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EBM WORKSHOP SERIES

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Rosiglitazone for the prevention of T2 diabetes – Risks and Benefits

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What we will cover today

- **Topic:** Rosiglitazone for the prevention of T2 diabetes – Risks and Benefits

- **Our EBM lessons will be**:
  - relative risk vs. absolute risk
  - number needed to treat and number needed to harm
  - Cost-benefit
  - .. and anything else you care to ask.

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Our case scenario

A new patient who has been taking rosiglitazone since 2007 stumbles upon media articles showing an increased risk of death. They are asking you if they should come off the drug. You are considering the safety of rosiglitazone and whether you should start the person on pioglitazone instead.

These are the articles you find….

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Papers

A trial that looks at the efficacy of Rosiglitazone, and a later systematic review that looked at long-term safety.

- **RCT:** Gerstein HC, Yusuf S, Bosch J, et al; DREAM (Diabetes REduction Assessment with ramipril androsiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006;368(9541):1096-1105.

- **Meta-Analysis:** Nissen SE, Wolski K (2010). "Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality". Arch. Intern. Med. **170** (14): 1191–1201. doi:10.1001/archinternmed.2010.207. PMID 20656674.

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Study Design

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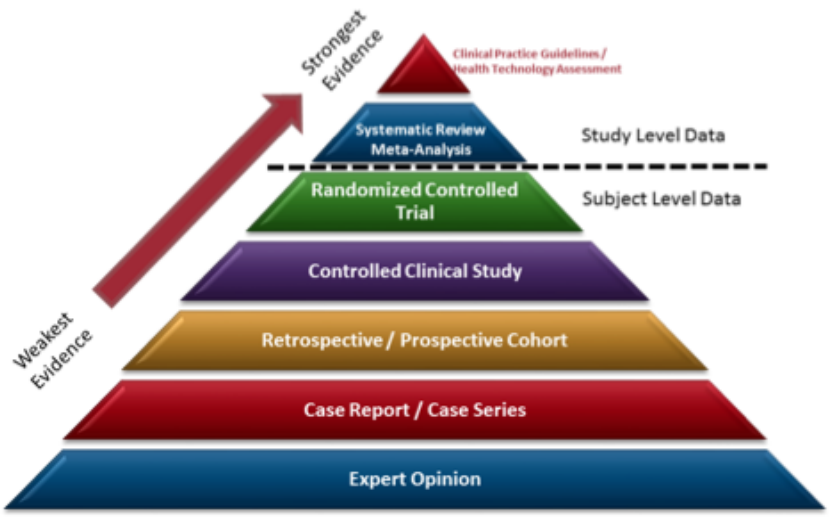

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Types of Studies

1. **Literature Reviews**
   - Literature Syntheses
   - Systematic Reviews
   - **Meta Analyses**
2. Qualitative Studies
3. Quantitative Observational Studies
4. **Intervention/Experimental Studies**
5. Case Studies

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Intervention/Experimental Studies

- **Aim:** To gain understanding of general causation (X effect on Y). Usually informed by obs. research.
  - Scope: Entire population of interest.
- **Methods:**
  - Control matching, randomization, temporal.
- **Sampling:**
  - Usually small to medium size samples.
  - Usually comparable populations.
  - Representativeness SHOULD matter.
- **Examples:** RCT, pre-post within group, comparative research

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Trial phases..

Phase	Primary goal	What you get..
Phase I	Testing of drug on healthy volunteers for dose	Determines whether drug is safe
Phase II	Testing of drug on patients to assess **efficacy** and **obvious side effects** (DRUG APPROVAL)	Determines whether drug can have any efficacy
Phase III	Testing of drug on patients to assess **efficacy (hopefully effectiveness)** and **safety**	Determines a drug's therapeutic effect in more real word conditions
Phase IV	Testing of drug on patients to assess true **effectiveness** and **safety**	Determines real world short term and long-term effects

