Rosiglitazone Cardiovascular Safety Meta-Analysis

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Outline

1. Background
2. Goals of analyses
3. Statistical analysis plan
4. Trial and patient summaries
5. Results
6. Summary

Background

- Previous FDA rosiglitazone meta-analysis (2007)
  - 42 trials
  - Total myocardial ischemia, OR=1.4, 95% CI [1.1, 1.8]
  - Serious myocardial ischemia, OR=1.4, 95% CI [1.0, 2.1]
  - MACE, OR=1.2, 95% CI [0.8, 1.9]
    - MACE (major adverse cardiovascular event): a composite endpoint comprised of MI, Stroke, CV death.
  - MI, OR=1.5, 95% CI [0.9, 2.7]
- No previous FDA pioglitazone meta-analysis

Goals of Rosiglitazone and Pioglitazone Meta-Analyses

1. To update the 2007 FDA meta-analysis of rosiglitazone of 42 trials with 10 additional trials
2. To conduct a parallel pioglitazone meta-analysis in order to compare indirectly the cardiovascular safety of the rosiglitazone and pioglitazone in short-term trials

Trial Inclusion: General Considerations

- Overall safety picture from clinical trials requires consideration of both short-term and long-term trials for each drug
- 2007 FDA analyses considered large and small trials separately.
  - Large trials (DREAM, ADOPT, RECORD) viewed as independent sources of information and were analyzed individually
  - These large trials would dominate meta-analyses
  - Meta-analysis was used to evaluate the information provided from the smaller trials
- 2010 FDA meta-analyses did not include large trials
  - Large trials continued to be viewed as independent sources of information
  - Large trials were not comparable between the drugs

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Statistical Analysis Plan: General Considerations

- Parallel plans for rosiglitazone and pioglitazone meta-analyses
- Recognition that trial designs and patient populations differ between the two drugs
- Use of trial-level groups to aid comparability between the two drugs
- Stratifying by trial to preserve randomized comparisons between treatment groups

Statistical Analysis Plan: Outline

- Trial inclusion criteria
- Endpoints
  - Primary
  - Secondary
- Trial-level groups
- Subgroups
- Methods
  - Primary
  - Sensitivity

Trial Inclusion Criteria

- All trials taken from GSK (rosiglitazone) and Takeda (pioglitazone) databases
- Inclusion criteria:
  - Randomized comparator
  - 2 months-2 years
  - Current diabetics
  - Double blind
  - Total daily dose
    - Rosiglitazone: 4 and 8 mg
    - Pioglitazone: 30 and 45 mg
  - Centrally monitored
  - Patient level data available
  - Investigative drugs were FDA approved

Endpoints

- Primary
  - MACE: CV death, stroke or myocardial infarction (MI)
- Secondary
  - CV death
  - Stroke
  - MI
  - All-cause death
  - Serious myocardial ischemic events
  - Total myocardial ischemic events
  - Congestive heart failure (CHF)

Example of Trial-Level Groups

- Example: rosi. + met. vs. placebo + met.
  - Placebo controlled trial
  - Metformin add-on trial
- Multi-arm trials (≥ 3) may contribute to more than one trial-level group.

Trial-Level Groups (1)

- Randomized comparator groups
  - Placebo controlled
  - Active controlled
  - Sulfonylurea controlled
  - Metformin controlled

Trial-Level Groups (2)

- Add-on therapy groups
  - Monotherapy
  - Background medication
  - Sulfonylurea add-on
  - Metformin add-on
  - Insulin add-on
  - Sulfonylurea+Metformin add-on
  - Add-on or background therapy trials
- Trial duration
  - ≤6 months, 6- ≤12 months, 12- ≤24 months

