

# Rosiglitazone increased heart failure but did not differ from metformin plus sulfonylurea for other CV outcomes at interim analysis

Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. *N Engl J Med*. 2007;357:28-38.

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

## QUESTION

In patients with type 2 diabetes, is rosiglitazone (RGZ) as add-on therapy noninferior to metformin (MFN) plus sulfonylurea (SFU) for cardiovascular (CV) outcomes?

## METHODS

**Design:** Randomized controlled trial (RCT) (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes [RECORD] trial).

**Allocation:** Unclear allocation concealment.\*

**Blinding:** Blinded (outcome assessors).\*

**Follow-up period:** Mean 3.75 years.

**Setting:** 338 centers in 23 countries in Europe and Australasia.

**Patients:** 4458 patients 40 to 75 years of age (mean age 58 y, 52% men, 99% white, based on 4447 patients) who had type 2 diabetes, body mass index > 25 kg/m<sup>2</sup>, and hemoglobin (Hb) A<sub>1c</sub> level > 7% to 9% while taking maximum doses of MFN or SFU. Exclusion criteria were use of other glucose-lowering drugs, hospitalization for major CV events in the past 3 months, planned CV intervention, heart failure (HF), hepatic disease, renal impairment, and uncontrolled hypertension.

**Intervention:** RGZ, 4 mg/d, plus MFN or SFU, with starting doses determined by local practices (*n* = 2220); or MFN plus SFU (control) (*n* = 2227). After 8 weeks, if HbA<sub>1c</sub> levels were > 7%, patients were given maximum daily drug doses (RGZ, 8 mg/d; MFN, 2550 mg/d; glyburide, 15 mg/d; gliclazide, 240 mg/d; and glimepiride, 4 mg/d). If HbA<sub>1c</sub> levels were > 8.5% with maximum doses, the RGZ group received a third agent and the control group started insulin therapy (IT). In the RGZ group, if HbA<sub>1c</sub> levels were

> 8.5% with triple therapy, RGZ therapy was replaced with IT.

**Outcomes:** Composite endpoint of hospitalization or death from CV causes. Secondary outcomes were a composite endpoint of CV death, myocardial infarction (MI), or stroke, and individual outcomes of CV death, all-cause death, MI, and congestive HF. The study needed 4000 patients followed for a median 6 years to have 99% power to detect non-inferiority (upper limit of the 2-sided 95% CI for the hazard ratio of the primary endpoint < 1.2 at study completion) when the control group had an annual event rate of 11% (3% CV death and 8% hospitalizations).

**Patient follow-up:** 90% (intention-to-treat analysis).

## MAIN RESULTS

The interim analysis at a mean 3.75 years showed that the RGZ and control groups

did not differ for the composite endpoint of hospitalization or death from CV causes (Table). The RGZ group had a higher incidence of congestive HF than did the control group, but groups did not differ for other secondary outcomes (Table).

## CONCLUSION

At interim analysis (mean 3.75 y), rosiglitazone as add-on therapy increased risk for heart failure but did not differ from metformin plus sulfonylurea for other cardiovascular outcomes in patients with type 2 diabetes.

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\*See Glossary.

## Rosiglitazone (RGZ) as add-on therapy to metformin or sulfonylurea vs metformin plus sulfonylurea (control) in type 2 diabetes at interim analysis (mean 3.75 y)†

Outcomes	RGZ	Control	RRI (95% CI)	NNH (CI)
Composite endpoint of death or hospitalization from CV causes	9.8%	9.1%	7.6% (-10 to 29)	Not significant
Acute MI‡	1.9%	1.7%	16% (-25 to 80)	Not significant
Congestive heart failure‡	1.7%	0.8%	123% (27 to 293)	107 (45 to 488)
			RRR (CI)	NNT (CI)
Composite endpoint of CV death, MI, or stroke	4.2%	4.3%	2.9% (-28 to 27)	Not significant
CV death	1.3%	1.6%	17% (-36 to 49)	Not significant
All-cause death	3.3%	3.6%	6.9% (-26 to 33)	Not significant

†CV = cardiovascular; MI = myocardial infarction; other abbreviations defined in Glossary. RRI, RRR, NNH, NNT, and CI calculated from control event rates and hazard ratios in article based on adjudicated events.

‡Included hospitalizations and deaths.

## COMMENTARY (continued from page 66)

So, what can we conclude? Clearly, RGZ can worsen HF, but available evidence is not yet definitive about risk for cardiac death and MI. In light of safety concerns, it is reasonable to consider alternative agents until this question can be better resolved by ongoing RCTs.

The RGZ controversy underscores the limitations of using surrogate outcomes. Studies of diabetes therapy use glucose control as the endpoint, but better glucose control does not translate into reduced macrovascular events. Because CV disease is the major cause of death in diabetes, the endpoint of RCTs for diabetes drugs should include CV outcomes in addition to glucose control. Similarly, developers of clinical guidelines and performance measures should weigh the risk for increasing CV events when setting benchmarks for tighter glucose control.

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## References

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