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DREAM

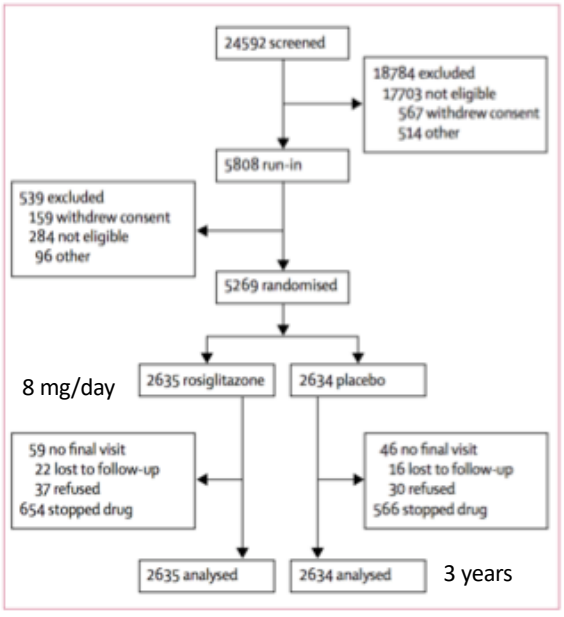
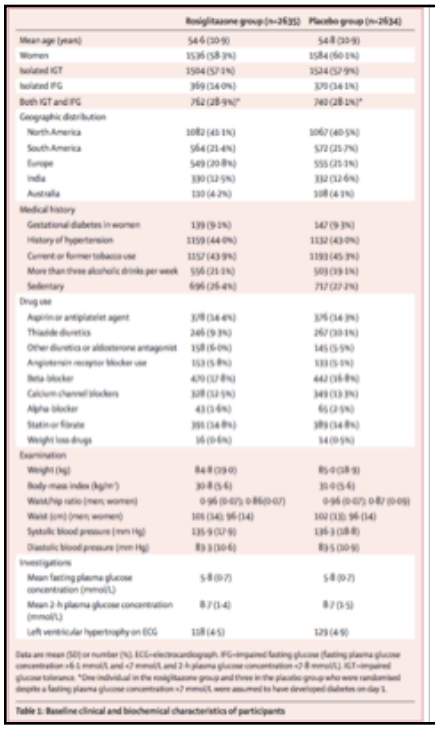


Figure 1: **Trial profile**
Data were censored at time of last follow-up for all participants.



	Rosiglitazone group (n=2635)	Placebo group (n=2634)
Mean age (years)	54·6 (10·9)	54·8 (10·9)
Women	1536 (58·3%)	1584 (60·1%)
Isolated IGT	1504 (57·1%)	1524 (57·9%)
Isolated IFG	369 (14·0%)	370 (14·1%)
Both IGT and IFG	762 (28·9%)*	740 (28·1%)*
Geographic distribution		
North America	1082 (41·1%)	1067 (40·5%)
South America	564 (21·4%)	572 (21·7%)
Europe	549 (20·8%)	555 (21·1%)
India	330 (12·5%)	332 (12·6%)
Australia	110 (4·2%)	108 (4·1%)
Medical history		
Gestational diabetes in women	139 (9·1%)	147 (9·3%)
History of hypertension	1159 (44·0%)	1132 (43·0%)
Current or former tobacco use	1157 (43·9%)	1193 (45·3%)
More than three alcoholic drinks per week	556 (21·1%)	503 (19·1%)
Sedentary	696 (26·4%)	717 (27·2%)
Drug use		
Aspirin or antiplatelet agent	378 (14·4%)	376 (14·3%)
Thiazide diuretics	246 (9·3%)	267 (10·1%)
Other diuretics or aldosterone antagonist	158 (6·0%)	145 (5·5%)
Angiotensin receptor blocker use	153 (5·8%)	133 (5·1%)
Beta-blocker	470 (17·8%)	442 (16·8%)
Calcium channel blockers	328 (12·5%)	349 (13·3%)
Alpha-blocker	43 (1·6%)	65 (2·5%)
Statin or fibrate	391 (14·8%)	389 (14·8%)
Weight loss drugs	16 (0·6%)	14 (0·5%)
Examination		
Weight (kg)	84·8 (19·0)	85·0 (18·9)
Body-mass index (kg/m²)	30·8 (5·6)	31·0 (5·6)
Waist/hip ratio (men; women)	0·96 (0·07); 0·86(0·07)	0·96 (0·07); 0·87 (0·09)
Waist (cm) (men; women)	101 (14); 96 (14)	102 (13); 96 (14)
Systolic blood pressure (mm Hg)	135·9 (17·9)	136·3 (18·8)
Diastolic blood pressure (mm Hg)	83·3 (10·6)	83·5 (10·9)
Investigations		
Mean fasting plasma glucose concentration (mmol/L)	5·8 (0·7)	5·8 (0·7)
Mean 2-h plasma glucose concentration (mmol/L)	8·7 (3·4)	8·7 (3·5)
Left ventricular hypertrophy on ECG	118 (4·5)	129 (4·9)

Data are mean (SD) or number (%). ECG=electrocardiograph. IFG=impaired fasting glucose (fasting plasma glucose concentration >6·1 mmol/L and <7 mmol/L and 2-h plasma glucose concentration <7·8 mmol/L). IGT=impaired glucose tolerance. *One individual in the rosiglitazone group and three in the placebo group who were randomised despite a fasting plasma glucose concentration >7 mmol/L were assumed to have developed diabetes on day 1.

