Review: Rosiglitazone increases risk for MI but does not differ from other drugs for CV death in type 2 diabetes

Nissen SE, Wolski K. **Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes.** N Engl J Med. 2007;356:2457-71.

Clinical impact ratings: GIM/FP/GP ★★★★★★★ Cardiology ★★★★★★☆ Endocrinology ★★★★★☆☆

QUESTION

In patients with type 2 diabetes, how does rosiglitazone (RGZ) compare with placebo or other drugs for cardiovascular (CV) outcomes?

METHODS

Data sources: U.S. Food and Drug Administration (FDA) Web site; clinical trial registry of the drug manufacturer; and 2 large, recently published trials (Diabetes REduction Assessment with ramipril and rosiglitazone Medication [DREAM] trial and A Diabetes Outcome Prevention Trial [ADOPT]).

Study selection and assessment: Randomized controlled trials (RCTs) that compared RGZ with placebo or other drugs (control) for > 24 weeks and reported myocardial infarction (MI) or CV death as outcomes. 42 RCTs (n = 27 847, mean age 56 y) met the selection criteria.

Outcomes: MI and CV death.

MAIN RESULTS

Meta-analysis showed that RGZ increased risk for MI more than placebo or other drugs, but groups did not differ for CV death (Table).

CONCLUSION

Rosiglitazone increases risk for myocardial infarction and cardiovascular death in patients with type 2 diabetes.

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For correspondence: Dr. S.E. Nissen, Cleveland Clinic, Cleveland, OH, USA. E-mail nissens@ccf.org.

Rosiglitazone vs placebo or other drugs (control) in type 2 diabetes*

Outcomes	Weighted event rates		RRI (95% CI)	NNH (CI)
	Rosiglitazone	Control		
Myocardial infarction	0.88%	0.62%	43% (3 to 97)	380 (167 to 5422)
Cardiovascular death	0.38%	0.23%	64% (–2 to 173)	Not significant

*Abbreviations defined in Glossary. Weighted event rates, RRI, NNH, and CI calculated from control event rates and odds ratios in article using a fixed-effects model.

COMMENTARY

Recent controversy over the CV safety of RGZ was sparked by the online publication of the meta-analysis by Nissen and Wolski, which received considerable attention in the lay press and led to a congressional hearing and calls to reform drug regulation. It also spurred Home and colleagues to publish the interim analysis of the RECORD trial. Both studies have substantial limitations, so no simple answers are forthcoming.

The meta-analysis by Nissen and Wolski was based on a large number of low-quality studies and used flawed methods. Almost all studies analyzed were small, short-duration RCTs that were not designed to assess CV outcomes and therefore did not prospectively ascertain or blindly adjudicate cardiac events. Most of these studies are unpublished, so the data (which were not peer-reviewed) were abstracted from documents on the Internet.

The analysis of these low-quality data had numerous methodological flaws. First, 6 of 48 eligible studies were excluded because they reported no cardiac deaths or MIs, which biases estimated CV risk upwards. Second, because cardiac events were rare, most RCTs reported zero outcomes in 1 or both groups, which may lead to inaccurate risk estimates with the meta-analysis method used. Third, a fixed-effects model was used despite obvious differences between RCTs, which exaggerate statistical significance. Finally, a separate FDA meta-analysis found only a nonsignificant trend toward more CV deaths, MIs, and strokes (odds ratio 1.2, 95% CI 0.7 to 1.8) (1). The low-quality data and technical flaws make the meta-analysis by Nissen and Wolski far from conclusive—at best, it is a hypothesis-generating study.

Even if the review by Nissen and Wolski had stronger methods, it would need to be interpreted cautiously because meta-analyses based on many small studies may not predict the results of subsequent definitive trials (2). In general, replicated results from well-designed, adequately powered RCTs provide the most reliable guide to clinical practice. Unfortunately, there are few such results available to assess the effect of RGZ on cardiac death and MI.

The DREAM trial (3), 1 of the studies included in the meta-analysis, randomized 5269 patients without CV disease to RGZ or placebo and found a nonsignificant trend toward more CV events with RGZ (hazard ratio 1.37, CI 0.97 to 1.94). The RECORD trial by Home and colleagues used CV events as the primary outcome and found the risk for MI to be slightly higher in the RGZ group (hazard ratio 1.23, CI 0.81 to 1.86), whereas risk for CV death was slightly lower (hazard ratio 0.80, CI 0.52 to 1.24); neither result was statistically significant, but the interim analysis had low statistical power.

The results on the cardiac risk associated with RGZ are suggestive but not definitive—more data from other large, well-conducted RCTs are needed. The ACCORD trial of > 10 000 patients with diabetes and high CV risk and the BARI-2D trial of > 2300 patients with diabetes and coronary disease are ongoing, but results will not be available for several years. Importantly, the data and safety monitoring boards of ACCORD and BARI-2D examined their interim outcomes in light of these 2 publications about RGZ and voted to continue their trials without modification; because patient safety is their paramount responsibility, presumably these data and safety monitoring boards did not detect significant excess CV risk.

The possible adverse effects of RGZ on cardiac death and MI should be distinguished from its established effect on exacerbation of HF, which is because of fluid retention and is reversible on discontinuation of the drug.

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