Drug utilization, safety and clinical use of Actos and Avandia

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Abstract.
BACKGROUND AND OBJECTIVE: The impetus for this review was recent increased warnings of cardiovascular toxicity, fractures and bladder cancer associated with glitazone use.
METHODS: A drug utilization review was performed regarding the use of Actos (pioglitazone) and Avandia (rosiglitazone) at Cooper Green Mercy Hospital (CGMH), an inner city safety net hospital in Birmingham, Alabama. Pharmacy records were reviewed hospital-wide to determine usage patterns of all anti-diabetic medications. Medline and the FDA websites were searched for articles on safety and efficacy of pioglitazone and rosiglitazone. Considerations were relative utilization profile, comparative efficacy, indications, relative cost, and safety profile of the two available medications in this drug class.
RESULTS: On the basis of all of these factors, a hospital-wide switch of all rosiglitazone prescriptions to all pioglitazone was implemented, which was estimated to result in savings of $83,000 for the first year. No episodes of worsening of control of diabetes were anticipated, nor were episodes of decreased efficacy or adverse effects as a result of automatically switching patients from rosiglitazone to pioglitazone at the time of prescription filling.
CONCLUSIONS: The conclusions can be summarized in a number of key points.
• Clinicians should follow the American Diabetes Association guidelines [1] for treatment.
• The basis for diabetic control is weight loss, diet and exercise.
• Initial medication management for type II Diabetes Mellitus includes metformin and insulin.
• There are no circumstances in which use of glitazone medications is preferable to other medication groups, and there are no clinical circumstances in which use of glitazone medications is absolutely necessary, as opposed to other classes of diabetic medication.
• There are significant contraindications, warnings and precautions to use of glitazones, which must be taken into consideration before use in every individual patient.
• Glitazones in particular should not be used in the following circumstances: congestive heart failure (CHF), concurrent bladder cancer or severe osteoporosis.

Keywords: Diabetes, thiazolidinediones, glitazone, Actos, pioglitazone, Avandia, rosiglitazone

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1. Introduction

The thiazolidinediones (GLITAZONES), also known as glitazones, are a class of medications used in the treatment of type II diabetes mellitus. The glitazone class of oral diabetes medications has been available since the late 1990s as one of many alternative treatments available for type II diabetes mellitus. Two drugs in this class are currently available in the United States: Actos (pioglitazone, Takeda and Lilly) and Avandia (rosiglitazone, GSK). A third glitazone, Rezulin (troglitazone, Pfizer) was removed from the market in 2000 due to its potential to cause liver toxicity and liver failure.

The glitazones are neither chemically nor functionally related to the sulfonylureas, the biguanides, or the alpha-glucosidase inhibitors. The glitazones mechanism of action is activation of peroxisome proliferator-activated receptors (PPARs), which are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR-gamma-nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. The glitazones act by increasing insulin sensitivity in muscle and adipose tissue and by inhibiting hepatic gluconeogenesis.

Unlike the sulfonylureas, the glitazone agents are not insulin secretagogues which trigger insulin release by direct action on the pancreatic beta cells. They may improve glycemic control while reducing circulating insulin levels. Thus, glitazones depend on the presence of insulin for their mechanism of action. They can decrease insulin resistance in the periphery and in the liver, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output.

Recently, a number of efficacy (pioglitazone vs. rosiglitazone, and glitazones vs. classical therapies such as metformin and glipizide) and safety (pioglitazone – increasing fractures, bladder cancer; rosiglitazone – increased cardiovascular CV death rates) issues have been raised for the glitazones. These concerns prompted an evaluation by the Pharmacy and Therapeutics (P&T) Committee at CGMH concerning the appropriateness of continuing both rosiglitazone and pioglitazone on the hospital formulary, as reported in this paper.

