

Effect of rosiglitazone on coronary events in the RECORD study

Discussant

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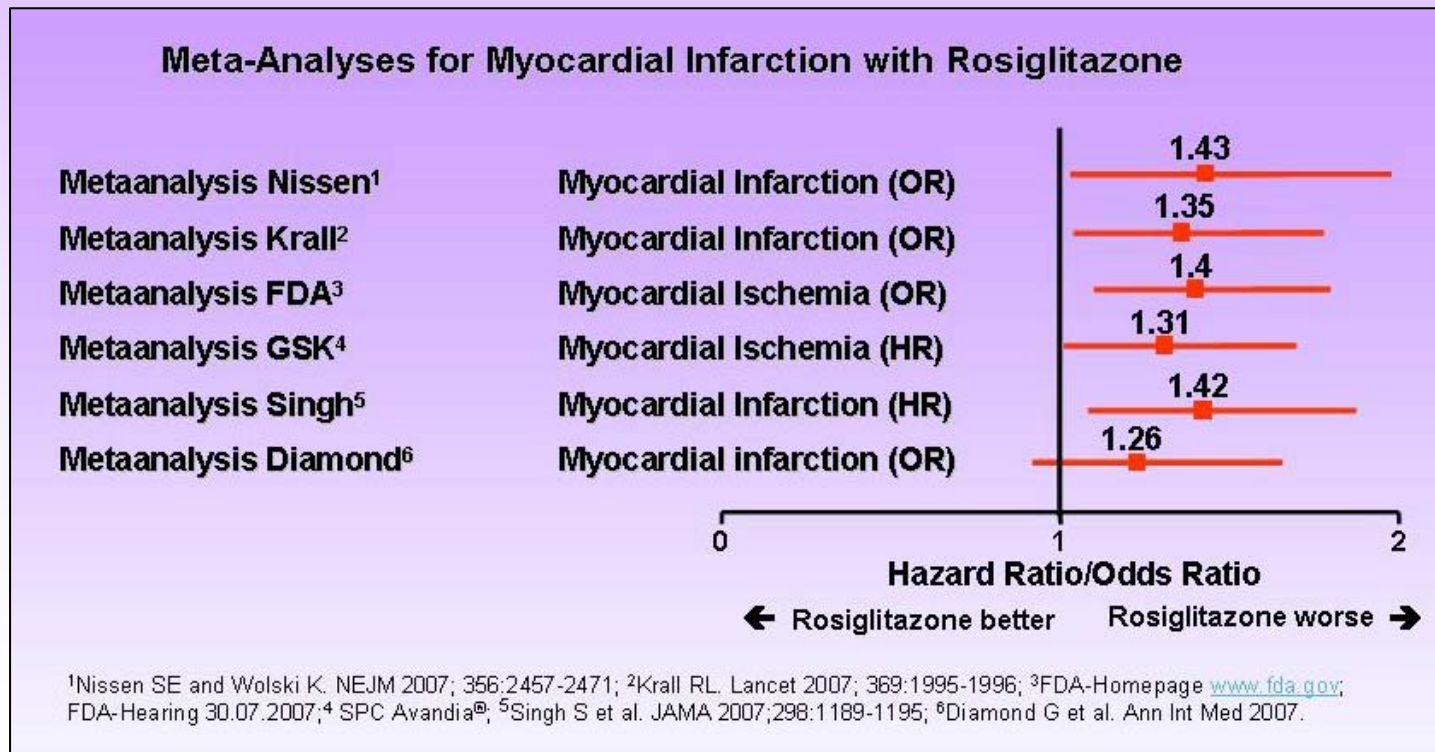
France

Dualities of interest : BC has received fees for consultancy, speaking, travel or accommodation from Takeda, GlaxoSmithKline, Merck Sharpe & Dohme, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Novo Nordisk, Roche, Sanofi -Aventis, Novartis.

Why RECORD is an important study

Within the general uncertainty regarding whether currently available glucose-lowering medications can reduce the increased risk of CVD,

for rosiglitazone (a PPAR γ agonist), various combined analyses of several studies, not designed to evaluate CV events, suggested that rosiglitazone might *increase (by 30 - 40%) myocardial ischaemia* and perhaps CV death, which has raised considerable uncertainty about the effects of rosiglitazone on cardiovascular disease.



