Rosiglitazone and Cardiovascular Safety

Rosiglitazone, an antidiabetic agent, belongs to the class of drugs known as the thiazolidinediones, and is a widely used agent for the treatment of type 2 diabetes. Rosiglitazone was approved by the Food and Drug Administration in 1999 based on the surrogate endpoints of decreased fasting blood glucose and glycated hemoglobin levels.

In the United States, there are about 1.5 million new cases of type 2 diabetes per year, with microvascular and macrovascular disease representing major complications of the disease. Both of these complications have been associated with elevated fasting blood glucose and glycated hemoglobin. Macrovascular complications are especially important because greater than 65% of deaths in diabetics are due to cardiovascular complications. Recently, emphasis has been placed on the safety of rosiglitazone, with concerns over its effects on the risk of cardiovascular events. Two conflicting papers have been published—a meta-analysis by Nissen and colleagues and an interim analysis of the RECORD trial by Home.

Findings of the meta-analysis

In the meta-analysis, 116 trials were screened for inclusion and 42 trials were subsequently included to assess the risk of myocardial infarction or death from cardiovascular causes. To be included in the analysis, trials must have had a randomized comparator group (placebo or active control [primarily a sulfonylurea, metformin, or insulin]), a comparable duration of treatment in both groups, and more than 24 weeks of drug exposure. Most of the 42 studies included in the analysis were small or short-term trials. There were a total of 15,560 patients given rosiglitazone and 12,283 given comparator treatment. The Peto method was used to combine data from the 42 trials. The primary outcomes evaluated were myocardial infarction and death from cardiovascular causes.

There were 86 myocardial infarctions and 39 deaths from cardiovascular causes in the rosiglitazone group versus 72 myocardial infarctions and 22 deaths from cardiovascular causes in the comparator group. Rosiglitazone was associated with a statistically significant increase in the risk of myocardial infarction, with an odds ratio (OR) of 1.43 (95% CI, 1.03 to 1.98; p=.03) versus comparator treatments. The OR for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; p=.06). The authors concluded that rosiglitazone was associated with a significant increase in the risk of myocardial infarction and a borderline significant increase in the risk of death from cardiovascular causes even after short-term exposure (24 to 52 weeks) to the drug.

Although this study was the first to report cardiovascular outcomes with rosiglitazone, there are several important limitations. A meta-analysis is not as strong as a randomized control trial to assess cause and effect regarding an outcome. The comparator group included both placebo and active treatment control groups, which could confound results. Most of the trials included in the analysis were small and, perhaps most importantly, were not designed to assess the risk of cardiovascular complications with rosiglitazone. In addition, the cardiovascular outcomes of interest were not adjudicated in most trials, hence subjects may have been missed or misclassified. The researchers only had access to public summary data, but not the original source data. Because of this, they were not able to conduct time-to-event analyses or to ascertain the time course of risks.

Interim analysis of the RECORD trial

In response to the results of the meta-analysis, Home and colleagues published an unplanned interim analysis of
a randomized, open-label, non-inferiority trial assessing the relationship between rosiglitazone and the risk of hospitalization or death from cardiovascular causes. The Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial consists of patients with type 2 diabetes treated with rosiglitazone plus metformin or a sulfonylurea (the rosiglitazone group) and patients treated with metformin plus a sulfonylurea (the control group). Patients included in the study had to have a glycated hemoglobin level between > 7% and 9% while on maximum doses of metformin or a sulfonylurea. Patients were then randomized to receive either rosiglitazone or metformin if they were currently being treated with a sulfonylurea. If the subjects were currently on metformin, they were randomized to receive either rosiglitazone or a sulfonylurea.

The primary outcome was the composite of hospitalization or death from cardiovascular causes analyzed as time to first occurrence. After 3.75 years of a planned total of 6 years, data were available for 4447 patients (2220 in the rosiglitazone group and 2227 in the control group). No difference was seen in the primary outcome between rosiglitazone and the control group, with a hazard ratio (HR) of 1.08 (95% CI, 0.89 to 1.31; p=0.43) for adjudicated events. For adjudicated and non-adjudicated events, an HR for the primary outcome was 1.11 (95% CI, 0.93 to 1.32; p=0.26). Rosiglitazone was associated with a statistically significant increase in heart failure with a HR of 2.15 (95% CI, 1.30 to 3.57; p=0.003) for all adjudicated and non-adjudicated events. An increased risk of heart failure was also seen for adjudicated events alone (HR 2.24; 95% CI, 1.27 to 3.97; p=0.006). The authors concluded that the interim findings were inconclusive regarding an overall risk of hospitalization or death from cardiovascular causes, but that rosiglitazone was associated with an increased risk of heart failure.

