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Clinical Development**

Presentation Outline

- Myocardial Ischemia
- Myocardial Infarction
- Stroke
- Cardiovascular Mortality

Myocardial Ischemia

Integrated Clinical Trial Analysis (ICT)

- 42 double-blind, controlled trials
 - Majority placebo controlled
- Efficacy studies primarily 6 months duration in differing patient populations
- Not designed to assess cardiovascular events
- Ascertainment bias
- Weak case definition

Definitions of Myocardial Ischemic Events in ICT

- AE terms broad & inclusive
 - Minimize likelihood of missing potential signal
 - Maximize number of events for modelling
- Acute Coronary Syndrome, Acute Myocardial Infarction (AMI), Angina Pectoris, Angina Unstable, Arteriospasm Coronary, Coronary Artery Occlusion, Coronary Artery Reocclusion, Coronary Artery Thrombosis, Coronary Bypass Thrombosis, Myocardial Infarction, Myocardial Ischemia, Papillary Muscle Infarction, Postinfarction Angina, Prinzmetal Angina, Silent Myocardial Infarction, Subendocardial Ischemia, Electrocardiogram ST Segment Elevation, Electrocardiogram ST-T Segment Elevation, Cardiac Arrest, Cardiac Death, Ventricular Tachycardia, Ventricular Fibrillation, Sudden Cardiac Death, Sudden Death, Ventricular Asystole
- All adverse events with preferred term which included “Chest Pain”
- All deaths including deaths due to unknown cause

Myocardial Ischemia: Evidence to Address ICT Questions

- ADOPT
 - AE Investigator Reports

Summary of Events of Myocardial Ischemia

	Treatment	# of Patients with Events	Rate / 100 PY	HR (95% CI)
ICT	RSG (n=8604)	171	4.13	
	Comp (n=5633)	85	3.18	1.31 (1.01 - 1.70)
ADOPT	RSG (n=1456)	106	2.14	
	MET (n=1454)	111	2.26	0.99 (0.76 - 1.30)
	SU (n=1441)	82	1.93	1.18 (0.88 - 1.57)

Examples: Short Term Studies May Not Predict Cardiovascular Outcomes

	Short Term (<1yr)	Long Term CV Outcomes
Metformin*	Cardiovascular events vs control 128 vs 80 per 1000PY	UKPDS Cardiovascular benefit in 342 obese subjects at 10yrs
Glimepiride*	Mortality vs control 5/1523 (0.3%) vs 0/294	UKPDS No excess risk for glyburide at 10 yr
Pioglitazone	PROactive 6 mos ** Primary endpoint (& most components) favored pbo	PROactive Neutral / trend to benefit for macrovascular outcomes

*data from SBAs ** FDA briefing document

Conclusions for Myocardial Ischemia

- There was no increase in myocardial ischemia in the long term comparator study (ADOPT)
- There was no difference in reporting for events of myocardial ischemia in AERS for either RSG and pioglitazone

Myocardial Infarction

Myocardial Infarction: Evidence to Address ICT Questions

- RECORD interim analysis
 - In-stream adjudication
- ADOPT
 - Investigator-reported Serious Adverse Events
 - Post-study adjudication
- DREAM
 - In-stream adjudication
- Study in high risk patients
 - In-stream adjudication
- Three epidemiology studies
 - ICD-9 codes, validated by chart review

Events of Myocardial Infarction

	Treatment	# of Patients with Events	Rate / 100 PY	HR (95% CI)
ICT	RSG (n=8604)	45	1.09	
	Comp (n=5633)	20	0.75	1.59 (0.93 - 2.71)
RECORD	RSG (n=2220)	43	0.52	
	Comp (n=2227)	37	0.45	1.16 (0.75 - 1.80)
ADOPT	RSG (n=1456)	24	0.48	
	MET (n=1454)	20	0.41	1.23 (0.68 - 2.22)
	GLY (n=1441)	14	0.33	1.52 (0.79 - 2.94)
DREAM	RSG (n=1325)	5	0.12	0.83 (0.25 - 2.71)
	RSG+RAM (n=1310)	11	0.26	1.85 (0.68 - 4.99)
	RAM (n=1313)	3	0.07	
	Placebo (n=1321)	6	0.14	

