Cardiovascular risks associated with anti-diabetic drugs, pioglitazone and rosiglitazone

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Workshop on New Directions in Postmarket Surveillance

University of Ottawa

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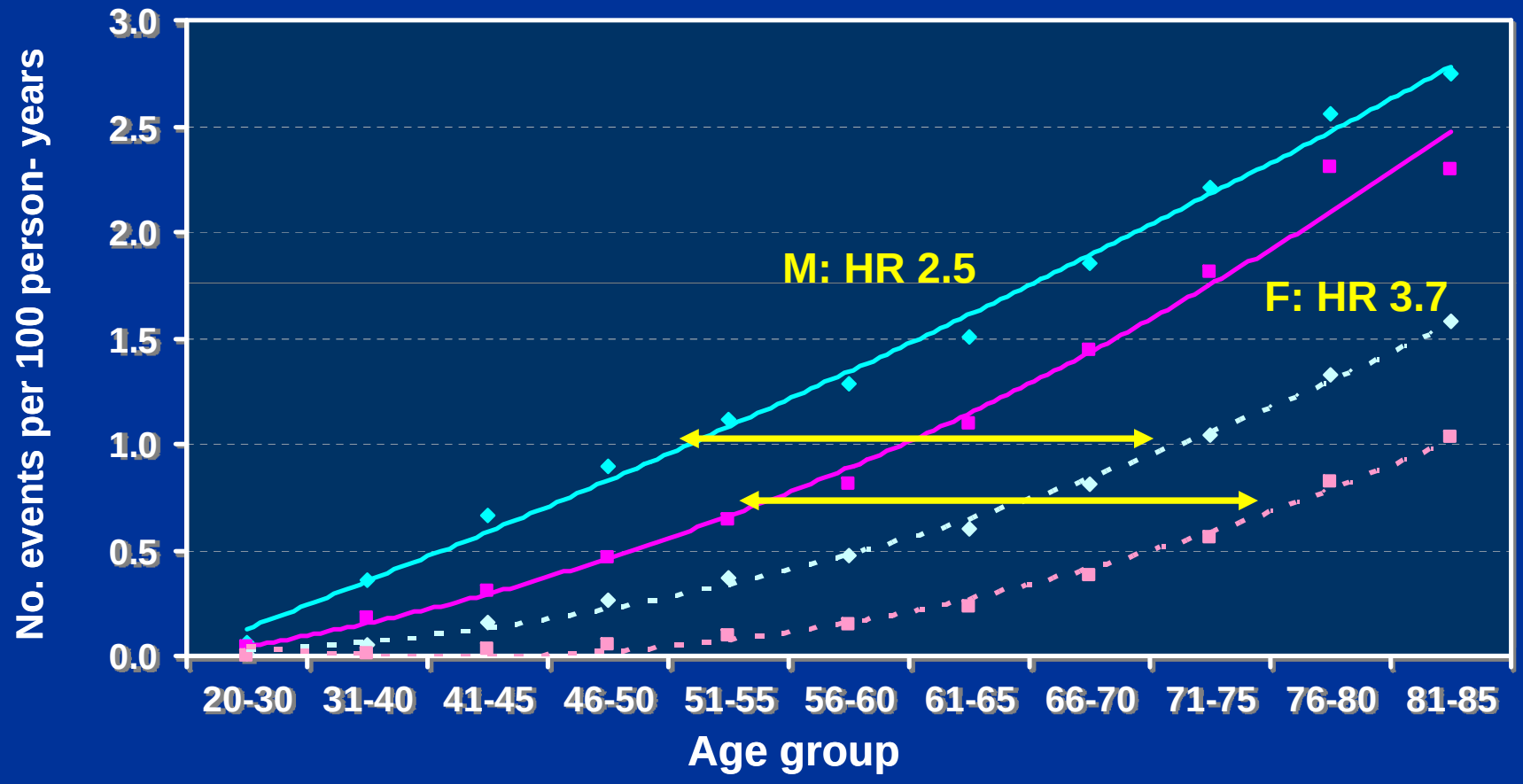
Objectives

- After attending this session, participants will be able to:
  - Appreciate clinical trial evidence of thiazolidinediones (TZDs) and cardiovascular events
  - Summarize data on TZDs and cardiovascular risk in ‘real-world’ diabetes patients

Diabetes

- Inadequate insulin
- Accumulation of glucose in blood
- Leads to long-term complications
  - Microvascular
  - Macrovascular
- >90% type 2
  - Insulin resistant
  - High risk of cardiovascular disease

Risk of AMI by gender and diabetes status



Booth GL, et al. *Lancet*. 2006;367:29-36

Goals of Type 2 Diabetes Treatment

- Short-term treatment of hyperglycemia
- Long-term prevention of microvascular and macrovascular complications
- Cardiovascular disease most important source of morbidity and mortality for type 2 DM
- Reduction of cardiovascular events primary treatment goal

Type 2 Diabetes Therapies

- Diabetes drugs approved based on efficacy for glycemic control
- Larger studies, longer follow-up needed to demonstrate reduction in complications
- Glycemic control considered a surrogate marker for long-term benefit

Does Glycemic Control Improve CV Outcomes?

- Evidence linking glycemic control to CV benefit limited
- UKPDS – benefit primarily on microvascular disease
- More intensive glycemic control
  - Advance - only microvascular risk reduction
  - Accord - may be increase CV mortality

Method of Lowering Glucose May be Important

- Metformin
  - MI and CV mortality reduction in UKPDS
  - First-line
  - Often need additional drugs with disease progression
- Sulfonylureas and Insulin
  - No convincing data on benefit or harm
- TZDs?

