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Quick Pulse

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GLITAZONES FOR TYPE 2 DIABETES:
Safety of Avandia Again Questioned, but Actos Appears Safer

The two FDA-approved thiazolidinediones (TZDs) for Type 2 diabetes – GlaxoSmithKline's Avandia (rosiglitazone) and Takeda's Actos (pioglitazone) are effective in reducing the surrogate endpoints of blood glucose and hemoglobin, but both are associated with a substantial increase in the risk of heart failure. New data confirm earlier reports that Avandia increases cardiovascular (CV) risk and find that Actos does ***not*** increase CV risk. In fact, Actos may be cardioprotective.

In May 2007, Dr. Steven Nissen and Kathy Wolski MPH of the Cleveland Clinic published a 42-trial meta-analysis of Avandia in the ***New England Journal of Medicine*** which showed a 43% increase in the risk of myocardial infarction (MI) (p=0.03). That ignited a firestorm over the safety of TZDs in general and Avandia in particular. TZDs had previously been shown to have an increased risk of heart failure, and the FDA added a black box warning to both Actos and Avandia in August 2007.

The FDA held an advisory committee meeting on Avandia on July 30, 2007, with the panel voting (a) 20 to 3 that Avandia is associated with an increased CV risk, but (b) 22 to 1 that Avandia should remain on the market with a black box warning about the CV risk. The FDA has yet to announce what it plans to do about Avandia or Actos with respect to CV risk, but it appeared unlikely that the agency would withdraw Avandia from the market. That may no longer be a safe assumption.

Two new meta-analyses, published in the September 12, 2007, issue of the ***Journal of the American Medical Association***, may play into that decision. Those studies reported that Avandia and Actos both cause heart failure but differ strikingly in their CV safety profile, but they raise questions about the risk:benefit of both drugs.

1. Avandia. A study – by Dr. Sonal Singh and Dr. Curt Furberg of Wake Forest University School of Medicine and Dr. Yoon Loke of the University of East Anglia in the U.K. – once again suggests the risk:benefit profile that led to Avandia's approval has been reversed. They concluded that safer treatment alternatives are available, regulatory agencies should reevaluate whether Avandia should remain on the market, and health plans and physicians should avoid using it in diabetics at risk of CV events.

The Singh et al meta-analysis looked only at long-term Avandia studies (those of at least 12 months' duration) which prospectively collected information on CV events (4 trials of 14,291 patients). It found Avandia was associated with:

- 42% ***increase*** in MI (p=0.02).
- 109% increase in the risk of heart failure (p=0.001).

- No significant increase in CV mortality (relative risk 0.90, p=0.53).
- No effect on all-cause mortality (relative risk 0.99, p=0.92)

With the Cox-2 inhibitors it initially appeared that only long-term use raised the CV risk, but more recent data indicate that even short-term use of Cox-2 inhibitors can be dangerous. Dr. Singh and his colleagues said it is "not possible to determine whether the harmful effects are immediate or if there is a lag time to harm (with Avandia)," but they called the public health impact of potential harm associated with Avandia "substantial."

Assuming the event rate for MI of 0.29%/year and a heart failure rate of 0.24%/year found in the ADOPT trial, Dr. Singh and colleagues estimated the number needed to harm (NNH) for Avandia was 822 for MI and 383 for heart failure. Using these rates, they estimated that, with about 3.5 million current Avandia users in the U.S., there could be more than 4,000 excess MIs and 9,000 excess heart failures annually. However, using other large observational studies, they found lower NNH rates:

- **MI.** Assuming a baseline rate of 10.8 per 1,000 person-years (PYs) in adult Type 2 diabetics with no history of MI, they estimated the NNH was 220/year.
- **Heart failure.** Assuming a baseline rate of 30.8 per 1,000 PYs in adult Type 2 diabetics with no history of heart failure, they estimated the NNH was 30/year.

Another serious adverse event with TZDs that has gotten little attention is macular edema leading to blindness. Dr. Singh et al noted that only one case of macular edema was reported in the long-term clinical trials they evaluated, and that was in the control group. But during a recent 12-month period the FDA received 66 reports of macular edema – 40 with Avandia and 26 with Actos – and Health Canada has received 16 reports with Avandia and none with Actos.