Myocardial Infarction Including Sudden Death

Events of Myocardial Infarction or Sudden Death

	Treatment	# of Patients with Events	Rate / 100 PY	HR (95% CI)
ICT	RSG (n=8604)	45	1.09	
	Comp (n=5633)	20	0.75	1.59 (0.93 - 2.71)
RECORD	RSG (n=2220)	43	0.52	
	Comp (n=2227)	37	0.45	1.16 (0.75 - 1.80)
ADOPT	RSG (n=1456)	24	0.48	
	MET (n=1454)	20	0.41	1.23 (0.68 - 2.22)
	GLY (n=1441)	14	0.33	1.52 (0.79 - 2.94)
DREAM	RSG (n=1325)	5	0.12	0.83 (0.25 - 2.71)
	RSG+RAM (n=1310)	11	0.27	1.85 (0.68 - 4.99)
	RAM (n=1313)	3	0.07	
	Placebo (n=1321)	6	0.14	

[] = previous

Events of Myocardial Infarction or Sudden Death

	Treatment	# of Patients with Events	Rate / 100 PY	HR (95% CI)
ICT	RSG (n=8604)	45	1.09	
	Comp (n=5633)	20	0.75	1.59 (0.93 - 2.71)
RECORD	RSG (n=2220)	[43] 49	0.59	
	Comp (n=2227)	[37] 45	0.54	[1.16] 1.09 (0.73 - 1.63)
ADOPT	RSG (n=1456)	24	0.48	
	MET (n=1454)	20	0.41	1.23 (0.68 - 2.22)
	GLY (n=1441)	14	0.33	1.52 (0.79 - 2.94)
DREAM	RSG (n=1325)	5	0.12	0.83 (0.25 - 2.71)
	RSG+RAM (n=1310)	11	0.27	1.85 (0.68 - 4.99)
	RAM (n=1313)	3	0.07	
	Placebo (n=1321)	6	0.14	

[] = previous

Events of Myocardial Infarction or Sudden Death

	Treatment	# of Patients with Events	Rate / 100 PY	HR (95% CI)
ICT	RSG (n=8604)	45	1.09	
	Comp (n=5633)	20	0.75	1.59 (0.93 - 2.71)
RECORD	RSG (n=2220)	[43] 49	0.59	
	Comp (n=2227)	[37] 45	0.54	[1.16] 1.09 (0.73 - 1.63)
ADOPT	RSG (n=1456)	24	0.48	
	MET (n=1454)	20	0.41	1.23 (0.68 - 2.22)
	GLY (n=1441)	14	0.33	1.52 (0.79 - 2.94)
DREAM	RSG (n=1325)	[5] 5	0.12	[0.83] 0.71 (0.23 - 2.24)
	RSG+RAM (n=1310)	[11] 12	0.29	[1.85] 1.73 (0.68 - 4.39)
	RAM (n=1313)	[3] 5	0.12	
	Placebo (n=1321)	[6] 7	0.17	

[] = previous

ADOPT & ICT: Post-study Adjudication

Post Study Adjudication ICT and ADOPT

Definitions of Myocardial Infarction

- Non-Fatal Myocardial Infarction
 - Definite:
 - Sudden onset of chest pain (or other acute cardiac symptom) accompanied by either typical ECG changes and/or the release of cardiac-specific enzymes without death within 30 days
 - Non-Confirmed:
 - Clinical course that is likely to represent an acute myocardial infarction, but insufficient information regarding the nature of symptoms, ECG changes or serum cardiac-specific enzymes to make the diagnosis of a definite non-fatal myocardial infarction
- Fatal Myocardial Infarction
- Sudden Death

Events of Myocardial Infarction or Sudden Death: Adjudicated

	Treatment	# of Patients with Events	Rate / 100 PY	HR (95% CI)
ICT	RSG (n=8604)	45	1.09	
	Comp (n=5633)	20	0.75	1.59 (0.93 - 2.71)
RECORD	RSG (n=2220)	49	0.59	
	Comp (n=2227)	45	0.54	1.09 (0.73 - 1.63)
ADOPT	RSG (n=1456)	24	0.48	
	MET (n=1454)	20	0.41	1.23 (0.68 - 2.22)
	GLY (n=1441)	14	0.33	1.52 (0.79 - 2.94)
DREAM	RSG (n=1325)	5	0.12	0.71 (0.23 - 2.24)
	RSG+RAM (n=1310)	12	0.29	1.73 (0.68 - 4.39)
	RAM (n=1313)	5	0.12	
	Placebo (n=1321)	7	0.17	