2. Drug utilization

A Drug Utilization Review (DUR) was performed by the P&T Committee for use of pioglitazone and rosiglitazone at Cooper Green Mercy Hospital (CGMH) for a twelve month period in 2006. The goal was to decide whether to automatically fill all prescriptions in this drug class with only one drug, based upon issues of efficacy and safety.

The clinical use data discussed above are categorized in Table 1.

Table 1 represents the doses of the various oral Diabetic Medications dispensed during a 1 month period at CGMH.

3. Relative cost savings

As illustrated in Table 1, although both pioglitazone and rosiglitazone were both on formulary for CGMH, only rosiglitazone was being used at the start of the DUR. At the beginning of the DUR, it was estimated there would be no annual cost savings by switching from rosiglitazone to pioglitazone. In fact, a potential increased cost to do so was identified during the DUR.
Table 1
Oral diabetic medication usage during 1 month period at CGMH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actos, pioglitazone</td>
<td>Glitazone/thiazolidinedione, Takeda</td>
<td>0</td>
</tr>
<tr>
<td>Avandia, rosiglitazone</td>
<td>Glitazone/thiazolidinedione, GSK</td>
<td>34</td>
</tr>
<tr>
<td>Metformin</td>
<td>Biguanide</td>
<td>310</td>
</tr>
<tr>
<td>Glucotrol, glipizide</td>
<td>Sulfonylurea/glipizide (Pfizer)</td>
<td>116</td>
</tr>
<tr>
<td>Diabeta, gliburide</td>
<td>Sulfonylurea/glyburide (Aventis)</td>
<td>124</td>
</tr>
</tbody>
</table>

Table 2
Estimated yearly cost savings by eliminating use of glitazones

<table>
<thead>
<tr>
<th>Cost Description</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra annual cost of using all pioglitazone</td>
<td>$5,000</td>
</tr>
<tr>
<td>Est. cost of one acute fracture of forearm</td>
<td>$2,700</td>
</tr>
<tr>
<td>Est. cost of one CHF exacerbation</td>
<td>$10,400</td>
</tr>
<tr>
<td>Est. cost of one new onset bladder cancer</td>
<td>$65,158</td>
</tr>
<tr>
<td>Potential yearly cost savings</td>
<td>$83,258</td>
</tr>
</tbody>
</table>

3.1. Savings by averting potential adverse effects

The DUR looked at estimated cost of treated patients who might experience an adverse event from use of glitazone medication: fractured forearm, exacerbation of CHF, and new onset bladder cancer. The costs described below do not include loss of wages and productivity.

The average cost (2006) to treat a fracture of forearm [2], as an example of the type of fracture attributable to glitazone use, which includes ER visit, orthopedic time and surgery costs, is at least $2,700. The average cost of treating an exacerbation of CHF [3] requiring hospitalization (2009) was $10,400. The average cost (2005) to evaluate and treat new onset bladder cancer was $65,158 [4].

The P&T Committee estimated that there was an additional cost for all pioglitazone instead of mixed glitazone. We also anticipated the additional cost of one major adverse event in the areas of fracture, CHF and bladder cancer from using glitazones.

Table 2 lists the yearly cost savings and the projected potential additional costs due to treatment of adverse effects from use of glitazones.

4. Discussion

4.1. Comparative efficacy

The glitazones can be indicated as medication therapy as an adjunct to diet and exercise to improve glycemic control in patients with type II diabetes mellitus (non-insulin-dependent diabetes mellitus, NIDDM). They are approved as monotherapy, and also can be used in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus a single agent do not result in adequate glycemic control. Rosiglitazone is generally used as an additional agent in combination with metformin, glipizide
(Glucotrol) or gliburide (Diabeta). Rosiglitazone is also used at our institution as a potential way to increase cell sensitivity to insulin.

Bolen et al. [5] recently compared thiazolidinediones, α-glucosidase inhibitors, and meglitinides against older agents (second-generation sulfonylureas and metformin). They found that the older agents have similar or superior effects on glycemic control, lipids, and other intermediate end points than newer agents, including glitazones.