Thiazolidinediones (TZDs)

- Rosiglitazone (Avandia), pioglitazone (Actos)
- Decrease insulin resistance
  - Key defect in type 2 DM
  - Risk factor for CV disease
- Benefit on surrogate CV markers

Benefit on Clinical CV Outcomes?

- Pioglitazone - ProActive trial
  - Pioglitazone vs. placebo x 3 yrs
  - Benefit only on secondary endpoint of death, MI, stroke
    - HR 0.84 (0.72-0.98, p=0.027)

Dormandy et al., Lancet 2005;366:1279

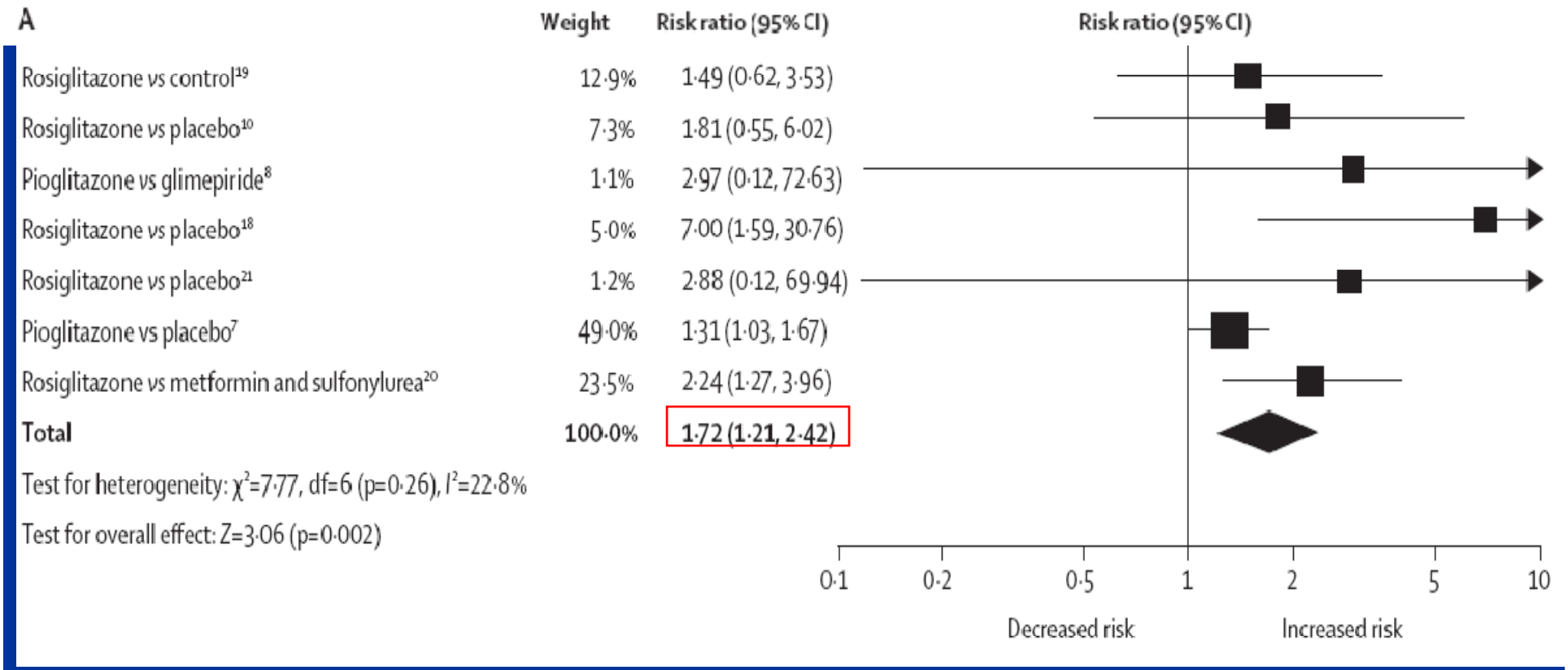
- Pioglitazone - meta-analysis of 19 RCTs
  - MI/death/stroke:
    - 4.4% pioglitazone vs. 5.7% controls
    - HR 0.82 (0.72-0.94, p=.005)

Lincoff et al., JAMA 2007; 298:1180

CV Risk with TZDs: CHF

- Evidence of increased congestive heart failure from clinical trials
  - Absolute risk low
  - Non-fatal, reversible
- Benefits on glycemia, ischemic CV events thought to outweigh risk of CHF

Risk of CHF: Meta-analysis of RCTs



- Rosiglitazone RR 2.18 (1.44-3.32)
- Pioglitazone RR 1.32 (1.04-1.68)
- NNH 107 per year

Lago et al. Lancet 2007; 370:1129

Does CV Benefit Outweigh CHF Risk?

