

Assessment of the cardiovascular risks and health benefits of rosiglitazone

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The questions of greatest importance to OSE

- 1° Does RSG increase the risk of CV events, most importantly, cardiac death, AMI, and stroke?
- 2° Does CV risk with RSG differ from that of PIO?
- 3° Does CV risk with RSG differ from that of other oral anti-diabetic agents (e.g., Met, SU)?

If answer to any question is "yes"

- Do the documented health benefits of RSG justify its cardiovascular risks?

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Randomized clinical trials data and the OSE question they help to address

Study	Comparison group	Of relevance to Question #
ADOPT	Active	3?
BARI 2D	Active	3?
DREAM	PBO	1,2
GLAI	PIO	2
PIO meta	Mixed	2
PROactive	PBO	2
RECORD	Active	3?
RSG meta	PBO	1,2

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Does rosiglitazone use increase the risk of cardiac death, AMI and stroke?

RSG meta-analysis
DREAM

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Overview of RSG meta-analysis and DREAM

RSG meta-analysis

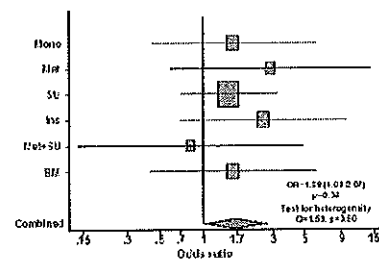
- 1° outcome: total and "serious" Ischemic Heart Disease
- Mean duration DM 5 yrs
- PBO add-on control accounted for 86% of RSG exposure-time; mean f/u ~6 mos
- *Post hoc* adjudication of routinely reported events

DREAM

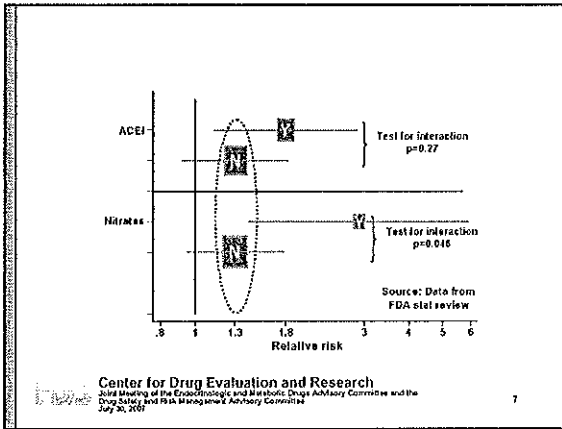
- Pre-diabetics; PBO-controlled; f/u ~4.5 years
- Adjudicated CV outcomes

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Meta-analysis of "serious" IHD risk with rosiglitazone from placebo-controlled clinical trials



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CV outcomes from DREAM by treatment arm

	RSG + ACEI	ACEI only	RSG only	PBO only
N	1310	1313	1325	1321
CV composite (%)	3.4	1.8	2.4	2.4
AMI (%)	0.8	0.2	0.4	0.5
CHF (%)	0.8	0.1	0.2	0.1

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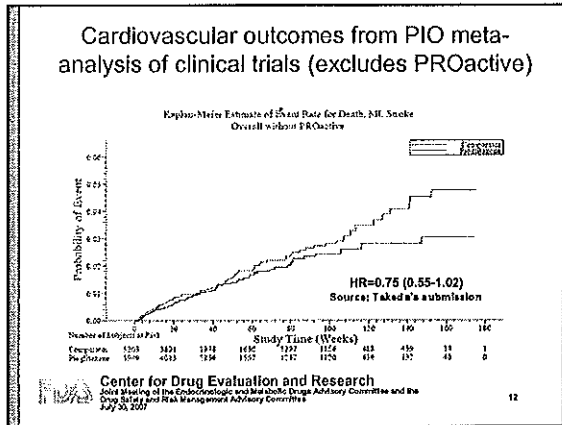
- Does RSG increase CV risk?
- Yes
 - FDA meta-analysis shows 20%-68% increased risk with 6-12 months RSG use compared to non-use, especially noticeable in the placebo-controlled analysis
 - DREAM shows ~40% increased risk with RSG
 - Relatively low-risk population; placebo-controlled
 - Uncertainty about what the possible ACEI "interaction" findings mean, but CV risk is increased
 - In 2006, 54% of RSG users took concomitant ACEIs or ARBs, and there is evidence to suggest that all patients with T2DM might benefit from their use
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Does rosiglitazone increase CV risk compared to pioglitazone?