Although this was a prospective trial designed to measure cardiovascular outcomes, there are several limitations. This study was an open-label study with non-blinded treatment allocation; however, an independent, blinded committee did review the outcomes. Also, a large number of patients were lost to follow-up (approximately 10%), and the event rate in the study was much lower than originally predicted (estimated at 11% vs. 3.1% in the trial)—both of these factors lessened the power of the study. The composite outcome of hospitalization or death from cardiovascular causes has been described as being a “weak” primary outcome. This is because hospitalization from cardiovascular causes may not be related to the treatments, resulting in an increased chance of non-inferiority findings. The full results of the RECORD study may allow for a better assessment of the cardiovascular risks of rosiglitazone.

**FDA warning - a class effect?**

The Food and Drug Administration (FDA) has issued an alert on this topic, but the agency is in the process of analyzing data and has not recommended any action at this point. The rosiglitazone data raise the question of whether or not the potential for cardiovascular events is a class effect of the thiazolidinediones. To date, the main difference between the drugs involves their effects on the lipid profile. Pioglitazone exhibits positive effects on the lipid profile, whereas rosiglitazone can have negative effects. At this time, no definitive conclusion can be made about a class effect. Pioglitazone, the other marketed thiazolidinedione, is also known to cause edema and heart failure. Thus far, no evidence has pointed to an increased risk of myocardial infarction with pioglitazone. Data from PROactive, a randomized, double-blind trial comparing pioglitazone to placebo in patients with diabetes and evidence of macrovascular disease, demonstrate that pioglitazone significantly reduced the incidence of the secondary composite endpoint of all-cause mortality, non-fatal myocardial infarction, and stroke. This trial has been criticized for the use of a composite endpoint and the fact that there was no significant difference between groups in the primary outcome, a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle.

**Summary**

At this point, based on the above data, it can be concluded that rosiglitazone does not appear to have a favorable effect on the reduction of adverse cardiac outcomes. Whether or not it leads to an increase in such events may be clarified when the full results of RECORD are available. Pioglitazone may have benefit on certain cardiac endpoints; however, this is based on data from patients with diabetes at high risk for macrovascular complications.

**Community-acquired Methicillin-resistant Staphylococcus Aureus**

The risks of methicillin-resistant *Staphylococcus aureus* (MRSA) in the inpatient setting are well known. The prevalence of infection with this organism has increased dramatically over the last 30 years—now accounting for over 60% of *S aureus* infections in the healthcare setting—and poor outcomes are not uncommon. In addition, today, MRSA has become a concern in the community setting, referred to as community-associated MRSA (CA-MRSA). The origins of CA-MRSA remain unclear, but data indicate that CA-MRSA is genetically distinct from healthcare-associated MRSA (HA-MRSA), suggesting emergence of a resistant strain in the community rather than migration from the healthcare setting. Differences also exist in antibiotic susceptibility between CA-MRSA and HA-MRSA.

**Current trends in CA-MRSA**

To assess the status and factors that could potentially contribute to acquiring an infection with CA-MRSA, Hota and colleagues conducted an epidemiologic study of CA-MRSA in the Chicago area. Electronic records were surveyed to identify cases of CA-MRSA among patients with no prior
A parallel, but less dramatic increase was also seen in the use of antibiotics (erythromycin and clindamycin) was seen to steadily increase during the time period studied. Resistance to 2 commonly used antibiotics — (African-American), recent incarceration, young age, and residence within a specific public housing complex.

Factors identified in the case-control study as significant risks for infection with CA-MRSA included race (≥80%), intermediate (40-79%), and low (<40%). The primary outcome assessed was long-term mortality. A total of 31,455 patients meeting inclusion criteria were identified. Statins, and beta-blockers—are well documented as reducing mortality in these patients. Although, although the Joint Commission and CMS use of core performance measures for assessing hospitals’ adherence to recommended treatment will improve inpatient care, continued use of medications by patients on an outpatient basis is needed for a therapy to be optimally effective.

Medication adherence is essentially a patient’s compliance with a prescribed therapy. Poor adherence by a patient can have negative effects not only for the individual patient, but for the healthcare system. It has been reported that 33 to 69% of medication-related hospital admissions are a result of poor adherence to therapy. The cost associated with these admissions has been estimated at $100 billion annually. Poor adherence to medications can also impact disease outcome, including mortality.

