If you are on metformin (MF) or a sulfonylurea (SU), is adding rosiglitazone (AVANDIA) inferior to moving to a combination of both MF and a SU?

**Background**

- Controversy and concern has surrounded the cardiovascular risk (CV) profile of rosiglitazone (AVANDIA) since GSK’s submission to the FDA and Nissen and Wolski’s Meta-analysis suggested increased CV events. (Concerns heightened as other PPAR agonists under development failed due to CV problems in humans or bladder cancer in animals.)

**Trial Background Data**

- Prospective, randomized, multicentre, open label, funded by GSK. Non-inferiority trial.
  - 7428 screened, 4458 randomized
  - Inclusion: age 40-75; BMI ≥25kg/m²; already on max tolerated dose of MF or SU; A1C control less than optimal (>7-9%)
  - Exclusion: CV hospitalization in last 3 months, planned CV intervention, any heart failure (HF)

**Treatment group vs Active Control group**

- Target A1C: ≤7.0%. Daily dose: Rosi: 4-8mg; MF: ≤2550mg; glibenclamide: ≤15mg; gliclazide ≤240mg; glimepiride ≤4mg.
- Rosette therapy (3rd agent added) if A1C ≥8.5%. If already on 3 agents including rosiglitazone, rosi stopped & insulin started.
- n=4447, T2DM; age mean 57 SU, ~60 MF; A1C mean ~7.9%
  - Prospective, randomized, multicentre, open label, funded by GSK. Non-inferiority trial.
  - Dropout rate at trial’s end for the Tx & control groups is reported to be 40% & 50% respectively. Report does not provide these numbers but notes an excess of 32 people (1.4%) in the rosiglitazone group withdrew from treatment.
  - Patients were treated differently (e.g. rate of statin and loop diuretic use in rosi arm may also be considered bias after transfer from dual therapy.)
- **Clinical endpoints**
  - CV death or CV hosp: 1.46% vs 1.50% NS
  - All-cause death: 6.13% vs 7.04% NS
  - CV death or CV hosp (1°): 2.75% vs 1.30% NS
  - MI: 2.88% vs 2.51% NS
  - Stroke: 2.07% vs 2.83% NS
  - Fractures, All (From Table 7): 8.33% vs 5.30% NS

**Strengths, Limitations & Uncertainties**

**Strengths**

- Important clinical endpoints rather than surrogate; reasonable duration; best powered rosi trial to date

**Limitations**

- Open label & funding source leave room for bias; limited statistical power for non-inferiority endpoints; non-compliance or other bias a potential factor after publication of the Nissen meta & interim RECORD analysis.
- Dropout rate at trial’s end for the Tx & control groups is reported to be 40% & 50% respectively. Report does not provide these numbers but notes an excess of 32 people (1.4%) in the rosiglitazone group withdrew from treatment.
- Patients were treated differently (e.g. rate of statin and loop diuretic use in rosi arm may also be considered bias after transfer from dual therapy.)
- **Groups were treated differently** (e.g. rate of statin and loop diuretic use in rosi arm may also be considered bias after transfer from dual therapy.)

**Other considerations & unanswered questions:**

- How would addition of rosiglitazone to a SU or MF compare to adding insulin to MF?
- How does rosiglitazone compare to pioglitazone (ACTOS)? (Pioglitazone has uncertain CV benefit based on the RECORD-1 trial.)
- Cost ($/day/100days): MF 2.550mg/day=$60; Gliclazide MR 60-240mg/day=$40-140; Rosiglitazone 4mg/day=$260-360

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**Results - over the mean 5 years of follow-up**

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>Rosiglitazone (n=1117)</th>
<th>Active Control (n=1108)</th>
<th>NNT/NNH (95% CI) Comments</th>
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<tr>
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**Cost ($/day/100days):**

- MF 2.550mg/day=$60
- Gliclazide MR 60-240mg/day=$40-140
- Rosiglitazone 4mg/day=$260-360

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**Bottom Line:**

**We have UNCERTAINTY about somewhat REASSURING CV results & concerns about HF & fracture.**

- Adding rosiglitazone to patients on either MF or SU seems to be no worse on CV endpoints than combining MF & a SU.
- Rosiglitazone may not reduce CV risk in patients who do not have HF, recent CV related hospital admission or ischemic heart disease. Although somewhat reassuring, when the significant trial limitations are considered along with the results of previous trials, there is still uncertainty. (Remember we are still talking about uncertain harm; ideally we’d be talking about benefit.)
- Adding rosiglitazone may reduce CV risk in patients who do not have HF, recent CV related hospital admission or ischemic heart disease. Although somewhat reassuring, when the significant trial limitations are considered along with the results of previous trials, there is still uncertainty. (Remember we are still talking about uncertain harm; ideally we’d be talking about benefit.)
- Adding rosiglitazone may not be beneficial in patients with a high risk of CV events who are already on a combination of both MF and a SU.
- Other considerations & unanswered questions:
  - How would addition of rosiglitazone to a SU or MF compare to adding insulin to MF?
  - Does it matter which SU is used or what dose of SU is used? (Higher SU doses may be associated with hypoglycemia & adverse outcomes)
  - Cost ($/day/100days): MF 2.550mg/day=$60; Gliclazide MR 60-240mg/day=$40-140; Rosiglitazone 4mg/day=$260-360

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**Notes:**

- Time to 1° event; **Other endpoints: no difference in malignancies, pneumonia; possible in non-serious but not serious macular edema.**
- Per Protocol Analysis: HR: 1.02 (0.85-1.22) but excluded if 30days after transfer from dual treatment.
- **Cost ($/day/100days):**
  - MF 2.550mg/day=$60; Gliclazide MR 60-240mg/day=$40-140; Rosiglitazone 4mg/day=$260-360

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**Chart:**

- Clinical endpoints vs other endpoints
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Update – July 2010:
The RECORD trial has come under increasing criticism since publication.

- E.g. an FDA researcher “found at least a dozen instances in which patients taking Avandia suffered serious heart problems that were not counted in the trial’s tally of adverse events” NY Times – Accessed 12Jul10 http://www.nytimes.com/2010/07/13/health/13avandia.html.
- This criticism is in the context of company data from 1999 showing signs of CV concerns relative to Pioglitazone; data that was not made public.
- Additional information: FDA review – 13Jul10 FDA Briefing: http://www.fda.gov/AdvisoryCommittees/CommitteeMeetingMaterials/Drugs/EndocrinologyMetabolismDrugsAdvisoryCommittee/ucm218491.htm

References

See also:


Additional references:

Prepared by L.oren Regier & Brent Jensen. The authors declare no conflicts of interest with any pharmaceutical companies. Thanks to those who contributed to this Q&A.

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