# RECORD - Rosiglitazone for cardiovascular outcomes in T2DM [1]

**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[2007] and Nissen and Wolski's Meta-analysis[2007] suggested increased CV events.[2,3,4] {Concerns heightened as other PPAR $\alpha\gamma$ 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
  - 2228 already taking MF; 2230 already taking SU. 11 did not receive study med. (Apr 2001 – Dec 2008)
  - Inclusion: age 40-75; BMI >25kg/m$^2$; 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:** (**$MF_{n=1117}$ or $SU_{n=1103}$ + rosiglitazone**) **versus** (**MF + SU**)$_{n=2227}$
  - Target A1C: ≤7.0%. Daily dose: Rosi: 4-8mg; MF: ≤2550mg; glibenclamide (= glyburide) ≤15mg; gliclazide ≤240mg; glimepiride ≤4mg.
  - Rescue 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%⇨7.4-7.9%; white; ♂ $_{49\text{-}53\%}$; weight 93kg $_{MF,}$ 85kg $_{SU}$
  - background SU $_{vs\ MF}$ group: rate of -heart disease $_{20\%\ vs\ 15\%}$, -retinopathy ~13% vs ~7%; longer hx of T2DM $_{7.9\ vs\ 6.2yrs}$
  - rosi. arms @baseline⇨5yrs vs control: ↑statins 18⇨55% vs19⇨46%;↑loop diuretic 3.1%$_{both}$⇨13% vs 8%; ↑weight 3.8-4.1kg

## Results - over the mean 5.5 years of follow-up {modified ITT analysis: those who were randomized but never got study drug (11) not included.}

| Clinical Endpoints *,** | Rosiglitazone n=2220 | Active Control n=2227 | ARR | NNT/NNH (95% CI) | Comments |
|---|---|---|---|---|---|
| CV death or CV hosp (1°)* | 14.46 % n=321 | 14.50 % n=323 | NS | - | ◆1°: HR: 0.99 (0.85-1.16) p = 0.9 {HR at 3.75yrs was 1.11 (0.93-1.32)}[5] {to claim non-inferiority, upper limit of CI had to be ≤1.2} ◆Subgroup analysis: trend for worse outcomes with rosiglitazone if previous ischemic heart disease (HR=1.26. CI:0.95-1.68) ◆event rate was lower than predicted ◆study visit withdrawals: 7.2% person-yrs |
| All-cause death | 6.13 % | 7.04 % | NS | - | |
| CV death | 2.70 % | 3.19 % | NS | - | |
| MI | 2.88 % | 2.51 % | NS | - | |
| Stroke | 2.07 % | 2.83 % | NS | - | |
| CV death, MI or stoke | 6.94 % | 7.41 % | NS | - | |
| HF admission to hospital or death | 2.75 % n=61 | 1.30 % n=29 | ↑ 1.45 % | NNH=69 (44-162) | |
| Fractures, All (From Table 7) Serious only Table 6 | 8.33 % n=185 2.2 % | 5.30 % n=118 1.6% | ↑ 3.03 % NS | NNH=33 (22-66) | Mostly upper & distal lower limb & ♀ (RR:↑57%; ↑82% in ♀ & 23% in ♂) |

*Time to 1st event; **Other endpoints: no difference in malignancies, pneumonia; possible ↑ in non-serious but not serious macular edema. Per Protocol Analysis: HR: 1.02 (0.85-1.21) but excluded if 30days after transfer from dual treatment

## 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 non1° 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.[6] Report does not provide these numbers but notes an excess of 32 people (1.4%) in the rosiglitazone group withdrew from treatment. 2.8% of patients were totally lost to follow-up. (Curiously, interim report stated ~ 10% lost to follow-up.)[5]
- Groups were treated differently (e.g. ↑ rate of statin and loop diuretic use in rosi arm may also be ↑dose of statin use?; higher rate of dropout in rosi arm after 2007 meta-analysis controversy); open label design together with the potential impact of a rosiglitazone controversy in the middle of the trial could affect trial outcome significantly. Of interest: the hazard ratio (HR) and Kaplan-Meier plots show a trend for worse outcome with rosiglitazone until the latter year of the trial.
  {The per-protocol analysis can not be used to assess this given complexity of study design (number of potential concomitant treatments and exclusion of any events occurring more than 30days after transfer from dual therapy.}
- SU dosing: quite high (e.g. gliclazide dose ≤240mg/day 2x higher than used in ADVANCE); {MF dose OK; 2550mg/day beneficial in UKPDS-34}; varied by local practice, adjustment only allowed after 8 wks
- Would outcome results change if: a 3rd agent was added before the A1C was ≥8.5? What if insulin was the 2nd agent?
- Uncertain is the complexity of a potential impact for two rosiglitazone arms & two active control arms (those with baseline SU vs baseline MF) on the results; this cannot be totally evaluated by subgroup analysis. For instance in the UKPDS-34 $_{10yr}$, MF reduced CV & mortality risk overall in obese patients; however, when MF was added to SU patients, the risk ↑'d.[7] This raises the issue of whether baseline group characteristics, choice & timing for drugs initiated could affect the outcomes.

## 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 ↑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$_{/\sim 5.5yrs}$: ↑ heart failure $_{NNH=69}$, fractures $_{NNH=33}$ & weight gain $_{\sim 4kg}$ more than MF or a SU but ↓hyperglycemia.
- 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 PROACTIVE trial so debate has been over whether neutral or beneficial for CV. Similar HF and fracture concerns)[8]
  - Does it matter which SU is used or what dose of SU is used? (Higher SU doses may be associated with hypoglycemia & adverse outcomes.[9,10])
  - Cost $_{SK\text{-}Canada}$/100days: MF 2,550mg/day=$60; Gliclazide MR 60-240mg/day=$40-140; Rosiglitazone 4-8mg/day=$260-360

**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/policy/13avandia.html?_r=1
- 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 NY Times – Accessed 12Jul10 http://www.nytimes.com/2010/07/13/health/policy/13avandia.html?_r=1
- Additional information FDA review – 13Jul10 FDA Briefing: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm218491.htm

## References

See also:

- RxFiles Chart - Diabetes Landmark Trials & Links at: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf
- RxFiles Rosiglitazone (Avandia) – CV Controversy Links: http://www.rxfiles.ca/rxfiles/uploads/documents/Rosiglitazone-CV-Controversy.htm
- RxFiles Chart – Oral Hypoglycemics: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-diabetes.pdf (Available only to online subscribers or in RxFiles Drug Comparison Charts book - 7th Edition. www.RxFiles.ca


[1] Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (**RECORD**): a multicentre, randomised, open-label trial. Lancet. 2009 Jun 20;373(9681):2125-35.

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