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Quick Pulse

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FDA Asking Advisers If Avandia Should Stay On The Market

On Monday, July 30, 2007, the FDA will ask a joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee whether GlaxoSmithKline's diabetes drug, Avandia (rosiglitazone), should remain on the market. The agency is concerned that the drug, used by millions of people worldwide, can cause heart attacks or other cardiovascular problems. According to the FDA, the safety concerns with Avandia also apply to GSK's combination products, Avandamet (rosiglitazone + metformin) and Avandryl (rosiglitazone + glimepride).

Airing the issue at an FDA panel meeting may be enough to satisfy the FDA that doctors are aware of the risks as well as the benefits of Avandia – if the panel doesn't recommend that Avandia be pulled from the market. The FDA has been concerned that Avandia and the other FDA-approved PPAR-γ agonist, Takeda Pharmaceuticals' Actos (pioglitazone), are being used "in a manner inconsistent with labeling and what is known about risk of heart failure." At the June 2007 American Diabetes Association (ADA) meeting, a long session on Avandia safety helped diabetes specialists understand why this drug has become so controversial.

The FDA is posing four questions to the panel, two of which require a vote:

Question 1. GSK submitted a meta-analysis of 42 controlled clinical studies on defining cardiac ischemic risk for Avandia. The panel is being asked to comment on:

- Types of studies selected (e.g., comparison groups).
- Patient populations.
- Treatment duration of studies.
- Endpoints (total ischemic events, composite of stroke/MI/CV death) and their ascertainment.

Question 2. Can cardiac ischemic risk identified in the meta-analysis be addressed by these trials:

- DREAM
- ADOPT
- RECORD
- BARI-2D

Question 3. Does Avandia increase cardiac ischemic risk in Type 2 diabetes mellitus (***VOTE requested***)? If yes, is there evidence that this risk is greater than other available therapies for the treatment of Type 2 diabetes mellitus?

Question 4. Does the overall risk:benefit profile of Avandia support its continued marketing in the U.S. (***VOTE requested***)? If yes, please comment on what FDA should do to maximize the risk:benefit considerations (e.g., limit to certain patients, incorporate a boxed warning, etc.).

Available Agents for the Treatment of Type 2 Diabetes

Drug Class	Route of Administration	Expected Hb_{A1c} reduction with monotherapy	Side Effects
Insulin	Subcutaneous injection or inhaled	>1.5% - 2.5% (no dose limit)	Hypoglycemia, weight gain
Sulfonylurea (SU)	Oral	1.5%	Hypoglycemia, weight gain, probable cardiac ischemic risk with some SUs
Biguanide/metformin	Oral	1.5%	Rare lactic acidosis, contraindicated in patients with renal impairment
Alpha-glucosidase inhibitors	Oral	0.5% - 0.8%	Gastrointestinal (GI) side effects
TZDs/PPAR agonists	Oral	0.5% - 1.5%	Anemia, weight gain, edema, heart failure, cardiac ischemic risk, potential cancer risk (bladder cancer signal with pioglitazone)
Glinides	Oral	1.0% - 1.5%	Hypoglycemia
Amylin analogues	Subcutaneous injection	0.5% - 1.0%	GI side effects
GLP-1 analogue [Amylin's Byetta (exenatide)] *	Subcutaneous injection	0.4% - 0.8% as add-on therapy to metformin or SU	GI side effects
DPP-IV-inhibitor [Merck's Januvia (sitagliptin)]	Oral	0.5% - 0.9%	Limited clinical experience, non-clinical safety signals for many in development