Table 3. Cardiovascular Event Rates for Combined Trials Stratified by Study Type[a]

	No. (%)			
	Pioglitazone (n = 8554)	Control (n = 7836)	Hazard Ratio (95% Confidence Interval)	*P* Value
Death/myocardial infarction/stroke	375 (4.38)	450 (5.74)	0.82 (0.72-0.94)	.005
Death	209 (2.44)	224 (2.86)	0.92 (0.76-1.11)	.38
Myocardial infarction	131 (1.53)	159 (2.03)	0.81 (0.64-1.02)	.08
Death/myocardial infarction	309 (3.61)	357 (4.56)	0.85 (0.73-0.99)	.04
Stroke	104 (1.22)	131 (1.67)	0.80 (0.62-1.04)	.09
Serious heart failure	200 (2.34)	139 (1.77)	1.41 (1.14-1.76)	.002
Death/serious heart failure	361 (4.22)	321 (4.10)	1.11 (0.96-1.29)	.17
Death/myocardial infarction/stroke/ serious heart failure	508 (5.94)	523 (6.67)	0.96 (0.85-1.09)	.54

[a] Very short-term, short-term, midterm, long-term, and PROactive studies were used as stratification variables.

Lincoff et al., JAMA 2007; 298:1180

CV Risk with TZDs: AMI

- Risk-benefit ratio questioned
- Further concern:
  - Emerging evidence of higher myocardial infarction risk with rosiglitazone
- Challenged widely-held assumption
  - Control of glucose supposed to lower CV risk
  - Benefit on surrogate CV markers
  - Evidence of clinical benefit with pioglitazone

Rosiglitazone and AMI risk

- WHO report (2003)
  - Possible increase in ‘cardiac events’ with rosiglitazone
- GSK meta-analysis (2006)
  - AMI HR 1.31 (1.01-1.70) (AR 1.99% vs. 1.51%)
- Nissen meta-analysis (NEJM 2007)
  - AMI OR 1.43 (1.03-1.98)
- Meta-analysis of long-term studies (JAMA 2007)
  - 4 rosiglitazone trials
  - AMI RR 1.42 (1.06-1.91)

FDA Advisory Panel

- FDA conducted own meta-analysis
  - Significant RR 1.4 of AMI with rosiglitazone
- Panel agreed by a 20-3 margin that available data support an increased MI risk
- Voted 22-1 to recommend against withdrawal of rosiglitazone due to insufficient data
- Recommended black box warning

November 19 2007: FDA Black Box Warning

WARNING: CONGESTIVE HEART FAILURE AND MYOCARDIAL ISCHEMIA

- Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients (5.1). After initiation of AVANDIA, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of AVANDIA must be considered.
- AVANDIA is not recommended in patients with symptomatic heart failure. Initiation of AVANDIA in patients with established NYHA Class III or IV heart failure is contraindicated. (4, 5.1)
- A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing AVANDIA to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive. (5.2)

Health Canada Endorsed Important Safety Information on rosiglitazone (PrAVANDIA®, PrAVANDAMET® and PrAVANDARYL™)

November 1, 2007

Dear Health Care Professional:

Subject: **New restrictions on the use of rosiglitazone products due to cardiac safety concerns (AVANDIA®, AVANDAMET® and AVANDARYL™)**

Restrictions on Rosiglitazone

- Rosiglitazone (AVANDIA®) is no longer approved as monotherapy for type 2 diabetes, except when metformin use is contraindicated or not tolerated.
- Rosiglitazone is no longer approved for use in combination with a sulfonylurea, except when metformin is contraindicated or not tolerated.
- Treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure (i.e., NYHA Class I, II, III or IV).

Risk Underestimated in Clinical Trials?

- Impact in ‘real world’?
  - Clinical trial patients healthier, less comorbidity
  - Higher risk of adverse events in real world?
- Risk in older populations?
  - Seniors under-represented in clinical trials
  - 40% of diabetes patients in Ontario 65+ yrs

Thiazolidinediones and Cardiovascular Outcomes in Older Patients With Diabetes

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Context Thiazolidinediones (TZDs), used to treat type 2 diabetes, are associated with an excess risk of congestive heart failure and possibly acute myocardial infarction. However, the association between TZD use and cardiovascular events has not been adequately evaluated on a population level.

Objective To explore the association between TZD therapy and congestive heart failure, acute myocardial infarction, and mortality compared with treatment with other oral hypoglycemic agents.

JAMA, December 12, 2007; 298(22): 2634-2643

Objectives and Design

- Objectives
  - Compare risk of CHF, AMI, death between older patients on TZDs vs. other OHAs
- Design
  - Linkable, population-based Ontario health care databases
  - Retrospective cohort design using nested case control analysis

