



Pioglitazone and Rosiglitazone Cardiovascular Safety Meta-Analyses

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Outline

1. Background
2. Pioglitazone Meta-Analysis
3. Pioglitazone and Rosiglitazone Meta-Analyses
 - Trial summary
 - Patient summary
 - Overall results
 - Randomized comparator
 - Insulin add-on trials
 - Patient subgroups
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Goals of the Pioglitazone and Rosiglitazone Meta-Analyses

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

Background

- FDA has not performed a meta-analysis investigating the cardiovascular safety of pioglitazone
- Previous pioglitazone meta-analyses
 - Takeda: 2006(2), 2008
 - Lincoff et al 2007

Pioglitazone Trial Selection

- All trials taken from Takeda database
- 2010 FDA meta-analyses did not include large trials
 - Large trials viewed as independent sources of information
 - Large trials were not comparable between the drugs
- 29 trials satisfied primary inclusion criteria
 - 11774 patients enrolled
- Sensitivity analysis including two large trials (PROactive & OPI-506) was performed
 - The 2 trials enrolled 7335 patients

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Pioglitazone Trial Summary: Randomized Comparator Groups

Randomized comparator	Trials N=29 n	Control N=5462 n (%)	Pioglitazone N=6132 n (%)	Total N=11774 n (%)
Placebo	18	2097 (37)	2477 (40)	4574 (39)
Active	12	3682 (65)	3668 (60)	7350 (62)
Sulfonylurea	8	2189 (39)	2194 (36)	4383 (37)
Metformin	3	1127 (20)	1105 (18)	2232 (19)

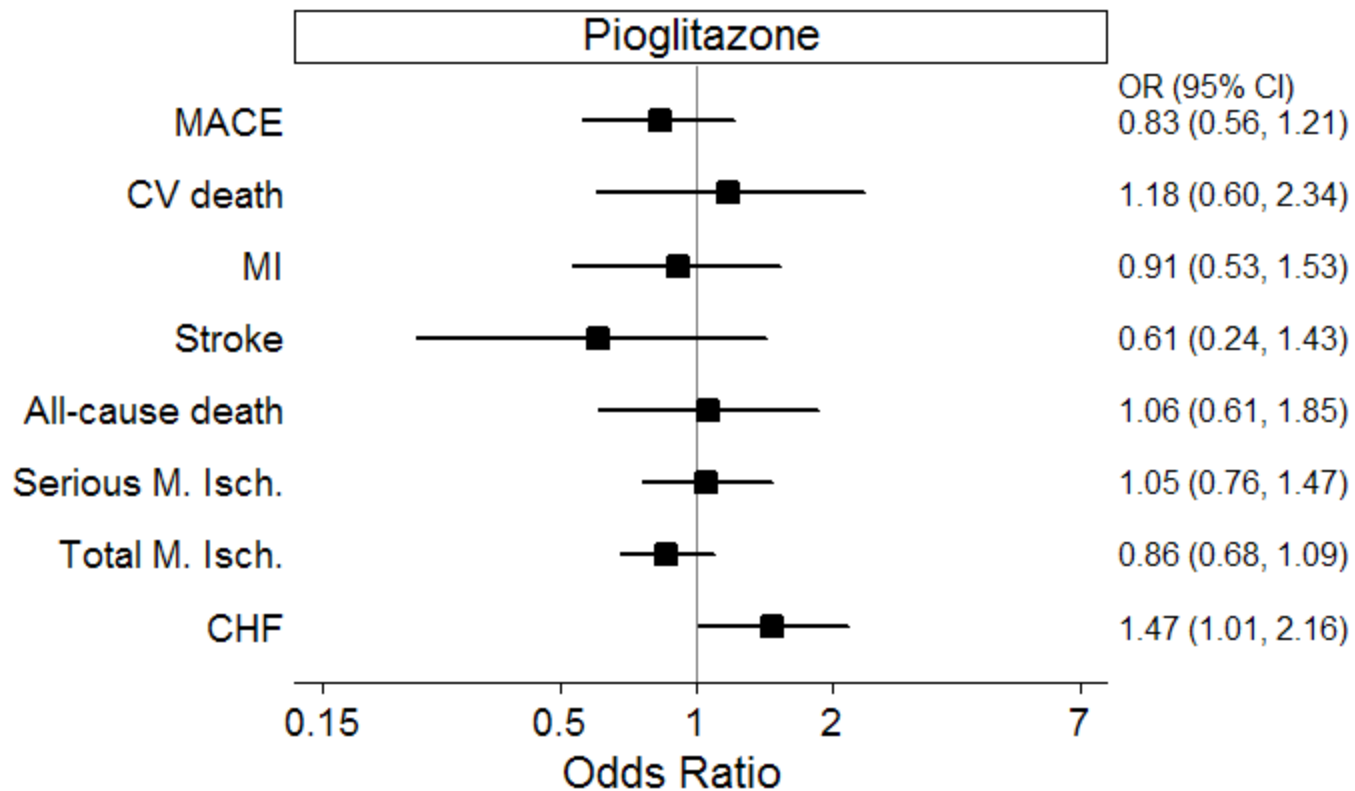
Pioglitazone Patient Summary: Treatment Duration

Treatment duration (d)	Control N=5642	Pioglitazone N=6132	Total N=11774
Mean (std)	273 (197)	258 (190)	265 (194)
Range (min-max)	(1-758)	(1-758)	(1-758)
Least-Squares Mean	213	209	

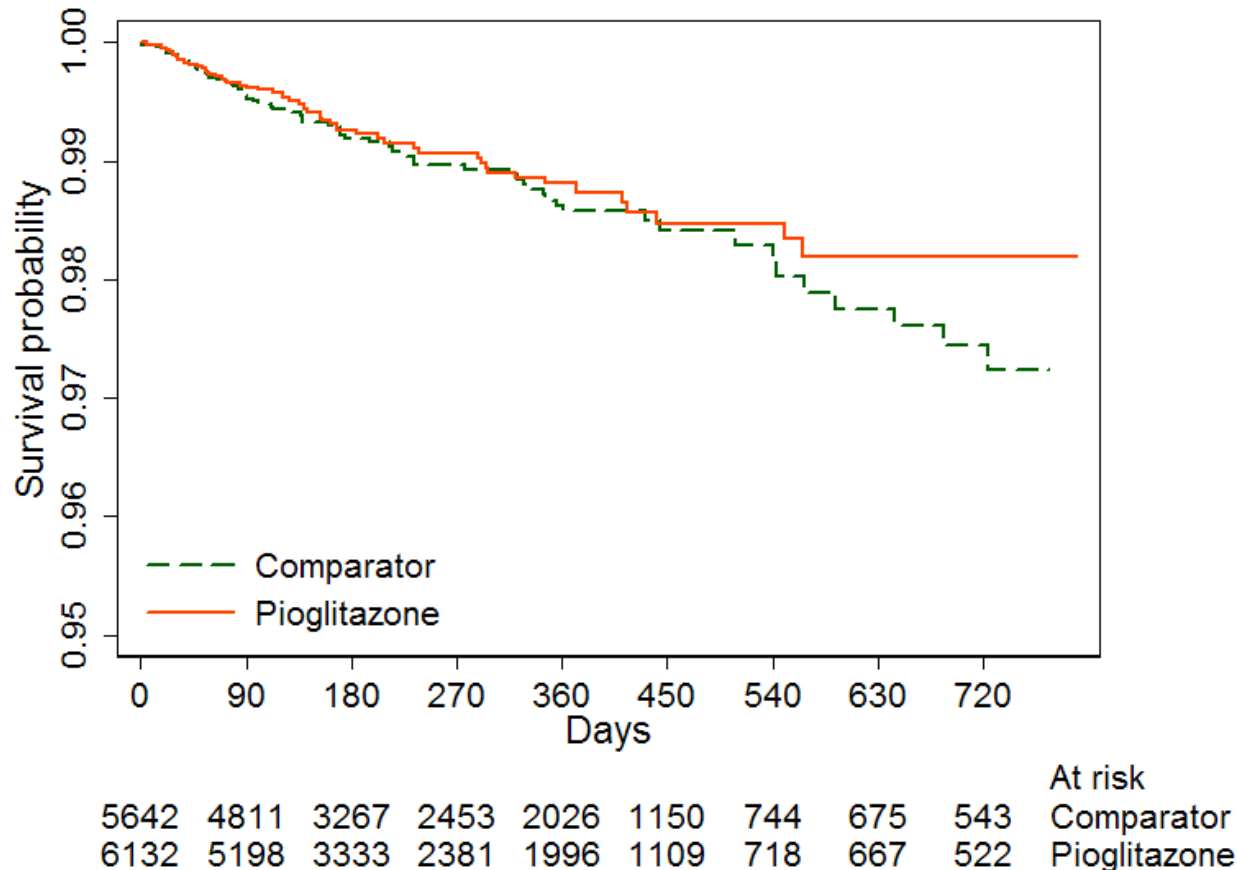
Pioglitazone Event Summary: Primary Analysis Set

