# Advisory Committee Meeting
# Avandia® (rosiglitazone maleate)
## June 5 and 6, 2013

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**Division of Metabolism and Endocrinology Products**
**Office of Drug Evaluation II**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**

# Outline of Presentation

- **2007**
  - **Events leading up to the 2007 AC meeting for Avandia**
  - **Data presented at 2007 AC meeting***
  - **Recommendations from 2007 AC meeting**
  - **Regulatory decisions made**
- **2010**
  - **Events leading up to the 2010 AC meeting**
  - **Data presented at 2010 AC meeting***
  - **Recommendations from 2010 AC meeting**
  - **Regulatory decisions made**
- **2013**
  - **Events leading up to today's AC meeting**
  - **Purpose of 2013 AC meeting**
- **Discussion Points/Questions to AC panel members**

*http://www.fda.gov/ohrms/dockets/ac/cder07.htm#EndocrinologicMetabolic

# Genesis of Ischemic Risk Potential Associated with Rosiglitazone

- December 2003 WHO report of data mining signal for increased cardiac risk, including heart failure, for the TZDs
- GSK initiated a meta-analysis (MA) of rosiglitazone controlled clinical trials w/ final report of MA on 42 controlled clinical trials submitted to FDA in August 2006
- Separate MA published in NEJM in June 2007 by Nissen and Wolski
- Together, these meta-analyses were viewed as a signal for CV risk associated with rosiglitazone

# July 30, 2007 Joint Advisory Committee Meeting on Avandia®

**FDA presentations focused on:**

- **Meta-analysis of 42 controlled clinical trials***
- **CV safety data from long-term controlled clinical trials (DREAM, ADOPT, RECORD)**
- **CV safety data from observational studies comparing rosiglitazone to other anti-diabetic therapies**
- **Cross-study comparisons between rosiglitazone and pioglitazone**

***FDA presentations on meta-analyses for 2013 AC will focus <u>only</u> on those MAs performed by FDA**

# Characteristics of FDA's MA Presented in 2007

- Comprised of 14,237 patients (8604 RSG; 5633 nonRSG)
- All studies were randomized, double-blind, and controlled
- 38 studies were </= 6 mos
- No prospective adjudication of CV events by blinded endpoints committee (except one study) --- trials were designed to assess glycemic control
- CV events were collected from AEs reported on CRFs; reviewed retrospectively with many terms nonspecific for cardiac ischemia
- Heterogenous patient population (tx-naïve vs long-standing DM, monotx vs combination tx)
- Control group varied (placebo, active - only metformin and/or SUs served as comparator)

# Results of FDA 2007 Meta-analysis

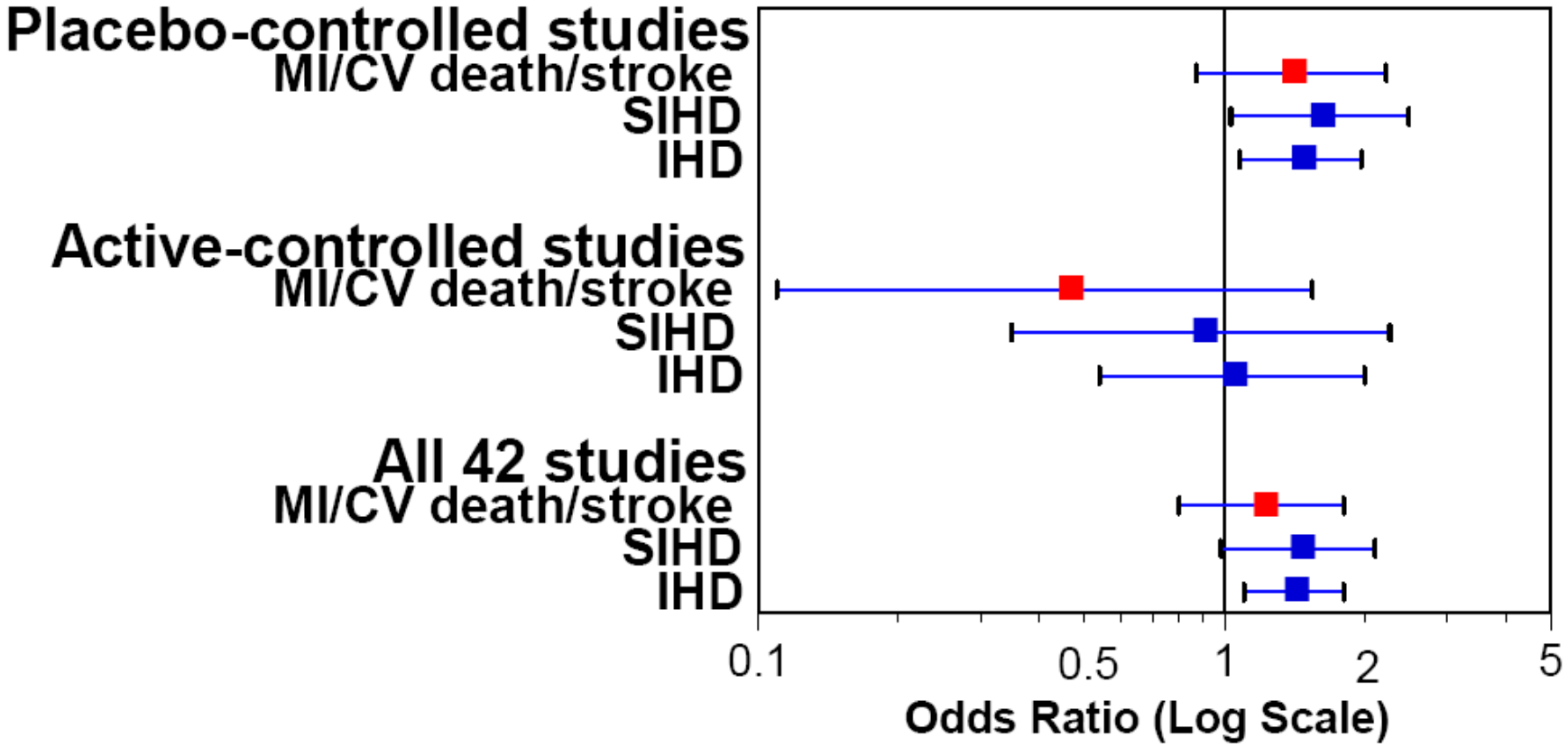
| | RSG N=8604 | Control N=5633 | OR (95% CI) | p-value |
|---|---|---|---|---|
| **IHD** | 2% | 1.5% | 1.4 (1.1-1.8) | 0.02 |
| **SIHD** | 1% | 0.8% | 1.44 (0.98-2.1) | 0.06 |
| **MACE** | 0.73% | 0.67% | 1.2 (0.7-1.8) | 0.4 |



**IHD = ischemic heart disease; SIHD = serious ischemic heart disease; MACE = CV death, NFMI, NFstroke**
**Events based on non-specific AE terms**

# Results of FDA 2007 Meta-analysis

## RSG vs Placebo or Active Control (met/su)




**Increased CV ischemic risk w/ RSG observed in placebo-controlled trials but not observed in active-controlled trials which compared RSG to metformin or SUs**

# Long-term Controlled Trials (LCCT)

## N=14,067

**DREAM**

- 2x2 factorial design in prediabetics comparing rosi vs pbo and rosi+ramipril vs ramipril in the prevention of T2DM
- N=5269; median duration of f/u 3.0 yrs
- Primary endpoint: composite of progression to diabetes and all-cause mortality
- Secondary endpoints included CV events adjudicated by a blinded CEC

**ADOPT**

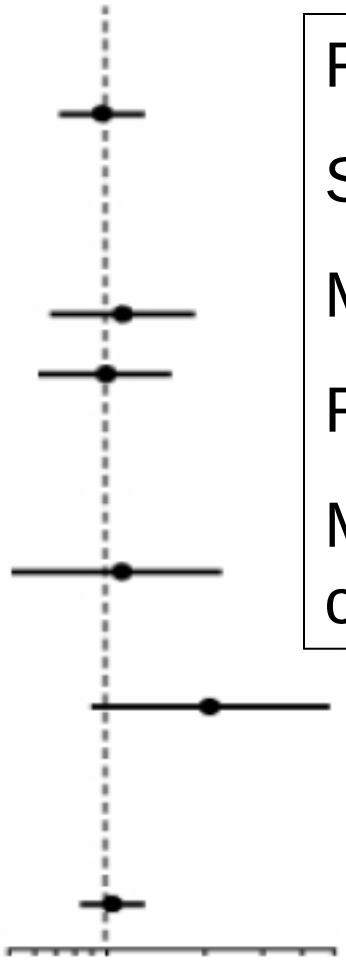
- Active control trial in treatment naïve diabetics to evaluate rate of monotherapy failure (rosi vs metformin or SU
- N=4351; median duration of tx 4 .0 yrs
- Primary endpoint: time to glycemic control failure of monotherapy
- CV events collected as adverse events, not adjudicated by blinded CEC

**RECORD (interim analysis as of 2007)**

- Ongoing, active control trial evaluating CV events between Met+RSG vs Met+SU and SU+RSG vs SU+Met
- N=4447, current status 3.75 yrs mean follow-up
- Primary endpoint: composite of CV death and CV hospitalization
- CV events adjudicated by blinded CEC

# Overall Findings from 3 LCCTs: MACE (2007)

| | N | n % |
|---|---|---|
| **RECORD** (interim data) | | |
| RSG+SU or MET | 2220 | 93 (4.2%) |
| vs SU+MET | 2227 | 96 (4.3%) |
| **ADOPT** | | |
| RSG | 1456 | 35 (2.4%) |
| vs SU | 1441 | 28 (1.9%) |
| vs MET | 1454 | 36 (2.5%) |
| **DREAM** | | |
| RSG | 1325 | 15 (1.1%) |
| vs placebo | 1321 | 14 (1.1%) |
| RSG+RAM | 1310 | 18 (1.4%) |
| vs RAM | 1313 | 9 (0.7%) |
| **All** | | |
| RSG | 6311 | 161 (2.6%) |
| vs control | 7756 | 183 (2.4%) |



favors rosiglitazone ← 0.5 1 5 → favors controls

RSG – rosiglitazone

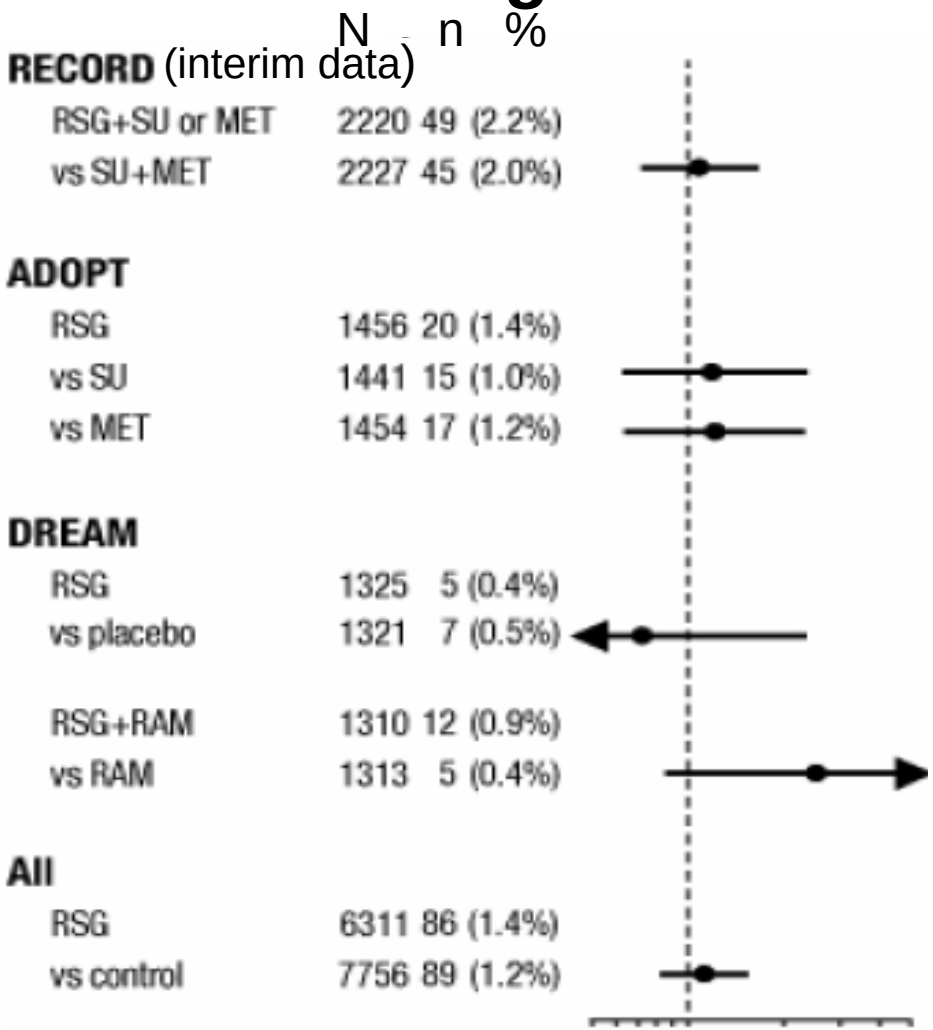
SU – sulfonylurea

MET – metformin

RAM – ramipril

MACE – major adverse cardiovascular events

# Overall Findings from 3 LCCTs: MI (2007)




RSG – rosiglitazone

SU – sulfonylurea

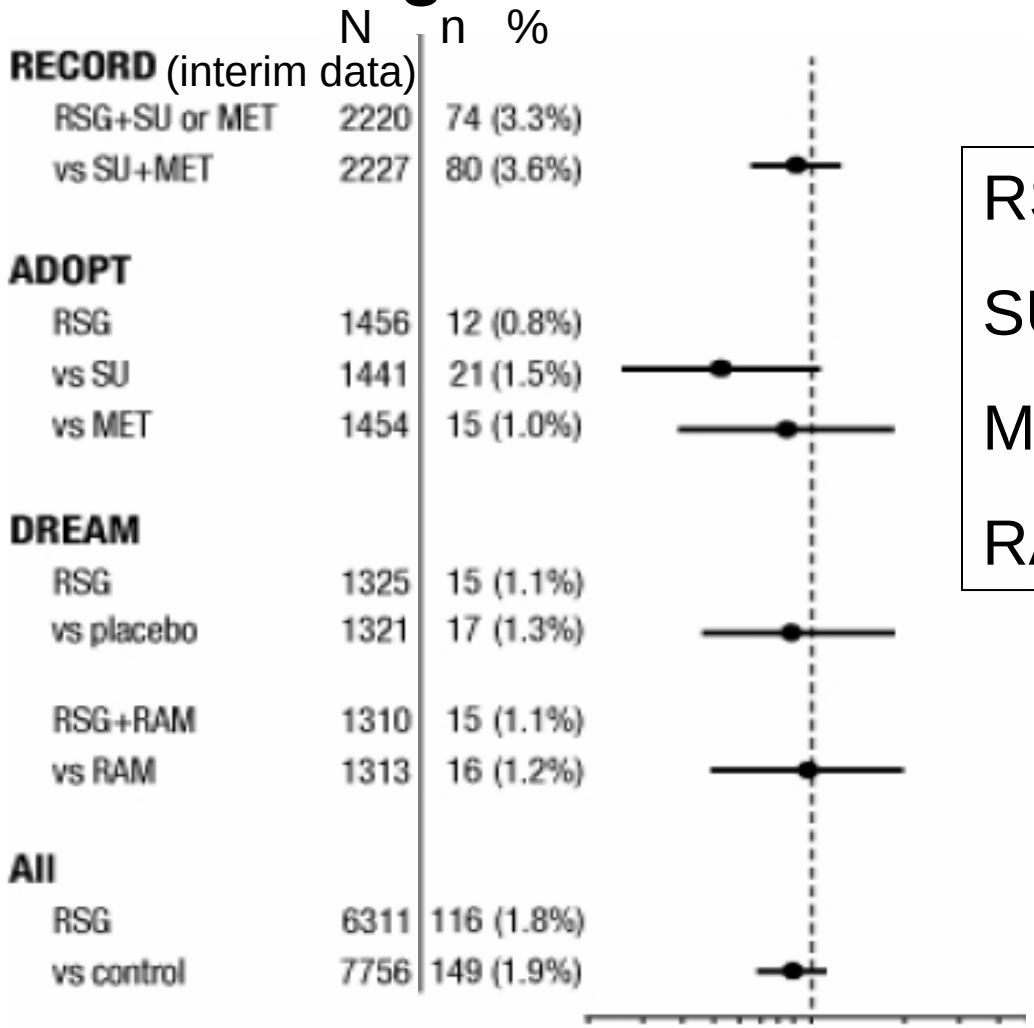
MET – metformin

RAM – ramipril

MI – myocardial infarction

favors rosiglitazone ← 0.5 1 5 → favors controls

# Overall Findings from 3 LCCTs: Mortality (2007)




RSG – rosiglitazone

SU – sulfonylurea

MET – metformin

RAM – ramipril

favors rosiglitazone ← 0.2 0.5 1 5 → favors controls

# Rosiglitazone vs Pioglitazone, 2007

- Pioglitazone (Actos) is the only other marketed TZD
- PROactive (Prospective Clinical Trial in Macrovascular Events)
  - CV outcomes trial in 5238 patients w/ T2DM and macrovascular disease comparing pioglitazone to placebo added on to current anti-diabetic therapies
  - Primary endpoint: composite of all-cause death, NFMI (including silent MI), stroke, ACS, cardiac intervention (CABG or PTCA), major leg amputations (AKA), or bypass surg/revasc procedure in the leg.
  - Late amendment to protocol 4 mos after trial cessation made all-cause death, NFMI, and stroke a major $2^0$ endpoint
  - FDA updated labeling of pioglitazone in 2/07 to include results from PROactive. No claim of CV benefit granted but labeling noted 'no increase in mortality or in total macrovascular events with Actos'
- No CVOT directly comparing the two TZDs

# PROactive Results*

| Endpoint | Add-On PIO N=2605 n (%) | Add-on PBO N=2605 n (%) | HR (95% CI), p-value |
|---|---|---|---|
| Primary composite | 514 (19.7%) | 572 (21.7%) | 0.90 (0.80, 1.02), p=0.10 |
| CV mort (predefined II°) | 127 (4.9%) | 136 (5.2%) | 0.94 (0.74, 1.20), p=0.62 |
| All-cause mort + MI + stroke (II°) | 301 (11.6%) | 358 (13.6%) | 0.84 (0.72, 0.98), p=0.03 |

***Presented by Dr. Karen Mahoney at July 2007 Avandia AC meeting**

# Results of 2007 AC Panel Voting Questions

**Panel was asked to comment on the strengths and limitations of the data presented followed by two voting questions:**

1. **Do the available data suggest* a conclusion that Avandia increases cardiac ischemic risk in T2DM?**

   **20 voted yes; 3 voted no**

2. **Does the overall risk-benefit profile of Avandia support its continued marketing in the U.S.?**

   **22 voted yes; 1 voted no**

***Original question had "support" which was changed by panel members to "suggest"**

# Regulatory Decisions Post 2007 AC Meeting

- October 13, 2007 –Center-Level decision that rosi would remain on the market
- In a memo dated January 2, 2008, to OND and OSE Directors, the Center Director concluded that:
  - Rosiglitazone should not be withdrawn from the market
  - A boxed warning to discuss the risk of MI was needed
  - A Medication Guide was needed
  - The Warnings section of labeling needed to discuss individual risk factors which might contribute to excess CV harm with rosiglitazone
  - "The firm should be required to begin and promptly execute a study comparing their drug to pioglitazone…"
- GSK initiated the required postmarketing trial, Thiazolidinedione Intervention and Vitamin D Evaluation (TIDE) in 2009

# Guidance for Industry

## Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

# July 13-14, 2010 Joint Advisory Committee Meeting on Avandia®

- **Prompted by the completion of RECORD and submission of results to FDA in August 2009**
- **FDA presentations focused on:**
  - **RECORD results with presentations given by Division of Metabolism/Endocrine (DMEP), Office of Biostatistics (OB), and Division of Cardio/Renal (DCRP), and Office of Scientific Investigations (OSI)**
  - **An updated MA of 52 controlled trials of rosi using patient-level data performed by FDA**
  - **MA of 29 controlled trials of pio using patient-level data performed by FDA**
  - **Update on new epi data since 2007 with studies specifically evaluating rosi and pio**
  - **Retrospective cohort study of claims data from CMS to compare rosi to pio on selected CV endpoints**

# July 13-14, 2010 Joint Advisory Committee Meeting on Avandia®

- In addition to FDA presentations, guest presentations were given by:
  - Dr. Steve Nissen (Cleveland Clinic)
    - His updated MA and Personal Overview/Perspective
  - Dr. Maria Brooks (Univ of Pittsburgh)
    - BARI-2D – Bypass Angioplasty Revascularization Investigation 2 Diabetes
  - Dr. Thomas Moritz (Edward Hines Jr. VA Hospital)
    - VADT – Veterans Affairs Diabetes Trial
  - Dr. Hertzel Gerstein (McMaster University)
    - TIDE – Thiazolidinedione Intervention and Vitamin D Evaluation
  - Dr. Dean Follman (NIAID/NIH)
    - Strengths/limitations of data from controlled trials, observational studies, meta-analyses
  - Dr. Ruth Faden (Johns Hopkins Berman Institute of Bioethics)
    - IOM (Institute of Medicine) Report
  - Dr. Steven Goodman (Johns Hopkins School of Medicine)
    - IOM Report

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

- **A CVOT designed to meet EMA postmarketing requirement; not conducted under U.S. IND (trial was initiated in 2001)**
- **Open-label trial designed to evaluate the CV safety of rosi plus either met or SU to met+SU**
- **Primary endpoint was composite of CV death and CV hospitalization**

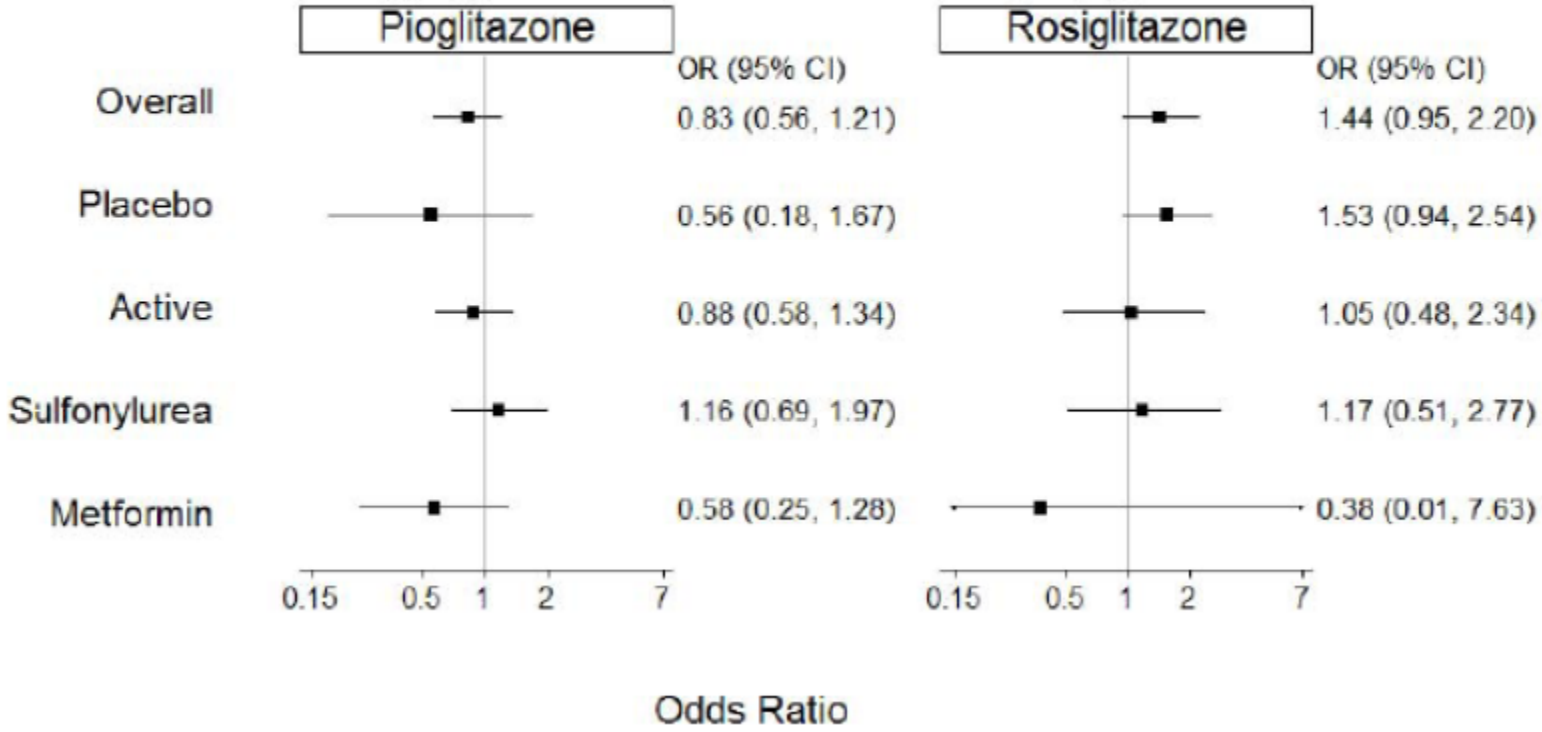
# RECORD
## (results from final study report)

| | HR (95% CI) |
|---|---|
| CV death and CV hospitalization | 0.99 (0.85, 1.16) |
| CV death | 0.84 (0.59, 1.18) |
| Myocardial infarction | 1.14 (0.80, 1.63) |
| Stroke | 0.72 (0.49, 1.06) |

**The design and conduct of RECORD led some to question the interpretability of the results**

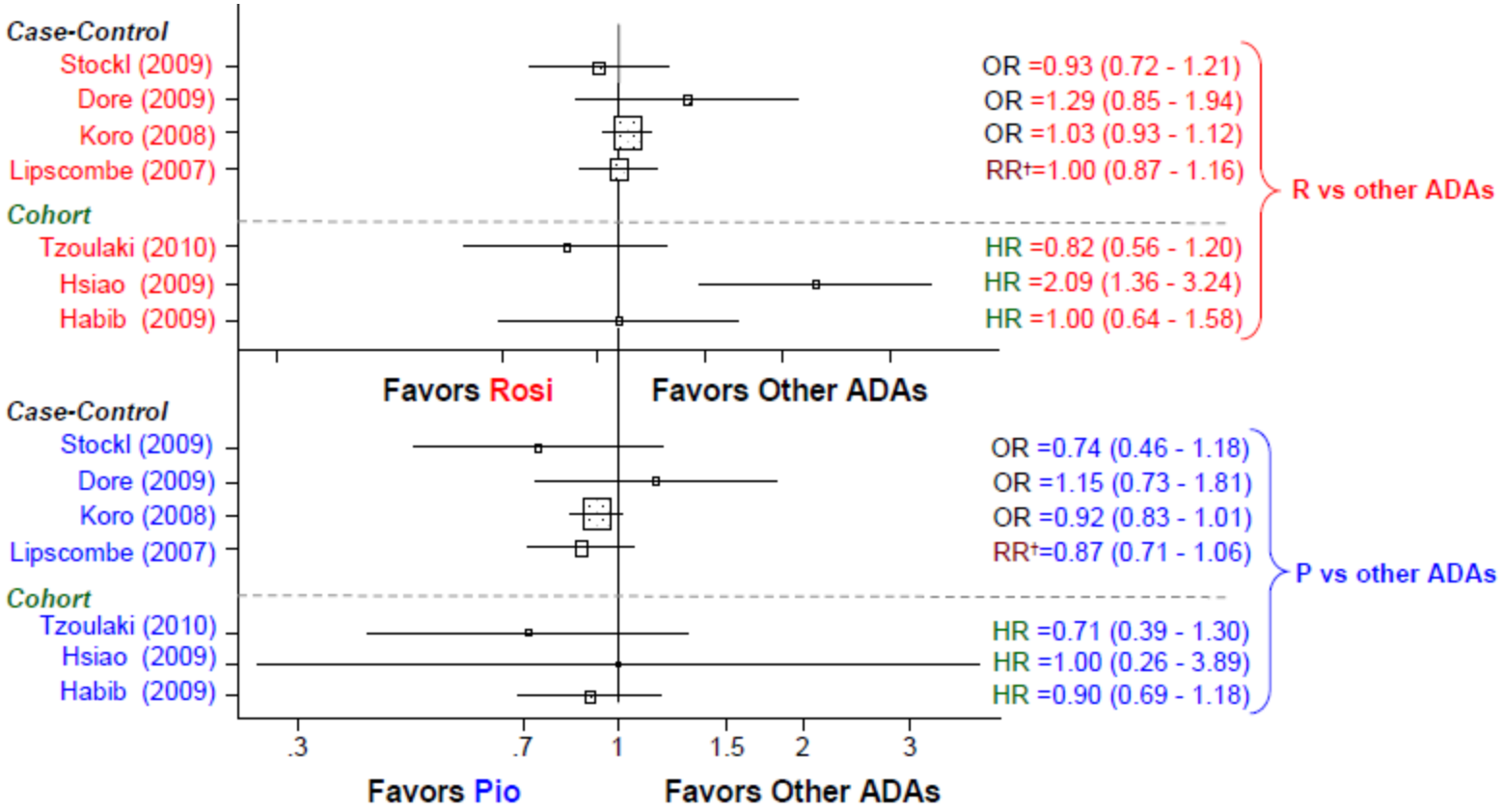
# Updated FDA Meta-analyses of Rosi and Pio Trials (2010)

**Figure 1. Overall Results of Meta-analyses for Pioglitazone and Rosiglitazone on MACE Endpoints (Forest Plot created by Dr. Bradley McEvoy and presented at July 13 and 14, 2010 advisory committee meeting)**

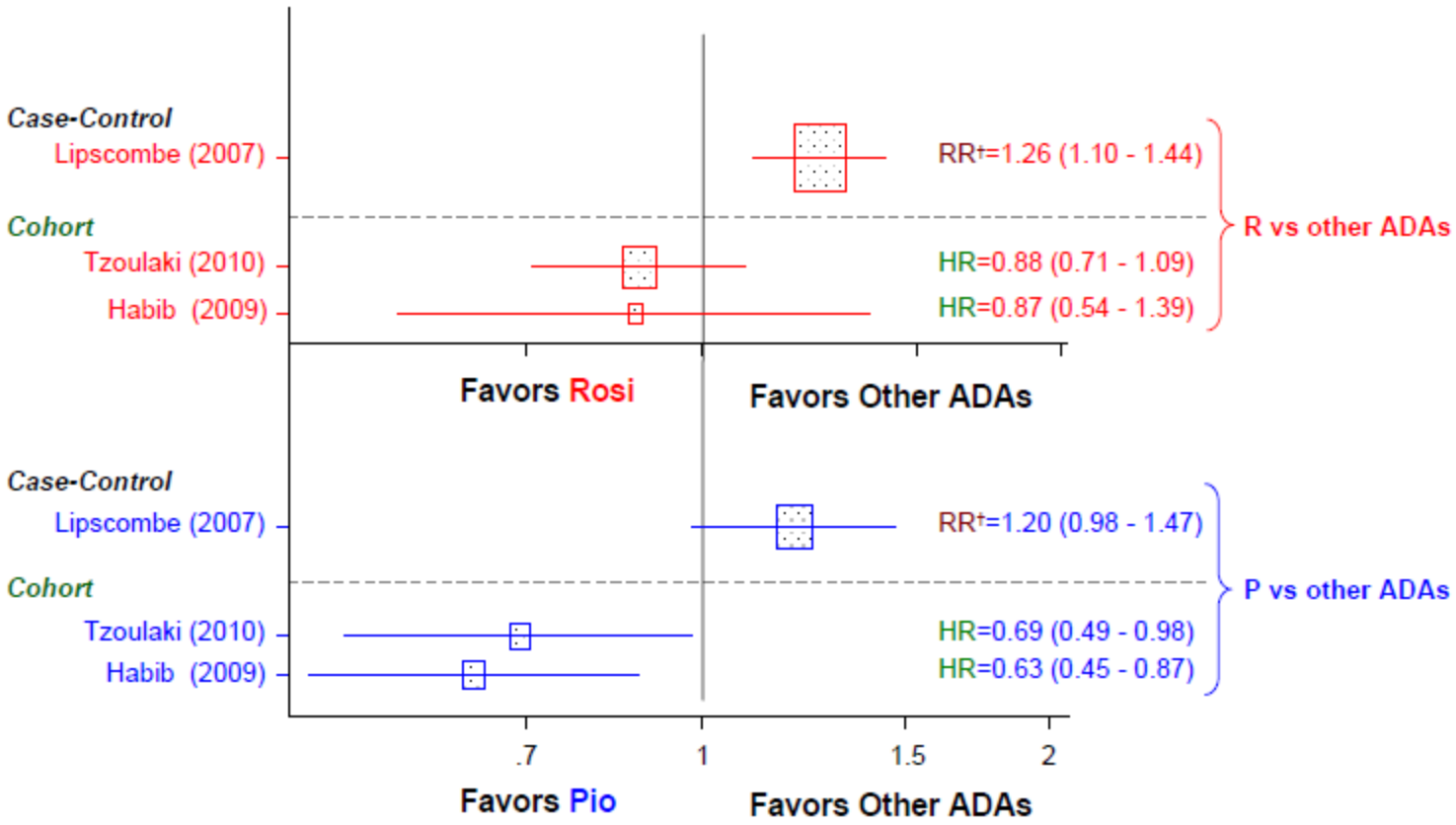


# Observational Studies: Review of Published Literature

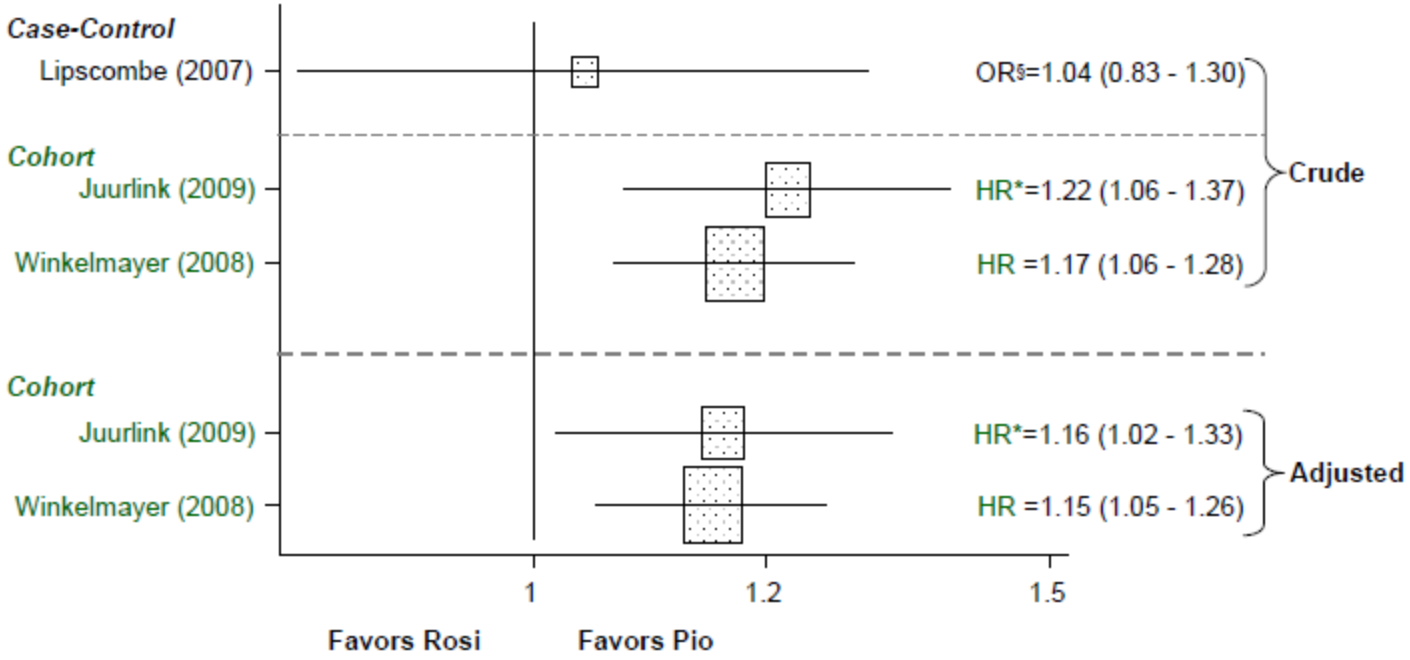
- 21 studies meeting selection criteria included
  - 7 nested case-control, 14 cohort
- Compared rosi or pio with other anti-diabetic agents on acute MI, CHF, and all-cause mortality
- Compared rosi to pio on acute MI, CHF and all-cause mortality



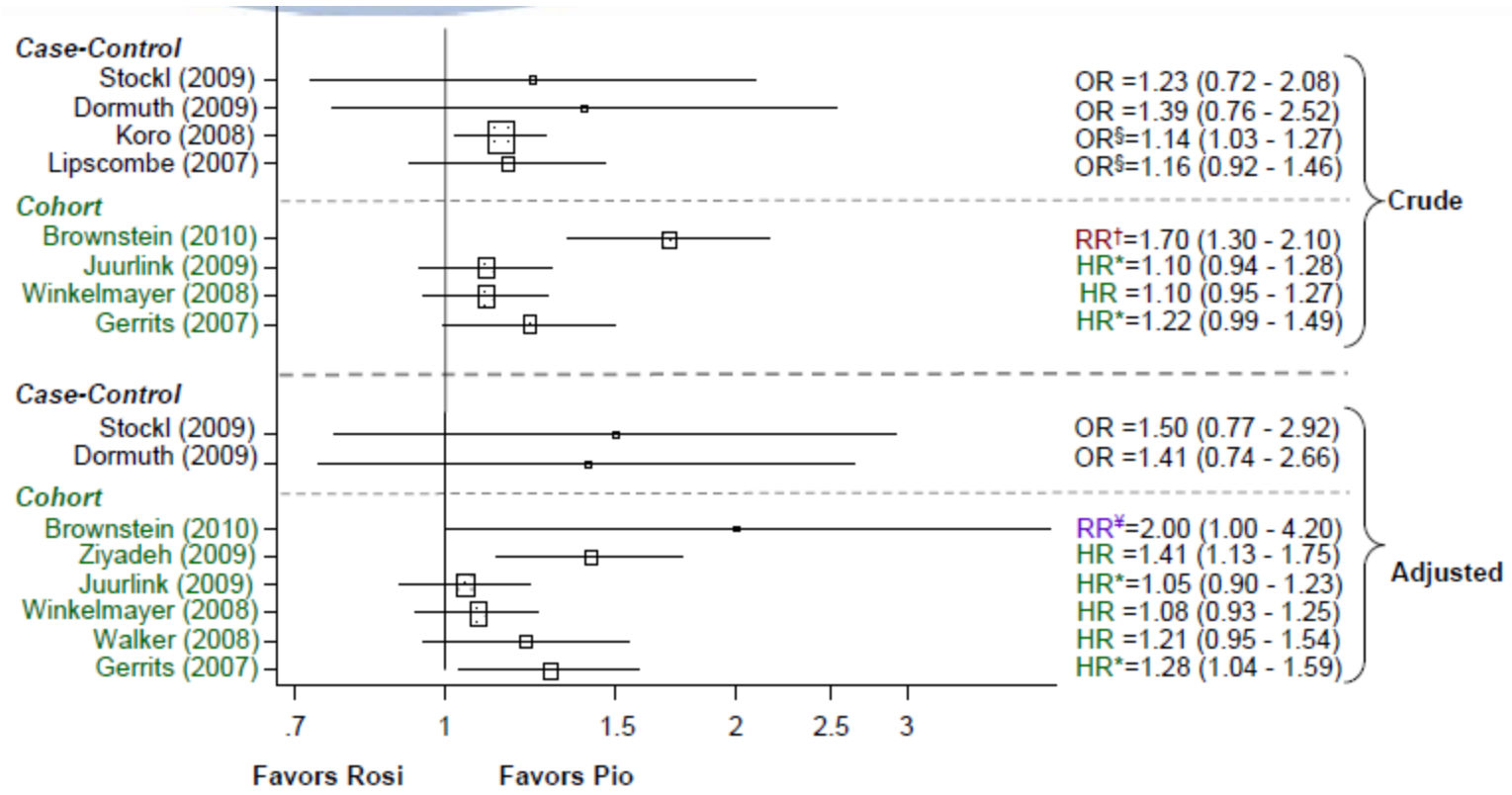

# Outcome AMI: R *or* P vs. other antidiabetic agents (ADAs)




# Outcome all-cause mortality: R *or* P vs. other ADAs




# Outcome all-cause mortality: R versus P




# Outcome acute myocardial infarction (AMI): R versus P

# Observational Studies: CMS Database

Hazard ratios (95% CI) for AMI, stroke, heart failure, death, and composites in Medicare elderly treated with rosiglitazone compared with pioglitazone

| End point | Unadjusted hazard ratio (95% CI) | Adjusted† hazard ratio (95% CI) |
|---|---|---|
| AMI | 1.07 (0.97-1.19) | 1.06 (0.96-1.18) |
| Stroke | 1.31 (1.15-1.49) | 1.27 (1.12-1.45) |
| Heart failure | 1.27 (1.18-1.37) | 1.25 (1.16-1.34) |
| Death | 1.17 (1.07-1.27) | 1.14 (1.05-1.24)‡ |
| AMI or death | 1.13 (1.06-1.21) | 1.11 (1.04-1.19)‡ |
| AMI, stroke, or death | 1.17 (1.10-1.24) | 1.15 (1.08-1.22)‡ |
| AMI, stroke, heart failure, or death | 1.20 (1.14-1.26) | 1.18 (1.12-1.23)‡ |

† Adjusted for all covariates in AC briefing document; same model for all end points
‡ test for PH assumption not met

# Results of 2010 AC Panel Voting Questions

- 6 voting questions
  - CV ischemic risk
    - Rosiglitazone vs non-TZD anti-diabetic therapies (metformin/su)
    - Rosiglitazone vs Pioglitazone
  - Mortality
    - Rosiglitazone vs non-TZD anti-diabetic therapies (metformin/su)
    - Rosiglitazone vs Pioglitazone
  - Regulatory Action Recommended for rosi
  - Recommendation on TIDE

# AC Vote on CV Ischemic Risk and Mortality (2010)

| | CV Ischemic Risk | | All Cause Mortality | |
|---|---|---|---|---|
| | Rosi vs nonTZD drugs | Rosi vs Pio | Rosi vs nonTZD drugs | Rosi vs Pio |
| A. These data are sufficient to raise significant safety concerns for ….. | 18 | 21 | 1 | 7 |
| B. These data are not sufficient to raise significant safety concerns for….. | 6 | 3 | 20 | 12 |
| C. I am not able to make a finding of A or B | 9 | 9 | 12 | 14 |

# Results of 2010 AC Panel Voting Questions

**Based on the available data, which of the following regulatory actions do you recommend FDA pursue regarding rosiglitazone?**

- **Allow continued marketing and revise the current label to remove the boxed warning and other warnings regarding an increased risk of ischemic CV events N=0**
- **Allow continued marketing and make no changes to the current label N=3**
- **Allow continued marketing and revise the current label to add additional warnings (e.g., contraindications for certain patient populations, recommendation for second-line use in patients intolerant of or uncontrolled on other anti-diabetic agents) N=7**
- **Allow continued marketing, revise the current label to add additional warnings, and add additional restrictions on use (such as restricting prescribing to certain physicians or requiring special physician and patient education) N=10**
- **Withdrawal from the U.S. market N=12**
- **Abstention N=1**

# Results of 2010 AC Panel Voting Questions

**If rosiglitazone remains on the U.S. market, do you recommend that the TIDE trial be continued in order to provide further data on the comparative CV safety of rosiglitazone, pioglitazone, and standard-of-care management of type 2 diabetes (placebo add-on)?**

- **19 yes**
- **11 no**
- **2 abstention**
- **1 non-voting (early departure of member)**

# Regulatory Decisions Post 2010 AC Meeting

1. Rosi-containing products would remain on the market but through a restricted distribution plan under a Risk Evaluation and Mitigation Strategy (REMS) which includes a MedGuide and Elements to Assure Safe Use (ETASU)
2. Safety Labeling Changes in accordance with Section 505(o)(4) of the FDCA
3. TIDE was placed on a full clinical hold
4. GSK was required to commission an independent re-adjudication of RECORD.

# Center Director Decisional Memo September 23, 2010

While both a majority of the Advisory Committee members and OND recommend continuation of TIDE, I do not believe it should proceed at this time, given the restrictions I have determined are necessary for rosiglitazone and the level of concern about its cardiovascular safety. In many cases, when a drug safety issue arises, conduct of a randomized trial is an appropriate step to resolve the question. However, the results of RECORD, which are currently in question, directly affect the ethics of conducting TIDE. I believe that re-adjudication of RECORD is the appropriate next step, with decisions on whether to conduct further studies or take additional regulatory actions to be based on the results of the re-adjudication and any other data that may become available in the interim. FDA is not rescinding the post-market requirement for the sponsor to study the safety of rosiglitazone compared to pioglitazone, if feasible and appropriate, but is stopping the current trial until all existing information is evaluated, including the data from RECORD, if possible.