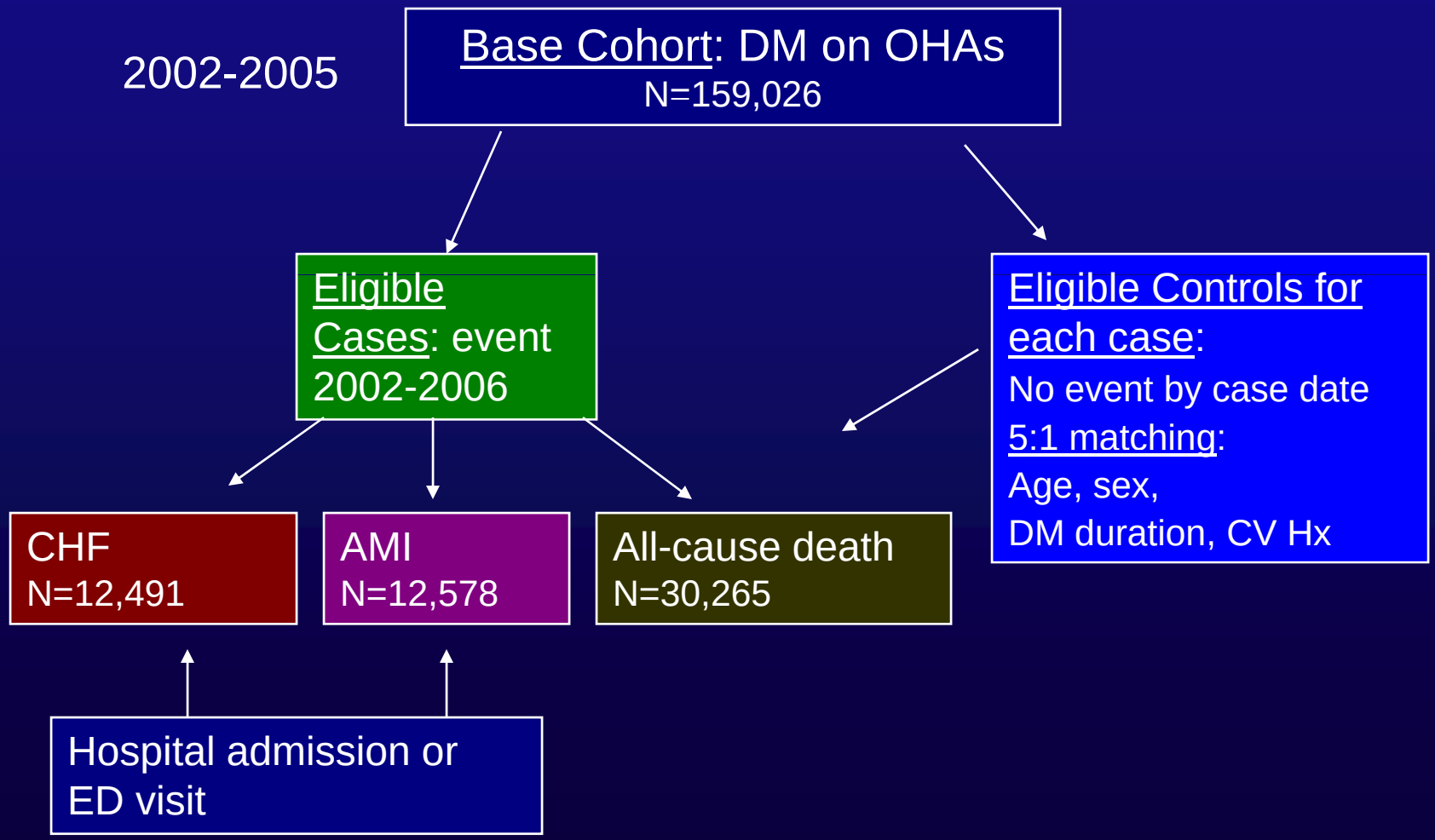
Linkable Databases

- *Ontario Diabetes Database*
  - *Validated diabetes registry*
- *Ontario Drug Benefit Database*
  - Prescriptions for Ontario residents ≥ age 65
- *CIHI*
  - *Hospital discharge abstracts*
- *NACRS*
  - *Emergency department visits*

Population

- Study cohort
  - Diabetes patients age 66+ yrs on at least one OHA
- Exclusion
  - Patients prescribed insulin before cohort entry
  - Patients started on insulin *during follow-up* included

Methods: Cases and Controls



TZD Exposure: Ontario Context

- TZDs only available through ODB Section 8 2000-2006
- Eligible if:
  - Inadequate control on maximal doses of glyburide and metformin
  - Intolerance or contraindication to glyburide or metformin
- 10-13% rejected

TZD Exposure

- Patients receiving drug via ODB may be older, at more advanced stage of diabetes
  - More an issue if TZD due to inadequate control = *combination therapy*
  - TZD due to contraindication/intolerance = *monotherapy*
- Could not assess treatment duration

Mutually Exclusive DM Drug Exposure Categories

- Primary: TZD monotherapy or combination
- Secondary: rosiglitazone and pioglitazone
- Comparison: Other OHA combination
  - At least 2 non-TZD drugs
- Defined at event date
  - Current exposure
  - Past exposure (stopped 15-365 days before)
  - No exposure (no script in last yr)

Analysis

- 3 NCC analyses
  - CHF, AMI, All-cause mortality
- TZD treatment vs. other OHA combination
- Rate ratios adjusted for:
  - Comorbidity, renal disease, income, other DM drugs, cardiac drugs, baseline CV disease, long-term care residence
- Stratified analyses:
  - DM duration, baseline CV disease