	Control N=5642	Pioglitazone N=6132	Total N=11774
Endpoint	n (%)	n (%)	n (%)
MACE	63 (1.1)	54 (0.9)	117 (1.0)
CV death	18 (0.3)	22 (0.4)	40 (0.3)
MI	33 (0.6)	31 (0.5)	64 (0.5)
Stroke	16 (0.3)	10 (0.2)	26 (0.2)
All-cause death	28 (0.5)	31 (0.5)	59 (0.5)
Serious M. Isch.	76 (1.3)	81 (1.3)	157 (1.3)
Total M. Isch.	162 (2.9)	143 (2.3)	305 (2.6)
CHF	50 (0.9)	75 (1.2)	125 (1.1)

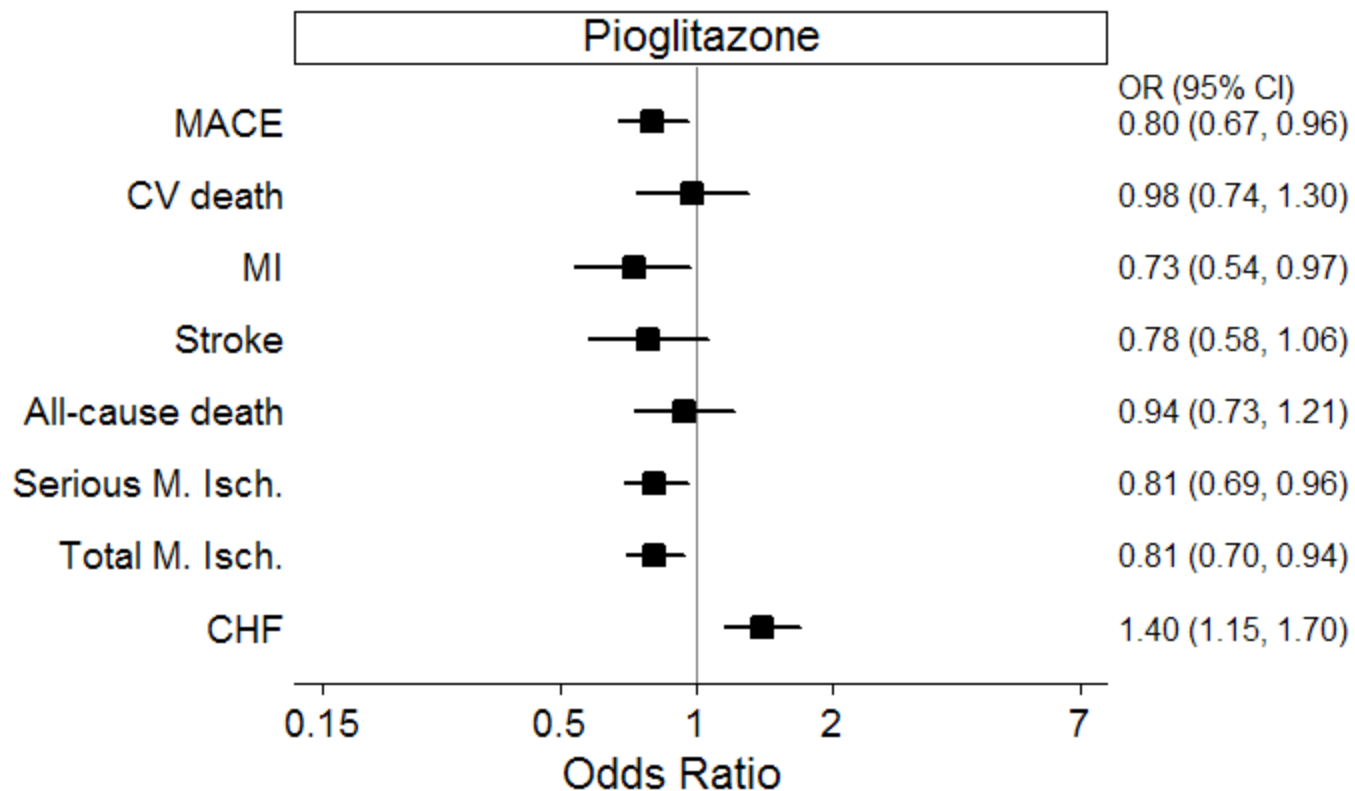
Pioglitazone Meta-Analysis Results: Primary Analysis Set, All Outcomes



