Quantitative Safety Assessment During the Post-Marketing Phase Examples at FDA/CDER

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Examples

1. Rosiglitazone/Pioglitazone Meta-Analyses
2. Rosiglitazone/Pioglitazone CMS Cohort Study
3. LABA Safety Trials
4. Sentinel: Oral Hypoglycemic Agents and Acute Myocardial Infarction

Avandia (Rosiglitazone)

- AVANDIA is a thiazolidinedione (TZD) antidiabetic agent indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Marketed by GSK.
- Only other approved TZD: Actos (pioglitazone). Marketed by Takeda.

Nissen and Wolski

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

Objectives of Rosiglitazone and Pioglitazone Meta-Analyses

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

Statistical Analysis Plan: General Considerations

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

Rosiglitazone and Pioglitazone Trials

Trial	Patients	Events	Duration	Notes
Rosi short-term trials (52)	16995	109	2 m – 2 y	
RECORD (Rosi)	4447	319	5 y	active control, open label, NI
Pio short-term trials (29)	11774	117	2 m – 2 y	
PROACTIVE (Pio)	5238	500	3 y	placebo controlled, high CV risk pop

Trial Inclusion: General Considerations

- Large trials (DREAM, ADOPT, RECORD, PROACTIVE) viewed as independent sources of information
  - These large trials would dominate meta-analyses
  - Large trials were not comparable between the drugs
- Meta-analysis was used to evaluate the information provided from the smaller trials

Trial-Level Groups (1)

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

Trial-Level Groups (2)

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

Trial Summary : Randomized Comparator

	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
Randomized comparator	Trials N=29 n	Sample size N=11774 n (%)	Trials N=52 n	Sample size N=16995 n (%)
Placebo	18	4574 (39)	46	13760 (81)
Active	12	7350 (62)	13	4037 (24)
Sulfonylurea	8	4383 (37)	8	3106 (18)
Metformin	3	2232 (19)	4	613 (4)