* not approved for monotherapy

Avandia Timeline

Date	Event
1997	Warner Lambert's Rezulin (troglitazone) is first thiazolidinedione (TZD) to get FDA approval.
1999	FDA approves GSK's Avandia and Takeda's Actos.
2000, March	Rezulin withdrawn from the market due to hepatotoxicity (liver failure).
2003	World Health Organization publishes an analysis of adverse reaction reports from the WHO Database that included a general discussion of TZDs and a data mining signal for "cardiac disease" overall (including both heart failure and ischemic events).
2005	FDA begins review of a 52-week study of Avandia given to patients with pre-existing heart failure. While there were no differences between Avandia and placebo in echocardiographic assessments, there was a numerical disadvantage in cardiac events, both in terms of congestive heart failure (CHF) and ischemic events.
2005, October	GSK submitted summary slides to the FDA showing preliminary results from a pooled analysis of Avandia randomized clinical trials (RCTs) that further raised concerns that Avandia may be associated with ischemic cardiac events. GSK proposed a formal analysis plan to provide a more definitive, formal examination of the pooled data RCTs.
2006, February	An FDA medical epidemiologist said GSK's suggested wording was not strong enough.
2006, April	FDA adds warning about adverse cardiac effects to Avandia label.
2006, August	GSK submitted to the FDA its meta-analysis of 42 Phase II and Phase III Avandia RCTs which found a 31% increase in cardiac ischemic events with Avandia vs. the comparator group. GSK also submitted an observational cohort study (Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents) based on an insurance company database that showed no increased risk of cardiac ischemic risk. GSK requests the FDA add a warning about MI to the Avandia label.
2006, September	European regulators revise label for Avandia and Actos.
2006, December	Phase IV ADOPT study published. ADOPT found CV ischemic outcomes with Avandia compared favorably to metformin, with both appearing somewhat less favorable than glyburide.
2007, February	ADOPT data submitted to the FDA, and the data are still being analyzed by the FDA.
2007, April	FDA issues boxed warning (not a black box) about heart failure and edema for both Avandia and Actos.
2007, May	***New England Journal of Medicine*** publishes meta-analysis by Dr. Steven Nissen and Ms. Kathy Wolski, which found a 43% increase risk of cardiac ischemia – with Avandia.
2007, May	FDA meets with GSK to discuss the CV risk of Avandia and to see if the company "could provide other data or information that would better clarify or quantify the signal of risk."
2007, June	Interim analysis of CV safety in ongoing RECORD trial finds an increased risk with Avandia of CHF but no increased risk of MI or CV death.
2007, June	FDA tells congressional committee that it is ordering a black box warning for both Avandia and Actos about the risk of MI and warns that patients with heart disease or who are taking insulin should not use Avandia.
2007, July	FDA advisory committee meeting on Avandia safety.

The Key Perspectives

#1 Nissen. So far, there have been 42 studies of Avandia that were more than 24 weeks in duration, but together or alone they don't settle the issue. Dr. Steven Nissen (past president of the American College of Cardiology) and Kathy Wolski MPH, both of the Cleveland Clinic, performed a meta-analysis of those 42 trials. Their study was published in the ***New England Journal of Medicine*** on May 21, 2007. They found Avandia increases the risk of myocardial infarction (MI) and perhaps cardiovascular (CV) death by 43%. In an accompanying editorial, Dr. Bruce Psaty of the University of Washington and Dr. Curt Furberg of Wake Forest University compared Avandia to Merck's Vioxx (rofecoxib) – which was withdrawn from the U.S. market in 2004 due to CV risks – saying Vioxx "represented a similar regulatory failure to insist on large trials of public health importance in a timely fashion."

#2 GSK. GSK has been defending Avandia, and it has disputed the Nissen findings. A GSK official said, "The totality of the data show that Avandia has a comparable cardiovascular profile to other oral anti-diabetic medicines. GSK stands firmly behind the safety of Avandia when used appropriately, and we believe its significant benefits continue to outweigh any treatment risks."

GSK's analysis of the 42 trials found a 31% increased risk with Avandia (1.99% risk of MI with Avandia vs. 1.51% with comparators), but an observational analysis from a managed care database of >33,000 diabetics found no difference in ischemic cardiovascular events (including MI) with Avandia compared to other oral anti-diabetic medicines. GSK also asked the FDA to add a warning to the Avandia label nearly a year ago – in August 2006. However, in its briefing documents, GSK argued there is "no consistent or systematic evidence that rosiglitazone increases the risk of myocardial infarction or cardiovascular death in comparison to other anti-diabetic agents. Therefore, the benefit:risk profile of rosiglitazone continues to be favorable."

#3 FDA. The FDA did its own meta-analysis and found about a 38% increase in the risk of cardiac ischemic events.

#4 Congress. House and Senate committees are investigating the handling of the Avandia matter by both GSK and the FDA.