# Events Leading to 2013 Advisory Committee Meeting

- GSK commissioned Duke Clinical Research Institute to undertake re-adjudication of RECORD
- Results for re-adjudicated mortality submitted to FDA on Dec 20, 2011
- Results for re-adjudicated MACE submitted to FDA March 28, 2012

# Agenda of 2013 Advisory Committee Meeting

- Present re-adjudicated results from RECORD with updated statistical analyses
- Update panel members on any available data for rosiglitazone CV safety since 2010 AC
- Describe the REMS program for rosiglitazone
- Provide overview of current marketing status of rosiglitazone
- Present feasibility of conducting CVOT with TZDs
- Revisit regulatory decisions made in 2010 given data presented today

# Discussion Point #1

1. At the July 2010 advisory committee meeting, questions were raised about the reliability and interpretability of the results from RECORD. As part of the regulatory actions taken by FDA in September 2010, CDER required GSK to commission a re-adjudication of the RECORD trial to determine if the results could be relied upon for the assessment of cardiovascular (CV) safety for rosiglitazone. Based on the re-adjudication conducted by Duke Clinical Research Institute (DCRI) and other presentations and discussions at this meeting, please discuss if the results of RECORD are reliable and interpretable. In your discussion, please comment on questions related, but not limited to:
   - Trial design
   - Trial conduct
   - Informative censoring
   - The conduct of the readjudication
   - The reliability and interpretability of the various CV endpoints assessed; e.g., mortality, nonfatal MI, nonfatal stroke

# Discussion Point #2

2. **Please comment on how each of the following clinical data sources should be weighed in the overall consideration of CV risk evaluation for rosiglitazone:**
   - **Observational studies**
   - **FDA's meta-analysis of 52 rosiglitazone controlled clinical trials**
   - **The cardiovascular outcomes trial, RECORD**

# Discussion Point #3

3. **Based on the totality of available data, do you recommend any additional clinical trial(s) be conducted to evaluate the CV safety of rosiglitazone? For any trial you might propose, please:**
   - **describe the objective(s) of such a trial;**
   - **discuss the feasibility of conducting such a trial; and**
   - **discuss the ethics of conducting such a trial**

# Voting/Discussion Question

4. **Rosiglitazone and rosiglitazone-containing products are currently marketed in the U.S. under a Risk Evaluation and Mitigation Strategy (REMS) with Elements To Assure Safe Use (ETASU). Based on the totality of available data, including the re-adjudicated results of RECORD, do you recommend:**

   A. **Removal of the REMS/ETASU.**
   B. **Continuation of the REMS/ETASU without changes.**
   C. **Modification of the REMS/ETASU. Please specify what you recommend be modified.**
   D. **Withdrawal of rosiglitazone from the market.**

# A Critical Review of the RECORD Re-adjudication

Thomas A. Marciniak, M.D.
Division of Cardiovascular and Renal Products
FDA

# Disclaimers

- The opinions expressed are my professional opinions as an FDA employee but not the official views of the FDA.

- After I communicated to DMEP problems with the readjudication design in Jan ’11 DMEP stopped sending me readjudication material and meeting invitations.

# Comment on Readjudication Plan

*Email to DMEP Deputy Director 01/18/11*

"But, if GSK is doing the redacting, there is the possibility for differential dropping of critical information. I documented with hard examples how differential dropping of patients and events prior to adjudication is found in RECORD. I believe that argues that GSK involvement in this readjudication should be minimized: Any activity that can be carried out by another group should be. However, no group funded by GSK is completely independent of GSK."

# Outline of Presentation

1. Anil Potti
2. Co-dependence
3. Little new
4. Extreme mishandling
5. Informative censoring
6. Dead horse

# *Who was Anil Potti?*

Answer: The Duke researcher whose scientific fraud went undetected by Duke for several years

*Question: What does Anil Potti have to do with the readjudication?*

# 1. Limitations of AROs

## How Duke missed the Potti Fraud
## *60 Minutes* Feb 12, 2012

***60 Minutes:*** "How could they have found nothing wrong, nothing suspicious about the work at that point?"

**DCRI founder**: "They were analyzing a data set that had been prepared by Dr. Potti. So, the data set they got was one that produced the same results that had been seen in our own analyses."

# FDA Tcon with Chief Statistician for RECORD May 25, 2010

*Q: Please discuss what it means to "have full access to the interim data and vouch for the accuracy and completeness of the data reported?" Does this mean access to the database, study level data or individual subject level data?*

A: GSK provided the data to Dr. [redacted] at the London School of Hygiene and Tropical Medicine. Dr. [redacted] wrote a program according to the statistical analysis plan supplied by GSK and ran the data provided by GSK though his program. Dr. [redacted]'s program was recreated to perform an analysis; not a complex plan.

# A Recent DCRI CV Trial: PLATO

- Ticagrelor vs. clopidogrel in acute coronary syndromes
- DCRI:
  - Executive committee co-chair
  - Operations committee member
  - US national coordinator
  - Co-chair of adjudication committee (re-adjudication PI)
  - Academic coordinating center (one of two)

# PLATO Problems 1
# Incomplete Follow-up

CRDAC Meeting July 28, 2010

- Incomplete follow-up: **13%**
- AdComm member: “I would say a 13 percent loss to follow-up in a trial where the follow-up is between 6 and 12 months is just way high.”
- DCRI Director: “I would agree with you, Dr. Neaton, that the 13 percent is not a very good standard.”

# PLATO Problems 2
# Adjudication Recording Blunder

| Event adjudication | |
|---|---|
| What is the result of the event adjudication? | Myocardial infarction |
| Adjudicator comments | Patient immediately had ST cl |
| Date: | 2007- |
| Time: | 23:45 |
| Date (yyyy-mm-dd) | 2005- |
| Time (hh:mm) | 11:45 |
| Type of myocardial infarction? | MI within 24 hours of CABG |
| Classification of Myocardial Infarction? | STEMI |
| Subclassification of Myocardial Infarction? | Q-wave |
| Is this endpoint related to a stent thrombosis? | No |

**MI in ticagrelor patient not counted in NEJM paper because year off by 2! Two other endpoints dropped for date/time blunders.**

# PLATO Problems 3 to 26

- 7 more in RECORD readjudication review dated 05/15/12 (Attachment 2)
- 26 problems detailed in ticagrelor review available at:
  - http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433Orig1s000MedR.pdf

# Another DCRI Trial & Tribulations

- ARISTOTLE – apixaban vs. warfarin in afib
- DCRI lead author on NEJM article + operations team & adjudicators
- FDA first round non-approval because of data quality issues
- DCRI founder blog June 25, 2012:
  - *"While DCRI did not do the data management or monitoring for this trial, we have a copy of the database and our statisticians have performed the independent analyses."*

# 2. Co-Dependence

## Readjudication was NOT independent

**Clinical Events Classification (CEC) Charter**

**Re-Adjudication Protocol AVD115170**
**"RECORD"**

**2.0 Role of the DCRI RECORD CEC Group**

The DCRI RECORD CEC group is responsible for the conduct of the CEC operations for the RECORD Re-Adjudication Protocol, in collaboration with the sponsor, GSK. The DCRI CEC group creates and maintains the CEC Charter and will develop the event

Version 1.0 2011May02 4

# Examples of GSK Dependence 1

- Protocol 4.2 Collection of Data "All data sent to the DCRI RECORD CEC group will have subject personal identifiers, treatment assignment, and glucose lowering agents redacted. This will include electronic datasets as well as source documents and paper CRFs. **GSK is responsible** for the redacting prior to delivery of data or documents to the DCRI."

- 4.2 "In addition, DCRI also screened all information **collected by GSK** between November 2010 and March 2011 regarding patients whose last contact was made during the survival status follow-up phase and recorded on pages 501, 502, and 506 of the CRF."

- 4.2.1 "Using the RECORD study data **supplied by GSK**, DCRI identified patients whose vital status at the end of the study was not clearly documented. MediciGlobal (King of Prussia, Pennsylvania), an independent vendor (third party) was employed to search for additional vital status information for these patients."

# Examples of GSK Dependence 2

- 4.2.2 “The CRF pages were the only information related to survival status that was collected by GSK, as the source documents were archived in the Investigator Site Files and not by GSK. **GSK retrieved available source documents** from the Investigators‘ Archive. . .”

- 4.2.2 “CRAs based at Quintiles and **GSK Sweden requested sites** where the 437 “survival status patients” were based to retrieve source documents for August 2008 through December 2008 (the study-visit close-out period), from their archive and **provide copies to GSK**.”

- 4.2.2 “The sites were asked to redact the paperwork (to remove person identifiable information) prior to **sending the information to GSK**.”

- 5 “Electronic data containing the raw data collected on the CRF in the original RECORD study were transferred in the form of SAS datasets **from GSK** to the DCRI . . .”

# Why were CV Endpoint CRFs "not databased"?

Information on this page was not databased

00000

SmithKline Beecham Pharmaceuticals

| Page | MIUA1 |
|---|---|

| Protocol | Centre Number | Patient Number | Patient Initials | Endpoint Number | Myocardial Infarction & Unstable Angina Endpoint Form |
|---|---|---|---|---|---|
| 49653/231 | | 0 0 0 0 0 | | E | |

***MYOCARDIAL INFARCTION AND UNSTABLE ANGINA ENDPOINT FORM***

Date of onset of event ___ Day Month Year

Where there any typical ischaemic symptoms ?

☐ No

☐ Yes

**(**Biomarkers, etc.)

- GSK omitted these CRFS (hospitalizations, deaths, MIs, strokes, HF, & other CV) from the initial sNDA submission
- We finally received some complete CRFs including CV EP CRFs starting March 23, 2010.
- We have never received data sets with the complete contents of these critical CRFs.

# DCRI Is Financially Co-Dependent

**The Chronicle**

## The Research Industrial Complex

By Caroline McGeough | April 23, 2010

In one tower of an nondescript, nine-story white building on Fulton Street, just across from Duke University Hospital, operates the world's largest academic clinical research institute, generating more than $125 million in revenue per year from the research grants and contracts it receives from both government sources and from industry. Its more than 218 clients in the pharmaceutical and medical device sectors include corporate giants Johnson & Johnson, Pfizer, GlaxoSmithKline and GE Healthcare. The Duke Clinical Research Institute, composed of more than 1,000 employees supporting the worldwide

# The PI Is Financially Co-Dependent

Mahaffey *et al. Circulation* 2011, 124:544-554

Dr Mahaffey has received consulting fees from AstraZeneca, Bayer, Boehringer Ingleheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmith-Kline, Johnson & Johnson, Merck, Ortho/McNeill, Sanofi-Aventis, and Schering-Plough (now Merck); he has also received research funding from Bayer, Boehringer Ingleheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Portola Pharmaceuticals, Pozen, Regado, Sanofi-Aventis, Schering-Plough (now Merck), and The Medicines Company.

# Selected GSK Payments

*From GSK US Website*

Research payments - YTD December 2012

| | | | | |
|---|---|---|---|---|
| 115170 | DUKE CLINICAL RESEARCH INSTITUTE | MAHAFFEY, KENNETH | DURHAM | NC |

[Readjudication] 2,994,163

Fees Paid to US Based Healthcare Professionals for Consulting & Speaking Services

1st through 3rd Quarter 2012

| | | | | | |
|---|---|---|---|---|---|
| Mahaffey, Kenneth | DURHAM, NC | FACULTY CONNECTION LLC | $11,625 | $0 | $11,625 |

**[Consultant Speaker]**

Grants & Charitable Contributions to US Based Healthcare Organizations

2nd Quarter 2012

| | | |
|---|---|---|
| Duke Clinical Research Institute | CSRC Annual Membership | $25,000.00 |

# MediciGlobal Is Financially Co-Dependent

Website doesn't post COIs or client listings but a former employee's news release states:

http://www.bizjournals.com/prnewswire/press releases/2012/04/10/PH84859[5/3/2012 8:16:21 AM]

"[redacted]'s previous position was Vice President of Operations for MediciGlobal, a clinical trials marketing company. There, she led the project team in the implementation of patient recruitment and retention programs for major pharmaceutical companies such as **GlaxoSmithKline**, Pfizer and Sepracor."

## History of MediciGlobal 2008

http://mediciglobal.com/press/category/company_history

EMEA orders a major Pharma Company (and Medici client) to withdraw its product from the market. The company removes the product from 47 countries. MediciGlobal adjusts headcount as a result of this regulatory decision and the loss of two global studies and one domestic one.

# 3. Little New: MediciGlobal Web Claims

*(mediciglobal.com & l2fu.net)*

LTFU® can result in study delays, increased patient recruitment costs and compromised study data. To improve efficiency Sponsors seek the services of MediciGlobal in proactively recovering LTFU study subjects. Our success in recovering lost follow-up patients ensures that **nearly all patient data is accounted for**.

## Global Patient Retention

With over a decade of designing and implementing highly effective patient retention programmes, ours are the best in the industry, delivering 100% success rate.

Before working with L2FU, the sponsor had little hope of achieving its goal of 80 % compliance required by the FDA. The collaboration between study sites and the L2FU team resulted in 78 % of the subjects being found and completing the medical outcomes assessment – enough to satisfy the FDA's expectations and save the trial.

# MediciGlobal's Methodology

## MediciGlobal's L2FU tracks down, contacts missing clinical trials patients

Tuesday, September 7, 2010 07:08 AM

Moench says L2FU recently took only one month to track down and contact about 30 patients who were three to five years disconnected from a particular study. How? Moench won't say; it's proprietary, of course, but it involves "billions of data" in a series of networked databases that L2FU has licensed. Some of the

*(http://jforcs.com/jcs/risk-mitigation-and-due-diligence-in-overcoming-lost-to-follow-up-ltfu-subjects-in-a-clinical-trial-2/)*

# MediciGlobal RECORD Reality

- Of 343 patients tracked in March 2012 submission (*a_medici.xpt*):
  - 82 patients with new alive date (24%)
  - Five death changes (4:1 favoring ros)
  - New follow-up beyond study end date in 20 ros, 9 control (>2:1 favoring ros)
- Overall new useful data (5+20+9)/343 =

10% success rate

# DCRI Query Reality - Death

**6.2 CEC Query of Suspected Events**

It was necessary to issue 127 CEC queries for additional information to follow up on death events classified as "unknown" and "insufficient information."

Of 127 CEC queries issued—

- 43 queries were closed with no response from site;
- 61 queries were closed with a response from the site that no additional data is available;
- 23 queries were closed with additional data received from the site.
  Of these 23 queries—
  - 16 events were re-reviewed with no change to adjudication result;
  - 7 events were re-reviewed with a change to the adjudication result from "unknown" to a known cause of death.

Hence 7/127 = 5.5% useful data success rate

# 4. Extreme Mishandling

**1.1 Extreme mishandling of events (Cases A-D)**

These four cases represent what we judge to be the worst mishandling of events in RECORD, mishandlings that we judge should not be found even as single occurrences and that suggest serious flaws with trial conduct. They are four among 70 mishandlings we have documented based on reviews of CRFs for 549 patients. We provide representative examples of the other 66 in Section 1.3.

A. The non-adjudicated deleted MI
B. The non-adjudicated pulmonary edema
C. The non-adjudicated stroke (ICH)
D. The 36-day hospitalization non-stroke

*(Marciniak, "Cardiovascular events in RECORD, NDA 21-071/S-035", 06/14/10, p. 27)*

# Case A: The Deleted MI

REF INVDCF15 OH 17MAR2007

121B SCR12 OH 15JAN2007

SmithKline Beecham Pharmaceuticals

A1

Page ~~125~~

| Protocol | Centre Number | Patient Number | Patient Initials | SB Receipt Date Day Month Year |
|---|---|---|---|---|
| 49653/231 | | | | |

**SERIOUS ADVERSE EXPERIENCE (SAE)**

| | |
|---|---|
| Person Reporting SAE (Please print clearly) | REGIS Number |
| Serious Adverse Experience (Please print clearly) | myocardial infarction |
| For SmithKline Beecham | |
| Onset Date and Time | 24 Day NK NK 24hr:min |
| End Date and Time (If ongoing please leave blank) | 0,5 Day NK NK 24hr:min |

→ Specify reason(s) for considering this a serious AE. Mark all that apply.

- [1] ☐ fatal
- [2] ☒ life threatening
- [3] ☐ disabling/incapacitating
- [4] ☐ results in hospitalisation (excluding elective surgery or routine clinical procedures)
- [5] ☒ hospitalisation prolonged

This patient underwent PTCA and died of HF 22 days later.

# Case A:The MI Vanishes!

CLINICAL DATA CLARIFICATION FORM **A3** Page 1 of 1

| | | | |
|---|---|---|---|
| Investigator Name: | Site Number: | | Protocol Number/Study Identification: 49653 /231 |
| Subject Number: | Subject Initials: | | DCF Tracking Number: |
| Requestor Name: | Requestor Signature: | | Date sent to the Site for Resolution: |

**Why?**

| Subject Visit | CRF Page/ File ID No. | Data Item/Field/ Record No. | Current CRF Entry/Description of Query | Corrected Entry/Resolution | For DM Use Only: Entered (initials/date) |
|---|---|---|---|---|---|
| | | | | | |
| | | EP 12735 | ⇒ Herewith I confirm the deletion of SAE page 125- | | |
| | | | | UD CH 17MAR2007 | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

Investigator Signature (or approved signatory/authorized designate):

Date Signed: 25.02.2007

**15 months after the MI!**

The event was never referred for adjudication.

# Case B: The Curious Case of Lack of Curiosity

furosemide for pulmonary edema on admission

B1 Royal Hospital NHS

This lady presented back to the [redacted] with shortness of breath. She was treated with Frusemide for pulmonary oedema and her breathing improved. She had a protracted stay in the hospital whilst long term oxygen therapy was established and some of her medications were titrated. Unfortunately on about the 5th June her breathing got worse and she started to retain CO2. She had a short spell on BIPAP but unfortunately she failed to respond and passed away on the [redacted] The cause of death was:

1a) pneumonia

This patient had NO CV events adjudicated!
The pulmonary edema was ignored.

If you have any further queries please do not hesitate to contact us. Many thanks.

This brief letter is the total information submitted for this 46-day hospitalization terminating in death!

# Case C: The Stroke Vanishes!

DRQ 572786 AL 07MAR2007

EPILEPSY ~~DUE TO HAEMATOMA IN INTRACEREBRAL LEFT TEMPORAL REGION~~

EP NO: [redacted]
FOC 16DEC2004

SmithKline Beecham Pharmaceuticals

C1

A.S. [redacted]

Page 119

| Protocol | Centre Number | Patient Number | | SB Receipt Date Day | Month | Year |
|---|---|---|---|---|---|---|
| 49653/231 | [redacted] | | | | | |

CODING AL 09DEC2004 SEE PAGE 120

AEMOD: 1)EPILEPSY 2)CEREBRAL HAEMATOMA

SAE REC SW21JAN2005

## SERIOUS ADVERSE EXPERIENCE (SAE)

Person Reporting SAE [redacted]
(Please print clearly)

10.08.2004.

AEGIS Number B0342093A

Serious Adverse Experience
(Please print clearly) [redacted]

CEREBRAL HAEMATOMA ~~WITH HAEMATOMA IN INTRACEREBRAL LEFT TEMPORAL REGION~~

A.S.

→ Specify reason(s) for considering this a serious AE. Mark all that apply.

[1] ☐ fatal
[2] ☑ life threatening
[3] ☐ disabling/incapacitating
[4] ☑ results in hospitalisation

[redacted]

A.S.

For SmithKline Beecham [redacted]

Onset Date and Time

Day Month Yr 24hr:min

# Case D: A Stroke SAE

SmithKline Beecham Pharmaceuticals

D1

Page 199

| Protocol | Centre Number | Patient Number | | SB Receipt Date Day Month Year | |
|---|---|---|---|---|---|
| 49653/231 | | | | | |

SAE REC MB26JAN2009

**SERIOUS ADVERSE EXPERIENCE (SAE)**

| | | |
|---|---|---|
| **Person Reporting SAE** *(Please print clearly)* | | **AEGIS Number** |
| **Serious Adverse Experience** *(Please print clearly)* | CEREBRAL STROKE | → *Specify reason(s) for considering this a serious AE. Mark all that apply.* |
| **For SmithKline Beecham** | | |
| **Onset Date and Time** | Day Month Yr 24hr:min | |
| **End Date and Time** *(If ongoing please leave blank)* | 21 SEP 08 UNK<br>Day Month Yr 24hr:min | |
| **Outcome** *If patient died, please complete Form D* | [1] [X] Resolved<br>[2] [X] Ongoing<br>[3] [ ] Died | |
| **Experience Course** | [1] [ ] Intermittent No. of episodes [ ]<br>[2] [X] Constant | |
| **Intensity** *(maximum)* | [1] [ ] Mild<br>[2] [ ] Moderate<br>[3] [X] Severe | |

[1] [ ] fatal
[2] [ ] life threatening
[3] [ ] disabling/incapacitating
[4] [X] results in hospitalisation (excluding elective surgery or routine clinical procedures)
[5] [ ] hospitalisation prolonged
[6] [ ] congenital abnormality
[7] [ ] cancer
[8] [ ] overdose
[9] [ ] Investigator considers serious or a significant hazard, contraindication, side effect or precaution

# Case D: Another Stroke Vanishes!

**Remarks** *(Please provide a brief narrative description of the SAE, attaching extra pages eg. hospital discharge summary if necessary)*

Patient was admitted to hospital due to stroke cerebral from [redacted] to [redacted]

Information obtained from family member and document not available.

***Adjudicated non-CV insufficient information***

For a severe stroke with 36-day hospitalization, the site couldn't have queried the family member about onset? Paralysis? Speech?

# Extreme Mishandling Confirmed!

| Case | GSK | OSI | Mine | DCRI |
|---|---|---|---|---|
| A | Not adjudicated | OK | MI | MI |
| B | Not adjudicated<br>Non-CV death | OK | HF hospitalization<br>Non-CV death | HF hospitalization<br>Non-CV death |
| C | Not adjudicated | OK | Stroke | Stroke |
| D | Non-CV (insufficient information) | OK | Stroke | Insufficient information |

DCRI adjudication agrees with mine in 3 of 4 cases.
See next slide for comments on the 4th(D)—and B.

# DCRI Comments on 2 Cases

- Case B: “Committee: Died of pneumonia > 1 month after admitted for CHF wich was reportedly improving.”

- Case D: “Committee:  Patient hospitalized due to stroke according to family members.  There is not enough information to adjudicate this event as a stroke.”

# DSI* Explains Case A

## *(DSI Branch Chief Email 07/08/10)*

**From:** Purohit-Sheth, Tejashri **[DSI Branch Chief]**
**Sent:** Thu 7/8/2010 6:57 PM
**To:** Leibenhaut, Susan; Ball, Leslie; Mahoney, Karen M (Endocrine Clinical Reviewer)
**Cc:** Unger, Ellis; Marciniak, Thomas; U, Khin M; Parks, Mary H
**Subject:** RE: Case examples that were reviewed in audit

Good Evening All,

1 = [Case A]: this was not cited on the 483 because GSK stated that the endpoint of MI was "deleted by the investigator, which resulted in this endpoint not being sent to the CEC for adjudication." For us to fully evaluate this, we would have to have gone to the site to see why this was "deleted." (we did not inspect this site) Therefore, we can't make any conclusions/assumptions about this case.

*DSI = Division of Scientific Investigations now Office of Scientific Investigations

# DSI Explains Cases B & C

*(DSI Branch Chief Email 07/08/10 continued)*

2 = [Case B]: this subject was hospitalized for pulmonary edema and later died from pneumonia. This patient had Myelodysplastic Syndrome (MDS) and during the inspection, Khin felt that the pneumonia could have been from the MDS, and it was felt that this was adjudicated appropriately as a non-CV death.

3 = [Case C]: this subject was not cited as the neurologic symptoms were considered to be as a result of hemangioma resulting in epilepsy. It was felt that this was non-CV (non-atherosclerotic) in origin, and per the protocol, was not specifically required to be reported ("rapidly developed clinical signs of focal (or global) disturbance or cerebral function lasting more than 24 hours….with no apparent cause other than vascular origin." The cause of the hematoma was thought to be as a result of the hemangioma (not atherosclerotic in origin).

# DSI Explains Case D

*(Leibenhaut & Purohit-Sheth, "Clinical Inspection Summary", 09/29/10, p. 13)*

"For the issues pertinent to Subjects [Case D] and [Case A], the protocol specified required hospital summaries were not available for adjudication; as such, they were not adjudicated. Quintiles responded adequately in a letter dated June 4, 2010."

# 5. Informative Censoring

*Informative censoring in RECORD is expected:*

- RSG produces more heart failure (HF)
- By protocol HF patients were to be d/c'd
- HF patients have heart problems—more cardiac events are expected in them
- F/U was incomplete in patients who d/c'd

*A later presentation will document that more RSG patients d/c'd than control.*

# Differential Informative Censoring

## Patients with HF during the RTP

| Yrs in RTP | n | | Any HF during RTP | | Any HF but no PEP during RTP | |
|---|---|---|---|---|---|---|
| | CTL | ROS | CTL | ROS | CTL | ROS |
| 1 | 175 | 168 | 1 | 9 | 0 | 1 |
| 2 | 169 | 124 | 3 | 10 | 0 | 5 |
| 3 | 172 | 111 | 6 | 11 | 0 | 5 |
| 4 | 178 | 131 | 2 | 10 | 0 | 1 |
| 5 | 190 | 167 | 4 | 17 | 2 | 7 |
| 6 | 791 | 861 | 19 | 30 | 3 | 8 |
| 7 | 513 | 607 | 9 | 21 | 5 | 9 |
| 8 | 44 | 57 | 1 | 1 | 0 | 0 |
| Total | 2232 | 2226 | 45 | 109 | 10 | 36 |

HF = heart failure; PEP = GSK primary endpoint; RTP = randomized treatment phase

More early HF dropouts without PEP with ROS

More missed PEPs with ROS

# 6. Dead Horse (1): Design Flaws '07

*(Graham & Dal Pan, "Review of protocol for RECORD", FDA, 07/06/07)*

1. No placebo group
2. Unacceptable noninferiority margin
3. Open label
4. Too broad composite outcome
5. Low power

*"The preliminary and final results of RECORD should not be considered reliable or valid and should not be used by FDA in any consideration of risk or benefit associated with RSG use."*

# Dead Horse 2: Design Flaws '10

*(Marciniak, RECORD AC presentation, 07/13/10, slide 11)*

Red shading indicates key issue

| # | Issue | Bias |
|---|---|---|
| 1 | Open label | rosiglitazone |
| 2 | Two studies | null |
| 3 | Active controls | null |
| 4 | Post-randomization determination of treatment phases | null |
| 5 | Treatment crossovers | null |
| 6 | Investigator determination of visit frequencies and types | rosiglitazone |
| 7 | Lower CV risk population | null |
| 8 | CV hospitalizations in primary endpoint | null |
| 9 | Ambiguities regarding endpoint definition of amputations | null |
| 10 | Strict MI definition | null |

The potential biases favoring rosiglitazone all stem from the open label design of RECORD.

# Dead Horse 2: Design Flaws ’10 (Continued)

*(Marciniak, RECORD AC presentation, 07/13/10, slide 12)*

| # | Issue | Bias |
|---|---|---|
| 11 | Primary endpoint not reflecting suspected problems | null |
| 12 | Endpoint date definition | null |
| 13 | Minimal documentation on rationale for adjudication of cases | neutral |
| 14 | Analysis populations | null |
| 15 | Endpoint reporting | null |
| 16 | SAE reporting | neutral |
| 17 | Concomitant medication reporting | null |
| 18 | Handling of withdrawals | rosiglitazone |

If consulted in advance, I would have rejected this study design as inappropriate and biased.

# Dead Horse 3: Design Flaws ‘12

*(Dunnmon, Grant, & Stockbridge, DCRP consult regarding RECORD readjudication mortality findings, 5/13-14/12, p. 21)*

“Though we commend the DCRI for an impressive re-analysis effort, it must be recognized that what comes out of an analysis directly depends on what goes in. There is no amount of analytical rigor that can compensate for a weak trial design that is exacerbated by elements of poor execution, both of which afflicted RECORD. Its openlabel non-inferiority design was simply problematic, especially for ascertainment of nonmortality MACE during trial execution. Of the 313 deaths that DCRI identified and readjudicated, there was insufficient evidence to determine cause of death (cardiovascular vs. non-cardiovascular) in 120 cases (38% of all deaths).

**“Thus, while we agree with the analytical findings of the DCRI mortality re-analysis, we would emphasize that RECORD’s design irreparably hampers its ability to characterize definitively the CV risk of rosiglitazone.”**

# Limitations of the Readjudication

[*Black DCRI, Red my additions*]

- Reliance largely on the original database and source documents **in collaboration with GSK**
- ~~Modest amount of~~ Little additional information obtained in this retrospective futile effort
- Little Additional follow-up primarily about vital status; limited additional information about MI or stroke
- Old extreme mishandling confirmed—but DCRI not chartered to identify additional extreme mishandling
- Study design flaws not overcome

# Conclusions

## *[From ’10 AC and still valid today]*

*(Marciniak, RECORD AC presentation, 07/13/10, slide 33)*

- RECORD was inadequately designed and conducted to provide any reassurance about the CV safety of rosiglitazone
- RECORD confirms and extends the recognized concerns regarding increased HF and HF deaths with rosiglitazone
- RECORD suggests that rosiglitazone increases the risk for MI

# Systematic review of epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone – update since 2010

Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, June 5 - 6, 2013

Kate Gelperin, MD, MPH
Division of Epidemiology-1
Office of Surveillance and Epidemiology, CDER

# Outline

- **Introduction**
- Criteria for selecting studies
- Summary of previous systematic review
- Findings of current review
- Forest plots: comparisons with other antidiabetic agents
- Forest plots: comparisons of rosiglitazone and pioglitazone
- Strengths and limitations
- Conclusions

# FDA Review Team

Kate Gelperin, OSE/DEPI-1, Epidemiology Reviewer
Esther Zhou, OSE/DEPI-1, Epidemiology Reviewer
John Yap, Statistics Reviewer, OTS/OB/DB7
Patricia Bright, OSE/DEPI-2, Epidemiology Reviewer
Tarek Hammad, Deputy Director, OSE/DEPI-1
Solomon Iyasu, Director, OSE/DEPI-1
Mark Levenson, Statistics (TL), OTS/OB/DB7
Aloka Chakravarty, Director, OTS/OB/DB7
Margarita Tossa, OSE Project Manager

# Introduction

- Cochrane-type systematic review - methods
- Protocol developed in 2010 by FDA team using Cochrane approach (copy in background package)
- Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomized studies. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK). John Wiley & Sons, 2008.
- Study quality assessed using standard instrument; data extraction; independent statistical review of individual studies; summary results displayed in forest plots based on pre-specified rules

# Outline

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# Studies eligible for inclusion:

- Endpoints describe cardiovascular risks associated with the use in population settings of rosiglitazone or pioglitazone;
- Case-control or cohort design; and
- Published in a peer-reviewed journal (studies excluded if abstract only).
- Cross-sectional studies, case-series, and studies based on a single institution's experience are excluded. Randomized clinical trials and nonclinical studies are excluded.
- Individual patient-level data were not available for this review.

# Systematic review of epidemiologic studies of cardiovascular risk with rosiglitazone or pioglitazone

- The summary of the systematic review is qualitative, no quantitative meta-analysis was planned.
- Summary results of cardiovascular endpoints for the individual studies are displayed using tables and forest plots.
- The primary summary measures for the individual studies are odds ratio (OR), relative risk (RR), or hazard ratio (HR), and associated 95% confidence interval (CI), when available.
- For studies of rosiglitazone versus other treatments, the ratio is expressed as the comparison of rosiglitazone versus the comparator treatment.
- For studies of pioglitazone versus other treatments (not including rosiglitazone), the ratio is expressed as the comparison of pioglitazone versus the other treatment.

# Systematic review of epidemiologic studies of cardiovascular risk with rosiglitazone or pioglitazone

- Results of new studies identified in this current review were combined with results from the previous systematic review for display in a series of forest plots.
- The outcomes of interest for which forest plots were prepared include:
  - Acute myocardial infarction (AMI)
  - Heart failure
  - All-cause mortality
  - Stroke
- In addition, forest plots were prepared for the subset of studies which reported outcomes of interest for direct comparisons of rosiglitazone and pioglitazone in older patients (≥65 yrs. of age).

# Outline

- Introduction
- Criteria for selecting studies
- **Summary of previous systematic review**
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# Previous Systematic Review: studies published before July 2010 AC (n=21)

- Design
  - Nested case-control (n= 7)
  - Cohort (n=14)
- Statistical methods
  - Logistic regression (n=8)
  - Cox proportional hazards model (n=12)
  - Poisson generalized linear model (n=1)
- Definition of outcome: ICD-9 or ICD-10 codes; Read codes
- Geographic settings: US (n=13), Canada (n=4), UK (n=3), Taiwan (n=1)

# Results of the previous Systematic Review:

- Comparisons of rosiglitazone and pioglitazone for outcomes including acute myocardial infarction, heart failure, and all-cause mortality tended to favor pioglitazone.
- Results of comparisons of rosiglitazone with other antidiabetic agents in observational studies were consistent with those of the meta-analyses of randomized clinical trials conducted by FDA staff and presented at the 2010 AC meeting, which suggested increased cardiovascular risk with rosiglitazone, but were not definitive.

# Outline

- Introduction
- Criteria for selecting studies
- Summary of previous systematic review
- **Findings of current review**
- Forest plots: comparisons with other antidiabetic agents
- Forest plots: comparisons of rosiglitazone and pioglitazone
- Strengths and limitations
- Conclusions

# Studies published after July 2010 AC (n = 7)

- Design
  - All retrospective cohort studies
- Statistical methods
  - Cox proportional hazards model (6 studies)
  - Poisson regression (1 study)
- Two of these studies (Graham 2010, and Wertz 2010) were discussed at the previous Advisory Committee meeting in 2010, but were not included in the previous systematic review because they were published after the datalock. *(Note that results from both of these studies were considered during regulatory decision-making in 2010.)*

# Included new studies (n=7)

- Outcomes (one, or more than one, per individual study):
  - acute myocardial infarction (AMI)
  - stroke
  - coronary revascularization (CRV)
  - congestive heart failure (CHF) or heart failure (HF)
  - angina
  - cerebral vascular accident (CVA)
  - acute coronary syndrome (ACS)
  - death or all-cause mortality (ACM)
  - composites of these outcomes

- Patient deaths were not described in some of the studies
- Definition of outcome: ICD-9 or ICD-10 codes; Read codes

# Data sources and geographic setting (n=7)

| Country | Database |
|---|---|
| United States | Translating Research Into Action for Diabetes (TRIAD)<br>Medicare<br>HealthCore Integrated Research Database – WellPoint |
| Israel | Maccabi Healthcare Services |
| Taiwan | Longitudinal Health Insurance Database |
| United Kingdom | General Practitioner Research Database (GPRD)<br>The Health Information Network in United Kingdom (THIN) |

# Outline

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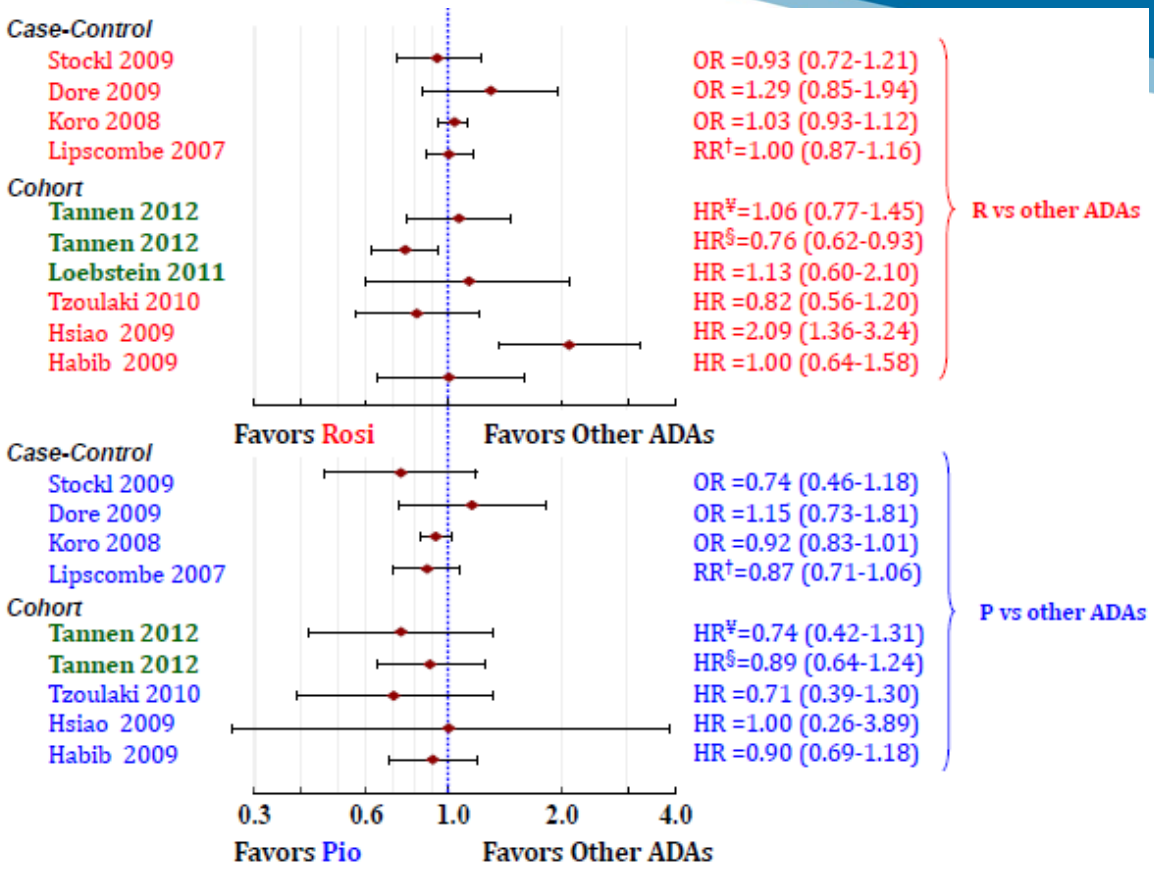
- Forest plots: comparisons of rosiglitazone and pioglitazone
- Strengths and limitations
- Conclusions

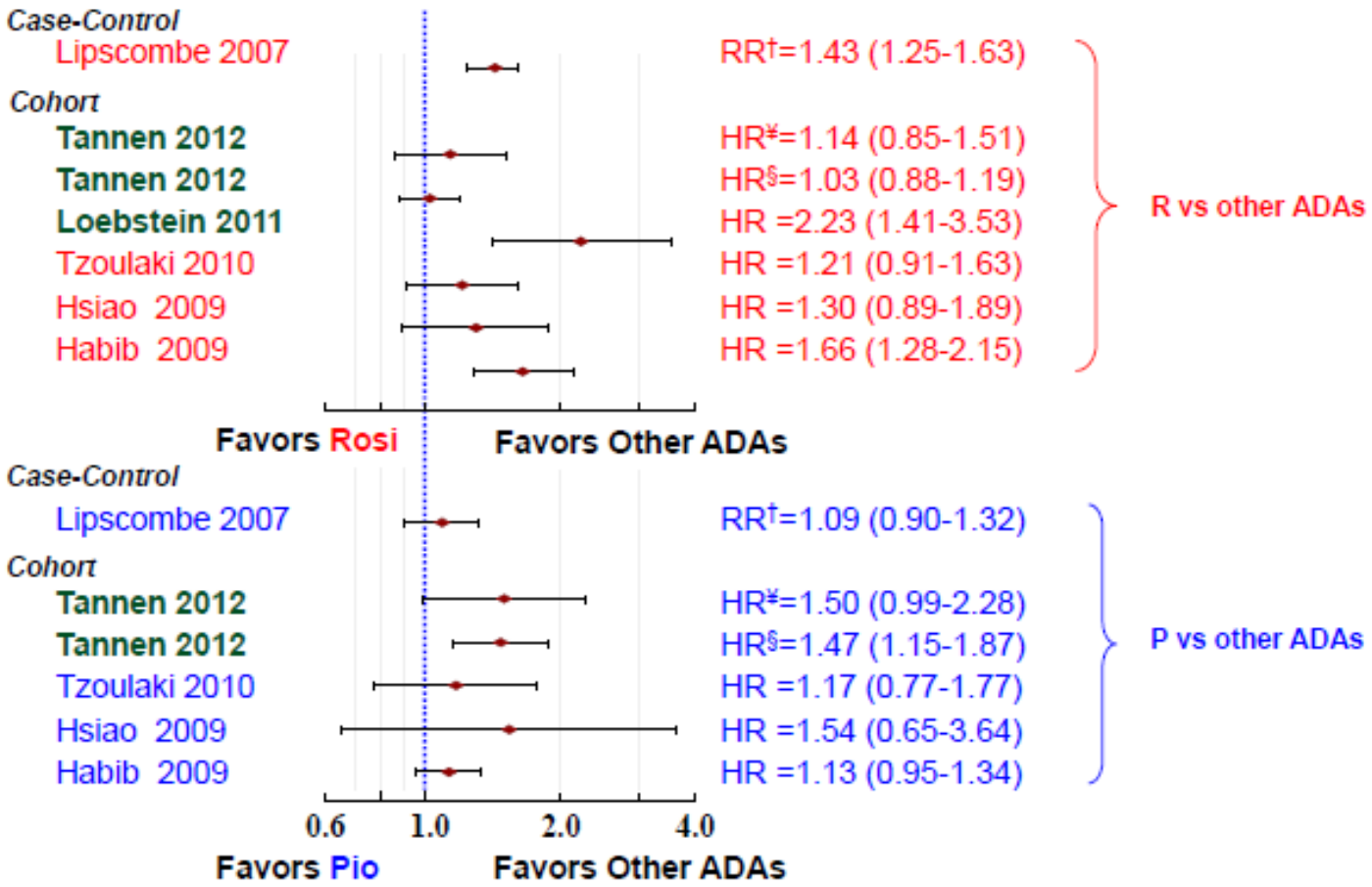



# AMI: R *or* P vs other antidiabetic agents (ADAs)

Notes: drugs included in the category "other ADAs" differ across studies; results displayed on this slide are the adjusted estimates; **dark green font color indicates new studies.**

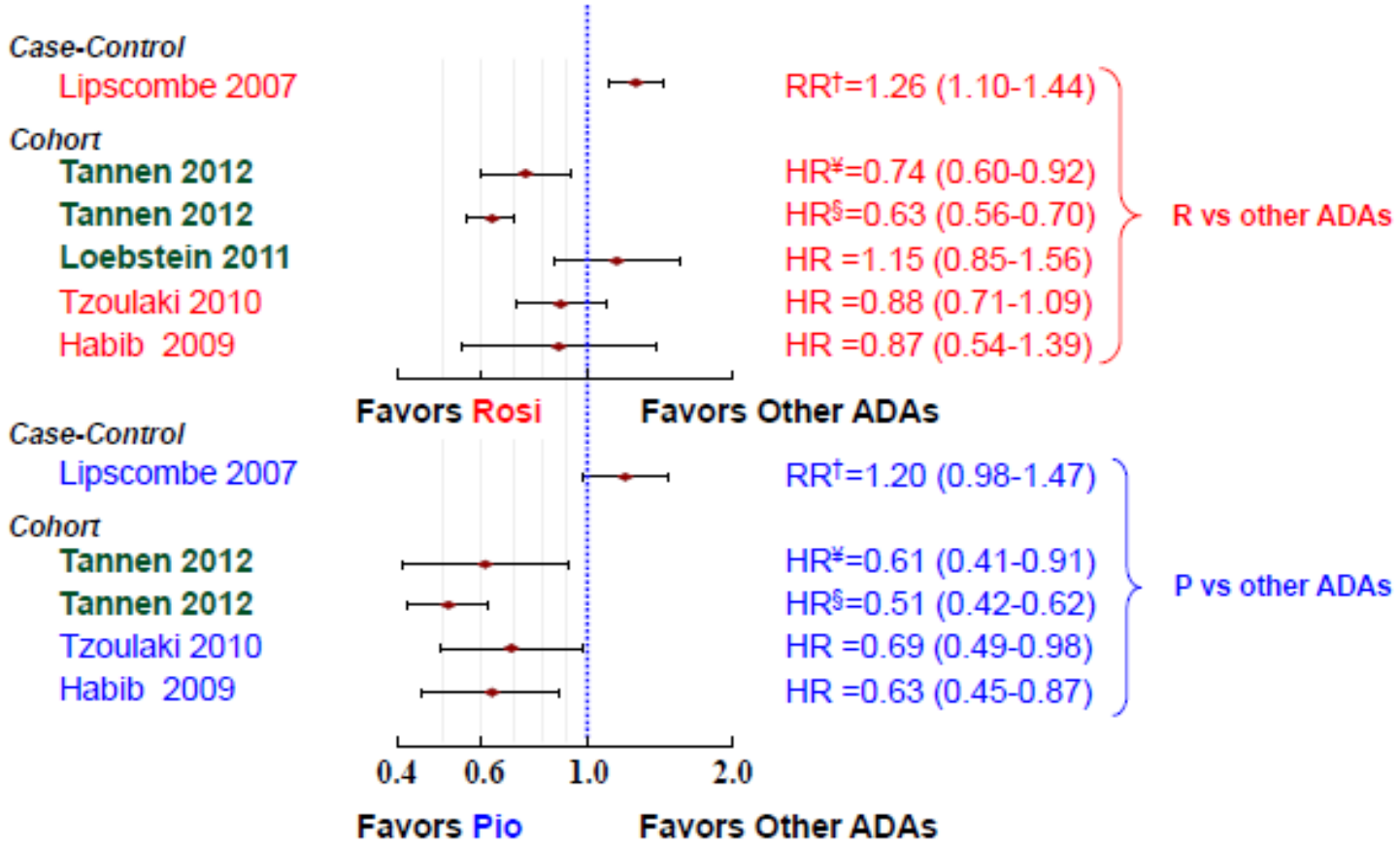
† Rate Ratio

For Tannen 2012: ¥ Replication Studies; § Expanded Studies



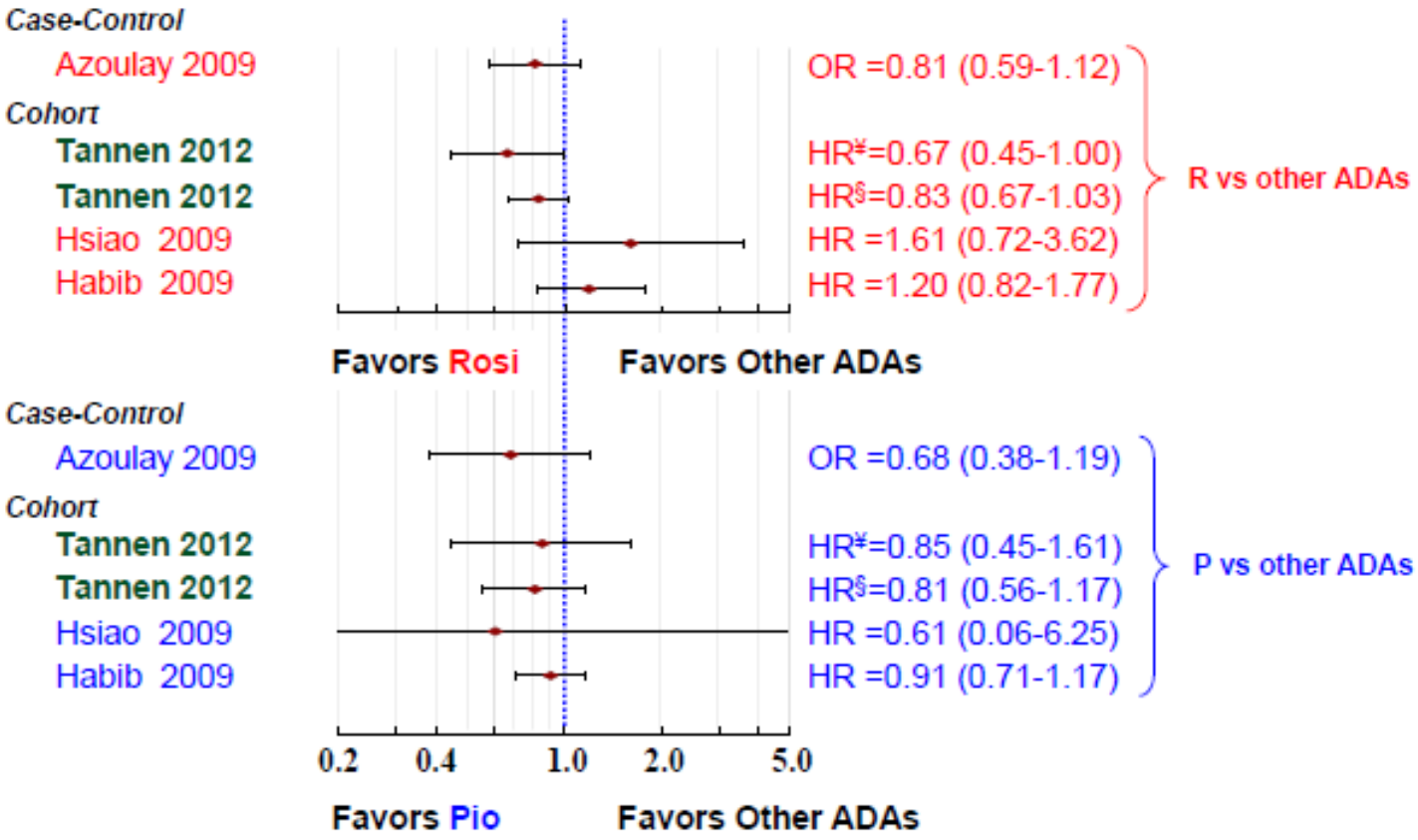

# Heart failure: R *or* P vs other ADAs

Notes: drugs included in the category "other ADAs" differ across studies; results displayed on this slide are the adjusted estimates; **dark green font color indicates new studies.**
† Rate Ratio
For Tannen 2012: ¥ Replication Studies; § Expanded Studies




# All-cause mortality: R *or* P vs other ADAs

Notes: drugs included in the category "other ADAs" differ across studies; results displayed on this slide are the adjusted estimates; **dark green font color indicates new studies.**
† Rate Ratio
For Tannen 2012: ¥ Replication Studies; § Expanded Studies




# Stroke: R *or* P vs other ADAs

Notes: drugs included in the category "other ADAs" differ across studies; results displayed on this slide are the adjusted estimates; **dark green font color indicates new studies.**
For Tannen 2012: ¥ Replication Studies; § Expanded Studies

# Challenges

- Epidemiologic studies of rosiglitazone or pioglitazone versus other antidiabetic agents may be challenging to interpret:
  - Important baseline differences in patient characteristics → unmeasured confounding
  - Frequent changes in diabetes treatment strategy for individual patients over time and unknown adherence → misclassification bias (random misclassification error may bias study results toward null effect)
- Gallagher et al (2011)
  - Conducted a bias analysis in GPRD data, and concluded that "comparisons of different classes of diabetes medications are likely to be prone to substantial confounding, while the within class comparison of rosiglitazone versus pioglitazone is less prone to selection bias and confounding."