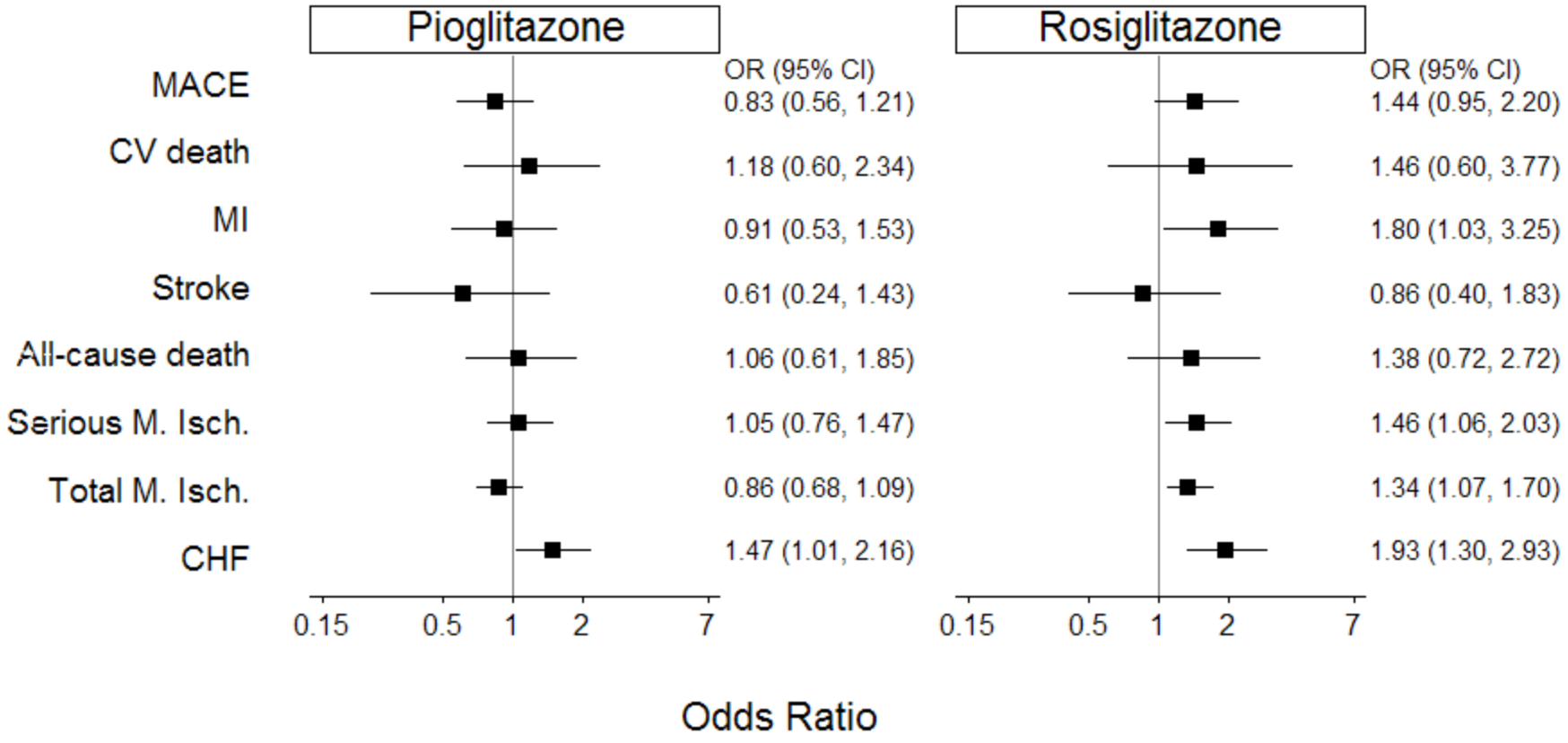
Trial Summary: Treatment Add-On Group

	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials N=29	Sample size N=11774	Trials N=52	Sample size N=16995
Treatment add-on	n	n (%)	n	n (%)
Monotherapy	13	5786 (49)	18	5484 (32)
Background	3	1301 (11)	5	904 (5)
Sulfonylurea	3	1164 (10)	16	4471 (26)
Metformin	6	2244 (19)	11	4064 (24)
Insulin	5	1190 (10)	7	1183 (11)
Sulfonylurea and Metformin	1	299 (3)	1	837 (5)

Trial Summary: Trial Duration

	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials N=29	Sample size N=11774	Trials N=52	Sample size N=16995
Trial duration	n	n (%)	n	n (%)
> 2m to ≤ 6m	18	5497 (47)	40	11784 (69)
> 6 m to ≤ 1y	6	3505 (30)	10	4316 (25)
> 1y to ≤ 2y	5	2772 (24)	2	895 (5)