4.2. Comparative safety of glitazones

4.2.1. Adverse effects which apply to the glitzone drug class

Microvascular disease. The two glitazones currently marketed, although both members of the same drug class, have strikingly different adverse event profiles in their effects on ischemic cardiovascular outcomes. Both agents reduce blood glucose levels and glycosylated hemoglobin levels to a similar degree and both appear to cause excess heart failure risk. Their effects on cardiovascular ischemic events differ, based on the currently available data. Since much of the morbidity and mortality associated with diabetes is due to macrovascular ischemic complications, even small increases in relative risks translate into major decrements in public health. Moreover, with many other available oral agents for diabetes, the potential benefit of glitazones requires re-evaluation.

Results of several long-term studies by the United Kingdom Prospective Diabetes (UKPD) study group indicate that effects of metformin on mortality and macrovascular outcomes vary considerably depending on the patient population evaluated. In one study [6], intensive therapy (target fasting plasma glucose of less than 108 mg/dL) initiated with metformin or other anti-diabetic agents (chlorpropamide, gliburide, or insulin) was compared with conventional therapy (target fasting plasma glucose of less than 270 mg/dL) consisting of diet and supplemental therapy with the same anti-diabetic agents for marked hyperglycemia in overweight (exceeding 120% of ideal body weight) patients. Cardiovascular disease accounted for 62% of the total mortality observed in patients receiving conventional therapy. Intensive therapy initiated with metformin in these overweight patients was associated with a 36% reduction in all-cause mortality and a 30% lower risk of developing macrovascular disease (myocardial infarction, sudden death, angina, stroke, peripheral vascular disease) compared with conventional therapy; the reduction in macrovascular disease was similar among intensive therapies employing other anti-diabetic agents.

In another UKPDS study [7], metformin was given as supplemental therapy in overweight and non-overweight patients who were poorly controlled on existing sulfonylurea therapy, or sulfonylurea therapy alone was continued. In this study, intensive metformin and sulfonylurea therapy was associated with an increase in the risk of diabetes-related death or death from any cause compared with that in patients continuing to receive sulfonylurea therapy alone. Similarly, another study by the UKPD Study Group found no decrease in mortality when metformin was added to sulfonylurea therapy (i.e., chlorpropamide or gliburide) or insulin alone in an intensive regimen in obese and non-obese patients. A pooled analysis of both UKPD trials and epidemiologic analysis of other non-overweight and overweight patients from UKPD studies who received metformin and sulfonylurea therapy because of progressive hyperglycemia showed a small reduction in diabetes-related death, all-cause mortality, myocardial infarction, and stroke.

Because the reasons for the inconsistent effects of metformin are unclear, further comparative studies of metformin alone or in combination with a sulfonylurea may be helpful to determine the long-term safety and efficacy of metformin in the treatment of type II diabetes mellitus. Pending the results of such studies, the ADA does not recommend changing current guidelines regarding the use of metformin as
monotherapy or in combination with sulfonylureas. ADA currently recommends that clinicians continue to emphasize dietary management and weight reduction as the principal therapy for the management of type II diabetes mellitus and that oral anti-diabetic agents or insulin be used only after these measures have failed. The decision to use an oral anti-diabetic agent or insulin should be made by the clinician in consultation with the patient.

As helpful as they may be, the administration of oral hypoglycemic drugs has also been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. The cardiovascular warning was initially based on a study conducted by the University Group Diabetes Program (UGDP), which involved 823 patients who were randomly assigned to one of four treatment groups [8]. This long-term prospective clinical trial was designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2.1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. Patients should be informed of the potential risks and advantages of various oral hypoglycemic therapies.