Table 1: Baseline clinical and biochemical characteristics of participants

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DREAM

…. Randomization is a beautiful thing!

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Literature Reviews

- Literature Syntheses
  - Broad-based questions used to understand the nature of the clinical issue and who and how others have approached it before.
- Systematic Reviews
  - Narrow review of a specific clinical topic with explicit a-priori criteria for whether to include research in review.
- **Meta Analyses**
  - Very narrow perspective seeking to examine a specific clinical question, usually by collating randomized controlled trials

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Meta-Analysis (Nissen 2010)

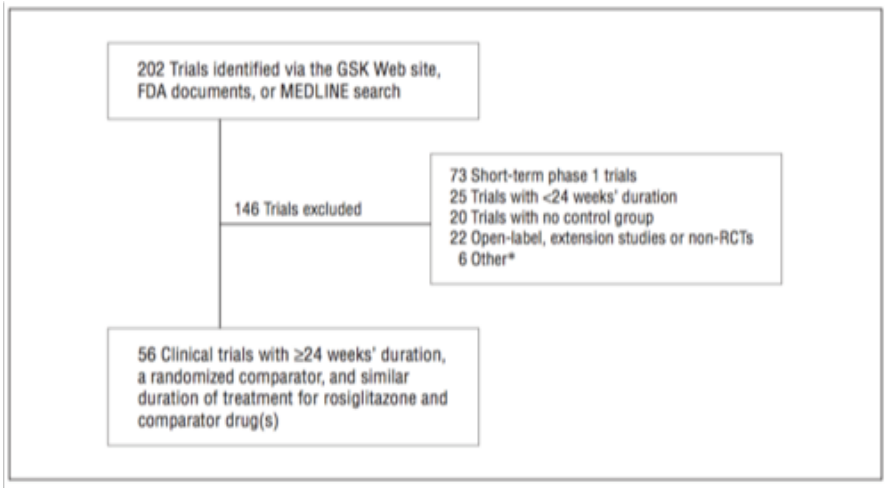

Figure 1. Flow diagram showing the numbers of studies included and excluded from the analysis and the reasons for exclusion. FDA indicates Food and Drug Administration; GSK, GlaxoSmithKline; and RCT, randomized controlled trial. *Includes pediatric studies, terminated early, or summary analysis.

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Meta-Analysis (Nissen 2010)

Table 2. Dosages, Baseline Demographic Characteristics, Study Periods, and Hemoglobin A_{1c} (HbA_{1c}) Levels