Meta-Analysis Results: Primary Analysis Set, All Outcomes



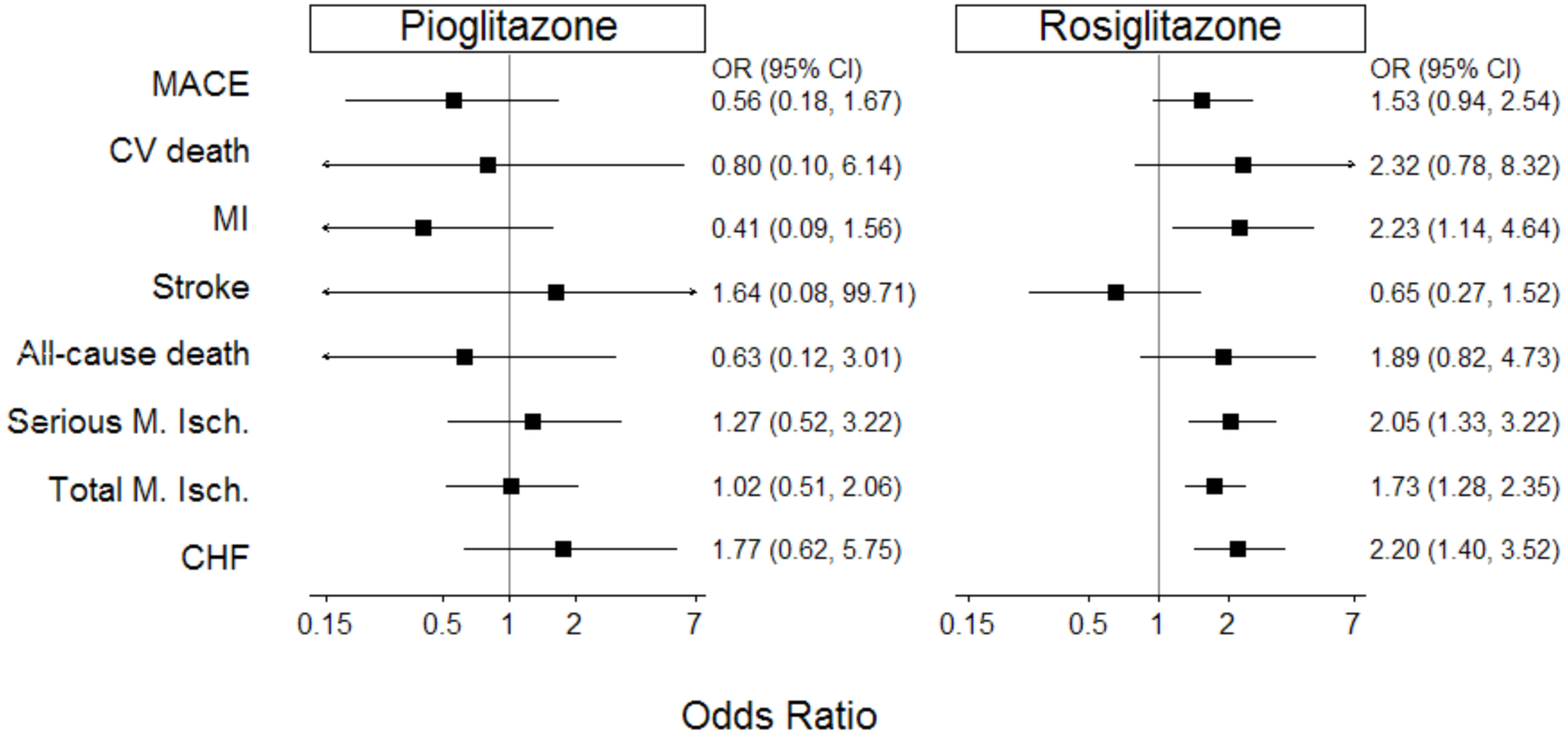
Placebo Controlled Trial Summary: Treatment Add-On Groups

	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials N=18	Sample size N=4574	Trials N=46	Sample size N=13760
Treatment add-on	n	n (%)	n	n (%)
Monotherapy	6	1115 (24)	11	2787 (20)
Background	-	-	5	904 (7)
Sulfonylurea	2	528 (12)	16	4481 (33)
Metformin	5	1614 (35)	8	2925 (21)
Insulin	4	1018 (22)	7	1833 (13)
Sulfonylurea and Metformin	1	299 (7)	1	837 (6)

Placebo Controlled Trial Summary: Durations

	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials N=18 n	Sample size N=4574 n (%)	Trials N=46 n	Sample size N=13760 n (%)
Trial duration				
> 2m to ≤ 6m	15	3813 (83)	38	11347 (82)
> 6 m to ≤ 1y	3	761 (17)	7	2186 (16)
> 1y to ≤ 2y	-	-	1	227 (2)
range (w)		12-52		8-104
Treatment duration				
Mean (std) (d)		140 (71)		165 (91)

Meta-Analysis Results: Placebo Controlled, All Outcomes



Limitations of Meta-Analyses

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

Examples

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4. Sentinel: Oral Hypoglycemic Agents and Acute Myocardial Infarction