Why RECORD is an important study

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

N Engl J Med 2007;356:2457

CONCLUSIONS

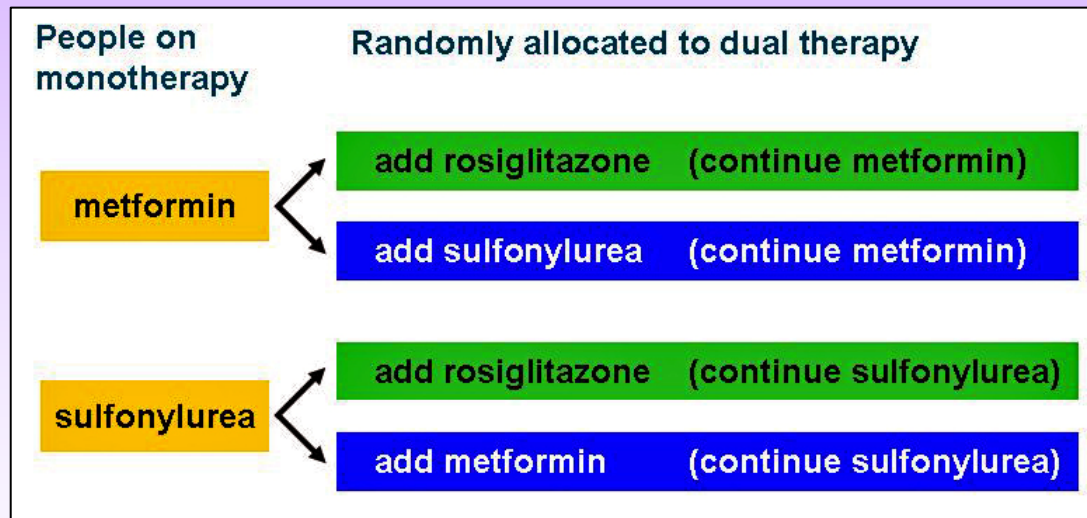
Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance.

Such meta-analyses may raise legitimate concerns, but have many flaws/limitations

The RECORD study is a large (4447 patients with type 2 diabetes) CV clinical trial, specifically designed to assess the effect of rosiglitazone on cardiovascular outcomes.

What is the RECORD study

The RECORD study design is a pragmatic design approach comparing a *rosiglitazone-based regimen* to the traditional and most commonly used regimen



RECORD compares:

- ❖ **rosiglitazone in combination with metformin or sulfonylurea**
with
- ❖ **a combination of metformin and a sulfonylurea**

Is the comparator appropriate?

RECORD compares (randomized, open label study) :

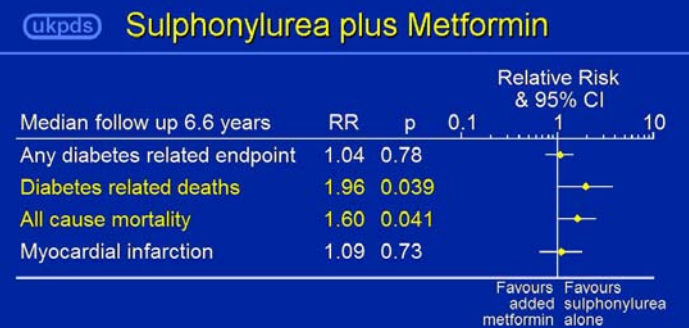
- ❖ rosiglitazone in combination with metformin or sulfonylurea
with
- ❖ a combination of metformin and a sulfonylurea

This metformin + sulfonylurea combination is the usually recommended combination (ADA/EASD statement 2009) but there is uncertainty about its CV benefits/safety.

Is the Combination of Sulfonylureas and Metformin Associated With an Increased Risk of Cardiovascular Disease or All-Cause Mortality?