PIO meta-analysis
 PROactive
 GLAI

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- Pioglitazone meta-analysis of clinical trials
- All randomized, double-blind, controlled trials in Takeda's clinical trials database excluding PROactive
 - 10,199 PIO patients; 11,247 PIO person-years
 - Submitted in Oct 2006; FDA review completed Jan 2007; FDA re-analysis not performed
 - Pre-specified patient-level, time-to-event analysis, stratified by category of study duration
 - 1st outcome: all deaths + nonfatal AMI + nonfatal CVA
 - Identified from standard RCT AE reporting process
 - N of adjudicated
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PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive)

- Randomized, double-blind, add-on PBO-controlled
- Mean follow-up: 34.5 months
- 1° outcome:
 - All-cause mortality, nonfatal AMI, nonfatal CVA, coronary revascularization, acute coronary syndrome, leg amputation, leg revascularization
 - HR = 0.90 (0.80-1.02)
- 2° outcome:
 - All-cause mortality, nonfatal AMI, nonfatal CVA
 - HR = 0.84 (0.72-0.98)

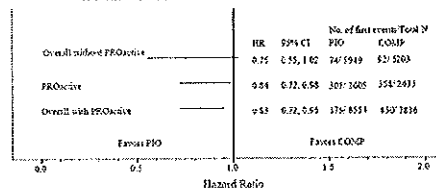
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Summary of meta-analysis of pioglitazone clinical trials including PROactive

Source: Takeda's submission

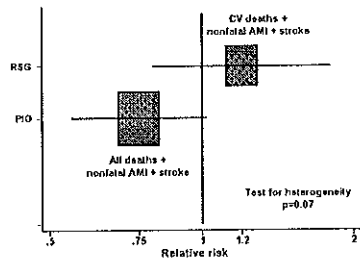
Figure 4.a Time to Composite Endpoint Events of All-cause Death, Nonfatal MI, or Nonfatal Stroke



No. Number of randomized subjects; PBO=Pioglitazone; COMP=Comparator.

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Study H6E-US-GLAI: head-to-head RSG vs. Pio

- Study results submitted to FDA Feb 2005 by Takeda
- FDA review completed November 2005
- Randomized, double-blind; 24 wks
- Assessment of lipid effects
- CV events collected; not adjudicated
 - Case report descriptions very convincing
- Balanced with respect to age (56 years), duration of T2DM (4 years), HgbA1c (7.6%); BMI (33)

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Does CV risk with RSG differ from that with PIO?

- Yes
 - From DREAM, relatively low-risk population: RSG increased risk by ~40% c/w PBO
 - From PROactive, high risk population: PIO decreased risk by ~15% c/w PBO
 - From RSG meta-analysis: RSG increased risk of serious IHD by ~40% c/w all comparators & by ~70% c/w PBO
 - From PIO meta-analysis: PIO decreased risk by ~25% c/w all comparators
 - From head-to-head GLAI: RSG increased risk 3.5-fold c/w PIO

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Does CV risk with rosiglitazone differ from that of metformin and sulfonylurea oral anti-diabetic agents?

ADOPT
RECORD
BARI 2D

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A Diabetes Outcome Progression Trial (ADOPT)

- Recently diagnosed T2DM (mean=1.1 yrs)
- All outcomes were efficacy-related
- No pre-specified CV outcomes
- No CV adjudication; *post hoc* arbitration of CHF

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Pertinent adverse event data from ADOPT

Source: N Engl J Med 2006; 355:2427-43

	RSG	Met	SU	Met+SU
N	1456	1454	1441	2895
CV disease (%)	3.4	3.2	1.8	2.5
AMI (%)	1.8	1.5	1.2	1.4
CHF (%)	1.5	1.3	0.6	1.0
CVA (%)	1.1	1.3	1.2	1.2
PVD (%)	2.5	1.9	2.2	2.0
Edema (%)	14.1	7.2	8.5	7.8

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Limitations of BARI 2D

- BARI 2D not designed to answer questions about specific drugs
- Assignment to RSG or metformin not blinded or random
- BARI 2D will not meaningfully inform the issue of RSG's CV risk *vis a vis* other oral anti-diabetes meds
- Markedly low statistical power for drug-specific CV risk questions
- The finding of increased risk in RSG + insulin meta-group may have implications for BARI 2D

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Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD)

- Randomized, non-inferiority, open-label, active-control
- Concerns:
 - *N oninferiority design has intrinsic limitations for safety
Suboptimal study execution related to AE identification and reporting could mask differences between groups
 - *N oninferiority margin too large (20%) & rationale not provided
 - *Open-label (increases bias potential)
 - *1° endpoint not focused on most important CV outcomes
 - *V ery low to absent statistical power