#5 Patients and doctors. Before the Nissen meta-analysis, Avandia slightly outsold Actos, but more recent data indicate that Actos now is outselling Avandia almost 2:1, and prescriptions for the entire PPAR-γ class have fallen. The ADA has been urging patients to "stay calm, talk to their doctor, and figure out the best course for themselves." Since 2004, Dr. Sidney Wolfe, Director of Health Research Group at Public Citizen, has been strongly urging patients not to use Avandia, except as a "last resort."

If There Is An Increased CV Risk With Avandia, Is It A Class Effect?

The FDA panel is discussing only Avandia, not Actos. But all of the warnings issued by the FDA so far have been for both Avandia and Actos. The known side effects of Avandia and Actos are weight gain, edema, anemia, and liver toxicity. And remember that Bristol-Myers Squibb's Pargluva (muraglitazar), a dual PPAR-γ/PPAR-α agonist, was rejected by the FDA because of an increase in CV events, including MI.

Dr. Nissen warned against making the conclusion that there is a class effect, even though this is not the first PPAR to have toxicity problems. He said, "This is not the first drug to show a problem…(But) pioglitazone appears to have a more favorable effect on lipids, particularly triglycerides, so we probably need to look at each PPAR individually…The jury is still out on pioglitazone, but so far the trends are in a favorable direction…The PPARs all activate somewhat different genes, and they must be considered individually. The overlap of rosiglitazone, pioglitazone, and troglitazone are about 50%."

But the MI risk findings with Avandia may ***not*** be a class effect, since the large, prospective PROactive trial found Actos was significantly better than placebo (p=0.027) on the ***secondary*** endpoint of combined MI, stroke, and death, though it only trended better (p=0.095) on the primary endpoint of combined coronary and peripheral vascular events.

The PROactive trial of high dose (45 mg) Actos vs. placebo missed its primary endpoint. The trial was powered to show a 20% improvement in time from randomization to first occurrence of any cardiovascular event (defined as the composite of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, coronary revascularization, revascularization in the leg, or amputation above the ankle), but it showed only a 10% improvement (21.0% Actos vs. 23.5% placebo, p=0.095).

Actos did show a 16% reduction in the major secondary endpoint – the composite of heart attacks, stroke, and premature death (12.3% Actos vs. 14.1% placebo, p=0.027) – but Actos also was associated with a ***doubled*** risk of heart failure. Each of the composites of the primary and secondary endpoints except one trended in favor of Actos, but none of these alone met statistical significance, though an investigator said the trial was not powered to show a difference in the individual measurements. Leg bypass was the one exception; it was slightly worse with Actos.

The study chairman, Dr. John Dormandy, Professor of Vascular Science at St. Georges Hospital, University of London, U.K., estimated that adding Actos to other diabetic medications in 1,000 people would avoid 21 first MIs, strokes, or deaths. Looked at another way, 48 patients would need to be treated for three years to avoid one first major cardiovascular event.

W***ould the FDA take Avandia off the market and leave Actos the only PPAR-γ agonist available?*** After the Nissen meta-analysis was published, the FDA asked Takeda to do a meta-analysis of all Actos trials, but that analysis is not yet available. In the panel briefing documents, the FDA appears to agree that a class effect should not be assumed, saying that, in contrast to Avandia, Actos "although clearly associated with increased risk of heart failure, has not been shown to result in increased risk of myocardial ischemia (MI), even in patients receiving concomitant insulin therapy."

FDA Briefing Documents

The FDA briefing documents released before the panel meeting contain 436 pages, with an almost overwhelming amount of data for panel members to wade through and interpret. In addition, GSK submitted 192 pages of its own analyses. At the meeting, the panel will hear a 75-minute presentation by GSK, followed by a 135-minute briefing by FDA officials. Public witnesses have been given 90 minutes to plead their cases, and that will be followed by 45 minutes of panel questions for presenters and a discussion. Then, 90 minutes are allotted for the panel to consider and vote on the FDA's questions.

In the FDA documents, the FDA said the Nissen analysis, which was based on study-level data, is ***not*** a focus of the panel meeting "because we believe the results of the analysis performed by GSK and subsequently by the FDA on the more granular individual datasets do not greatly differ from that of Dr. Nissen and Ms. Wolski in a qualitative sense." However, the FDA believes its analysis, which includes patient level data, is more robust.