A meta-analysis of observational studies

Diabetes Care 31:1672–1678, 2008



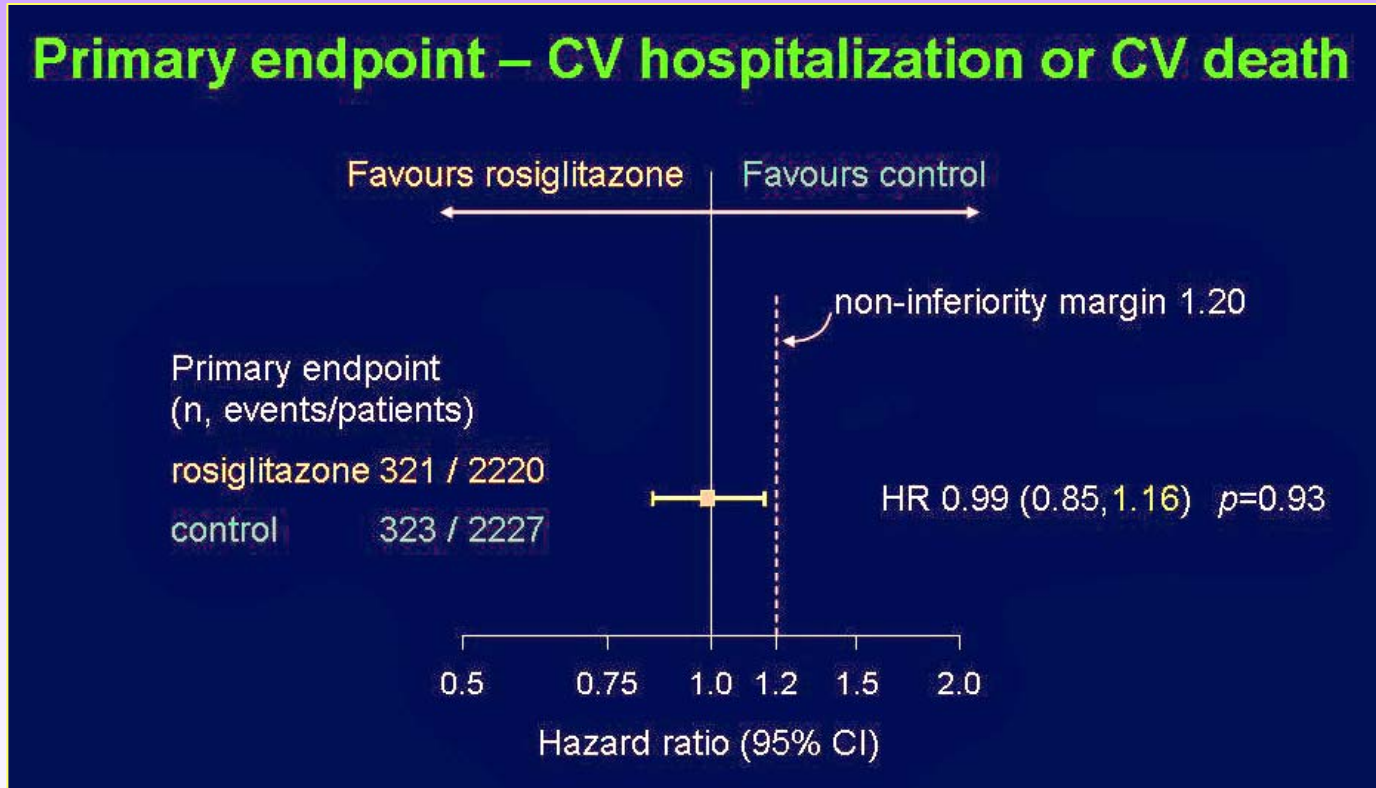
Observational studies about the sulfonylurea + metformin combination and risk of CVD have reported conflicting results: some studies have reported an increase in the risk, while others have reported a decrease or no association.

It is generally assumed it is neutral.