Results

Baseline Data

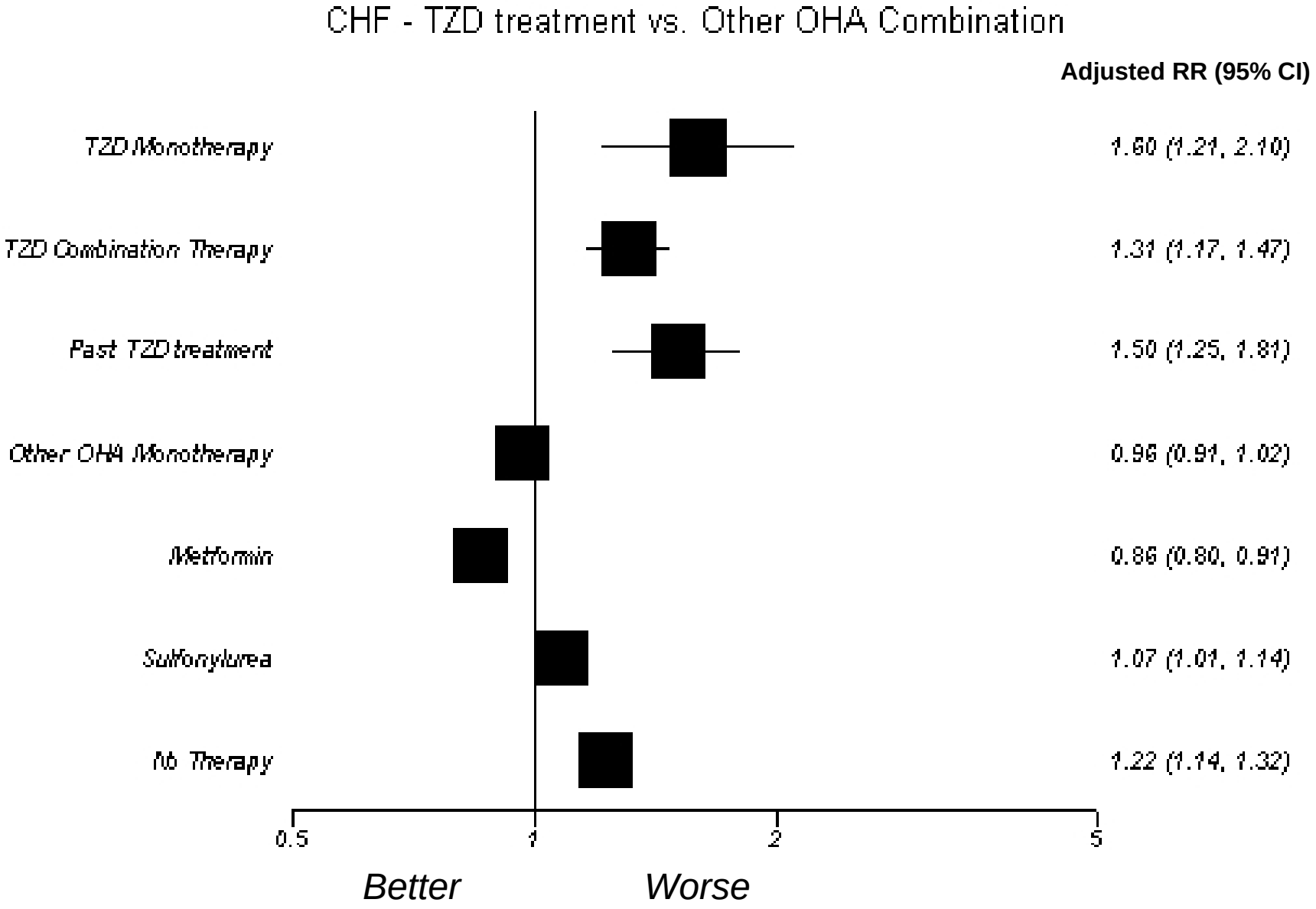
- Base cohort: 159 026 persons
- Median follow-up 3.8 years

- Events
  - 12 491 CHF cases (7.9%)
  - 12 578 AMI cases (7.9%)
  - 30 265 deaths (19%)

Baseline Variables: Cases vs. Controls

Characteristics	CHF Controls	CHF Cases	AMI Controls	AMI Cases
Age, mean +/- SD (years)	76.9 ± 6.4	76.4 ± 6.4	76.4 ± 6.4	76.5 ± 6.4
Female	48.6%	48.6%	44.8%	44.8%
Charlson comorbidity ≥ 2	39.2%	51.3%	25.4%	22.1%
DM duration < 2 yrs	8.2%	8.5%	8.4%	8.5%
2-5 yrs	17.1%	17.3%	16.6%	16.7%
> 5 yrs	74.6%	74.2%	75.0%	74.8%
History of renal disease	5.5%	9.3%	4.1%	6.8%
History of CV disease (5 yrs)	34.3%	34.9%	26.4%	26.6%
AMI	16.0%	18.2%	16.9%	17.1%
CHF	16.5%	17.3%	6.1%	8.4%
Mean drugs prior 6 m (SD)	9.3 (5.2)	11.1 (5.6)	8.9 (5.0)	9.9 (5.4)