Although only one drug in the sulfonylurea class (tolbutamide) was included in the UGDP study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

Congestive heart failure CHF. An internal memo [9] from the FDA dated July 16, 2002 described a retrospective analysis of forty-seven reports of serious glitazone-associated CHF. Half of the reports represented older females, and fifty-five percent of the reports describe “New Onset” CHF. The remaining 45% were exacerbations of stable CHF due to edema or excessive weight gain. Data from this case series provided evidence as early as 2002 that glitazones may be causally [10] associated with CHF to an extent not clearly defined in the product labels which existed at that time. A causal link between the glitazones and CHF onset could not be established by the FDA at that time and based upon those data due to the uncontrolled nature and confounding factors in their spontaneous reporting system. Additionally, the FDA raised the possibility that glitazone initiation may facilitate a subsequent diagnosis of CHF, due to increased medical monitoring of the patient.

FDA findings in their 2002 memo:
1) Post marketing reports of glitazone-associated CHF resulting in hospitalization exist.
2) Case series suggested that CHF may be occurring in individuals without previously diagnosed disease.
3) Reports suggested that glitazones may be associated with CHF to an extent not clearly defined in the product labels as they existed at that time.

Based upon their retrospective analyses, the FDA recommended in 2002:
1) The prescribing information for both pioglitazone and rosiglitazone should include mention of these post marketing reports.
2) Additional studies (e.g., Phase IV cohort study to elucidate possible increased risk of incident CHF among both pioglitazone and rosiglitazone users relative to other oral hypoglycemic medications) should be considered.

In 2002, the FDA [11] required glitazones to include warnings on their respective drugs’ labels citing an increased risk of congestive heart failure (CHF). The strengthened warning advised health care professionals to observe patients taking these medications for the signs and symptoms of heart failure, including excessive, rapid weight gain, shortness of breath, and edema after starting drug therapy. The warning also stated that people with severe heart failure, those who have marked activity limitations, and those who are comfortable only at rest or who are confined to bed should not use glitazones.

Case reports and studies conducted independent of the drug makers began to be analyzed shortly thereafter. In 2003, a retrospective case study [12] found that glitazones could cause edema and cause or exacerbate heart failure. CHF resolved with discontinuation of the drug and administration of diuretics. Another study conducted by Srivastava et al. in 2004 [13] noted that glitazones are associated with nearly 5% increase in peripheral edema, but data for increased CHF were limited. They suggested screening patients with an echocardiogram prior to initialization of pioglitazone or rosiglitazone. A much larger case control study conducted by Filion et al. in 2011 [14] showed an increased risk of incident CHF with glitazones. The literature concerning increased edema and CHF incidence in patients taking glitazones is well established, and there are many studies that lend credence to this. Additionally, two studies [15] involving 611 patients compared insulin plus rosiglitazone and insulin plus placebo. These studies showed an increase in heart failure in the insulin plus rosiglitazone group compared to insulin plus placebo. A similar trial was conducted in patients with pioglitazone at doses of 15 mg and 30 mg plus insulin and insulin alone [11]. This trial showed 1.1% of patients in each of the Pioglitazone plus insulin groups developed heart failure compared to 0% of the patients receiving insulin alone. Therefore, the risk of glitazones in patients with CHF exceeds the benefits conferred by this class of medications and is not recommended in these patients. Furthermore, the administration of glitazones to patients with New York Heart Association class III or IV heart failure is contraindicated.

In a very important report, Nissen et al. [16] studied 42 clinical trials of rosiglitazone which had outcome data on myocardial infarction and death from cardiovascular causes. Using meta-analysis, they determined that rosiglitazone was associated with a significant increase (40%) in the risk of myocardial infarction compared to metformin or sulfonylurea or to placebo. They also found an increase in the risk of death from cardiovascular causes that had borderline significance. Their study was limited by a lack of access to original source data, which could have enabled time-to-event analysis. A patient level analysis performed by GSK (GSK no. ZM2005/00181/01) confirmed the increased CV risk.