In its briefing documents, the FDA also said, "These various datasets present an array of somewhat inconsistent findings that complicate the interpretation of the available data regarding the effect of Avandia on cardiac ischemic events. Nonetheless, given the findings from the RCT (randomized clinical trial) meta-analysis, FDA views this signal with considerable concern…Current available information points to an increased risk of CV adverse effects, including heart failure, myocardial ischemia, and cardiovascular death in diabetic patients treated with Avandia. ***A critical question to be resolved in determining appropriate regulatory action is whether the anticipated therapeutic benefit of Avandia outweighs the demonstrated CV risks***."

The FDA reviewers, summarizing their findings, said, "An increased risk of cardiac ischemia was identified in a pooled analysis of 42 controlled clinical studies of Avandia in patients with T2DM (Type 2 diabetes)…The studies…involved diverse treatment regimens including monotherapy, combination therapy, placebo vs. active comparator, add-on vs. initial therapy, etc." The reviewers found:

- Avandia was associated with a greater risk of ischemia in previously-treated patients than in treatment-naïve patients.
- The risk of cardiac ischemia was increased in placebo-controlled studies with an overall risk (OR) of 1.6 whereas active-controlled studies had an OR of 0.8.
- Combined use of Avandia and metformin is associated with a higher risk of ischemia than metformin alone. However, these findings are not consistent across all 10 combination studies.
- A consistent increase in risk of cardiac ischemia was observed in all studies in which Avandia was added to insulin.
- Longer-term studies in the meta-analysis had similar risks between Avandia and comparators.

An FDA reviewer wrote: "Both this reviewer's and the applicant's (GSK's) analyses produced statistically significant overall estimates of risk of about 1.3 to 1.4 for both total (non-serious plus serious) myocardial ischemic events and serious myocardial ischemic events." The reviewers also found:

- **The addition of CV medications to Avandia may put patients at high risk of an ischemic event**, which the reviewer called "a concern."
- **Inconsistencies were seen across subgroups.**
- **Avandia + metformin has an OR of 3.2.** "The Avanda-met (combination pill of metformin + Avandia) studies showed a statistically significant OR of MI of about 5," the highest seen from any of the reviewer's analyses.

FDA Summary of Serious Ischemic Events in 7 Meta-Groups

Medication	Avandia events	Control events	OR	p-value
Avandia + metformin + sulfonylurea vs. metformin + sulfonylurea (Study 137 only)	1.5%	3.2%	0.4	0.32
Avandia + metformin + sulfonylurea	0.9%	1.1%	0.8	>.99
Avandia + sulfonylurea	0.9%	0.8%	1.4	0.3
Avandia	1%	0.6%	1.5	0.4
Avandia + biguanide/metformin	3.3%	2.1%	1.5	0.18
Avandia + insulin	1.4%	0.6%	2.6	0.12
Avandia + metformin	0.6%	0.2%	2.9	0.1
Overall (weighted by meta-groups)	1.0%	0.8%	1.44	0.06

FDA Mortality Findings

Mortality	Avandia deaths	Control deaths	OR	p-value
Total	0.3%	0.2%	1.7	0.15
Cardiac (IHD)	0.1%	0.1%	1.3	0.6
Cardiac (IHD+CHF)	0.2%	0.1%	1.6	0.4

- **Avandia + insulin doubled the risk**, and this was a consistent finding across all endpoints, but the insulin population was small (about 11% of the database) and short-term studies. The reviewer concluded that "the indication for use with insulin should be carefully reassessed …The results for the combination with insulin are particularly concerning since these results were seen to be consistent across the five studies provided and were consistent considering both total ischemic events and more serious ischemic events including heterogeneity in the designs and in the results. Studies where Avandia plus metformin is compared to placebo plus metformin showed a higher risk due to Avandia across all three measures of ischemia."
- **A statistically significant risk for Avandia over comparators was only seen for the endpoint of total MI events**, which included both non-serious and serious events. The results for serious myocardial events were borderline significant when considering all 42 short-term trials but not significant when excluding the five insulin trials.
- **Nitrate users constitute a high-risk population in general but also show increased risk of an ischemic event** when Avandia is added to nitrates.

AMERICAN DIABETES ASSOCIATION SESSION ON AVANDIA SAFETY

The ADA added a special session to its June 2007 meeting program to talk about the safety of Avandia. Before that session, diabetes specialists were animatedly criticizing Dr. Nissen for raising this issue with his meta-analysis of Avandia.