Medicare Study Goal

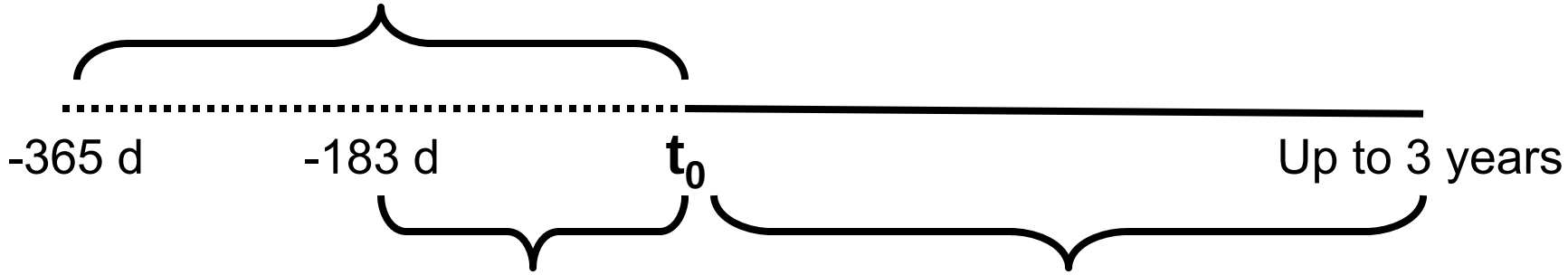
- Compare the risk rosiglitazone versus pioglitazone in patients aged 65 years or older
  - AMI
  - Stroke
  - Heart failure
  - Death
  - Composites

Medicare Data

- FDA access to Medicare and Medicaid data through CMS SafeRx initiative
- Data management & programming via Acumen LLC
- Medicare
  - Part A: hospitalization, inpatient, SNF
  - Part B: physician, outpatient
  - Part D: prescription drugs, started in 2006

Study design: inception cohort, time-to-event

Medical covariates
Not in hospital, NH, SNF, hospice on t_0
Age ≥ 65 on t_0



No TZD use
DM therapy
Drug covariates

Censor: TZD switch, therapy gap, endpoint, non-endpoint hospitalization, study end
(14-day extended follow-up for endpoints)

Selected baseline covariates (1)

Characteristic	Rosiglitazone (67 593)	Pioglitazone (159 978)	Standardized mean difference
Female (%)	60.8	59.5	0.03
Age (mean)	74.4	74.4	0.00
Vascular disease (%)			
AMI†	1.1	1.0	0.01
Coronary revasc	8.1	8.0	0.01
Heart failure†	6.9	6.0	0.04
Other IHD	21.0	20.8	0.01
Stroke†	1.3	1.1	0.02
Micro disease	36.5	37.3	0.02
PVD	5.8	5.6	0.01

† hospitalized only

Selected baseline covariates (2)