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Statistical power of ADOPT, BARI 2D, and RECORD to exclude a 20% increase in risk of cardiovascular death + AMI + stroke for RSG vs. Met

	ADOPT	BARI 2D	RECORD
Power to exclude RR=1.2	<10%	<10%	<10%

None of these studies will provide meaningful evidence about the comparative cardiovascular risk of rosiglitazone and metformin

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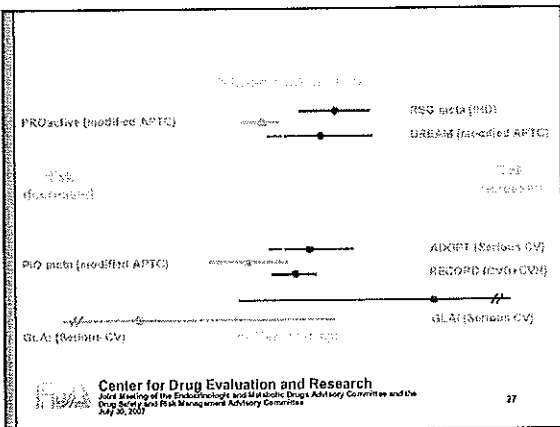
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The hidden dangers of low statistical power when dealing with a comparative safety issue

- Low power = high "type II" error rate
 - Probability of concluding that treatments are similar when they really differ
- Consequences of low power
 - Failure to conclude that treatments are similar when important differences in risk exist
 - Promotes a false sense of security and complacency
 - Leads to failure to take appropriate measures to protect patients from unnecessary harm
- "Absence of evidence is not evidence of absence"

Does the CV risk of RSG differ from that of metformin or sulfonylurea?

- The data provide inadequate and insufficient evidence to conclude that RSG does not increase CV risk compared to metformin or sulfonylureas
- Neither RECORD nor BARI 2D will provide meaningful answers to this question



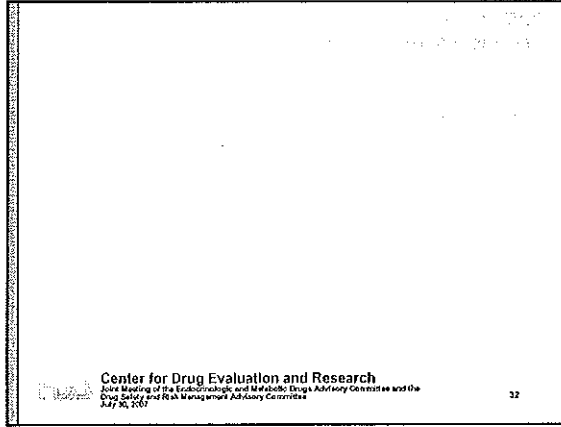
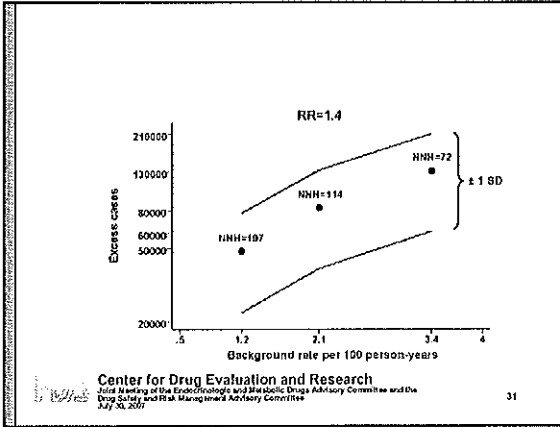
Population impact of cardiovascular risks and benefits of rosiglitazone use

Sources of data for estimation of excess cases of cardiovascular deaths and nonfatal AMI (1)