- ❖ **Yes** : from a pragmatic clinical point of view
- ❖ **±** : from an evidence-based point of view

What RECORD has shown : key points

Primary endpoint non-inferiority criterion satisfied

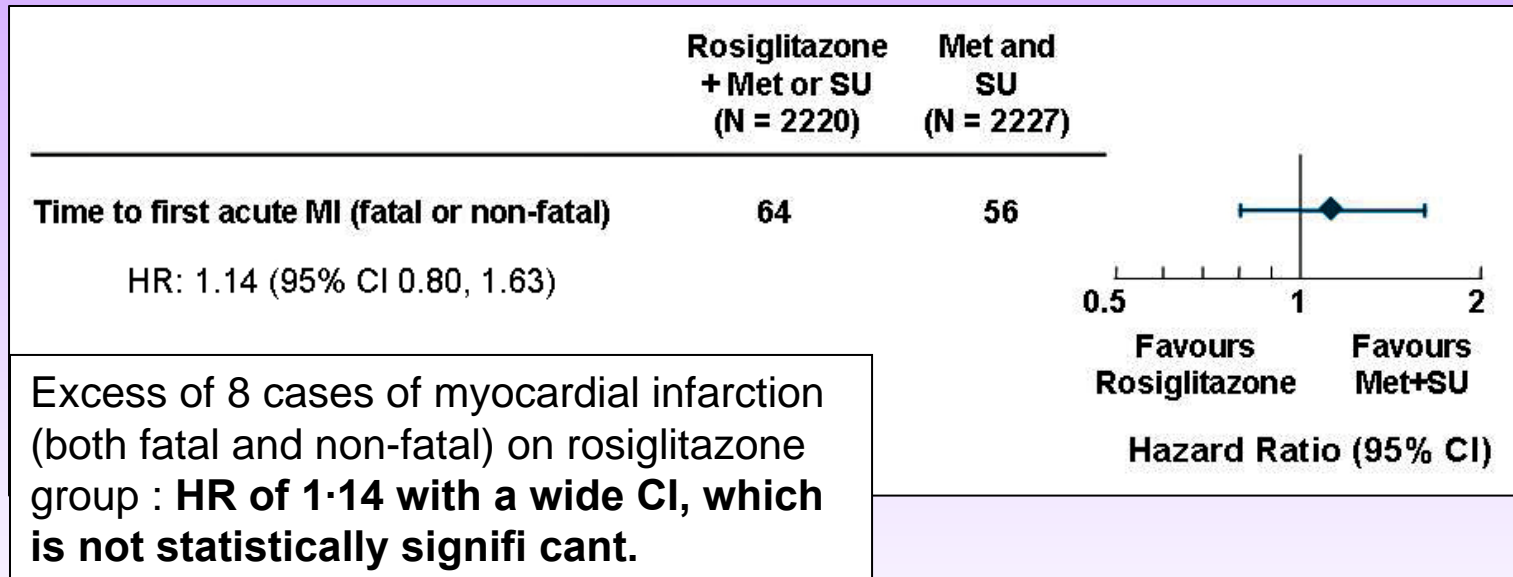


Addition of **rosiglitazone** to metformin or sulfonylurea **does not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs** (metformin/sulfonylurea in dual combination therapy).

What RECORD has shown : key points

Secondary endpoints :

