Rosiglitazone Registration (May 1999)

- Major concerns had emerged about hepatic toxicity of troglitazone (Rezulin)
- Both rosiglitazone and pioglitazone appeared free of life-threatening liver toxicity.
- The registration “package” for rosiglitazone consisted of 5 trials (2902 patients), mostly short-term (24 weeks) glycemic-control studies.
- The drug was presented to an FDA Advisory Panel on May 22, 1999 and approved.
### Rosiglitazone Advisory Panel: CV Events

<table>
<thead>
<tr>
<th>Ischemic Heart Disease Events</th>
<th><strong>RSG</strong> n=2902</th>
<th><strong>Placebo</strong> n=601</th>
<th><strong>Metformin</strong> n=225</th>
<th><strong>SU</strong> n=626</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 (1.2%)</td>
<td>3 (0.5%)</td>
<td>3 (1.3%)</td>
<td>4 (0.6%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rosiglitazone</th>
<th>Comparators</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>36/2902 (1.24%)</td>
<td>10/1452 (0.69%)</td>
<td>1.8 (0.9-3.6)</td>
</tr>
</tbody>
</table>

The FDA reviewer adjusted for “time-on-drug” and the signal became less dramatic (8.8 vs. 7.9 per 1000 pt yrs, RR=1.11)

### Rosiglitazone Approval Package (1999)

<table>
<thead>
<tr>
<th>Percent Change from baseline in LDL-C*</th>
<th><strong>Baseline LDL</strong></th>
<th><strong>Study 011</strong></th>
<th><strong>Study 024</strong></th>
<th><strong>Study 020</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>24%</td>
<td>20%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>LDL&lt;130</td>
<td>32%</td>
<td>24%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>LDL 130-160</td>
<td>14%</td>
<td>11%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>LDL&gt;160</td>
<td>7%</td>
<td>5%</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

FDA-approved rosiglitazone product insert: 18.6% LDL-C increase for patients with mean baseline of 125 mg/dL

*Statistical Review. Joy D. Mele M.S. Mathematical Statistician
Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis

Cholesterol Treatment Trialists’ (CTT) Collaborators

Summary

Background and objectives The Cholesterol Treatment Trialists’ (CTT) Collaboration has combined individual patient data from 14 large randomised trials of statins for cholesterol lowering. The trialists’ Collaborative have published analyses of the effect of LDL cholesterol reduction on major coronary events in people with and without diabetes, and for different baseline levels of LDL cholesterol. We reanalysed the data to examine the effect of LDL cholesterol reduction on major coronary events in people with diabetes, with a view to informing secondary prevention.

Methods We analysed data from 18,686 individuals with diabetes (14,666 with type 1 and 1722 with type 2) in the context of a further 71370 without diabetes in 14 randomised trials of statin therapy. Weighted estimates were obtained of effects on clinical outcomes per 1·0 mmol/L reduction in LDL cholesterol.

Findings During a mean follow-up of 4·3 years, there were 3247 major vascular events in people with diabetes. There was a 9% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol in participants with diabetes (rate ratio [RR] 0·91, 99% CI 0·82–1·01; p=0·02), which was similar to the 15% reduction in those without diabetes (0·87, 0·82–0·92; p<0·0001). This finding reflected a significant reduction in vascular mortality (0·87, 0·76–1·00; p=0·008) and no effect on non-vascular mortality (0·97, 0·82–1·16; p=0·7) in participants with diabetes. There was a significant 21% proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol in people with diabetes (0·79, 0·72–0·86; p<0·0001), which was similar to the effect observed in those without diabetes (0·79, 0·76–0·82; p<0·0001). In diabetic participants there were reductions in myocardial infarction or coronary death (0·78, 0·69–0·87; p<0·0001), coronary revascularisation (0·75, 0·64–0·88; p<0·0001), and stroke (0·79, 0·67–0·93; p<0·0002). Among people with diabetes the proportional effects of statin therapy were similar irrespective of whether there was a prior history of vascular disease and irrespective of other baseline characteristics. After 5 years, 42 (95% CI 30–55) fewer people with diabetes had major vascular events per 1000 allocated statin therapy.