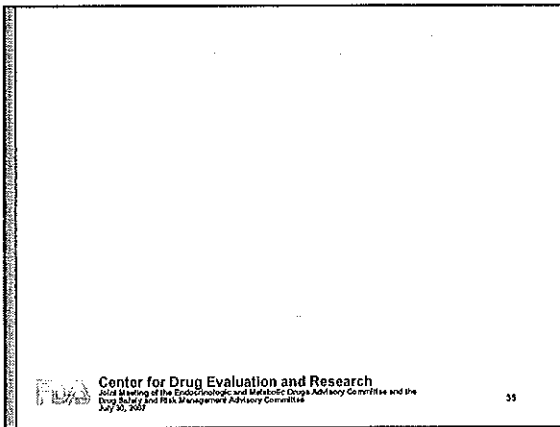
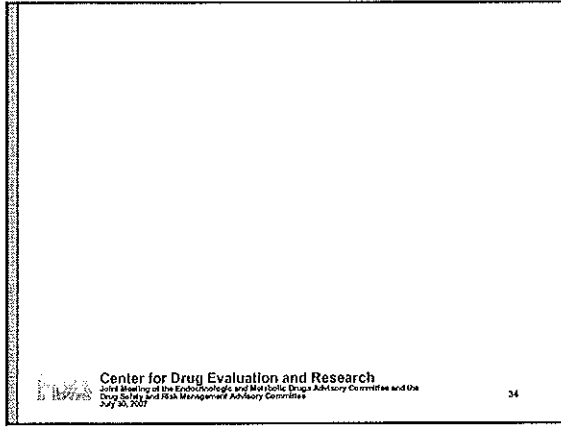
- Estimates of the relative risk for CV events obtained from RSG meta-analysis & DREAM
- Background rates of CV death + nonfatal AMI, and CV death + nonfatal AMI + nonfatal stroke from published literature
- National prescription data used to estimate person-years of RSG use (time at-risk)

Sources of data for estimation of excess cases of cardiovascular deaths and nonfatal AMI (2)

- Analysis accounted for variability in level of excess risk while focusing on range of most likely risk
 - By using three point estimates of relative risk
 - RR=1.2 ("MACE" RSG meta-analysis)
 - RR=1.4 (RSG meta-analysis; DREAM)
 - RR=1.7 (RSG meta-analysis of PBO-controlled data)
 - ± 1 standard deviation (68% confidence intervals)
- By using the inter-quartile range for the background event rates in diabetic patients



- ### RSG health benefit assessment (1)
- What benefits are we interested in?
 - How does RSG compare to PIO?
 - How does RSG compare to Met or SU?
 - Are there benefits unique to RSG?
 - Two systematic reviews provide insight
 - Bolen et al. Ann Intern Med 2007
Oral anti-diabetes agents
 - Bandeira-Echler et al. Cochrane Collaboration 2007
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- ### RSG health benefit assessment (4)
- No major clinical health benefits have been demonstrated for RSG
 - No macrovascular benefits
 - No microvascular benefits
 - RSG confers no clear advantage over other oral anti-diabetes drugs for a variety of intermediate outcomes
 - RSG confers no unique advantage over PIO and appears to be inferior to PIO with respect to some intermediate outcomes (HDL-C, LDL-C, triglycerides)
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Risks, benefits, and degree of certainty (1)

- At approval, "definitive proof" of efficacy obtained; health benefit is assumed, not demonstrated or "proven"
 - But efficacy measures often don't translate into long-term benefits
- When postmarketing safety concerns arise, reappraisal of "assumed benefit" is necessary; benefit-risk assessment must be made at the population-level
- "Actionable" threshold of evidence for serious risk is not "definitive proof"
 - Rarely possible due to statistical power (at least 95% power needed to minimize false negative conclusion)
 - Unreasonably high threshold, considering obligation to protect public from serious harm

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Risks, benefits, and degree of certainty (2)

- Despite uncertainty, the analysis must take into account the potential consequences of the risk, as well as the magnitude and certainty of health benefits
- Prior measures of efficacy often inadequate to justify serious risk; actual health benefits are essential
- For a health benefit to justify a serious risk, it must be clinically important and meaningful, of comparable or greater health-value, and of greater frequency of occurrence than the risk; and there must be definitive evidence to support the benefit.

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Decision analysis of RSG risks and benefits

- The cost of a wrong decision is not symmetric
 - First, absolutely no evidence of major clinical health benefits with RSG
 - If RSG increases CV risk, wrong decision will cost thousands of lives
 - If RSG doesn't increase CV risk, wrong decision causes no population harm; other therapies are available
- The data on RSG CV risk, though not definitive, strongly suggest the following:
 - RSG CV risk is increased (3 studies: RSG meta-analysis, DREAM, GLA1)
 - PIO CV risk is not increased, and may be decreased compared to other therapies including RSG (3 studies: PIO meta-analysis, PROactive, GLA1)
 - Other studies such as BARI 2D and RECORD will not provide adequate evidence to refute these findings

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Conclusions

- RSG increases cardiovascular risk compared to its non-use
- PIO does not increase cardiovascular risk
- RSG has no unique short-term benefits related to glycemic control
- RSG has no demonstrated long-term health benefits related to cardiovascular disease, diabetic retinopathy, nephropathy, or neuropathy
- Given these conclusions, are there definitively documented population-level health benefits of RSG to justify its continued marketing?
 - N o
 - R SG should be removed from the market

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