Yet, Dr. Singh and his colleagues did not let Actos completely off the hook. They noted that there is a lack of information on adverse events with Actos, which is known to increase the risk of heart failure, although Avandia may have more MI risk than Actos. They wrote, "While rosiglitazone increases the risk of MI (from 31% to 43%), pioglitazone does not adversely increase this risk…Firm conclusions about the risk differences between the two agents cannot be made because of the absence of head-to-head comparisons…The cardiovascular differences between rosiglitazone and pioglitazone may be partly explained by a difference in effects on lipids and lipoprotein particles and subclass."

They also suggested that concomitant use of cardioprotective drugs might help to reduce the likelihood of harm from Avandia, "If the excess of MIs is mediated through the unfavorable effects of rosiglitazone on low-density lipoprotein cholesterol (LDL-C) and triglycerides, it is possible that adequate lipid control with statins would reduce the MI risk… Similarly, aspirin use could also reduce this risk in patients with diabetes and coronary disease. Patients with hypertension and diabetes who are treated with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) may be at a lower risk of heart failure."

Singh et al Avandia Meta-Analysis

Trial	Avandia	Comparator
Heart Failure		
Gerstein et al, 2006	0.5%	0.1% (control)
Kahn et al, 2006	1.5%	1.0% (metformin or glyburide)
Home et al, 2007	2.1%	1.0% (metformin or glyburide)
Dargie et al, 2007	17%	8.8% (placebo)
Total	**2.09 RR**	**---**
MI		
Gerstein et al, 2006	0.6%	0.3%
Kahn et al, 2006	1.8%	1.2%
Home et al, 2007	2.2%	1.8%
Dargie et al, 2007	4.5%	0
Total	**1.42 RR**	**---**
CV mortality		
Gerstein et al, 2006	0.5%	0.4%
Kahn et al, 2006	0.3%	0.4%
Home et al, 2007	1.7%	2.1%
Dargie et al, 2007	4.5%	3.6%
Total	**0.90 RR**	**---**

2. Actos. The first independent, pooled analysis of Actos data – by Cleveland Clinic researchers Dr. A. Michael Lincoff, Kathy Wolski MPH, Stephen Nicholls PhD, and Dr. Steven Nissen – found Actos has a better risk:benefit profile than Avandia. They reported that Actos is associated with a significantly lower risk of death, MI, and stroke. Though heart failure is increased, it was not associated with an increase in mortality in their analysis.

In their review, Dr. Lincoff and his colleagues examined patient-level data from 19 randomized, double-blind, active- or placebo-controlled trials with a total of 16,390 patients with a treatment duration of 4 months to 3.5 years. They made two key findings, and these were consistent across all subgroups:

- 18% ***reduction*** in the composite of death, MI, and stroke (p=0.005). The time-to-event curves separated progressively after about 1 year.
- 41% ***increase*** in the risk of heart failure (p=0.002). The time-to-event curve separation stabilized at about 1.5 years.

Dr. Lincoff and his colleagues concluded that Actos has a cardioprotective effect in diabetics, regardless of whether or not they had established CV disease, "These findings suggest that the net clinical cardiovascular benefit with pioglitazone

therapy is favorable, with an important reduction in irreversible ischemic events that is not attenuated by the risk of more frequent heart failure complications…(This meta-analysis) constitutes reasonably strong evidence that this agent (Actos) does, in fact, reduce the risk of cardiovascular ischemic endpoints among patients with Type 2 diabetes mellitus …This analysis also provides reassuring information that although fluid retention and heart failure are more frequent with pioglitazone treatment, the offsetting risks do not appear to negate the beneficial effects of the drug on irreversible ischemic and fatal endpoints."