Clinical Trial No.	Study	Dosage	Population	Study Period	Age, y	% Male Sex	% Race*	Baseline HbA_{1c} Level
100684	Rsg/Gly	4-8 mg	Korean patients with type 2 DM	Dec 2003-Jul 2005	55.2	53.5	100 (A)	NA
	Gly	5-15 mg			54.5	45.6	100 (A)	
49653/143	Rsg/Gly	8 mg	Type 2 DM poorly controlled with Gly	Jul 2005-Jan 2003	52	45.3	44:56 (B:H)	9.2
	Gly	Per usual			53	48.3	38:62 (B:H)	9.4
49653/211	Rsg	4 mg	Type 2 DM with CHF	Jul 2001-Nov 2003	64.3	84.3	99	7.7
	Plc	NA			63.9	79.0	99	7.8
49653/284	Rsg/Met	4-8 mg/1 g	Type 2 DM	Jun 2001-Feb 2003	55.5	51.1	72	8.1
	Met	1-2 g			55.6	51.0	71	7.9
712753/008	Rsg/Met	8 mg/1 g	Type 2 DM poorly controlled with Met	Jun 2003-Dec 2005	54.6	63.2	70	Baseline not reported
	Rsg/Met	4 mg/2 g			56.0	65.2	78	
	Met	2 g			56.9	53.4	69	
AVM100264	Rsg/Met	4-8 mg/2 g	Overweight type 2 DM poorly controlled with Met	Jul 2004-Jan 2006	58.5	52.7	94	8.0
	Met/Su	2 g/titrated			59.3	52.5	95	8.0
BRL49653C/185	Rsg/Elm/Met	4 mg/1.5 g	Type 2 DM	May 2000-May 2002	58.0	65.2	76	7.5
	Rsg/Elm	4 mg			59.0	60.2	78	7.4
	Met/Elm	1.5 g			60.0	56.4	78	7.5
	Elm	NA			57.0	60.9	83	7.4
BRL 49653/334	Rsg	4-8 mg	Type 2 DM or Ins resistance syndrome	Mar 2002-Nov 2004	67.7	44.8	99	6.3
	Plc	NA			67.3	47.7	100	6.3
BRL 49653/347	Rsg/Ins	4 mg	Type 2 DM poorly controlled with Ins	Nov 2002-Apr 2004	52.6	48.1	57	9.0
	Rsg/Ins	2-4 mg			52.7	60.0	57	8.9
	Ins/Plc	Per usual			53.8	46.2	57	9.1
49653/011	Rsg	8 mg	Type 2 DM	Sep 1996-Sep 1997	60.7	66.9	73	8.8
	Rsg	4 mg			59.6	64.5	75	9.0
	Plc	NA			58.8	65.8	74	9.0
49653/015	Rsg/Su	4 mg	Type 2 DM	Aug 1996-Mar 1998	60.6	53.2	98	9.2
	Rsg/Su	2 mg			61.0	62.8	86	9.2
	Su	NA			61.9	57.3	97	9.2
49653/020	Rsg	8 mg	Type 2 DM	Oct 1996-May 1998	60.9	57.6	97	8.2
	Rsg	4 mg			60.4	68.2	99	8.1
	Gly	Titrated			60.1	70.4	99	8.2
49653/024	Rsg	4 mg/d	Type 2 DM	Jan 1997-Feb 1998	57.5	58.6	76	8.9
	Rsg	2 mg BD			56.8	59.1	78	8.9
	Rsg	8 mg/d			58.9	65.7	80	8.9
	Rsg	4 mg BD			56.5	59.9	71	9.0

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Meta-Analysis (Nissen 2010)

Table 3. Myocardial Infarction (MI) and Cardiovascular (CV) Death in Rosiglitazone Trials

	Rosiglitazone			Comparators		
GSK Trial No.	No. of Patients	MI	CV Death	No. of Patients	MI	CV Death
Trials Included in Original Registration Package						
49653/011	357	2	1	176	0	0
49653/020	391	2	0	207	1	0
49653/024	774	1	0	185	1	0
49653/093	213	0	0	109	1	0
49653/094	232	1	1	116	0	0
Additional Phase 2, 3, and 4 Efficacy Trials						
100684	43	0	0	47	1	0
49653/143	121	1	0	124	0	0
49653/211	110	5	5	114	2	4
49653/284	382	1	0	384	0	0
712753/008	284	1	0	135	0	0
AVM100264	294	0	2	302	1	1
BRL 49653C/185	563	2	0	142	0	0
BRL 49653/334	278	2	0	279	1	1
BRL 49653/347	418	2	0	212	0	0
49653/015	395	2	2	198	1	0
49653/079	203	1	1	106	1	1
Published Large Prospective Randomized Trials						
DREAM trial[18]	2635	15	12	2634	9	10
ADOPT[19]	1456	27	2	2895	41	5
RECORD trial[4]	2220	64	60	2227	56	71

Abbreviations: ADOPT, A Diabetes Outcome Progression Trial; APPROACH, Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients With Cardiovascular History; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes.

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Point Estimates

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Point Estimates

- **Definition**: A one-number summary of clinical effect or association.

- Examples:
  - Dose finding trials: MTD (maximum tolerable dose)
  - Safety and Efficacy Trials: response rate, median survival
  - Comparative Trials: Odds ratio, hazard ratio

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Types of Point Estimates

- For Continuous Outcomes:
  - Examples: change in tumor volume or tumor diameter
  - Commonly used point estimates: mean, median
- For Binary Outcomes:
  - Examples: response, events
  - Commonly used point estimate: proportion, relative risk, odds ratio
- Time-to-Event (Survival) Outcomes:
  - Examples: time to progression, time to death, time to relapse
  - Commonly used point estimates: median survival, hazard ratio

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Common Point Estimates

1. Odds ratio
2. Relative Risk/Risk ratio
3. Hazard ratio

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The Relative Risk/Risk Ratio

- The risk of an event or disease relative to exposure

- What does it mean?
- "protective" relative risk is < 1
- "increased risk" relative risk is > 1