An interim analysis of data from the RECORD trial was recently published [17], to shed light on the work of Nissen et al. [16]. The RECORD trial was designed specifically to measure the effects on CV outcomes of treatment with rosiglitazone compared to other treatments. Somewhere between a 7% decrease to a 32% increase in CV risk was found, but the data at the interim point were inconclusive, and for methodological reasons were unlikely to be so even at the trial’s completion. Despite this, it is fair to say that the RECORD trial results are not at all in disagreement with the findings of Nissen et al. [16]. Drazen et al. [18] have pointed out in an editorial that there were problems with the noninferiority structure of the RECORD trial which were evident at the time of the interim analysis of Home et al. [17]. A diabetologist, a cardiovascular epidemiologist, and a drug-safety expert were asked to review the available data, and they all expressed in associated (to Drazen) articles uncertainty about the safety of
rosiglitazone. The use of metformin plus a sulfonylurea (the comparator group) may be associated itself
with an increased rate of CV mortality.

Based on calculations of medication use at CGMH, it is estimated that less than 5 patients will suffer a
cardiac event that is directly related to or exacerbated by thiazolidinediones use over the next 5 years. Yet,
the cost of diagnosis and treatment of these cardiac events, should they occur, could run in the hundreds
of thousands of dollars.

Singh and colleagues [19] performed a meta-analysis of rosiglitazone trials and (unlike the previous
meta-analysis of Nissen) included only studies of at least 12 months’ duration that prospectively collected
information on cardiovascular events. The findings of the Singh study also found a 42% increase in risk
of myocardial infarction ($P = 0.02$). In addition, the authors observed a more-than-doubling of the risk of
heart failure with rosiglitazone (hazard ratio, 2.18; $P = 0.001$). Still, no significant increase in the risk of
cardiovascular mortality was detected.

Lincoff et al. [20] performed a pooled analysis of cardiovascular events using patient-level data from
trials comparing pioglitazone with a range of alternative regimens. The manufacturer of pioglitazone
provided the data from 19 randomized, double-blinded trials that were available, but the analyses were
conducted independent of the drug manufacturer. Among patients randomized to receive pioglitazone, the
rate of death, myocardial infarction, or stroke was reduced by 18% compared with controls ($P = 0.005$).
Similar to the meta-analysis of rosiglitazone, the risk of heart failure was significantly increased in
pioglitazone users (hazard ratio, 1.41; $P = 0.002$).

The studies discussed above are summarized in Table 3.

Table 3 compares the various types of clinical studies evaluating the cardiovascular risk outcomes
attributable to treatment with rosiglitazone compared to treatment with other medications.

The Prescribing Information for Actos (pioglitazone) now clearly warn of the potential for exacerbations
of CHF.

### 4.3. Actos black box warning

**WARNING: CONGESTIVE HEART FAILURE**

- Thiazolidinediones, including ACTOS, cause or exacerbate congestive heart failure in some patients
  (see WARNINGS). After initiation of ACTOS, and after dose increases, observe patients carefully
  for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or
  edema). If these signs and symptoms develop, the heart failure should be managed according to

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type</th>
<th>Risk MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nissen</td>
<td>Meta-analysis from 42 clinical studies</td>
<td>30%</td>
</tr>
<tr>
<td>RECORD</td>
<td>Unplanned interim analysis of a randomized,</td>
<td>−7% to +32%, inconclusive</td>
</tr>
<tr>
<td></td>
<td>multicenter, open-label, noninferiority trial</td>
<td></td>
</tr>
<tr>
<td>GSK</td>
<td>Pooled data from 42 clinical studies</td>
<td>+1.99% relative incidence,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+1.31% hazard = +30%</td>
</tr>
<tr>
<td>FDA</td>
<td>Retrospective</td>
<td>Risk CHF</td>
</tr>
<tr>
<td>ADOPT</td>
<td>Randomized, patients with CV risk were excluded</td>
<td>No increase</td>
</tr>
<tr>
<td>DREAM</td>
<td>Randomized, to prevent onset DM</td>
<td>No increase</td>
</tr>
</tbody>
</table>
the current standards of care. Furthermore, discontinuation or dose reduction of ACTOS must be considered.