[] = previous

Events of Myocardial Infarction or Sudden Death: Adjudicated

	Treatment	# of Patients with Events	Rate / 100 PY	HR (95% CI)
ICT	RSG (n=8604)	[45]24	0.58	
	Comp (n=5633)	[20]11	0.41	[1.59] 1.53 (0.75 - 3.15)
RECORD	RSG (n=2220)	49	0.59	
	Comp (n=2227)	45	0.54	1.09 (0.73 - 1.63)
ADOPT	RSG (n=1456)	24	0.48	
	MET (n=1454)	20	0.41	1.23 (0.68 - 2.22)
	GLY (n=1441)	14	0.33	1.52 (0.79 - 2.94)
DREAM	RSG (n=1325)	5	0.12	0.71 (0.23 - 2.24)
	RSG+RAM (n=1310)	12	0.29	1.73 (0.68 - 4.39)
	RAM (n=1313)	5	0.12	
	Placebo (n=1321)	7	0.17	

[] = previous

*Definite MI or Sudden death

Events of Myocardial Infarction or Sudden Death: Adjudicated*

	Treatment	# of Patients with Events	Rate / 100 PY	HR (95% CI)
ICT	RSG (n=8604)	[45]24	0.58	
	Comp (n=5633)	[20]11	0.41	[1.59] 1.53 (0.75 - 3.15)
RECORD	RSG (n=2220)	49	0.59	
	Comp (n=2227)	45	0.54	1.09 (0.73 - 1.63)
ADOPT	RSG (n=1456)	[24]12	0.24	
	MET (n=1454)	[20]12	0.24	[1.23] 1.03 (0.46 - 2.28)
	GLY (n=1441)	[14]11	0.26	[1.52] 1.00 (0.44 - 2.27)
DREAM	RSG (n=1325)	5	0.12	0.71 (0.23 - 2.24)
	RSG+RAM (n=1310)	12	0.29	1.73 (0.68 - 4.39)
	RAM (n=1313)	5	0.12	
	Placebo (n=1321)	7	0.17	

[] = previous

*Definite MI or Sudden death

Events of Myocardial Infarction or Sudden Death: Adjudicated*

	Treatment	# of Patients with Events	Rate / 100 PY	HR (95% CI)
ICT	RSG (n=8604)	[45]36	0.87	
	Comp (n=5633)	[20]18	0.67 [1.59]	1.47 (0.83 – 2.60)
RECORD	RSG (n=2220)	49	0.59	
	Comp (n=2227)	45	0.54	1.09 (0.73 - 1.63)
ADOPT	RSG (n=1456)	[24]20	0.40	
	MET (n=1454)	[20]17	0.35 [1.23]	1.21 (0.64 - 2.32)
	GLY (n=1441)	[14]15	0.35 [1.52]	1.20 (0.62 - 2.35)
DREAM	RSG (n=1325)	5	0.12	0.71 (0.23 - 2.24)
	RSG+RAM (n=1310)	12	0.29	1.73 (0.68 - 4.39)
	RAM (n=1313)	5	0.12	
	Placebo (n=1321)	7	0.17	

[] = previous

*Definite or unconfirmed MI or Sudden death

Myocardial Infarction: Study in High Risk Patients

High Risk Patients: PPAR Study

Objectives & Design

Design:

- 1 year, randomized, double-blind
- 200 obese subjects with CAD undergoing PCI
 - Hypertension, dyslipidemia or dysglycemia
 - >35% prior MI, >20% prior CABG, >50% with angina

Primary Endpoint:

- Progression rate of carotid intima media thickness
 - No difference between groups on intima media thickness progression

CV Events:

- Adjudicated

In High CV Risk Patients Rosiglitazone Was Not Associated With an Increase in CV Events

Endpoints	RSG (n = 102)	Placebo (n = 98)
Death / MI / Stroke	6	11
Death	1	2
MI	5	8
Stroke	1	2
New CHF	1	0

Myocardial Infarction: Epidemiology Studies

Epidemiology Studies

Design:

- Three US managed care database studies
 - IHCIS: Nested case control
 - 891,901 diabetes pts
 - Ingenix: Cohort Study (propensity score methodology)
 - 33,363 diabetes pts
 - PharMetrics: Cohort Study (propensity score methodology)
 - 402,845 diabetes pts