# Outline

- Introduction
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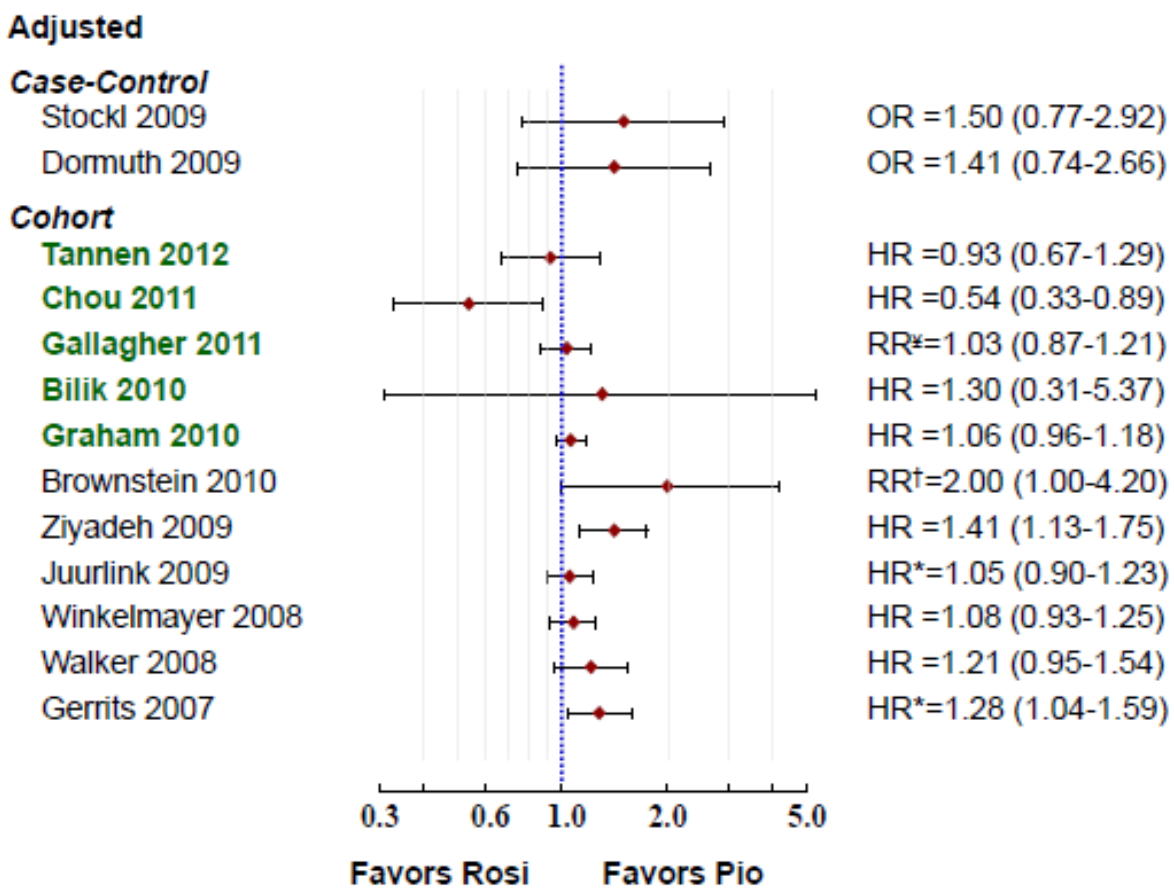
- Forest plots: comparisons of rosiglitazone and pioglitazone
- Strengths and limitations
- Conclusions

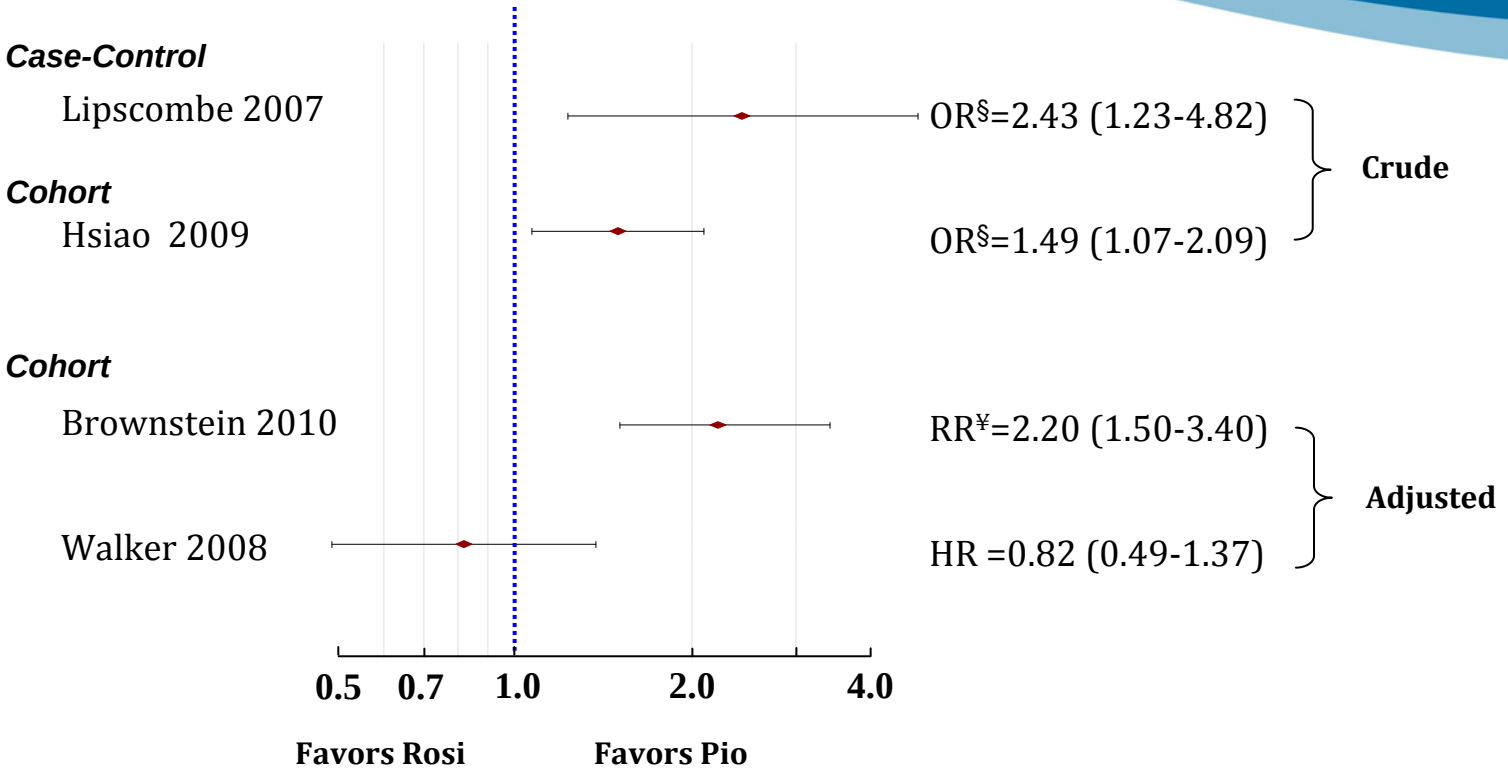



# AMI: R vs P (adjusted estimates)

Notes: outcome in Gallagher 2011 is ACS; Wertz 2010 not included in figure since primary analysis is composite (AMI, AHF, ACD) with HR=1.03 (95% CI 0.91-1.15); **dark green font color indicates new studies.**

† Rate Ratio ¥ Relative Risk

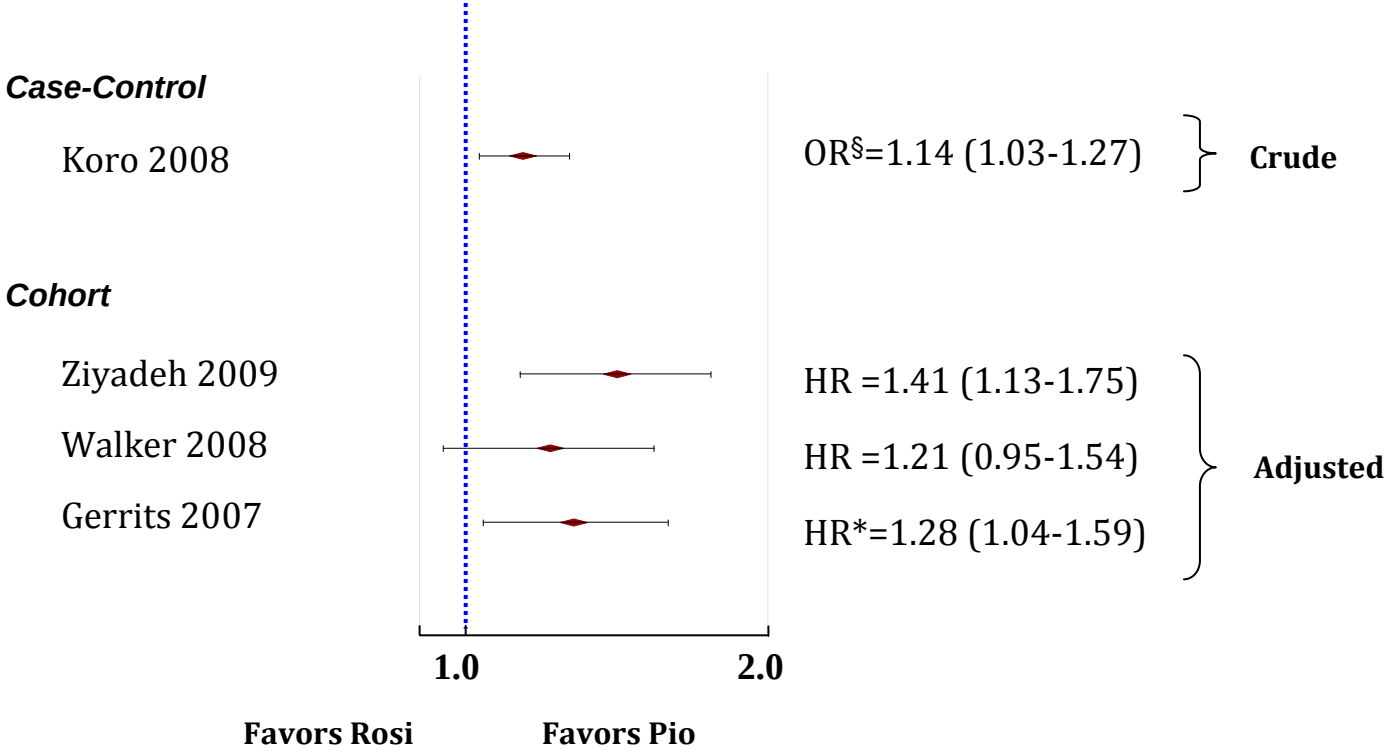
* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)




# AMI: R vs P (monotherapy only)

§ Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article.

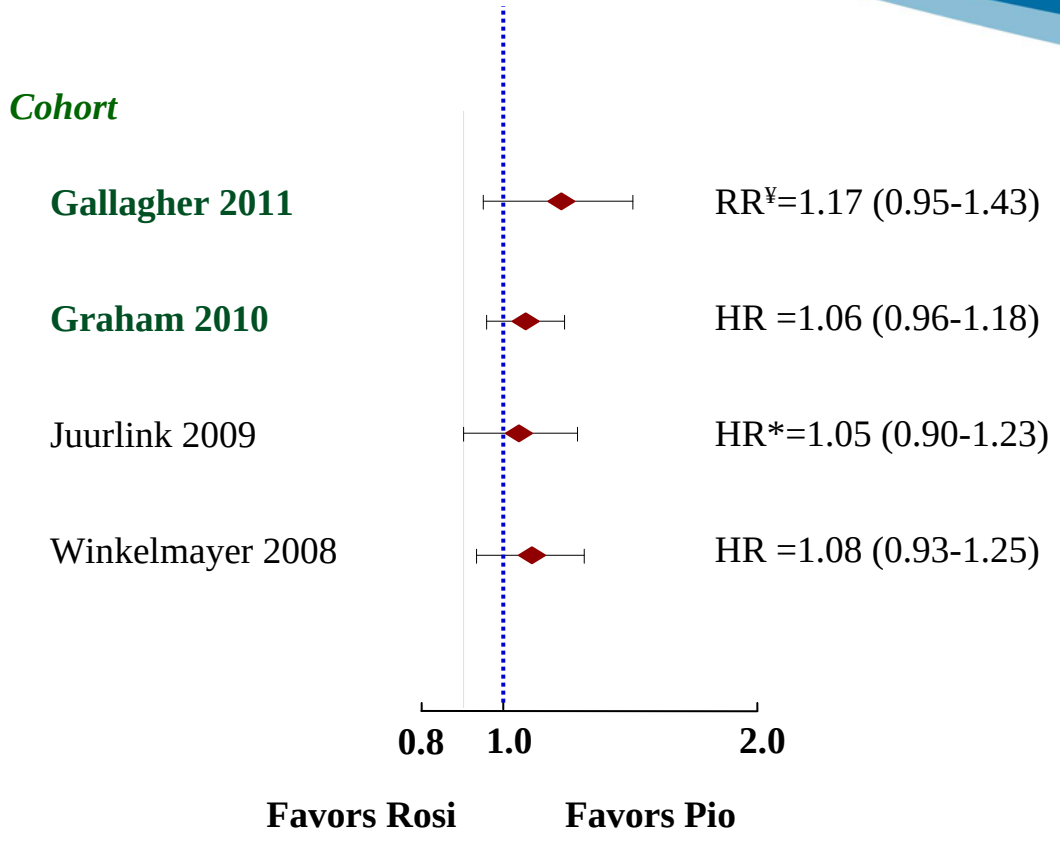
† Rate Ratio ¥ Relative Risk




## AMI: R vs P (studies sponsored by drug manufacturers)

§ Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article.

* HR=reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)



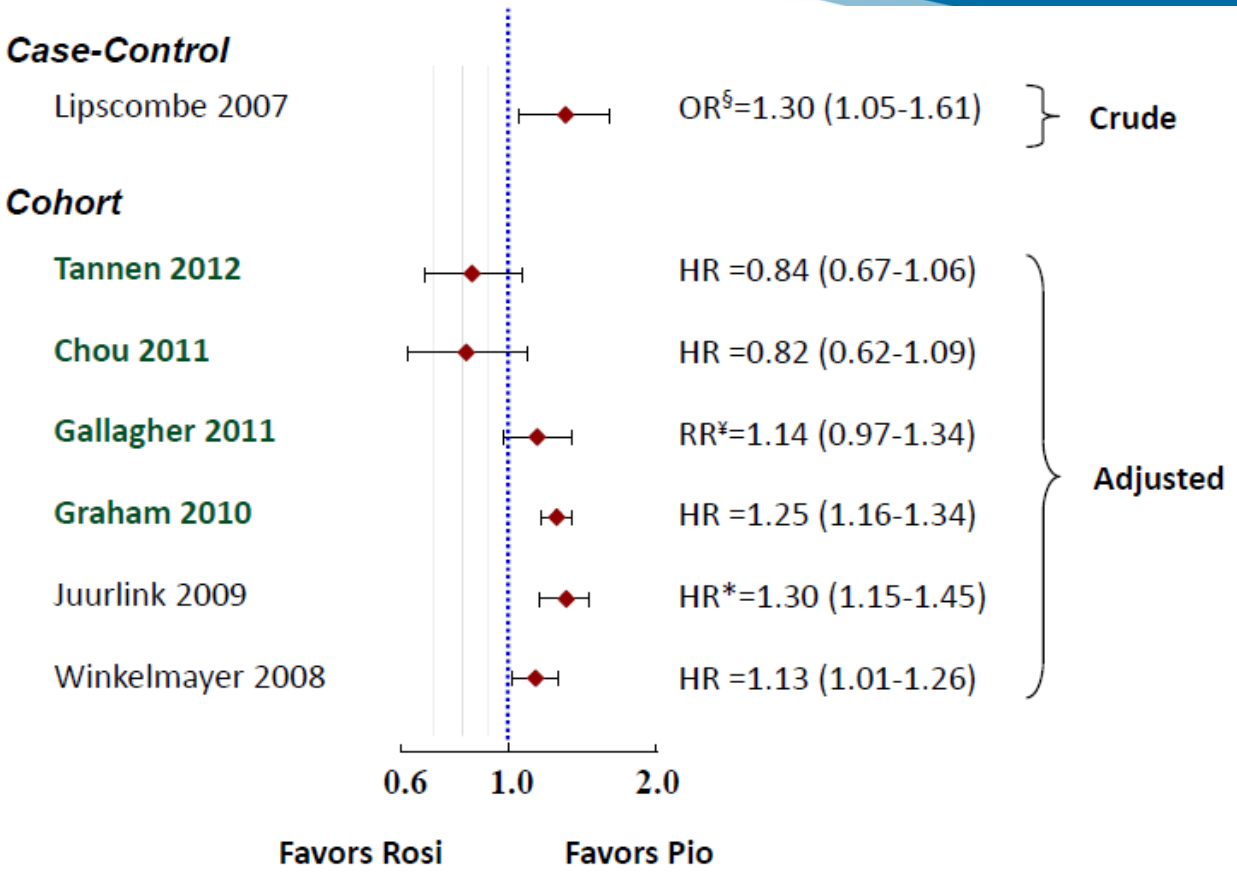

# AMI: R vs P (older patients)

**Dark green font color indicates new studies.**

* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)

¥ Relative Risk

*Note: Wertz 2010 is not included in the forest plot because primary analysis results only included composite (AMI, AHF, ACD); HR=0.97 (95% CI 0.83-1.12).*




# Heart failure: R vs P

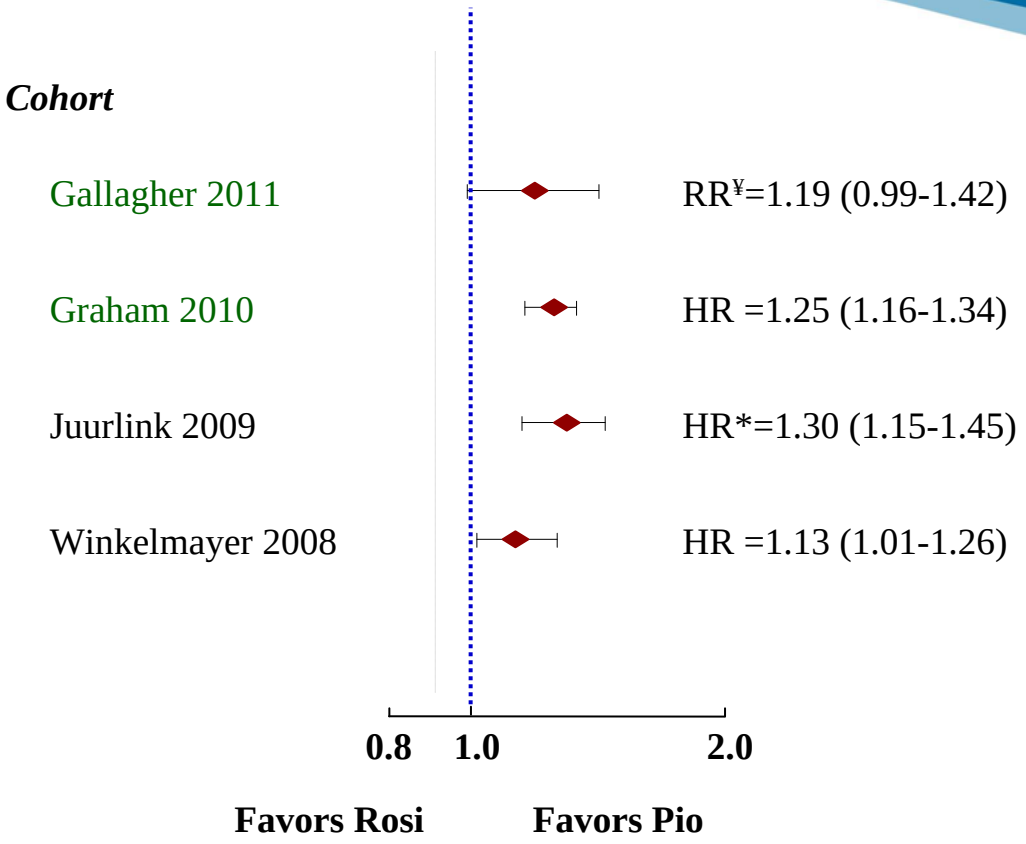
**Dark green font color indicates new studies.**

§ Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article

¥ Relative Risk

* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)

*Note: Wertz 2010 is not included in the forest plot because primary analysis results only included composite (AMI, AHF, ACD); HR=1.03 (95% CI 0.91-1.15).*



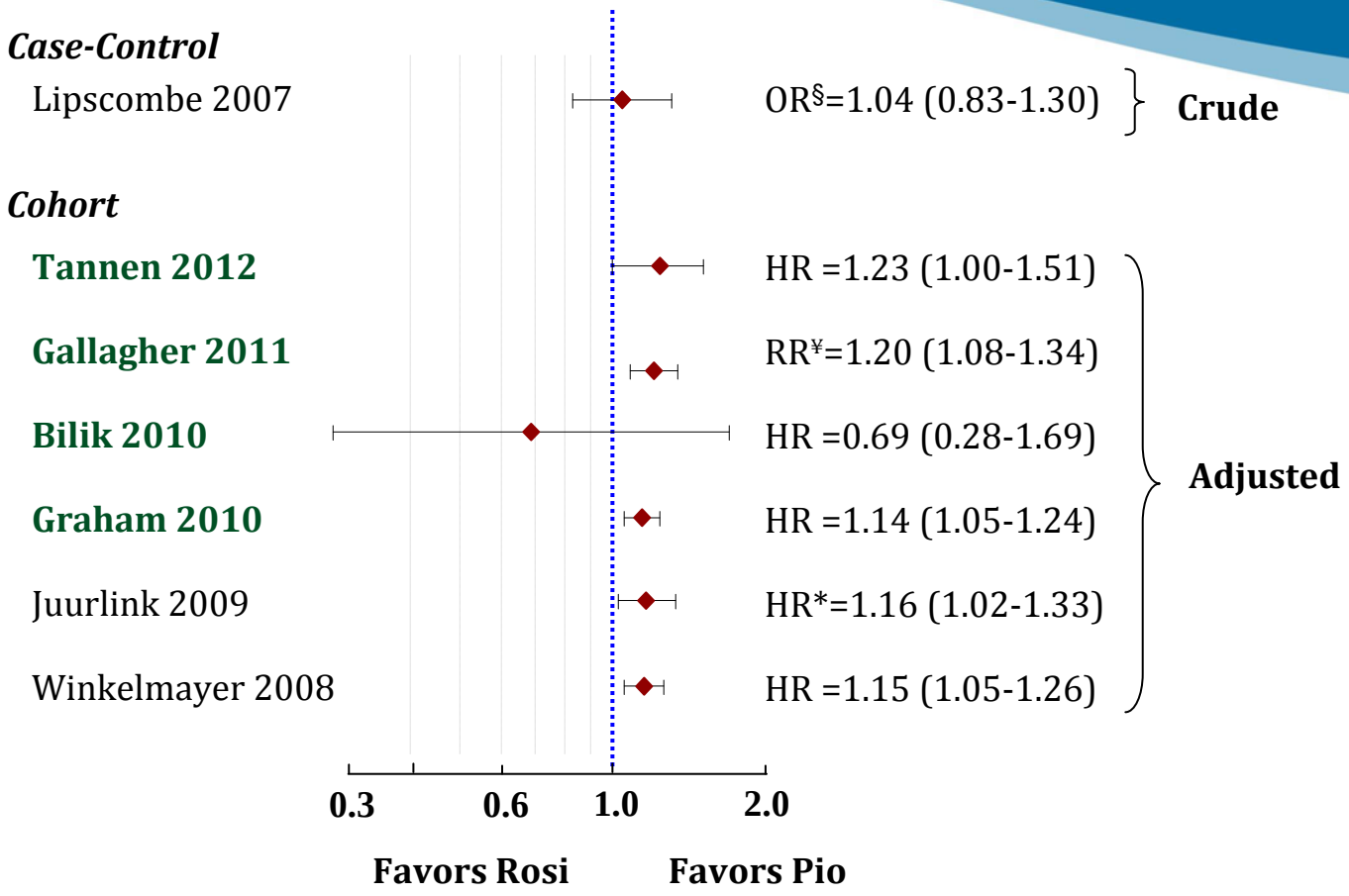

# Heart failure: R vs P (older patients)

**Dark green font color indicates new studies.**

* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)

¥ Relative Risk

*Note: Wertz 2010 is not included in the forest plot because primary analysis results only included composite (AMI, AHF, ACD); HR=0.97 (95% CI 0.83-1.12).*




# All-cause mortality: R vs P

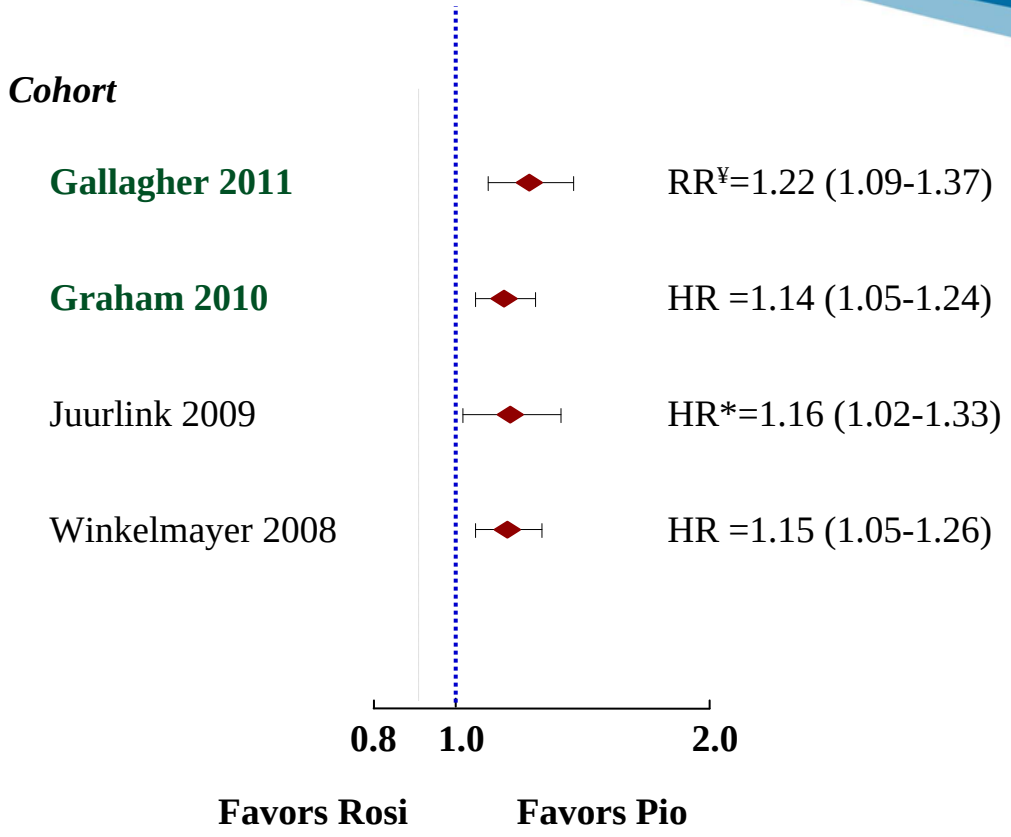
**Dark green font color indicates new studies**

§ Estimated unadjusted OR comparing rosi vs pio calculated from data provided in published article

¥ Relative Risk

* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)

*Note: Wertz 2010 is not included in the forest plot because primary analysis results only included composite (AMI, AHF, ACD); HR=1.03 (95% CI 0.91-1.15).*



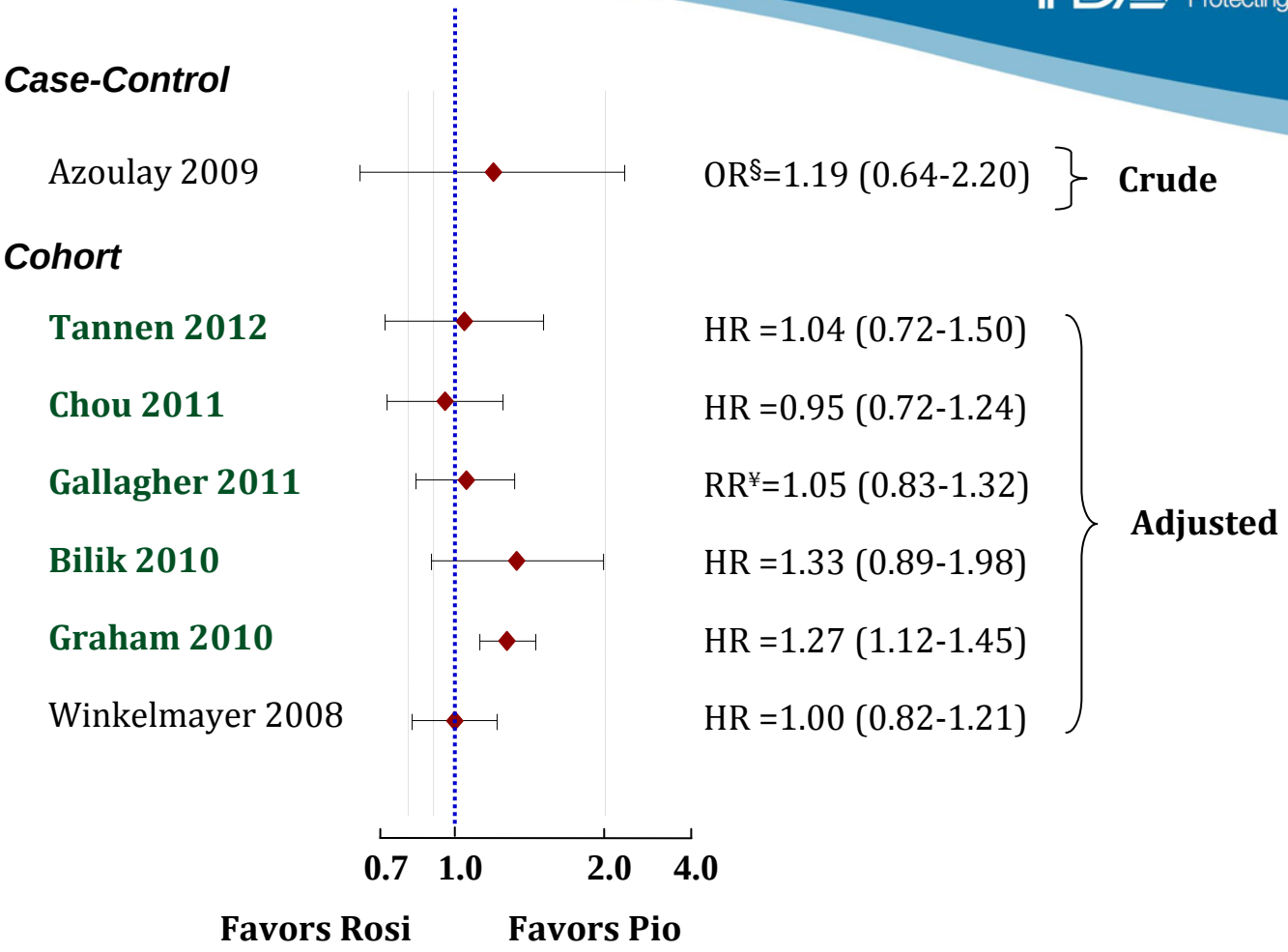

# All-cause mortality: R vs P (older patients)

**Dark green font color indicates new studies.**

* HR = reciprocal of point estimate (reciprocal of upper 95%CI – reciprocal of lower 95%CI)

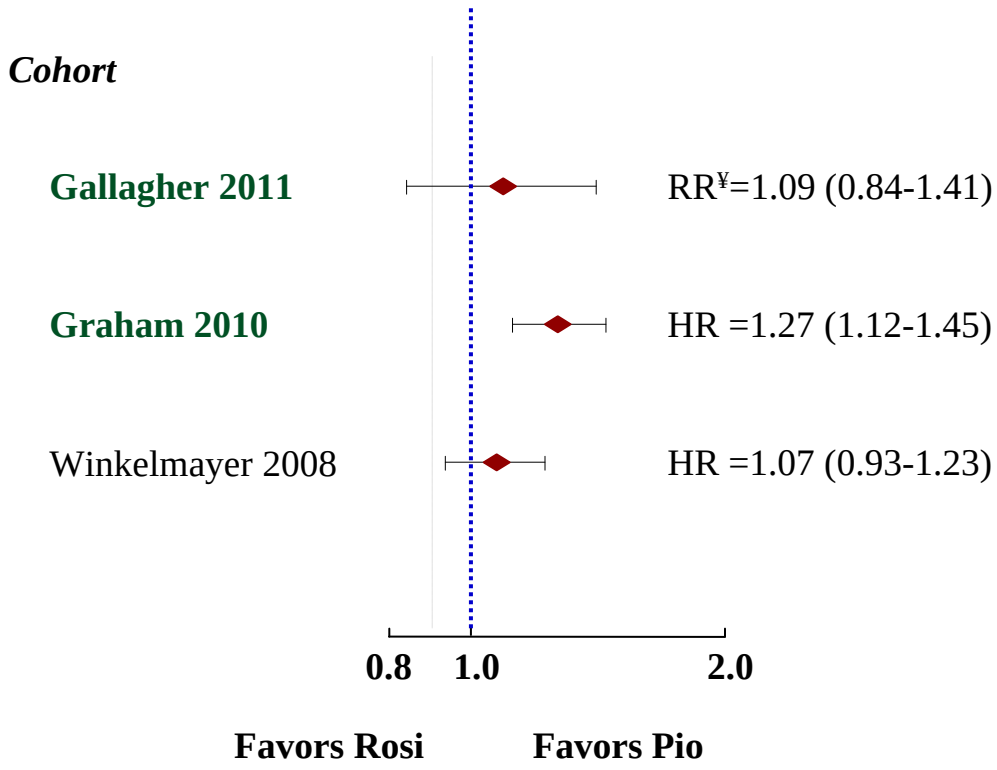
¥ Relative Risk

*Note: Wertz 2010 is not included in the forest plot because primary analysis results only included composite (AMI, AHF, ACD); HR=0.97 (95% CI 0.83-1.12).*




# Stroke: R vs P

Note: definition of stroke in Winkelmayer 2008 study includes TIA
§ Estimated unadjusted OR calculated from data provided in published article
**Dark green font color indicates new studies**
¥ Relative Risk




# Stroke: R vs P (older patients)

**Dark green font color indicates new studies.**

Note: definition of stroke in Winkelmayer 2008 study includes TIA

¥ Relative Risk

# Statistically significant risk estimates in subset of studies in older patients - comparison

| Endpoint | Number of Studies | Rosiglitazone vs. Pioglitazone Statistically Significant Risk Estimates | |
|---|---|---|---|
| | | General Population | Subset of studies in older patients |
| **AMI** (including combo + monotherapy studies) | 15 | 1 ↓risk, 3 ↑risk | none |
| **Heart failure** | 6 | 3 ↑risk | 3 ↑risk |
| **All-cause mortality** | 6 | 4 ↑risk | 4 ↑risk |
| **Stroke** | 6 | 1 ↑risk | 1 ↑risk |

*Statistically significant results (only adjusted estimates included) are from the following studies*:

**AMI**: Chou 2011, Brownstein 2010, Ziyadeh 2009, Gerrits 2007; **HF**: Graham 2010, Juurlink 2009, Winkelmayer 2008; **ACM**: Gallagher 2011, Graham 2010, Juurlink 2009, Winkelmayer 2008; **Stroke**: Graham 2010

# Published meta-analysis of observational studies

- A random effects meta-analysis was used to calculate the odds ratios for CV outcomes in studies with direct comparisons of rosiglitazone and pioglitazone in patients with T2DM*
- Review identified 16 observational studies (4 case-control and 12 cohort studies) comprising 810,000 exposed patients
- Compared to pioglitazone, rosiglitazone was associated with a statistically significant increased risk of
  - myocardial infarction (OR 1.16, 95% CI 1.07-1.24; $p<0.001$)
  - heart failure (OR 1.22, 95% CI 1.14-1.31; $p<0.001$)
  - all-cause mortality (OR 1.14, 95% CI 1.09-1.20; $p<0.001$)

* Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. BMJ 2011;342: 1-9.

# Outline

- Introduction
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- Forest plots: comparisons with other antidiabetic agents
- Forest plots: comparisons of rosiglitazone and pioglitazone
- **Strengths and limitations**
- Conclusions

# Summary

## Strengths:

- Comprehensive and systematic data collection process
- Methods pre-specified by Cochrane-type protocol
- Multi-disciplinary FDA team including statistics and epidemiology reviewers
- Literature searches and adjudication conducted independently by two reviewers
- Includes studies with direct comparisons of rosiglitazone and pioglitazone, addressing an important knowledge gap

## Limitations:

- Non-randomized study design
- Individual studies may be subject to various types of bias such as misclassification or confounding by disease severity
- Function of limitations of individual studies
- Study-level data, not patient-level
- Unknown publication bias

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# Conclusions

- Overall, comparisons of rosiglitazone and pioglitazone for outcomes including acute myocardial infarction, heart failure and all-cause mortality tended to favor pioglitazone.

- These results suggest that the cardiovascular safety profile of pioglitazone is favorable compared to that of rosiglitazone, especially in older patients ≥65 years of age.

- A signal for increased all-cause mortality with rosiglitazone in older patients (>65 years of age), which was demonstrated in four observational studies, may be a reflection of increased cardiovascular risk with rosiglitazone compared to pioglitazone.

# Studies included in previous review (n=21)

1. Brownstein, J.S.; Murphy, S.N.; Goldfine, A.B.; Grant, R.W.; Sordo, M.; Gainer, V.; Colecchi, J.A.; Dubey, A.; Nathan, D.M.; Glaser, J.P.; Kohane, I.S. Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records. Diabetes Care, vol 33, no. 3; 2010.
2. Azoulay, L.; Schneider-Lindner, V.; Dell'aniello, S.; Filion, K. B.; Suissa, S. Thiazolidinediones and the risk of incident strokes in patients with type 2 diabetes: a nested case-control study. Pharmacoepidemiol and Drug Safety, 2009.
3. Dore, D. D.; Trivedi, A. N.; Mor, V.; Lapane, K. L. Association between extent of thiazolidinedione exposure and risk of acute myocardial infarction. Pharmacotherapy. 29(7):775-783; 2009.
4. Dormuth, C.R.; Maclure, M.; Carney, G.; Schneeweiss, S.; Bassett, K.; Wright, J. M. Rosiglitazone and myocardial infarction in patients previously prescribed metformin. PLoS One, vol 4(6), e6080; 2009.
5. Habib, Z.A.; Tzogias, L.; Havstad, S.L.; Wells, K.; Divine, G.; Lanfear, D.E.; Tang, J.; Krajenta, R.; Pladevall, M.; Williams, L.K. Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: A time-updated propensity analysis. Pharmacoepidemiol and Drug Safety, 18:437-447; 2009.
6. Hsiao, F.Y.; Huang, W.F.; Wen, Y.W.; Chen, P.F.; Kuo, K.N.; Tsai, Y.W. 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 Safety, 32(8):675-690, 2009.
7. Juurlink, D.N.; Gomes, T.; Lipscombe, L.L.; Austin, P.C.; Hux, J.E.; Mamdani, M. M. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: Population based cohort study. BMJ 339:b2942; 2009.