However, Dr. Nissen did an excellent job explaining why he did the study, why it was published in the ***New England Journal of Medicine***, and why there are safety questions about Avandia. Physicians had a lot of questions, but Dr. Nissen fielded them well. From physician comments afterwards, it appeared he diffused much of the anger that had been directed at him personally. Doctors were still angry with the situation, but their anger shifted somewhat from Dr. Nissen to the FDA and to GSK for not revealing the issue earlier when, they postulated, it might have remained a relatively minor issue.

It wasn't easy for the ADA to put the program together. Dr. Steve Haffner of the University of Texas Health Science Center in San Antonio was listed as providing the counterpoint to Dr. Nissen, but he declined to participate. So did more than a dozen experts who were invited, but Prof. Philip Home of the U.K. finally accepted, and three other experts agreed to participate in a panel discussion with Dr. Nissen and Dr. Home as well as answer questions from the audience: Dr. John Buse of the University of North Carolina, Dr. Barry Goldstein of Thomas Jefferson University in Philadelphia, and Dr. David Nathan of Harvard.

The case against Avandia

Dr. Nissen cited several problems that contributed to the need for his meta-analysis:

- **An early signal was ignored.** Dr. Nissen said there "was a signal from the very beginning of a problem" with Avandia. He pointed to the data at the FDA Advisory Committee meeting in 1999 which indicated that cardiovascular (CV) event rates might be elevated with Avandia: 1.2% with Avandia, 0.6% with a sulfonylurea, 0.5% with placebo, and 1.3% with metformin. He said, "A strong safety signal of excess ischemic CV events was ignored at the time of drug launch. That was a mistake in my view."
- **FDA approval was too quick.** Dr. Nissen said the FDA "rushed to approve a new glitazone because of concerns with troglitazone toxicity. In my view that was a regulatory mistake. Each agent must be carefully and individually evaluated."
- **Recommended post-marketing outcome trials were not performed by GlaxoSmithKline.** The FDA reviewer recommended a four-year safety study to evaluate long-term safety be ***required***, and in the approval letter the FDA's "strongly worded statement" was that it wanted a long-term, four-year safety study, to look at, among other things, CV safety. That study still has not been done, eight years after approval.
- **An internal GSK study was not shared with providers.** GSK informed the FDA about the study first in 2005 and then in more detail in 2006, but neither GSK nor the FDA told physicians about the findings.
- **The results of some post-marketing studies were "concerning."**
  - DREAM, a 3-year diabetes prevention study. The overall CV hazard ratio was 1.37 for Avandia vs. placebo, but this was not statistically significant.
  - ADOPT, a 4-year glycemic durability study. The MI odds ratio was 1.33 for Avandia but not statistically significant.
  - RECORD, an open-label, 6-year, European regulatory cardiovascular outcome study. The results are not due out until 2009.
- **There was a consistent signal of a CV problem in the clinical trials.** Dr. Nissen said, "None of the studies reaches statistical significance, but the consistent pattern to me was very worrisome."

As a result of all this, Dr. Nissen decided to perform a meta-analysis, and this was easier because then New York Attorney General Eliot Spitzer (now governor of New York) had required that GSK publicly disclose all clinical trial results

with Avandia. Again the results suggested a problem with Avandia. Dr. Nissen said, "When you see this kind of consistency in data, it makes you believe there is something real going on."

The findings of the meta-analysis are well-known by now. Dr. Nissen said, "We concluded rosiglitazone is associated with a significant increase in the risk of MI and an increase in the risk of death from CV causes that had borderline significance…Patients and providers should consider the potential for serious adverse CV effects of treatment with rosiglitazone for Type 2 diabetes…We didn't call for withdrawal."

Strengths of the meta-analysis:

- Large size – 42 trials.
- Use of hard endpoints (MI and CV death), not revascularization or hospitalization.
- Analysis included every appropriate randomized clinical trial and used data disclosed by the company itself.
- Inclusion of both published and unpublished trials avoided the common problem of publication bias (studies with favorable outcomes).

Weaknesses of the meta-analysis:

- Access only to study level data, not patient-level data, which precluded measuring composite CV outcomes.
- No time-to-event data, so no Kaplan-Meier curves.
- CV outcomes were not the primary endpoint in any of the trials. Dr. Nissen called this an "important weakness."
- Events not adjudicated in most trials.
- Small number of actual events observed, which resulted in wide confidence intervals.