- Example: RR = 2.14
- "The risk of men dying before 85 years of age is 2.14 times higher than that of women." or "The risk of men dying before 85 years of age is 114% greater than that of women"

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The Odds Ratio

- The ratio of the odds of an event occurring in one group to the odds of it occurring in another group

- What does it mean?
- "protective" odds ratios < 1
- "increased risk" odds ratios > 1
- Example: OR = 1.88
  - "The odds of women living to 85 is 1.88 higher than that of men" or "The odds of women living to 85 is 88% greater than that of men"

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Risk v.s Odds .. Not the same

Risk (probability)	Odds
0.80	**4.0** ⌂⌂⌂⌂/⌂
0.67	**2.0** ⌂⌂/⌂
0.50	**1.0** ⌂/⌂
0.20	**0.25** ⌂/⌂⌂⌂⌂
0.10	**0.11** ⌂/⌂⌂⌂⌂⌂⌂⌂⌂⌂

Conversion:
Odds = Risk/(1-Risk)
Risk = Odds / (1 + Odds)

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OR and RR: What's the difference?

ORs and RRs can give quite different magnitude.

No one thinks in terms of odds (esp. odds ratios). Most interpret odds in terms of risk (probability). Don't make that mistake.

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The Hazard Ratio

- The **instantaneous** risk of an event or disease relative to exposure.

- What does it mean?
- "protective" hazard ratio is < 1
- "increased risk" hazard ratio is > 1

- Example:
- "The risk of men dying of MI is 2.14 times higher than that of women, over the age of 50"

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The P Value

- What does it tell you?
  - How probable the point estimate (effect) in the study reflects a true difference/value in the population studied.
  - Doesn't tell you the size of the effect
  - e.g., P=0.05 – The probability of their being a true difference is 95% (95 times out of 100)
- Influenced by:
  - Sample size.
    - Small samples gives you larger (worse) p-values intervals.
  - Weakness or inconsistency of the effect.

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Significance: Statistical v. Clinical

- Measures of association can lie!
- What's the difference?

Event Rate TREATMENT	Event Rate Control	RR (Relative Risk)	Absolute Risk Reduction
10%	20%	0.5	10%
1%	2%	0.5	1%

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Number needed to treat (NNT)

- Number Needed to Treat (NNT):
  - Number of persons who would have to receive an intervention for 1 to benefit.
- Number Needed to Harm(NNH):
  - Number of persons who would have to receive an intervention for 1 to be experience a adverse event.

NNT= 1/ARR OR 100/ARR%

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The Confidence Interval

- What does it tell you?
  - How reliable/precise the point estimate (effect) is in the study population (measure of certainty).
  - The true point estimate (effect) can be any value within in the confidence interval.
  - Doesn't tell you if the effect is valid
- Influenced by:
  - Sample size used.
    - Small samples give you larger confidence intervals.
  - Reliability of the effect.

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How to evaluate the evidence …

(this is a generalization)

1
- Do the results **directly relate** to my question/patients/practice?
- Is the **study quality** good enough?

YES

2
- Are the effects **statistically significant**? (i.e., based on p-value, relative risk/benefit)

YES

3
- Are the results **clinically significant**? (i.e., based on change in absolute risk/NNT, precision)
- Are the harms small enough to justify?

YES

CONSIDER IT*

*Consider the cost-benefit compared to **all other** options.

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DREAM

Summary

Background Rosiglitazone is a thiazolidinedione that reduces insulin resistance and might preserve insulin secretion. The aim of this study was to assess prospectively the drug's ability to prevent type 2 diabetes in individuals at high risk of developing the condition.

Methods 5269 adults aged 30 years or more with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease were recruited from 191 sites in 21 countries and randomly assigned to receive rosiglitazone (8 mg daily; n=2365) or placebo (2634) and followed for a median of 3 years. The primary outcome was a composite of incident diabetes or death. Analyses were done by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT00095654.

Findings At the end of study, 59 individuals had dropped out from the rosiglitazone group and 46 from the placebo group. 306 (11·6%) individuals given rosiglitazone and 686 (26·0%) given placebo developed the composite primary outcome (hazard ratio 0·40, 95% CI 0·35–0·46; p<0·0001); 1330 (50·5%) individuals in the rosiglitazone group and 798 (30·3%) in the placebo group became normoglycaemic (1·71, 1·57–1·87; p<0·0001). Cardiovascular event rates were much the same in both groups, although 14 (0·5%) participants in the rosiglitazone group and two (0·1%) in the placebo group developed heart failure (p=0·01).