Subgroup Analysis

- Demographics
  - Age: <65, ≥ 65
  - Sex
  - BMI: ≤ 30, >30
  - Location: US, Non-US
- Baseline medications
  - Nitrates
  - ACE Inhibitors
  - Loop diuretic
  - Beta-blockers
  - No. of CV medications: ≤ 2, >2
- Prior conditions
  - History of coronary heart disease (CHD)
  - History of CHD and nitrates
  - History of CHF
  - Previously treated for diabetes vs. naïve
  - No. of major CV risk conditions: 0,1, ≥ 2
  - Duration of diabetes
- Dose
  - Rosi: 4, 8 mg
  - Pio: 30, 45 mg

Primary Statistical Analysis Method

- Exact stratified odds ratio (OR)
  - Consistent with 2007 FDA meta-analysis
  - Assumes common OR across trials
  - Stratified by trial to maintain within-trial randomization
  - Trials with zero events in both arms do not contribute to estimate

Sensitivity Analyses: Statistical Methods

- Mantel-Haenszel risk difference
  - Incorporates information from trials with zero events
  - Stratified by trial
- Proportional hazards regression
  - Accounts for different follow-up times and hazard patterns
  - Stratified by trial
- Generalized linear mixed model
  - Used to examine the effect of trial heterogeneity
- Kaplan-Meier survival curves

Limitations of Meta-Analyses

- Most trials were not prospectively designed to evaluate cardiovascular endpoints
- Results of trials were known before statistical analysis plan was developed
- Statistical significance was not adjusted for multiple testing
- Comparisons between the two meta-analyses are subject to the deficiencies of cross-trial comparisons

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Rosiglitazone Trial Summary: Randomized Comparator Groups

Randomized control	Trials N=52	Control N=6956 n (%)	Rosiglitazone N=10039 n (%)	Total N=16995 n (%)
Placebo	46	5636 (81)	8124 (81)	13760 (81)
Active	13	1918 (28)	2119 (21)	4037 (24)
Sulfonylurea	8	1457 (21)	1649 (16)	3106 (18)
Metformin	4	302 (4)	311 (3)	613 (4)

Rosiglitazone Trial Summary: Duration Groups

Trial duration	Trials N=52	Control N=6956 n (%)	Rosiglitazone N=10039 n (%)	Total N=16995 n (%)
> 2 m to ≤ 6 m	40	4716 (68)	7068 (70)	11784 (69)
> 6 m to ≤ 1 y	10	1792 (26)	2524 (25)	4316 (25)
> 1 y to ≤ 2 y	2	448 (6)	447 (4)	895 (5)

Rosiglitazone Patient Summary: Baseline Characteristics

Characteristic		Total N=16995 n (%)
Age	< 65	12069 (71)
	Mean (Std.)	58 (10)
	Range (min-max)	(26-88)
Gender	Male	10059 (59)
Location	United States	7450 (44)
Body mass index	< 30	8822 (52)
	Mean (Std.)	30 (6)
	Range (min-max)	(16-75)

Rosiglitazone Patient Summary: Treatment Duration

Treatment Duration (d)	Control N=6956 n (%)	Rosiglitazone N=10039 n (%)	Total N=16995 n (%)
Mean (Std.)	191 (122)	186 (112)	188 (116)
Range (min-max)	(1-758)	(1-758)	(1-758)
Least-squares mean	174	179	

Rosiglitazone Event Summary: Primary Analysis Set (52 trials)

Endpoint	Control N=6956 n (%)	Rosiglitazone N=10039 n (%)	Total N=16995 n (%)
MACE	39 (0.6)	70 (0.7)	109 (0.6)
CV death	9 (0.1)	17 (0.2)	26 (0.2)
MI	20 (0.3)	45 (0.4)	65 (0.4)
Stroke	16 (0.2)	18 (0.2)	34 (0.2)
All-cause death	17 (0.2)	29 (0.3)	46 (0.3)
Serious M.Isch.	66 (0.9)	118 (1.2)	184 (1.1)
Total M.Isch.	132 (1.9)	221 (2.2)	353 (2.1)
CHF	40 (0.6)	88 (0.9)	128 (0.8)

