Pioglitazone and rosiglitazone are both members of the thiazolidinedione (TZD) class of antihyperglycemic agents. While they share several pharmacologic similarities, laboratory analyses of their effects on gene expression show that there are marked differences between the agents.\textsuperscript{1-4} While the clinical significance of these differences is not fully understood, there is evidence from clinical-trial and real-life experience with these two agents showing important clinically relevant distinctions as well. With the recent Health Canada endorsed restrictions on the use of rosiglitazone for reasons of cardiovascular safety, it is particularly important to emphasize that pioglitazone does not share the characteristics that led to these restrictions. In this short review, cardiovascular safety data for these agents are presented, as well as some practical tips for switching patients from rosiglitazone to pioglitazone. First, however, we discuss the place of TZDs in therapy.

\textbf{Place of TZDs in Therapy for Type 2 Diabetes}

For pharmacotherapy in Type 2 diabetes, the Canadian Diabetes Association’s 2008 guidelines recommend metformin as first-line treatment for most patients.\textsuperscript{5} The guidelines also recognize that combination antihyperglycemic therapy is often required to get patients to their glycemic goals. The choice of agent to use in combination is left to the discretion of the individual physician, although the guidelines do recommend using classes of agents with differing mechanisms of action.

TZDs are appealing drugs in that regard, as their mechanism of action is complementary to that of metformin; they act by directly reducing insulin resistance at the sites of insulin action (e.g., in muscle, adipose tissue, and the liver).\textsuperscript{6} Of all currently available oral antidiabetic agents, TZDs have the most durable effect, maintaining A1C at goal for a longer period of time compared to glyburide and metformin. Clinical studies with metformin in combination with pioglitazone or rosiglitazone have shown each therapy to be effective.\textsuperscript{7,8}

\textbf{Cardiovascular Safety of TZDs}

Recent restrictions on the use of rosiglitazone reflect the findings that this drug increases the risk of myocardial ischemia.\textsuperscript{9} In a meta-analysis of 52 rosiglitazone trials involving 16,995 patients, there was a statistically significant increase in the risk of serious myocardial ischemia (odds ratio [OR] 1.5, 95\% confidence interval [CI] 1.1-2.0) and overall myocardial ischemia (OR 1.3, 95\% CI 1.1-1.7). There was also a trend towards an increased risk of overall cardiovascular events (OR 1.4, 95\% CI 0.9-2.2).

With two prospective trials (RECORD and BARI 2D), the FDA found the cardiovascular risk with rosiglitazone to be inconclusive (study subjects included patients at high cardiovascular risk who were exposed to rosiglitazone for many years). A full discussion of these two prospective studies can be found on the FDA’s Web site.\textsuperscript{10} While the Thiazolidinedione Intervention With Vitamin D Evaluation (TIDE) trial was designed to compare the long-term cardiovascular effects of rosiglitazone and pioglitazone, its results will never be known following termination of the trial due to the questionable safety of rosiglitazone.\textsuperscript{11}

In contrast, pioglitazone has been shown to reduce the risk of cardiovascular events. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) study (n=5,238 patients with evidence of macrovascular disease), pioglitazone therapy was associated with a statistically significant reduction in risk for the combined endpoint of myocardial infarction, stroke or death, the secondary endpoint of the study (hazard ratio [HR] 0.84, 95\% CI 0.72-0.98; Figure 1).\textsuperscript{12}
the primary endpoint was not significant, there was a significant effect in the secondary endpoint. Initially, many physicians viewed the study results as being negative; however, following a meta-analysis by Nissen, pioglitazone’s safety data became more apparent.

A retrospective cohort study using Ontario data found that patients taking pioglitazone had a significantly lower risk of the primary composite endpoint (death or hospital admission for either acute myocardial infarction or heart failure) compared to those taking rosiglitazone (HR 0.83, 95% CI 0.76-0.90). The risks were also significantly lower for pioglitazone in the individual endpoints of death and heart failure. These data are supported by another retrospective, observational comparison of rosiglitazone and pioglitazone, wherein investigators have also shown that pioglitazone therapy is associated with significantly lower rates of stroke, heart failure, and death. The risk for fracture and CHF appears to be equivalent for rosiglitazone and pioglitazone.

The dose equivalent for rosiglitazone 4 mg is pioglitazone 30 mg, and for rosiglitazone 8 mg, the equivalent is pioglitazone 45 mg. There are no formal switching guidelines available, but if tolerability is thought to be a concern, one might consider switching to a lower dose of pioglitazone (e.g., start with 15 or 30 mg and titrate to the target dose of 30 or 45 mg). Since rosiglitazone and pioglitazone are not necessarily equivalent drugs, we would also suggest that the physician monitor for rapid weight gain (fluid retention) during the first few weeks following a medication switch. Depending on the province and the patient’s reimbursement situation, a switch to pioglitazone from rosiglitazone may also be easier on a practical level, as there may be fewer obstacles to reimbursement.

Conclusions
TZDs are effective medications for the control of hyperglycemia in Type 2 diabetes. Their mechanism of action is complementary to that of metformin, making them attractive options for inclusion in combination strategies. The safety concerns with rosiglitazone are legitimate, but the data with pioglitazone show it to be a safer agent in terms of cardiovascular risk. Unfortunately, the study to determine the extent of pioglitazone’s comparative safety, the TIDE trial, will never be completed. Nonetheless, pioglitazone should continue to be considered as a potential choice for combination therapies in patients requiring more than metformin to control their hyperglycemia, and can be considered as a reasonable replacement for patients being taken off rosiglitazone therapy.

One of the important lessons learned from the rosiglitazone experience is that the entire safety picture may take some time...
The most obvious choice for those patients who were doing well on rosiglitazone is to switch to pioglitazone—an agent that is as effective as rosiglitazone for glycemic control, but it is associated with a more favourable safety profile.

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References

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