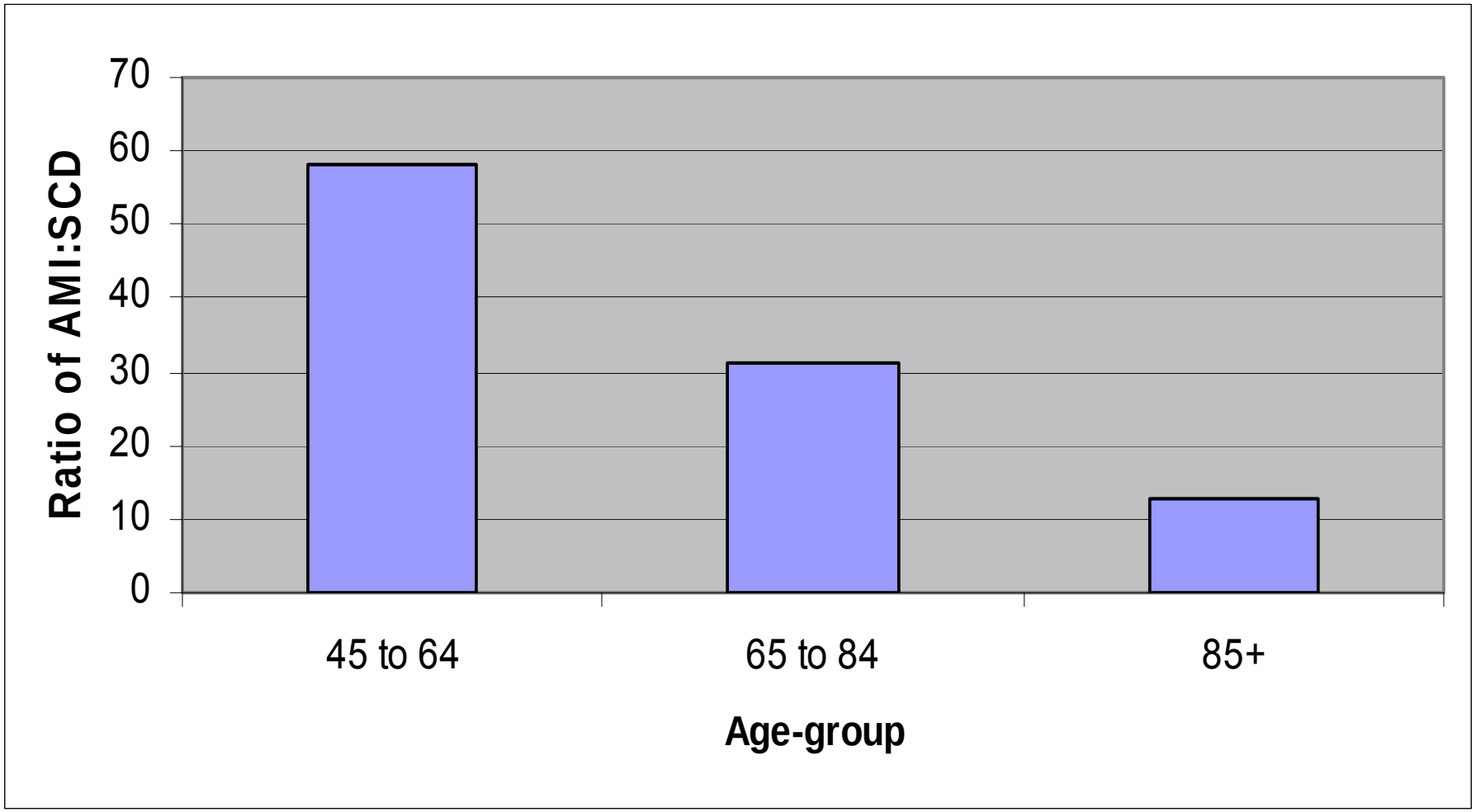
Medications (%)	Rosiglitazone (67 593)	Pioglitazone (159 978)	Standardized mean difference
ACEIs and ARBs	66.3	67.4	0.02
Antiarrhythmics	1.9	1.8	0.01
Anti-coagulants	8.3	8.6	0.01
Anti-platelets	14.3	14.3	0.00
Beta-blockers	41.9	43.0	0.02
CCBs	32.5	32.9	0.01
Digoxin	7.1	6.9	0.01
Loop diuretics	21.7	21.4	0.01
Thiazides	35.3	35.7	0.01
Nitrates	11.1	10.4	0.02
Insulin	13.7	13.7	0.00
Metformin	48.8	52.3	0.07
Sulfonylureas	48.2	49.8	0.03
Statins	57.4	59.2	0.04

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

Ratio of hospitalized AMI to sudden cardiac death (SCD) by age



Source: National underlying cause of death data (CDC) and HCUP National Inpatient Sample (AHQR)

Study Limitations and Strengths

Limitations

- Not randomized
- Potential misclassification
- Potential unmeasured confounding
- Endpoints not independently validated
- Part D data not used previously for research
- Limits of observational study in terms of estimate sizes?