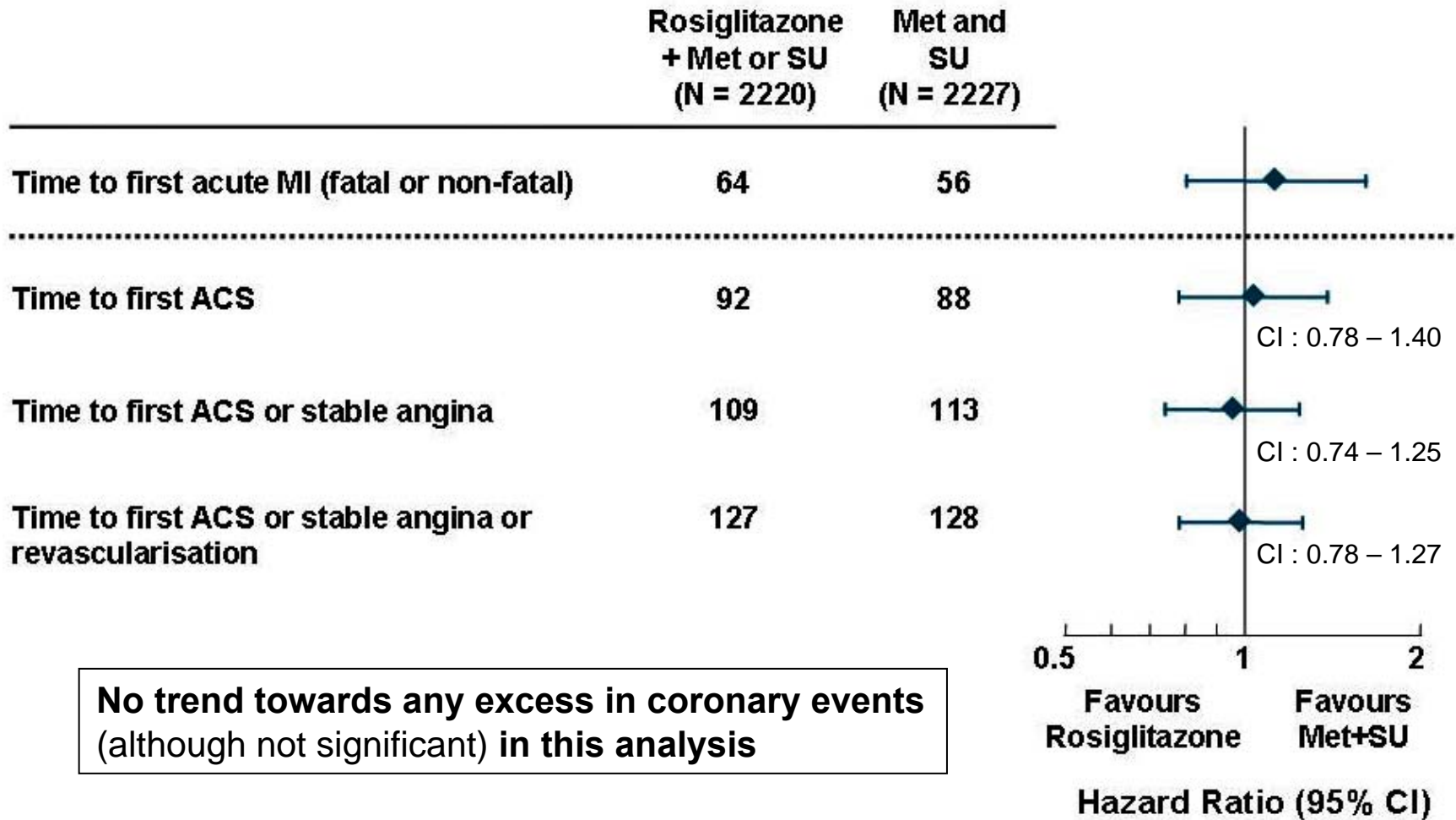
effect on myocardial infarction inconclusive



The study had limited statistical power for individual components of the primary endpoint, including MI, and was not intended to answer this question.

Furthermore, the overall cardiovascular event rate was lower than anticipated, which enhances this statistical limitation.