- ACTOS is not recommended in patients with symptomatic heart failure. Initiation of ACTOS in patients with established NYHA Class III or IV heart failure is contraindicated”.

As is the practice in the general medical community, CGMH emphasizes a multimodal approach, with nutritional counseling, weight reduction as needed, and exercise for all diabetic patients. Because of the high prevalence of diabetes in our patient population, CGMH has established a Center of Excellence for diabetes care. These efforts are important not only in the primary treatment of type II diabetes, but also to maintain the efficacy of drug therapy.

4.4. Lipid effects

Members of the glitazone class, metformin, and repaglinide each improved glycemic control to the same degree as sulfonylureas [5]. Glitazones were the only class that had a beneficial effect on high-density lipoprotein cholesterol levels but a harmful effect on low-density lipoprotein (LDL) cholesterol levels compared with other oral agents. Metformin decreased LDL cholesterol levels by about 0.26 mmol/L, whereas other oral agents had no obvious effects on LDL cholesterol levels. Most agents other than metformin increased body weight by 1 to 5 kg. Sulfonylureas and repaglinide were associated with greater risk for hypoglycemia, and metformin with greater risk for gastrointestinal problems compared with other oral agents. Lactic acidosis was no more common in metformin recipients without co-morbid conditions than in recipients of other oral diabetes agents.

4.5. Edema

A 16-week clinical trial of pioglitazone plus a sulfonylurea versus placebo plus a sulfonylurea concluded that there was increased risk of edema in patients receiving pioglitazone plus a sulfonylurea. The trial showed that the incidence of edema increased with increasing dose of pioglitazone. Results demonstrated 1.6% of patients taking pioglitazone 15 mg plus a sulfonylurea had edema versus 12.7% for patients on the 30 mg dose plus a sulfonylurea, and 2.1% of patients taking placebo plus a sulfonylurea developed edema [15]. A 24-week non-controlled double-blind trial showed similar results with 10.5% of patients taking 30 mg pioglitazone plus a sulfonylurea developed edema versus 23.1% on the 45 mg dose plus a sulfonylurea. Similar dose related edema development was noted in clinical trials examining pioglitazone plus metformin, pioglitazone plus insulin and pioglitazone alone. Dose related edema development was also noted in patients taking rosiglitazone versus placebo, suggesting that this is class effect. Edema-related prescribing information for Actos is provided as follows from the manufacturer and FDA:

“Edema: ACTOS should be used with caution in patients with edema. In all U.S. clinical trials, edema was reported more frequently in patients treated with ACTOS than in placebo-treated patients and appears to be dose related. In post marketing experience, reports of initiation or worsening of edema have been received. Since thiazolidinediones, including ACTOS, can cause fluid retention, which can exacerbate or lead to congestive heart failure, ACTOS should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure”.
4.6. Fractures of bones

In March 2007, the manufacturer of pioglitazone (Takeda) announced [21] that female patients with diabetes who were taking pioglitazone experienced an increased incidence of fractures of the distal upper limb (forearm, hand and wrist) or distal lower limb (foot, ankle, fibula and tibia). The fracture incidence calculated was 1.9 fractures per 100 patient-years in the pioglitazone-treated group and 1.1 fractures per 100 patient-years in the comparator-treated group. The observed excess risk of fractures for women in this data set on pioglitazone is therefore 0.8 fractures per 100 patient-years of use. This was based on analysis of data from their clinical trial database. In their 2007 letter, Takeda mentioned that the cumulative worldwide post-marketing exposure was more than 7 million patient-years for ACTOS. Apparently the estimated fracture incidence estimates did not include post-marketing AE reports, so it is possible that the incidence of fracture due to Actos is actually much higher.