Strengths

- Large size
- Entire eligible population
- Close similarity in baseline characteristics
- Previously validated end points
- Complete death ascertainment
- Consistency across sub-analyses

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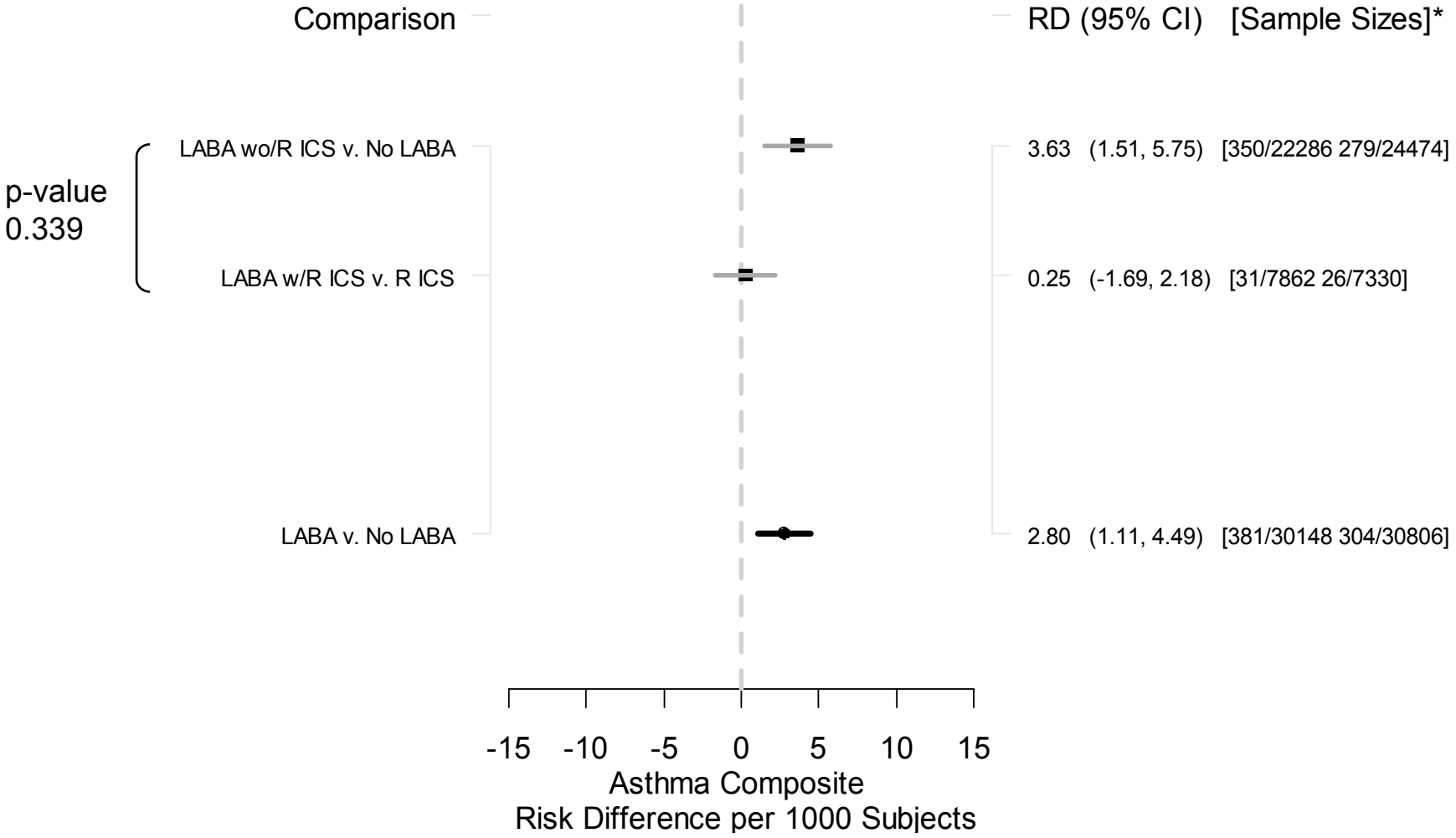
LABA: Background

