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Do thiazolidinediones increase the risk of cardiovascular events?

A 56-year-old woman, a non-smoker, presents to your office seeking better control of her type 2 diabetes mellitus (DM). The diagnosis was made 6 years ago. She has been controlling her diabetes with a combination of exercise (going to the gym 3 times per week, including 30-45 minutes of walking/jogging), diet (reduced carbohydrates), and metformin, 500 mg twice daily initially, then 1,000 mg twice daily; plus glyburide, 10 mg twice daily, for the past 2 years. She monitors her blood glucose levels twice daily (before breakfast and before dinner), and in the past 2 months the levels have sometimes been 170 to 210 mg/dL. The patient is asymptomatic, but she is concerned about her increasing blood glucose levels. Her medical history is negative for cardiovascular disease. Her family history is positive for DM, dyslipidemia, and hypertension. Her height is 5 ft 4 in, and her weight is 150 lb. The physical examination is within normal limits. The patient does not wish to start using insulin.

You are considering adding a thiazolidinedione (TZD) to the patient's regimen, but because an FDA Advisory Committee recently stated that rosiglitazone (Avandia, a TZD) should remain on the market but warned about an increased risk of cardiac ischemic events with its use,¹ you are concerned that TZDs may increase this patient's cardiovascular risk.

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CLINICAL QUESTION

Do TZDs increase the risk of cardiovascular events?

SEARCH CRITERIA AND RESULTS

The data sources for this article included the PubMed database (2005-2008) and Cochrane Central (2005-2008). Inclusion criteria were humans, meta-analysis, randomized controlled trials, English, and core clinical journals. The searched terms included *thiazolidinediones AND cardiovascular risk*. A total of 15 articles were retrieved using this strategy. To ensure the inclusion of all pertinent articles, a secondary search using *pioglitazone AND cardiovascular risk* and *rosiglitazone AND cardiovascular risk* was done. This secondary search did not reveal any additional articles. A total of five articles were chosen to review. First we will discuss the two randomized trials, but because of the stated limitations of these trials, including one being an interim analysis, we deemed it necessary also to include three meta-analyses for this review. The randomized controlled trials were chosen because they used cardiovascular events or hospitalization for cardiac events as their primary end point. Randomized trials that looked only at heart failure or did not include cardiovascular events as a primary end point were excluded.

EVALUATING THE EVIDENCE

Dormandy and colleagues published the only completed prospective randomized controlled trial that was specifically designed and properly powered to evaluate the efficacy of pioglitazone

(Actos, a TZD) in reducing cardiovascular outcomes.² The authors looked at 5,238 patients with type 2 DM who had evidence of macrovascular disease over an average of 34 to 35 months. Their primary end point was the composite of all-cause mortality, nonfatal MI (including silent MI), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the knee. This study failed to show a significant benefit of pioglitazone treatment on the primary composite end points (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.80-1.02; $P = .095$). However, pioglitazone reduced risk for the main secondary end points, including death from any cause, nonfatal MI, and stroke (HR, 0.84; 95% CI, 0.72-0.98; $P = .027$).

No similar studies have been done on rosiglitazone. Home and colleagues did publish an unplanned interim analysis of an ongoing randomized, open-label clinical trial comparing rosiglitazone with metformin or a sulfonylurea in 4,447 patients.³ These were patients with type 2 DM who had inadequate glycemic control. The primary end point of this study was hospitalization (for acute MI, heart failure, stroke, unstable angina, transient ischemic attack, unplanned cardiovascular revascularization, amputation of extremities, or another definite cardiovascular reason) or death from cardiovascular causes (including heart failure, acute MI, sudden death, and death caused by acute vascular events including stroke). For adjudicated primary end points, the HR was 1.08 (95% CI, 0.89-1.31), indicating that rosiglitazone had a small, statistically nonsignificant

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increase in the risk of primary outcomes. An additional 91 patients had potential primary events reported by investigators, but these events were pending adjudication. The inclusion of these events resulted in an HR of 1.11 (95% CI, 0.93-1.32). Given that the mean follow-up was only 3.75 years, however, the study was underpowered to detect treatment differences. Both of these randomized clinical trials^{2,3} found a significantly increased risk of heart failure with pioglitazone and rosiglitazone versus their respective comparison group, but mortality rates did not differ for both groups.