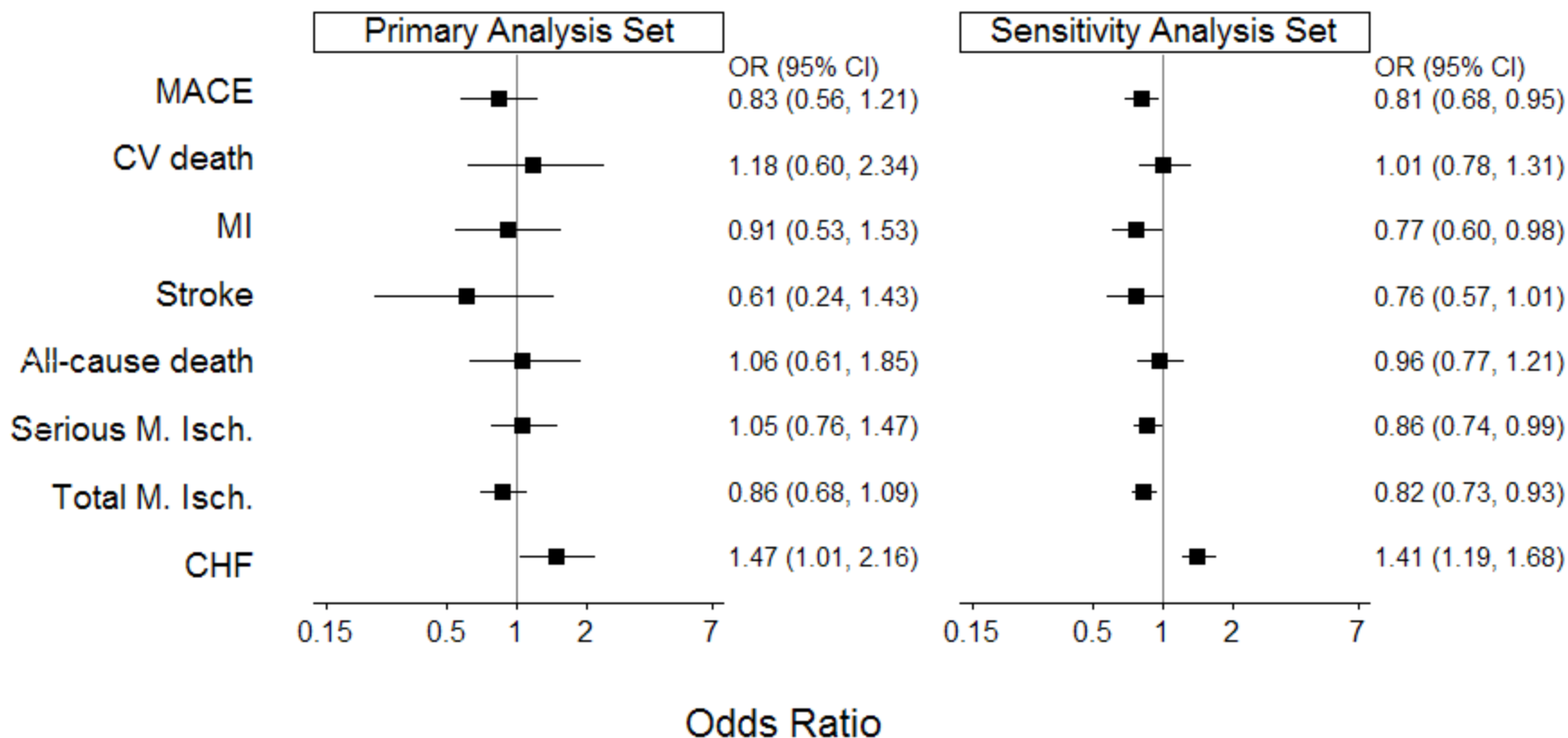
Pioglitazone Kaplan-Meier, Primary Analysis Set: MACE



Pioglitazone Sensitivity Analysis: Large Trials (OPI-506 & PROactive)



Pioglitazone Sensitivity Analysis: Contribution of Large Trials



Pioglitazone Meta-Analysis Summary

- Pioglitazone tended to have lower or similar estimated risks as control across the safety endpoints, except for congestive heart failure
- For congestive heart failure pioglitazone had a statistically significant greater risk compared to control
- Findings from the two large trials were consistent with the primary analysis set
 - Analyses including large trials had more precise estimates

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Trial Summary : Randomized Comparator

Randomized comparator	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials	Sample size	Trials	Sample size
	N=29 n	N=11774 n (%)	N=52 n	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

Treatment add-on	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials N=29	Sample size N=11774	Trials N=52	Sample size N=16995
	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

Trial duration	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials	Sample size	Trials	Sample size
	N=29	N=11774	N=52	N=16995
	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)

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Baseline Patient Characteristics

Characteristic		Pioglitazone N=11774 n (%)	Rosiglitazone N=16995 n (%)
Age	≥ 65	2888 (25)	4926 (29)
	Mean (Std.)	57 (10)	58 (10)
	Range (min-max)	(18-91)	(26-88)
Gender	Male	6496 (55)	10059 (59)
	Female		
Location	United States	3532 (30)	7450 (44)
	Other	6675 (57)	9545 (56)
	Missing	1567 (13)	0 (0)
Body mass index	≥ 30	6119 (52)	8173 (48)
	Missing	14 (0)	11 (0)
	Mean (Std.)	31 (5)	30 (6)
	Range (min-max)	(14-84)	(16-75)

Baseline Patient CV Medications

Baseline CV medication use	Pioglitazone N=11774 n (%)	Rosiglitazone N=16995 n (%)
Nitrates	958 (8)	901 (5)
ACE inhibitors	3636 (31)	5912 (35)
Loop diuretics	802 (7)	831 (5)
Beta-blockers	2114 (18)	2692 (16)

Baseline CV Risk Factors

Characteristic		Pioglitazone N=11774 n (%)	Rosiglitazone N=16995 n (%)
Duration Diabetes (y)	≥ 10 y	2651 (23)	4241 (25)
	Missing	35 (0)	4 (0)
	Mean (Std.)	6 (7)	7 (6)
	Range (min-max)	(0-70)	(0-45)
Naive	Yes	4065 (35)	3737 (22)
	Missing	774 (7)	10 (0)
History of CHD	Yes	1749 (15)	2806 (17)
	Missing	289 (2)	0 (0)
History of CHF	Yes	662 (6)	523 (3)
	Missing	289 (2)	0 (0)

Treatment Duration

	Pioglitazone	Rosiglitazone
Treatment duration (d)	N=11774	N=16995
Mean (std)	265 (194)	188 (116)
Range (min-max)	(1-758)	(1-758)