One of the most recent studies assessing the effects of medication adherence was by Rasmussen and colleagues. The purpose of the trial was to evaluate the effects of adherence to 3 medications (calcium channel blockers, statins, and beta-blockers) among patients with a recent history of acute myocardial infarction. Patients included in the study cohort were at least 66 years of age and remained alive at least 15 months after hospitalization for an acute myocardial infarction. Data on prescription compliance, mortality, and other patient characteristics (e.g., age, income level, physician specialty, concurrent disease conditions and hospital readmissions) were taken from prescription claims and medical records databases. Adherence to prescribed medications was determined for a 1-year period based on the number of pills dispensed and number of days supplied per prescription. The rates of adherence were classified as high (≥80%), intermediate (40-79%), and low (<40%). The primary outcome assessed was long-term mortality. A total of 31,455 patients meeting inclusion criteria were identified. Statins were dispensed for 57%, a beta-blocker for 77%, and a calcium channel blocker for 30% within 3 months of hospital discharge. Although the mean rates of adherence were high for all 3 drug therapies (~80-87%), there was an association between medication adherence and treatment outcomes.
compliance and mortality for statins and beta-blockers. For statins, intermediate and poor adherence resulted in higher rates of mortality—12% and 25% higher, respectively (p=.03 and p=.001)—compared to high adherence. A significant association was also seen between low adherence to beta-blockers and mortality—a 13% higher mortality compared to high adherence (p=.008). However, no relationship was seen between calcium channel blocker adherence (either dihydropyridine or nondihydropyridine) and mortality (p=.12). The authors concluded that the benefits with adherence were related to specific drug effects, rather than by “generic” adherence to a medication.

Simpson and colleagues conducted a meta-analysis to determine the effects of medication adherence on mortality. Data from randomized controlled trials, retrospective analyses, and observational studies were included. A total of 21 trials (46,847 patients) were included in the analysis. In the trials, drug therapy was evaluated for a number of different medical conditions, including heart disease, human immunodeficiency virus infection, type 2 diabetes, and hyperlipidemia. Good medication adherence was defined as 75 to 90% or better compliance to prescribed therapy. Mortality was higher among patients with poor adherence to therapy compared to those with good adherence (8.5% vs. 4.7%; OR 0.56 [95% CI 0.5-0.63]). As would be expected, patients who exhibited good adherence to therapies that were found to be harmful for the medical condition under treatment had a higher mortality rate than patients non-adherent to such therapies (OR 2.90 [95%CI 1.04-8.11]).

**Strategies to assess and improve medication adherence**

Several methods can be used to assess a patient’s adherence to medication. The patient can be directly observed, probably the most accurate method. Measuring plasma or serum drug levels or biologic markers can be done, as in clinical trials. However, these may not be practical approaches for patients in the outpatient setting and may be expensive. Various indirect methods have been suggested, including pill counts, questionnaires, patient diaries, and electronic medication monitors.

In addition to direct and indirect measures of assessing a patient’s adherence, patient education can be used to improve adherence. This may be especially important for medical conditions that are generally asymptomatic, such as hypertension and osteoporosis. Often patients who do not experience the effects of a medical condition may not fully understand the need for medication. Patient education has been shown to improve adherence to medication regimens. The impact of education has been greater when it was provided as direct patient counseling or written plus audio educational materials, rather than given only as written information. Any educational intervention should be ongoing. Regular reinforcement of the need for medication and monitoring of a patient’s medical condition can provide proof of the effectiveness of treatment.

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### Table. Strategies to assess or improve medication adherence

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**Summary**

Adherence to prescribed medications has been shown to improve disease outcomes, including mortality. Assessment of adherence should be done, and patient education provided to ensure consistent use of medications by patients.

**FDA Update—Revisions to Antidepressant Black Box Warnings**

Antidepressants have been under considerable evaluation by the Food and Drug Administration (FDA) due to the increased incidence of suicidal behavior among children and adolescents. In March 2004, the FDA required a black box warning to be placed on all antidepressants indicating increased risk of suicidal ideation or suicidal behavior in children. This action was based on an analysis of 24 trials involving over 4400 children and adolescents with various psychiatric conditions (including major depression and obsessive compulsive disorder) treated with antidepressants. An increased risk of suicidal behavior was seen during the first few months of therapy with these agents—4% versus 2% with placebo. Although the mechanism for suicidal behavior with antidepressants is not known, it is thought that antidepressants may have an early activation effect that may give depressed patients the energy to follow through on suicidal thoughts before the mood improvement associated with the antidepressants treatment has a chance to take effect.