# Studies included in previous review (n=21, cont'd)

8. Shaya, F.T.; Lu, Z.; Sohn, K.; Weir, M.R. Thiazolidinediones and cardiovascular events in high-risk patients with type-2 diabetes mellitus: a comparison with other oral antidiabetic agents. P&T, vol 34, no 9; 2009.
9. Stockl, K.M.; Le, L.; Zhang, S.; Harada, A.S. Risk of acute myocardial infarction in patients treated with thiazolidinediones or other antidiabetic medications. Pharmacoepidemiol and Drug Safety, 18:166-174, 2009.
10. Tzoulaki, I.; Molokhia, M.; Curcin, V.; Little, M.P.; Millett, C.J.; Ng, A.; Hughes, R.I.; Khunti, K.; Wilkins, M.R.; Majeed, A.; Elliott, P. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: Retrospective cohort study using UK general practice research database. BMJ, 339: b4731; 2009.
11. Vanasse, A.; Carpentier, A.C.; Courteau, J.; Asghari, S. Stroke and cardiovascular morbidity and mortality associated with rosiglitazone use in elderly diabetic patients. Diabetes & Vascular Disease Research, 6(2) 87-93; 2009.
12. Ziyadeh, N.; McAfee, A.T.; Koro, C.; Landon, J.; Chan, K.A. The thiazolidinediones rosiglitazone and pioglitazone and the risk of coronary heart disease: A retrospective cohort study using a US health insurance database. Clinical Therapeutics, vol 31, 2665-2677; 2009.
13. Koro, C.E.; Fu, Q.; Stender, M. An assessment of the effect of thiazolidinedione exposure on the risk of myocardial infarction in type 2 diabetic patients. Pharmacoepidemiol and Drug Safety, 17:989-996; 2008.
14. Margolis, D.J.; Hoffstad, O.; Strom, B.L. Association between serious ischemic cardiac outcomes and medications used to treat diabetes. Pharmacoepidemiol and Drug Safety, 17:753-759; 2008.

# Studies included in previous review (n=21, cont'd)

15. Walker, A.M.; Koro, C.E.; Landon, J. Coronary heart disease outcomes in patients receiving antidiabetic agents in the PharMetrics database 2000-2007. Pharmacoepidemiol and Drug Safety, 17:760-768; 2008.
16. Winkelmayer, W.C.; Setoguchi, S.; Levin, R.; Solomon, D.H. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. Arch Intern Med, 168(21): 2368-2375; 2008.
17. Gerrits, C.M.; Bhattacharya, M.; Manthena, S.; Baran, R.; Perez, A.; Kupfer, S. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. Pharmacoepidemiol and Drug Safety, 16:1065-1071; 2007.
18. Lipscombe, L.L.; Gomes, T.; Levesque, L.E.; Hux, J.E.; Juurlink, D.N.; Alter, D.A. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA, vol 298, no 22; 2007.
19. McAfee, A.T.; Koro, C.; Landon, J.; Ziyadeh, N.; Walker, A.M. Coronary heart disease outcomes in patients receiving antidiabetic agents. Pharmacoepidemiol and Drug Safety, 16:711-725; 2007.
20. Karter, A.J.; Ahmed, A.T.; Liu, J.; Moffet, H.H.; Parker, M.M. Pioglitazone initiation and subsequent hospitalization for congestive heart failure. Diabet Med, 22, 986-993; 2005.
21. Rajagopalan, R.; Rosenson, R.S.; Fernandes, A.W.; Khan, M.; Murray, F. T. Association between congestive heart failure and hospitalization in patients with type 2 diabetes mellitus receiving treatment with insulin or pioglitazone: A retrospective data analysis. Clinical Therapeutics, 26:9; 2004.

# Studies included in update (n=7)

1. Tannen R, Xie D, Wang X, Menggang Y, Weiner MG. A new "Comparative Effectiveness" assessment strategy using the THIN database: Comparison of the cardiac complications of pioglitazone and rosiglitazone. Pharmacoepi Drug Saf 2012 Oct 16.
2. Chou CC, Chen WL, Kao TW, Chang YW, Loh CH, Wang CC. Incidence of cardiovascular events in which 2 thiazolidinediones are used as add-on treatments for type 2 diabetes mellitus in a Taiwanese population. Clin Ther 2011; 33(12):1904-13.
3. Gallagher AM, Smeeth L, Seabroke S, Leufkens H, van Staa TP. Risk of death and cardiovascular outcomes with thiazolidinediones: A study with the general practice research database and secondary care data. PLoS ONE 2011; 6(12):e28157 [pages1-9].
4. Loebstein R, Dushinat M, Vesterman-Landes J, Silverman B, Friedman N, Katzir, I, Kurnik D, Lomnicky Y, Kokia E, Halkin H. Database evaluation of long-term rosiglitazone treatment on cardiovascular outcomes in patients with Type 2 diabetes. J Clin Pharmacol 2011; 51:173-180.
5. Bilik D, McEwen LN, Brown MB, Selby JV, Karter AJ, Marrero DG, HsiaoVC, Tseng CW, Mangione CM, Lasser NL, Crosson JC, Herman WH. Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD). Pharmacoepidemiol Drug Saf 2010; 19:715-21.
6. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA 2010; 304(4):411-418.
7. Wertz DA, Chang CL, Sarawate CA, Willey VJ, Cziraky MJ, Bohn RL. Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed-care population. Circ Cardiovasc Qual Outcomes 2010; 3:538-45.

# The Re-adjudication of Mortality and MACE from the RECORD Trial

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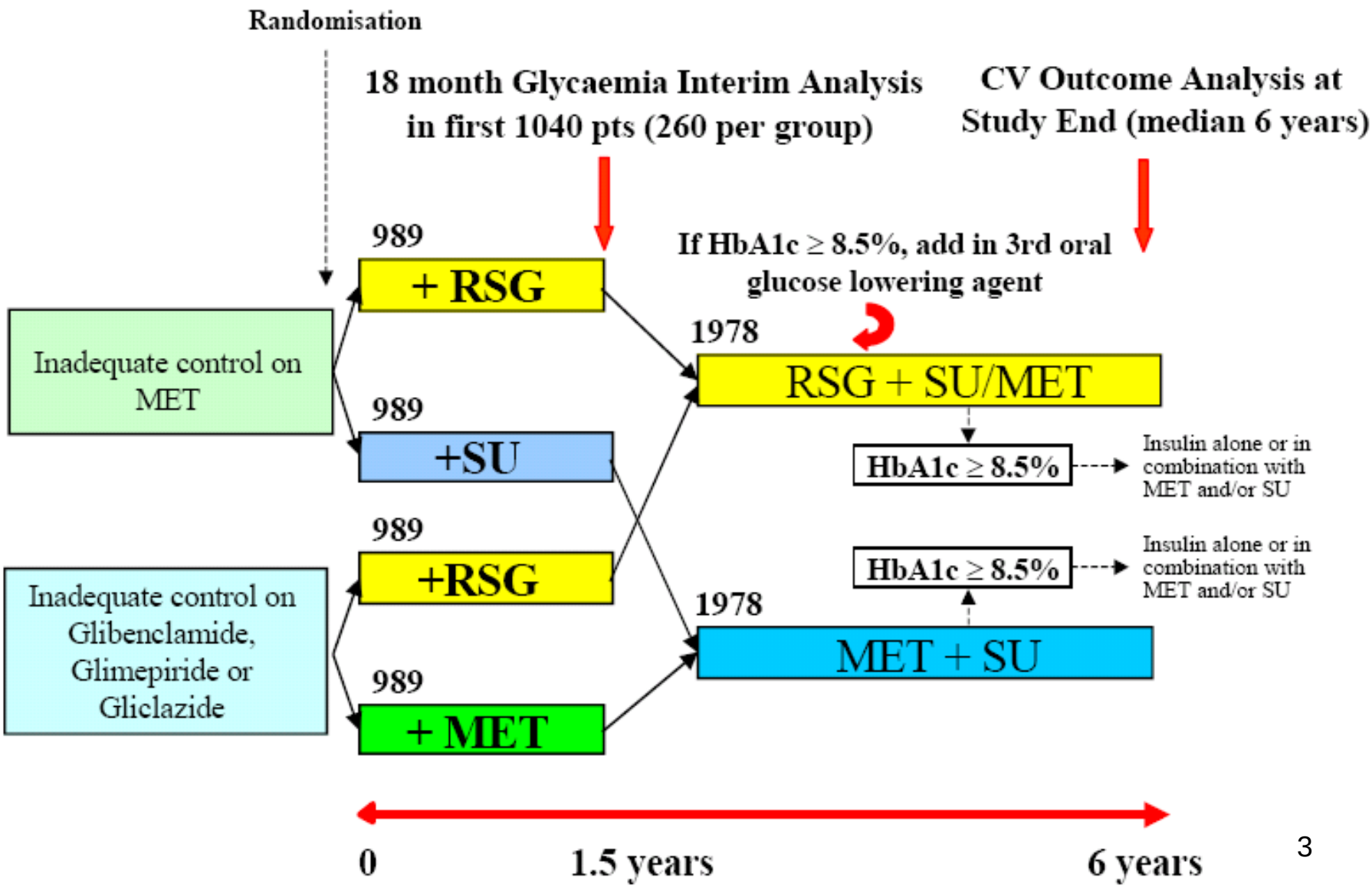
Division of Cardiovascular and Renal Products
US Food and Drug Administration

June 5, 2013

# Overview

- RECORD design characteristics
- Priorities for FDA in the re-adjudication
- The Duke Clinical Research Institute (DCRI) re-adjudication
  - Ascertainment
  - Methodology and Quality Control
  - Results
- Conclusions

# RECORD


Randomisation
18 month Glycaemia Interim Analysis in first 1040 pts (260 per group)
CV Outcome Analysis at Study End (median 6 years)
Inadequate control on MET
989
+ RSG
989
+SU
Inadequate control on Glibenclamide, Glimepiride or Gliclazide
989
+RSG
989
+ MET
If HbA1c ≥ 8.5%, add in 3rd oral glucose lowering agent
1978
RSG + SU/MET
HbA1c ≥ 8.5%
Insulin alone or in combination with MET and/or SU
1978
MET + SU
HbA1c ≥ 8.5%
Insulin alone or in combination with MET and/or SU
0
1.5 years
6 years

# RECORD: 364 Centers in 25 Countries

- Australia (10)
- Belgium (11)
- Bulgaria (8)
- Croatia (8)
- Czech Republic (11)
- Denmark (9)
- Estonia(12)
- Finland (18)
- France (38)
- Germany (18)
- Greece (13)
- Hungary (18)
- Italy (19)
- Latvia (10)
- Lithuania (8)
- Netherlands (17)
- New Zealand (8)
- Poland (17)
- Romania (7)
- Russia (6)
- Slovakia (18)
- Spain (9)
- Sweden (19)
- Ukraine (7)
- United Kingdom (45)

# Re-adjudication Priorities for FDA

- Independent
  - Unfettered access to all information sources
  - Robust re-ascertainment of CV events
- Complete
  - Mortality
  - MACE
  - Using event definitions from RECORD
  - Using standardized definitions of MACE events being developed by FDA

# Re-adjudication Priorities for FDA

- Rigorous statistical analysis plans
  - Mortality
  - MACE
  - Submitted to FDA in advance concurrence
- Stringent Internal quality controls during the re-adjudication process
- Clear identification of analysis limitations

# Prospective RECORD Re-adjudication Statistical Plans

- Re-adjudication Protocol for RECORD
  - Version 1, 28 January 2011
  - Amendment Version 2, 24 June 2011
- Statistical Analysis Plans
  - First Phase (Mortality), 13 July 2011
  - Second Phase (MACE), 24 January 2012

# Information Sources for DCRI

- GSK provided
  - Electronic datasets (sent to the DCRI prior to the event packet files)
  - Paper CRFs
  - Source
- MediciGlobal provided
  - Third party survival data forms
- DCRI requests directly to sites
  - 2 attempts
  - Independent vendor for translation services

# Ascertainment - Limitations

- Time effects
  - RECORD initiation: 13 Apr 2001
  - RECORD completion: 26 Dec 2008
- Investigative sites effects
  - Sites close
  - Coordinators leave
  - Investigators retire
  - Inadequate resources to re-process decade-old records
- Patients effects
  - Move
  - Become unable to return to the investigative site
  - Obtain medical care for CV events at non-investigative sites (e.g., the closest hospital)

# Ascertainment – Limitations

## Poor site responses to DCRI CEC queries of suspected events

- Mortality – 127 queries of death classification
  - 43 closed with no response from site
  - 61 closed with response that no additional data available
  - 23 closed with additional data (18% response rate)
    - 16 no change to adjudication result
    - 7 changed death from "unknown" to a known cause
- MI/CVA – 70 queries
  - 31 closed with no response from site
  - 20 closed with response that no additional data available
  - 19 closed with additional data (27% response rate)
    - 9 no change to adjudication result
    - 2 changed MI (one from MI yes to no; and one from MI no to yes)
    - 8 had no adjudication prior to receiving the additional information

# Ascertainment
# Incomplete Vital Status Data

- DCRI definition of completers
  - Died
  - F2F with vitals recorded on or after 24 Aug 08
  - F2F in 2008 and phone visit after 24 Aug 08
- On this basis
  - 3843 completed patients
  - 604 patients deemed incomplete
    - Included 127 patients from the original RECORD trial with unknown vital status

# Vital Status
# 604 Incomplete Subjects

- 298 subjects – additional source documentation obtained by GSK/Quintiles in the 2010-11 post-study time frame that confirmed last follow-up date
- 298 subjects – referred to MediciGlobal for vital status search
- 8 additional deaths discovered in the 2010-11 post-study time frame sent to DCRI for adjudication

# Vital Status
# 308 Known Deaths

- 43 known deaths with partial or unknown death dates
- Referred to MediciGlobal for vital status search

# Ascertainment – Vital Status

- Of the 341 subjects referred to MediciGlobal for vital status investigation
  - Vital status determined for 254 subjects
  - Year of death known for all deaths
  - Month/day required imputation on only 10 deaths
  - Vital status remained unknown for 87 patients (1.96% of the enrolled population)

# Ascertainment - MACE
## Automated Triggers

- All AE and SAE forms
  - MedDRA coded PT reviewed by Clinical, Clinical Event Committee (CEC), and Safety experts
  - Identify terms indicative of potential endpoints with a low threshold
  - Death forms when present in database
- Trigger specifications documented
  - RECORD Re-Adjudication Trigger Specifications

# Ascertainment – Manual Triggers

## DCRI coordinators – Manual/paper Review

- All source docs used in original adjudication
- Unscheduled visit forms resulting in hospitalization or ER visit
- Additional source docs collected during re-adjudication (discharge summaries, progress notes, pertinent lab values, and physician narratives)

# Ascertainment – Manual Triggers

- Investigator verbatim terms
- All SAE and AE forms
- All cases sent to the original RECORD CEC
- All death endpoint forms
- All myocardial infarction/unstable angina endpoint forms
- All stroke/TIA endpoint forms
- All hospitalizations

# Ascertainment – Manual Triggers

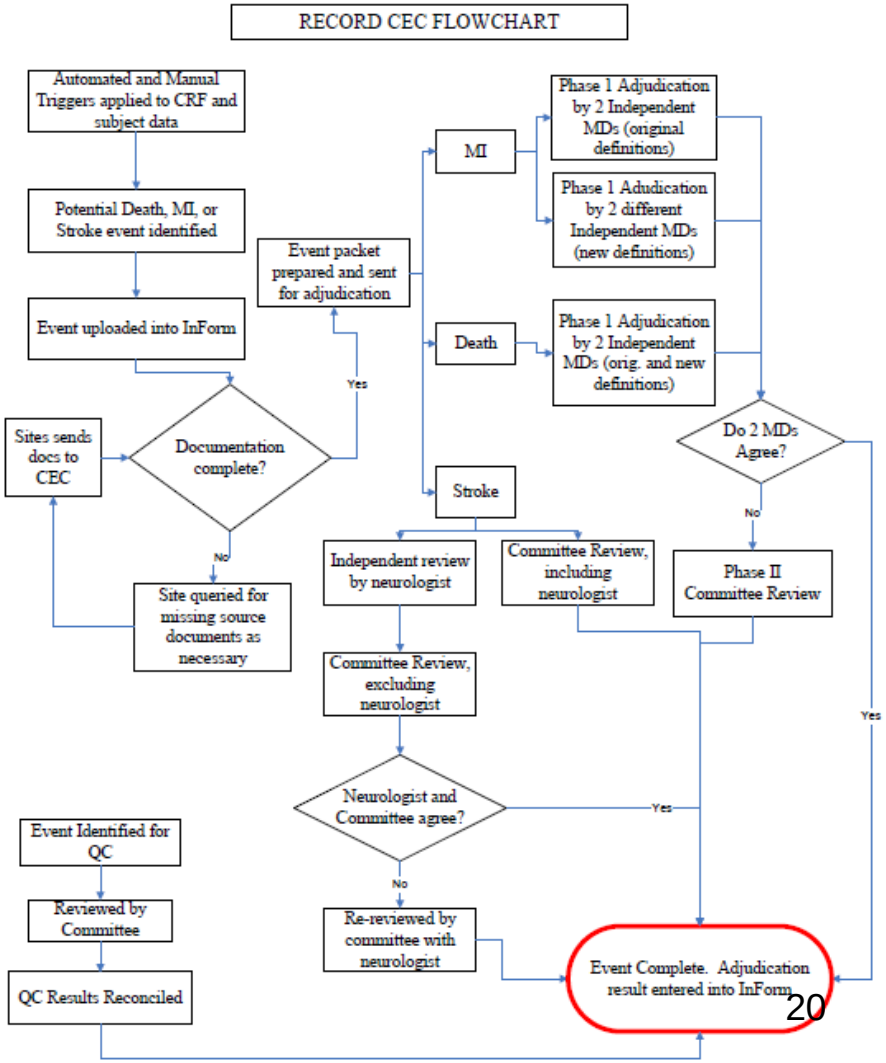
- All survival status forms
- All tracking forms for completely withdraw patients
- All study completion forms
- SAEs and AEs that were deleted by RECORD investigators
- All documentation of third party survival data forms

# Process and Quality Control

## The Re-adjudication of RECORD

# DCRI Clinical Event Committee

- Phase I review
  - Two physicians
- Phase II review
  - Three faculty physicians
  - All disagreements from Phase I
  - All suspected stroke events



# MACE Re-adjudication Quality Control

- Data for 110 re-adjudicated stroke and MI events (5% sample of the total re-adjudicated events) randomly/blindly re-re-adjudicated:
  - 103 events: no discrepancy
  - 4 events: minor discrepancy, date/time
  - 2 events: minor discrepancy, q wave classification
  - 1 event: major discrepancy, event classification

# MACE Manual Trigger Quality Control – Stage 1

- 165 (5%) of patients without automated or manual triggers randomly/blindly reviewed by CEC MD
  - 163 patients – no discrepancy
  - 2 patients – new additional manual triggers
    - both adjudicated as “no event”

# MACE Manual Trigger Quality Control – Stage 2

- 10 patients (5%) with manual triggers by CEC coordinator re-re-adjudicated by a CEC MD
- Manual triggers identified by the RECORD CEC physician were then compared to the manual triggers identified by the RECORD CEC coordinator
  - 5 subjects – no manual triggers confirmed
  - 2 subjects – same trigger identified
  - 3 subjects – same trigger identified, plus additional triggers
    - All new triggers adjudicated as “no-event”

# Results

## The Re-adjudication of RECORD

# Estimated Hazard Ratios of Death

## Original vs. DCRI vs. FDA

| | **RSG** events N=2220 | **MET/SU** events N=2227 | HR (95% CI) RSG/Comparator |
|---|---|---|---|
| **All Cause Death** | | | |
| **Original** report | 136 | 157 | 0.86 (0.68, 1.08) |
| **DCRI:** Deaths before 31-Dec-08 | 139 | 160 | 0.86 (0.69, 1.07) |
| **DCRI:** Including deaths after 31-Dec-08 | 147 | 167 | 0.87 (0.70, 1.08) |
| **Cardiovascular + Undetermined Death** | | | |
| **Original** report | 60 | 71 | 0.84 (0.59, 1.18) |
| **DCRI:** original or new definitions | 88 | 96 | 0.91 (0.68, 1.21) |
| **DCRI:** including deaths after 31-Dec-08 | 96 | 101 | 0.94 (0.71, 1.24) |
| **FDA 2010:** CV Death - all CV follow-up | | | 0.92 (0.65, 1.31) |
| **Cardiovascular Only** | | | |
| **DCRI:** Deaths before 31-Dec-08 | 35 | 42 | 0.82 (0.53, 1.29) |

*Note: the DCRI re-adjudication of deaths by original definition and new definition matched perfectly for all deaths. The old definition uses “unknown”, the new definition uses “undetermined”

## RSG (139 +8 deaths)

## MET + SU (160 +7 deaths)

DCRI: Original/New Definition of Death

Original Adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV + Undetermined | 32 | 5 | 23 |
| Non-CV | 1 | 42 | 8 |
| Not Adjudicated | 2 | 4 | 22 +8 |

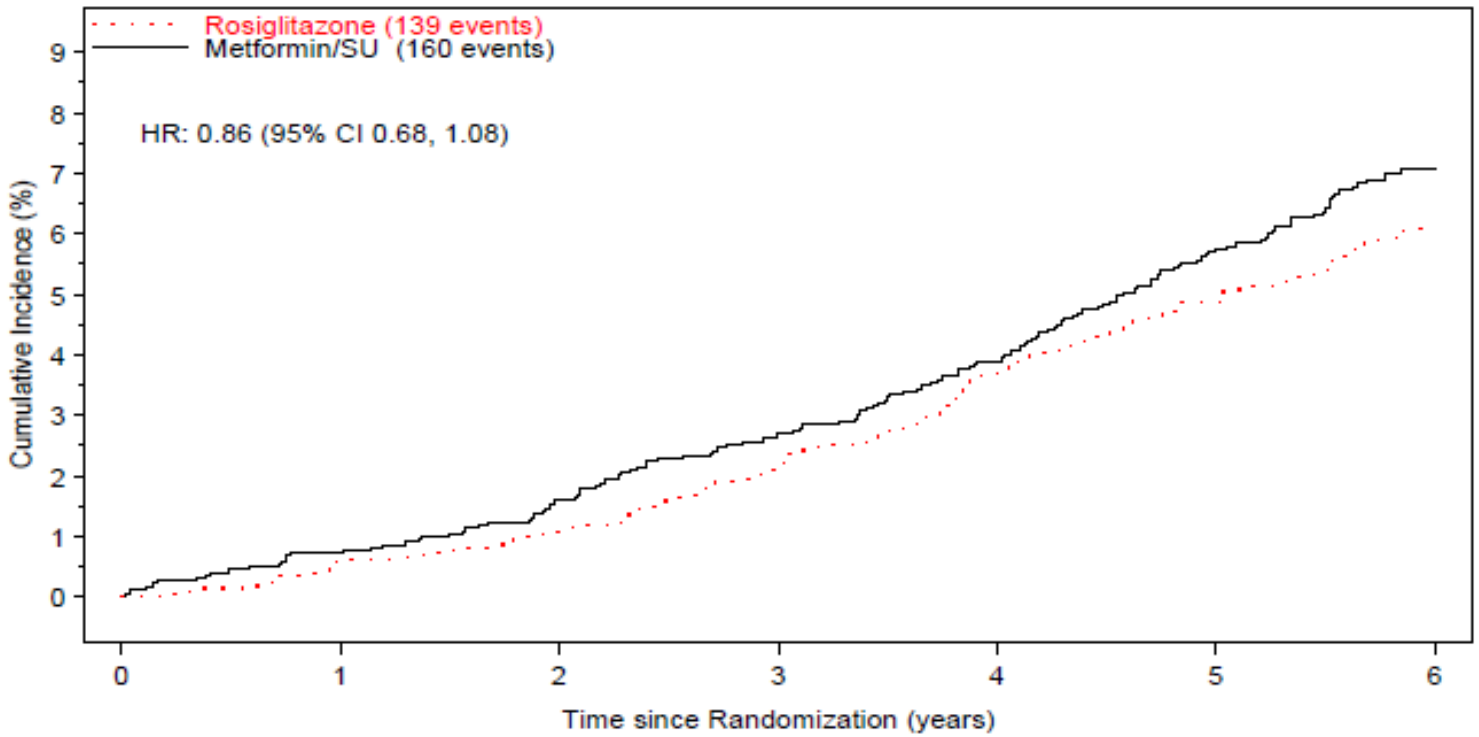
| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV + Undetermined | 41 | 7 | 23 |
| Non-CV | 0 | 56 +1 | 11 +1 |
| Not Adjudicated | 1 | 1 +1 | 20 +4 |

Discordant death classifications

Deaths after 12/31/2008

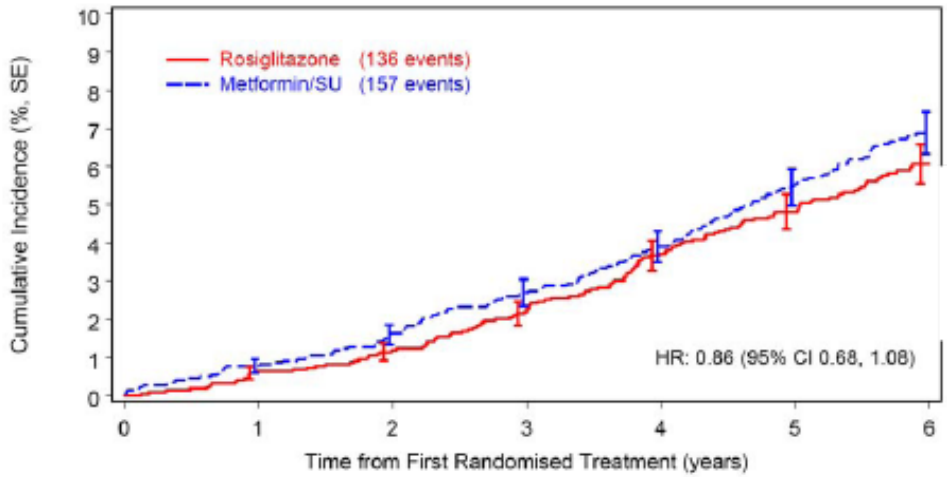
# DCRI: All Death

## Survival f/u (Original Def)




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rosaglitazone | | | | | | | |
| Events | 0 | 13 | 24 | 46 | 81 | 106 | 129 |
| At Risk | 2220 | 2190 | 2165 | 2130 | 2087 | 2048 | 988 |
| Metformin/SU | | | | | | | |
| Events | 0 | 16 | 35 | 59 | 85 | 125 | 150 |
| At Risk | 2227 | 2181 | 2140 | 2110 | 2079 | 2019 | 953 |

# Sponsor's original analysis: All-Cause Death, ITT

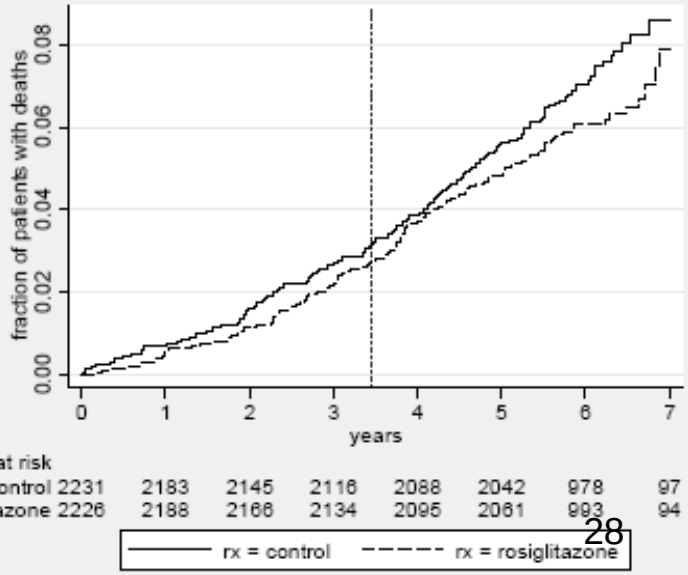



Subjects at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Rosiglitazone | 2220 | 2189 | 2166 | 2134 | 2096 | 2062 | 1137 |
| Metformin/SU | 2227 | 2183 | 2147 | 2117 | 2088 | 2046 | 1115 |

Data Source: DS Figure 7.32

# FDA 2010 re-adjudication: All-Cause Death




Number at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| rx = control | 2231 | 2183 | 2145 | 2116 | 2088 | 2042 | 978 | 97 |
| rx = rosiglitazone | 2226 | 2188 | 2166 | 2134 | 2095 | 2061 | 993 | 94 |

# Sensitivity Analyses – Mortality

| | |
|---|---|
| All-Cause, LDRT + 30 days, 60 days | No treatment effect, no interaction |
| CV+U, LDRT + 30 days, 60 days | No treatment effect, no interaction |
| CV , new FDA definitions | No treatment effect, no interaction |
| All-cause, amendment 7 | No treatment effect, no interaction |
| All-cause, landmark amend 7 | No treatment effect, no interaction |
| CV+U, prior to amend 7 | No treatment effect, no interaction |
| CV+U, landmark amend 7 | No treatment effect, no interaction |
| All-cause, before interim report | No treatment effect, no interaction |
| All-cause, following interim report | No treatment effect, no interaction |
| CV+U (new defs), prior to interim rpt | No treatment effect, no interaction |
| CV+U (new defs), following interim | No treatment effect, no interaction |
| All-cause, three EoF defs | No treatment effect, no interaction |
| CV+U, three EoF defs | No treatment effect, no interaction |
| All-cause, 24 Aug 2008 censoring | No treatment effect, no interaction |
| CV+U (new defs), 24 Aug 2008 censoring | No treatment effect, no interaction |

# Estimated Hazard Ratios of MACE

## Original adjudication vs DCRI re-adjudication

| | **RSG** events N=2220 | **MET/SU** events N=2227 | HR (95% CI) RSG/Comparator |
|---|---|---|---|
| **CV Death, Undetermined Death, MI, and Stroke** | | | |
| **Original** report | 154 | 165 | 0.93 (0.74, 1.15) |
| **DCRI** original definition | 181 | 188 | 0.96 (0.78, 1.17) |
| **DCRI** new definition | 186 | 191 | 0.97 (0.79, 1.18) |
| **FDA 2010:** MACE all CV follow-up | | | 1.07 (0.86, 1.33) |
| **MI (fatal and non-fatal)** | | | |
| **Original** report | 64 | 56 | 1.14 (0.80, 1.63) |
| **DCRI** original definition | 68 | 60 | 1.13 (0.80, 1.59) |
| **DCRI** new definition | 72 | 62 | 1.15 (0.82, 1.62) |
| **FDA 2010:** all CV follow-up | | | 1.38 (0.99, 1.93) |
| **Stroke (fatal and non-fatal)** | | | |
| **Original** report | 46 | 63 | 0.72 (0.49, 1.06) |
| **DCRI** original definition | 50 | 63 | 0.79 (0.54, 1.14) |
| **DCRI** new definition | 53 | 64 | 0.82 (0.57, 1.18) |
| **FDA 2010:** all CV follow-up | | | 0.89 (0.63, 1.28) |

## RSG

## MET + SU

### DCRI: Original Definition of MI

Original Adjudication — MI

| | MI | Non-MI |
|---|---|---|
| MI | 63 | 1 |
| Non-MI / Not reported | 5 | - |

| | MI | Non-MI |
|---|---|---|
| MI | 54 | 2 |
| Non-MI / Not reported | 6 | - |

### DCRI: Original Definition of Stroke

Original Adjudication — Stroke

| | Stroke | Non-Stroke |
|---|---|---|
| Stroke | 43 | 3 |
| Non-Stroke / Not reported | 7 | - |

| | Stroke | Non-Stroke |
|---|---|---|
| Stroke | 59 | 4 |
| Non-Stroke / Not reported | 4 | - |

Discordant MACE adjudications

# Missing Observations from RECORD
# A Conservative (Parsimonious) Estimate

| | RSG | Met/SU |
|---|---|---|
| Total Follow-up (person-years) | 11913 | 11808 |
| Person-years unobserved for MACE | 926 | 1011 |
| N (%) of patients with incomplete follow-up for MACE | 346 / 2220 (15.6) | 398 / 2227 (17.9%) |

- 744 total patients with some missing data (~8% of p-y exposure)
- Limited ascertainment of MACE events in this sub-population
- DCRI simulation suggests HR $\geq$ 1.5 required in this sub-pop to cause HR > 1.0 for the MACE result of the overall trial

# Conclusions-1

- Well-conceived, well-executed, and comprehensive re-adjudication of the available RECORD MACE data by the DCRI
- Small number addit'l MACE events identified during re-adjudication did not change the overall findings that were originally reported for RECORD
- For the RSG group
  - HR for MI numerically higher
  - HR for CVA numerically lower
  - HR for MACE numerically lower

# Conclusions-2

- Missing observation time/people for MACE outcomes
  - 744 / 4447 (16.7%) of patients
  - Approximately 8% of total patient-year exposure
  - Balanced observation loss
    - pt-year exposure
    - number (%) of patients
- Vital Status unknown on 87 / 4447 patients (1.96%)
- DCRI lacked sufficient evidence to determine CV versus non-CV causality for 120 deaths
  - 107 deaths prior to 12/31/2008

# Conclusions-3

- Simulations by DCRI demonstrate that a HR for MACE in the unobserved data would have to be $\geq$ 1.5 to produce a probability of the HR for the overall trial MACE to exceed 1.0 which FDA agrees would be unlikely

- Sensitivity analysis by FDA demonstrates that extreme imbalance of mortality among 87 patients missing vital status would not cause the all-cause mortality HR to exceed 1.0

# Conclusion-4

- The aforementioned conclusions do not consider the impact that the open-label design may or may not have had on what the investigators entered into the source documents with respect to CV outcomes
- Regarding the allegation of data mishandling
  - No dataset from a large, long, complex trial is perfect, and the examples sited here most likely reflect isolated operational errors or lack of clarity at the site level
  - There is no convincing evidence for systemic, systematic, or intentional manipulation of efficacy or safety outcomes in RECORD

# The FDA Review of Cardiovascular Outcomes – An Overview

Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

**Rosiglitazone – June 5-6, 2013**

**Ellis F. Unger, MD**

Director
Office of Drug Evaluation-I
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration

# Outline

- Why are we here?
- Meta-analyses: general thoughts
- RECORD: key features
- RECORD: re-adjudication results
- Conclusions

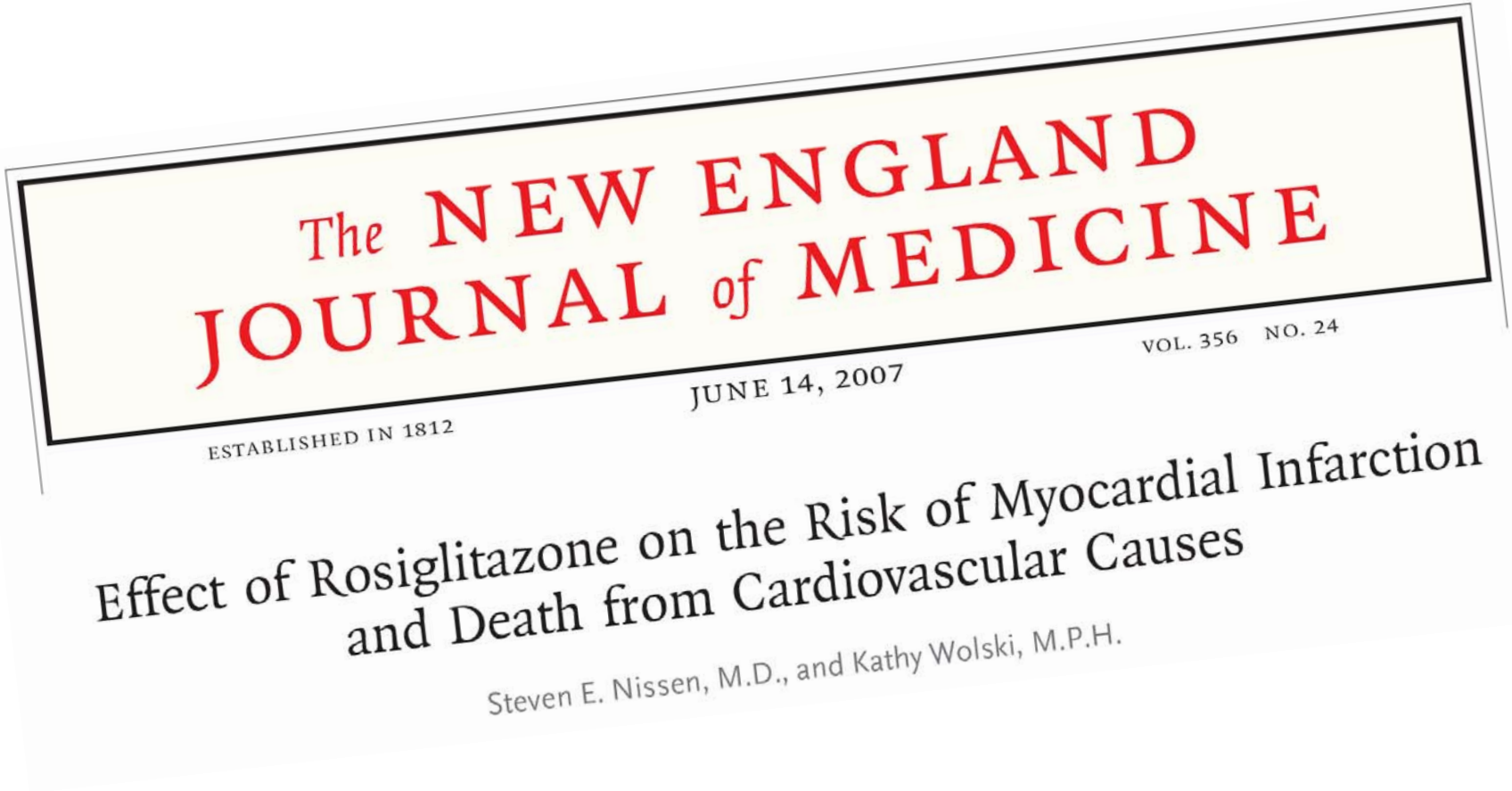
# Why are we here?

The Nissen-Wolski meta-analysis suggested that rosiglitazone could cause heart attacks and perhaps cardiovascular death.

Although rosiglitazone (and other drugs in this class) are well-known to cause fluid retention and heart failure, these effects are not related to myocardial infarction.

The findings of the meta-analysis led to labeling changes for rosiglitazone that markedly limited its use.

# Nissen/Wolski Meta-analysis



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

# Nissen/Wolski Meta-analysis

**Table 4.** Rates of Myocardial Infarction and Death from Cardiovascular Causes.

| Study | Rosiglitazone Group | Control Group | Odds Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of events/total no. (%)* | | | |
| **Myocardial infarction** | | | | |
| Small trials combined | 44/10,285 (0.43) | 22/6106 (0.36) | 1.45 (0.88–2.39) | 0.15 |
| DREAM | 15/2,635 (0.57) | 9/2634 (0.34) | 1.65 (0.74–3.68) | 0.22 |
| ADOPT | 27/1,456 (1.85) | 41/2895 (1.42) | 1.33 (0.80–2.21) | 0.27 |
| Overall | | | 1.43 (1.03–1.98) | 0.03 |
| **Death from cardiovascular causes** | | | | |
| Small trials combined | 25/6,845 (0.36) | 7/3980 (0.18) | 2.40 (1.17–4.91) | 0.02 |
| DREAM | 12/2,635 (0.46) | 10/2634 (0.38) | 1.20 (0.52–2.78) | 0.67 |
| ADOPT | 2/1,456 (0.14) | 5/2895 (0.17) | 0.80 (0.17–3.86) | 0.78 |
| Overall | | | 1.64 (0.98–2.74) | 0.06 |

Overall findings: statistically significant difference ($p$=0.03) on MI; trend ($p$=0.06) on cardiovascular death

# Meta-analyses: General Issues (1)

- Meta-analyses are almost always conducted with data in-hand:
  - There is usually an interest in several endpoints, e.g., cardiovascular death, stroke, MI, MACE.
  - There is inevitably some multiplicity, unless a particular finding triggered assessment of a single endpoint of interest.
  - Even then, there are decisions as to <u>what</u> to assess and <u>how</u> to assess it.

# Meta-analyses: General Issues (2)

- Such analyses usually don't consider multiplicity, i.e., the search for any of many safety findings that would pose a concern.
- For an effectiveness trial with a single endpoint, a *p*-value of 0.05 is considered meaningful, although it would usually call for substantiation.
- In meta-analyses, given the risk of false-positive findings, it can be difficult to consider $p<0.05$ equally persuasive.

# Multiplicity: Multiple Ways to Find a Signal

Assess 1 drug in a class?  Or a whole class?

# Multiplicity: Multiple Ways to Find a Signal

## Pool all studies? Or eliminate some of them?

| include? | Study # | Dose (mg) | Population | Study length | N treated | HR |
|---|---|---|---|---|---|---|
| Y | Study 1 | 5 | Type 2 DM | 12 months | 452 | 2.3 |
| Y | Study 2 | 5-15 | Type 2 DM | 6 months | 561 | 1.9 |
| Y | Study 3 | 5, 10 | DM renal | 12 months | 121 | 0.7 |
| Y | Study 4 | 10 | Type 2 DM | 6 months | 62 | 0.9 |
| Y | Study 5 | 5 | Type 2 DM | 3 months | 240 | 1.0 |
| N | Study 6 | 10 | DM poor control | 3 months | 68 | 1.2 |
| Y | Study 7 | 5-15 | Type 2 DM | 18 months | 98 | 0.8 |
| Y | Study 8 | 5 | Type 2 DM | 18 months | 122 | 0.7 |
| N | Study 9 | 5 | DM poor control | 36 months | 140 | 0.3 |
| Y | Study 10 | 10 | Type 2 DM | 3 months | 64 | - |
| Y | Study 11 | 2-16 | Type 2 DM | 12 months | 98 | 1.2 |
| Y | Study 12 | 5, 10 | Type 2 DM | 24 months | 120 | 1.4 |
| Y | Study 13 | 10 | Type 2 DM | 6 months | 32 | 0.2 |
| Y | Study 14 | 5 | Type 2 DM | 24 months | 118 | 1.1 |

# Multiplicity: Multiple Ways to Find a Signal

Include study(ies) that generated initial concern? Or not?

| include? | Study # | Dose (mg) | Population | Study length | N treated | HR |
|---|---|---|---|---|---|---|
| ? | Study 1 | 5 | Type 2 DM | 12 months | 452 | 2.3 |
| ? | Study 2 | 5-15 | Type 2 DM | 6 months | 561 | 1.9 |
| Y | Study 3 | 5, 10 | DM renal | 12 months | 121 | 0.7 |
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# Multiplicity: Multiple Ways to Find a Signal

Consideration of more than 1 concern:

1. heart failure
2. death (all-cause)
3. death (cardiovascular)
4. myocardial infarction (fatal and/or nonfatal)
5. stroke (fatal and/or non-fatal)
6. MACE (3 + 4 + 5)

7. suicidality

8+ cancer: (lung, colon, breast, others, all)

# Multiplicity: Multiple Ways to Analyze

1. on-treatment
2. intent-to-treat
3. way to handle studies with no events
4. models: random effects; fixed effects

# Multiplicity: Multiple Ways to Consider a Signal

Sometimes, subsets are considered:

1. demographic (age, sex, etc.)
2. underlying disease(s)
3. drug dose
4. length of treatment

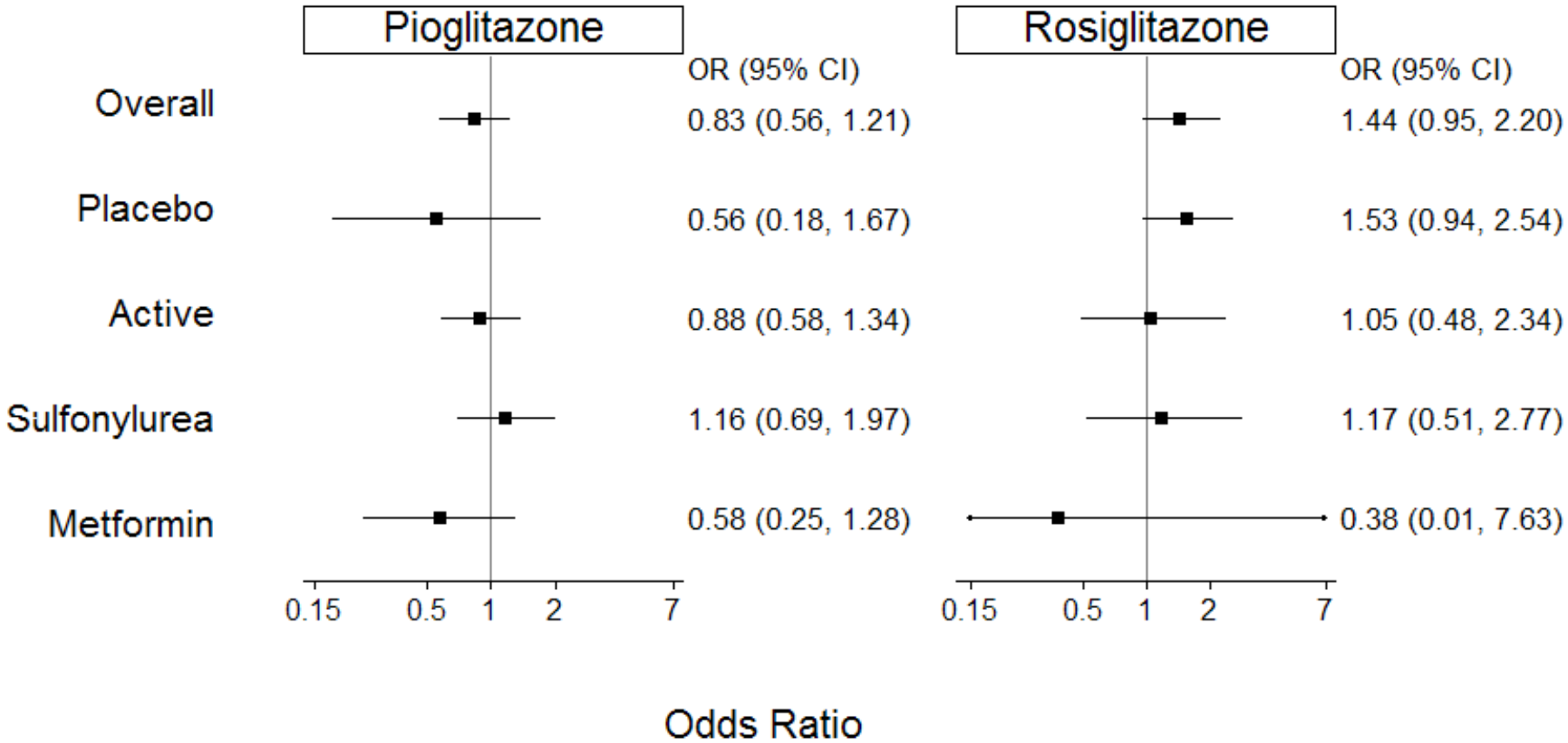
# Thus, with meta-analyses, the potential for false positive findings can be <u>extreme</u>

- Drug alone, versus drug class
- Many ways to include (or not include) studies
- Numerous endpoints of interest
- Numerous subgroups
- To consider the overall multiplicity, the various choices must be multiplied together:

>2 X "many" X "many" X "many" = hundreds!