Rosiglitazone Event Summary: 10 New Trials

Endpoint	Control N=1323 n (%)	Rosiglitazone N=1435 n (%)	Total N=2758 n (%)
MACE	8 (0.6)	13 (0.9)	21 (0.8)
CV death	3 (0.2)	1 (0.1)	4 (0.2)
MI	4 (0.3)	7 (0.5)	11 (0.4)
Stroke	2 (0.2)	5 (0.4)	7 (0.3)
All-cause death	8 (0.6)	6 (0.4)	14 (0.5)
Serious M. Isch.	26 (2.0)	23 (1.6)	49 (1.8)
Total M. Isch.	50 (3.8)	41 (2.9)	91 (3.3)
CHF	6 (0.5)	8 (0.6)	14 (0.5)

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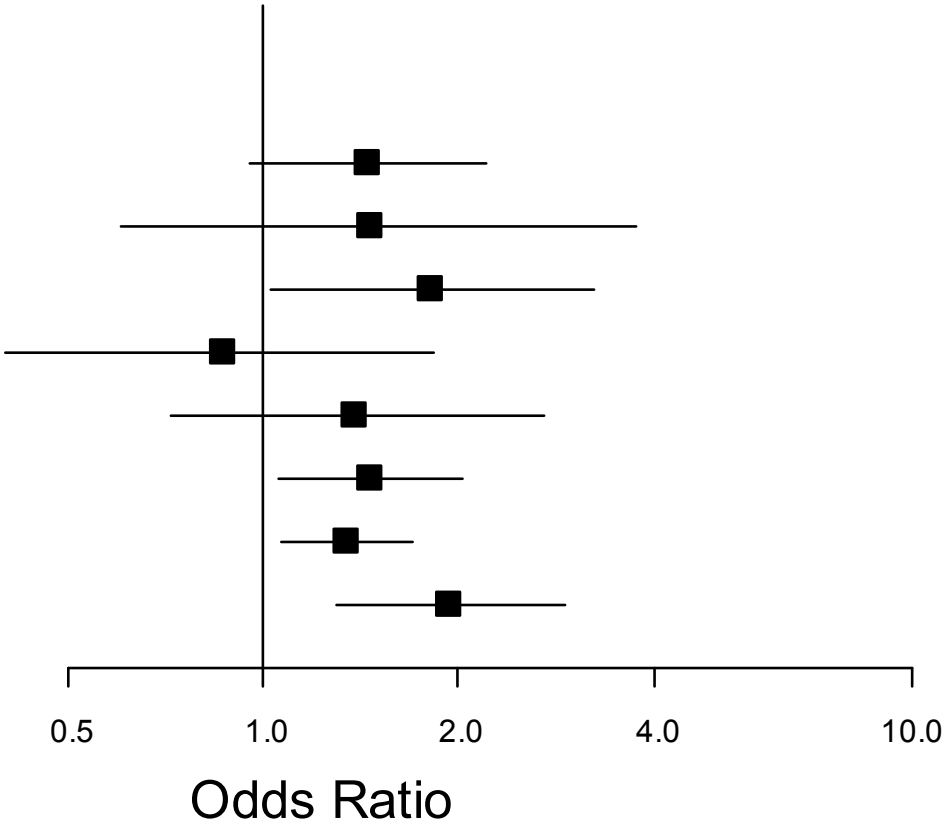
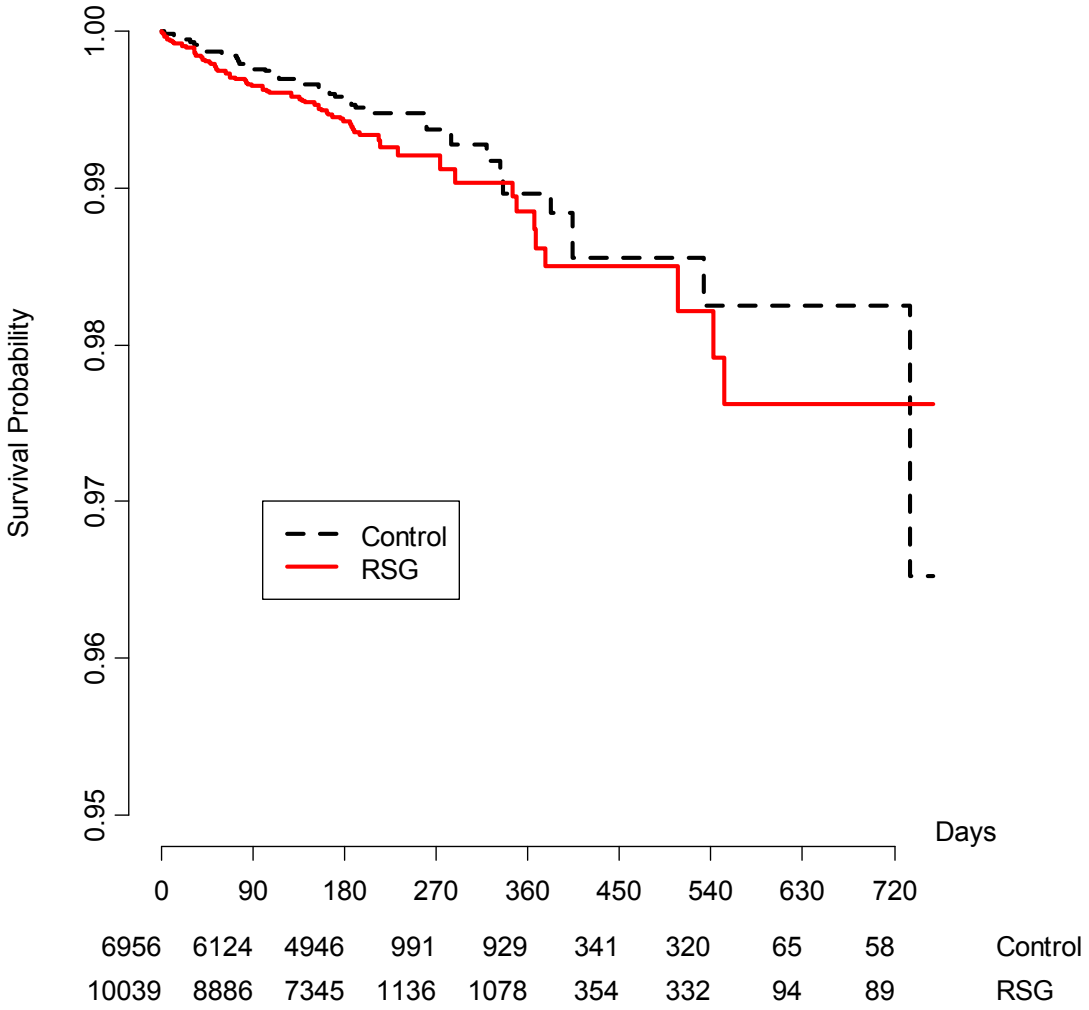
Rosiglitazone Meta-Analysis Results: Primary Analysis Set, All Outcomes

Outcome	OR (95%CI)
MACE	1.44 (0.95,2.20)
CV death	1.46 (0.60,3.77)
MI	1.80 (1.03,3.25)
Stroke	0.86 (0.40,1.83)
All-cause death	1.38 (0.72,2.72)
Serious M.Isch.	1.46 (1.06,2.03)
Total M.Isch.	1.34 (1.07,1.70)
CHF	1.93 (1.30,2.93)