Interpretation Rosiglitazone at 8 mg daily for 3 years substantially reduces incident type 2 diabetes and increases the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance, or both.

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DREAM

	Rosiglitazone group (n=2635)	Placebo group (n=2634)	HR (95% CI)	p
Composite primary outcome*	306 (11·6%)	686 (26·0%)	0·40 (0·35–0·45)	<0·0001
Diabetes	280 (10·6%)	658 (25·0%)	0·38 (0·33–0·44)	<0·0001
Diagnosed by FPG/OGTT	231 (8·8%)	555 (21·1%)	0·38 (0·33–0·44)	<0·0001
Physician diagnosed	49 (1·9%)	103 (3·9%)	0·47 (0·33–0·66)	<0·0001
Death	30 (1·1%)	33 (1·3%)	0·91 (0·55–1·49)	0·7
Regression (FPG <6·1 mmol/L)†	1330 (50·5%)	798 (30·3%)	1·71 (1·57–1·87)	<0·0001
Regression (FPG <5·6 mmol/L)†	1016 (38·6%)	540 (20·5%)	1·83 (1·65–2·04)	<0·0001
Cardiovascular events composite*	75 (2·9%)	55 (2·1%)	1·37 (0·97–1·94)	0·08
Myocardial infarction	15 (0·6%)	9 (0·3%)	1·66 (0·73–3·80)	0·2
Stroke	7 (0·3%)	5 (0·2%)	1·39 (0·44–4·40)	0·6
Cardiovascular death	12 (0·5%)	10 (0·4%)	1·20 (0·52–2·77)	0·7
Confirmed heart failure‡	14 (0·5%)	2 (0·1%)	7·03 (1·60–30·9)	0·01
New angina	24 (0·9%)	20 (0·8%)	1·20 (0·66–2·17)	0·5
Revascularisation	35 (1·3%)	27 (1·0%)	1·29 (0·78–2·14)	0·3
Myocardial infarction, stroke, or cardiovascular death	32 (1·2%)	23 (0·9%)	1·39 (0·81–2·37)	0·2

Data are number (%). *Rows are not mutually exclusive for components of the composite—if a participant had more than one component of the composite then they are counted in the relevant row. †Regression implies achieving a normal fasting glucose concentration (as defined in both rows) and 2-h plasma glucose level. ‡Defined as acute treatment with at least two of the following criteria: typical signs and symptoms, typical radiological evidence, use of diuretics, vasodilators, or inotropes. FPG=fasting plasma glucose. OGTT=oral glucose tolerance test.

Table 2: Primary and other outcomes

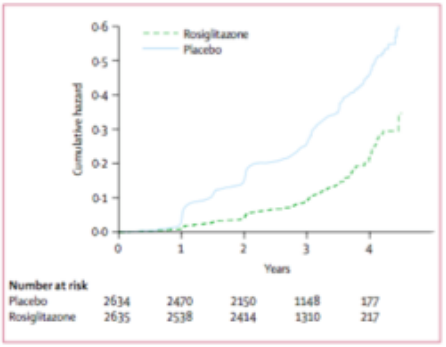

Figure 2: Time to occurrence of primary outcome

NNT? **NNH?** **Cost-benefit?**

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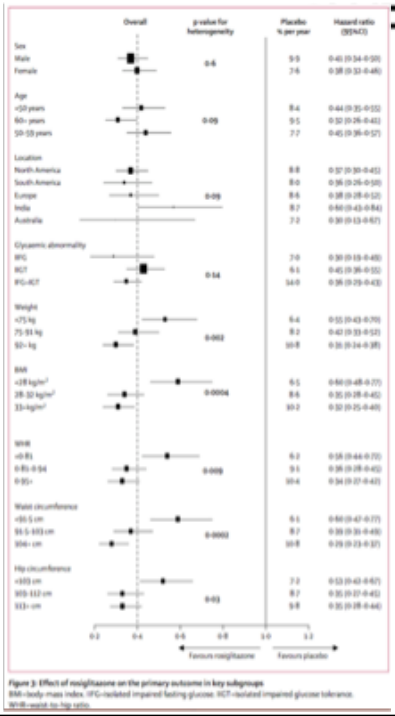

Figure 3: Effect of rosiglitazone on the primary outcome in key subgroups
BMI=body-mass index. IFG=isolated impaired fasting glucose. IGT=isolated impaired glucose tolerance. WHR=waist-to-hip ratio.

