ROSIGLITAZONE (AVANDIA) AND CARDIOVASCULAR (CV) RISK
To Be Concerned, Or Not To Be Concerned?

There are many opinions regarding how much concern to give to the current rosiglitazone controversy. The morbidity and mortality associated with diabetes creates the desire for effective agents. With some of the data that is uncertain and marginal, interpretations are varied and recommendations are guarded. Many who are reassuring do not want to be too reassuring, and many who are alarmist, do not want to be too alarmist. The whole area is confounded by potential adverse effects that are shared by both drug treatment and the natural history of type 2 diabetes. The following table sorts out some possible reasons for more, or less concern.

<table>
<thead>
<tr>
<th>Favouring Less Concern</th>
<th>Favouring More Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The meta-analysis has severe limitations, very few events and is open to interpretation; therefore concerns are “overblown”.</td>
<td>• Clinical outcomes (e.g. MI) are more important than surrogate measures (e.g. A1C).</td>
</tr>
<tr>
<td>• A re-analysis of various data, including DREAM, is reported to be reassuring.</td>
<td>• Clinical outcome benefits should be apparent before widespread use of any drug.</td>
</tr>
<tr>
<td>• The fact that RECORD and ACCORD trials are ongoing is somewhat reassuring as patient safety monitoring boards are following outcomes. (Some may note however that the stop rules do not rule out a hazard of the magnitude found in the meta-analysis.)</td>
<td>• ↑HF, edema &amp; weight gain are well recognized.</td>
</tr>
<tr>
<td>• The absolute cardiovascular (CV) harm found in the analysis, even if true, is very small.</td>
<td>• Since HF is seen in lower-risk patients DREAM, there is more concern for those at higher risk.</td>
</tr>
<tr>
<td>• The value of blood glucose management offsets the questionable concern about CV safety.</td>
<td>• No published clinical trials show a reduction in adverse CV outcomes with rosiglitazone.</td>
</tr>
<tr>
<td>• The authors of both the analysis and editorial that occurred in the NEJM have a history of focusing on drug safety concerns (e.g. Nissen played a key role in bringing forward Vioxx safety issues).</td>
<td>• Much debate seems to be about how much or little harm there may be. If an OR of 1.4 was applied to a higher-risk population with a 2% MI risk per year it would result in an NNH of 125/yr. Drugs for diabetes need to offer CV benefit, not harm.</td>
</tr>
<tr>
<td>• A small risk in the initial years may be offset by benefits of lowering glucose over many years.</td>
<td>• Even the one CV outcome trial PROactive with pioglitazone did not meet its primary endpoint.</td>
</tr>
<tr>
<td>• The limited number of hypoglycemic drug options may make achievement of A1C targets difficult.</td>
<td>• Concerns have been raised about a degree of “cover-up” regarding CV outcome data.</td>
</tr>
<tr>
<td>• The risk/benefit profile must be individualized for each patient.</td>
<td>• Interventions known to reduce CV endpoints may be eclipsed with a narrow focus on glucose.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Considerations In Light of the Recent Meta-analysis (NEJM, May 2007) 1,2

What did we know prior to May 21, 2007?

For patients with type 2 diabetes:
• Intense management of glucose has not resulted in macrovascular benefit (MI, stroke, CV Death); however microvascular benefit (e.g. eye, renal) has been seen (UKPDS-33 over ~10yrs).3
• Macrovascular benefit has been demonstrated with some other therapies such as metformin in obese patients (UKPDS-34) 4 as well as in various blood pressure and lipid management trials.

For glitazones in type 2 diabetes (T2D): why has there been some uncertainty over their role?
• Approvals are based on trials for glucose control rather than clinical outcomes. Avandia approved: 1999 FDA; 2000 CAN
• A significant increased risk of heart failure has been seen in larger placebo controlled glitazone trials
  o DREAM {rosiglitazone vs placebo in pre-diabetes without CV disease: 0.5% vs 0.1%; NNH=250/3yrs}5
  o PROActive {pioglitazone ACTOS vs placebo in diabetes & established CV disease: 11% vs 8%; NNH=34/~3y}6
  A trend toward CV harm with rosiglitazone was seen in DREAM 12.9 vs 2.5%; HR 0.97-1.94.7 Trial was stopped early based on a decrease in newly diagnosed diabetes although all CV outcomes signalled potential harm.
• Muraglitazar was associated with adverse CV outcomes and was never approved.
•Troglitazone was withdrawn due to liver toxicity.
• Weight gain ~3kg/3yrs, edema especially if with insulin cotherapy and anemia are also potential adverse effects.

Abbreviations in this Q&A: CV=cardiovascular  HF=heart failure  MI=myocardial infarction  NNH=number of patients needed to treat for 1 extra harm  OR=odds ratio
The Nissen, Wolski Rosiglitazone Meta-analysis (NEJM May 2007)

- This recent rosiglitazone meta-analysis raises concern of an increased risk of MI and CV Death.
  - Meta-analysis compared rosiglitazone to both placebo & active control groups
  - MI 66 vs 72 events in over 26,000 patients (p=0.06) OR 1.43 CI 1.03-1.98 CV DEATH OR 1.64 CI 0.98-2.74
  (Note: a low rate of events is partly due to inclusion of many unpublished trials being short duration in a lower risk population.
  If a 43% relative increase in MI persisted in higher CV risk patients, long term absolute risk would be quantitatively higher.
  For example: An MI rate of 2% per year may be seen in higher-risk diabetes populations. In such a case the absolute increase in risk would be approximately 0.8% per year or a number need to harm of 125 per year. Thus, absolute risk would vary greatly with patient risk.)