Takeda claimed that the explanation for the fractures was not known to them in 2007. In fact, it is clear from several recent publications [22–24] that using pioglitazone results in decreased mineral density. Fracture-related prescribing information for Actos is provided as follows from the manufacturer and the FDA:

“...The risk of fracture should be considered in the care of patients, especially female patients, treated with pioglitazone and attention should be given to assessing and maintaining bone health according to current standards of care”.

Based on this increased risk of fractures, we evaluated our own hospital records for the following:

1) Number of female patient years of glitazone use
2) Identification of fractures in female patients with diabetes

Females using glitazone during the time period analyzed were not identified who suffered a fracture of the distal upper limb or distal lower limb. It was estimated that perhaps 5 patients in our hospital clinics could suffer a fracture that is consistent with glitazone use over the next 5 years. The monetary cost of diagnosis and treatment of these fractures could be significant.

4.7. Hepatic effects

While post-marketing reports of patients developing hepatic failure while taking Actos have been reported, no causal association has been determined. Actos [15] and Avandia warnings both state that therapy should not be initiated in patients with liver enzymes 2.5 times greater than normal. Interestingly a recent study by Chang [25] concluded that the use of Actos and Avandia in diabetic patients is actually associated with a decreased risk of liver cancer incidence.

4.8. Bladder cancer

The incidence rate for Bladder cancer (http://www.cancer.gov/statistics) is 20 per 100,000 (70,530 new cases per year) and is highest in diabetics and Caucasians. 91% of bladder cancer for the pioglitazone group vs. in humans is uroepithelial, and is strongly associated with cigarette smoking.

The Prescribing Information for Actos notes that, “Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible,
and the drug is excreted primarily as metabolites and their conjugates”. Similar results were not obtained in mice. The manufacturer of Actos also notes that, “During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors were identified. In two 3-year studies in which pioglitazone was compared to placebo (or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14 vs. %) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six, (0.16%) cases on pioglitazone and two (0.05%) on placebo”.

In a prospective, randomized controlled trial in 5238 patients with type 2 diabetes who had evidence of macrovascular disease, Dormandy et al. [26] found more cases of bladder cancer for the pioglitazone group vs placebo (14 vs. 6).

To put context in the disclaimer from the manufacturer that Actos does not cause bladder cancers, an interim report [27] was recently published for a ten-year cohort study comprised of 193,099 patients taking Actos for more than 12 months. The investigators concluded, “In this cohort of patients with diabetes, short-term use of pioglitazone was not associated with an increased incidence of bladder cancer, but use for more than 2 years was weakly associated with increased risk”. Their data translates to an increase of 3 cases of bladder cancer per 10,000 patients taking Actos for greater than 1 year.

Azoulay et al. [28] in a nested case-control study involving 115,727 patients, also found an increased risk for the development of bladder cancer in type II diabetic patients taking Actos. The risk was highest in patients taking Actos for greater than 24 months and in patients who had a cumulative dose of greater than 28,000 mg.

Mamtani et al. [29] similarly found that the risk of bladder cancer was increased among patients with the longest duration of glitazone vs. SU therapy (≥5 years of use, and among those with the longest time since initiation of therapy. Risk of bladder cancer also increased with increasing time since initiation of pioglitazone and rosiglitazone. Comparison of pioglitazone to rosiglitazone use did not demonstrate difference in cancer risk. Mamtani et al. were therefore in agreement with other published research that long-term (≥5 years) glitazone therapy in patients with type II diabetes may be associated with an increased risk of bladder cancer, which may be common to all glitazones, including both Actos and Avandia.

As noted by Panikar [30], FDA recommendations include:

- Do not use pioglitazone in patients with active bladder cancer.
- Use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.
- Counsel patients to report any signs or symptoms of blood in the urine, urinary urgency, pain on urination, or back or abdominal pain, as these may be due to bladder cancer.

A consistent viewpoint is given by the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP), which concluded [31] that the small increased risk of bladder cancer could be reduced by appropriate patient selection and exclusion, including a requirement for periodic review of the efficacy and safety of the individual patient’s treatment.