Endpoints:

- Hospitalization for myocardial infarction or coronary revascularization
 - Head to head comparisons of RSG vs other OADs
 - Includes comparison of RSG vs pioglitazone

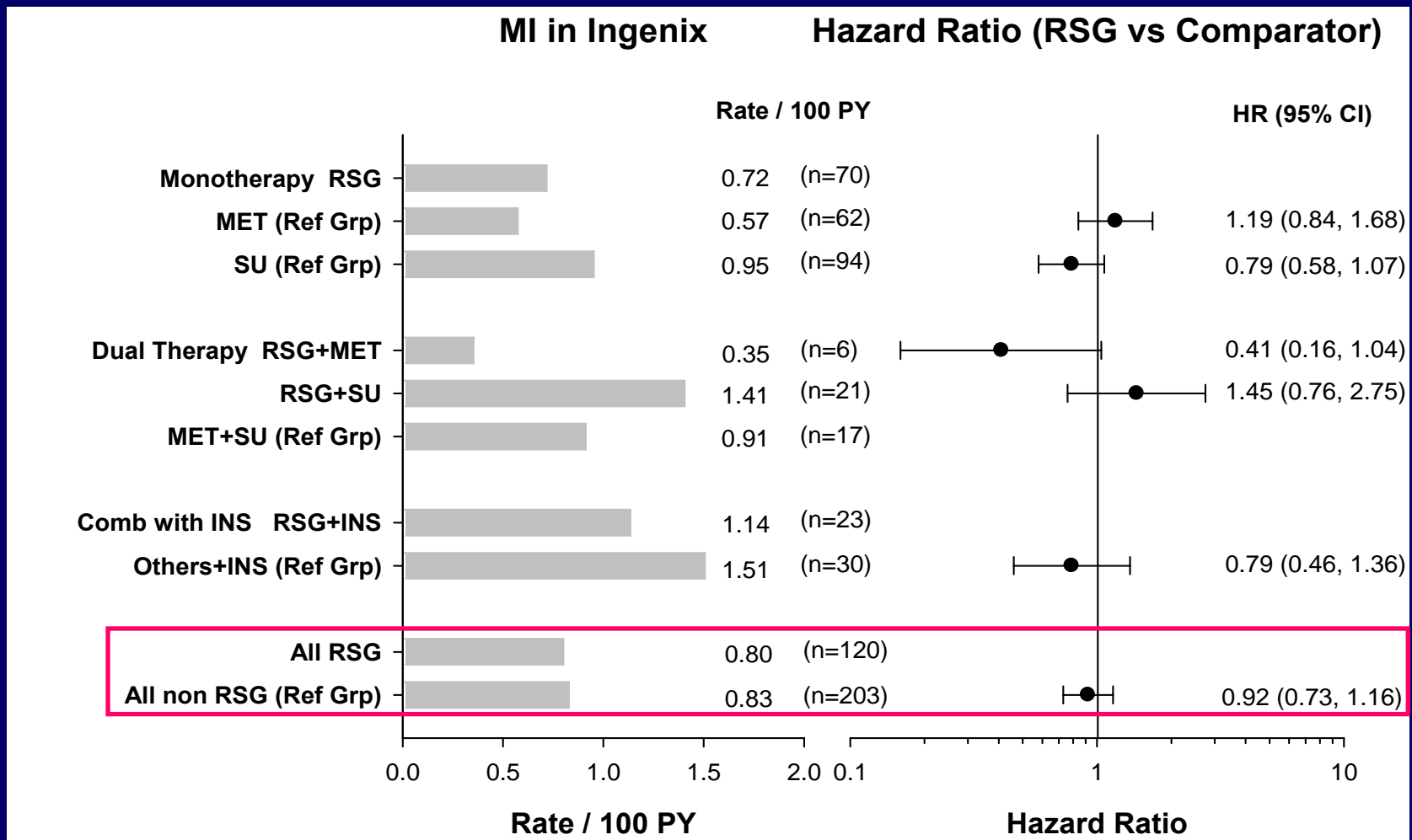
IHCIS Nested Case-Control Study: Myocardial Infarction