- Long-acting beta-agonists (LABAs) — drugs provide bronchodilation for 12 hours or longer for asthma patients
- LABAs have been associated with asthma-related: hospitalization, intubation, and death
- 2008 FDA Advisory Committee discussed a FDA meta-analysis of LABAs and serious asthma-related events

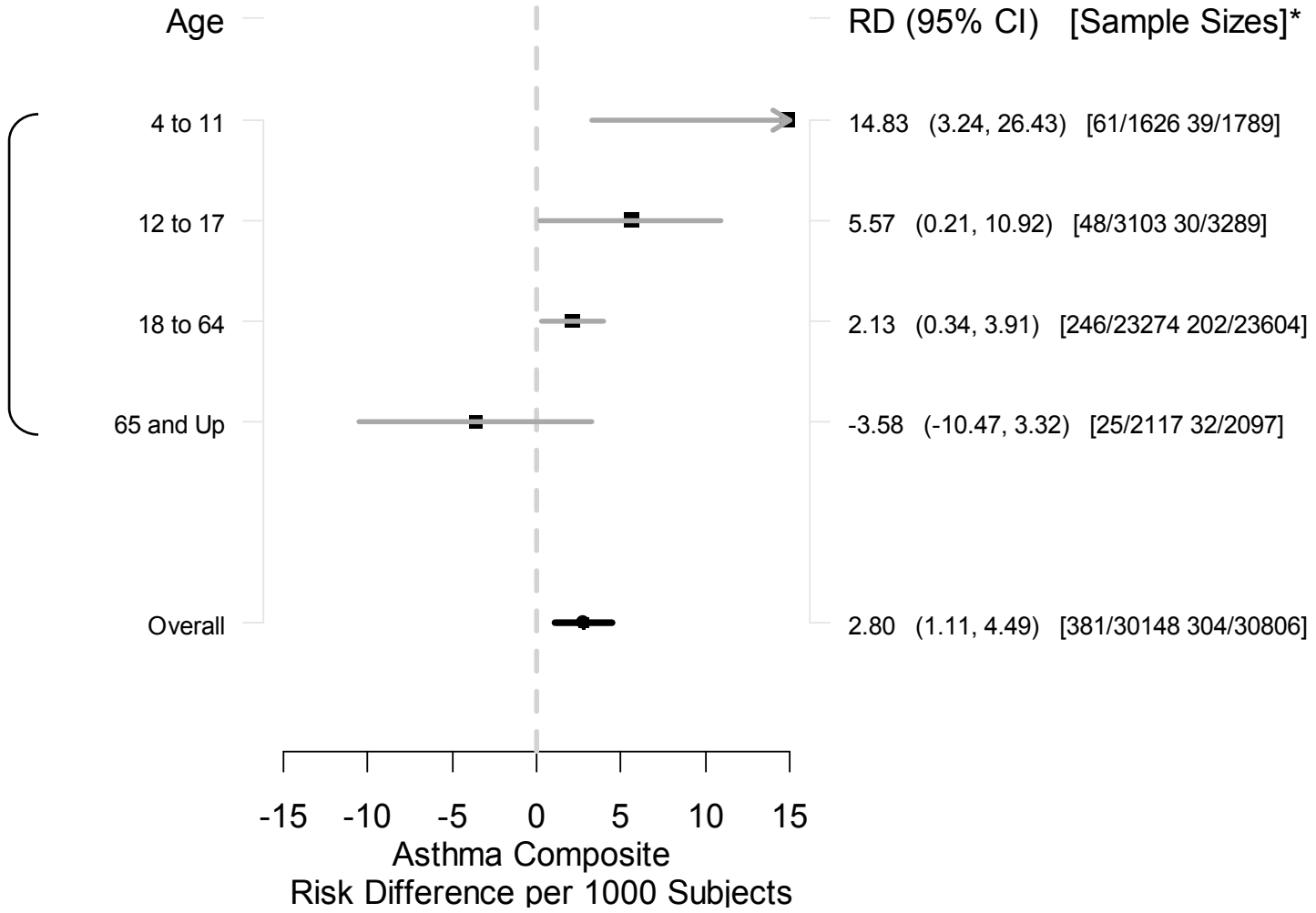
Asthma Composite by Assigned ICS Comparison Risk Difference Estimates