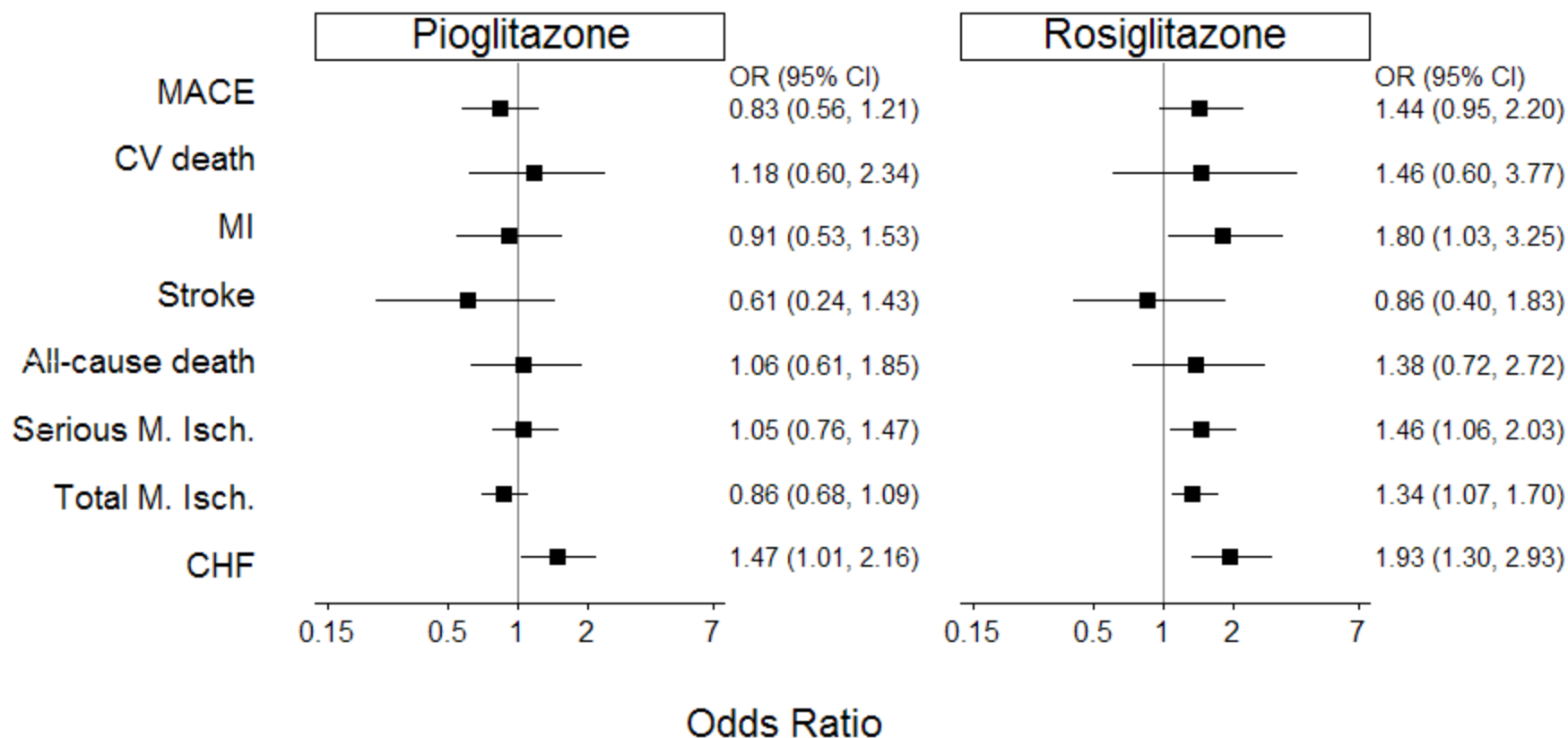
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Event Summary: Primary Analysis Set

Endpoint	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Control N=5642 n (%)	Pioglitazone N=6132 n (%)	Control N=6956 n (%)	Rosiglitazone N=10039 n (%)
MACE	63 (1.1)	54 (0.9)	39 (0.6)	70 (0.7)
CV death	18 (0.3)	22 (0.4)	9 (0.1)	17 (0.2)
MI	33 (0.6)	31 (0.5)	20 (0.3)	45 (0.4)
Stroke	16 (0.3)	10 (0.2)	16 (0.2)	18 (0.2)
All-cause death	28 (0.5)	31 (0.5)	17 (0.2)	29 (0.3)
Serious M. Isch.	76 (1.3)	81 (1.3)	66 (0.9)	118 (1.2)
Total M. Isch.	162 (2.9)	143 (2.3)	132 (1.9)	221 (2.2)
CHF	50 (0.9)	75 (1.2)	40 (0.6)	88 (0.9)

Meta-Analysis Results: Primary Analysis Set, All Outcomes



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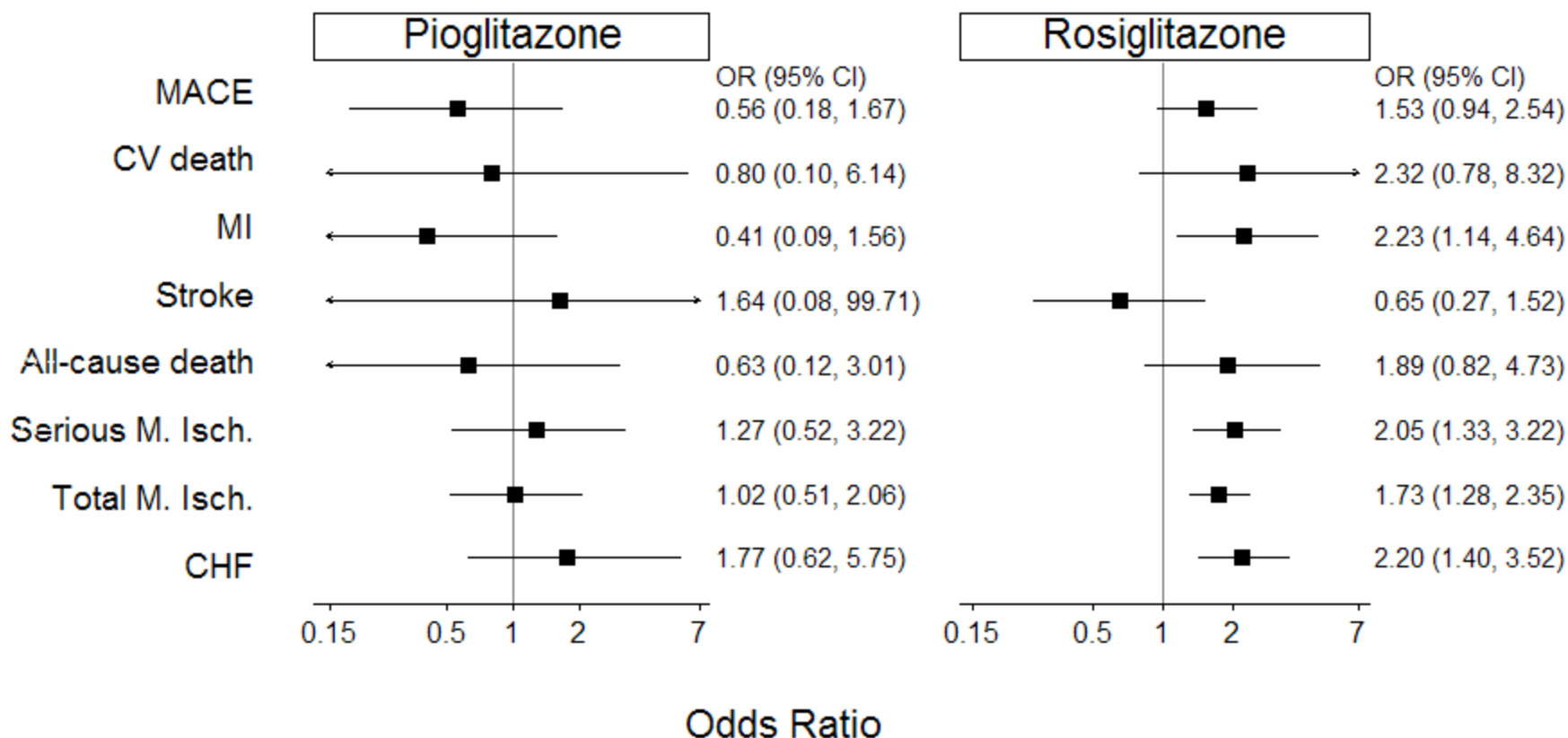
Placebo Controlled Trial Summary: Treatment Add-On Groups

Treatment add-on	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials N=18	Sample size N=4574	Trials N=46	Sample size N=13760
	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 (%)
<i>Trial duration</i>				
> 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
<i>Treatment duration</i>				
Mean (std) (d)		140 (71)		165 (91)