	Case (n)	Control (n)	Adjusted OR* [95% CI]
Antidiabetic therapy (oral and/or insulin excluding TZD)	5644	13702	1.00 Reference group
Rosiglitazone (mono or combination therapy)	1149	2690	1.02 [0.94-1.11]
Pioglitazone (mono or combination therapy)	910	2433	0.90 [0.82-0.98]

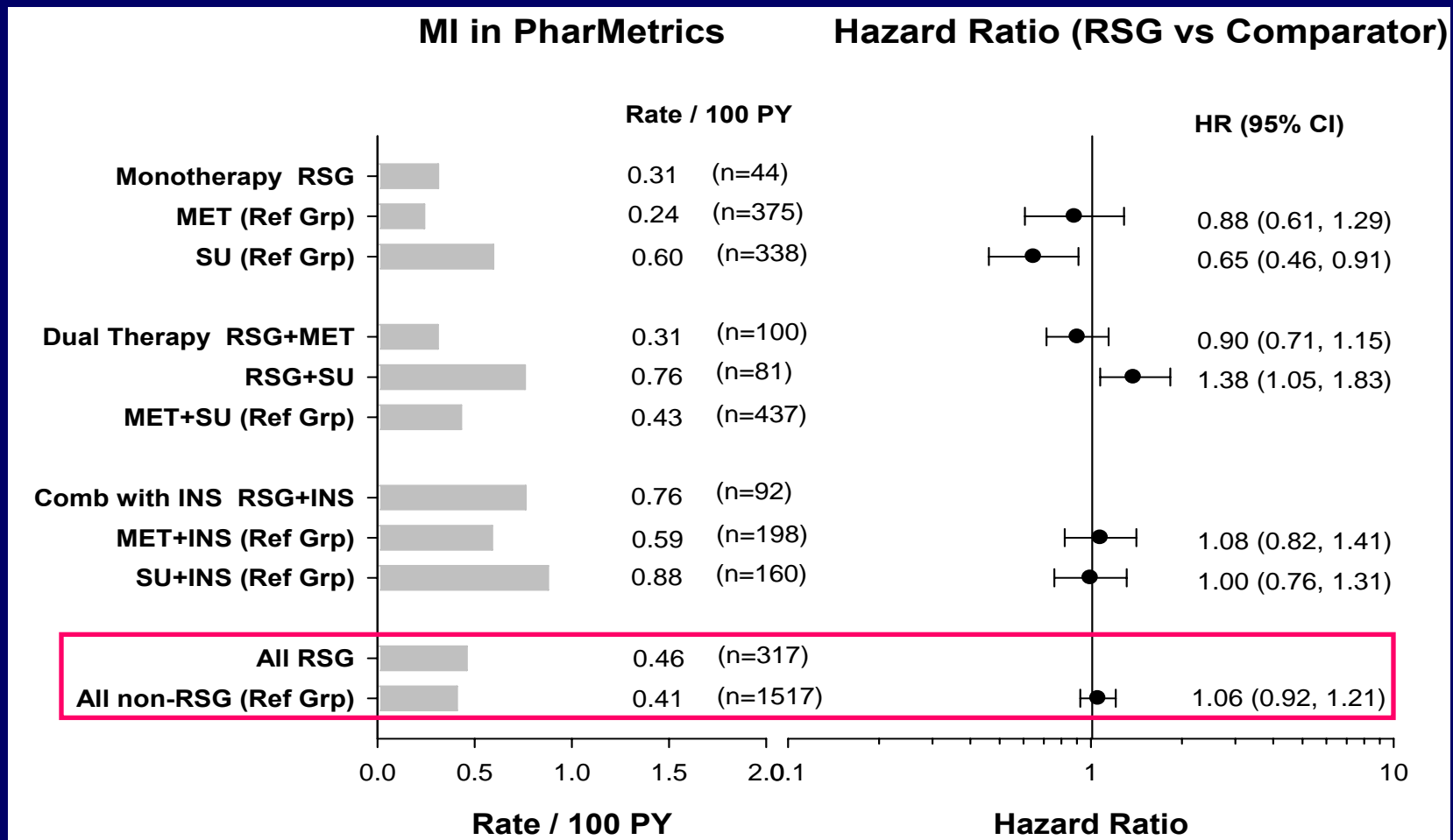
*Adjusted for age, gender, index-year, ACE inhibitor use, Beta-blocker use, diuretic use, nitrate use, drugs to treat hyperlipidemia, hyperlipidemia diagnosis, hypertension diagnosis.