Yet few consider multiplicity when interpreting M-A; Considerable potential for false positive findings

# Results of Meta-Analyses for Pioglitazone and Rosiglitazone on MACE Endpoints




**From Dr. Bradley McEvoy, July 13-14, 2010 advisory committee meeting**

# RECORD

The RECORD study, a 4400-patient randomized controlled trial with many cardiovascular endpoints and long duration, could help inform whether rosiglitazone causes myocardial infarction and CV death.

There were criticisms of RECORD's performance and analysis; therefore, the manufacturer was asked to conduct, as an explicit part of Dr. Woodcock's 2010 decision, a re-adjudication of the critical endpoints, to see whether the study could better contribute to the assessment of whether rosiglitazone did, in fact, increase the rate of myocardial infarction and CV death.

# RECORD: Key Features

- Aim was to show non-inferiority of combination therapy with rosiglitazone to therapy without rosiglitazone with respect to CV outcomes.
- Open-label trial – key limitation
- Primary endpoint: time-to-first cardiovascular hospitalization or cardiovascular death
- Adjudication of potential endpoint events by a Clinical Endpoint Committee (CEC), blinded to treatment assignment, but…
- Potential ascertainment bias with open-label design (whether potential events were sent to the CEC)

# RECORD: Re-Adjudication

- Discussion at 2010 Advisory Committee Meeting highlighted a number of concerns, principally:
  - Open-label design with potential for bias
  - Questions about completeness of follow-up
- These concerns led to restrictive labeling for rosiglitazone and re-adjudication of RECORD

# RECORD Re-Adjudication: Critique from Dr. Marciniak of the Division of Cardiovascular and Renal Products

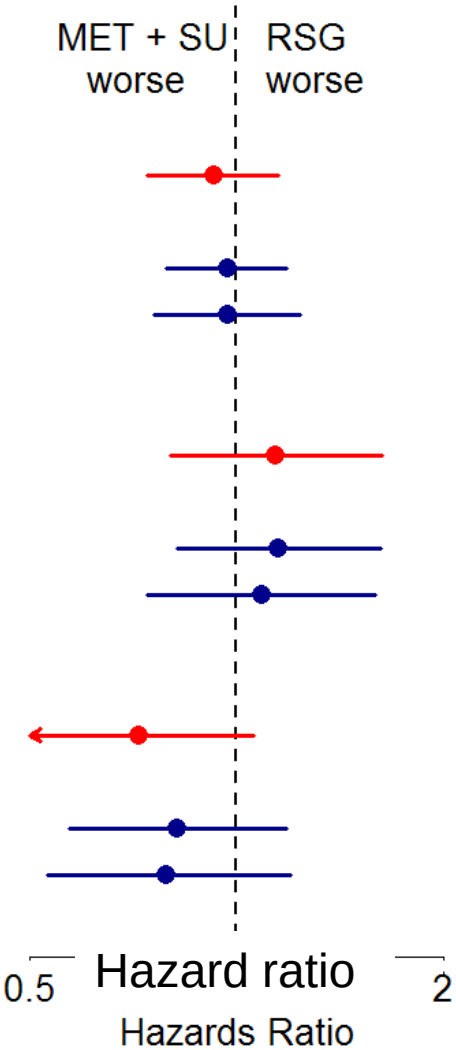
- Academic research organizations have limitations and are not independent:
  - Lack access to primary source data
  - Paid by company
- There is little new information post-re-adjudication

# RECORD Re-Adjudication: Critique from Dr. Marciniak of the Division of Cardiovascular and Renal Products

- Academic research organizations have limitations and are not independent:
  - Lack access to primary source data
  - Are paid by company
- There is little new information post-re-adjudication

# RECORD: Little Change in Hazard Ratios for MACE – Original vs. Re-adjudicated Analyses

| | MET + SU (N=2227) | RSG (N=2220) | HR (95% CI) |
|---|---|---|---|
| **CV death + MI + Stroke** | | | |
| Original | 165 | 154 | 0.93 (0.74, 1.15) |
| Re-adjudicated: | | | |
| Full follow-up | 191 | 186 | 0.97 (0.79, 1.18) |
| Dual Trt + 90 days | 134 | 118 | 0.97 (0.76, 1.24) |
| **MI** | | | |
| Original | 56 | 64 | 1.14 (0.80, 1.63) |
| Re-adjudicated: | | | |
| Full follow-up | 62 | 72 | 1.15 (0.82, 1.62) |
| Dual Trt + 90 days | 53 | 53 | 1.09 (0.75, 1.60) |
| **Stroke** | | | |
| Original | 63 | 46 | 0.72 (0.49, 1.06) |
| Re-adjudicated: | | | |
| Full follow-up | 64 | 53 | 0.82 (0.57, 1.18) |
| Dual Trt + 90 days | 54 | 39 | 0.79 (0.53, 1.20) |



# Major Adverse Cardiovascular Events (MACE) in RECORD

- Additional MACE events were found, but the new events were not disproportionately indentified in either treatment group
- Hazard ratios were little changed by re-adjudication

# All-cause Mortality in RECORD – Worth Considering Because…

- All-cause mortality is a “hard” endpoint, not influenced by open-label design
- Objective
- Insensitive to bias
- Little need for adjudication
- Verifiable, using public records

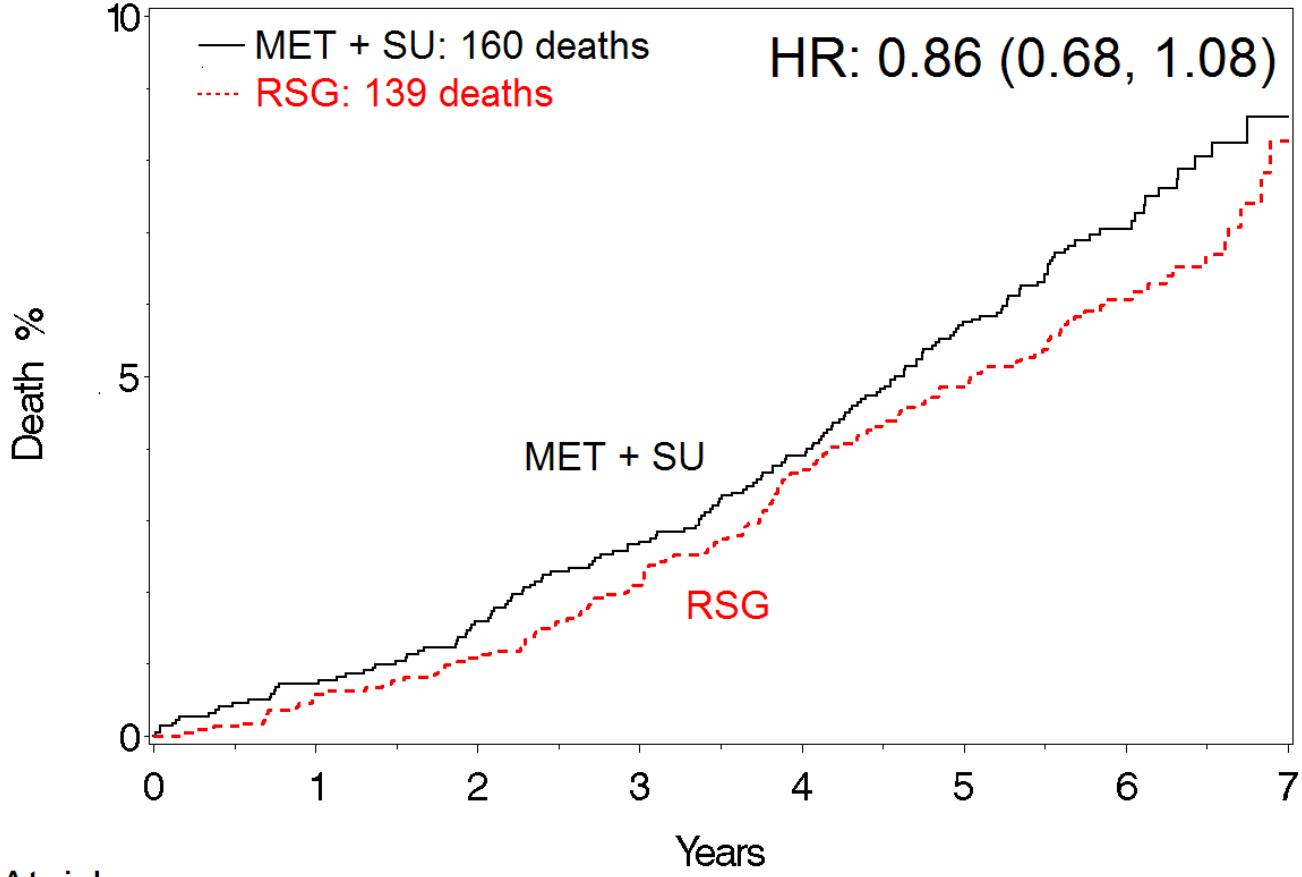
# All-Cause Mortality: Full Follow-up (DCRI Primary Endpoint)

| | |
|---|---|
| Rosiglitazone | 139/2220 (6.3%) |
| Control | 160/2227 (7.2%) |

Hazard ratio = 0.86

95% confidence interval = 0.68, 1.08

# DCRI: All-cause Mortality in RECORD, Full Follow-up




At risk:

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| MET+SU: | 2227 | 2183 | 2143 | 2114 | 2084 | 2026 | 974 | 126 |
| RSG: | 2220 | 2191 | 2167 | 2136 | 2093 | 2055 | 1015 | 110 |

# Mortality in RECORD

- Multiple ways to consider the findings:
  - Cardiovascular mortality or all-cause mortality
  - Intent-to-treat population or various definitions of “on treatment” populations

# All-cause Mortality; Cardiovascular Mortality in RECORD

- Irrespective of the specific analysis selected, the hazard ratio is in the favorable to neutral range, which seems reassuring.

# Conclusions on RECORD (1)

- RECORD with its re-adjudicated results can be viewed as a means to test two hypotheses:
  1. Rosiglitazone increases the risk of MI
  2. Rosiglitazone increases the risk of cardiovascular mortality

# Conclusions on RECORD (2)

- The results of the re-adjudication of RECORD do <u>not</u> substantiate these hypotheses:
  - Results for myocardial infarction are indeterminate
  - Results for all-cause mortality seem reassuring

# FDA Statistical Analyses of RECORD based on Re-adjudicated Outcomes

**June 5, 2013**

**Eugenio Andraca-Carrera, PhD**
Division of Biometrics 7
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

# Outline

- **Disposition and Exposure**
- Original vs. Re-adjudicated Events
- Updated Statistical Analyses
- Sensitivity Analyses
- Summary

# Disposition

| | RSG (*N* = 2220) | MET + SU (*N* = 2227) |
|---|---|---|
| Completed to last visit | 1835 (82.7%) | 1797 (80.7%) |
| Died before completion or withdrawal | 111 (5.0%) | 138 (6.2%) |
| Withdrew /lost to FU/ followed for survival | 274 (12.3%) | 292 (13.1%) |
| Alive | 210 (9.5%) | 216 (9.7%) |
| Died | 30 (1.4%) | 23 (1.0%) |
| Unknown vital status | 34 (1.5%) | 53 (2.4%) |

# Disposition

| | RSG (*N* = 2220) | MET + SU (*N* = 2227) |
|---|---|---|
| Completed to last visit | 1835 (82.7%) | 1797 (80.7%) |
| Died before completion or withdrawal | 111 (5.0%) | 138 (6.2%) |
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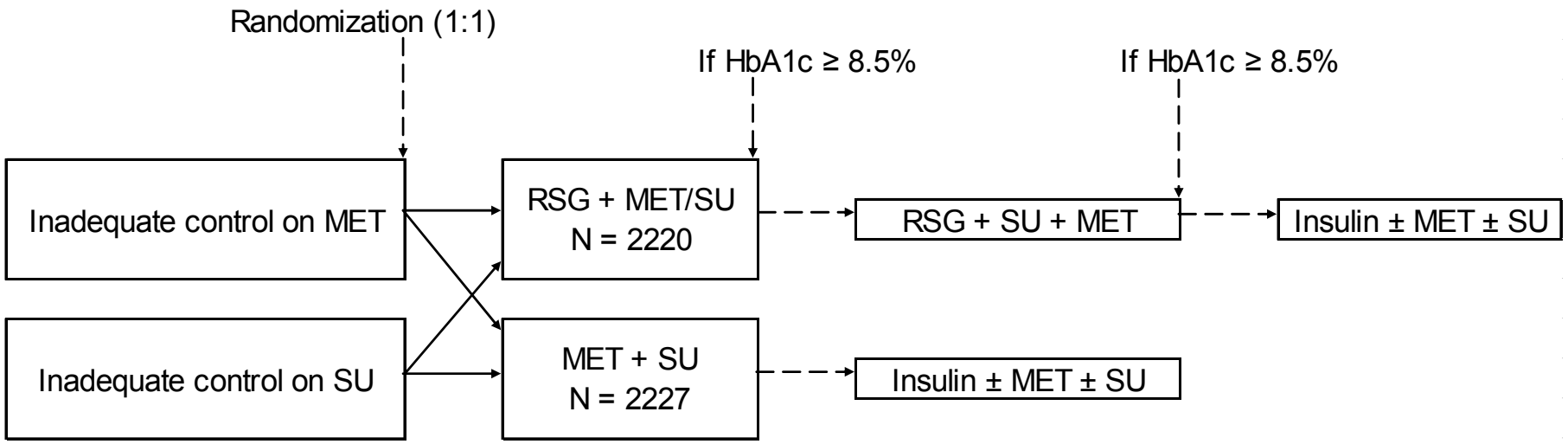
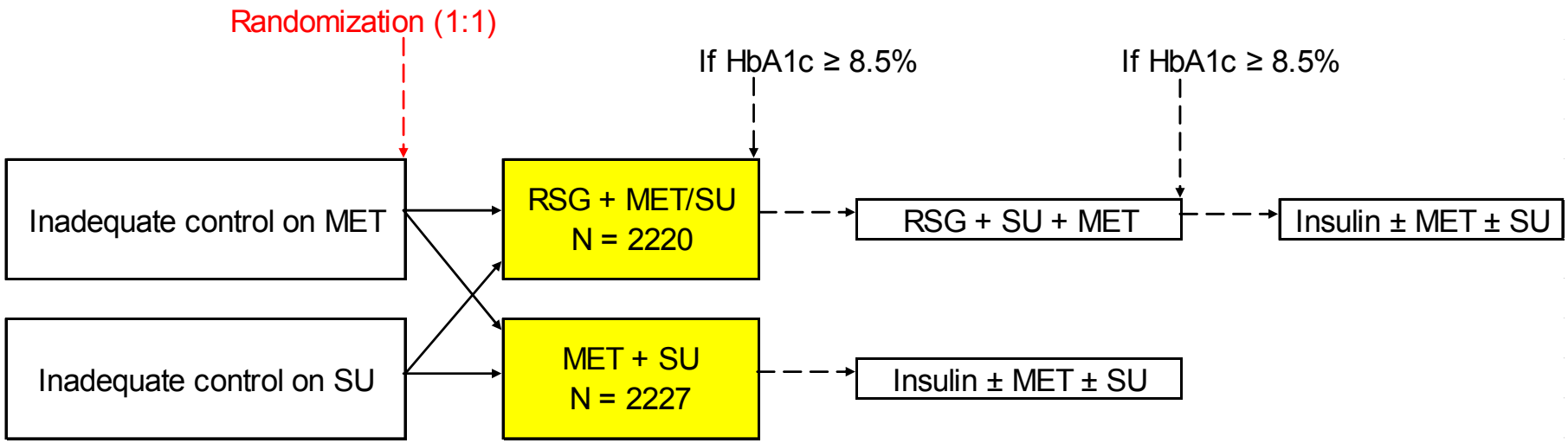
| Alive | 210 (9.5%) | 216 (9.7%) |
| Died | 30 (1.4%) | 23 (1.0%) |
| **Unknown vital status** | **34 (1.5%)** | **53 (2.4%)** |

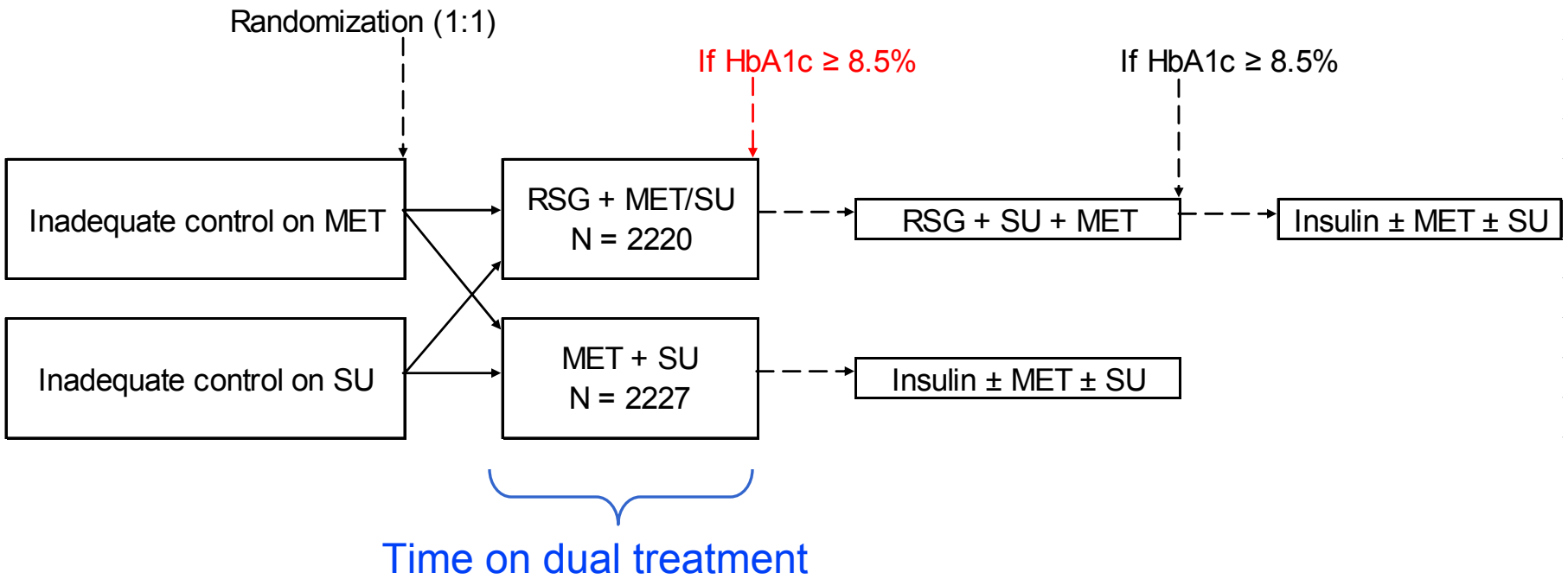
# Randomization Scheme



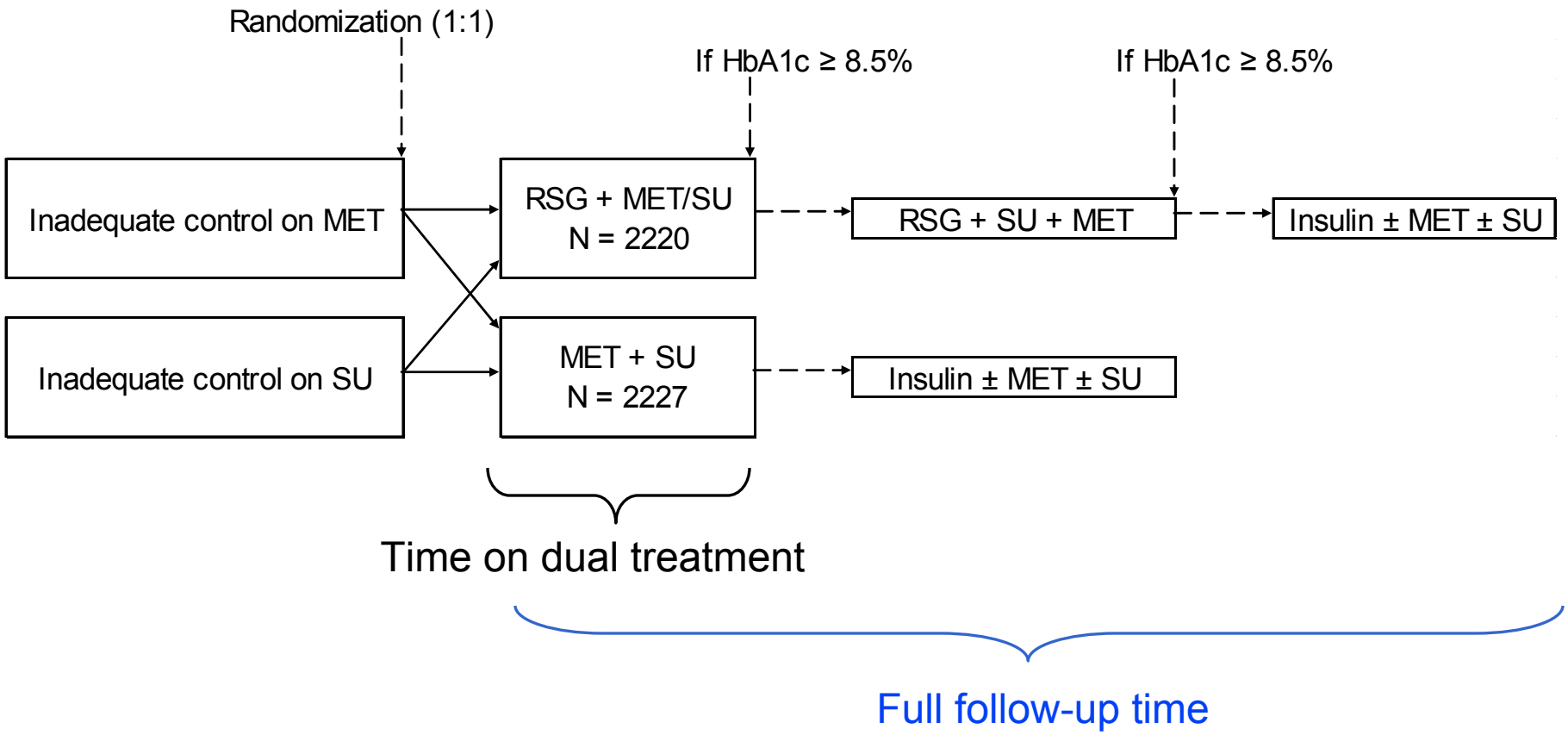
# Randomization Scheme



# Randomization Scheme



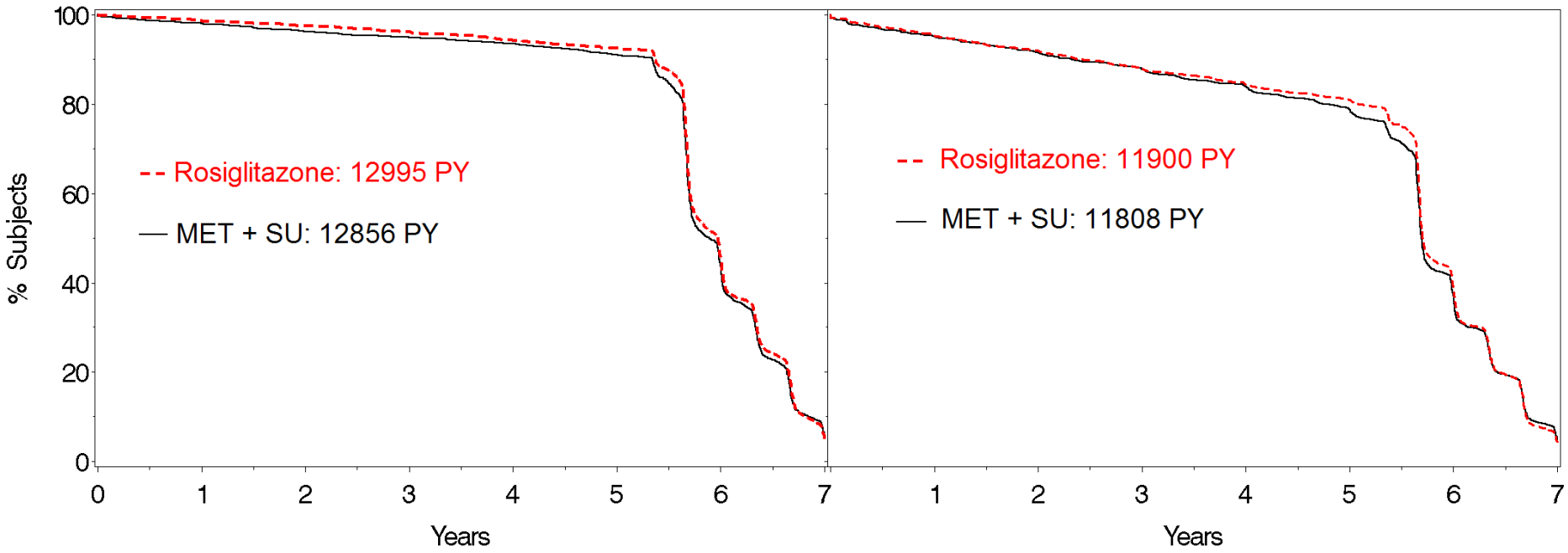
# Randomization Scheme



# Survival and CV Follow-Up "Full follow-up" Population

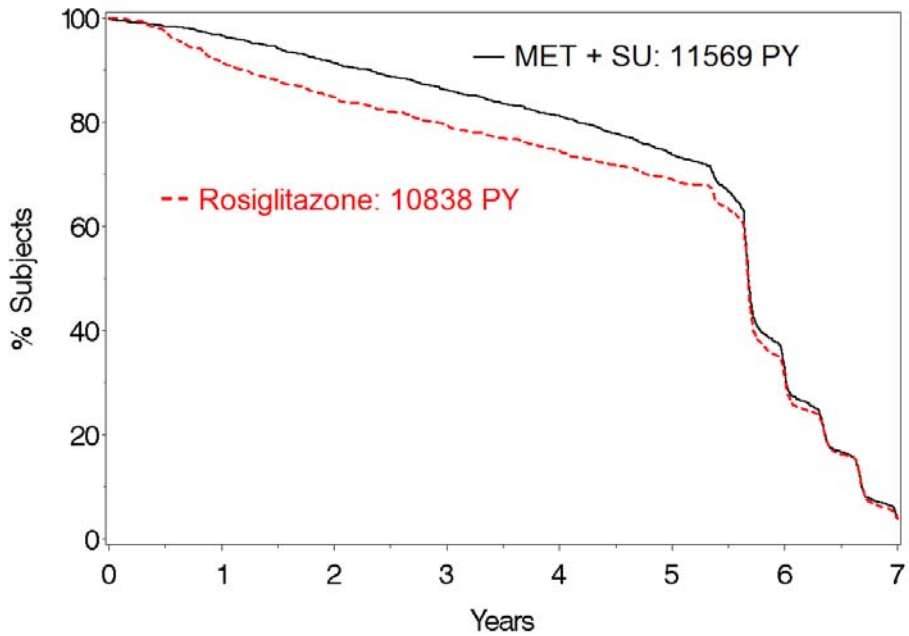
Time to **death** or discontinuation from **survival follow-up**

Time to **MACE** or discontinuation from **CV follow-up**



# Survival Follow-Up "On Dual Treatment" Population

Time to **discontinuation from dual therapy** or death




| | RSG (N = 2220) | MET + SU (N = 2227) |
|---|---|---|
| Years of follow-up (mortality) | 12995 | 12856 |
| Years on dual therapy (%) | 72% | 80% |
| Added triple therapy or insulin (%) | 33% | 24% |

# Disposition and Exposure

- Disposition (completed, died or withdrew) was similar in both treatment arms
- Vital status is unknown for 87 subjects (1.96%): 34 RSG, 53 MET + SU
- Full follow-up (as randomized) for CV outcomes and survival were similar in both treatment arms
- Subjects randomized to RSG were more likely to use rescue medication or discontinue randomized (dual) treatment

# Outline

- Disposition and Exposure
- **Original vs. Re-adjudicated Events**
- Updated Statistical Analyses
- Sensitivity Analyses
- Summary

# Outcome Definitions

- Original adjudication using original definition
- DCRI Re-adjudication using original definition
- DCRI Re-adjudication using new definition: FDA standardized definitions for endpoints in cardiovascular trials

# Re-adjudication of Deaths

## RSG (139 deaths)

**DCRI re-adjudication (new/original definition)**

Original Adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 28 | 1 | 3 |
| Non-CV | 1 | 42 | 8 |
| Unknown | 4 | 4 | 20 |
| Not Adjudicated | 1 | 4 | 18 |
| Not Identified | 1 | 0 | 4 |
| Column Total | 35 | 51 | 53 |

## MET + SU (160 deaths)

**DCRI re-adjudication (new/original definition)**

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 33 | 1 | 4 |
| Non-CV | 0 | 56 | 11 |
| Unknown | 8 | 6 | 19 |
| Not Adjudicated | 1 | 1 | 17 |
| Not Identified | 0 | 0 | 3 |
| Column Total | 42 | 64 | 54 |

*Deaths prior to 12/31/2008

# Re-adjudication of Deaths

## RSG (139 deaths)

DCRI re-adjudication

Original Adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 28 | 1 | 3 |
| Non-CV | 1 | 42 | 8 |
| Unknown | 4 | 4 | 20 |
| Not Adjudicated | 1 | 4 | 18 |
| Not Identified | 1 | 0 | 4 |
| Column Total | 35 | 51 | 53 |

## MET + SU (160 deaths)

DCRI re-adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 33 | 1 | 4 |
| Non-CV | 0 | 56 | 11 |
| Unknown | 8 | 6 | 19 |
| Not Adjudicated | 1 | 1 | 17 |
| Not Identified | 0 | 0 | 3 |
| Column Total | 42 | 64 | 54 |

*Deaths prior to 12/31/2008

# Re-adjudication of Deaths

## RSG (139 deaths)

**DCRI re-adjudication**

Original Adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| **CV** | 28 | 1 | 3 |
| **Non-CV** | 1 | 42 | 8 |
| **Unknown** | 4 | 4 | 20 |
| **Not Adjudicated** | 1 | 4 | 18 |
| **Not Identified** | 1 | 0 | 4 |
| Column Total | 35 | 51 | 53 |

## MET + SU (160 deaths)

**DCRI re-adjudication**

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| **CV** | 33 | 1 | 4 |
| **Non-CV** | 0 | 56 | 11 |
| **Unknown** | 8 | 6 | 19 |
| **Not Adjudicated** | 1 | 1 | 17 |
| **Not Identified** | 0 | 0 | 3 |
| Column Total | 42 | 64 | 54 |

*Deaths prior to 12/31/2008

# Re-adjudication of Deaths

## RSG (139 deaths)

**DCRI re-adjudication**

Original Adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 28 | 1 | 3 |
| Non-CV | 1 | 42 | 8 |
| Unknown | 4 | 4 | 20 |
| Not Adjudicated | 1 | 4 | 18 |
| Not Identified | 1 | 0 | 4 |
| Column Total | 35 | 51 | 53 |

## MET + SU (160 deaths)

**DCRI re-adjudication**

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 33 | 1 | 4 |
| Non-CV | 0 | 56 | 11 |
| Unknown | 8 | 6 | 19 |
| Not Adjudicated | 1 | 1 | 17 |
| Not Identified | 0 | 0 | 3 |
| Column Total | 42 | 64 | 54 |

*Deaths prior to 12/31/2008

# Re-adjudication of Deaths

## RSG (139 deaths)

**DCRI re-adjudication**

Original Adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 28 | 1 | 3 |
| Non-CV | 1 | 42 | 8 |
| Unknown | 4 | 4 | 20 |
| Not Adjudicated | 1 | 4 | 18 |
| Not Identified | 1 | 0 | 4 |
| Column Total | 35 | 51 | 53 |

## MET + SU (160 deaths)

**DCRI re-adjudication**

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 33 | 1 | 4 |
| Non-CV | 0 | 56 | 11 |
| Unknown | 8 | 6 | 19 |
| Not Adjudicated | 1 | 1 | 17 |
| Not Identified | 0 | 0 | 3 |
| Column Total | 42 | 64 | 54 |

*Deaths prior to 12/31/2008

# Re-adjudication of Deaths

## RSG (139 deaths)

DCRI re-adjudication

Original Adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 28 | 1 | 3 |
| Non-CV | 1 | 42 | 8 |
| Unknown | 4 | 4 | 20 |
| Not Adjudicated | 1 | 4 | 18 |
| Not Identified | 1 | 0 | 4 |
| Column Total | 35 | 51 | 53 |

## MET + SU (160 deaths)

DCRI re-adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 33 | 1 | 4 |
| Non-CV | 0 | 56 | 11 |
| Unknown | 8 | 6 | 19 |
| Not Adjudicated | 1 | 1 | 17 |
| Not Identified | 0 | 0 | 3 |
| Column Total | 42 | 64 | 54 |

*Deaths prior to 12/31/2008

# Re-adjudication of Deaths

## RSG (139 deaths)

**DCRI re-adjudication**

Original Adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 28 | 1 | 3 |
| Non-CV | 1 | 42 | 8 |
| Unknown | 4 | 4 | 20 |
| Not Adjudicated | 1 | 4 | 18 |
| Not Identified | 1 | 0 | 4 |
| Column Total | 35 | 51 | 53 |

## MET + SU (160 deaths)

**DCRI re-adjudication**

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 33 | 1 | 4 |
| Non-CV | 0 | 56 | 11 |
| Unknown | 8 | 6 | 19 |
| Not Adjudicated | 1 | 1 | 17 |
| Not Identified | 0 | 0 | 3 |
| Column Total | 42 | 64 | 54 |

*Deaths prior to 12/31/2008

# Re-adjudication of Deaths

## RSG (139 +8 deaths)

DCRI Adjudication

Original Adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 28 | 1 | 3 |
| Non-CV | 1 | 42 | 8 |
| Unknown | 4 | 4 | 20 |
| Not Adjudicated | 1 | 4 | 18 +1 |
| Not Identified | 1 | 0 | 4 +7 |

## MET + SU (160 +7 deaths)

DCRI Adjudication

| | CV | Non-CV | Undetermined |
|---|---|---|---|
| CV | 33 | 1 | 4 |
| Non-CV | 0 | 56 +1 | 11 +1 |
| Unknown | 8 | 6 | 19 |
| Not Adjudicated | 1 | 1 | 17 |
| Not Identified | 0 | 0 +1 | 3 +4 |

Deaths after 12/31/2008

# Re-adjudication of MI

## DCRI Re-adjudication (original definition)

Original Adjudication

### RSG

| | MI | Non-MI |
|---|---|---|
| MI | 63 | 1 |
| Non-MI / Not reported | 5 | - |

### MET + SU

| | MI | Non-MI |
|---|---|---|
| MI | 54 | 2 |
| Non-MI / Not reported | 6 | - |

# Re-adjudication of MI

## RSG

## MET + SU

### DCRI Re-adjudication (original definition)

Original Adjudication

| | MI | Non-MI |
|---|---|---|
| MI | 63 | 1 |
| Non-MI / Not reported | 5 | - |

| | MI | Non-MI |
|---|---|---|
| MI | 54 | 2 |
| Non-MI / Not reported | 6 | - |

# Re-adjudication of MI

## RSG

## MET + SU

### DCRI Re-adjudication (original definition)

Original Adjudication

| | MI | Non-MI |
|---|---|---|
| MI | 63 | 1 |
| Non-MI / Not reported | 5 | - |

| | MI | Non-MI |
|---|---|---|
| MI | 54 | 2 |
| Non-MI / Not reported | 6 | - |

### DCRI Re-adjudication (new definition)

| | MI | Non-MI |
|---|---|---|
| MI | 63 | 1 |
| Non-MI / Not reported | 9 | - |

| | MI | Non-MI |
|---|---|---|
| MI | 54 | 2 |
| Non-MI / Not reported | 8 | - |

# Re-adjudication of MI

## RSG

## MET + SU

### DCRI Re-adjudication (original definition)

Original Adjudication

| | MI | Non-MI |
|---|---|---|
| MI | 63 | 1 |
| Non-MI / Not reported | 5 | - |

| | MI | Non-MI |
|---|---|---|
| MI | 54 | 2 |
| Non-MI / Not reported | 6 | - |

### DCRI Re-adjudication (new definition)

| | MI | Non-MI |
|---|---|---|
| MI | 63 | 1 |
| Non-MI / Not reported | 9 | - |

| | MI | Non-MI |
|---|---|---|
| MI | 54 | 2 |
| Non-MI / Not reported | 8 | - |

# Re-adjudication of Strokes

## RSG

### DCRI Re-adjudication (original definition)

Original Adjudication

| | Stroke | Non-Stroke |
|---|---|---|
| Stroke | 43 | 3 |
| Non-Stroke / Not reported | 7 | - |

## MET + SU

| | Stroke | Non-Stroke |
|---|---|---|
| Stroke | 59 | 4 |
| Non-Stroke/ Not reported | 4 | - |

# Re-adjudication of Strokes

## RSG

### DCRI Re-adjudication (original definition)

Original Adjudication

| | Stroke | Non-Stroke |
|---|---|---|
| Stroke | 43 | 3 |
| Non-Stroke / Not reported | 7 | - |

### DCRI Re-adjudication (new definition)

| | Stroke | Non-Stroke |
|---|---|---|
| Stroke | 43 | 3 |
| Non-Stroke / Not reported | 10 | - |

## MET + SU

### DCRI Re-adjudication (original definition)

| | Stroke | Non-Stroke |
|---|---|---|
| Stroke | 59 | 4 |
| Non-Stroke / Not reported | 4 | - |

### DCRI Re-adjudication (new definition)

| | Stroke | Non-Stroke |
|---|---|---|
| Stroke | 59 | 4 |
| Non-Stroke / Not reported | 5 | - |

# Re-adjudication Summary

| | | Original Analysis[1] | DCRI Original Definition[2] | DCRI New Definition[2] |
|---|---|---|---|---|
| **All-Cause Death** | RSG | 136 | 139 | 139 |
| | MET + SU | 157 | 160 | 160 |
| **CV + Undetermined Death** | RSG | 60 | 88 | 88 |
| | MET + SU | 71 | 96 | 96 |
| **MI** | RSG | 64 | 68 | 72 |
| | MET + SU | 56 | 60 | 62 |
| **Stroke** | RSG | 46 | 50 | 53 |
| | MET + SU | 63 | 63 | 64 |

[1]Original analysis included some deaths occurring after 12/31/2008
[2]Excluding deaths occurring after 12/31/2008

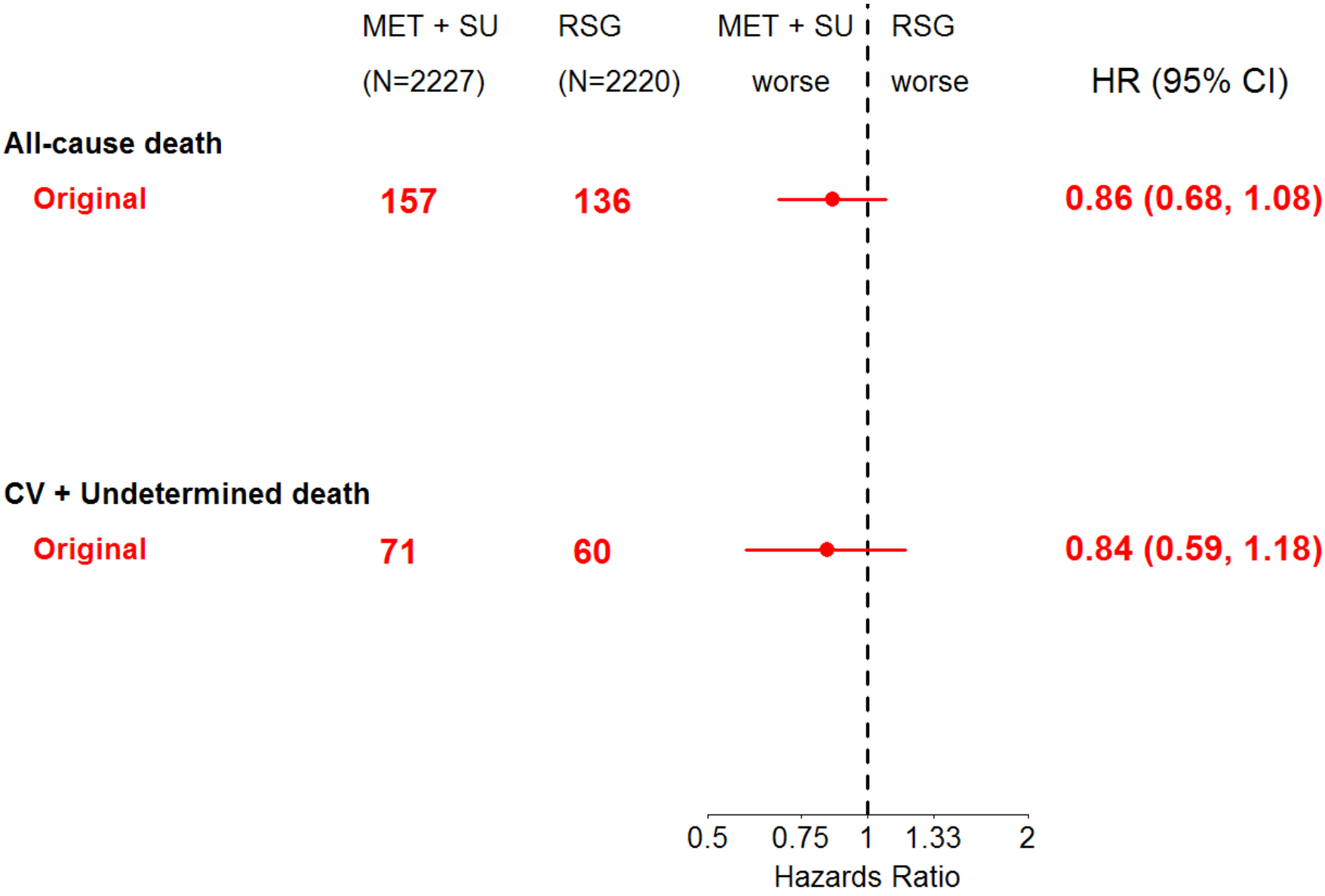
# Outline

- Disposition and Exposure
- Original vs. Re-adjudicated events
- **Updated Statistical Analyses**
- Sensitivity Analyses
- Summary

