Background
The anti-diabetic drug class thiazolidinediones (TZD) includes rosiglitazone (available as Avandia® and in the combination products Avandamet® and Avandaryl®) as well as pioglitazone (available as Actos®). These agents stimulate peroxisome proliferator-activated gamma (PPAR-γ) receptors which sensitize muscle and adipose tissue to insulin to decrease blood glucose (See Figure 1). In particular, products containing rosiglitazone have been under increasing scrutiny recently for safety and ethical reasons.

TZDs provoke fluid retention and heart failure because they stimulate renal PPAR-γ receptors, resulting in sodium and fluid retention.1 Rosiglitazone is a more potent PPAR-γ agonist than pioglitazone. Recent research has highlighted differential safety issues with both TZDs, forcing the Food and Drug Administration (FDA) to place restrictions on access and use of rosiglitazone. This paper will review key clinical trials leading up to the new regulations and guide practitioners on how to proceed in light of recent data and FDA restrictions.

Trials Related to TZDs and Cardiovascular Outcomes
The controversy began in 2007 when Nissen et al. published a meta-analysis of 42 trials which linked treatment with rosiglitazone with fluid retention, myocardial infarction and near-significant cardiovascular-related mortality.2 Before this article was published, a copy was faxed by a reviewer to GlaxoSmithKline (GSK), the manufacturer of Avandia®. Because of Nissen's findings, GSK decided to change the protocol of their ongoing "RECORD" trial to an open-label trial. The RECORD, or "Rosiglitazone Evaluated for Cardiovascular Outcomes in oral agent combination therapy for type 2 Diabetes,3" was a non-inferiority study of cardiovascular outcomes with Avandia® compared with other agents (See Table 1). When Nissen et al. published their analysis, the FDA ruled in favor of a black-box warning for both drugs in the TZD class, however there are less data supporting these risks with pioglitazone. The boxed warning cautions prescribers to avoid the use of TZDs in patients who have existing NYHA class III/IV heart failure.4 Although the boxed warning encompasses both TZDs, a recent systematic review and meta-analysis of observational studies concluded that the use of rosiglitazone is associated with significantly higher odds of congestive heart failure, risk of ischemic cardiovascular events (namely myocardial infarctions), and death compared with pioglitazone.5

Within the last few years, numerous clinical trials have fueled the debate on the safety of rosiglitazone. (See Table 1) While most of the data points to an increase in fluid retention and heart failure, data related to effects on mortality have been mixed. Still, there have not been any head-to-head trials to compare safety of rosiglitazone to pioglitazone until 2009 when the TIDE trial began enrolling patients. TIDE or "Thiazolidinedione Intervention with vitamin D Evaluation," was a trial designed by GSK who advocated that concrete evidence was needed in order to draw conclusions about the safety of their drug. However, the FDA recently pulled the plug on this trial, citing it unsafe and unethical given the published data on rosiglitazone. The FDA is requiring an independent examination team to re-evaluate the RECORD trial due to the uncertainty of its results and methods.6 (See Figure 2 below)

Next Steps
According to the ACC/AHA advisory paper published in February 20107, the current recommendations are aimed at using lifestyle modifications such as diet, exercise, and smoking cessation paired with the use of aspirin, lipid lower-
TZDs and Cardiovascular Outcomes: A Heart-to-Heart on Patient Safety (Continued)

Figure 2. Timeline of events

1999: Avanda® F.D.A. approved

2007: FDA issues black-box warning for both TZDs in patients with CHF, and 43% increase in MI with Avanda®

2007: FDA issues black-box warning for both TZDs in patients with CHF, and 43% increase in MI with Avanda®

2008: Avanda® removed from F.D.A. DM recommendations for 2nd line therapy

2010: RECORD, TRAD, ACCORD, update, TIDE trial (began but was discontinued)

2013: FDA places full hold on TIDE, ordered re-evaluation of RECORD, initiated restricted access program to use Avanda®