Cholesterol Treatment Trialists Collaborative: LDL-C and Major CV Events in Diabetics

<table>
<thead>
<tr>
<th>Effect of each 1 mmol/L LDL-C difference</th>
<th>Statin-treated</th>
<th>Controls</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>776 (8.3%)</td>
<td>979 (10.5%)</td>
<td>0.78 (0.69-0.87)</td>
</tr>
</tbody>
</table>

Estimated effect of an 18.6% (0.6 mmol/L) increase in LDL-C (baseline 125 mg/dL)

Estimated Hazard Ratio = 1.17
LDL-C and Cardiovascular Outcomes

Ezetimibe was approved in 2002 on the basis of a 15-18% reduction in LDL-C because this magnitude of LDL-C reduction is presumed by regulatory policy to confer cardiovascular benefits.

What should we presume about a drug that increases LDL-C by a similar amount?

Lipids: Rosiglitazone vs. Pioglitazone

Triglycerides

-12.0%
P<0.001

Non-HDL-cholesterol

14.9%
P<0.001

18.6%
3.8%
P<0.001

Goldberg et al. Diabetes Care 28:1547–1554, 2005
2003-4: Rosiglitazone Concerns Emerge

- The Upsala Drug Monitoring group of the World Health Organization informs GSK that spontaneous reports suggest that rosiglitazone may increase CHF and ischemic myocardial events.

- GSK, in consultation with the company's “Drug Safety Board” undertakes a comprehensive analysis of rosiglitazone and the risk of ischemic events (The Integrated Clinical Trial).

2004-5: The First GSK Integrated Analysis

37 randomized trials: Proportional hazards regression

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.29</td>
<td>0.99-1.89</td>
</tr>
<tr>
<td>Pre-existing CHD/nitrates</td>
<td>2.45</td>
<td>1.34-4.49</td>
</tr>
<tr>
<td>No CHD</td>
<td>1.25</td>
<td>0.84-1.87</td>
</tr>
</tbody>
</table>

These data were submitted to the FDA

However, neither GSK, nor the FDA, made any public statement warning physicians or patients of the findings.
2006: Updated GSK Integrated Analysis

42 randomized clinical trials enrolling 12,183 patients

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.31</td>
<td>1.01-1.70</td>
</tr>
<tr>
<td>Pre-existing CHD/nitrates</td>
<td>2.14</td>
<td>1.20-3.81</td>
</tr>
<tr>
<td>No CHD</td>
<td>1.42</td>
<td>0.96-2.11</td>
</tr>
</tbody>
</table>

These data were also submitted to the FDA

However, neither GSK, nor the FDA, made any public statement warning physicians or patients of the findings.

Why Did the FDA Fail to Warn in 2006?

• GSK supplied FDA with a quickly commissioned observational study performed by a commercial vendor, submitted with the “integrated analysis.”*

• This Ingenix Research Database study showed no significant hazard for rosiglitazone compared with other diabetes therapies or placebo.

• But there was a major issue – The study included data on all major comparator drugs except for pioglitazone!

*McAfee AT et al Pharmacoepidemiology and drug safety 2007; 16: 711–725
Later, the Pioglitazone Data Emerge

Same Ingenix Research Database: Study Sponsor Takeda

Multivariate Cox Proportional Hazards
Adjusted HR = 0.78
95% CI 0.63-0.96

Rosiglitazone Survives 2006

• In 2006, rosiglitazone survived the emergence of strong evidence of a cardiovascular hazard after the company submitted an observational study to FDA.
  – However, study was carefully constructed to avoid comparing rosiglitazone with pioglitazone!

• If the Agency had access to the rosiglitazone vs. pioglitazone data in 2006, they may well have acted decisively to warn physicians and patients.