Cohort Studies

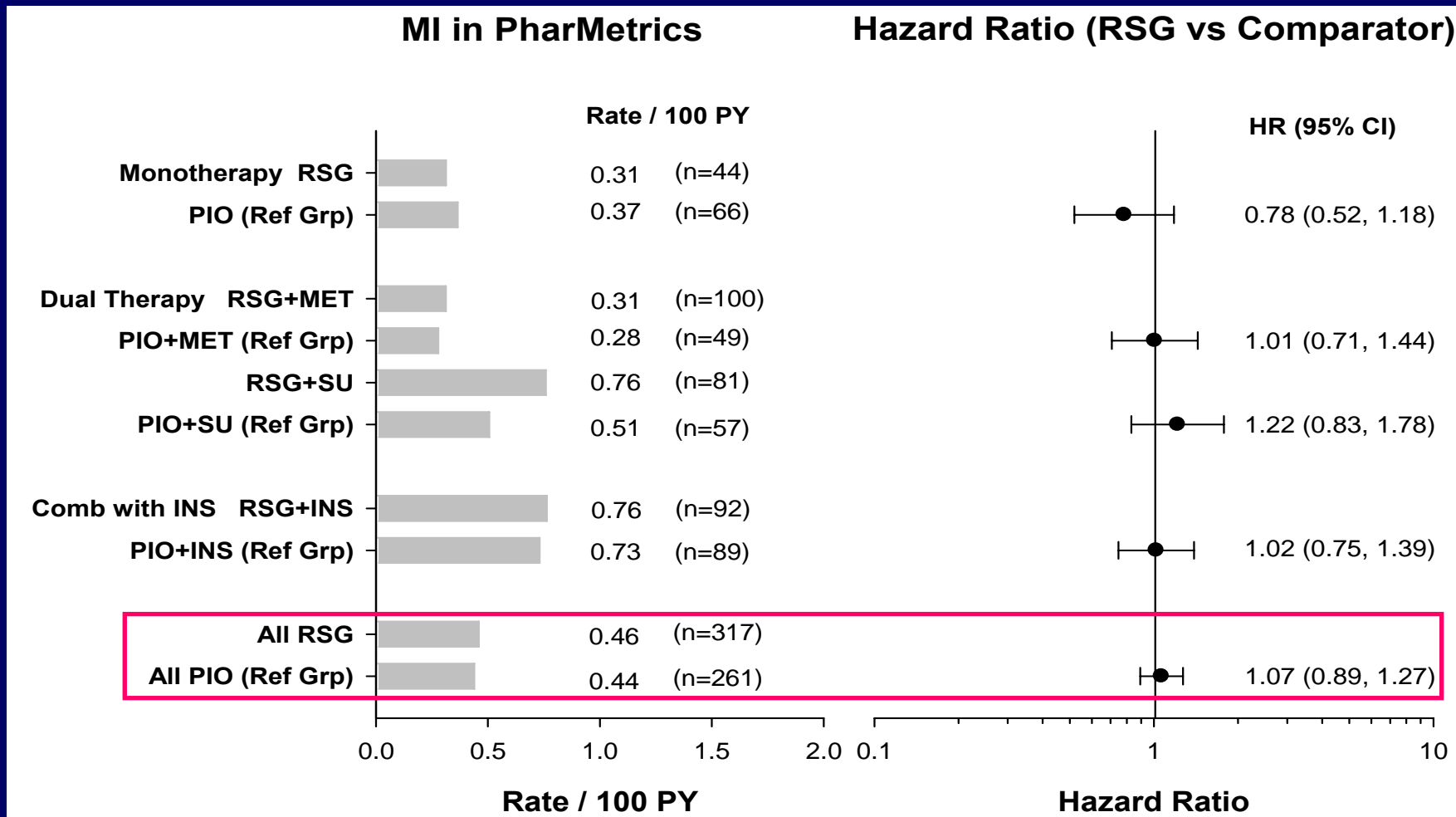
Ingenix Cohort Study: Myocardial Infarction (323 Events/33363 Patients)



PharMetrics Cohort Study: Myocardial Infarction (2095 Events/402845 Patients)



PharMetrics Cohort Study: Myocardial Infarction Comparison of Rosiglitazone & Pioglitazone