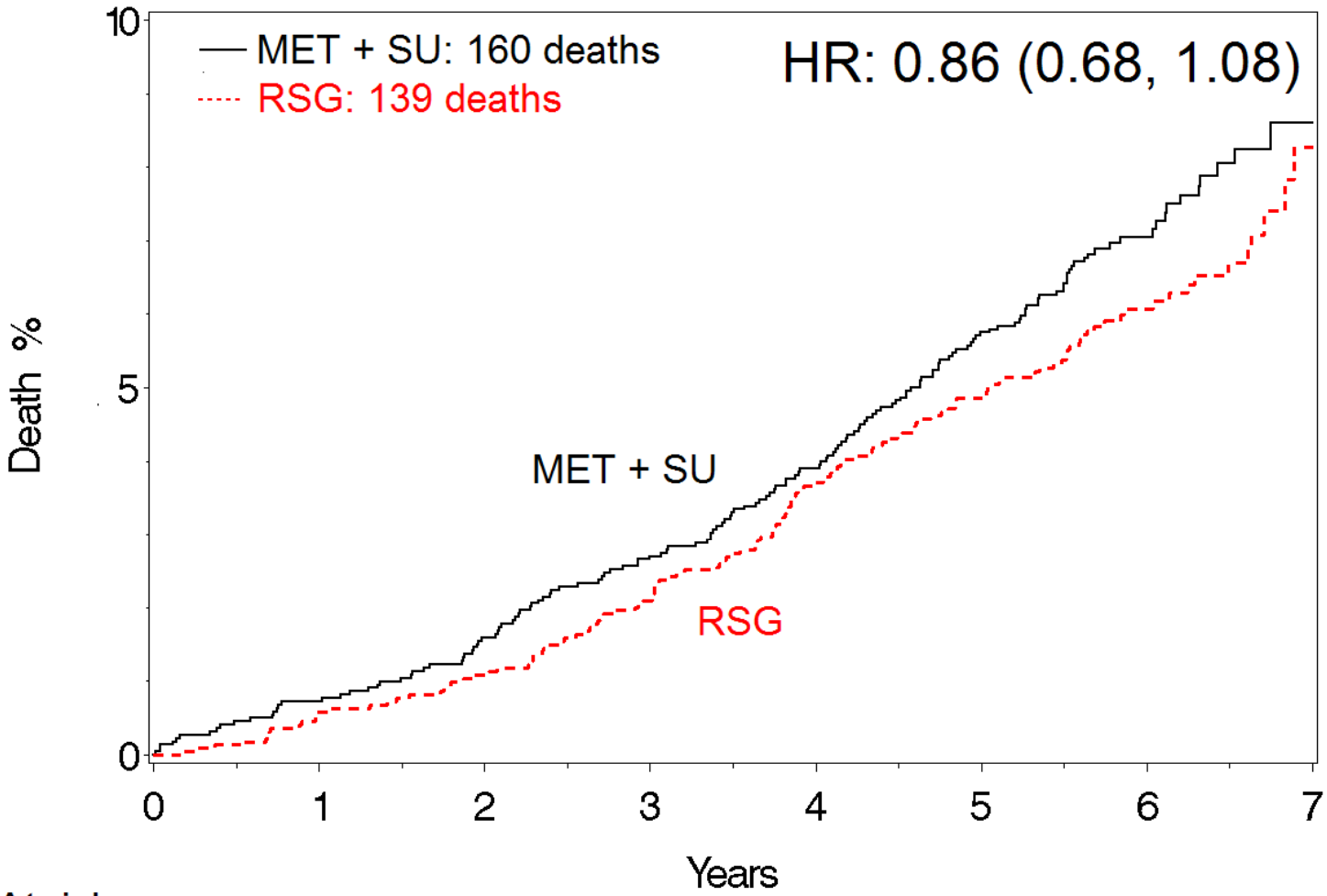
# Methodology

- Cox proportional hazards model stratified by background therapy (MET or SU) with a single covariate: rosiglitazone (yes / no)
- Endpoints:
  - Original Report
  - DCRI re-adjudicated events using new FDA Definition
- Populations:
  - Full follow-up time (i.e. as randomized)
  - On dual randomized treatment + 90 days

# Analysis of Deaths



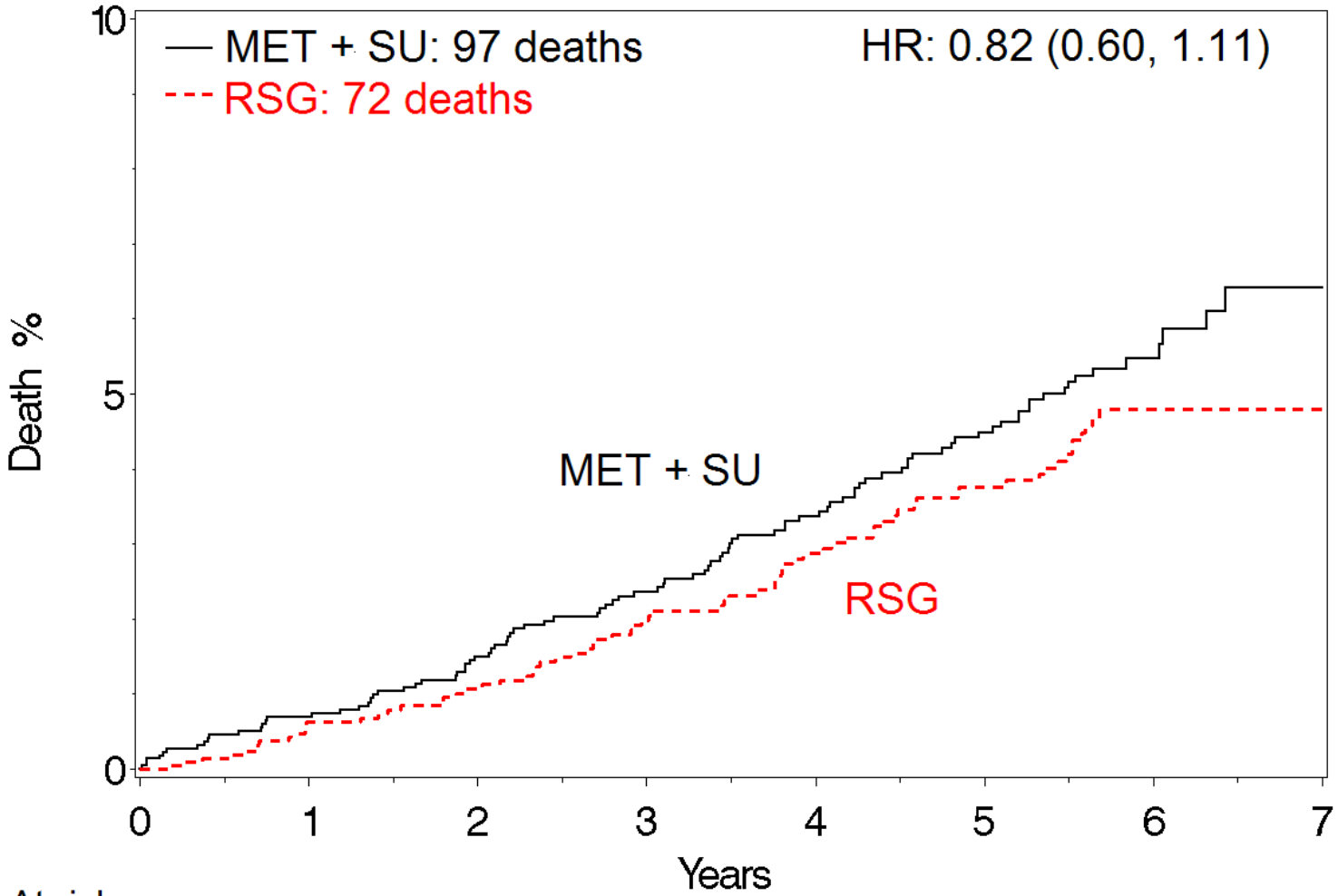
# DCRI All-Cause Mortality: Full Follow-Up




At risk:

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| MET+SU: | 2227 | 2183 | 2143 | 2114 | 2084 | 2026 | 974 | 126 |
| RSG: | 2220 | 2191 | 2167 | 2136 | 2093 | 2055 | 1015 | 110 |

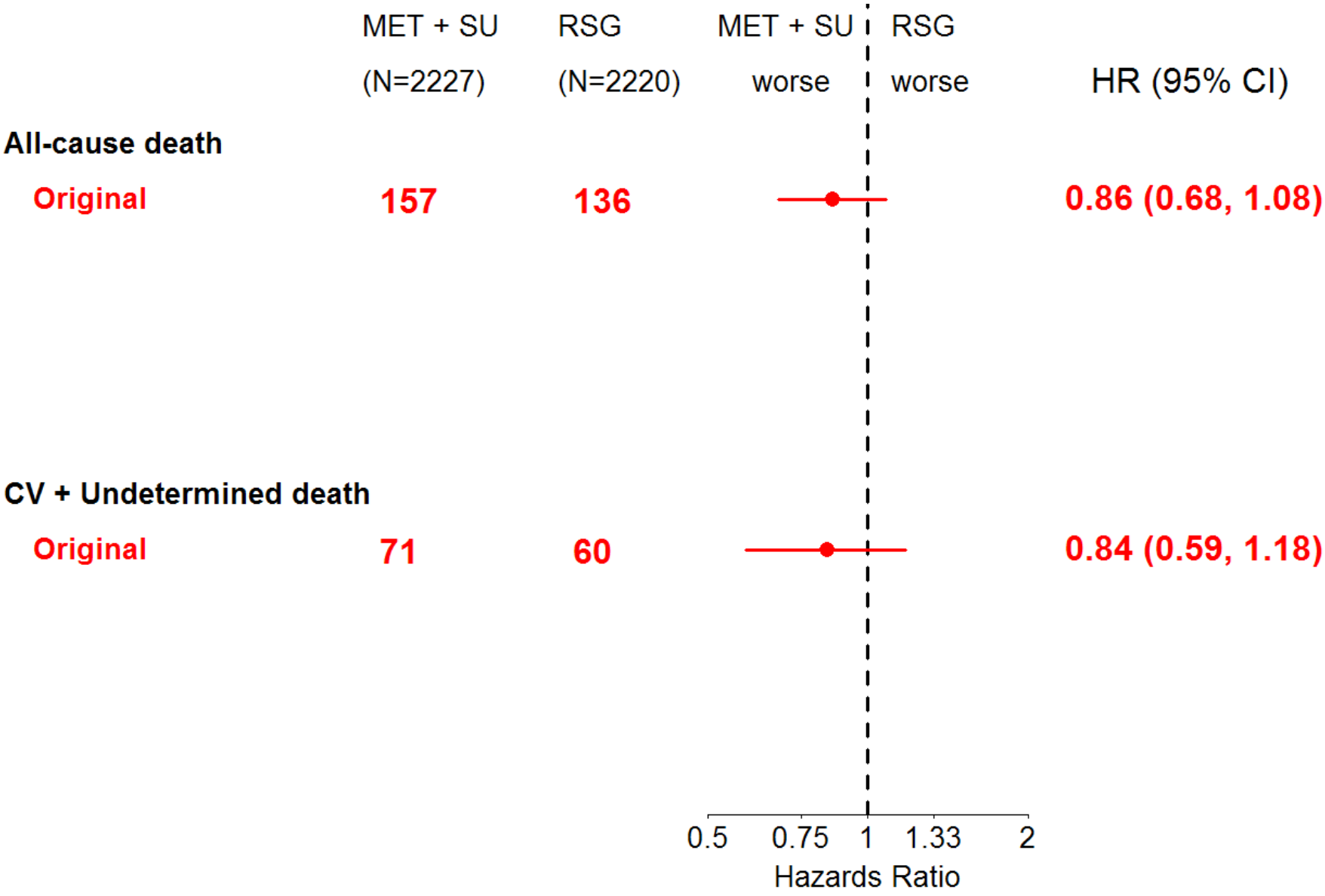
# DCRI All-Cause Mortality: On Dual Treatment + 90 Days




At risk:

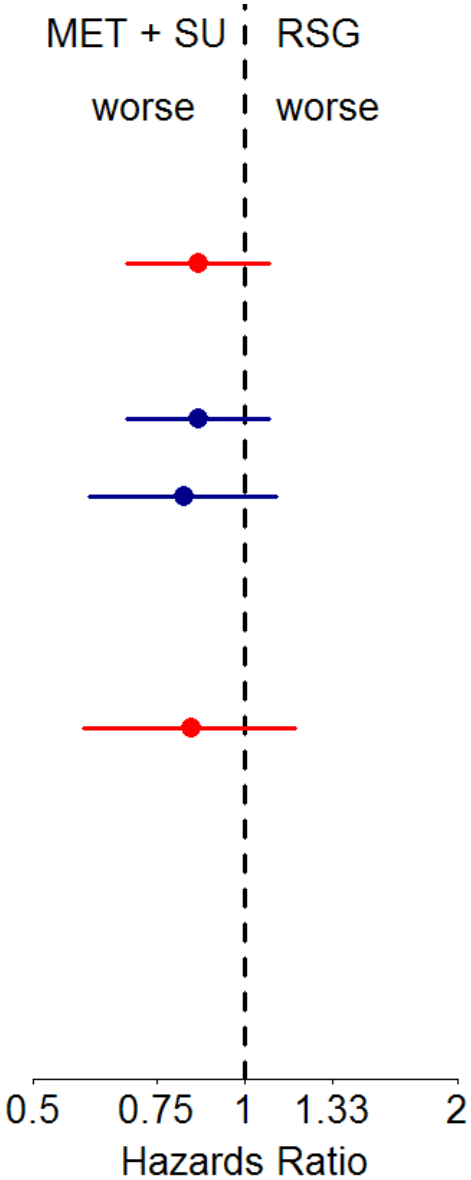
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| MET+SU: | 2227 | 2066 | 1892 | 1725 | 1539 | 1348 | 560 | 55 |
| RSG: | 2220 | 1960 | 1707 | 1533 | 1377 | 1192 | 492 | 48 |

# Analysis of Deaths



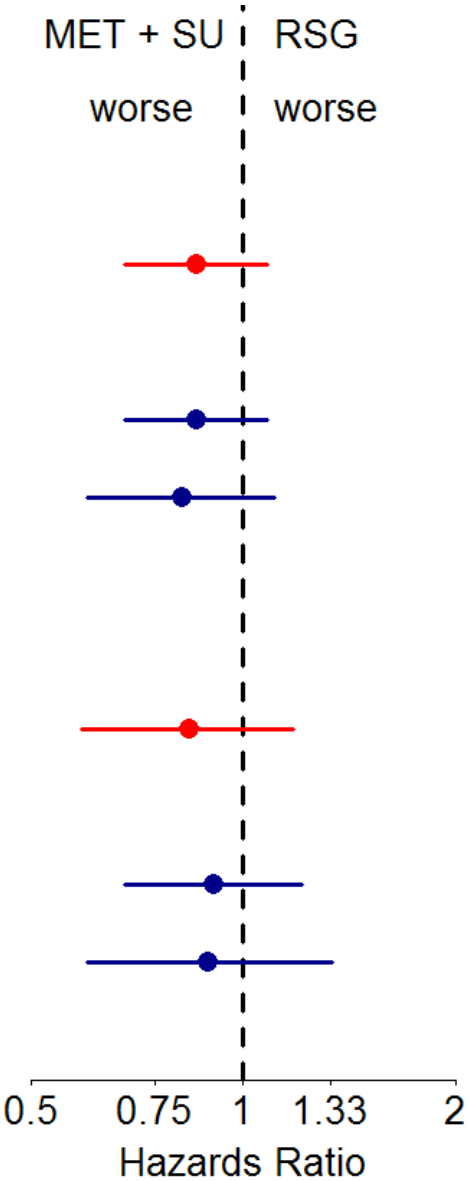
# Analysis of Deaths

| | MET + SU (N=2227) | RSG (N=2220) | HR (95% CI) |
|---|---|---|---|
| **All-cause death** | | | |
| Original | 157 | 136 | 0.86 (0.68, 1.08) |
| Re-adjudicated: | | | |
| Full follow-up | 160 | 139 | 0.86 (0.68, 1.08) |
| Dual Trt + 90 days | 97 | 72 | 0.82 (0.60, 1.11) |
| **CV + Undetermined death** | | | |
| Original | 71 | 60 | 0.84 (0.59, 1.18) |

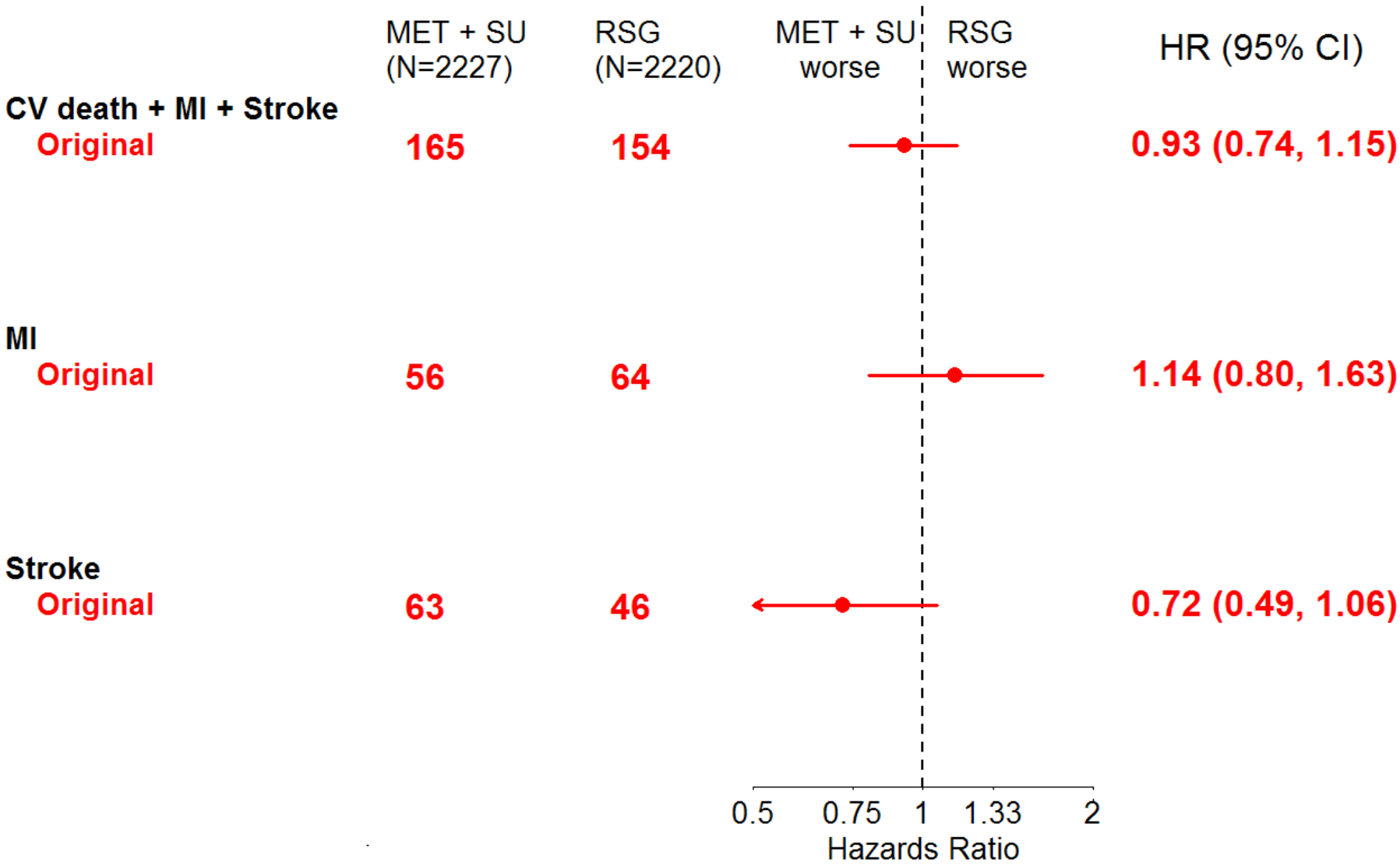


# Analysis of Deaths

| | MET + SU (N=2227) | RSG (N=2220) | HR (95% CI) |
|---|---|---|---|
| **All-cause death** | | | |
| Original | 157 | 136 | 0.86 (0.68, 1.08) |
| Re-adjudicated: | | | |
| Full follow-up | 160 | 139 | 0.86 (0.68, 1.08) |
| Dual Trt + 90 days | 97 | 72 | 0.82 (0.60, 1.11) |
| **CV + Undetermined death** | | | |
| Original | 71 | 60 | 0.84 (0.59, 1.18) |
| Re-adjudicated: | | | |
| Full follow-up | 96 | 88 | 0.90 (0.68, 1.21) |
| Dual Trt + 90 days | 53 | 43 | 0.90 (0.60, 1.34) |



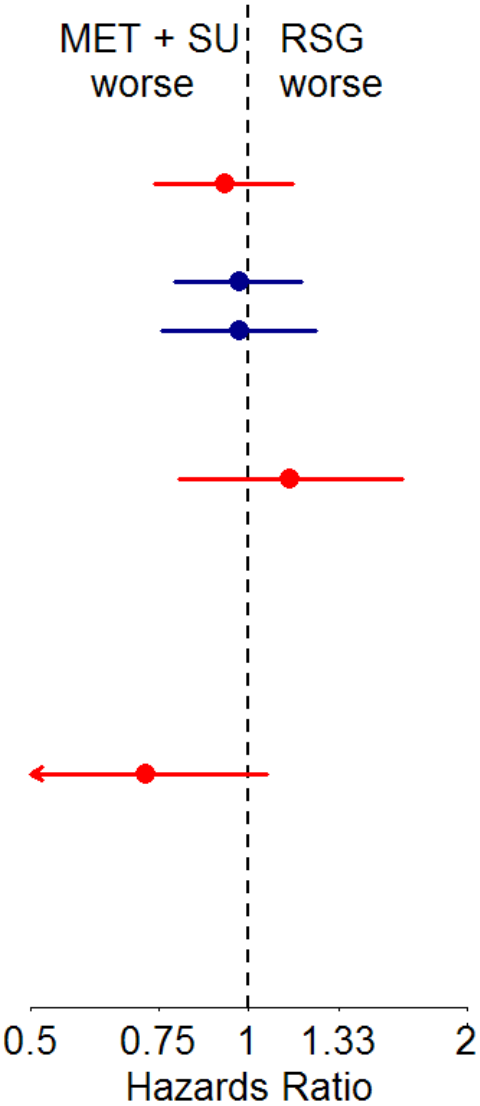
# Analysis of MACE




*"CV death" includes CV deaths + Undetermined deaths

# Analysis of MACE

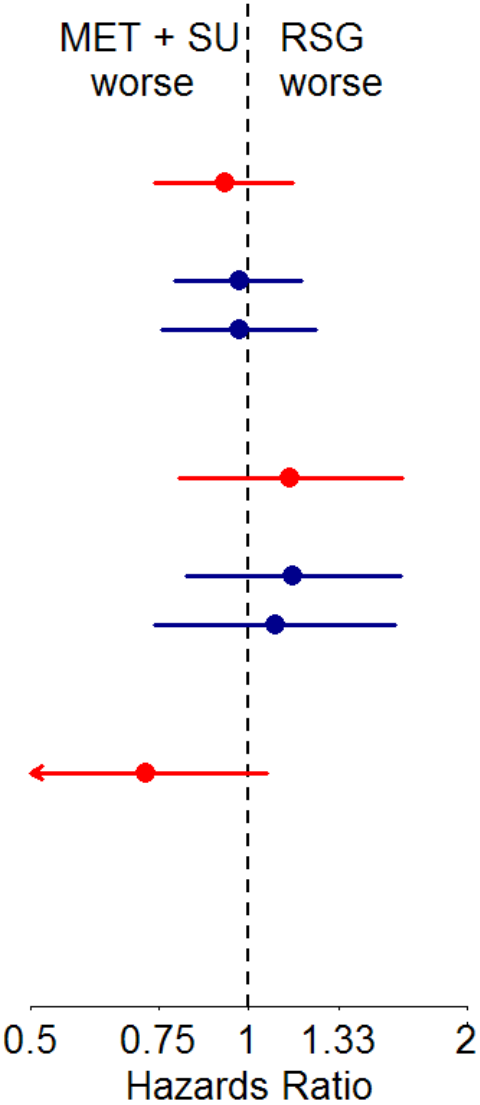
| | MET + SU (N=2227) | RSG (N=2220) | HR (95% CI) |
|---|---|---|---|
| **CV death + MI + Stroke** | | | |
| Original | 165 | 154 | 0.93 (0.74, 1.15) |
| Re-adjudicated: | | | |
| Full follow-up | 191 | 186 | 0.97 (0.79, 1.18) |
| Dual Trt + 90 days | 134 | 118 | 0.97 (0.76, 1.24) |
| **MI** | | | |
| Original | 56 | 64 | 1.14 (0.80, 1.63) |
| **Stroke** | | | |
| Original | 63 | 46 | 0.72 (0.49, 1.06) |




*"CV death" includes CV deaths + Undetermined deaths

# Analysis of MACE

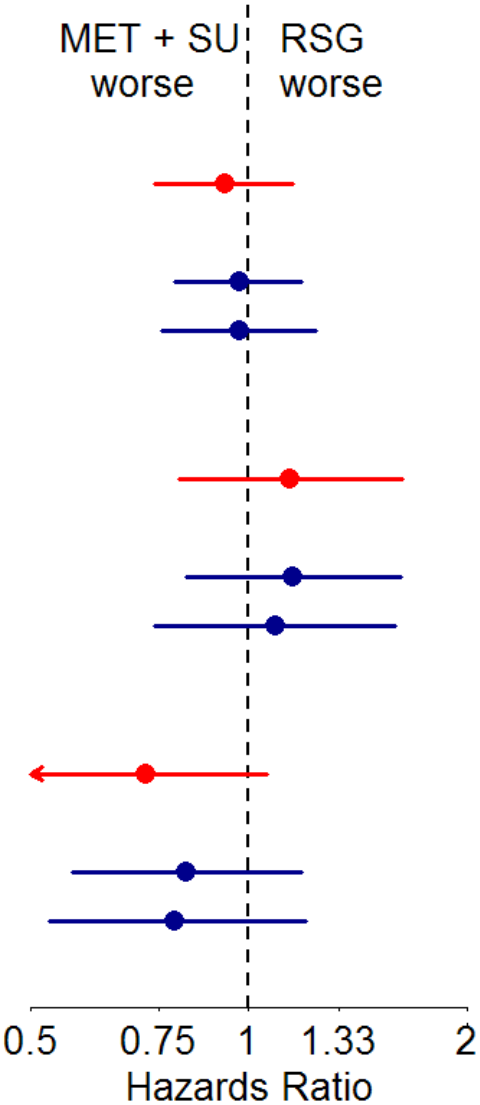
| | MET + SU (N=2227) | RSG (N=2220) | HR (95% CI) |
|---|---|---|---|
| **CV death + MI + Stroke** | | | |
| Original | 165 | 154 | 0.93 (0.74, 1.15) |
| Re-adjudicated: | | | |
| Full follow-up | 191 | 186 | 0.97 (0.79, 1.18) |
| Dual Trt + 90 days | 134 | 118 | 0.97 (0.76, 1.24) |
| **MI** | | | |
| Original | 56 | 64 | 1.14 (0.80, 1.63) |
| Re-adjudicated: | | | |
| Full follow-up | 62 | 72 | 1.15 (0.82, 1.62) |
| Dual Trt + 90 days | 53 | 53 | 1.09 (0.75, 1.60) |
| **Stroke** | | | |
| Original | 63 | 46 | 0.72 (0.49, 1.06) |




*"CV death" includes CV deaths + Undetermined deaths

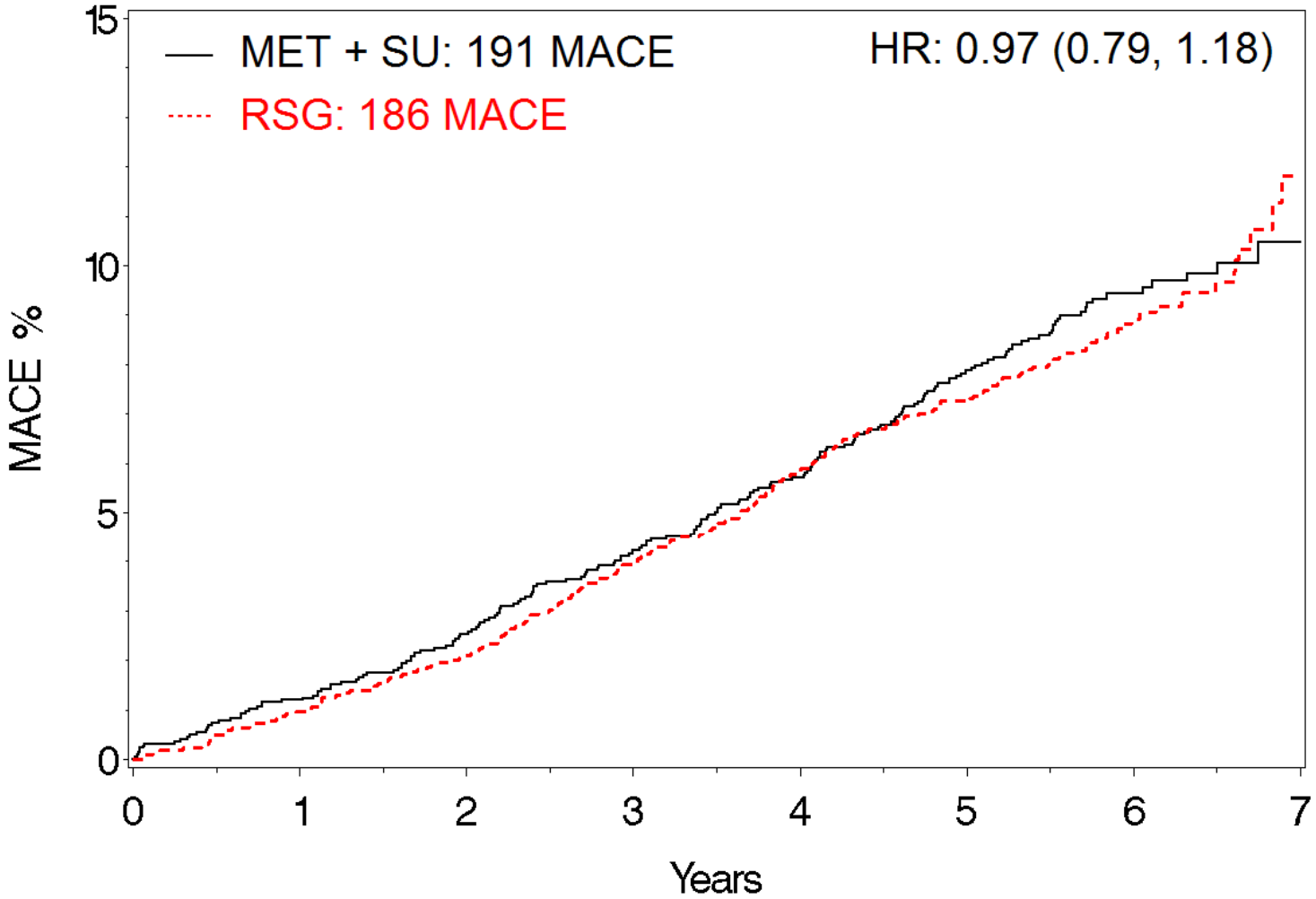
# Analysis of MACE

| | MET + SU (N=2227) | RSG (N=2220) | HR (95% CI) |
|---|---|---|---|
| **CV death + MI + Stroke** | | | |
| Original | 165 | 154 | 0.93 (0.74, 1.15) |
| Re-adjudicated: | | | |
| Full follow-up | 191 | 186 | 0.97 (0.79, 1.18) |
| Dual Trt + 90 days | 134 | 118 | 0.97 (0.76, 1.24) |
| **MI** | | | |
| Original | 56 | 64 | 1.14 (0.80, 1.63) |
| Re-adjudicated: | | | |
| Full follow-up | 62 | 72 | 1.15 (0.82, 1.62) |
| Dual Trt + 90 days | 53 | 53 | 1.09 (0.75, 1.60) |
| **Stroke** | | | |
| Original | 63 | 46 | 0.72 (0.49, 1.06) |
| Re-adjudicated: | | | |
| Full follow-up | 64 | 53 | 0.82 (0.57, 1.18) |
| Dual Trt + 90 days | 54 | 39 | 0.79 (0.53, 1.20) |




*"CV death" includes CV deaths + Undetermined deaths

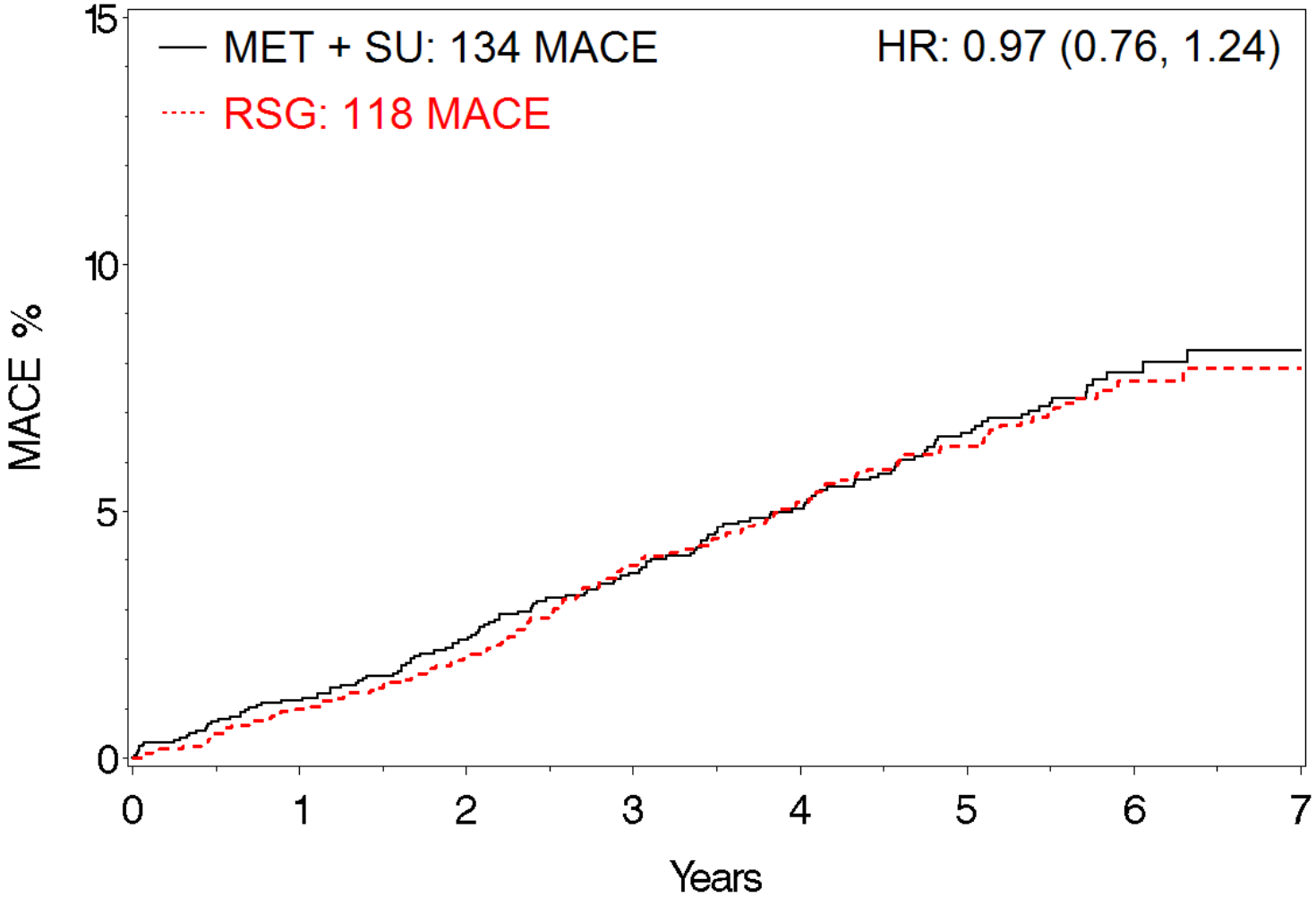
# DCRI MACE: Full Follow-Up Time




At risk:

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| MET+SU: | 2227 | 2118 | 2039 | 1955 | 1870 | 1753 | 823 | 106 |
| RSG: | 2220 | 2117 | 2041 | 1952 | 1872 | 1798 | 865 | 84 |

# DCRI MACE: On Dual Treatment + 90 Days

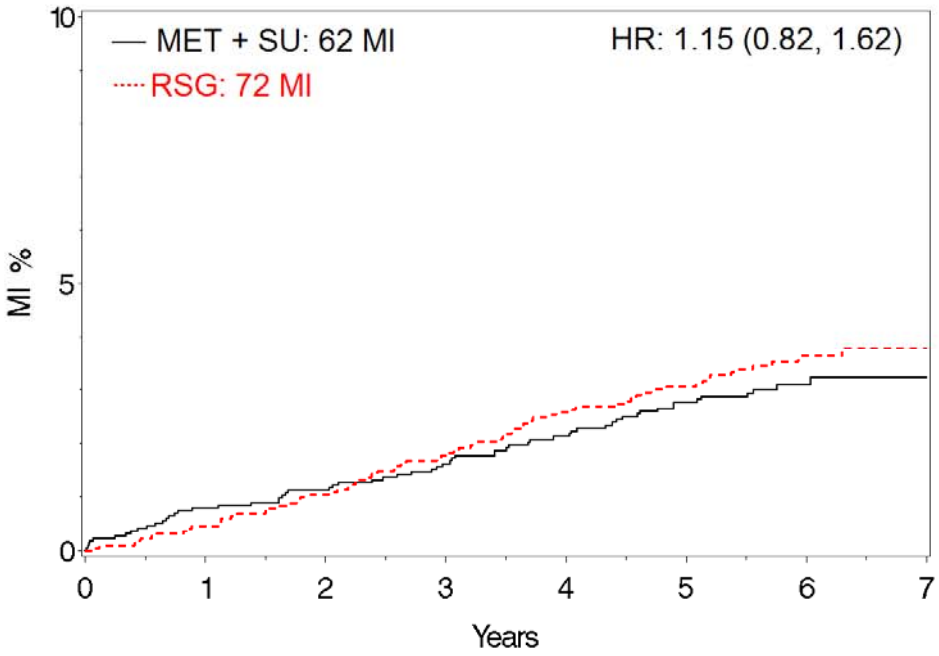



At risk:

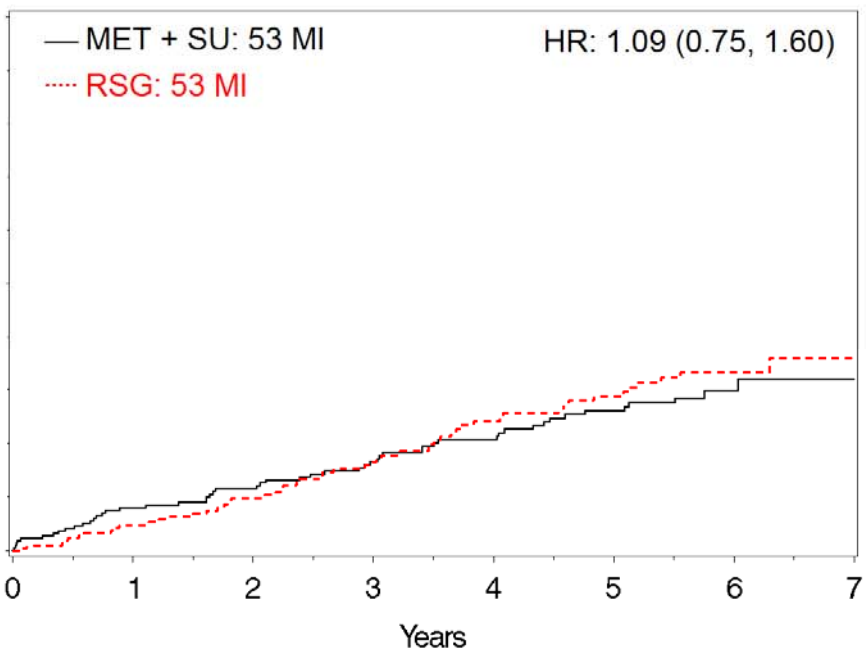
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| MET+SU : | 2227 | 2047 | 1860 | 1683 | 1497 | 1292 | 542 | 54 |
| RSG: | 2220 | 1940 | 1675 | 1489 | 1325 | 1139 | 469 | 46 |

# DCRI Myocardial Infarctions

Full Follow-Up

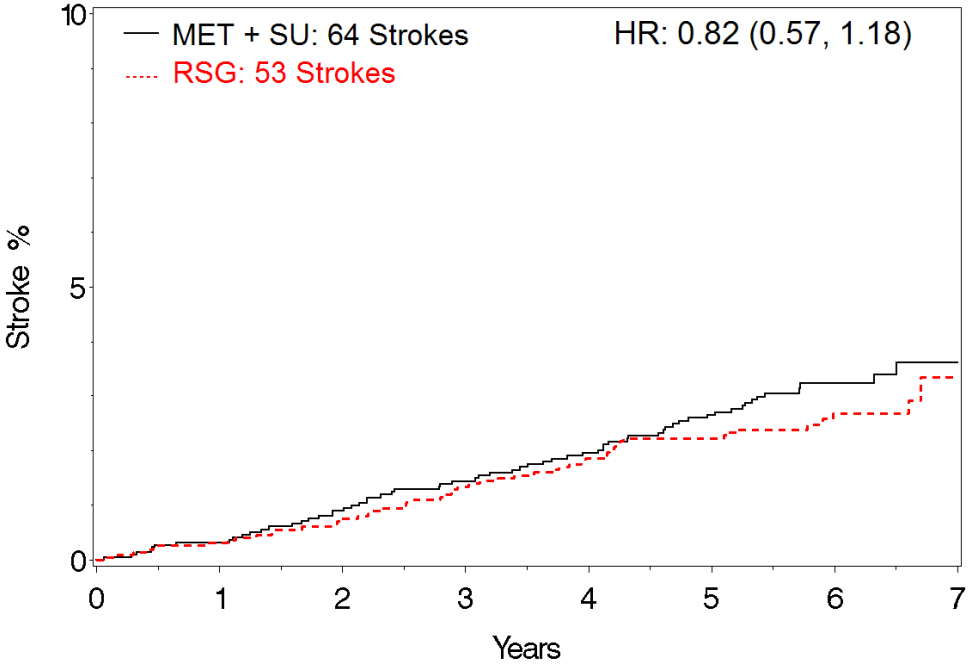



On Dual Trt + 90 Days

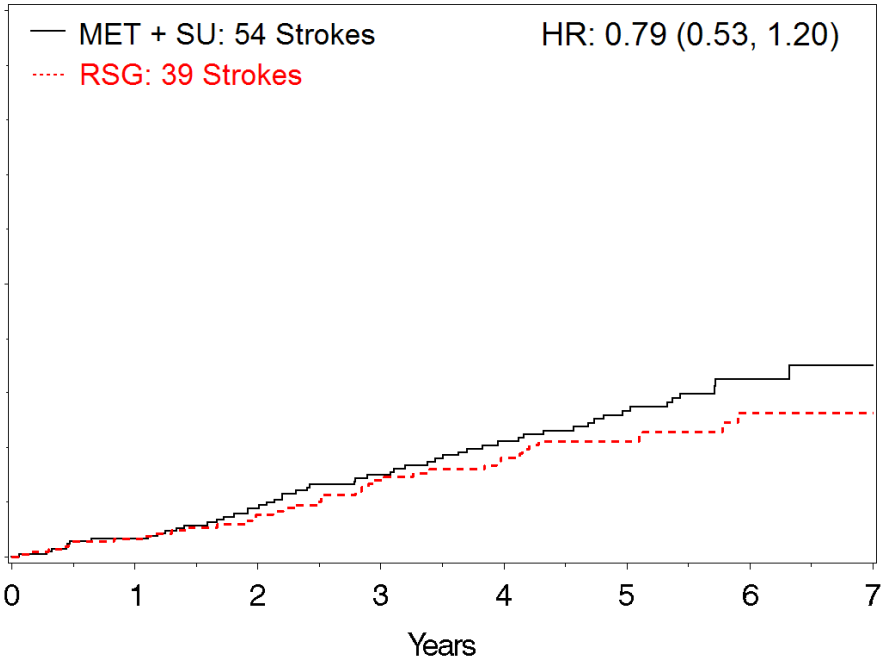


# DCRI Strokes

## Full Follow-Up




## On Dual Trt + 90 Days



# Updated Statistical Analyses

- Original and re-adjudicated analyses were consistent
- Full follow-up time analyses and on dual-treatment + 90 days were consistent:

| | HR (95% CI) | |
|---|---|---|
| **Endpoint** | **Full follow-up** | **Dual Trt + 90 days** |
| All-cause death | 0.86 (0.68, 1.08) | 0.82 (0.60, 1.11) |
| CV + Undetermined death | 0.90 (0.68, 1.21) | 0.90 (0.60, 1.34) |
| MACE | 0.97 (0.79, 1.18) | 0.97 (0.76, 1.24) |
| MI | 1.15 (0.82, 1.62) | 1.09 (0.75, 1.60) |
| Stroke | 0.82 (0.57, 1.18) | 0.79 (0.53, 1.20) |

# Outline

- Disposition and Exposure
- Original vs. Re-adjudicated Events
- Updated Statistical Analyses
- **Sensitivity Analyses**
  - **87 subjects with missing vital status**
- Summary

# Missing Vital Status

| Reason for discontinuation | MET + SU | RSG |
|---|---|---|
| Adverse Experience | 7 | 3 |
| Lost to follow-up | 10 | 9 |
| Other | 5 | 3 |
| Patient withdrew at his own request | 29 | 17 |
| Missing | 2 | 2 |
| **Total** | **53** | **34** |

**Goal:** Assess impact of these 87 subjects with missing vital status on mortality

# Sensitivity Analysis

87 subjects with missing vital status:

- 53 MET + SU subjects = 265 missing patient years
- 34 RSG subjects = 147 missing patient years

**Scenario 1:** HR=5 in the missing patient years

- Mortality rate in the 53 MET + SU subjects = 1.2%
- Mortality rate in the 34 RSG subjects = 6.0%

**Scenario 2:** worst case scenario for Rosiglitazone

- All 34 subjects on RSG died
- No additional deaths among 53 subjects on MET + SU

# Sensitivity Analysis

| | MET + SU | RSG | |
|---|---|---|---|
| Known vital status: | N = 2174 | N = 2186 | Rate Ratio (95% CI) |
| Unknown vital status: | N = 53 | N = 34 | |
| **All Cause Mortality** | | | |
| **Observed** | 160 | 139 | 0.86 (0.69, 1.08) |

# Sensitivity Analysis

| | MET + SU | RSG | |
|---|---|---|---|
| Known vital status: | N = 2174 | N = 2186 | Rate Ratio (95% CI) |
| Unknown vital status: | N = 53 | N = 34 | |
| **All Cause Mortality** | | | |
| Observed | 160 | 139 | 0.86 (0.69, 1.08) |
| Scenario 1 (HR = 5 in missing PY) | 160 + 3.2 | 139 + 8.8 | 0.90 (0.72, 1.13) |

*Expected deaths in the unobserved patient years in the 87 subjects with missing vital status under the assumptions of the Scenario

# Sensitivity Analysis

| Known vital status:<br>Unknown vital status: | MET + SU<br>N = 2174<br>N = 53 | RSG<br>N = 2186<br>N = 34 | Rate Ratio (95% CI) |
|---|---|---|---|
| **All Cause Mortality** | | | |
| Observed | 160 | 139 | 0.86 (0.69, 1.08) |
| Scenario 1 (HR = 5 in missing PY) | 160 + 3.2 | 139 + 8.8 | 0.90 (0.72, 1.13) |
| Scenario 2 (worst possible in missing PY) | 160 + 0 | 139 + 34 | 1.09 (0.88, 1.35) |

*Expected deaths in the unobserved patient years in the 87 subjects with missing vital status under the assumptions of the Scenario

# Outline

- Disposition and Exposure
- Original vs. Re-adjudicated Events
- Updated Statistical Analyses
- Sensitivity Analyses
- **Summary**

# Some limitations of RECORD

- Interpretation of analyses "On Treatment" is complicated by differential treatment discontinuation rate
- Many deaths re-adjudicated as "Undetermined": 53/139 (38%) on RSG, 54/160 (34%) on MET + SU
- Open-label design – not possible to resolve via re-adjudication

# Summary of Re-adjudication

- Full follow-up time was similar between treatments for both mortality and CV outcomes
- Some numerical differences were found between original and re-adjudicated outcomes; no evidence of systematic bias
- Updated estimates of hazard ratios of mortality, MACE, MI and Stroke were similar to the original reported hazard ratios
  - **Mortality**: Re-adjudicated HR = 0.86 (0.68, 1.08) for full FU
  - **MACE**: Re-adjudicated HR = 0.97 (0.79, 1.18) for full FU
  - **MI**: Re-adjudicated HR = 1.15 (0.82, 1.62) for full FU
  - **Stroke**: Re-adjudicated HR = 0.82 (0.57, 1.18) for full FU
- Hazard ratio estimates of **mortality** are **not** likely affected by the 87 subjects with missing vital status

# Acknowledgments:

- Mat Soukup
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# How the Readjudication of RECORD Addressed Some of the Concerns from the Original RECORD Reviews

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# What the Readjudication Could and Could Not Address

# Concerns that Could Not Be Addressed- Trial Design

- Open-label treatment (although randomization and adjudication blinded)
- Complexity of adverse event reporting process in original trial

# Concerns that Could be Addressed by Readjudication

- Allegations that there was widespread incorrect interpretation of cardiovascular adverse events
- Concern regarding percentage of patients not taking original randomized therapy at end of study
- Concern regarding noninferiority design
- Concern regarding asymmetry in use of insulin
- Concern regarding percentage of patients lost to follow-up
- Concern regarding dates of last follow-up

# Concerns that Could be Addressed by Readjudication (cont)

- Concern regarding potential effect of publicity and the published interim analysis
- Concerns regarding ascertainment
- Concern regarding inclusion of deaths with inadequate data as cardiovascular deaths
- Concern regarding inclusion of deaths due to unknown cause as cardiovascular deaths
- Concern regarding potential effect of unobserved time or possible missing data

# How Readjudication Could Address Concern Regarding Possible Widespread Incorrect Interpretation of Cardiovascular Adverse Events

# Addressing Cases of Concern from Original RECORD Review- Deaths

- During original RECORD review, Cardiorenal consultant requested additional information for approximately 475 cases of concern (not all cases involved death)
- During readjudication review, clinical reviewer examined these cases to see how often DCRI readjudication reached a different conclusion than the original adjudication
- In 39 of these cases, DCRI reached a different conclusion regarding death (either CV vs non-CV, or specific CV cause). Some discordance always expected.
- Asked this question: If one assumes that the DCRI readjudication was RIGHT, and the original adjudication was WRONG, how would that have affected the analysis outcome?