4.9. Macular edema

There is conflicting evidence available concerning glitazones and the development of macular edema. Ambrosius [32] reported on the ACCORD Eye study, which examined the visual acuity of 9,690 patients,
including fundus photographs of 3,473 patients. Cross-sectional data analysis concluded that there was no association between glitazones and diabetic macular edema. The authors did state in their conclusion, however, “we cannot exclude a modest protective or harmful association”.

A recent retrospective cohort study published by Idris et al. [33] demonstrated results to the contrary of Ambrosius. They reviewed records for 103,368 patients with type II diabetes and no macular edema. At year 1, macular edema incidence was 1.5% in patients taking GLITAZONES and 0.2% in patients who did not. The same increase among glitazone users was also seen at year 10. This study also showed an increased incidence of diabetic macular edema in patients taking glitazones plus insulin above those taking glitazones alone. A reduction of macular edema was noted in patients who were taking ACE inhibitors and/or aspirin.

Although the data are conflicting concerning macular edema, one could argue that the prudent action is to utilize anti-diabetic medications with similar efficacy and a lower risk profile. Additionally, all diabetic patients should undergo routine eye examinations per ADA guidelines.

4.10. Conflicts of interest

It is widely known [34] that academic investigators depend heavily on support from the pharmaceutical industry. As NIH funding continues to be difficult to obtain, researchers depend to an increasing extent on pharmaceutical industry support. This can certainly be said of the authors of the interim analysis of data [17] in the RECORD trial [16], where on page 36, the trial and presumably the cost of preparing the interim analysis and the publication itself were supported by the manufacturer of Avandia – GSK. This is followed by a long list of conflict disclosures, and then an astounding two page listing of participating investigators (this was a multi-center study), a list nearly three times as long as the referenced publications. Although I do not known this to be the case here [35], it is my own experience as Associate Director and Director of Clinical Research for multinational pharmaceutical companies that offering participation in clinical trials is one way of channeling rewards to “opinion leaders” and “decision makers” in the medical community. Such minimal investments often lead to significant product loyalty and increased sales.

4.11. Discussion and implications

Diabetes is a significant risk for CV disease, and it is not surprising that patients with DM develop CV disease. It is imperative that all primary care physicians control risk factors in their diabetic patients and not unnecessarily introduce new ones in this at-risk population [18]. Patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type II diabetes [16]. The FDA and others have noted that even switching diabetic patients to other therapies also can confer risks.

The ADA currently recommends [1] that clinical judgment in the management of type II diabetes mellitus should be based on the assessment of all available therapeutic information, including data on cardiovascular risk factors, the positive effect of metabolic control of diabetes on cardiovascular disease, the importance of dietary management and weight reduction in obese diabetic patients, the importance of regular physical activity, and objective reports in the scientific literature that pertain to the UGDP and other studies and to the long-term use of sulfonylureas and other medications.
4.12. Conclusions

Physicians should follow the American Diabetes Association guidelines [1] for treatment of diabetes. The basis for diabetic control remains weight loss, diet and exercise. Initial medication management for Diabetes Mellitus II includes metformin and insulin. The thiazolidinedione/glitazone therapeutic drug class has only equivalent efficacy to classic diabetic agents, significant safety concerns, and the availability of perfectly acceptable, safe and more economical alternative agents for treatment of Diabetes Mellitus type II. There are no circumstances in which use of glitazone medications is preferable to other medication groups, and there is no essential use of glitazone medications. In fact, there are significant contraindications, warnings and precautions to use of glitazones, which must be taken into consideration before use in every individual patient. Glitazones in particular should not be used in the following circumstances: CHF, concurrent bladder cancer, severe osteoporosis. The use of drugs in this therapeutic class is optional. Because of equivalent safety and efficacy, substitution within this group can be driven by considerations such as cost. Significant institutional cost savings can occur with automatic drug substitution during dispensing.

Conflict of interest

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References