• Instead, by the end of 2006, rosiglitazone became the largest selling diabetes drug in the world.
September 2006: DREAM Appears in Lancet, Placebo Controlled Diabetes Prevention Trial

<table>
<thead>
<tr>
<th></th>
<th>RSG n=2635</th>
<th>Placebo n=2634</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>15</td>
<td>9</td>
<td>1.66 (0.73-3.80)</td>
<td>0.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
<td>5</td>
<td>1.39 (0.44-4.40)</td>
<td>0.6</td>
</tr>
<tr>
<td>CV Death</td>
<td>12</td>
<td>10</td>
<td>1.20 (0.52-2.77)</td>
<td>0.7</td>
</tr>
<tr>
<td>Adj. CHF</td>
<td>14</td>
<td>2</td>
<td>7.03 (1.6-30.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>New Angina</td>
<td>24</td>
<td>20</td>
<td>1.2 (0.66-2.17)</td>
<td>0.5</td>
</tr>
<tr>
<td>Revasc.</td>
<td>35</td>
<td>27</td>
<td>1.29 (0.78-2.14)</td>
<td>0.3</td>
</tr>
<tr>
<td>Composite</td>
<td>75</td>
<td>55</td>
<td>1.37 (0.97-1.94)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Next Steps

- Concerned about the DREAM findings, we seek to perform a comprehensive meta-analysis of CV outcomes for rosiglitazone.

- Serendipity intervenes: As a result of a court settlement with the state of New York, GSK is required to post results of all of its clinical trials.

- We locate the website and obtain data from 42 clinical trials, 35 of which are unpublished.
Odds ratio for myocardial infarction
1.43 (95% CI 1.03-1.98)

Effect of Infarction
and Death from Cardiovascular Causes
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Odds ratio for cardiovascular death
1.64 (95% CI 0.98-2.74)

July 2007 FDA Advisory Committee

- FDA replicates the findings from the meta-analysis using patient level data:
  - Primary outcome measure – serious ischemic myocardial events HR 1.4 (1.1-1.8), p = 0.02

- Advisory Committee voted 20-3 that rosiglitazone “increases risk of myocardial ischemia”, but 22-1 that benefits exceed risks.

- However, FDA did not present any pioglitazone data at the 2007 Advisory Committee.

- Later, a non-public internal FDA Safety Board votes 8-7 to allow continued marketing of the drug.
Observational Studies (2007-2010)

- A series of observational studies published, nearly all of which confirm the risk of rosiglitazone compared with other diabetes therapies.

- The comparisons with pioglitazone are particularly striking:
  - Younger patients show excess myocardial infarction.
  - Older patients show an increase in CV death.

- These studies culminate in the large Medicare study published 2 weeks ago in JAMA.

2009 Consensus Statement of ADA and EASD

“...the consensus group members unanimously advise against using rosiglitazone.”

Diabetes Care 32:193–203
RECORD - How not to Perform a Safety Study

- An unblinded study – Patients and physicians knew who was taking rosiglitazone.

- Extraordinary unblinding – Unrestricted availability of treatment codes to Quintiles and GSK!

- The study leadership rejected silent MI’s from analysis AFTER analyzing RECORD data:
  - Silent MI’s split 10 to 5, rosiglitazone vs. control, inclusion changes the HR to 1.5 (1.0 to 2.2)

- Study leadership violated DSMB and SC Charter in decision to publish an interim analysis

---

**Time to First MI**

[Graph showing time to first MI with control and rosiglitazone groups, indicating good follow-up dropped below 90% after 4 years.]
European Medicines Agency Statement

The availability of recent studies has added to the knowledge about rosiglitazone and overall, the accumulated data support an increased cardiovascular risk of rosiglitazone. In view of the restrictions already in place on the use of rosiglitazone, the Committee could not identify additional measures that would reduce the cardiovascular risk. The Committee therefore concluded that the benefits of rosiglitazone no longer outweigh its risks and recommended the suspension of the marketing authorisation of the medicines. The suspension will remain in place unless the marketing authorisation holder can provide convincing data to identify a group of patients in whom the benefits of the medicines outweigh their risks.

RECORD Results (Corrected)

• Despite the serious flaws and inherent biases:

• Reported HR ratio for myocardial infarction:

  – HR = 1.14 (95% CI 0.80-1.63)

• MI hazard ratio recalculated by FDA reviewer:

  – HR = 1.38 (95% CI 0.99-1.93)
2010 Meta-Analyses

FDA approach: In the briefing document, analysis only includes trials of <2 years duration, which eliminates the majority of morbid and mortal events.