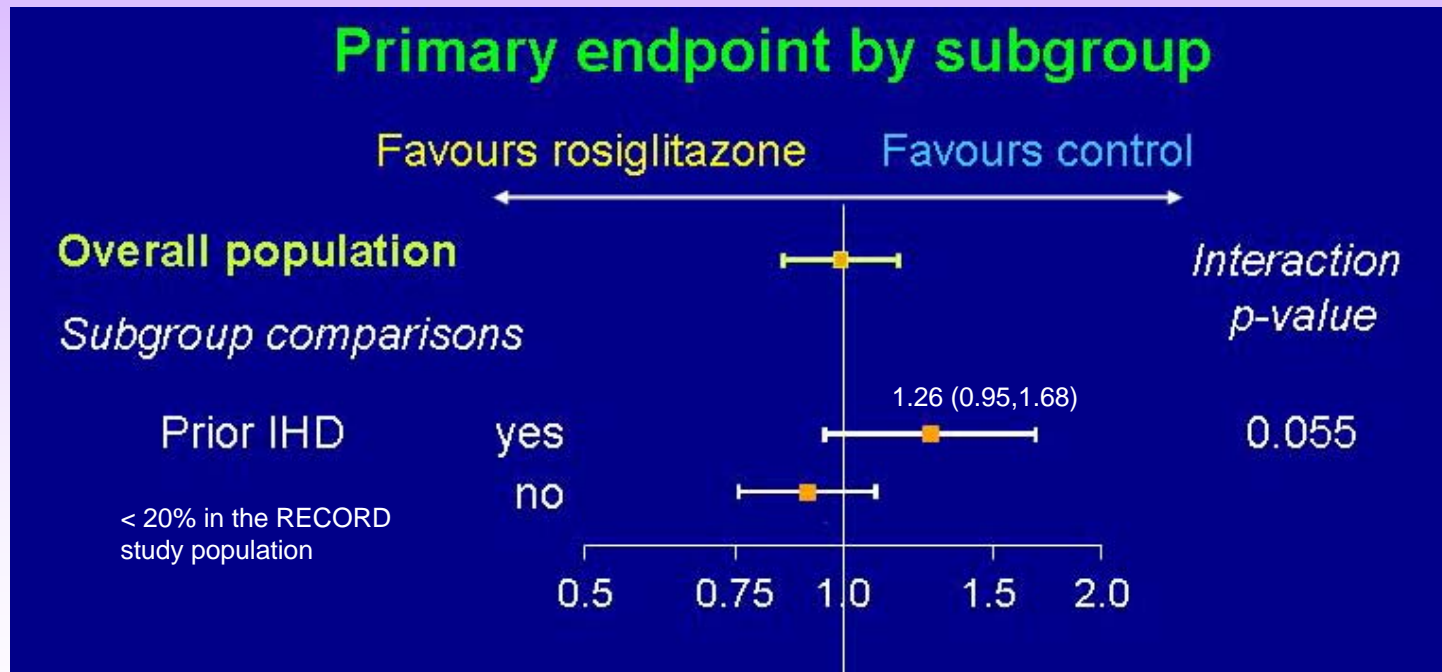
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Question raised by the “primary” study results :

