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.**

Favouring Less Concern	Favouring More Concern
• The meta-analysis has severe limitations, very few events and is open to interpretation; therefore concerns are "overblown". • A re-analysis of various data, including DREAM, is reported to be reassuring. • 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.} • The absolute cardiovascular (CV) harm found in the analysis, even if true, is *very small*. • The value of blood glucose management offsets the questionable concern about CV safety. • 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). • A small risk in the initial years may be offset by benefits of lowering glucose over many years. • The limited number of hypoglycemic drug options may make achievement of A1C targets difficult. The risk/benefit profile must be individualized for each patient.	• Clinical outcomes (e.g. MI) are more important than surrogate measures (e.g. A1C). • Clinical outcome benefits should be apparent before widespread use of any drug. • ↑HF, edema & weight gain are well recognized. • Since HF is seen in lower-risk patients [DREAM], there is more concern for those at higher risk. • No published clinical trials show a reduction in adverse CV outcomes with rosiglitazone. • 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. • Even the one CV outcome trial [PROactive] with pioglitazone did not meet its primary endpoint. • Concerns have been raised about a degree of "cover-up" regarding CV outcome data. • Interventions known to reduce CV endpoints may be eclipsed with a narrow focus on glucose. • Other concerns include macular edema, anemia and fractures in women. • Dropouts threaten the status of future trials. • Concern may be "overblown" but it is still there.

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

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 has 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
  - **DREAM** {rosiglitazone vs placebo in pre-diabetes without CV disease; 0.5% vs 0.1%; **NNH=250/3yrs**}[5]
  - **PROactive** {pioglitazone [ACTOS] vs placebo in diabetes & established CV disease; 11% vs 8%; **NNH=34/~3yr**}[6]

Previous CV concerns

- A trend toward CV harm with rosiglitazone was seen in DREAM {2.9 vs 2.1%; HR 0.97-1.94}. 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.

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.** (using published & unpublished data)
  - Meta-analysis compared **rosiglitazone** to both **placebo & active control** groups
  - **MI** 86 vs 72 events in over 26,000 patients (~0.6%) {OR 1.43[p=0.03]; CI 1.03-1.98}; **CV DEATH** {OR 1.64[p=0.06]; 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.**

Analysis criticized

  - 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.[7]
  - 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**
- ***Wait and see* is one option.** {Note: Sept07; most subsequent analysis consistent with ↑ CV risk for rosiglitazone; see Update box at bottom of page}
- **For proven cardiovascular outcome benefits in patients with diabetes, consider:**

Proven CV interventions

  - **Lifestyle** (e.g. weight loss, diet, exercise 30-60 minutes exercise, 4-7 times per week and smoking cessation)
  - **Blood pressure control** in diabetes – target 130/80 (e.g. ACEI or ARB, &/or a thiazide ≤25mg daily)
  - **Cholesterol control with statins** especially for high risk patients (e.g. CARDS atorvastatin 10mg daily [8]; HPS simvastatin 40mg daily [9])
  - **Metformin** especially if obese & no contraindications (only hypoglycemic with proven CV, & mortality NNT=14/10yr 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)[10]
    - Add insulin surrogate data; or sulfonylureas mixed/inconclusive CV data (concern with high doses?)[11], ADOPT CV reassuring[12]
    - Consider addition of other agents recognizing absence of clinical outcome evidence
  - **Pioglitazone** ACTOS: CV risk/benefit unclear; reductions in 2° CV endpoints but increased HF {in patients with CV disease (PROactive; Cochrane)}[6,13,14] {Note: Pioglitazone has a preferred lipid profile relative to rosiglitazone.}
- **In the prevention of diabetes, lifestyle interventions especially, and metformin offer benefit** DPP.[15]

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 data safety monitoring board has been completed 2007); **ACCORD** 2008?
  - Some concern has been raised over whether RECORD will be able to continue, given ↑ patient dropouts [16]
- **Randomized controlled trials to evaluate CV outcomes for such diabetes interventions are needed!**

Related weblinks:

FDA: http://www.fda.gov/cder/drug/infopage/rosiglitazone/default.htm ; CDA: http://www.diabetes.ca/section_main/newsreleases.asp?ID=194;
ADA: http://diabetes.org/diabetesnewsarticle.jsp?storyId=15115339&filename=20070521/comtex20070521pr00004113diabetesavandiariskEDIT.xml;
Heart.org: www.theheart.org; Lancet editorial May 23, 2007: http://www.thelancet.com. Canadian BP Guidelines CHEP 2007: www.hypertension.ca
RxFiles: select drug comparison charts, related newsletters, Q&A Trial Summaries available from www.RxFiles.ca or from our RxFiles Drug Comparison Charts Book
{e.g. various diabetes charts, DREAM Trial Overview}; **Updated Related Links**: http://www.rxfiles.ca/rxfiles/uploads/documents/Rosiglitazone-CV-Controversy.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 this Q&A.