Table 1. Summary of Important Avanda® Safety Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Subjects</th>
<th>Comparison</th>
<th>Endpoint</th>
<th>Results</th>
<th>Conclusions</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>TRAD</td>
<td>Prospective observational study</td>
<td>75,439</td>
<td>All had DM2</td>
<td>Avasia vs. Avanda® for several CV outcomes</td>
<td>No difference in any cardiovascular outcome</td>
<td>Avasia® and Avanda® are equivalent in their adverse effect profile</td>
<td>Subanalysis showed Avasia® group had less patients with history of CV disease and current smokers</td>
</tr>
<tr>
<td>TRAD</td>
<td>Randomized, controlled</td>
<td>13,251 subjects</td>
<td>All had DM2</td>
<td>CV death</td>
<td>Increased MI, CV death in Avasia® group, lower in control (p&lt;0.03)</td>
<td>Lead to black box warning in 2007</td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>Parallel randomized, intention to treat</td>
<td>77 sites</td>
<td>All had DM2</td>
<td>CV death</td>
<td>No mortality difference in primary outcomes</td>
<td>T2D seem to increase fluid retention, this did not appear to be a significant factor in mortality</td>
<td></td>
</tr>
<tr>
<td>RECORD</td>
<td>Prospective randomized, open-label, multicenter</td>
<td>4,447 subjects</td>
<td>All had DM2</td>
<td>Avasia® vs. Avanda® with metformin</td>
<td>No difference in outcomes</td>
<td>Patients with DM1, T2D, no previous heart failure were 2x as likely to develop a heart failure event when taking Avanda®</td>
<td></td>
</tr>
<tr>
<td>TIDE</td>
<td>Non-inferiority study of CV outcomes with Avanda® vs. other agents</td>
<td>1,612 75 years</td>
<td>Avasia® vs. Avanda® with metformin</td>
<td>CV death or cardiovascular death with CV deaths in Avasia® group, lower than control (p&lt;0.05)</td>
<td>Fluid restriction, visual acuity not reported</td>
<td></td>
<td></td>
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</table>

The figure and table above highlight the timeline of events related to the use of TZDs and their cardiovascular outcomes, along with a summary of important safety trials. It is important to note the timeline of events from 1999 to 2013, which includes the FDA approval of Avanda®, subsequent black-box warnings due to cardiovascular concerns, and the eventual withdrawal of Avanda® from the market. The table provides a detailed overview of the key safety trials, including design, subjects, comparison, endpoint, results, and conclusions. The panel warns against reliance on TZDs to prevent cardiovascular events and cautions to weigh the benefits and risks when considering TZD therapy. Metformin remains first-line therapy for diabetes. Sulfonylureas are a reasonable second-line monotherapy and can be used in combination with metformin to achieve glycemic control. If both classes are utilized at their maximal doses without achieving HbA1C levels less than 6.5%, the practitioner should reassess lifestyle and consider additional risk factors.
ing insulin or another glucose lowering agent to attain target reductions in HbA1c. In accordance with the 2007 black-box warning, TZDs are contraindicated in patients with NYHA class III and IV heart failure and should not be administered to patients on insulin or nitrates, as the combination of these drugs was shown to increase risk of cardiovascular events.

From the patient’s point of view
Thiazolidinediones have moved down the list of options for diabetic patients who are not candidates or not adequately controlled with first-line oral anti-diabetic agents. The goal for most patients will be to establish a regimen to maintain glycemic control long-term, however, the interim results of a longitudinal cohort study with pioglitazone pointing to an increased risk of bladder cancer are disconcerting.7

A July 2010 article8 published in The New York Times describes this issue to the layperson emphasizing the discrepancy between GSK and the FDA. After reading this article, patients may have questions and concerns with respect to their medications and the role of the FDA in approving safe medications. This will require the clinician to be well versed in the facts of this controversy in pursuit of optimal therapy.

FDA Actions and Clinical Practice
In addition to the continuation of the TIDE trial and the re-examination of the RECORD trial results, the FDA ruled that rosiglitazone should be reserved for patients who are already taking it, have documented knowledge of the risks, and when glycemic control cannot be maintained otherwise.9 A February 3, 2011 safety announcement from the FDA explains new additions to the package insert for Avandia® including a warning about the potential of the drug to cause myocardial infarction.10 After November 18, 2011, in order to prescribe and for patients to receive rosiglitazone, they will need to enroll in a risk evaluation and mitigation strategy (REMS) mandated by the FDA, called the “Avandia® Rosiglitazone Medicines Access Program.” Rosiglitazone products will only be available by mail order through pharmacies participating in the program.10

REFERENCES