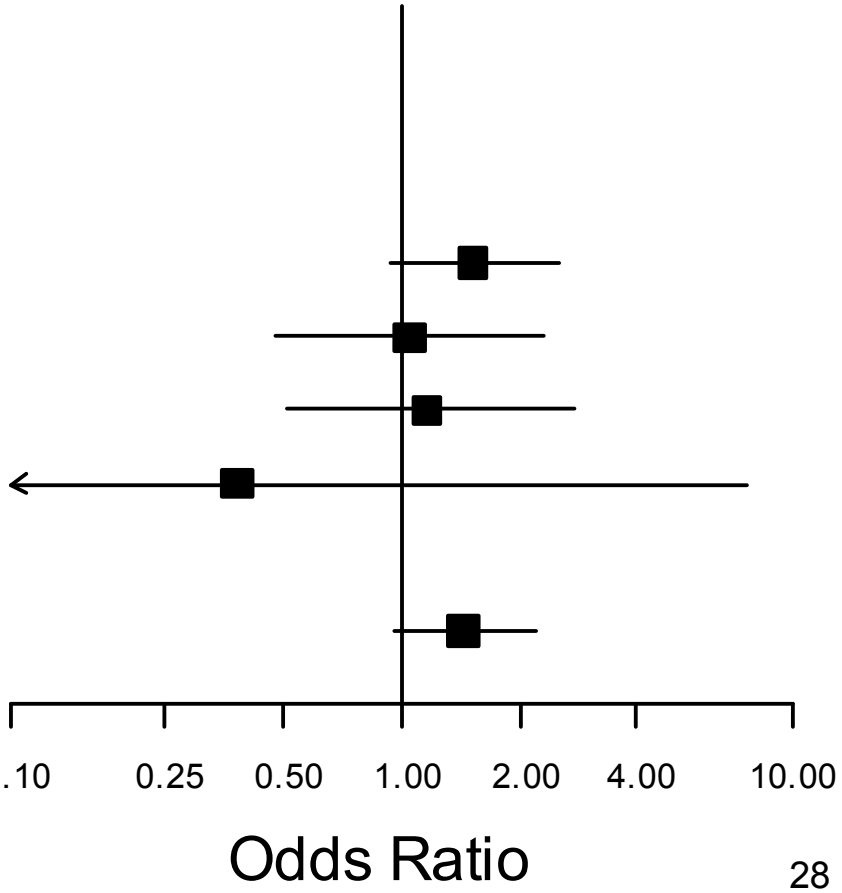


Rosiglitazone Kaplan-Meier, Primary Analysis Set: MACE



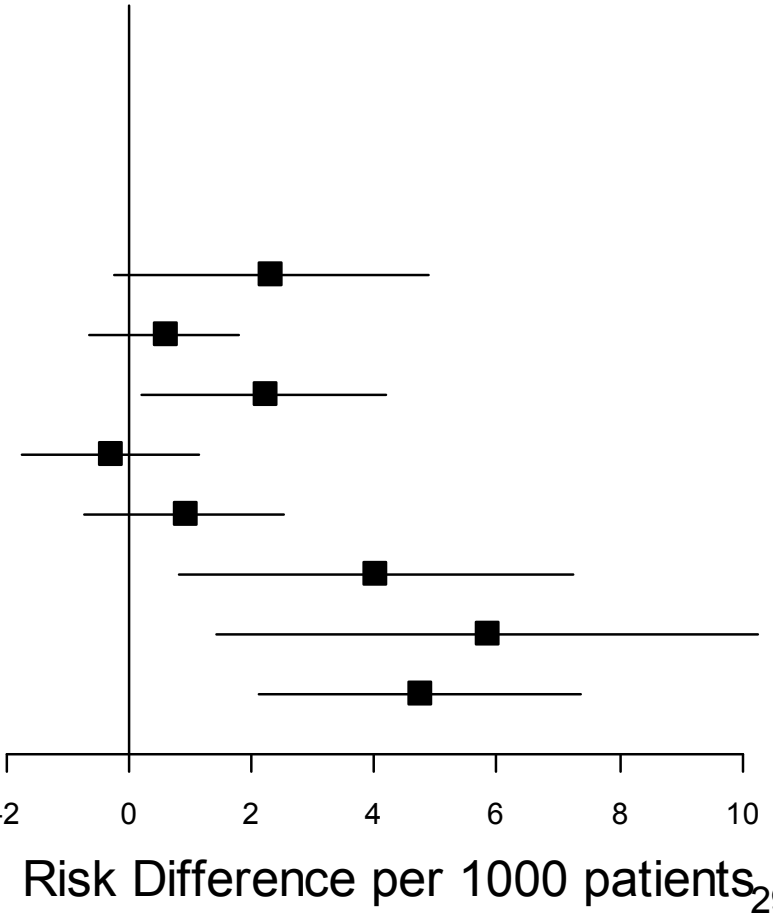
Rosiglitazone Meta-Analysis Results: MACE by Randomized Comparator Groups