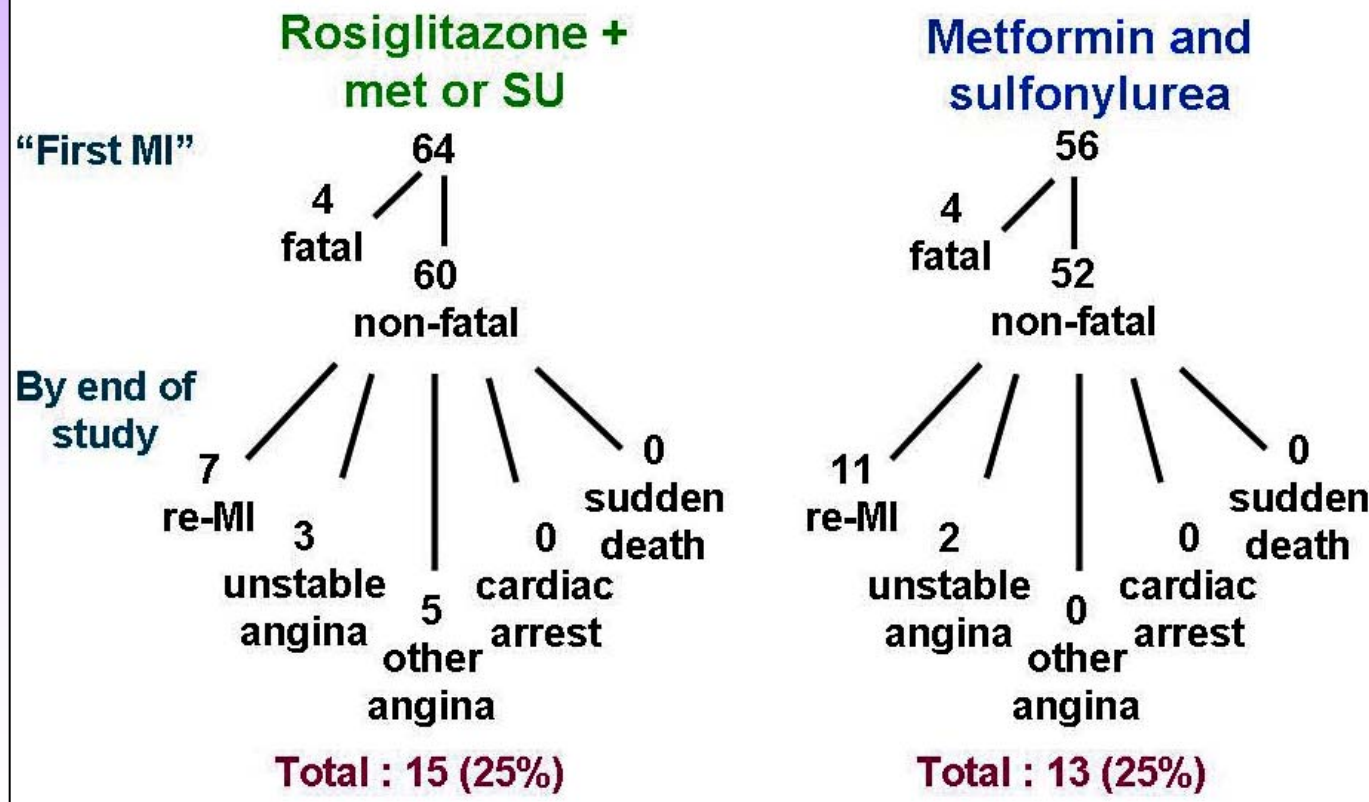
Should rosiglitazone be avoided in people with angina or a previous heart attack?



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Should rosiglitazone be avoided in people with angina or a previous heart attack?

Outcomes after "first" acute MI



No excess in recurrent coronary events after a 1st MI

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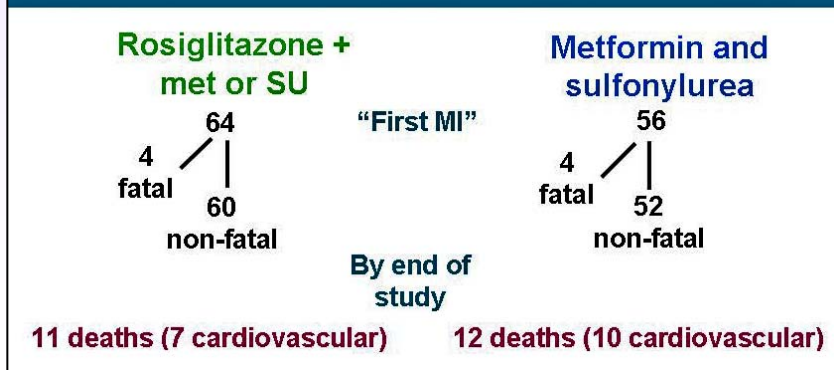
If MI is increased with rosiglitazone (and it cannot be ruled out), what effect does that have on death?

	Rosiglitazone+ Met or SU (n=2220) Patients	Metformin and sulfonylurea (n=2227) Patients
Deaths		
• Acute MI	7	10
• Sudden	8	12

excess fatal MI (n) –3

excess total CV deaths (n) -7

Outcomes after “first” acute MI



MI may be increased, or may not, on rosiglitazone, but it is not causing excess death

In summary

This current post hoc analysis of coronary events identified in RECORD tends to confirm and reinforce the conclusions of the main study results

1. Good news :

- ❖ Nissen's paper and subsequent meta-analyses were wrong : rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality, compared with standard glucose-lowering drugs.**
- ❖ If the data remain inconclusive on risk of myocardial infarction, this risk, if it exists, is low and does not increase the fatality rate.**

2. Disappointing news :

If rosiglitazone is not bad, it is not better than standard treatment, contrary to the expectations raised by the pre-clinical and surrogate end-points studies.