- Problems/limitations of the methodology have been acknowledged by both authors and critics.
  - e.g. study selection, limited access to patient level study data, lack of time to effect data, lack of event adjudication, very small number of events; due to weighting of data, some numbers do not add up. Data, including some additional data from the company, is currently being reanalysed by the FDA.
  - Meta-analysis authors called for further data, evaluation and consideration of CV risk with rosiglitazone.

What to do with the current rosiglitazone controversy

- Weigh the value of cardiovascular outcomes versus glucose control outcomes for the patient

- Blood pressure control in diabetes – target 130/80 (e.g. ACEI or ARB, &/or a thiazide)

- Cholesterol control with statins especially for high risk patients (e.g. CARDS, NNT=14/10yr)

- Metformin especially if obese & no contraindications (only hypoglycemic with proven CV & mortality benefit in T2D)

- ASA 81mg daily (especially for higher CV risk patients e.g. age >50yrs)

- Options for glucose control with consideration for macrovascular data in T2D

- Lifestyle + Metformin (1st line recommendation in recent ADA Position Statement 2007)
  - Add insulin surrogate data, sulfonylureas mixed/inconclusive CV data (concern with high doses?)
  - Consider addition of other agents recognizing absence of clinical outcome evidence
  - Pioglitazone ACTOS: CV risk/benefit unclear; reductions in 2CV endpoints but increased HF in patients with CV disease (PROactive; Cochrane)

- In the prevention of diabetes, lifestyle interventions especially, and metformin offer benefit

Looking to the future.

- Other data will likely soon be available!!! (e.g. FDA re-analysis; other post-surveillance data)

- We await the results of rosiglitazone randomized control trials designed to evaluate CV outcomes.

More to come

- RECORD 2009?
  - Interim analysis by safety data monitoring board has been completed 2007)
  - Some concern has been raised over whether RECORD will be able to continue, given ↑ patient dropouts 2008

- Randomized controlled trials to evaluate CV outcomes for such diabetes interventions are needed?

Related weblinks:

- FDA: http://www.fda.gov/cdrh/druginfo/rosglitazone/default.htm

Prepared by B. Jensen & L. Regier. The authors declare no conflicts of interest with any pharmaceutical companies. Thanks to the many reviewers from across Canada who contributed to the Q&A. Copyright 2007 RxFilms, Saskatoon Health Region. All Rights Reserved. DISCLAIMER: The content of this newsletter represents the research, experience and opinions of the authors and not those of the Board or Administration of SSH. Neither the authors nor SSH is any other party who has been involved in the preparation or publication of the work accepts or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or the results obtained from the use of such information. Any use of the newsletter will imply unconditional of the doctriptions and release any responsibility of SSH, its employees, owners or agents. Readers are encouraged to confirm the information contained herein with other sources.

---

Update Dec 2007: Glitazone Meta:

- FDA News: any ischemia Odds Ratio 1.4 (1.1-1.8) p=0.02
- WellPoint Observational study: increased MI Hazard Ratio 1.029 (0.886-1.194) Nov 2007
- Meta-reanalysis: discordant risk

Gerrits 2007:

- FDA Panel July 30, 2007: rosiglitazone for the treatment of type 2 diabetes was associated with a greater risk of MI than placebo, metformin or sulfonylureas
- Rosiglitazone Meta: company sponsored but lower risk of death, MI or stroke in diabetics (vs placebo) MI events Hazard Ratio 1.31 (1.1-1.7) P=0.044
- FDA Meta: any ischemia Odds Ratio 1.4 (1.1-1.8) p=0.02
- Heart failure 2.3 x 2.8 without increased mortality

Gerrits: increased risk of MI 1.42 & heart failure 2.3, without a significantly increased risk of cardiac mortality.

FDA Panel 2007: rosiglitazone for the treatment of type 2 diabetes was associated with a significantly increased risk of MI than placebo, metformin or sulfonylureas.

Gerrits 2007: rosiglitazone & pioglitazone ↑ risk of HF in prediabetes & type 2 diabetes; however no corresponding increase in CV death.

Gerrits: Case Control Study: further suggests glitazones, esp. rosiglitazone ↑ risk of MI & death in elderly pts treated in Ontario...
Additional references:


Graham David J; Ouellet-Hellstrom Rita; MaCurdy Thomas E.; et al. Risk of Acute Myocardial Infarction, Stroke, Heart Failure, and Death in Elderly Medicare Patients Treated With Rosiglitazone or Pioglitazone. JAMA. 2010;0(2010):jama.2010.920.

Hsiao FY, Huang WF, Wen YW, Chen PF, Kao KN, Tsai YW. Thiazolidinediones and Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: A Retrospective Cohort Study of over 473 000 Patients Using the National Health Insurance Database in Taiwan. Drug Saf. 2009;32(8):675-90.

Hollander P, Yu D, Cheu HS. Low-dose rosiglitazone in patients with insulin-requiring type 2 diabetes. Arch Intern Med. 2007 Jun 25;167(12):1284-90. The addition of low-dose rosiglitazone to insulin therapy is an effective and well-tolerated treatment option for patients with type 2 diabetes mellitus who continue to have poor glycemic control despite administration of exogenous insulin as monotherapy, but excess rates of cardiovascular events with rosiglitazone use (2.4% in the 2-mg/d group and 1.4% in the 4-mg/d group vs 0.9% in the placebo group.)