# Addressing Cases of Concern from Original RECORD Review- Deaths (cont)

- In 15 cases, the DCRI result was less favorable toward RSG (in terms of the outcome of analyses) than the original adjudication. Examples include original adjudication non-CV with readjudication CV or unknown (which counted as CV)
- In 18 cases, the DCRI result was more favorable toward RSG
- In 6 cases, the DCRI result was neither favorable nor unfavorable. Examples include original adjudication CV with readjudication unknown (still counted as CV death)
- Discordance equally distributed between RSG and comparator
- One might expect these subjects to represent an enriched population of “problem cases”
- Appears that there was not evidence of systematic favorable adjudication decisions regarding deaths, even in this previously suspect population

# Addressing Cases of Concern from Original RECORD Review- MACE

- Across the approx 475 patients for whom additional information was requested, there were 47 events (in 46 patients) for which DCRI readjudication results differed from the original adjudication result with regard to a MACE
- For MACE, if one assumes DCRI readjudication correct and original adjudication not correct, DCRI readjudication less favorable toward RSG in 19 cases, more favorable toward RSG in 23 cases, and in favor of neither in 5 cases
- For MI alone, DCRI readjudication resulted in 4 cases less favorable for RSG, and 5 cases more favorable for RSG
- For stroke alone, 3 cases each
- Even in this sample which one might expect to be enriched in “problem” cases, the DCRI readjudication did not support systematic event interpretation bias in favor of RSG in the original adjudication process

| Summary of Discordant Readjudication/Adjudication Results Among Cases of Concern from Original RECORD Review | | | | |
|---|---|---|---|---|
| | **Mortality** | **MACE** | **MI** | **Stroke** |
| Number of Cases Where ***DCRI*** Readjudication Reached a ***Different Conclusion Than Original*** Adjudication | **39** | **47 events in 46 pts** | **9** | **6** |
| Number of Cases Where DCRI Readjudication was ***Less Favorable Toward RSG*** than Original Adjudication, With Respect to Effect on Analysis Results | **15** | **19** | **4** | **3** |
| Number of Cases Where DCRI Readjudication was ***More Favorable Toward RSG*** than Original Adjudication, With Respect to Effect on Analysis Results | **18** | **23** | **5** | **3** |
| Number of Cases Where DCRI Readjudication Result, Although Different, was ***Neither Favorable Nor Unfavorable Toward RSG*** than Original Adjudication, With Respct to Effect on Analysis Results | **6** | **5** | | |

# Cases of Marked Concern From Original Review- Mortality Readjudication Results

- In original Cardiorenal review, 8 cases identified as "failure to refer events for adjudication"; 3 (or perhaps 4) of these also cited for "extreme mishandling of events"
- 5/8 cases had deaths; examined readjudication outcomes
- In 4/5 cases, readjudication result for death same as original RECORD adjudication
- In one case, original RECORD adjudication death due to unknown cause due to insufficient data; readjudication cause of death heart failure or cardiogenic shock
- Would not have changed outcome for rates of total mortality or CV death but would have increased the total number of RSG heart failure deaths from 8 to 9 (heart failure a class effect of thiazolidinediones)

# Cases of Marked Concern From Original Review- MACE Readjudication Results

- Again examining the 8 cases of marked concern
- 6/8 cases had same outcome for MACE readjudication as for original RECORD adjudication
- Includes the death readjudication difference mentioned on previous slide, in a patient who also had an MI
- One other RSG patient readjudicated to have had a stroke, but had not been in the original adjudication
- Blinded readjudication reached the same MACE result in most (6/8) cases, even in this sample of cases identified as having the most egregious problems

## Cases Identified in 2010 Cardiorenal Consult as "Failure to Refer"

| Patient ID | "Failure to Refer" Case # | "Extreme Mishandling" Case # | Original RECORD Adjud Result | DCRI Readjud Result | Effect on Analyses? |
|---|---|---|---|---|---|
| **18215** | 2 | B | Non-CV death | Non-CV death | **No** |
| **19079** | 1 | A | No MI | MI | **Yes** |
| | | | Unknown cause of death (insuff data) (counted as CV death in analysis) | Death due to heart failure or cardiogenic shock (counted as CV death in analysis) | |
| **19338** | 5 | | Non-CV death | Non-CV death | **No** |
| **20930** | 6 | N | Death occurred after end of study | Death due to unknown cause, after end of study | **No** |
| **21368** | 7 | | Non-CV death | Non-CV death | **No** |
| **31427** | 8 | | No MACE | No MACE | **No** |
| **43697** | 3 | C | Intracerebral hematoma called epilepsy; not referred for adjudication | Stroke | **Yes** |
| **98364** | 4 | | No MACE | No MACE | **No** |

# How Readjudication Could Address Concern Regarding Number of Patients Not on Original Randomized Therapy at End of Study

# Concerns About Number of Patients Not on Randomized Therapy at End of Trial

- Recall concern about noninferiority design; some advocated “as-treated” analysis rather than the prespecified intention-to-treat approach
- Recall that RSG patients couldn’t add insulin due to EU restriction, but MET/SU patients could add insulin. Led to more withdrawal from RSG arm.

# Intention-to-Treat vs "Last Date of Randomized Therapy" Analyses: All-Cause Mortality

| | LDRT + 30 Days | | LDRT + 60 Days | | ITT | |
|---|---|---|---|---|---|---|
| | RSG N=2220 PY=10919 | MET/SU N=2227 PY=10289 | RSG N=2220 PY=10983 | MET/SU N=2227 PY=10369 | RSG N=2220 PY=12954 | MET/SU N=2227 PY=12815 |
| n (%) | 57 (2.6%) | 70 (3.1%) | 69 (3.1%) | 83 (3.7%) | 139 (6.3%) | 160 (7.2%) |
| Rate/100 PY (95% CI) | 0.52 (0.38, 0.66) | 0.68 (0.52, 0.84) | 0.63 (0.48, 0.78) | 0.80 (0.62, 0.98) | 1.07 (0.89, 1.26) | 1.25 (1.05, 1.45) |
| HR (95% CI) | 0.76 (0.54, 1.08) | | 0.78 (0.57, 1.07) | | 0.86 (0.68, 1.08) | |
| Abs Rate Diff/100 PY (95% CI) | -0.16 (-0.37, 0.06) | | -0.17 (-0.40, 0.06) | | -0.18 (-0.44, 0.09) | |

# Intention-to-Treat vs "Last Date of Randomized Therapy" Analyses: Cardiovascular or Unknown Cause Mortality

| | LDRT + 30 Days | | LDRT + 60 Days | | ITT | |
|---|---|---|---|---|---|---|
| | RSG N=2220 PY=10919 | MET/SU N=2227 PY=10289 | RSG N=2220 PY=10983 | MET/SU N=2227 PY=10369 | RSG N=2220 PY=12954 | MET/SU N=2227 PY=12815 |
| n (%) | 34 (1.5) | 43 (1.9) | 41 (1.8) | 44 (2.0) | 88 (4.0) | 96 (4.3) |
| Rate/100 PY (95% CI) | 0.31 (0.20, 0.42) | 0.42 (0.29, 0.55) | 0.37 (0.25, 0.49) | 0.42 (0.29, 0.55) | 0.68 (0.53, 0.83) | 0.75 (0.59, 0.90) |
| HR (95% CI) | 0.74 (0.47, 1.16) | | 0.87 (0.57, 1.34) | | 0.90 (0.68, 1.21) | |
| Abs Rate Diff/100 PY (95% CI) | -0.11 (-0.27, 0.06) | | -0.05 (-0.23, 0.12) | | -0.07 (-0.28, 0.14) | |

# Intention-to-Treat vs "Last Date of Randomized Therapy" Analyses: Cardiovascular (or Unknown Cause) Mortality, Myocardial Infarction or Stroke

| | LDRT + 30 Days | | LDRT + 60 Days | | ITT | |
|---|---|---|---|---|---|---|
| | RSG N=2220 PY=10662 | MET/SU N=2227 PY=10080 | RSG N=2220 PY=10707 | MET/SU N=2227 PY=10140 | RSG N=2220 PY=11913 | MET/SU N=2227 PY=11808 |
| n (%) | 128 (5.8%) | 129 (5.8%) | 135 (6.1%) | 133 (6.0%) | 181 (8.2%) | 188 (8.4%) |
| Rate/100 PY (95% CI) | 1.20 (0.99, 1.41) | 1.28 (1.05, 1.51) | 1.26 (1.04, 1.48) | 1.31 (1.08, 1.54) | 1.52 (1.29, 1.75) | 1.59 (1.36, 1.82) |
| HR (95% CI) | 0.94 (0.73, 1.20) | | 0.96 (0.76, 1.22) | | 0.95 (0.78, 1.17) | |
| Abs Rate Diff/100 PY (95% CI) | -0.08 (-0.39, 0.23) | | -0.05 (-0.36, 0.26) | | -0.07 (-0.40, 0.25) | |

# Intention-to-Treat vs "Last Date of Randomized Therapy" Analyses: Fatal or Nonfatal Myocardial Infarction

| | LDRT + 30 Days | | LDRT + 60 Days | | ITT | |
|---|---|---|---|---|---|---|
| | RSG N=2220 PY=10756 | MET/SU N=2227 PY=10156 | RSG N=2220 PY=10800 | MET/SU N=2227 PY=10216 | RSG N=2220 PY=11965 | MET/SU N=2227 PY=11882 |
| n (%) | 63 (2.8%) | 51 (2.3%) | 64 (2.9%) | 52 (2.3%) | 68 (3.1%) | 60 (2.7%) |
| Rate/100 PY (95% CI) | 0.59 (0.44, 0.74) | 0.50 (0.36, 0.65) | 0.59 (0.44, 0.74) | 0.51 (0.37, 0.65) | 0.57 (0.43, 0.71) | 0.50 (0.37, 0.64) |
| HR (95% CI) | 1.17 (0.81, 1.70) | | 1.17 (0.81, 1.69) | | 1.13 (0.80, 1.59) | |
| Abs Rate Diff/100 PY (95% CI) | 0.08 (-0.12, 0.29) | | 0.08 (-0.12, 0.29) | | 0.06 (-0.13, 0.25) | |

# Intention-to-Treat vs "Last Date of Randomized Therapy" Analyses: Fatal or Nonfatal Stroke

| | LDRT + 30 Days | | LDRT + 60 Days | | ITT | |
|---|---|---|---|---|---|---|
| | RSG N=2220 PY=10772 | MET/SU N=2227 PY=10156 | RSG N=2220 PY=10818 | MET/SU N=2227 PY=10217 | RSG N=2220 PY=12009 | MET/SU N=2227 PY=11882 |
| n (%) | 42 (1.9%) | 52 (2.3%) | 42 (1.9%) | 54 (2.4%) | 50 (2.3%) | 63 (2.8%) |
| Rate/100 PY (95% CI) | 0.39 (0.27, 0.51) | 0.51 (0.37, 0.66) | 0.39 (0.27, 0.51) | 0.53 (0.38, 0.67) | 0.42 (0.30, 0.54) | 0.53 (0.39, 0.67) |
| HR (95% CI) | 0.76 (0.51, 1.14) | | 0.74 (0.49, 1.10) | | 0.79 (0.54, 1.14) | |
| Abs Rate Diff/100 PY (95% CI) | -0.12 (-0.31, 0.07) | | -0.14 (-0.33, 0.05) | | -0.11 (-0.29, 0.07) | |

# How Readjudication Could Address Concern Regarding Determination of Dates of Last Follow-up

## All-Cause Mortality Analyses Using Four Methods of Derivation of End of Follow-Up

| Approach to Derivation of End of Follow-Up | # Pts Who Died | | Rate per 100 PY | | HR (95%CI) | Absolute Rate Difference per 100 PY (95%CI) |
|---|---|---|---|---|---|---|
| | RSG N=2220 n(%) | MET/SU N=2227 n(%) | RSG Rate (95%CI) | MET/SU Rate (95%CI) | | |
| **Parsimonious** | 139 (6.3) | 160 (7.2) | 1.14 (0.94, 1.33) | 1.32 (1.11, 1.53) | 0.86 (0.68, 1.08) | -0.18 (-0.47, 0.10) |
| **Primary** | 139 (6.3) | 160 (7.2) | 1.07 (0.89, 1.26) | 1.25 (1.05, 1.45) | 0.86 (0.68, 1.08) | -0.18 (-0.44, 0.09) |
| **Primary + Test and Event Dates** | 139 (6.3) | 160 (7.2) | 1.07 (0.89, 1.26) | 1.25 (1.05, 1.45) | 0.86 (0.68, 1.08) | -0.18 (-0.44, 0.09) |
| **Primary + Test and Event Dates + Survival Status and Third Party Survival Data** | 139 (6.3) | 160 (7.2) | 1.06 (0.88, 1.25) | 1.24 (1.04, 1.44) | 0.86 (0.68, 1.08) | -0.18 (-0.44, 0.09) |

**Source: Sponsor's Tables 2 (pg 48), 3.1 (pg 93), 24.1 (pg 194), 26.1 (pg 200) and 28.1 (pg 206)**

## Cardiovascular Plus Unknown Cause Mortality Analyses Using Four Methods of Derivation of End of Follow-Up

| Approach to Derivation of End of Follow-Up | # Pts With CV or Unk Cause Death | | Rate per 100 PY | | HR (95%CI) | Absolute Rate Difference per 100 PY (95%CI) |
|---|---|---|---|---|---|---|
| | RSG N=2220 n(%) | MET/SU N=2227 n(%) | RSG Rate (95%CI) | MET/SU Rate (95%CI) | | |
| **Parsimonious** | 88 (4.0) | 96 (4.3) | 0.72 (0.56, 0.87) | 0.79 (0.63, 0.96) | 0.90 (0.68, 1.21) | -0.07 (-0.30, 0.15) |
| **Primary** | 88 (4.0) | 96 (4.3) | 0.68 (0.53, 0.83) | 0.75 (0.59, 0.90) | 0.90 (0.68, 1.21) | -0.07 (-0.28, 0.14) |
| **Primary + Test and Event Dates** | 88 (4.0) | 96 (4.3) | 0.68 (0.53, 0.83) | 0.75 (0.59, 0.90) | 0.90 (0.68, 1.21) | -0.07 (-0.28, 0.14) |
| **Primary + Test and Event Dates + Survival Status and Third Party Survival Data** | 88 (4.0) | 96 (4.3) | 0.67 (0.53, 0.82) | 0.74 (0.59, 0.90) | 0.90 (0.68, 1.21) | -0.07 (-0.28, 0.14) |

**Source: Sponsor's Tables 2 (pg 48), 5.1 (pg 109), 25.1 (pg 197), 27.1 (pg 203) and 29.1 (pg 209)**
**For these analyses, DCRI used the "new FDA" definitions**

**Results of Analyses for Myocardial Infarction and Stroke Using Original RECORD Approach to Derivation of Follow-up, and DCRI "Parsimonious" Approach**

| Analysis | Fatal or Nonfatal Myocardial Infarction | | | Fatal or Nonfatal Stroke | | |
|---|---|---|---|---|---|---|
| | RSG N=2220 n (%) | MET/SU N=2227 n (%) | HR (95% CI) | RSG N=2220 n (%) | MET/SU N=2227 n (%) | HR (95% CI) |
| Original RECORD approach | 64 (2.9%) | 56 (2.5%) | 1.14 (0.80, 1.63) | 46 (2.1%) | 63 (2.8%) | 0.72 (0.49, 1.06) |
| DCRI "parsimonious" approach, original definitions | 68 (3.1%) | 60 (2.7%) | 1.13 (0.80, 1.59) | 50 (2.3%) | 63 (2.8%) | 0.79 (0.54, 1.14) |
| DCRI "parsimonious" approach, "new" definitions | 72 (3.2%) | 62 (2.8%) | 1.15 (0.82, 1.62) | 53 (2.4%) | 64 (2.9%) | 0.82 (0.57, 1.18) |

Source: Table 12-A, pg 79 and pg 86, study report
Abbreviations: DCRI = Duke Clinical Research Institute; HR = hazard ratio; MET = metformin; RSG = rosiglitazone; SU = sulfonylurea

# Results of Efforts to Document Date of Death

- By conditions DCRI used to define completion of follow-up, 3843/4777 patients designated as having completed follow-up; 604 patients needed additional info about end of follow-up
- Collected additional source documents for 344 patients; data for 46 patients inadequate and cases referred to MediciGlobal
- For 252 patients, additional documents not obtained; referred to MediciGlobal
- Eight additional deaths had been found post-study by GSK; sent to DCRI CEC for adjudication
- At end of efforts, 21 patients needed imputation of death date. For all 21, year of death found; for 11/21, month of death found
- Therefore, the only imputation required for death dates was a month of death for ten patients

# How Readjudication Could Address Concern Regarding Inclusion of Deaths Due to Unknown Cause as Cardiovascular Deaths

## Cardiovascular Mortality, With and Without Deaths Due to Unknown Cause

| | With Unk Cause Deaths | | Without Unk Cause Deaths | |
|---|---|---|---|---|
| | RSG N=2220 PY=12815 | MET/SU N=2227 PY=12915 | RSG N=2220 PY=12954 | MET/SU N=2227 PY=12815 |
| n (%) | 88 (4.0) | 96 (4.3) | 34 (1.5%) | 42 (1.9%) |
| Rate per 100 PY (95% CI) | 0.68 (0.53, 0.83) | 0.75 (0.59, 0.90) | 0.26 (0.17, 0.36) | 0.33 (0.22, 0.43) |
| HR (95% CI) | 0.90 (0.68, 1.21) | | 0.80 (0.51, 1.25) | |
| Abs Rate Diff per 100 PY | -0.07 (-0.28, 0.14) | | -0.07 (-0.20, 0.07) | |

## Cardiovascular Deaths Excluding Deaths Due to Unknown Cause, Original RECORD Adjudication and DCRI Readjudication Results

| | RSG N=2220 n (%) | MET/SU N=2227 n (%) | Raw Ratio RSG:MET/SU |
|---|---|---|---|
| Orig adjud | 32 (1.4%) | 38 (1.7%) | 0.84 |
| DCRI readjud | 34 (1.5%) | 42 (1.9%) | 0.81 |

Source: Sponsor's Table 2, pg 49, current study report; and Table 53, pg 147, original RECORD study report (27 Aug 2009)

# MACE, With and Without Deaths Due to Unknown Cause

| | With Unk Cause Deaths | | Without Unk Cause Deaths | |
|---|---|---|---|---|
| | RSG N=2220 PY=11892 | MET/SU N=2227 PY=11800 | RSG N=2220 PY=11840 | MET/SU N=2227 PY=11746 |
| n (%) | 186 (8.4%) | 191 (8.6%) | 143 (6.4%) | 142 (6.4%) |
| Rate per 100 PY (95% CI) | 1.56 (1.33, 1.79) | 1.62 (1.38, 1.85) | 1.21 (1.00, 1.41) | 1.21 (1.01, 1.41) |
| HR (95% CI) | 0.97 (0.79, 1.18) | | 1.00 (0.79, 1.26) | |
| Abs Rate Diff per 100 PY | -0.05 (-0.38, 0.27) | | -0.00 (-0.29, 0.28) | |

# Exploration of a Difference Between Original Adjudication and DCRI Readjudication: Deaths Due to Unknown Cause

- In DCRI readjudication, there were 120 deaths (62 RSG, 58 MET/SU) adjudicated as due to unknown cause. 107/120 occurred prior to end of study.
- In original RECORD adjudication, there had been 61 (28 RSG, 33 MET/SU)
- This difference explored further by clinical reviewer
- The 61 original adjudication deaths due to unknown cause (DDTUC) not a perfect subset of the 120 DCRI readjudication DDTUC

# Exploration of a Difference Between Original Adjudication and DCRI Readjudication: Deaths Due to Unknown Cause (cont)

- Of the 120 DCRI DDTUC, 80 had not been originally adjudicated as DDTUC. These 80 DDTUC were evenly distributed between RSG (41) and MET/SU (39)
- Relatively even distribution not suggestive of systematic process in the original RECORD adjudication of assignment of cause of death in cases where data were actually insufficient
- Common reason for DDTUC: deaths had been identified in the Survival Status Update in the original RECORD study. This update collected survival status only, but patients did not consent to collection of all information necessary to determine cause of death
- Beyond this reason, recall that DCRI developed its own adjudication forms. Possible that these new forms, and consciousness of readjudicators of expected scrutiny of their process, could have been associated with increased stringency in requirements for events to meet definitions for cause of death.

# Exploration of Deaths Due to Unknown Cause (cont)

- Of the 61 deaths originally adjudicated as DDTUC, 22 (8 RSG, 14 MET/SU) were adjudicated by DCRI as having a known cause of death
- Of the 8 RSG deaths that DCRI changed from DDTUC to an identified cause of death, 4 changed to a CV death, and 4 changed to a non-CV death
- Of the 14 MET/SU deaths that DCRI changed from DDTUC to an identified cause of death, 8 changed to a CV death, and 6 changed to a non-CV death
- This relatively even distribution is not suggestive of deliberate misclassification in the original adjudication process, and is not weighted toward differing assignment away from either CV or non-CV death

# How Readjudication Could Address Concern Regarding Ascertainment

# Identification of Potential Events

Both electronic and manual triggering used to identify potential events

Automated methods included:

- Screening of all Adverse Experience and Serious Adverse Experience forms from the Case Report Form data fields from the RECORD datasets
- Use of a set of prespecified MedDRA terms, with the set of terms intended to have a low threshold for identification of events
- Identification of Death Forms (called Form D) in the RECORD database

# Manual Trigger Procedures: Source Documents Reviewed

- All source documents used as part of the original RECORD adjudication process
- All cases that were sent to the original RECORD Clinical Endpoints Committee, including endpoints that were adjudicated as non-endpoints and all cases that were later deleted by the investigator
- Unscheduled visit forms
- “Hospitalization or Accident and Emergency Department Visit Endpoint Form”
- Investigator verbatim terms

# Manual Trigger Procedures: Source Documents Reviewed (cont)

- All SAE and AE forms
- All Death Endpoint Forms
- All Myocardial Infarction/Unstable Angina Endpoint Forms
- All Stroke/TIA Forms
- All hospitalizations
- All Survival Status Forms

# Manual Trigger Procedures: Source Documents Reviewed (cont)

- All “Documentation of Third Party Survival Status” Forms
- All “Tracking Forms for Completely Withdrawn Patients”
- All Study Completion Forms
- Any SAEs or AEs that were deleted by RECORD investigators. These were identified from the audit trails of the study’s electronic datasets
- Additional source documents collected as part of the readjudication activities: e.g. discharge summaries, progress notes, lab reports, physician narratives

# Additional Information Sources

- Queries to original study sites (two attempts per request)
- MediciGlobal, a third party vendor, employed to search for additional vital status information for patients whose vital status at end of study had not been clearly documented

# Challenges to Identification of Additional Events

- Long period of time since original trial
- Closure of some research sites
- Inability to obtain current Institutional Review Board approval
- National regulations preventing additional follow-up
- Patients move or do not agree to additional contact

# How Readjudication Could Address Concern Regarding the Effect of Publicity and the Interim Analysis

## All-Cause Mortality
## Before and After Interim Publication

| | Before 5 Jun 2007 | | After 5 Jun 2007 | |
|---|---|---|---|---|
| | RSG N=2220 PY=10092 | MET/SU N=2227 PY=10010 | RSG N=2220 PY=2863 | MET/SU N=2227 PY=2808 |
| Number of patients with death (%) | 97/2220 (4.4) | 114/2227 (5.1) | 42/2057 (2.0) | 46/2032 (2.3) |
| Rate per 100 PY (95% CI) | 0.96 (0.76, 1.16) | 1.14 (0.92, 1.35) | 1.47 (1.02, 1.92) | 1.64 (1.16, 2.12) |
| Hazard ratio (95% CI) | 0.84 (0.64, 1.10) | | 0.89 (0.59, 1.35) | |
| Absolute rate difference per 100 PY (95% CI) | -0.18 (-0.47, 0.11) | | -0.17 (-0.83, 0.48) | |

Source: Sponsor's Tables 20.1 (pg 182) and 21.1 (pg 185), study report

# Withdrawal Without a Primary Event, Prior To and After Interim Publication

- Prior to interim publication: 1.9 withdrawals per 100 patient-years
- After interim publication: 2.5 withdrawals per 100 patient-years (65 patients each group)

## Cardiovascular Mortality Plus Unknown Cause Mortality Before and After Interim Publication

| | Before 5 Jun 2007 | | After 5 Jun 2007 | |
|---|---|---|---|---|
| | RSG N=2220 PY=10092 | MET/SU N=2227 PY=10010 | RSG N=2220 PY=2863 | MET/SU N=2227 PY=2808 |
| Number of patients with cardiovascular death or death due to unknown cause (%) | 55/2220 (2.5) | 68/2227 (3.1) | 33/2057 (1.6) | 28/2032 (1.4) |
| Rate per 100 PY (95% CI) | 0.55 (0.40, 0.69) | 0.68 (0.51, 0.85) | 1.15 (0.75, 1.55) | 1.00 (0.62, 1.37) |
| Hazard ratio (95% CI) | 0.80 (0.56, 1.14) | | 1.15 (0.70, 1.90) | |
| Absolute rate difference per 100 PY (95% CI) | -0.13 (-0.36, 0.09) | | 0.16 (-0.39, 0.70) | |

Source: Sponsor's Tables 22.1 (pg 188) and 23.1 (pg 191), study report

| MACE<br>Before and After Interim Publication | | | | |
|---|---|---|---|---|
| | Before 5 Jun 2007 | | After 5 Jun 2007 | |
| | RSG<br>N=2220<br>PY=9410 | MET/SU<br>N=2227<br>PY=9397 | RSG<br>N=2220<br>PY= 2466 | MET/SU<br>N=2227<br>PY=2391 |
| Number of patients with endpoint (%) | 142/2220 (6.4%) | 150/2227 (6.7%) | 44/1817 (2.4%) | 41/1782 (2.3%) |
| Rate per 100 PY (95% CI) | 1.51 (1.26, 1.76) | 1.60 (1.34, 1.86) | 1.78 (1.25, 2.32) | 1.71 (1.19, 2.24) |
| Hazard ratio (95% CI) | 0.95 (0.75, 1.19) | | 1.04 (0.68, 1.59) | |
| Absolute rate difference per 100 PY (95% CI) | -0.09 (-0.45, 0.27) | | 0.07 (-0.68, 0.82) | |
| Source: Tables 35.1 (pg 289) and 36.1 (pg 292), study report | | | | |

## Fatal or Nonfatal Myocardial Infarction Before and After Interim Publication

| | Before 5 Jun 2007 | | After 5 Jun 2007 | |
|---|---|---|---|---|
| | RSG N=2220 PY=9465 | MET/SU N=2227 PY=9446 | RSG N=2220 PY=2493 | MET/SU N=2227 PY=2432 |
| Number of patients with endpoint (%) | 59/2220 (2.7%) | 53/2227 (2.4%) | 13/1834 (0.7%) | 9/1805 (0.5%) |
| Rate per 100 PY (95% CI) | 0.62 (0.46, 0.79) | 0.56 (0.41, 0.72) | 0.52 (0.23, 0.81) | 0.37 (0.12, 0.62) |
| Hazard ratio (95% CI) | 1.11 (0.77, 1.61) | | 1.42 (0.60, 3.31) | |
| Absolute rate difference per 100 PY (95% CI) | 0.06 (-0.16, 0.29) | | 0.15 (-0.23, 0.53) | |

Source: Tables 37.1 (pg 295) and 38.1 (pg 298), study report

| Stroke<br>Before and After Interim Publication | | | | |
|---|---|---|---|---|
| | Before 5 Jun 2007 | | After 5 Jun 2007 | |
| | RSG<br>N=2220<br>PY=9493 | MET/SU<br>N=2227<br>PY=9449 | RSG<br>N=2220<br>PY=2510 | MET/SU<br>N=2227<br>PY=2434 |
| Number of patients with endpoint (%) | 45/2220<br>(2.0%) | 49/2227<br>(2.2%) | 8/1845<br>(0.4%) | 15/1809<br>(0.8%) |
| Rate per 100 PY (95% CI) | 0.47<br>(0.33, 0.62) | 0.52<br>(0.37, 0.67) | 0.32<br>(0.09, 0.54) | 0.62<br>(0.30, 0.93) |
| Hazard ratio (95% CI) | 0.92 (0.61, 1.37) | | 0.52 (0.22, 1.23) | |
| Absolute rate difference per 100 PY (95% CI) | -0.04 (-0.25, 0.16) | | -0.30 (-0.88, 0.09) | |
| Source: Tables 39.1 (pg 301) and 40.1 (pg 304), study report | | | | |

# How Readjudication Could Address Concern Regarding Potential Unobserved Patient Time and Missing Information

# Simulation and Sensitivity Analysis Using High Assumed Hazard Ratios for Unobserved Time

- For MACE, DCRI considered potential unobserved time between last recorded vital sign and other, later types of contacts
- Assumed a range of hazard ratios for the time period after the last recorded vital sign, up to HR of 2.0, for RSG vs MET/SU
- Little change in analysis result, even if assuming increase in hazard ratio during potential unobserved time

# Sensitivity Analysis Using High Assumed Hazard Ratios for Unobserved Time (cont)

- For all-cause mortality, Dr. Andraca-Carrera performed a sensitivity analysis regarding the 87 patients for whom vital status was missing at end of study
- Assumed a hazard ratio of 5 for RSG vs MET/SU for these patients
- For all-cause mortality, this would changed the rate ratio in the analysis from the observed 0.86 to 0.90

# Summary Comparison of Original Adjudication and DCRI Readjudication

# Original Adjud vs DCRI Readjud Comparison- Total Mortality

| Type of Analysis | HR (95% CI) |
|---|---|
| Original | 0.86 (0.68, 1.08) |
| DCRI Main | 0.86 (0.68, 1.08) |
| DCRI LDRT + 30 days | 0.76 (0.54, 1.08) |
| DCRI LDRT + 60 days | 0.78 (0.57, 1.07) |
| DCRI rand to Amendment 7 | 0.90 (0.64, 1.25) |
| DCRI Amendment 7 to end | 0.83 (0.60, 1.13) |
| DCRI rand to interim pub | 0.84 (0.64, 1.10) |
| DCRI interim pub to end | 0.89 (0.59, 1.35) |
| End of FU parsimonious | 0.86 (0.68, 1.08) |
| End of FU primary analysis + test + event dates | 0.86 (0.68, 1.08) |
| End of FU primary analysis + test + event dates + surv status | 0.86 (0.68, 1.08) |

# Original Adjud vs DCRI Readjud Comparison- Cardiovascular Mortality

| Type of Analysis | HR (95% CI) |
|---|---|
| Original | 0.84 (0.59, 1.18) |
| DCRI Main | 0.90 (0.68, 1.21) |
| DCRI LDRT + 30 days | 0.74 (0.47, 1.16) |
| DCRI LDRT + 60 days | 0.87 (0.57, 1.34) |
| DCRI rand to Amendment 7 | 0.79 (0.50, 1.24) |
| DCRI Amendment 7 to end | 1.00 (0.69, 1.46) |
| DCRI rand to interim pub | 0.80 (0.56, 1.14) |
| DCRI interim pub to end | 1.15 (0.70, 1.90) |
| End of FU parsimonious | 0.90 (0.68, 1.21) |
| End of FU primary analysis + test + event dates | 0.90 (0.68, 1.21) |
| End of FU primary analysis + test + event dates + surv status | 0.90 (0.68, 1.21) |

# Original Adjud vs DCRI Readjud Comparison- MACE

| Type of Analysis | HR (95% CI) |
|---|---|
| Original | 0.93 (0.74, 1.15) |
| DCRI Main | 0.95 (0.78, 1.17) |
| DCRI LDRT + 30 days | 0.94 (0.73, 1.20) |
| DCRI LDRT + 60 days | 0.96 (0.76, 1.22) |
| DCRI rand to Amendment 7 | 0.97 (0.74, 1.28) |
| DCRI Amendment 7 to end | 0.96 (0.71, 1.29) |
| DCRI rand to interim pub | 0.95 (0.75, 1.19) |
| DCRI interim pub to end | 1.04 (0.68, 1.59) |
| DCRI cut-off 24 Aug 2008 | 0.91 (0.74, 1.12) |

# Original Adjud vs DCRI Readjud Comparison- MI

| Type of Analysis | HR (95% CI) |
|---|---|
| Original | 1.14 (0.80, 1.63) |
| DCRI Main | 1.13 (0.80, 1.59) |
| DCRI LDRT + 30 days | 1.17 (0.81, 1.70) |
| DCRI LDRT + 60 days | 1.17 (0.81, 1.69) |
| DCRI rand to Amendment 7 | 1.15 (0.75, 1.77) |
| DCRI Amendment 7 to end | 1.16 (0.67, 2.02) |
| DCRI rand to interim pub | 1.11 (0.77, 1.61) |
| DCRI interim pub to end | 1.42 (0.60, 3.31) |
| DCRI cut-off 24 Aug 2008 | 1.14 (0.81, 1.61) |

# Original Adjud vs DCRI Readjud Comparison- Stroke

| Type of Analysis | HR (95% CI) |
|---|---|
| Original | 0.72 (0.49, 1.06) |
| DCRI Main | 0.79 (0.54, 1.14) |
| DCRI LDRT + 30 days | 0.76 (0.51, 1.14) |
| DCRI LDRT + 60 days | 0.74 (0.49, 1.10) |
| DCRI rand to Amendment 7 | 0.89 (0.55, 1.44) |
| DCRI Amendment 7 to end | 0.74 (0.43, 1.30) |
| DCRI rand to interim pub | 0.92 (0.61, 1.37) |
| DCRI interim pub to end | 0.52 (0.22, 1.23) |
| DCRI cut-off 24 Aug 2008 | 0.79 (0.55, 1.14) |

# Strengths of Readjudication

- Multiple meetings between DCRI and Agency to refine readjudication procedures
- All procedures for readjudication process predefined
- DCRI highly experienced in clinical trial procedures and cardiovascular event adjudication
- No GSK representatives on Clinical Events Classification committee
- Well-documented processes for blinding of adjudicators
- Two methods for redaction of treatment assignments from records

# Strengths of Readjudication (cont)

- In addition to being blinded to treatment assignment, readjudication reviewers were also blinded to other glucose-lowering agents
- Both electronic and manual triggers used to identify potential events
- Manual trigger procedures extensive
- Trigger procedures included review of all cases sent to original RECORD CEC, including those adjudicated as non-endpoints and those later deleted
- Numbers of triggered cases, and sources of triggering, were similar between RSG and MET/SU groups. Triggering process did not identify evidence of systematic over- or under- identification of potential events.

# Strengths of Readjudication (cont)

- Systematic effort made to identify events that had been deleted by investigators, by reviewing audit trails of study's electronic datasets
- Repeated efforts made to obtain missing data
- A separate contractor, MediciGlobal, was hired to track down patients who were lost to follow-up
- Quality control checks were prespecified and conducted
- Efforts were made to address as many of the concerns from the original review as possible

# Why RECORD is Important

- The only long-term, prospective, randomized, controlled cardiovascular outcomes trial for rosiglitazone
- In hierarchy of evidence, data from large, long-term, randomized, controlled trials with prospectively planned adjudication of predefined cardiovascular events are generally considered to be of higher value than meta-analyses of smaller trials without prospectively planned cardiovascular event adjudication, and of higher value than observational data
- In observational data, deliberate (rather than randomized) choice of treatment for each person is associated with risk that observed outcomes may be caused by differences among people being given the two treatments, rather than outcomes being due to the treatment alone
- With observational data, risk that unrecognized confounding factors interfere with attempts to correct for identified differences between groups

| RECORD vs Meta-analysis of 52 Trials | | |
|---|---|---|
| | RECORD | Meta-analysis (Across all 52 Trials) |
| Number of MACE | 369 | 109 |
| Mean duration of follow-up | 5.8 yrs | 0.5 yrs |
| Patient-years | 25,769 | 8,754 |

# Death in RECORD Readjudication

- All-Cause Mortality: HR 0.86 (0.68, 1.08)
- CV or Unknown Cause Mortality: HR 0.90 (0.68, 1.21)
- CV Mortality (without unk cause mort): HR 0.80 (0.51, 1.25)
- Fatal MI events contributing to “fatal or nonfatal MI” endpoint:
  6 RSG vs 11 MET/SU
- Total fatal MI events:
  8 RSG vs 12 MET/SU
- Fatal stroke events contributing to “fatal or nonfatal stroke” endpoint:
  0 RSG vs 6 MET/SU
- Total acute vascular event deaths (category which included stroke by original definitions):
  1 RSG vs 12 MET/SU

# Summary

- DCRI readjudication was well-planned, well-conducted and comprehensive
- DCRI readjudication analysis results consistent with original adjudication
- Myocardial infarction HR point estimate favored comparator; no stat sig treatment difference
- Total mortality, CV mortality, MACE and stroke HR point estimates favored RSG; no stat sig treatment difference
- Could not entirely address some concerns about trial design, although some aspects were addressed
- Could be used to address multiple other concerns; results of analyses remained consistent

# Summary (cont)

- RECORD is the only large, randomized, controlled cardiovascular outcomes trial of rosiglitazone
- RECORD contains a large amount of useful information regarding cardiovascular risk with rosiglitazone, including three times as many events and three times as much patient-time as all 52 meta-analysis trials combined
- Overall, readjudication appears to support the previous observation that, in this trial, rosiglitazone was not associated with an increased risk of death or major adverse cardiovascular events

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- Dr. Susan Leibenhaut
- Ms. Julie Marchick
- Ms. Jena Weber

# FDA Inspection of Duke Clinical Research Institute (DCRI) Re-adjudication of the RECORD Trial

Endocrinologic and Metabolic Drugs Advisory Committee
June 5, 2013

Ann Meeker O'Connell
Director (Acting), Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER/FDA

# Overview

- Review of previous inspections
- FDA inspection of DCRI
  - DCRI responsibilities and activities
  - Inspection scope
  - Inspection outcome
  - Examples of specific subjects reviewed

# Previous FDA Inspections (2010)

| Inspected Entity | Inspection Program |
|---|---|
| GlaxoSmithKline | Sponsor* |
| Quintiles | Contract Research Organization (CRO)* |
| Croatia (Tertiary Referral Center) | Clinical Investigator (CI) |
| Sweden (Primary care) | CI |
| Germany (Dedicated research site) | CI |

* Included Office (then Division) of Scientific Investigation (OSI) and Office of New Drugs (OND) subject matter experts at the request of the review division

# 2010 FDA Inspections

- No evidence of systemic or pervasive findings that would undermine the reliability of the data.
- General limitations:
  - Clinical Investigator inspections covered <1% of sites involved in the RECORD trial
  - Limited ability to detect bias in referral for adjudication in an open-label trial

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm218481.htm

# DCRI Inspection (2012)

- Covered conduct of #AVD 115170, “Re-adjudication Protocol for RECORD”
- Conducted August 20 to 24, 2012
- Included participation by OSI medical officer (S. Leibenhaut)

# DCRI Responsibilities

- Develop and implement Clinical Events Committee (CEC) charter and processes
- Develop and implement operational processes to track workflow and report adjudication results
- Develop and implement quality control procedures to ensure appropriate referral for re-adjudication and accuracy of results

# Scope of FDA Inspection

- Procedures for blinding:
  - Adequacy of redaction of paper files
  - Phase 1 (mortality) report
- Implementation of operational processes and CEC charter
- Implementation of quality control procedures
- Accuracy of data submitted to NDA
- Documentation of staff training and qualifications

# Summary FDA Inspection

- Overall, DCRI procedures appear to have been adequate and implemented adequately, except for isolated failures of redaction of paper subject records which were not documented according to the CEC charter, one of which went to adjudication.

# FDA Inspection Outcome

(1)

- Subject 97703 (met-su): Adjudicator returned package for redaction and re-adjudication by two new adjudicators because concomitant medication insulin was not redacted; DCRI result was “CV death” unchanged from previous.