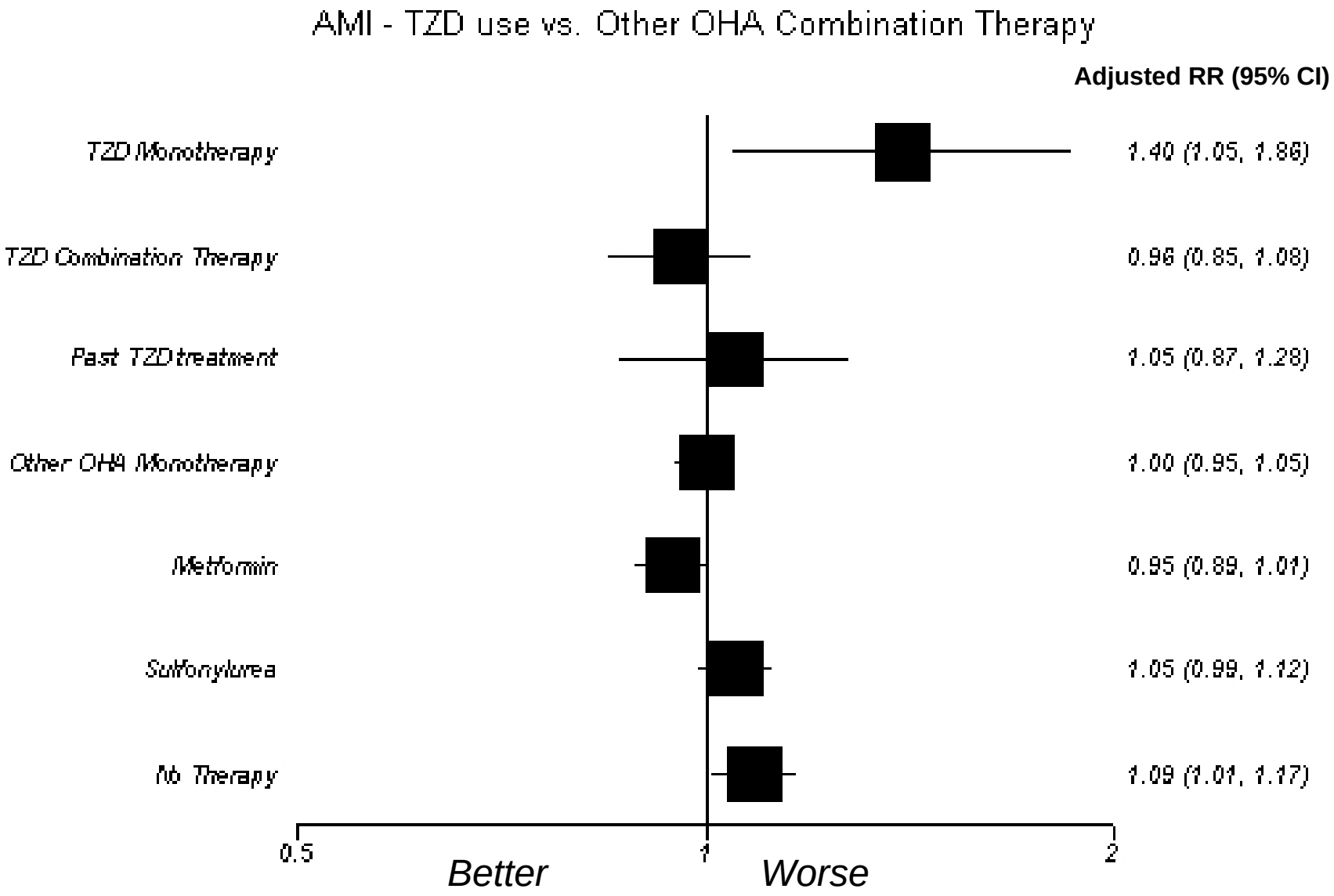
TZDs and CHF


CHF - TZD treatment vs. Other OHA Combination
Adjusted RR (95% CI)
TZD Monotherapy
1.60 (1.21, 2.10)
TZD Combination Therapy
1.31 (1.17, 1.47)
Past TZD treatment
1.50 (1.25, 1.81)
Other OHA Monotherapy
0.96 (0.91, 1.02)
Metformin
0.86 (0.80, 0.91)
Sulfonylurea
1.07 (1.01, 1.14)
No Therapy
1.22 (1.14, 1.32)
0.5
1
2
5
Better
Worse

CHF: Rosiglitazone vs. Pioglitazone

Pattern of Use	Cases No.	Controls No.	Adjusted RR (vs. OHA combo)	95% CI
TZD monotherapy	78	237	1.60	1.21-2.10
Rosiglitazone	62	151	1.98	1.44-2.72
Pioglitazone	16	86	0.91	0.52-1.59
TZD combination therapy	508	2013	1.34	1.20-1.49
Rosiglitazone	364	1330	1.43	1.25-1.63
Pioglitazone	144	683	1.09	0.90-1.32