**Revision of black box warnings**

In December 2006, the FDA’s Psychopharmacologic Drugs Advisory Committee made the decision to update the black box warning for antidepressants to include young adults age 18 to 24 years. This was based on the results of 319 short-term trials; 295 trials involved patients with major depressive disorders or other psychiatric disorders and 24 trials involved patients with obsessive compulsive disorder or other psychiatric disorders. The highest risk of suicidality was found in patients with major depressive...
disorder and patients that were less than 24 years old. In drug versus placebo trials, out of 1000 patients treated, 14 additional cases of suicidality in children and adolescents (< 18 years old) were seen in the antidepressant group compared to placebo and were considered a drug-related increase. In patients between 18 and 24 years old there were 5 additional cases associated with antidepressants out of 1000 patients treated. There was no increase in suicidal behavior with antidepressant use for patients over 24 years of age, and a decrease in suicide behavior was seen for patient 65 years or older.

As a result of these findings, the FDA mandated an update to existing black box warnings including:

- Increased risks of suicidality in young adults (18-24 years old) during initiation of therapy
- Information stating that an increased risk of suicidality was not observed in patients over 24 years of age
- Emphasis that suicidality in itself is an associated risk of major depressive disorder
- Revision of medication guides that are to be provided to the patient

Due to the short-term nature of the trials included in the analysis the risk of suicidal behavior or ideation is not known in patients treated for depression long term. The FDA states that there are sufficient maintenance, placebo-controlled trials that show antidepressants can delay the recurrence of depression. The FDA recommends that all patients who are treated with antidepressants regardless of reason for use should be closely monitored for any signs of suicidal behavior. If any patient experiences symptoms such as agitation, anxiety, panic attacks, insomnia, hypomania, or hostility, the physician or healthcare provider should consider changing therapy or tapering medication to discontinuation.

**Medication Safety**

*The complete details are available on the Medical Center Intranet under Clinical Care Guideline in the Medication Use section, G-13.5 High Alert Medication Guideline.*

**UIMC High-Alert Medications**

- Argatroban
- IV calcium salts
- Chemotherapeutic agents
- Chloral Hydrate
- Digoxin
- Dobutamine
- Dopamine
- Epinephrine
- Esmolol
- Heparin
- Hypertonic Saline
- Insulin
- Isoproterenol
- IV magnesium
- Midazolam
- Narcotics and opiates, including Patient-Controlled Analgesia (PCA)
- Neuromuscular blocking agents (e.g. vecuronium, pancuronium)
- Norepinehrine
- Phenylephrine
- IV phosphate salts (sodium and potassium)
- IV potassium chloride
- Propranolol (IV)
- Warfarin

**UIMC High-Alert Medication Safety Categories and Example Strategies**

**Access/Storage:**
- Apply warning labels
- Tall-man lettering

**Ordering:**
- Eliminate non-approved abbreviations from Gemini orders
- Utilize standard concentration for IV infusion medications included in the clinical care guideline “Adult Critical Care medications for continuous IV infusion” guideline

**Computer alerts – Clinical decision support:**
- Rules, pop-ups and multum alerts for drug-drug, drug-allergy and duplicate therapy

**Perform independent double checks:**
- Recalculate the dose
- Use peer review process for unusual drug, dose, regimen

**Preparation and dispensing:**
- Use commercially available premixed IV solutions
- Use drug preparation guidelines
- Dispense the drug from pharmacy only or emergency stock (drug box or crash cart)

**Administration:**
- Use dosing charts for IV administration or calculation function on infusion control devices
- Use infusion control devices for continuous IV infusions
- Use oral syringes for administration of oral products

**Monitoring:**
- Require cardiac monitoring and/or pulse oximetry
- Have antidotes and/or resuscitation equipment close at hand
UIMC Look-alike / Sound-alike Drugs

1. Cisplatin-Carboplatin
2. Ephedrine-Epinephrine
3. Fentanyl-Sufentanil
4. Amphotericin B - Amphotericin B lipid form (Abelcet)
6. Vinblastine - Vincristine
7. Folic Acid - Leucovorin calcium (Folinic Acid)
8. Doxorubicin - Daunorubicin
9. Lamivudine - Lamotrigine
10. Retrovir - Ritonavir
11. Glyburide - Glipizide
12. Concentrated liquid morphine products – Conventional liquid morphine concentrations
13. Hydroxyzine - Hydralazine

The complete details regarding implemented safety strategies are located on the Medical Center Intranet under Clinical Departments / Hospital Pharmacy

P&T Committee Formulary Action

Additions
- Gadobenate dimeglumine
- Pioglitazone
- Aripiprazole injection – Restricted to Psychiatry and ED for use in patients with significant risk of experiencing extrapyramidal side effects

Deletions
- Rosiglitazone
- Ziprasidone injection

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