# FDA Inspection Outcome

(2)

- Re-adjudication Protocol and CEC Charter both state, "GSK is responsible for the redacting prior to delivery of data or documents to the DCRI. If during the course of DCRI activities it is noted that information that should have been redacted was not then DCRI RECORD CEC Coordinators, Clinical Data Assistant, and/or Clinical Trial Assistants will redact the information, document the event and notify GSK." Section 4.2 of charter; 6.4.2 of protocol

# Redaction in RECORD trial

- Inspection of Quintiles Clinical Event Validation and Adjudication Committee (CEVA) 2010
  - Included review of 53 subject records
  - One instance of inadequate redaction
- Conclusion: “Failure to redact treatment information occurred rarely.”

# Original RECORD trial events not referred for adjudication

- The following slides review DCRI's re-adjudication results for six subjects discussed in the original OSI review for whom events were not referred for adjudication.

# Original RECORD trial events not referred for adjudication

**Subject 18215:**

- Original reviews documented concerns regarding lack of referral by CI for hospitalization and adequacy of adjudication concerning hospitalization and death.
- **Re-adjudication Outcome:** Cause of hospitalization listed as pneumonia in CEC spreadsheet; DCRI adjudicated the death as non-cardiovascular (unchanged).

**Subject 19079:**

- Event of myocardial infarction (MI) was withdrawn from consideration as an endpoint at discretion of investigator
- **Re-adjudication Outcome:** DCRI adjudication added MI.

# Original RECORD trial events not referred for adjudication

**Subject 20930**

- Event of collapse attributed to atrial fibrillation was not sent for adjudication by the CI.
- **Re-adjudication Outcome:** Two MI triggers adjudicated by DCRI as no MI

**Subject 31427**

- Hospitalization for facial paralysis not referred because CT scan ruled out a stroke
- **Re-adjudication Outcome:** At DCRI, diagnosis on CEC spreadsheet is peripheral facial paralysis, event was not sent to DCRI CEC for adjudication

# Original RECORD trial events not referred for adjudication

**Subject 43697**

- Event of transient ischemic attack (TIA) or stroke withdrawn by CI.
- **Re-adjudication Outcome:** DCRI adjudicated as hemorrhagic stroke.

**Subject 98364**

- Hospitalization for Congestive Heart Failure (CHF) withdrawn by CI; referral issue cited by FDA in 2010
- **Re-adjudication Outcome:** DCRI adjudicated as no MI (unchanged)

# Summary

- For six subjects that had not been referred for adjudication in the original RECORD trial, two subjects had addition of CV death or MACE endpoint
- Based on FDA on-site inspection, data generated at DCRI are considered reliable

# Rosiglitazone REMS

**Joyce Weaver, PharmD**
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**Office of Medication Error Prevention and Risk Management**
**Division of Risk Management**

# Rosiglitazone REMS

- REMS with restricted distribution approved for rosiglitazone-containing drugs May 18, 2011
  - Six-month phase-in period to allow patients and prescribers to transition
- Generic products added to REMS January 2013

# Goals of Rosiglitazone REMS

- To restrict access to rosiglitazone so that only prescribers who acknowledge the potential increased risk of myocardial infarction associated with the use of rosiglitazone are prescribing rosiglitazone.

# Goals of Rosiglitazone REMS

- To restrict access to patients who have been advised by a healthcare provider about the potential increased risk of myocardial infarction associated with the use of rosiglitazone and are one of the following:
  - either already taking rosiglitazone or
  - if not already taking rosiglitazone, they are unable to achieve glycemic control on other medications and, in consultation with their healthcare provider, have decided not to take pioglitazone for medical reasons

# Elements of Rosiglitazone REMS

- Medication Guide
- Elements to Assure Safe Use
  - Healthcare providers who prescribe rosiglitazone for outpatient or long-term care use are specially certified
  - Rosiglitazone will be dispensed only by specially certified pharmacies
  - Rosiglitazone will only be dispensed to patients with evidence or other documentation of safe-use conditions

# Safe-use Condition

- Patients receiving rosiglitazone at the time of REMS approval
  - Myocardial infarction risk discussion between patient and prescriber
- Patients new to rosiglitazone
  - Prescriber must determine that they are unable to achieve glycemic control on other meds
  - Myocardial risk discussion between patient and prescriber

# May 2012 Assessment Report

- Submitted by GSK May 17, 2012.
- Presents data from May 19, 2011 through March 12, 2012.
- Key Distribution Milestone: After **November 18, 2011**, patients could obtain rosiglitazone-containing products (RCPs) only by mail from a specially certified pharmacy participating in the REMS Program and not from local pharmacies.

# Findings from May 2012 Assessment Report

- Basic Information (cumulative data):
  - 2,231 total prescribers enrolled
  - 2,758 total patients total (2,654 were already on RCPs upon enrolling in REMS)
  - 4 total certified pharmacies
  - 63% of prescriptions for Avandia, 31% for Avandamet (rosiglitazone + metformin)

# Key Utilization Findings

| Parameter | 1st Assessment Report | 2nd Assessment Report | | Most Recent Assessment Report |
|---|---|---|---|---|
| | MAY 18 2011 to SEP 19 2011 | SEP 20 2011 to NOV 18 2011 | NOV 19 2011 to MAR 19 2012 | MAR 20 2012 through MAR 18 2013 |
| Total Prescriptions dispensed | 257,223 | 93,285 | 3,661 | 12,791 |
| Prescriptions/month | 64,306 | 46,463 | 915 | 1,066 |
| Prescriptions written by non-enrolled prescribers | 257,075 | 93,279 | 37 | Not Reported |
| Prescriptions written for non-enrolled patients | 257,075[a] | 93,279[a] | 308[a] | 64 |
| Number of times specialty pharmacies dispensed RCPs from a prescription written by a non-enrolled prescriber | 23,009 | 10,080 | **1**[b] | **2** |
| Number of times specialty pharmacies dispensed RCPs to non-enrolled patients | 23,088 | 10,086 | **1**[b] | **1** |

**a** - "*This process of checking the REMS system more than one time for the same prescription resulted in overstated numbers in the previous reports* "

**b** - Number was revised from "0" to "1" based on report submitted 5/1/13. The Sponsor reports that one non-certified pharmacy (parent company of a certified pharmacy) inadvertently dispensed 40 prescriptions after November 18, 2011, 9 of which were intercepted prior to patient receipt.

# Dispensing outside of the REMS

- After REMS implementation, dispensing of rosiglitazone by non-certified pharmacies (e.g., retail pharmacies) remained a source of product.
- Dispensing by non-certified pharmacies has been decreasing over time.
- As of last month of data available, few prescriptions dispensed by non-certified retail pharmacies.

# Key Risk Message of REMS

- Both prescribers and patients demonstrated good knowledge regarding potential risk of myocardial infarction (MI) with rosiglitazone
- Patients had a good understanding of MI symptoms as well as need to seek immediate medical attention

# FDA Conclusions on May 2012 Assessment Report

- The Sponsor's submitted assessment report was complete in addressing all issues outlined in the REMS assessment plan
- Overall, the REMS was determined to be meeting its goals

# Back-Up Slides

# Key Findings from Prescriber Survey (1)

- Survey conducted Feb 2012 – March 2012
- 155 Prescribers enrolled in the REMS of which:
  - 56% reported treating >50 patients with diabetes in a typical month
  - 87% were physicians (MD or DO)
  - Medical specialties:
    - 54% primary care/family practice
    - 22% internal medicine
    - 19% endocrinology

# Key Findings from Prescriber Survey (2)

- % understanding:
  - Increased risk of myocardial infarction (MI) with RCPs (83-92%)
  - limiting rosiglitazone use to patients who have been advised of the risks (91%)
  - Before starting a new patient on a rosiglitazone medicine, prescribers must determine that the patient is unable to achieve glycemic control on other diabetes medications … (78%)

# Key Findings from Prescriber Survey (3)

- % understanding:
  - can prescribe rosiglitazone to new patients (63% )
  - a local pharmacy can not dispense rosiglitazone (59%)

# Key Findings from Patient Survey

- Survey conducted Feb 2012 – March 2012
- N= 305 (96% patients, 4% caregivers) who were enrolled in the RCP REMS program
- % understanding:
  - Need to seek immediate medical attention for heart attack symptoms (99%)
  - Heart attack symptoms (80-94%)
  - REMS administrative aspects (80-89%)

# Goals of the REMS

- To restrict access to rosiglitazone so that only prescribers who acknowledge the potential increased risk of myocardial infarction associated with the use of rosiglitazone are prescribing rosiglitazone.

# Goals of the REMS

- To restrict access to patients who have been advised by a healthcare provider about the potential increased risk of myocardial infarction associated with the use of rosiglitazone and are one of the following:
  - either already taking rosiglitazone or
  - if not already taking rosiglitazone, they are unable to achieve glycemic control on other medications and, in consultation with their healthcare provider, have decided not to take pioglitazone for medical reasons

# Drug Utilization Patterns for Rosiglitazone- and Pioglitazone-Containing Products, July 2007-December 2012

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**Division of Epidemiology II**
**Office of Surveillance and Epidemiology**
FDA/CDER

Joint Meeting of the Drug Safety and Risk Management (DSaRM) and Endocrine and Metabolic Drugs Advisory Committee (EMDAC)

June 5-6, 2013

# Outline

- Sales Distribution
- Prescription and Patient Trends
- Prescriber Specialty
- Diagnoses Associated with Use
- Limitations
- Summary

# Products Included

- Rosiglitazone-containing Products
  - Avandia (rosiglitazone)
  - Avandamet (rosiglitazone/metformin)
  - Avandaryl (rosiglitazone/glimepiride)

- Pioglitazone-containing Products
  - Actos (pioglitazone) and generics
  - Actoplus Met, Actoplus Met XR (pioglitazone/metformin) and generics
  - Duetact (pioglitazone/glimepiride)

# Sales Distribution Analysis

IMS Health, IMS National Sales Perspective™

# IMS Health, IMS National Sales Perspectives™

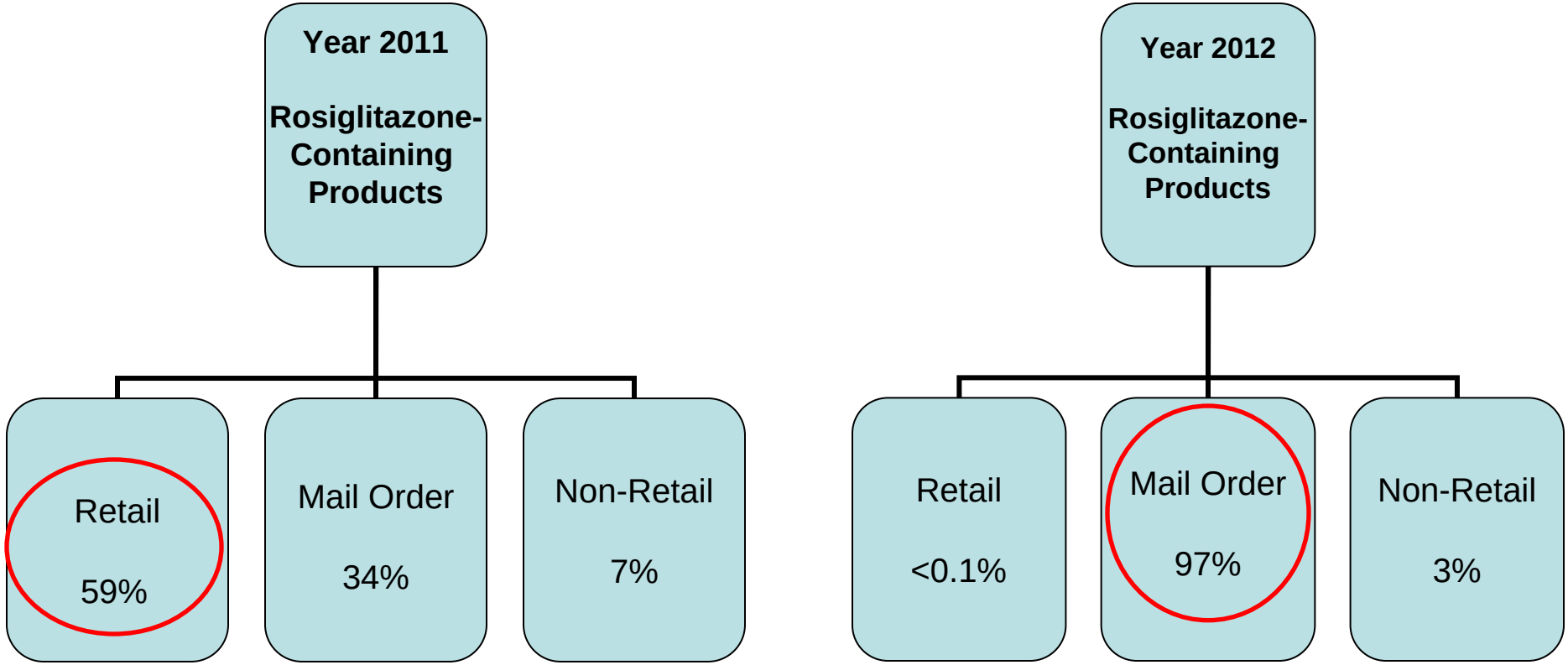
## Measures sales data from *manufacturer to retail and non-retail channels of distribution*

- Retail Channels - chain, independent, mass merchandisers, food stores with pharmacies
- Non-Retail Channels - federal facilities, non-federal hospitals, clinics, long-term care facilities, home health care, HMOs, miscellaneous channels (prisons, universities, other)
- Mail Order/Specialty Channels

# Sales Data

## Year 2011 & 2012*

*IMS Health, National Sales Perspective™*






** Total may add to more than 100% due to rounding*

# Prescription and Patient-Level Data

## Outpatient Retail Pharmacies

Symphony Healthcare Analytics': PHAST Prescription™ and ProMetis Lx®

IMS Health, Vector One®: VONA and Total Patient Tracker (TPT)

# Outpatient Analysis

- July 2007 – December 2012
  - Post Advisory Committee 1 (AC1):
    - July 2007 – July 2010
  - Post Advisory Committee 2 (AC2):
    - August 2010 – April 2011
  - Post REMS:
    - May 2011 – December 2012

# Prescriptions

- ***IMS Health, Vector One®: National***
  - Prescriptions captured from a sample of approximately 59,000 retail pharmacies throughout the US.
  - Sourced from:
    - Chain Pharmacies
    - Independent Pharmacies
    - Food Stores
    - Mass Merchandisers

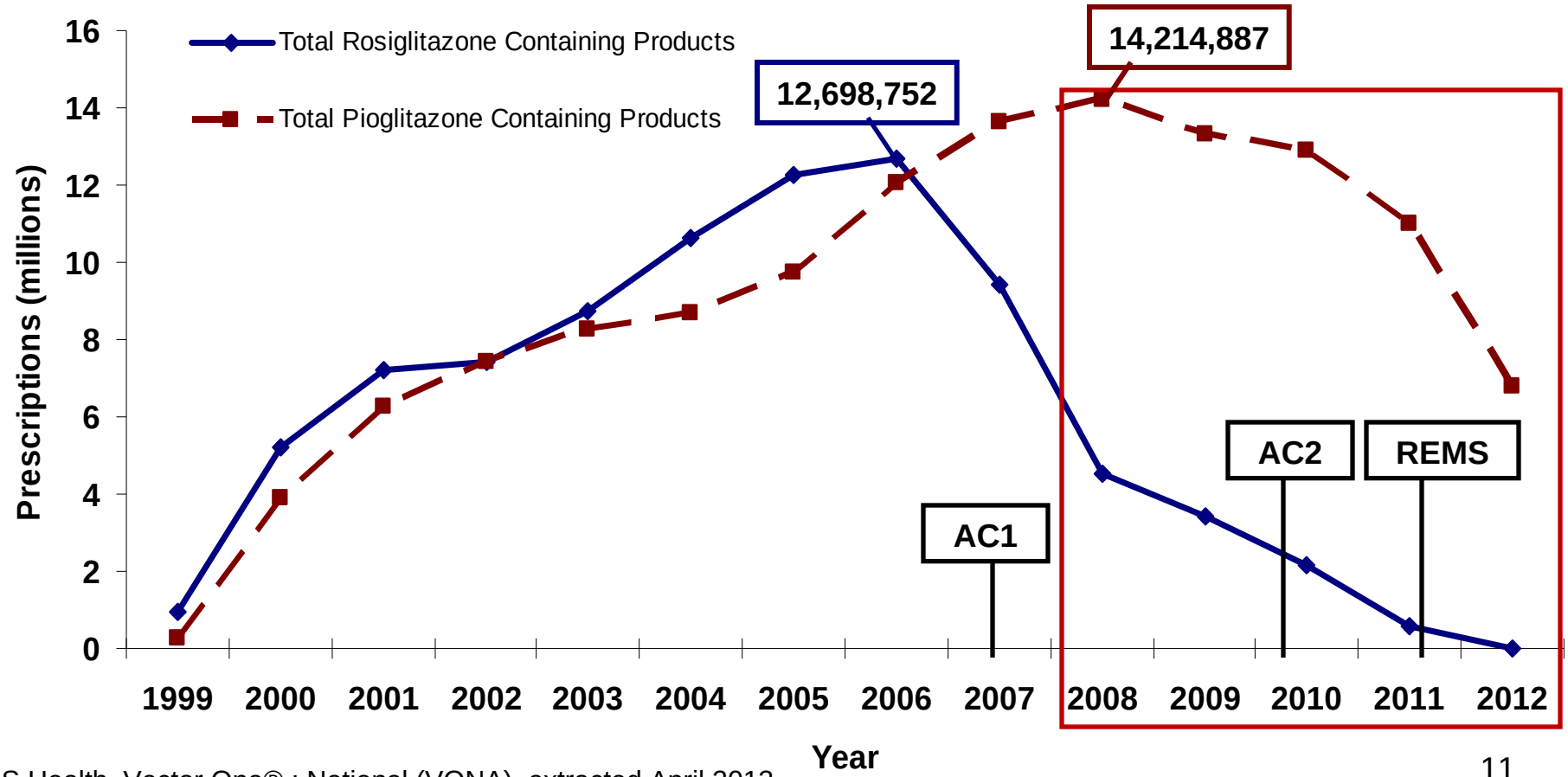
- ***The Symphony Healthcare Analytics PHAST Prescription Monthly™***
  - Prescriptions captured from a sample of approximately 42,000 retail and *mail-order/specialty* pharmacies
  - Sourced from:
    - PBM's and Plan Organizations
    - Chain Pharmacies
    - Independent Pharmacies
    - Mail-Order/Specialty Pharmacies

# Patients

- ***IMS Health, Vector One®: Total Patient Tracker (TPT)***
  - **Measures the number of unique patients receiving a dispensed prescription from outpatient retail pharmacies**

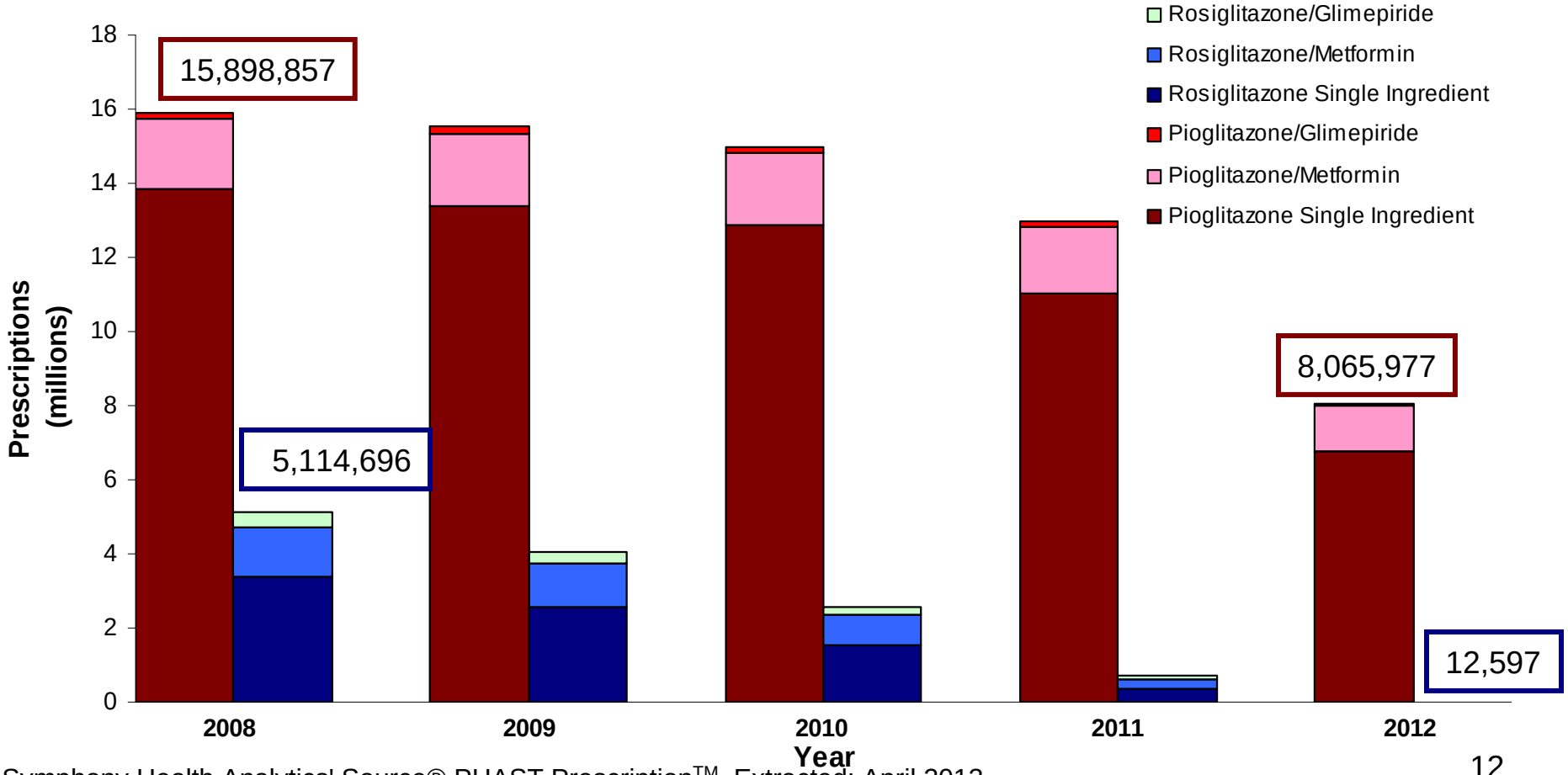
- ***Prometis Lx®***
  - **Measures *longitudinal* patient data based on medical and prescription claims**
    - Commercial plans
    - Medicare Part D plans
    - Medicaid claims
    - Cash

# Nationally estimated number of prescriptions for rosiglitazone- and pioglitazone-containing products dispensed through U.S. retail pharmacies, years 1999-2012



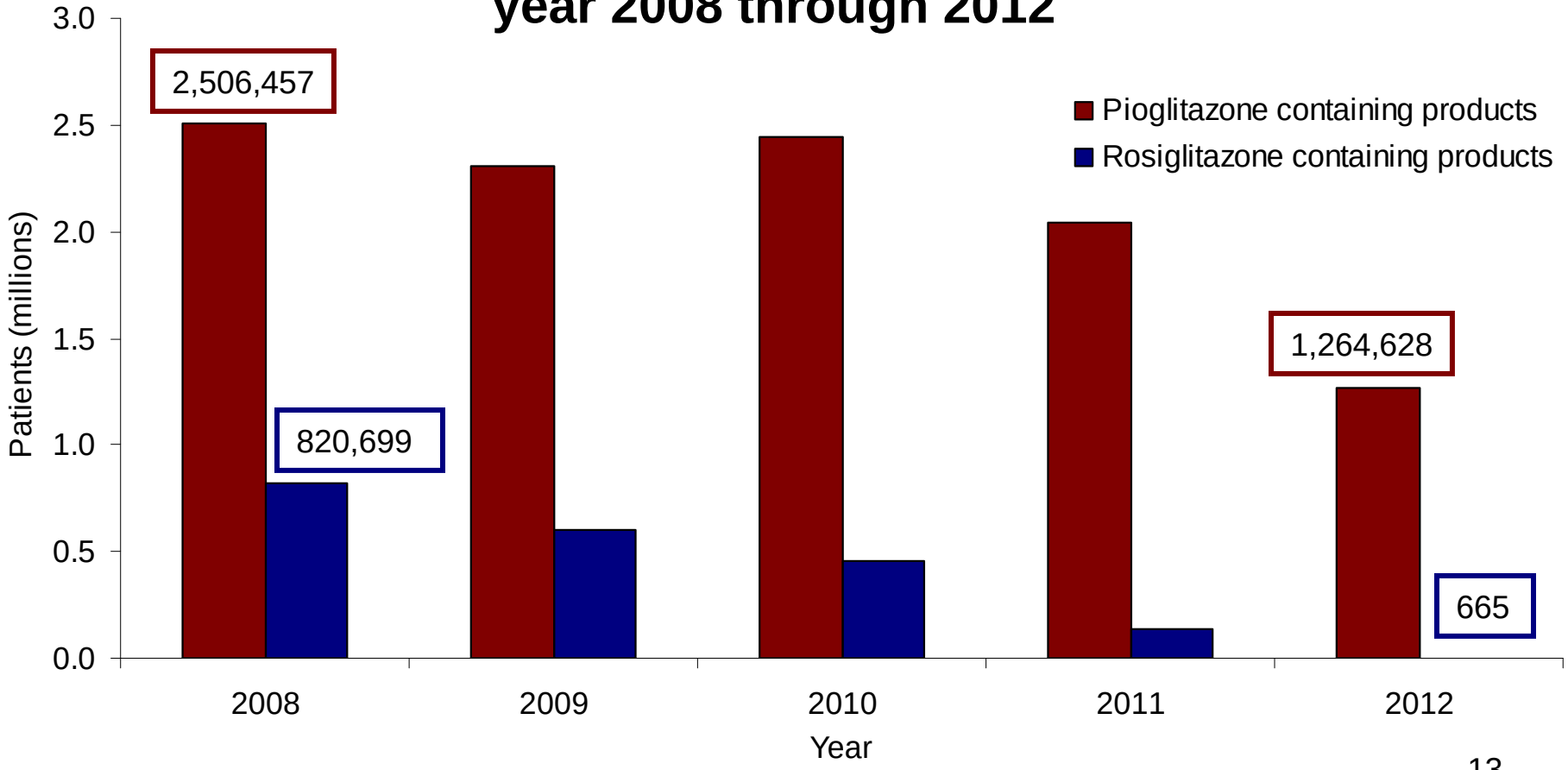

IMS Health, Vector One® : National (VONA), extracted April 2013

# Nationally estimated number of prescriptions for rosiglitazone-containing and pioglitazone-containing products dispensed through U.S. retail and mail-order/specialty pharmacies, year 2008 through 2012



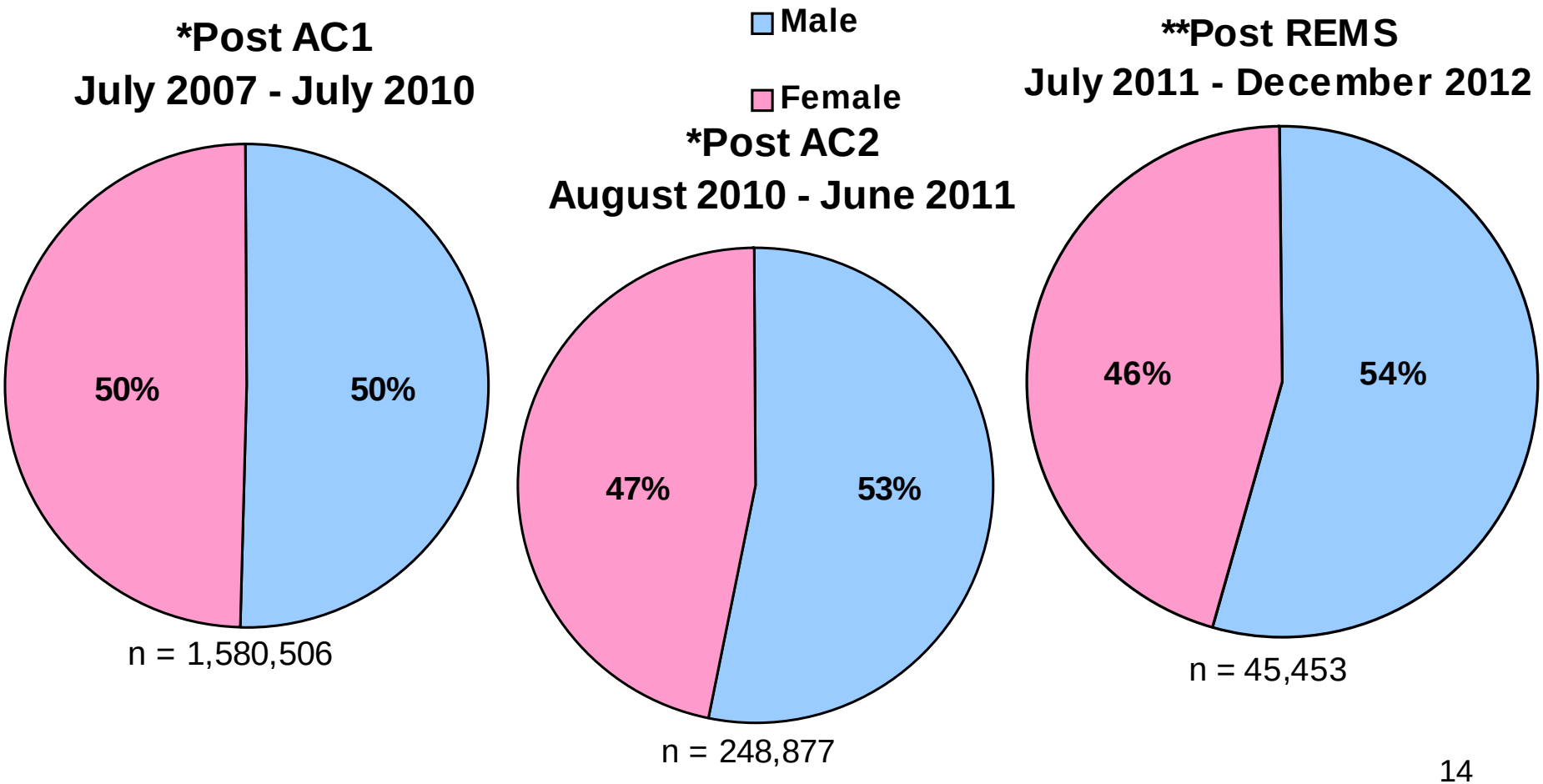

Symphony Health Analytics' Source® PHAST Prescription™. Extracted: April 2013.

# Nationally estimated number of patients who received a prescription for rosiglitazone- or pioglitazone-containing products dispensed through U.S. retail pharmacies from year 2008 through 2012




IMS Health, Vector One®:Total Patient Tracker, extracted April 2013

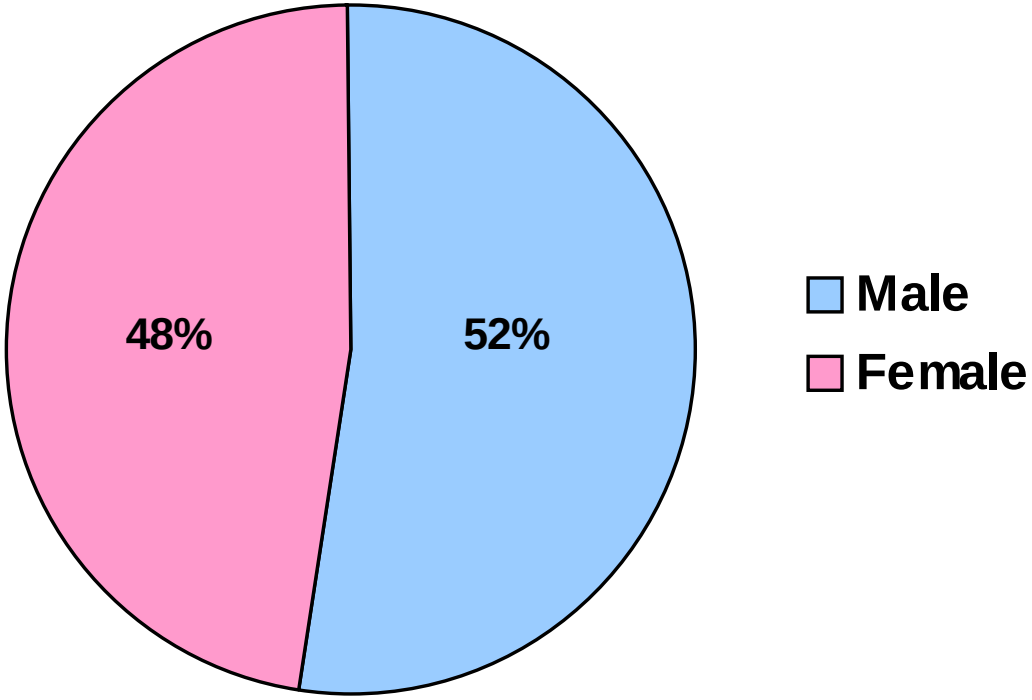
# Number of patients who received a dispensed prescription for rosiglitazone-containing products, stratified by patient sex




*IMS Health, Vector One®: Total Patient Tracker, extracted April 2013
**Symphony Health Analytics Prometis Lx CPA Analyzer, extracted April 2013

# Number of patients who received a dispensed prescription for rosiglitazone-containing products, stratified by patient sex, Year 2012

## January 2012 - December 2012

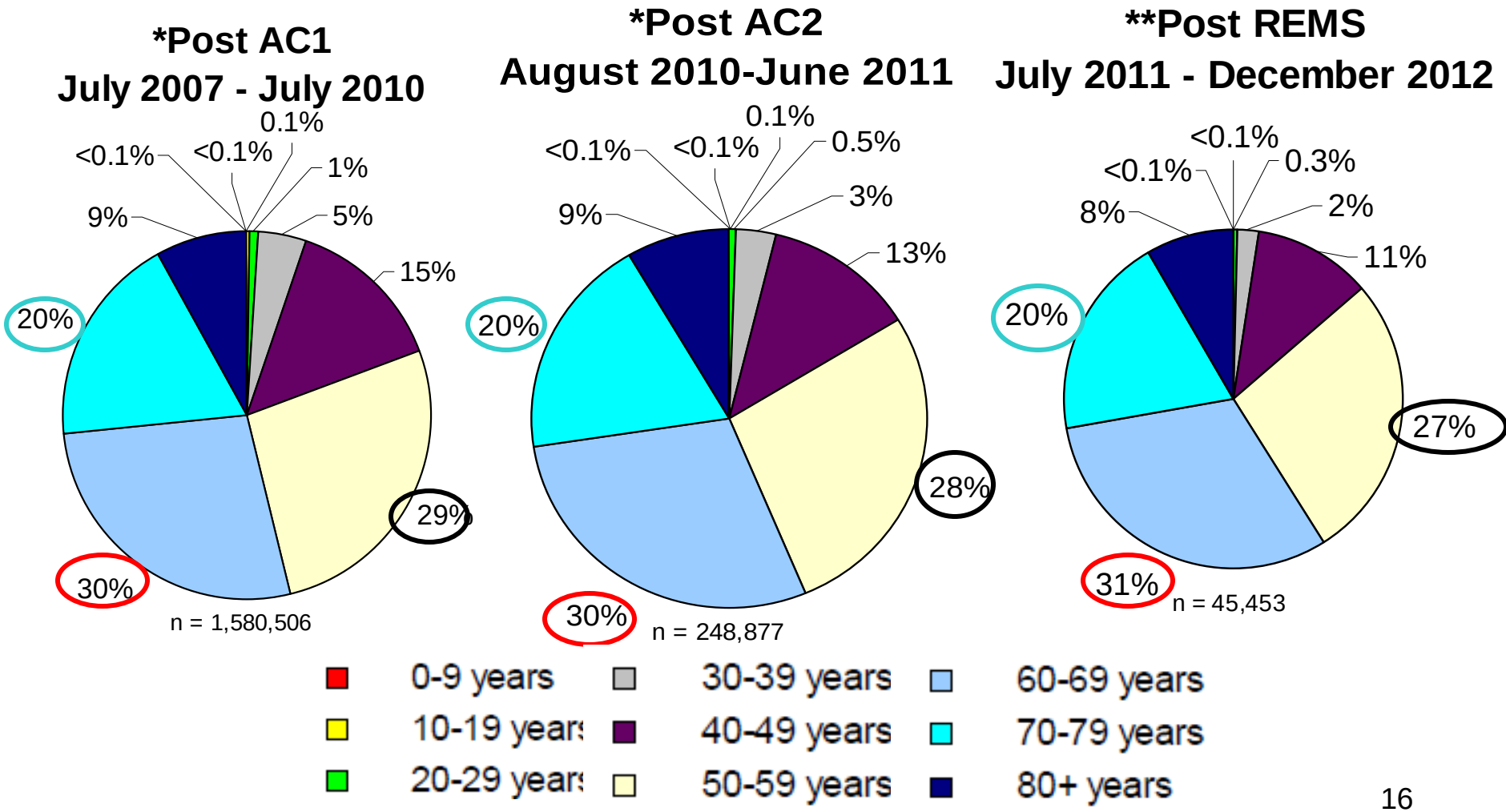



n = 4,637



Symphony Health Analytics Prometis Lx CPA Analyzer, extracted April 2013

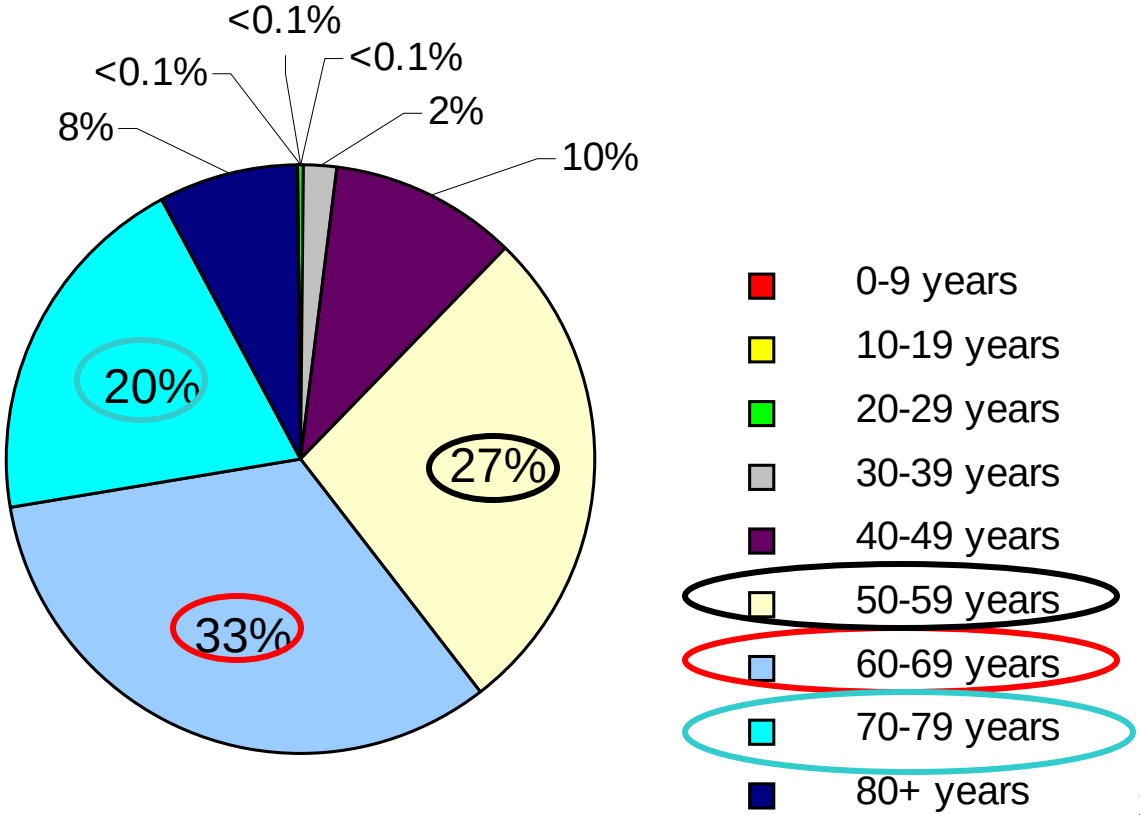
# Number of patients receiving dispensed prescriptions for rosiglitazone-containing products stratified by patient age




*IMS Health, Vector One®:Total Patient Tracker, extracted April 2013
**Symphony Health Analytics Prometis Lx CPA Analyzer, extracted April 2013

# Number of patients receiving dispensed prescriptions for rosiglitazone-containing products stratified by patient age, Year 2012

## January 2012 - December 2012




n = 4,637



Symphony Health Analytics Prometis Lx CPA Analyzer, extracted April 2013

# Prescriber Specialty Data

## Outpatient Retail and Mail Order Pharmacies

*Symphony Healthcare Analytics' PHAST Prescription™*

# Nationally estimated number of prescriptions dispensed for rosiglitazone-containing products from U.S. outpatient retail and mail-order/specialty pharmacies by top 10 prescribing specialties from July 2007 – December 2012

| | Post AC1 July 2007- July 2010 | Post AC2 August 2010-April 2011 | Post REMS May 2011 - December 2012 |
|---|---|---|---|
| | TRx (14,651,961) | TRx (1,090,955) | TRx (364,714) |
| **Total** | **100.0%** | **100.0%** | **100.0%** |
| FAMILY PRACTICE/GENERAL PRACTICE | 51.2% | 53.1% | 52.6% |
| INTERNAL MEDICINE | 34.0% | 32.4% | 32.9% |
| ENDOCRINOLOGY-DIABETES-METABOLISM | 4.9% | 4.6% | 3.9% |
| OTHER | 2.8% | 2.8% | 3.1% |
| EMERGENCY MEDICINE | 1.4% | 1.5% | 1.7% |
| CARDIOLOGY | 1.4% | 1.3% | 1.4% |
| RESIDENT | 0.9% | 0.9% | 1.0% |
| GERIATRICS | 0.6% | 0.5% | 0.6% |
| SURGERY | 0.5% | 0.4% | 0.4% |
| PEDIATRICS | 0.5% | 0.5% | 0.5% |
| All Others | 1.8% | 1.9% | 1.9% |

Symphony Health Analytics' Source® PHAST PrescriptionTM. Extracted: April 2013.

# Diagnosis Data

Encuity Research TreatmentAnswers™

# Diagnosis Data

**Encuity Research, Treatment Answers™**

- Monthly survey that monitors disease states and physician intended prescribing habits on a national-level
- 3,200 panelists, 30 specialties, 115 pain specialists
- Includes diagnoses, patients characteristics, and treatment patterns

# Top Diagnoses Associated with the Use of Rosiglitazone-Containing Products by U.S. Office-Based Physician Surveys, from July 2007 to December 2012

| | Post AC1 July 2007 - July 2010 | Post AC2 August 2010 - April 2011 | Post REMS May 2011 - December 2012 |
|---|---|---|---|
| | Uses (4,511,000) | Uses (255,000) | Uses (118,000) |
| **Total Market** | 100.0% | 100.0% | 100.0% |
| 2500 DIABETES MELLITUS UNCOMP | 96.3% | 81.3% | 100.0% |
| 4019 HYPERTENSION NOS | 0.4% | -- | -- |
| 4140 CORONARY ATHEROSCLEROSIS | 0.3% | -- | -- |
| 5838 NEPHRITIS NOS W OTH LES | 0.3% | -- | -- |
| 5854 CHRONIC KIDNEY DIS IV | -- | 5.3% | -- |
| 5818 NEPHROTIC SYN W OTH LES | -- | 5.3% | -- |
| 2504 DIAB W RENAL MANIFEST | 0.3% | 5.3% | -- |
| 2506 DIAB W NEUROLOGIC MANIF | 0.3% | 2.9% | -- |
| 2714 RENAL GLYCOSURIA | 0.2% | -- | -- |
| 2509 DIABETES W COMPLIC NOS | 0.2% | -- | -- |
| 2512 HYPOGLYCEMIA NOS | 0.2% | -- | -- |
| 3572 NEUROPATHY IN DIABETES | 0.2% | -- | -- |
| All Others | 1.4% | -- | -- |

*Source: Encuity Research, Treatment Answers LLC, July 2007 - December 2012 Extracted April 2012.File Encuity Total Diagnosis 2013-427 Rosiglitazone.xls*

# Strengths & Limitations

- Numerous data sources were used to provide national-level prescription and patient counts.
  - Patient counts that include mail-order/specialty pharmacy data are not nationally projected

- No statistical tests were performed to determine statistically significant changes over time

# Summary

- Rosiglitazone Prescriptions
  - Pre- REMS (Year 2008-2011): U.S. outpatient retail pharmacies
  - Post-REMS (Year 2012): mail-order/specialty pharmacies

- Unique Patients
  - Post AC1 period (July 2007-July 2010 ): ~1.6 million patients
  - Post AC2 (August 2010-June 2011): ~249,000 patients
  - Post-REMS (July 2011-December 2012): ~45,000 patients (~4,600 patients in year 2012)

- Top Prescribing Specialties
  - Family Practice/General Practice and Internal Medicine

- Top Diagnosis:
  - “Diabetes Mellitus Uncomp”