Meta-Analysis Results: Placebo Controlled, All Outcomes



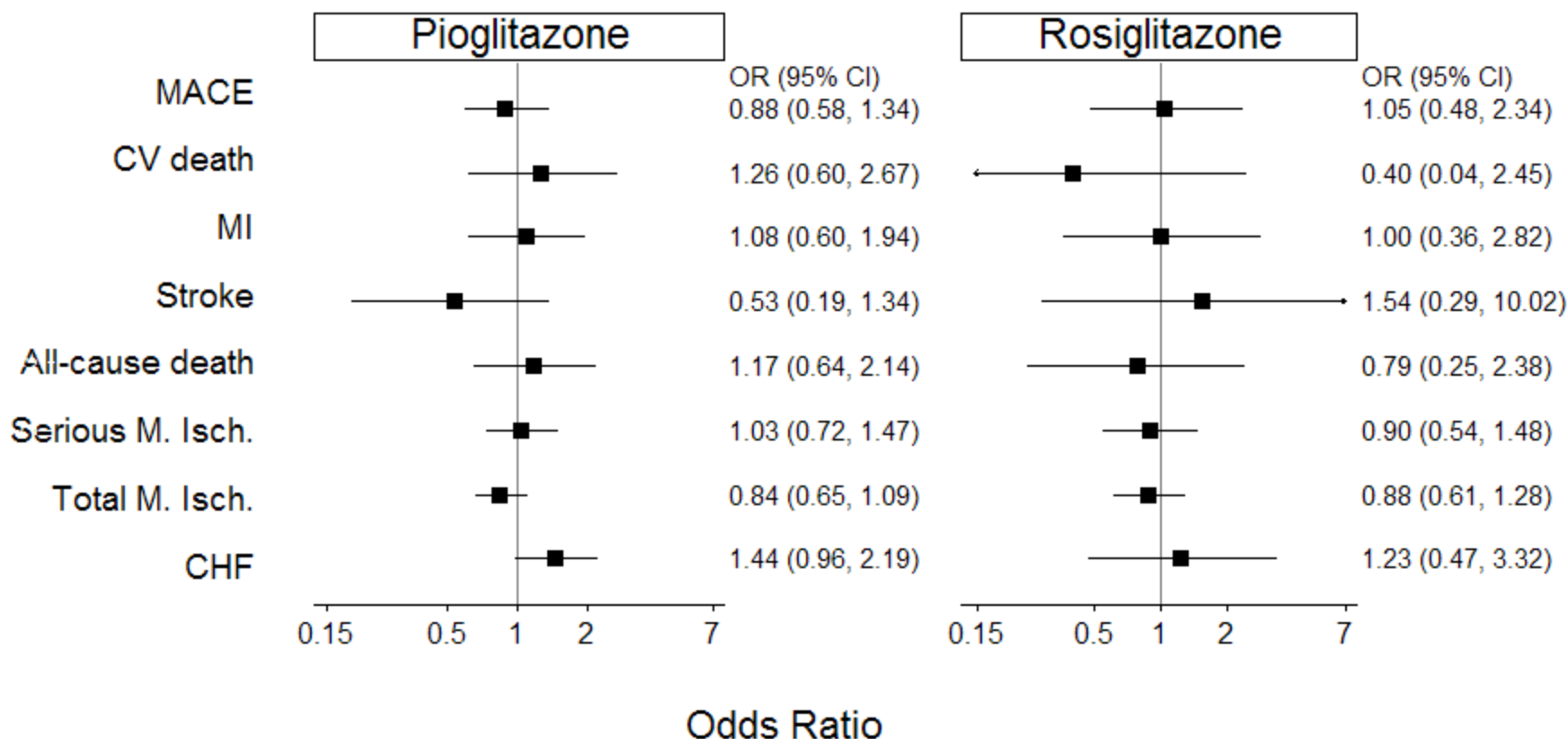
Active Controlled Trial Summary: Treatment Add-On Groups

Treatment add-on	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials N=12	Sample size N=7350	Trials N=13	Sample size N=4037
	n	n (%)	n	n (%)
Monotherapy	7	4608 (63)	10	2908 (72)
Background	3	1301 (18)	-	-
Sulfonylurea	1	639 (9)	-	-
Metformin	1	630 (9)	3	1129 (28)
Insulin	1	172 (2)	-	-
Sulfonylurea and Metformin	-	-	-	-

Active Controlled Trial Summary: Duration

	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials N=12 n	Sample size N=7350 n (%)	Trials N=13 n	Sample size N=4037 n (%)
<i>Trial duration</i>				
> 2m to ≤ 6m	4	1834 (25)	6	704 (17)
> 6 m to ≤ 1y	3	2744 (37)	6	2665 (66)
> 1y to ≤ 2y	5	2772 (38)	1	668 (17)
range (w)		24-104		12-77
<i>Treatment duration</i>				
Mean (std) (d)		342 (203)		263 (147)

Meta-Analysis Results: Active Controlled, All Outcomes



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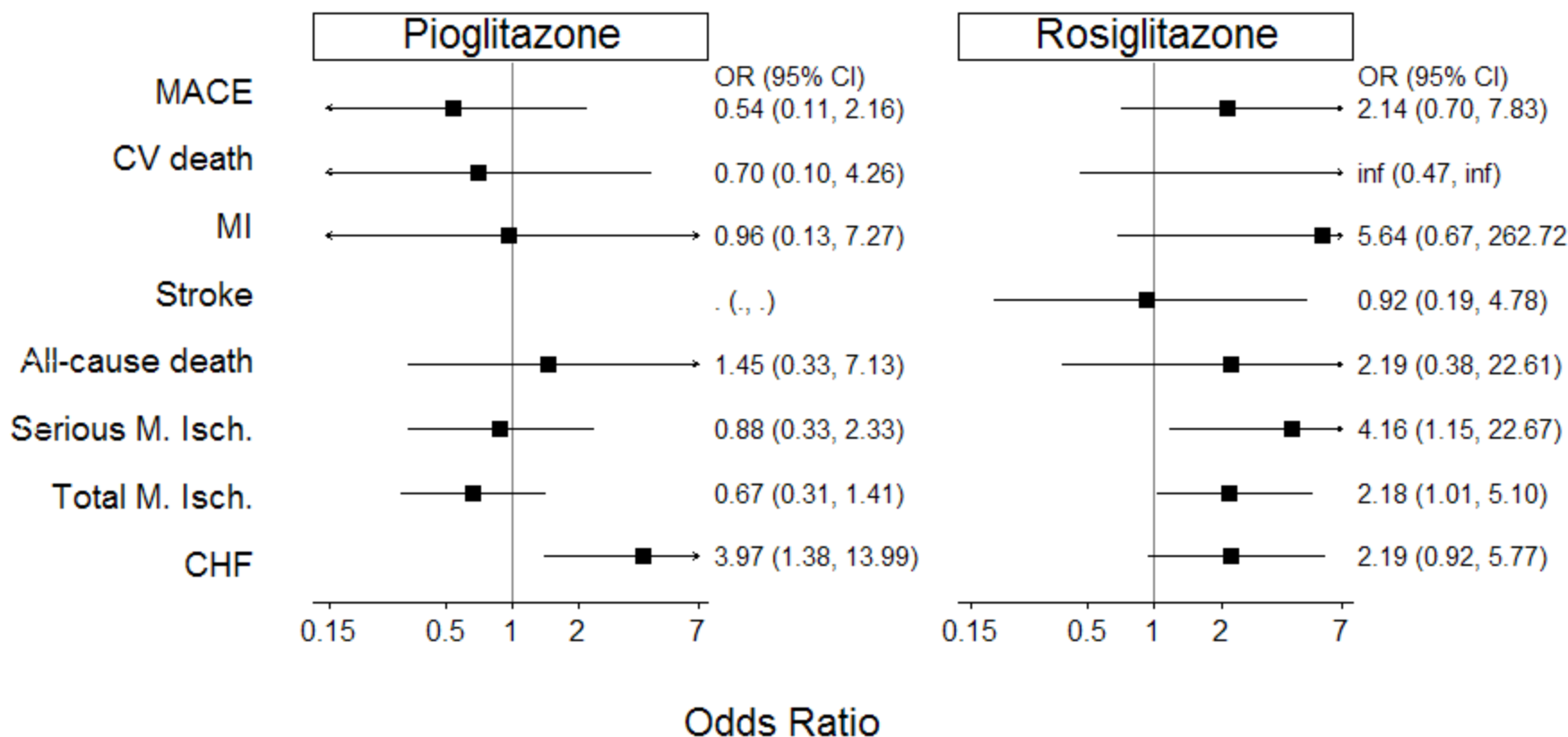
Insulin Add-On Trial Summary: Randomized Comparator

