim results from the large RECORD trial, which was designed to investigate cardiovascular outcome, showed that RSG was associated with increased risk of HF, but the findings were inconclusive with respect to AMI and cardiovascular death. Overall, it appears there is increased risk of HF with RSG. Completion of the RECORD study may provide a better assessment of the long-term cardiovascular effects of treatment with RSG and thus assist in determining appropriate therapies for patients with type 2 DM. In the mean time, in

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deciding a treatment for a type 2 DM patient, it may be worthwhile to take into consideration the potential risks and benefits, the profile of adverse events and the cost of RSG.

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References:


Appendix 1: Details of RCTs

<table>
<thead>
<tr>
<th>RCT</th>
<th>Treatment and Duration</th>
<th>Patients</th>
<th>Event type</th>
<th>Number of Patients having an Event in the Treatment Group</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dargie et al., 2006⁹</td>
<td>RSG (N = 110) vs placebo (N = 114); 1 year</td>
<td>Type 2 DM with NYHA class I or II HF</td>
<td>MI</td>
<td>5 0</td>
<td>11.40 (0.64, 203.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HF</td>
<td>19 10</td>
<td>1.97 (0.96, 4.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular mortality</td>
<td>5 4</td>
<td>1.30 (0.36, 4.70)</td>
</tr>
<tr>
<td>Home et al., 2007¹⁰ - RECORD</td>
<td>RSG + (Met or SU) (N = 2220) versus Met + SU (N = 2227); 3.75 years*</td>
<td>Type 2 DM Exclusion: recent hospitalization for cardiovascular event, planned cardiovascular procedure, HF</td>
<td>MI</td>
<td>49 40</td>
<td>1.23 (0.81, 1.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HF</td>
<td>47 22</td>
<td>2.14 (1.30, 3.54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular mortality</td>
<td>37 46</td>
<td>0.81 (0.53, 1.24)</td>
</tr>
<tr>
<td>Kahn et al., 2006⁷ - ADOPT</td>
<td>RSG (N = 1456) versus Met or Glyb (N = 2895); 4 years</td>
<td>Type 2 DM, diagnosed within the past 3 years and not taking any oral hypoglycemic drugs. Exclusion: unstable or severe angina, any degree of heart failure</td>
<td>MI</td>
<td>24 34</td>
<td>1.40 (0.84, 2.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HF</td>
<td>22 28</td>
<td>1.56 (0.90, 2.72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular mortality</td>
<td>5 12</td>
<td>0.83 (0.29, 2.35)</td>
</tr>
</tbody>
</table>

Interim analysis

ADOPT = A Diabetes Outcomes Progression Trial, Glyb = glyburide, HF = heart failure, Met = metformin, MI = myocardial infarction, N = number of patients in each treatment group, NYHA = New York Heart Association, RECORD = Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes, SU = sulfonylurea