Why are Actos and Avandia different? Dr. Lincoff et al wrote, "It is not clear why these two thiazolidinediones should have disparate effects on cardiovascular outcomes. Various PPAR agonists can yield markedly different patterns of gene modulation, resulting in complex and largely unknown differences in effects on metabolic pathways…Although pioglitazone and rosiglitazone have similar effects on glycemic control, for example, pioglitazone produces greater reductions in serum triglycerides and increases in high-density lipoprotein cholesterol (HDL-C) levels…The 15% relative increase in high-density lipoprotein observed with pioglitazone is similar in magnitude to that which has been associated with coronary atheroma regression or reduction in the incidence of coronary heart disease with other lipid modifying agents."

The bottom line, according to the Lincoff meta-analysis, is that the CV problems with Avandia are not a class effect. They wrote, "The findings of this study illustrate that drugs of the same 'class' may in fact have quite different therapeutic profiles and highlight the potential hazards involved in using surrogate endpoints such as glycosylated hemoglobin rather than assessing safety and efficacy in relation to unequivocal clinical endpoints…The findings of this meta-analysis provide evidence of a favorable effect of pioglitazone on ischemic vascular complications, which is distinct from the efficacy of thiazolidinediones in reducing blood glucose levels."

Lincoff et al Actos Meta-Analysis

Trial	Actos	Comparator	p-value	HR
Primary endpoint: Death, MI, or stroke	4.38%	5.74%	0.005	0.82
Death	2.44%	2.86%	Nss, 0.38	0.92
MI	1.53%	2.03%	Nss, 0.08	0.81
Stroke	1.22%	1.67%	Nss, 0.09	0.80
Serious heart failure	2.34%	1.77%	0.002	1.41
Death/MI	3.61%	4.56%	0.04	0.85
Death/serious heart failure	4.22%	4.10%	Nss, 0.17	1.11
Death, MI, stroke, or serious heart failure	5.94%	6.67%	Nss, 0.54	0.96
Composite of death, MI, and stroke by gender				
Men	5.1%	6.4%	Nss, 0.06	0.85
Women	3.4%	4.8%	0.04	0.77
Serious heart failure by gender				
Men	1.9%	2.5%	0.01	1.41
Women	2.1%	1.6%	Nss, 0.06	1.41

Overview

In a ***JAMA*** editorial in accompanying the two studies, Dr. Daniel Solomon, a rheumatologist and epidemiologist at Brigham & Women's Hospital, and Dr. Wolfgang Winkelmayer, an assistant professor of medicine at Harvard Medical School and an associate physician in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham & Women's Hospital, were extremely critical of the split vote by the July 2007 FDA advisory committee that Avandia has CV safety issues but should remain on the market. They concluded, "With many other available oral agents for diabetes, the potential benefit of TZDs requires reevaluation."

Drs. Solomon and Winkelmayer described the TZD situation as a replay of the Cox-2 situation two years ago. The Cox-2s, they noted, have "some potential benefits with respect to gastrointestinal toxic effects, (but) their benefit:risk ratio was and is still unclear." Likewise, the TZDs have "known benefits on glycemic control but potential cardiovascular toxic effects" and both Actos and Avandia increase the risk of heart failure. They also cited five lessons from the Cox-2 and TZD situations for designing a better drug safety system, and warned that public trust in the FDA rides on fixing the current system:

1. Early safety concerns must prompt **strong and clear regulatory action**, not just new warning labels.

2. **New adverse events should be expected** to be seen in the post-marketing setting when there is incomplete understanding of the mechanism of action of a drug, so "systematic and targeted post-marketing surveillance or randomized trials in high-risk patient groups should be strongly considered. Timely delivery of such studies can be required as a condition of approval and for continued marketing."

3. The **same risk:benefit equation used for approval of a drug should be applied to decisions on continued marketing.** They noted that Avandia probably would not have been approved based on the data presented to the July 2007 advisory committee. Drs. Solomon and Winkelmayer wrote, "Although removal of a medication creates tremendous patient inconvenience, the public expects that FDA approval is a seal of safety."

4. **Approval of me-too drugs should be based on improvement in clinical outcomes, not surrogate measures.** Drs. Solomon and Winkelmayer wrote, "The use of surrogate measures as proxies for clinical outcomes may yield timelier results at lower cost, but the fallacies of this approach have been well demonstrated. Even though TZDs may be a useful step up in therapy, allowing patients to control their blood glucose levels without use of insulin, this may be doing patients a disservice if the complications of diabetes are not reduced through better glycemic control." They urged the

FDA to consider changing the requirements for diabetes trials, especially for me-too drugs.