Randomized comparator	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials	Sample size	Trials	Sample size
	N=5 n	N=1190 n (%)	N=7 n	N=1833 n (%)
Placebo	4	1018 (86)	7	1833 (100)
Active	1	172 (14)	-	-
Sulfonylurea	1	172 (14)	-	-
Metformin	-	-	-	-

Insulin Add-On Trial Summary: Duration

	Pioglitazone meta-analysis		Rosiglitazone meta-analysis	
	Trials N=5 n	Sample size N=1190 n (%)	Trials N=7 n	Sample size N=1833 n (%)
<i>Trial duration</i>				
> 2m to ≤ 6m	4	901 (76)	7	1833 (100)
> 6 m to ≤ 1y	1	289 (24)	-	-
> 1y to ≤ 2y	-	-	-	-
range (w)		16-52		16-26
<i>Treatment duration</i>				
Mean (std) (d)		171 (103)		157 (48)

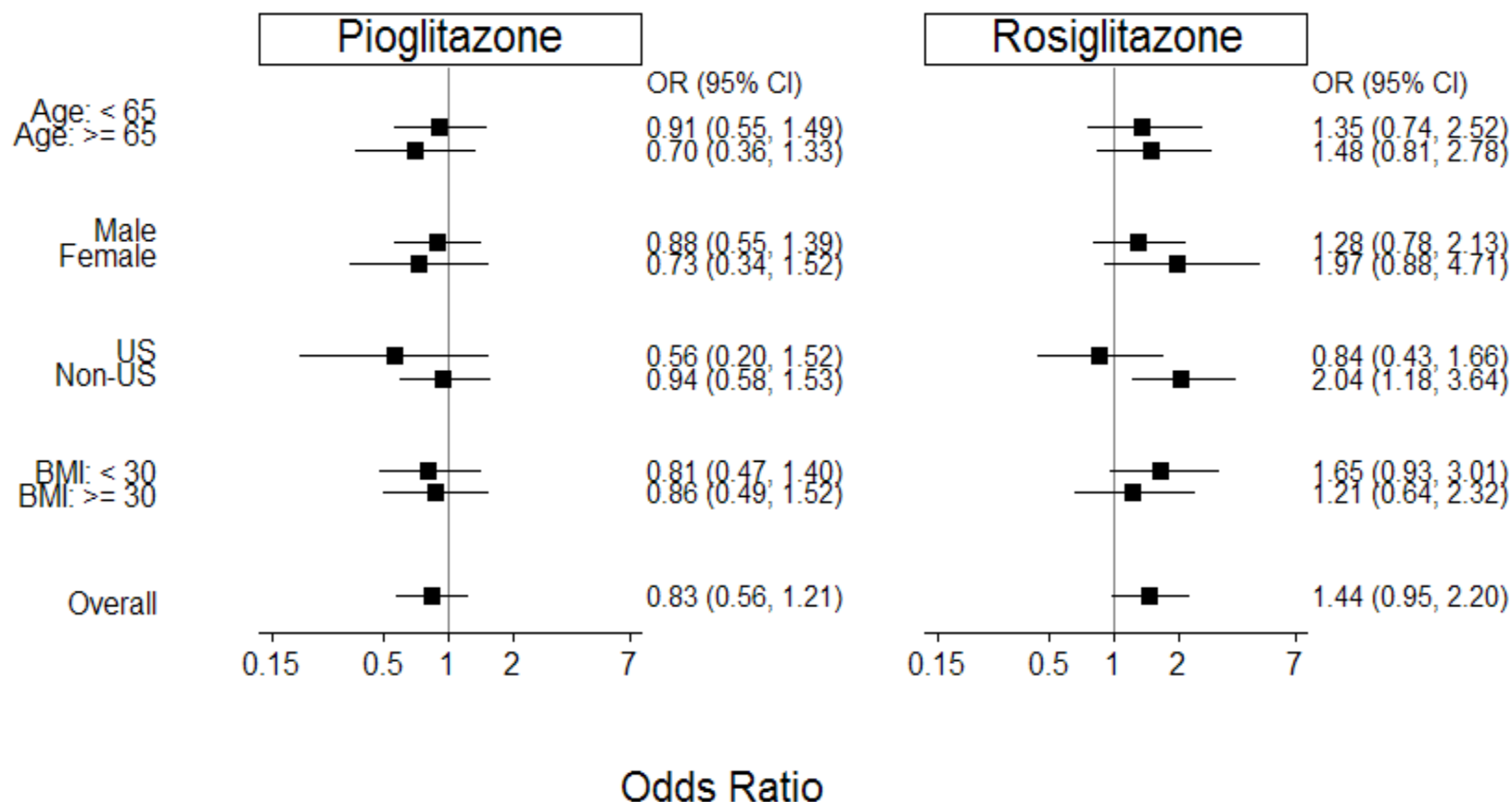
Meta-Analysis Results: Insulin Add-On, All Outcomes