Should Dr. Nissen's meta-analysis have been published at all? Dr. Nissen said there was no choice, and after the session, doctors appeared to agree, if grudgingly. He addressed that directly, saying, "The alternative to us was unacceptable – to keep the scientific community in the dark, to not tell you a pooled analysis showed a pretty substantial increase in the most serious complication of diabetes."

Aren't GSK's own meta-analysis and an observational study of a managed care database reassuring about the safety of Avandia? Dr. Nissen argued they aren't: "Near the completion of the meta-analysis, we learned that GSK had done a similar study that was not published, initially in 2005 and updated in 2006, not including DREAM and ADOPT, and it showed a 31% greater incidence of MI ischemic events. The GSK analysis used more powerful patient-level data not available to us. And recently, the FDA announced they conducted their own meta-analysis which showed an "approximately 40%" greater rate of ischemic events…Then, GSK commissioned a retrospective observational study of CV outcomes…which they said was to allay concerns about their meta-analysis. This was a ***very*** limited study, using an insurance claims database, looking only at MI and revascularization, with incomplete assessment of covariates, such as smoking or aspirin use. That found no apparent increased CV hazard, but there were few events, wide confidence intervals, and follow-up that was far too short to answer the question. In my view, this study is very weak."

Nissen Meta-Analysis of Avandia

Measurement	Odds ratio (number of events)		p-value
	Avandia	Control	
Primary endpoint #1: MI	1.43 (86 events)	(72 events)	0.03
MI vs. placebo	1.80	---	0.07
Primary endpoint #2: CV death	1.64 (39 deaths)	(22 deaths)	0.06 *
CV death vs. placebo	1.22	---	0.55
MI in all small trials	1.45	---	0.15
MI in DREAM trial	1.65	---	0.22
MI in ADOPT trial	1.33	---	0.20
CV death in small trials	2.40	---	0.02
CV death in DREAM trial	1.20	---	0.67
CV death in ADOPT trial	0.80	---	0.67

* Described as "borderline significant"

Comparison of MI with Avandia vs. Other Diabetes Drugs

Avandia vs.	Odds ratio for MI	p-value
Metformin	1.14	0.59
Sulfonylurea	1.24	0.39
Insulin	2.78	0.29
Placebo	1.80	0.07
Overall	1.43	0.03

Won't the ongoing RECORD trial, which is looking at CV outcomes, settle the safety issue? Again, Dr. Nissen said no: "Major errors in design have likely rendered this study futile. It is an open-label, unblinded, non-inferiority study with an upper confidence interval (CI) of <1.2. Instead of hard CV outcomes, the endpoint is death plus CV hospitalization, with a postulated 11% annual event rate…(But) the observed rate was only 2.5%. This miscalculation results in a huge problem because, when it is completed in 2009, current event rates indicate there is only 45% statistical power for the primary endpoint and <1% power to detect non-inferiority for MI. The bottom line is RECORD will not give us an answer…Ten years after the launch of rosiglitazone, we still may not know whether this agent benefits or harms."

Isn't the interim analysis of RECORD that was performed recently reassuring? Dr. Nissen argued it isn't: "The primary endpoint showed a hazard ratio of 1.11. Up to this point in time, it is consistent with up to a 7% benefit or a 32% hazard. For MI, the hazard ratio was 1.2, and the heart failure hazard ratio was 2.15 (p=0.003). There was no evidence of increased

mortality but <1% power to detect a difference in the interim analysis. The authors described the results appropriately as inconclusive."

In defense of Avandia

Prof. Philip Home of Newcastle University in the U.K., the chair of the RECORD Steering Committee, defended both that trial and Avandia. He said, "My view is that by or around the time of licensing, these medications (Avandia and Actos) were shown to have (numerous benefits)…so strong wave pushing these drugs along…By comparison with other medications believed to improve cardiovascular outcomes, rosiglita-zone appears to behave similarly for CV death, all-cause death, and a CV composite. This suggests that there is no reason rosiglitazone should not continue to have a role in our glucose lowering armory…(But) a clinically significant increase in MI, not causing death, cannot be ruled out for the RECORD data, and there is the known problem of CHF."