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Meta-Analysis (Nissen 2010)

Context: Controversy regarding the effects of rosiglitazone therapy on myocardial infarction (MI) and cardiovascular (CV) mortality persists 3 years after a meta-analysis initially raised concerns about the use of this drug.

Objective: To systematically review the effects of rosiglitazone therapy on MI and mortality (CV and all-cause).

Data Sources: We searched MEDLINE, the Web site of the Food and Drug Administration, and the GlaxoSmithKline clinical trials registry for trials published through February 2010.

Study Selection: The study included all randomized controlled trials of rosiglitazone at least 24 weeks in duration that reported CV adverse events.

Data Extraction: Odds ratios (ORs) for MI and mortality were estimated using a fixed-effects meta-analysis of 56 trials, which included 35 531 patients: 19 509 who received rosiglitazone and 16 022 who received control therapy.

Results: Rosiglitazone therapy significantly increased the risk of MI (OR, 1.28; 95% confidence interval [CI], 1.02-1.63; $P=.04$) but not CV mortality (OR, 1.03; 95% CI, 0.78-1.36; $P=.86$). Exclusion of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial yielded similar results but with more elevated estimates of the OR for MI (OR, 1.39; 95% CI, 1.02-1.89; $P=.04$) and CV mortality (OR, 1.46; 95% CI, 0.92-2.33; $P=.11$). An alternative analysis pooling trials according to allocation ratios allowed inclusion of studies with no events, yielding similar results for MI (OR, 1.28; 95% CI, 1.01-1.62; $P=.04$) and CV mortality (OR 0.99; 95% CI, 0.75-1.32; $P=.96$).

Conclusions: Eleven years after the introduction of rosiglitazone, the totality of randomized clinical trials continue to demonstrate increased risk for MI although not for CV or all-cause mortality. The current findings suggest an unfavorable benefit to risk ratio for rosiglitazone.

Arch Intern Med. 2010;170(14):1191-1201. Published online June 28, 2010. doi:10.1001/archinternmed.2010.207

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Meta-Analysis (Nissen 2010)

Table 4. Primary Analysis of Risk for Myocardial Infarction and Cardiovascular Mortality

Method	No. of Studies	Rosiglitazone Group	Control Group	Peto OR (95% CI)	*P* Value
Risk for Myocardial Infarction[a]					
Including RECORD trial[a]	41	159/17 258	136/14 449	1.28 (1.02-1.63)	.04
Excluding RECORD trial	40	95/15 038	80/12 222	1.39 (1.02-1.89)	.04
Risk for Cardiovascular Mortality[b]					
Including RECORD trial	26	105/13 672	100/12 175	1.03 (0.78-1.36)	.86
Excluding RECORD trial	25	45/11 452	29/9949	1.46 (0.92-2.33)	.11

Abbreviations: CI, confidence interval; OR, odds ratio; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes.

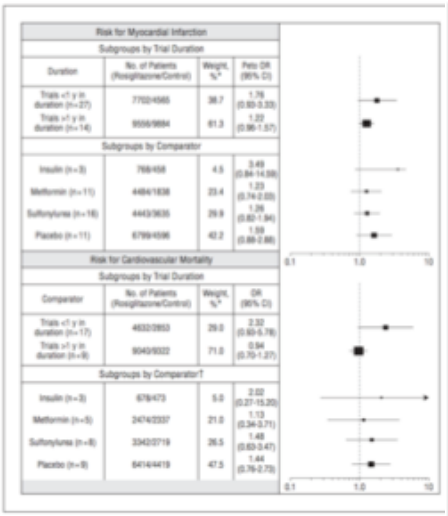
[a] Including RECORD trial: Q statistic, 30.3; $P=.87$; $I^2=0\%$, Excluding RECORD trial: Q statistic, 29.7; $P=.86$; $I^2=0\%$.

[b] Including RECORD trial: Q statistic, 16.2; $P=.91$; $I^2=0\%$. Excluding RECORD trial: Q statistic, 12.8; $P=.97$; $I^2=0\%$.

NNH?