Epidemiology Studies in Patients with T2DM

- Studies of over 1.35 million diabetic patients have shown
 - The risk of myocardial infarction is similar for RSG compared to other antidiabetic agents
 - The risk of myocardial infarction is no different between RSG and pioglitazone

Myocardial Infarction: Conclusions

The number of myocardial infarctions in the clinical trials is small, the data are inconsistent, and there is no overall evidence that rosiglitazone is different from other oral antidiabetic agents

Stroke

Stroke:

Evidence to Address ICT Questions

- RECORD interim analysis
 - In-stream adjudication
- ADOPT
 - SAE Investigator Reports
- DREAM
 - In-stream adjudication

Events of Stroke

	Treatment	# of Patients with Events	Rate / 100 PY	HR (95% CI)
ICT	RSG (n=8604)	13	0.31	
	Comp (n=5633)	18	0.67	0.48 (0.23 - 0.98)
RECORD	RSG (n=2220)	29	0.35	
	Comp (n=2227)	38	0.46	0.76 (0.47 - 1.23)
ADOPT	RSG (n=1456)	13	0.26	
	MET (n=1454)	17	0.35	0.77 (0.38 - 1.59)
	GLY (n=1441)	12	0.28	0.94 (0.43 - 2.07)
DREAM	RSG (n=1325)	5	0.12	1.66 (0.40 - 6.93)
	RSG+RAM (n=1310)	2	0.05	0.67 (0.11 - 4.02)
	RAM (n=1313)	2	0.05	
	Placebo (n=1321)	3	0.07	

Conclusions

Across data sources, fewer strokes are observed with rosiglitazone

Cardiovascular Mortality

CV Mortality: Evidence to Address ICT Questions

- RECORD interim analysis
 - In-stream adjudication
- ADOPT
 - Serious Adverse Event Reports
 - Post-Study Adjudication
- DREAM
 - In-stream adjudication

Events of CV Mortality

	Treatment	# of Patients with Events	Rate /100 PY	HR (95% CI)
ICT	RSG (n=8604)	18	0.43	
	Comp (n=5633)	7	0.26	1.91 (0.79 - 4.64)
RECORD	RSG (n=2220)	29	0.35	
	Comp (n=2227)	35	0.42	0.83 (0.51 - 1.36)
ADOPT	RSG (n=1456)	5	0.10	
	MET (n=1454)	4	0.08	1.30 (0.35 - 4.86)
	GLY (n=1441)	8	0.19	0.58 (0.19 - 1.78)
DREAM	RSG (n=1325)	5	0.12	0.99 (0.29 - 3.43)
	RSG+RAM (n=1310)	7	0.17	1.41 (0.45 - 4.44)
	RAM (n=1313)	5	0.12	
	Placebo (n=1321)	5	0.12	

Cardiovascular Mortality: Post-study adjudication

Post Study Adjudication ICT and ADOPT

Definitions of Cardiovascular Death

- Cardiovascular Death
 - Fatal Myocardial Infarction
 - Death while hospitalized following an acute myocardial infarction or within 30 days of an acute myocardial infarction
 - Sudden Death
 - Death that occurred unexpectedly, death without prior symptoms, witnessed sudden death
 - Other cardiovascular death
 - Death due to an identified cardiovascular cause, death following a vascular event, or fatal stroke

Events of CV Mortality: Adjudicated

	Treatment	# of Patients with Events	Rate /100 PY	HR (95% CI)
ICT	RSG (n=8604)	18	0.43	
	Comp (n=5633)	7	0.26	1.91 (0.79 - 4.64)
RECORD	RSG (n=2220)	29	0.35	
	Comp (n=2227)	35	0.42	0.83 (0.51 - 1.36)
ADOPT	RSG (n=1456)	5	0.10	
	MET (n=1454)	4	0.08	1.30 (0.35 - 4.86)
	GLY (n=1441)	8	0.19	0.58 (0.19 - 1.78)
DREAM	RSG (n=1325)	5	0.12	0.99 (0.29 - 3.43)
	RSG+RAM (n=1310)	7	0.17	1.41 (0.45 - 4.44)
	RAM (n=1313)	5	0.12	
	Placebo (n=1321)	5	0.12	