A meta-analysis was done by Nissen and Wolski.⁴ Published literature and clinical trial registries were searched for cardiovascular end points such as MI and death from cardiovascular causes. Data were combined by means of a fixed-effect model. Forty-two trials were selected. In the rosiglitazone group, as compared with the control group, the odds ratio (OR) for MI was 1.43 (95% CI, 1.03-1.98; $P=.03$), and the OR for death from cardiovascular causes was 1.64 (95% CI, 0.98-2.74; $P=.06$). The authors concluded that rosiglitazone was associated with a significant increase in the risk of MI and with an increased risk of death from cardiovascular causes that had borderline significance. The studies' limitations were lack of access to original data, which would have enabled time-to-event analysis.

Singh and colleagues conducted a meta-analysis of the relative risks (RRs) of MI, heart failure, and cardiovascular mortality using a fixed-effect meta-analysis of four randomized controlled trials (N = 14,291, including 6,421 subjects receiving rosiglitazone and 7,870 receiving control therapy, with a follow-up of 1-4 years).⁵ The study determined that rosiglitazone significantly increased the risk of MI (n = 94/6,421 vs 83/7,870; RR, 1.42; 95% CI, 1.06-1.91; $P=.02$) and heart failure (n = 102/6,421 vs 62/7,870; RR, 2.09; 95% CI, 1.52-2.88; $P<.001$) without a significant increase in risk of cardiovascu-

lar mortality (n = 59/6,421 vs 72/7,870; RR, 0.90; 95% CI, 0.63-1.26; $P=.53$). The authors therefore concluded that rosiglitazone use for at least 12 months is associated with a significantly increased risk of MI and heart failure, without a significantly increased risk of cardiovascular mortality.

“Patients considering TZDs need to be counseled about the possible cardiovascular risks surrounding this class of drugs.”

Lincoff and colleagues conducted a pooled analysis of cardiovascular events using patient-level data from randomized trials comparing pioglitazone with a range of alternative regimens.⁶ The manufacturer of pioglitazone provided the data from 19 randomized, double-blind trials, but the analysis was conducted independently. Study drug treatment duration ranged from 4 months to 3.5 years. The primary outcome was a composite of death, MI, or stroke. A fixed-effect approach was used. This study determined that death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,896 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72-0.94; $P=.005$). The authors concluded that treatment with pioglitazone was associated with a significantly lower risk of death, MI, or stroke compared with any of the alternative regimens. Serious heart failure was increased in patients on pioglitazone, although without an associated increase in mortality (HR, 1.41; 95% CI, 1.14-1.76; $P=.002$).

CLINICAL BOTTOM LINE

Currently, two TZDs are marketed in the United States. Both agents reduce blood glucose levels and glycated hemoglobin levels to a similar degree, and both appear to cause an increased risk of heart failure. Based on current

available data (as of January 2008), the effects on cardiovascular outcomes may be where these two drugs differ. Rosiglitazone has shown an increased risk for cardiovascular ischemic events. A head-to-head randomized comparative trial of the two TZDs using cardiovascular events as a primary end point

would be very useful. Studies evaluating whether complications such as ischemic cardiovascular events are reduced secondary to better glycemic control would also help with our clinical decision. This would provide us with useful information regarding clinical outcomes and not just surrogate outcomes. For now, patients who do not want to use insulin and are at the maximum dosage for non-TZD oral antidiabetic drugs need to be counseled about the possible cardiovascular risks surrounding rosiglitazone and told that pioglitazone has not shown the same risk profile but is from the same class of drugs. **JAAPA**

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