Meta-Analysis (Nissen 2010)

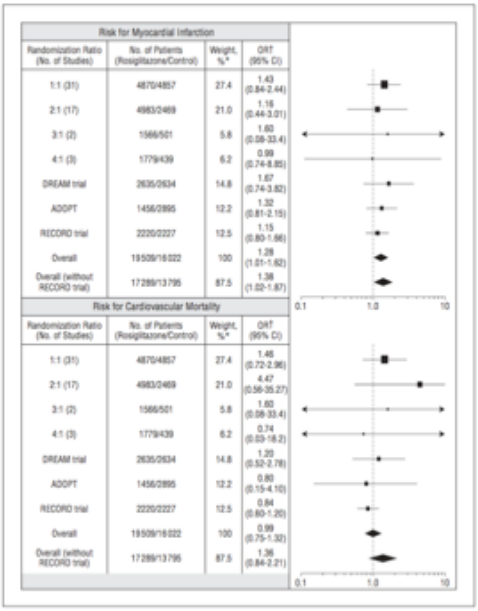
WRCResearch



Risk for Myocardial Infarction			
Subgroups by Trial Duration			
Duration	No. of Patients (Rosiglitazone/Control)	Weight, %*	Peto OR (95% CI)
Trials <1 y in duration (n=37)	7702/4565	38.7	1.79 (0.93-3.33)
Trials >1 y in duration (n=14)	9556/9884	61.3	1.22 (0.86-1.57)
Subgroups by Comparator			
Insulin (n=3)	768/458	4.5	3.49 (0.84-14.59)
Metformin (n=11)	4484/1838	23.4	1.33 (0.74-2.03)
Sulfonylurea (n=18)	4443/3635	29.9	1.26 (0.82-1.94)
Placebo (n=11)	6799/4596	42.2	1.59 (0.88-2.88)
Risk for Cardiovascular Mortality			
Subgroups by Trial Duration			
Comparator	No. of Patients (Rosiglitazone/Control)	Weight, %*	OR (95% CI)
Trials <1 y in duration (n=17)	4632/2853	29.0	2.32 (0.93-5.78)
Trials >1 y in duration (n=9)	9040/9022	71.0	0.94 (0.70-1.27)
Subgroups by Comparator†			
Insulin (n=3)	678/473	5.0	2.02 (0.27-15.20)
Metformin (n=5)	2474/2337	21.0	1.13 (0.34-3.71)
Sulfonylurea (n=8)	3342/2719	26.5	1.48 (0.69-3.47)
Placebo (n=9)	6414/4419	47.5	1.44 (0.79-2.73)

0.1 1.0 10

Figure 2. Risk for myocardial infarction and cardiovascular mortality in trials classified by study durati and comparator drug. CI indicates confidence interval; and OR, odds ratio. *Calculated by proportion of the total sample included in the meta-analysis. †The RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial[7] was not included in the analysis of the comparator subgroup because of the combination treatment assignment, and ADOPT (A Diabetes Outcome Progression Trial)[10] was included separately for both the metformin (n=1454) and the sulfonylurea (n=1441) subgroups, according to randomized assignment.



Risk for Myocardial Infarction			
Randomization Ratio (No. of Studies)	No. of Patients (Rosiglitazone/Control)	Weight, %*	OR† (95% CI)
1:1 (31)	4870/4857	27.4	1.43 (0.84-2.44)
2:1 (17)	4983/2469	21.0	1.16 (0.44-3.01)
3:1 (2)	1566/501	5.8	1.60 (0.08-33.4)
4:1 (3)	1779/439	6.2	0.99 (0.74-8.85)
DREAM trial	2635/2634	14.8	1.67 (0.74-3.82)
ADOPT	1456/2895	12.2	1.32 (0.81-2.15)
RECORD trial	2220/2227	12.5	1.15 (0.80-1.66)
Overall	19509/16022	100	1.28 (1.01-1.62)
Overall (without RECORD trial)	17289/13795	87.5	1.38 (1.02-1.87)
Risk for Cardiovascular Mortality			
Randomization Ratio (No. of Studies)	No. of Patients (Rosiglitazone/Control)	Weight, %*	OR† (95% CI)
1:1 (31)	4870/4857	27.4	1.46 (0.72-2.96)
2:1 (17)	4983/2469	21.0	4.47 (0.56-35.27)
3:1 (2)	1566/501	5.8	1.60 (0.08-33.4)
4:1 (3)	1779/439	6.2	0.74 (0.03-16.2)
DREAM trial	2635/2634	14.8	1.20 (0.52-2.78)
ADOPT	1456/2895	12.2	0.60 (0.15-4.10)
RECORD trial	2220/2227	12.5	0.84 (0.60-1.20)
Overall	19509/16022	100	0.99 (0.75-1.32)
Overall (without RECORD trial)	17289/13795	87.5	1.36 (0.84-2.21)

0.1 1.0 10

Figure 3. Alternative analysis of risk for myocardial infarction and cardiovascular mortality, including studies with no events. ADOPT indicates A Diabetes Outcome Progression Trial[10]; CI, confidence interval;