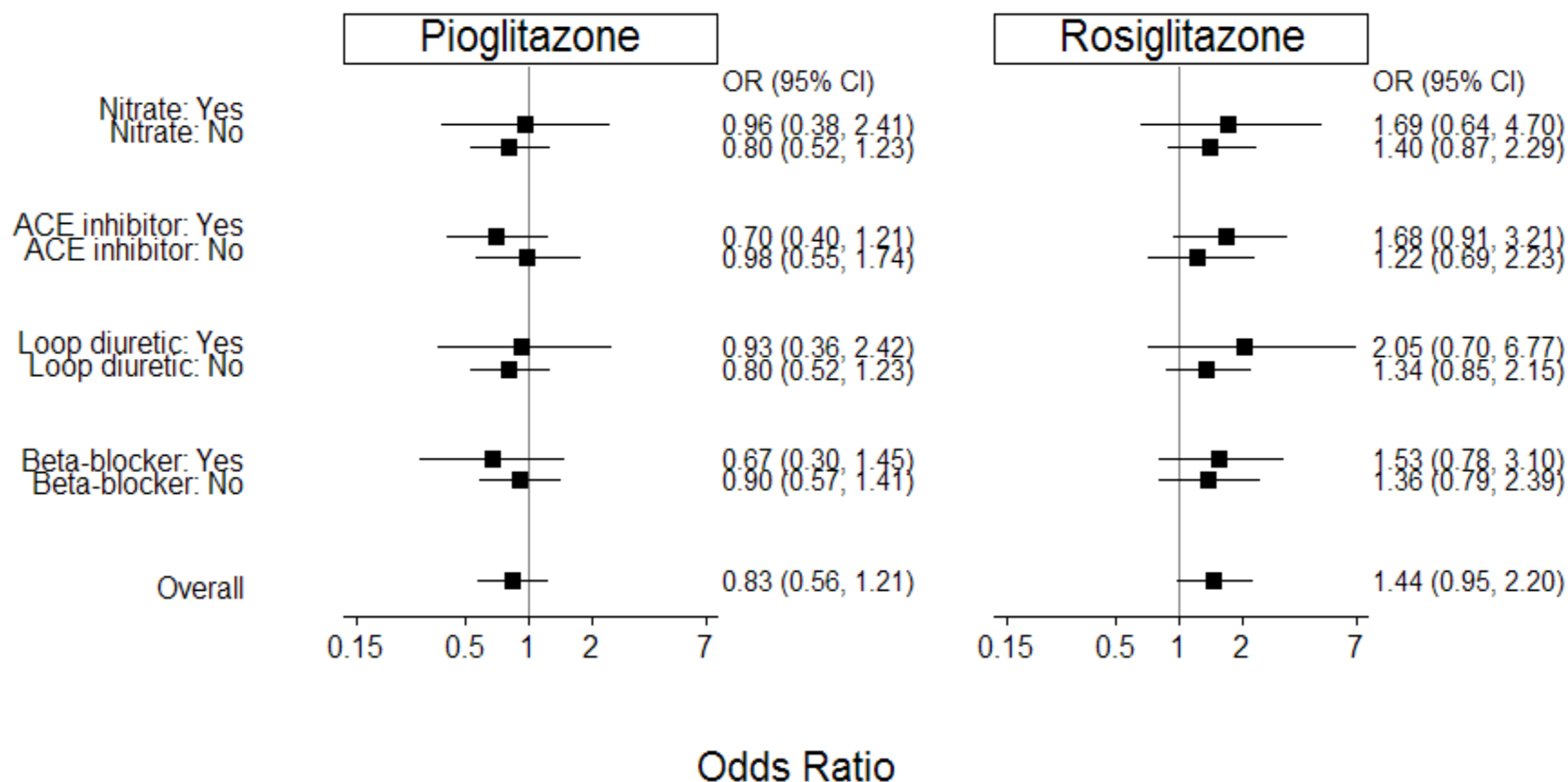
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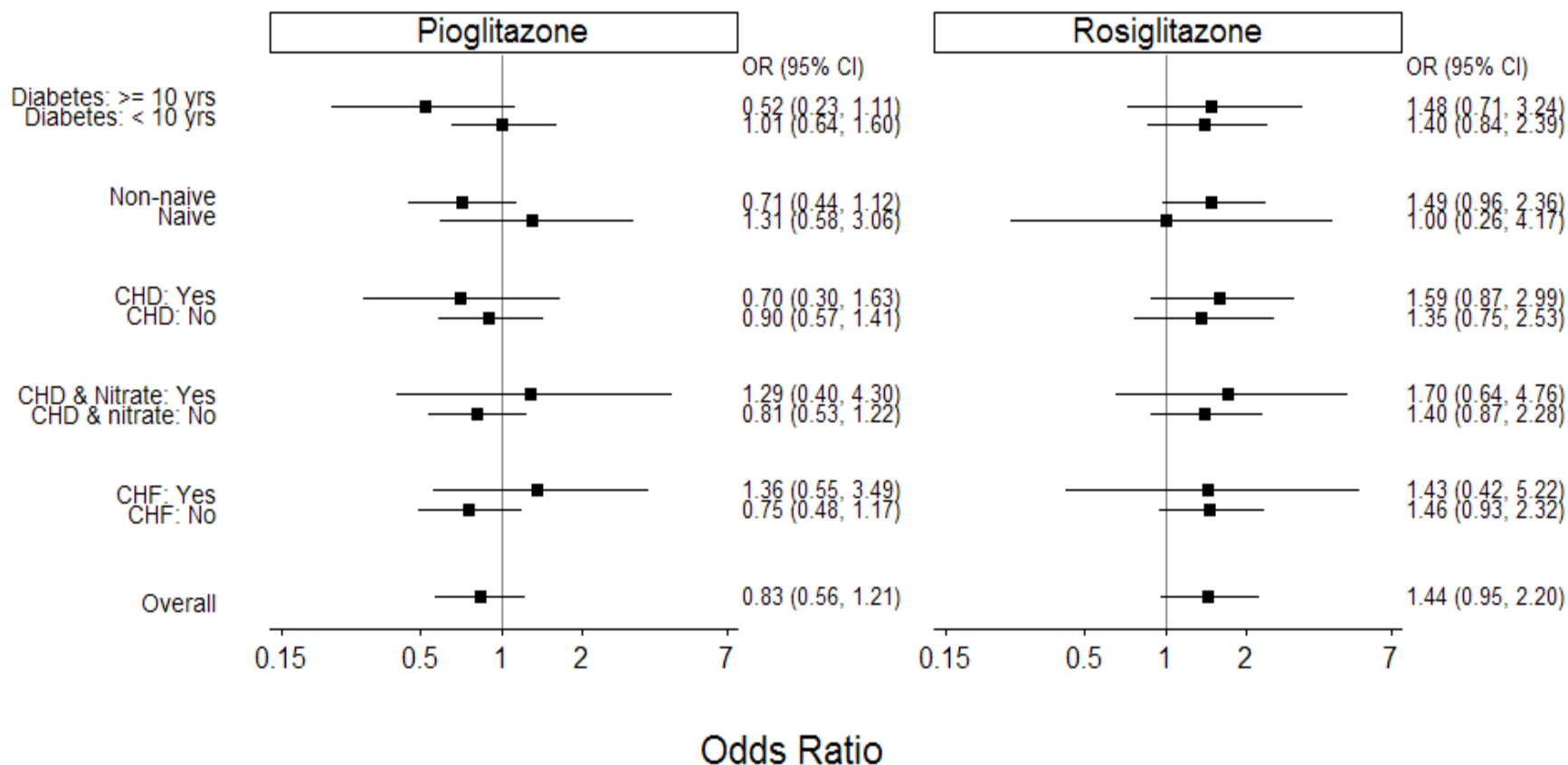
Meta-Analysis Results (1): Patient Characteristics, MACE



Meta-Analysis Results (2): Patient Characteristics, MACE



Meta-Analysis Results (3): Patient Characteristics, MACE



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Summary:

Limitations of Meta-Analyses

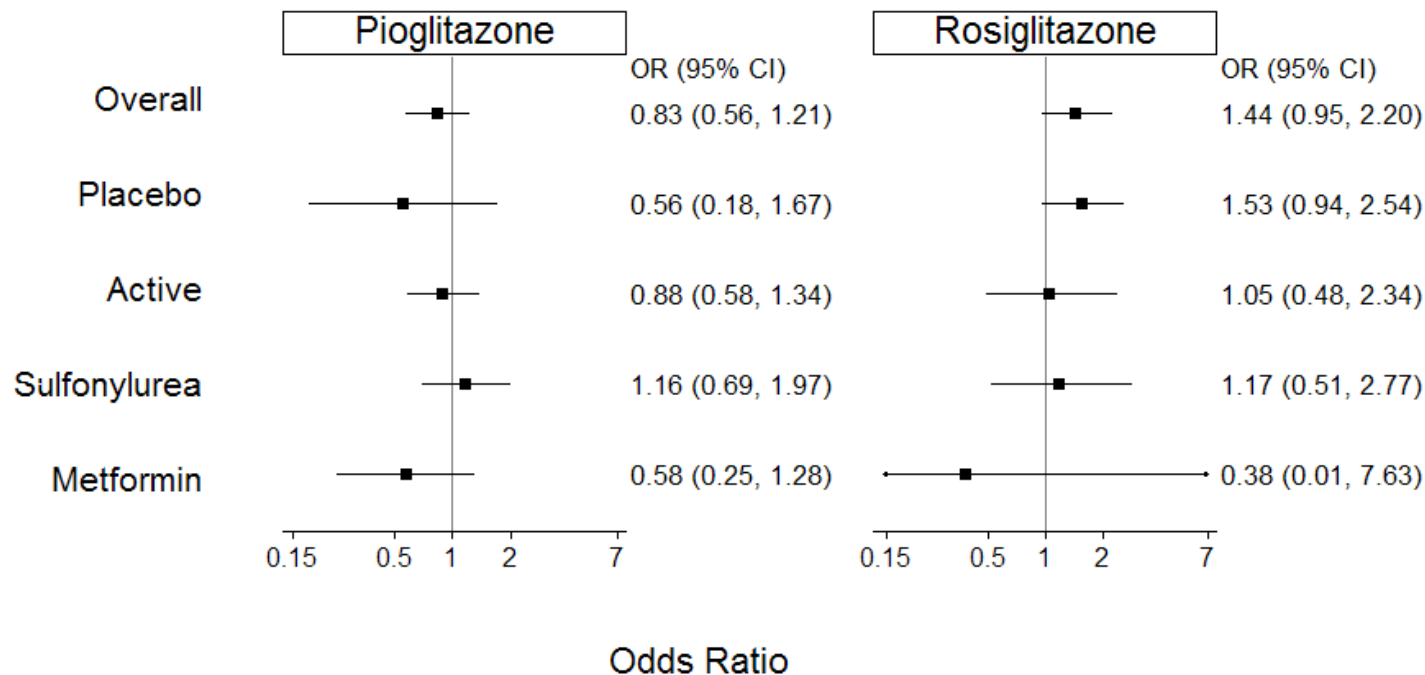
- Most trials were not prospectively designed to evaluate cardiovascular endpoints
- Results of trials were known before statistical analysis plan was developed
- Statistical significance was not adjusted for multiple testing
- Comparisons between the two meta-analyses are subject to the deficiencies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

Summary: Trials and Patients

- Differences in trial and patient characteristics between meta-analyses limit the comparability of the cardiovascular safety profile between rosiglitazone and pioglitazone
- Trial characteristics considered differed overall and within the different trial groups
 - Randomized comparator
 - Trial duration
 - Treatment add-on group
- Overall patient characteristics were not too different

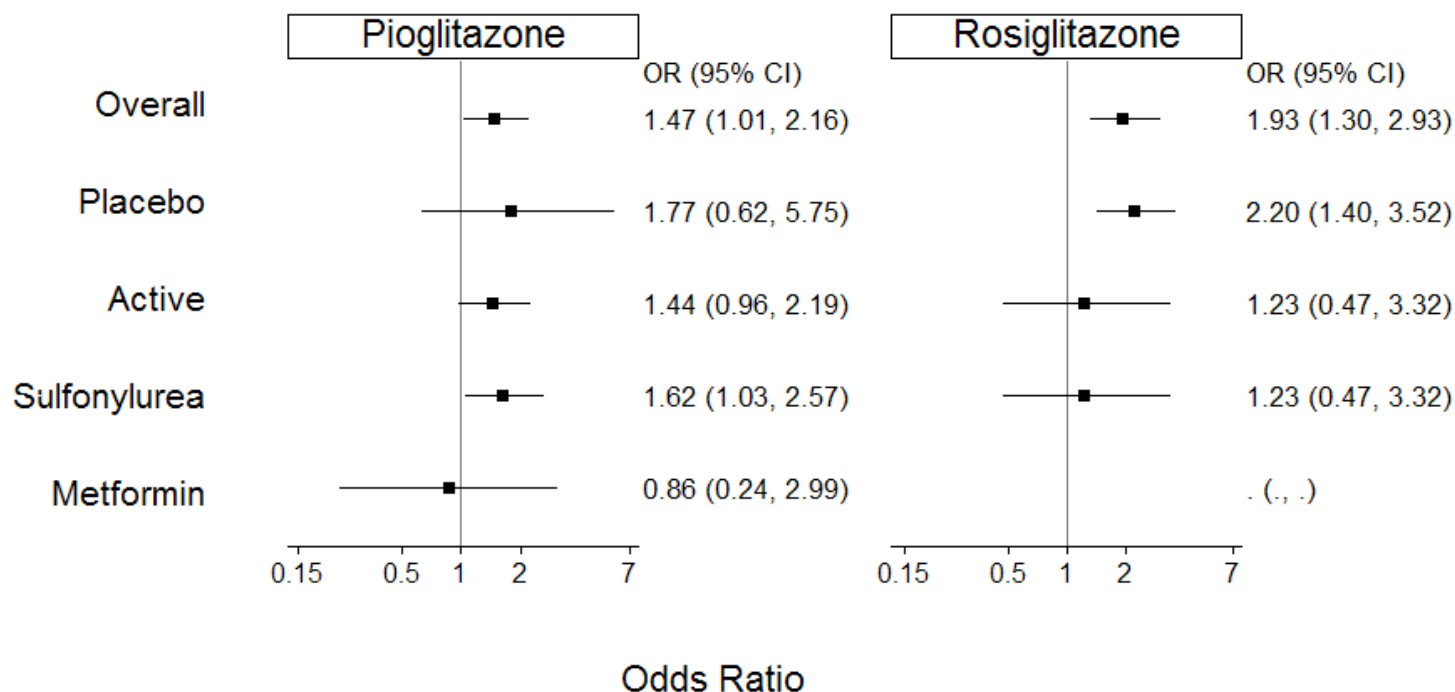
Summary: MACE

- For pioglitazone the risk tended to be less compared to control overall, and across different trial groups
- For rosiglitazone the risk tended to be greater compared to control overall, and across different trial groups



Summary: CHF

- Risk tended to be greater for both pioglitazone and rosiglitazone compared to control overall, and across different trial groups





QUESTIONS