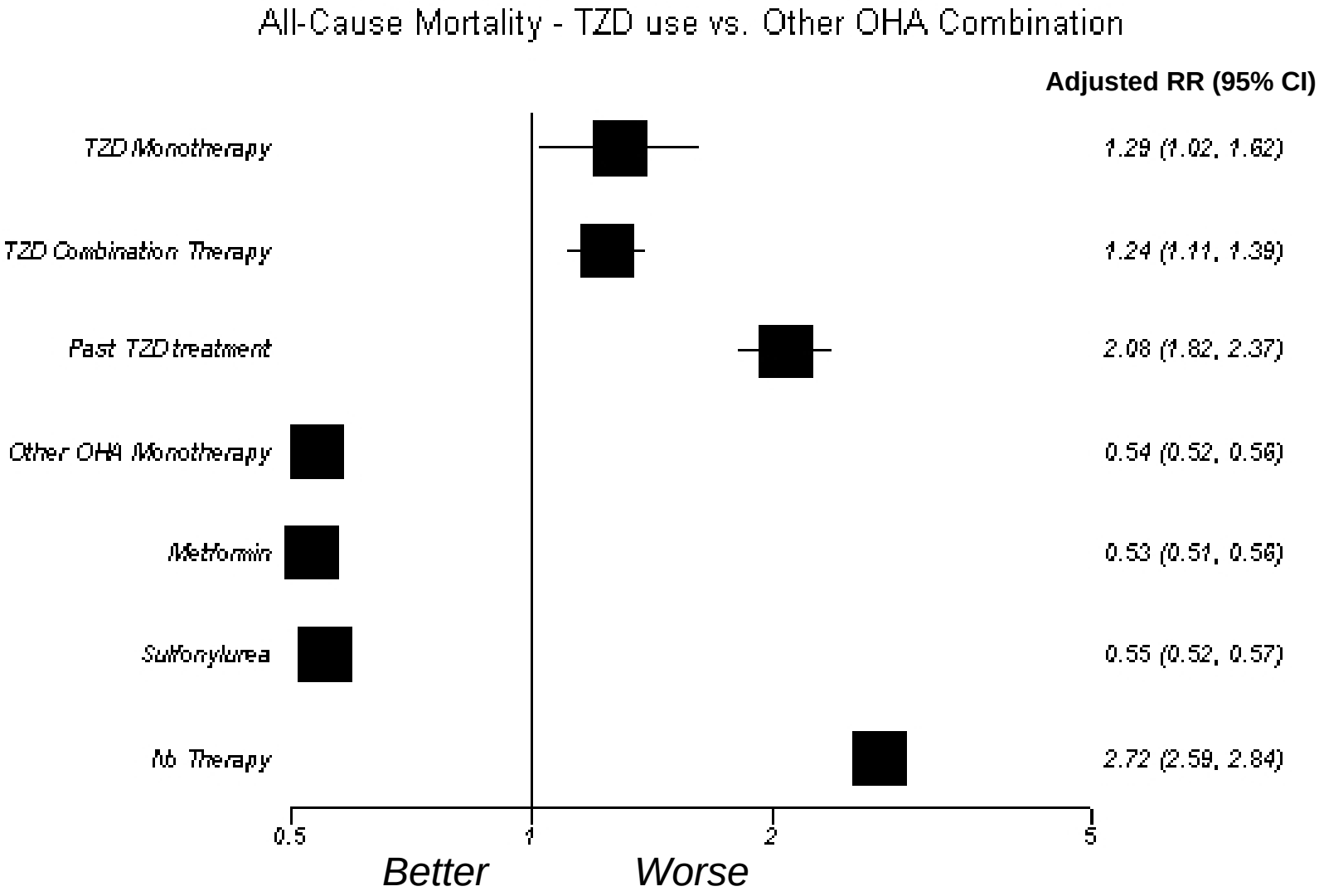
TZDs and AMI


AMI - TZD use vs. Other OHA Combination Therapy
Adjusted RR (95% CI)
TZD Monotherapy
1.40 (1.05, 1.86)
TZD Combination Therapy
0.96 (0.85, 1.08)
Past TZD treatment
1.05 (0.87, 1.28)
Other OHA Monotherapy
1.00 (0.95, 1.05)
Metformin
0.95 (0.89, 1.01)
Sulfonylurea
1.05 (0.99, 1.12)
No Therapy
1.09 (1.01, 1.17)
0.5
1
2
Better
Worse

AMI: Rosiglitazone vs. Pioglitazone

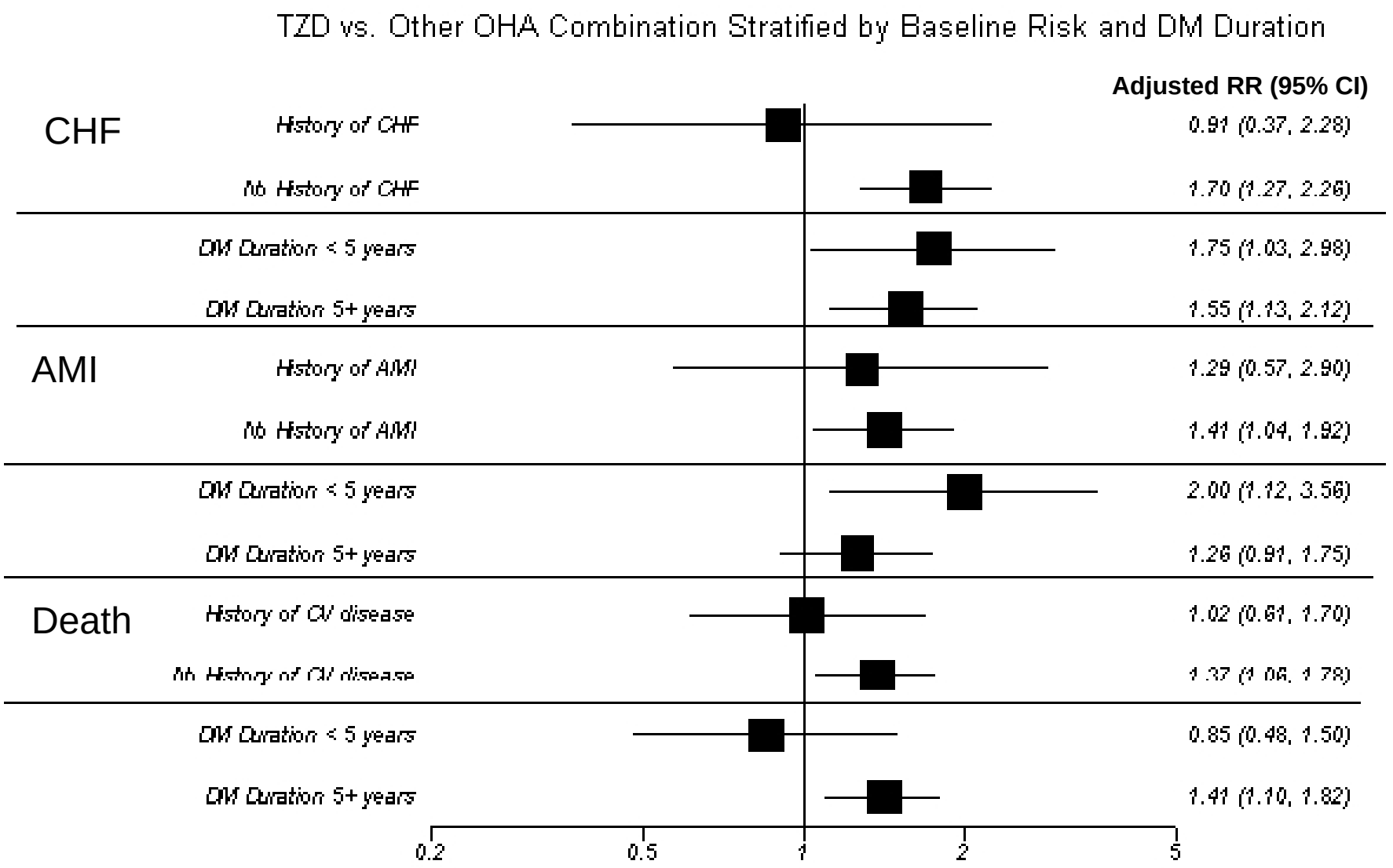
Pattern of Use	Cases No.	Controls No.	Adjusted RR (vs. OHA combo)	95% CI
TZD monotherapy	65	228	1.40	1.05-1.86
Rosiglitazone	53	147	1.76	1.27-2.44
Pioglitazone	12	81	0.73	0.40-1.36
TZD combination therapy	404	2109	0.96	0.85-1.08
Rosiglitazone	282	1404	1.00	0.87-1.16
Pioglitazone	122	705	0.87	0.71-1.06