5. The FDA should develop or codify **methods for weighing benefits vs. risk** and require their use as part of new drug applications (NDAs) or for continued marketing of drugs.

Physician reaction

The ***JAMA*** articles keep the discussion going about the safety and efficacy of glitazones, but they aren't definitive. That was the initial reaction from several diabetes specialists.

- *Dr. Alan Dalkin, a Virginia endocrinologist:* "On the issue of relative risk, let me illustrate why it is important. If I say to you that I am going to give you a medicine that may double your heart attack risk, you will not be happy…If I inform you that the risk will go from one in a trillion to 2 in a trillion, you may think that this is less of a critical issue. This is why absolute risk is more important, and it seems to me critical that we define that risk as precisely as possible."
- *Dr. Anthony McCall, UVA Health System:* "I do not expect the FDA to pull Avandia now because the conclusive information is still not there…Really, what is going on is an analysis of data similar to that done before. These are probably not entirely conclusive about an increased risk, as many of these observations are based upon adverse event reporting and not upon adjudicated endpoints that are pre-specified. Thus, they are less conclusive than a randomized controlled trial that pre-specifies certain endpoints. Some such studies are in progress and the FDA and the study investigators and almost all of the physicians wish to see them continue in order to obtain more definitive information about cardiovascular risk."

However, more doctors may start switching patients from Avandia to Actos – or away from glitazones altogether.

- *Dr. McCall:* "As Actos appears better in the meta-analysis, many will consider switching if they are concerned about Avandia, but frankly many patients have decided not to do so…Glitazones are likely to be more limited in use but will, I think, remain used, as they are effective medications…Some patients are switching. My own preference is to use Actos, probably because of some studies suggesting reduced cardiac risk and some comparative data suggesting some better lipid values. I am not personally starting new patients on Avandia, but I am not necessarily taking them off of it either, particularly if they are doing very well on it. With both I watch very closely for signs or risks of heart failure."
- *Dr. Ira Goldfine, University of California, San Francisco:* "I personally think all this publicity will cut down the use of (both Actos and Avandia)…(But) if a patient is doing well on a drug and not having problems, I would certainly discuss the risks with the patient. However, the risks are small and the numbers are small."
- *Dr. Dalkin:* "I have switched a couple of patients from Avandia to Actos, though I am not sure it made a difference. I tell patients that have cardiac disease and diabetes that it (a glitazone) may not be the best choice and would switch them to insulin before adding another pill. However, some patients still don't want insulin injections."

Is there really a difference between Avandia and Actos? Some doctors are not yet convinced there is. Dr. Dalkin said, "Whether two medications in the same class can act differently is unknown. I doubt either drug will come off of the market…I am not sure from the big picture safety perspective that there is a difference between the two medications. Actos may cause more fluid retention and a risk of congestive heart failure. It is hard to say." Dr. McCall said, "I do not know for sure whether there is a safety difference between the drugs. Like all physicians we are trying to decide with less than conclusive definitive information. The trend looks better for Actos now but I think we need to interpret these data cautiously because most of us view meta-analysis as having some limitations…One very important consideration here is relative vs. absolute risk. Relative risk with Avandia appears increased but absolute risk is really very low. Comparing the two we have no direct head to head comparison of outcome data and so we can not really say with certainty whether one is superior. One nonetheless may have to make decisions in the absence of definitive information. That is where we are now."

Will the glitazone problems cause doctors to opt for more off-label use of newer drugs such as Merck's Januvia (sitagliptin), an oral DPP-IV inhibitor? Dr. Goldfine would only say, "Januvia is an interesting drug with new mechanisms of action…and works reasonably well."

What will the effect be on new diabetes medications? The biggest impact of the safety concerns that have been raised with Avandia may be on new drugs in development. Dr. Goldfine said any new drugs in development "will require some long-term cardiac safety data to make sure this isn't a class effect."

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