The benefits Dr. Home cited for Avandia were:

- Effective glucose lowering.
- Improved insulin sensitivity.
- Fluid retention and occasional cardiac failures.
- Mixed effects on the lipid profile, differing between agents, with rosiglitazone raising LDL.

Subsequently and prior to ADOPT, Avandia and Actos were shown to:

- Improve CV risk markers.
- Improve blood pressure.
- Improve surrogate CV outcomes, e.g. CIMT (carotid intima-media thickness).

Dr. Home called Dr. Nissen's meta-analysis "hypothesis generating, not hypothesis testing." His criticisms of the meta-analysis included:

- Lack of a classic endpoint. "Instead, it was a somewhat 'waffle-y' statement."
- No hypothesis was tested in the study. "I think this is data snooping on quite a big scale."
- Of the 42 Avandia studies, some were excluded.
- Cardiovascular death is not a hard endpoint, even when adjudicated.
- Lack of a time-to-event analysis.

European regulators revised the Avandia label in September 2006 to include the statement: "In a retrospective analysis of data from pooled clinical studies, the overall incidence of events typically associated with cardiac ischemia was higher for rosiglitazone-containing regimens, 1.99% vs. 1.51, with a hazard ratio of 1.31."

Interim Analysis of RECORD Trial

Measurement	Avandia n=2,220	Metformin or sulfonylurea n=2,227	Hazard ratio (p-value)
Lost to follow-up	218 patients	223 patients	---
Length of follow-up	3.77 years	3.73 years	---
CV event rate	2.5%	3.1%	---
Evaluable	217 patients	202 patients	---
CV death	29	35	0.83 (Nss)
Any cause death	74	80	0.93 (Nss)
CV death/MI/stroke	93	96	0.97 (Nss)
Acute MI	43	37	1.16 (Nss)*
CHF	38	17	2.24 (0.006)

* Wide confidence interval

Dr. Home defended the decision to do an interim analysis of the RECORD trial: "Acute reactions of some investigators began to lead to withdrawals…The steering committee decided that publication of the interim analysis was the lesser of two evils...I like to think we have done our best to produce a good study."

Strengths of the RECORD trial include:

- Specifically designed to evaluate CV outcomes.
- Outcomes properly evaluated.
- Long-term trial in a large cohort.
- Active comparator study.

Weaknesses of RECORD include:

- Low event rate, which lowers the power. Dr. Home said, "It was much lower than anticipated, which is a good thing for patients if not for the study."
- 10%+ lost to follow-up.
- Open-label study.
- Broad primary endpoint that Dr. Home said was "in some ways rather unsatisfactory."
- Comparators may have differing efficacy.

Dr. Home also detailed another study that appeared in the ***American Heart Journal*** by Dr. Deepak Bhatt of the Cleveland Clinic on CV adverse events following percutaneous coronary revascularization in patients with metabolic syndrome (not diabetes). That study compared Avandia to placebo and found no increased CV risk.

CV Events with Avandia in PCI Patients

Measurement	Avandia n=102	Placebo n=98
Death, MI, stroke, or recurrent ischemia	30.2%	31.4%
Death, MI, stroke	6.4%	11.9%
MI	5.2%	8.4%
Stroke	1.2%	2.3%

Dr. Home concluded: "Studies such as Dr. Nissen's are important for raising issues, but are a poor basis for making decisions…Modern CV outcomes studies will now struggle to maintain power without large numbers and a long duration, but they are worthwhile and informative…Drug creators (pharmas) have a difficult task to perform, particularly in the area of drug safety, but they are best placed to make benefit:risk assessments, not the media, not Congress, and not editorials in major journals…TZDs have a continuing role to play in glucose-lowering therapy…and I don't believe individual physicians should assess the data…I think the guidelines committees need to redefine where they stand now."

Expert opinions

After hearing both Dr. Nissen and Dr. Home, the experts were asked to comment. Dr. Goldstein said, "It is worth considering that a signal of CV damage is associated with the class…There are issues that have limited TZD use: weight gain, fluid retention, CHF. There has been caution, and now we certainly need to sort out whether there is additional hazard in using the class…When I use them, it is unusual for me to go to the highest dose of either rosiglitazone or pioglitazone." Dr. Nathan added, "We don't control glycemia for CV disease but for microvascular and neurological complications…That is what drives our algorithms…When we look at rosiglitazone or the TZDs, their role in lowering glycemia is far from the most powerful. And as newer, brand names drugs, they are somewhat more expensive…My own attitude is that (Avandia) was never a first choice of mine in any case. The data on fluid retention and CHF made both drugs (Avandia and Actos) less attractive to me…And now the more recent data on fractures and decreased bone mineral density (BMD) also speaks against them."