[1] Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. N Engl J Med. 2007 May 21; [Epub ahead of print] http://content.nejm.org/cgi/content/full/NEJMoa072761
[2] Psaty BM, Furberg CD. Rosiglitazone and Cardiovascular Risk. N Engl J Med. 2007 May 21; [Epub ahead of print] http://content.nejm.org/cgi/content/full/NEJMe078099
[3] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53. Erratum in: Lancet 1999 Aug 14;354(9178):602.
[4] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65. Erratum.
5 Gerstein HC, Yusuf S, Bosch J, et al. DREAM; Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006 Sep 23;368(9541):1096-105. Erratum: Lancet. 2006 18;368(9549):1770.
[6] Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, et al; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study: a randomised controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89.
[7] Rosiglitazone maleate (marketed as Avandia, Avandamet, and Avandaryl) Information May 23, 2007; FDA Alert. Accessed online at: http://www.fda.gov/cder/drug/infopage/rosiglitazone/default.htm
[8] Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, et al; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004 Aug 21-27;364(9435):685-96.
[9] Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study(HPS) of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361(9374):2005-16.
[10] American Diabetes Association. Standards of medical care in diabetes--2007. Diabetes Care. 2007 Jan;30 Suppl 1:S4-S41. Online at http://care.diabetesjournals.org/cgi/content/full/30/suppl_1/S4
[11] Simpson SH, Majumdar SR, Tsuyuki RT, Eurich DT, Johnson JA. Dose-response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. CMAJ. 2006 Jan 17;174(2):169-74.
[12] Kahn SE, Haffner SM, Heise MA; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006 Dec 7;355(23):2427-43. Epub 2006 Dec 4. Erratum in: N Engl J Med. 2007 Mar 29;356(13):1387-8.
[13] Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD006060.
[14] Erdmann E, Dormandy JA, Charbonnel B, et al; PROactive Investigators. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive Study. J Am Coll Cardiol. 2007;1;49(17):1772-80.
[15] Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program (DPP). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002 Feb 7;346(6):393-403
[16] Reuters news accessed online May 28, 2007. http://www.reuters.com/article/governmentFilingsNews/idUSN26207206207052 6
[17] Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA. 2007 Sep 12;298(10):1180-8. Pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. Serious heart failure is increased by pioglitazone, although without an associated increase in mortality.
[18] Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA. 2007 Sep 12;298(10):1189-95. Among patients with impaired glucose tolerance or type 2 diabetes, rosiglitazone use for at least 12 months is associated with a significantly increased risk of myocardial infarction and heart failure, without a significantly increased risk of cardiovascular mortality.
[19] Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007 Sep 29;370(9593):1129-36.

Update Dec 2007: **Glaxo's Meta[Rosi]:** MI events Hazard Ratio **1.31** (1.01-1.7) Europe label changes: **Oct 2006** **FDA Meta [Rosi]:** any ischemia Odds Ratio **1.4** (1.1-1.8) p= 0.02
WellPoint Observational study[Rosi]: acute MI Hazard Ratio 1.029 (0.886-1.194) Rosen NEJM Aug 30/07 **Meta re-analysis[Rosi]:** uncertain risk Diamond AnnIntMed Aug 6/07
Gerrits et al Observational study: less acute MI or coronary revascularization with pioglitazone than rosiglitazone Hazard Ratio **0.78** (0.63-0.96) PharmacoDrugSafety Aug 3/07
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.
Pioglitazone Meta: company sponsored but lower risk of death, MI or stroke in diabetics HR 0.82. ↑heart failure 2.3 vs 1.8% without increased mortality. [17]
Rosiglitazone Meta: increased risk of MI RR 1.42 & heart failure RR 2.09, without a significantly increased risk of cardiovascular mortality. [18]
Glitazone Meta: both rosiglitazone & pioglitazone ↑ risk of HF in prediabetes & type 2 diabetes; however no corresponding increase in CV death. [19] (Lancet Lago et al; pooled data)
Glitazone Population Case Control Study: further suggests glitazones, esp. rosiglitazone ↑risk of HF,MI & death in elderly pts treated in Ontario Lipscombe JAMA Dec 12,07

Additional references:

Brownstein JS, Murphy SN, Goldfine AB, et al. Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records. Diabetes Care. 2010 Mar;33(3):526-31. Epub 2009 Dec 15.

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, Kuo 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, Chou 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.)

Juurlink David N. Rosiglitazone and the Case for Safety Over Certainty. JAMA. 2010;0(2010):jama.2010.954.

Nissen Steven E.; Wolski Kathy. Rosiglitazone Revisited: An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality. Arch Intern Med. 2010;0(2010):2010.207.

Wang Amy T, McCoy Christopher P, Murad Mohammad Hassan, Montori Victor M. Association between **industry affiliation** and position on cardiovascular risk with rosiglitazone: cross sectional systematic review. BMJ 2010;340:c1344, doi: 10.1136/bmj.c1344 (Published 18 March 2010).

Updated Related Links: http://www.rxfiles.ca/rxfiles/uploads/documents/Rosiglitazone-CV-Controversy.htm