TZDs and All-Cause Mortality


All-Cause Mortality - TZD use vs. Other OHA Combination
Adjusted RR (95% CI)
TZD Monotherapy
1.29 (1.02, 1.62)
TZD Combination Therapy
1.24 (1.11, 1.39)
Past TZD treatment
2.08 (1.82, 2.37)
Other OHA Monotherapy
0.54 (0.52, 0.56)
Metformin
0.53 (0.51, 0.56)
Sulfonylurea
0.55 (0.52, 0.57)
No Therapy
2.72 (2.59, 2.84)
0.5
1
2
5
Better
Worse

All-Cause Mortality: Rosiglitazone vs. Pioglitazone

Pattern of Use	Cases No.	Controls No.	Adjusted RR (vs. OHA combo)	95% CI
TZD monotherapy	102	392	1.29	1.02-1.62
Rosiglitazone	76	255	1.47	1.12-1.93
Pioglitazone	26	137	0.94	0.61-1.45
TZD combination therapy	497	1440	1.24	1.11-1.39
Rosiglitazone	358	1027	1.26	1.10-1.44
Pioglitazone	139	413	1.20	0.98-1.47


TZD vs. Other OHA Combination Stratified by Baseline Risk and DM Duration
Adjusted RR (95% CI)
CHF
History of CHF
0.91 (0.37, 2.28)
No History of CHF
1.70 (1.27, 2.26)
DM Duration < 5 years
1.75 (1.03, 2.98)
DM Duration 5+ years
1.55 (1.13, 2.12)
AMI
History of AMI
1.29 (0.57, 2.90)
No History of AMI
1.41 (1.04, 1.92)
DM Duration < 5 years
2.00 (1.12, 3.56)
DM Duration 5+ years
1.26 (0.91, 1.75)
Death
History of CV disease
1.02 (0.61, 1.70)
No History of CV disease
1.37 (1.06, 1.78)
DM Duration < 5 years
0.85 (0.48, 1.50)
DM Duration 5+ years
1.41 (1.10, 1.82)
0.2
0.5
1
2
5

Estimated Absolute Risk and NNH over 4 Years

	CHF	AMI	Death
Baseline event rate (%)	9.54	9.67	19.3
Estimated absolute risk with TZDs (%)	12.5	13.5	24.0
Absolute risk increase (%)	3.0	3.9	4.6
Number-needed-to-harm	34	26	22
95% Confidence Interval	21 - 52	12 - 105	13 - 47

Conclusions

In Ontario seniors with DM…

- TZD monotherapy vs. other OHA combo:
  - 60% increase in CHF
  - 40% increase in AMI
  - 29% increase in all-cause death
- TZD combo vs. other OHA combo:
  - 31% increase in CHF
  - 24% increase in all-cause death
- Estimated NNH 22-34 over 4 years

Conclusions

- Risk appeared limited to rosiglitazone
- Not affected by baseline risk or DM duration
- Findings generally consistent with previous studies
- Absolute risk may exceed benefits in this population

Advantages of an Observational Study

- Patterns of use in ‘real world’
- Large population
  - More power to detect uncommon events
- Population-based
- Seniors, patients with higher comorbidity better represented
  - Greater burden of diabetes
  - Absolute risk of adverse events higher

Limitations

- Potential for selection bias
  - Less an issue with unanticipated events
  - Concern with known or perceived benefits or risks
  - TZD use through ODB may be different
- No data on glycemic control, drug compliance
- Possible misclassification
- Generalizability limited to seniors
- Small numbers on pioglitazone

Summary

- Goal of type 2 DM treatment to prevent long-term complications especially CV disease
- Surrogate outcomes promising but not sufficient to ensure benefit or safety
- Neutral effect on clinical outcomes not enough
- Mounting evidence of worse rather than better CV outcomes with TZDs
- Harms may be underestimated in clinical trials

Summary

- Further studies needed
  - Class effect?
  - Effect of combination with other OHAs?
  - Other populations
- Need to weigh potential benefits and harms of TZDs for each patient
  - Harms may outweigh benefits in seniors and other high-risk populations
  - Recent evidence of fracture risk a further concern

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