The moderator posed three patient scenarios and asked panelists what they would do in each case. Generally, the experts agreed that they would not start a naïve patient on Avandia, but would continue patients doing well on it, and would switch patients taking Avandia who weren't doing well.

1. **A patient with poor glycemic control not on Avandia.** *Should Avandia be introduced?*
   - Dr. Buse said ***no***, "At this time I wouldn't choose to start someone on Avandia *de novo* until these issues are settled to the extent they are likely to be settled… After FDA panel we will know everything we are going to know in the next few months."
   - Dr. Goldstein said ***no***, "I would start metformin, not a TZD, unless the patient can't take metformin."
   - Dr. Nathan said ***no***, "I don't understand why, given the choice of other medications, one would start this patient on Avandia."
2. **A patient on Avandia who met the glycemic goals.** *Should Avandia be continued?*
   - Dr. Goldstein said ***yes***, "I'd maintain the patient on Avandia until we learn more."
   - Dr. Buse said ***yes***, "Personally, I think there would be more risk in switching a patient off Avandia than in staying with the current well-controlled situation."
   - Dr. Nathan said ***yes***, "There is a desire not to rock the boat, and I'd think twice about changing someone otherwise achieving the goals."
3. **A patient on Avandia not meeting the glycemic goal.** *Should the Avandia dose be increased?*
   - Dr. Buse said ***maybe***, "It is appropriate to re-think the Avandia…That doesn't mean I necessarily would switch. There are situations where it can be difficult to switch, based on other patient preferences, the patient's formulary, etc."
   - Dr. Goldstein said ***no***, "It is unusual to use three orals with insulin, so I would probably drop one (of the orals), and the weight gain is exacerbated with TZDs, so a TZD is often the one dropped."
   - Dr. Nathan said, "I would stop Avandia and change the regimen."

Questions and answers

Among the comments by doctors in the ADA audience were:

- *New York:* "I am deeply disturbed by the Nissen meta-analysis, particularly by the fact that it was not accompanied by the appropriate editorials…I think it is irresponsible to publish this kind of data in the face of an ongoing randomized clinical trial (RECORD)."
- *U.K.:* "I think we need to look at ourselves and why we are prescribing so many of these drugs. Perhaps our phones wouldn't have been ringing so much if we hadn't put so many patients on it (Avandia)."

Asked what the number needed to harm (NNH) is, Dr. Nissen said, "I deliberately didn't do…a meta-analysis is hypothesis-generating, and to leap to NNH went beyond what we had the available data to do. A NNH should only be done from a careful, prospective trial designed to answer the question of benefit:harm."

Asked about the small absolute risk, Dr. Nissen said, "It (the meta-analysis) is a tremendous underestimation of the potential issue…The actual MI rates are many fold higher than in these trials. The real population at risk is the much sicker population than what was studied in the trials."

Asked about the appropriateness of publication of the meta-analysis, Dr. Home said: "It seems to me…a considerable amount of harm has been done as a result (of the publication of the meta-analysis)…That doesn't mean it shouldn't have been published…but it means our ways of handling these things are inadequate….We get a half-baked editorial with an ax to grind…(audience applause)…What we seriously have to look at is how when something of this kind appears, which

affects millions of people, hundreds of thousands of people, it is handled so there is faster certainty around what it means, and faster interpretation, and that probably means a higher level of commentary with publication." Dr. Goldstein said, "Everyone thinks there should have been more balanced editorials. Beyond that it is impossible to control how this information is revealed…and it is difficult and dangerous to try to control the press." Dr. Nissen defended the press, saying, "We live in a free society with a free press. Diabetes is an important disease…and the idea that a drug ***might*** cause one of the most feared complications of diabetes is news. We can't change that."

Challenged about his statement that individual doctors should be making their own decisions about Avandia, Dr. Nissen explained, "I do think it is an individual decision. Every time you pull out a prescription pad to write a prescription, you are making a decision on whether the benefits of a drug exceed the risks…It does come down to your hand and your pen, and I wanted you to have the information…not publishing it was not an option."

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