[] = previous

Events of CV Mortality: Adjudicated

	Treatment	# of Patients with Events	Rate /100 PY	HR (95% CI)
ICT	RSG (n=8604)	[18] 19	0.46	
	Comp (n=5633)	[7] 8	0.30 [1.91]	1.68 (0.73 - 3.87)
RECORD	RSG (n=2220)	29	0.35	
	Comp (n=2227)	35	0.42	0.83 (0.51 - 1.36)
ADOPT	RSG (n=1456)	5	0.10	
	MET (n=1454)	4	0.08	1.30 (0.35 - 4.86)
	GLY (n=1441)	8	0.19	0.58 (0.19 - 1.78)
DREAM	RSG (n=1325)	5	0.12	0.99 (0.29 - 3.43)
	RSG+RAM (n=1310)	7	0.17	1.41 (0.45 - 4.44)
	RAM (n=1313)	5	0.12	
	Placebo (n=1321)	5	0.12	

[] = previous

Events of CV Mortality: Adjudicated

	Treatment	# of Patients with Events	Rate /100 PY	HR (95% CI)
ICT	RSG (n=8604)	[18] 19	0.46	
	Comp (n=5633)	[7] 8	0.30 [1.91]	1.68 (0.73 - 3.87)
RECORD	RSG (n=2220)	29	0.35	
	Comp (n=2227)	35	0.42	0.83 (0.51 - 1.36)
ADOPT	RSG (n=1456)	[5] 6	0.12	
	MET (n=1454)	[4] 8	0.16 [1.30]	0.79 (0.27 - 2.27)
	GLY (n=1441)	[8] 12	0.28 [0.58]	0.46 (0.17 - 1.23)
DREAM	RSG (n=1325)	5	0.12	0.99 (0.29 - 3.43)
	RSG+RAM (n=1310)	7	0.17	1.41 (0.45 - 4.44)
	RAM (n=1313)	5	0.12	
	Placebo (n=1321)	5	0.12	

[] = previous

Events of All Cause Mortality

	Treatment	# of Patients with Events	Rate / 100 PY	HR (95% CI)
ICT	RSG (n=8604)	23	0.56	
	Comp (n=5633)	9	0.34	1.80 (0.82 - 3.92)
RECORD	RSG (n=2220)	74	0.88	
	Comp (n=2227)	80	0.96	0.92 (0.67 - 1.26)
ADOPT	RSG (n=1456)	12	0.24	
	MET (n=1454)	15	0.31	0.82 (0.38 - 1.76)
	SU (n=1441)	21	0.49	0.51 (0.25 - 1.03)
DREAM	RSG (n=1325)	15	0.35	0.87 (0.44 - 1.75)
	RSG+RAM (n=1310)	15	0.36	0.89 (0.44 - 1.78)
	RAM (n=1313)	16	0.38	
	Placebo (n=1321)	17	0.40	

Conclusion on Cardiovascular Mortality

- Rosiglitazone is not associated with an increase in cardiovascular mortality
- No increase in all-cause mortality

Summary of MACE Events
RECORD + ADOPT + DREAM

MACE Events

RECORD + ADOPT + DREAM

	Treatment	# of Events	Rate / 100 PY	HR (95% CI)	Rate Difference/100PY (95% CI)
MI/SD	RSG (n=6311)	78	0.36		
	Comp (n=7756)	80	0.31	1.13 (0.82, 1.54)	0.05 (-0.06, 0.15)
Stroke	RSG (n=6311)	49	0.22		
	Comp (n=7756)	72	0.28	0.84 (0.58, 1.21)	- 0.05 (- 0.14, 0.04)
CV Mortality	RSG (n=6311)	47	0.22		
	Comp (n=7756)	65	0.25	0.84 (0.57, 1.22)	- 0.03 (- 0.12, 0.05)
MACE	RSG (n=6311)	153	0.70		
	Comp (n=7756)	174	0.67	1.03 (0.83, 1.28)	0.03 (- 0.12, 0.18)

Reflects Post Study Adjudication for ICT and ADOPT based on definite MI/SD and CV mortality

Overall Conclusion

The totality of the data show that:

- There was no increase in myocardial ischemia in the long term comparator study (ADOPT)
- For myocardial infarction, the data are inconsistent and there is no overall evidence that RSG is different from other oral antidiabetic drugs, including pioglitazone
- Across data sources, fewer strokes are observed with RSG
- Rosiglitazone is not associated with an increase in cardiovascular or all-cause mortality