*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

Asthma Composite by Age Subgroup Risk Difference Estimates

p-value
0.018



*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

LABA: Post-Market Safety Trials

- FDA issued a PMR to all LABA manufacturers to conduct an RCT to assess the safety of LABAs plus inhaled corticosteroids v. inhaled corticosteroids alone
- Each product trial is powered for a non-inferiority margin of HR=2 on a composite endpoint (11,700 adolescents and adults patients)
- Trials have common design and joint oversight board
- Trials will be pooled for the analysis of asthma-related deaths (46,800 patients)
- Separate pediatric trial of 6,200 patients

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Sentinel Initiative

- National electronic healthcare data system to track the safety of FDA-approved products
- Active surveillance: FDA can initiate safety evaluations of specific products and safety outcomes
- Currently
  - Federal Partners Collaboration
  - Mini-Sentinel Collaboration

Sentinel Initiative: Federal Partners

- Federal Partners
  - Centers for Medicare and Medicaid Services (CMS)
  - Veterans Health Administration
  - Department of Defense
- Each partner maintains its own data. No common data model. Common protocols.

Sentinel Initiative: MiniSentinel

- Purpose: to inform and facilitate development of a fully operational active surveillance system
- Consists of data partners (private health care systems) and academic partners
- Distributed data environment
  - Common Data Model (MSCDM) at all Data Partners
  - Single SAS program disseminated and implemented to all sites
- No transfer of individual level data for assessments
- Several ongoing surveillance and methods projects

Oral Hypoglycemic Agents and Acute Myocardial Infarction

- Protocol (by Selby, Fireman, and Butler) and study team deliberations available online
- Objectives:
  - Active surveillance of the risk of AMI from saxagliptin
  - Evaluation of several statistical approaches to active surveillance in the Sentinel environment

Design and Analysis

- Saxagliptin compared to each of 4 oral hypoglycemic agents
- New user cohort design
- Confounding adjustment
  - Propensity scores
  - Disease risk scores
  - Multivariate regression

Propensity Scores Approach

- Compares saxagliptin cohort to each of the other drug cohorts separately
- Propensity scores
  - Program developed centrally, common covariates
  - Propensity scores fit at each data partner
  - Propensity score updated quarterly
- Patients matched within quarter
- Sufficient (summary) statistics at each DP provided centrally to fit stratified Cox model
  - No patient-level data provide centrally
  - Alternative approach might use meta-analysis

Sequential Analysis

- Planned 10 sequential looks on a quarterly basis
- Each look based on test with same nominal p-value.
- Planned for 80% power to detect a HR=1.33 maintaining a one-sided of 0.05 type 1 error over the 10 looks
- Drug usage is lower than anticipated. Protocol is be simulated on previously approved drug

References

- Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, briefing materials and slides (July 13–14, 2010, FDA Website).
- Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone, Graham DJ et al, JAMA, 2010 Jul 28;304(4):411-8.
- Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee, briefing materials and slides (December 10, 2008, FDA Website).
- Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting, briefing materials and slides (March 10-11, 2010, FDA Website).
- Assessing the Safety of Adding LABAs to Inhaled Corticosteroids for Treating Asthma, Chowdhury BA, Seymour SM, Levenson MS, N Engl J Med 2011; 364:2473-2475.
- A Protocol for Active Surveillance of Acute Myocardial Infarction in Association with Use of Anti-Diabetic Agents, (http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_AMI-and-Anti-Diabetic-Agents_Protocol_v2.0.pdf).

Thank You

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