Our approach: Include all randomized controlled trials to provide a comprehensive assessment with narrowest possible confidence intervals.

Rosiglitazone: 2010 Meta-analysis

Analysis set: 56 studies enrolling 35,531 patients

<table>
<thead>
<tr>
<th></th>
<th>Myocardial Infarction (42 trials)</th>
<th>Cardiovascular Death (26 trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Including RECORD</td>
<td>1.28 (1.02-1.63)</td>
<td>1.03 (0.78-1.36)</td>
</tr>
<tr>
<td>Excluding RECORD</td>
<td>1.39 (1.02-1.89)</td>
<td>1.46 (0.92-2.33)</td>
</tr>
<tr>
<td>P value</td>
<td>0.04</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Archives of Internal Medicine. Published online June 28, 2010
2010 Analysis: Including Zero Event Trials

Including all 56 trials, including studies with no events

<table>
<thead>
<tr>
<th>Myocardial Infarction</th>
<th>Method</th>
<th>OR (95% CI)</th>
</tr>
</thead>
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<tr>
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<thead>
<tr>
<th>Cardiovascular Death</th>
<th>Method</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Including RECORD</td>
<td>0.99 (0.75-1.32)</td>
</tr>
<tr>
<td></td>
<td>Excluding RECORD</td>
<td>1.36 (0.84-2.21)</td>
</tr>
</tbody>
</table>

2010 Meta-analysis: NNH Calculations

For number-needed-to-harm (NNH) calculations, a background MI rate was estimated based on the ACCORD standard treatment group:

• High-quality government-sponsored trial
• MI incidence 6.9% during 5 years follow up

\[
\text{NNH}_{5\text{ year}} \text{ (including RECORD)} = 52
\]
\[
\text{NNH}_{5\text{ year}} \text{ (excluding RECORD)} = 37
\]
Are There Unique Benefits of Rosiglitazone to Counterbalance the Increased Risks?

- There are no unique benefits.
- Rosiglitazone produces modest glucose lowering, but is no more effective (or sustained) than pioglitazone or other available drugs.
- There are now 13 classes of drugs to reduce blood glucose levels.
- We have a safe alternative in the same class.

What Has Changed Since 2007?

- The observational study used to defend the drug in 2006-7 failed to include pioglitazone data.
- The Senate report reveals that GSK had concluded by 2005 that the rosiglitazone increased CV events.
- The completed RECORD Trial was so poorly conducted it cannot be used for regulatory purposes.
- A Medicare observational study (n=227,000) confirms an increase in the risk of death, MI, stroke and CHF.
- New 2010 meta-analyses confirm the very different CV event profiles for pioglitazone and rosiglitazone.
The TIDE Trial

- Approximately 1200 patients enrolled in 14 months. Total sample size = 16,000
- At current enrollment rate, it would take over 8 years to complete enrollment! The trial would report no earlier than 2020.
- Given the current usage of rosiglitazone, how many excess morbid events will occur prior to study completion?
- Because US and European physicians not willing to enroll, company adding sites in the 3rd World.

Ethics of TIDE: Myocardial Infarction

- Pioglitazone (Nissen, Wolski) (all 35 trials)
- Rosiglitazone (FDA briefing) (29 trials < 2 years)
- Rosiglitazone - Nissen, Wolski (55 trials excluding RECORD)

Two Questions for the Panel

1) If a family member asked you whether you approved of their enrollment in TIDE, what would you advise?
2) Are you willing to expose economically vulnerable 3rd world patients to a trial US physicians will not enroll?
Conclusions

Rosiglitazone still commonly used: More than 2.8 million prescriptions in Medicare patients during last decade

Rosiglitazone increases the risk of ischemic myocardial events

With an alternative in the same class (pioglitazone) with favorable effects on CV outcomes, can continued marketing of rosiglitazone be medically or ethically justified?

Conclusions

• Cleveland Clinic removed from the Formulary

• September 2010 FDA restricts use to Type 2 diabetes who cannot control their diabetes on other medications

• GSK required to develop a restricted access program

• February 2011 updated labeling and medication guide
Cleveland Clinic

Every life deserves world class care.