Randomized control	OR (95%CI)
Placebo	1.53 (0.94,2.54)
Active	1.05 (0.48,2.34)
Sulfonylurea	1.17 (0.51,2.77)
Metformin	0.38 (0.01,7.63)
Overall	1.44 (0.95, 2.20)



Rosiglitazone Sensitivity Analysis: Risk Difference, All Outcomes

Outcome	Risk Difference per 1000 patients (95% CI)
MACE	2.31 (-0.25,4.87)
CV death	0.57 (-0.66,1.81)
MI	2.20 (0.21,4.19)
Stroke	-0.32 (-1.77,1.13)
All-cause death	0.90 (-0.72,2.52)
Serious M.Isch.	4.02 (0.80,7.24)
Total M.Isch.	5.84 (1.44,10.25)
CHF	4.73 (2.10,7.37)



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Rosiglitazone 2007 and 2010 FDA Meta-Analyses, All Outcomes

Outcome	2007, 42 trials N=14237 OR (95% CI)	2010, 52 trials N=16995 OR (95% CI)
MACE	1.2 (0.8,1.9)	1.4 (0.9,2.2)
CV death	1.7 (0.7,5)	1.5 (0.6,3.8)
MI	1.5 (0.9,2.7)	1.8 (1.0,3.3)
Stroke	0.6 (0.2,1.2)	0.9 (0.4,1.8)
All-cause death	1.7 (0.8,4)	1.4 (0.7,2.7)
Serious M.Isch.	1.4 (1.0,2.1)	1.5 (1.1,2.0)
Total M.Isch.	1.4 (1.1,1.8)	1.3 (1.1,1.7)
CHF	-	1.9 (1.3,2.9)

GSK Analysis, 2010

- Patients pooled across all trials, randomized comparisons not preserved
- Proportional hazards regression to estimate hazard ratio (HR)
- Different definitions of outcomes

FDA Meta-Analysis and GSK Analysis, 2010 (52 trials)

Outcome	FDA N=16995 OR (95% CI)	FDA N=16995 HR (95% CI)	GSK N=16995 HR (95% CI)
MACE	1.4 (1.0, 2.2)	1.4 (1.0, 2.1)	1.1 (0.9,1.4)
Total Myocardial Ischemia	1.3 (1.1,1.7)	1.3 (1.1,1.6)	1.1 (0.8,1.6)

Summary

- No statistically significant increase in risk for MACE, lower limit close to 1:
  - OR=1.44, 95% CI (0.95, 2.20).
- 2010 FDA results reinforced 2007 FDA results:
  - MI: OR=1.80, 95% CI (1.03,3.25)
  - Serious M. Ischemia: OR=1.46, 95% CI (1.06,2.03)
  - Total M. Ischemia: OR=1.34, 95% CI (1.07,1.70)
  - CHF: OR=1.93, 95% CI (1.30,2.93)

QUESTIONS