

Rosiglitazone reduced type 2 diabetes but increased heart failure in patients with impaired glycemic control

Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet*. 2006;368:1096-105.

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

QUESTION

In patients with impaired fasting glucose or impaired glucose tolerance, does rosiglitazone reduce the incidence of type 2 diabetes mellitus?

METHODS

Design: Randomized placebo-controlled trial (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication [DREAM]).

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, data collectors, and outcome assessors).*

Follow-up period: Median 3.0 years (range 2.5 to 4.7 y).

Setting: 191 sites in 21 countries.

Patients: 5269 patients (mean age 55 y, 59% women) who had impaired fasting glucose (14%), impaired glucose tolerance (57%), or both (29%). Exclusion criteria were history of diabetes (except gestational diabetes), cardiovascular (CV) disease, or intolerance to angiotensin-converting enzyme inhibitors or thiazolidinediones (TZDs).

Intervention: Rosiglitazone, 4 mg once daily for 2 months and then 8 mg once daily ($n = 2635$), or placebo ($n = 2634$). At baseline and follow-up visits, all patients received advice from research staff about healthy diets and lifestyle habits to reduce diabetes.

Outcomes: A composite outcome of death from any cause or diagnosis of diabetes.

Secondary outcomes included regression to normal fasting and 2-hour postload glucose levels (fasting plasma glucose level < 6.1 mmol/L and 2-h plasma glucose level < 7.8 mmol/L), a composite of CV events (myocardial infarction, stroke, CV death, revascularization procedures, heart failure, new angina with evidence of ischemia, or ventricular arrhythmia needing resuscitation), individual components of the CV composite endpoint, and renal events and a composite cardiorenal endpoint.

Patient follow-up: 98% (intention-to-treat analysis).

MAIN RESULTS

Fewer patients who received rosiglitazone had the composite outcome of death or diabetes than did patients who received placebo (Table), a result of the large difference in incidence of diabetes (hazard ratio [HR] 0.38, 95% CI 0.33 to 0.44). The groups did not differ for deaths (HR 0.91, CI 0.55 to 1.49).

The effect of rosiglitazone on the primary outcome was similar in patients with impaired fasting glucose and impaired glucose tolerance. More patients who received rosiglitazone regressed to normoglycemia than did those who received placebo (51% vs 30%, HR 1.71, CI 1.57 to 1.87). Groups did not differ for any other secondary outcomes except heart failure, which was increased with rosiglitazone (Table).

CONCLUSION

In patients with impaired fasting glucose or impaired glucose tolerance, rosiglitazone reduced the incidence of type 2 diabetes but increased the incidence of heart failure.

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*See Glossary.

Rosiglitazone vs placebo to reduce death or diabetes at median 3 years†

Outcomes	Rosiglitazone	Placebo	RRR (95% CI)	NNT (CI)
Composite outcome‡	11.6%	26%	56% (50 to 62)	7 (7 to 8)
			RI (CI)	NNH (CI)
Heart failure	0.5%	0.1%	601% (60 to 2944)	167 (34 (1668))

†Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from hazard ratios in article.

‡Death from any cause (1.1% vs 1.3%) or diabetes (10.6% vs 25%).

COMMENTARY

The DREAM trial showed that rosiglitazone reduced the risk for being diagnosed with diabetes more than did placebo. The 60% reduction is of a magnitude similar to that achieved by intensive lifestyle changes (1) but greater than reductions reported with metformin (1) and acarbose (2). However, several unanswered questions remain: Should clinicians and patients be enthusiastic about a pill that prevents diabetes? Is delaying the diagnosis of diabetes enough of a positive outcome in itself to begin prescribing a medication, or should clinicians demand evidence that earlier introduction (i.e., before the diagnosis) of diabetes drugs improves health outcomes, especially CV events?

This study could not precisely measure the effect of the intervention on CV events, and considerable debate exists about the efficacy of TZDs in preventing macrovascular complications, as seen in the PROactive trial (3). Given the uncertainty about the benefits, side effects become critical. Both DREAM and PROactive found that TZDs increased risk for heart failure, and of the DREAM trial participants assigned to rosiglitazone, 4.8% stopped the medication because of development of edema compared with 1.6% of placebo recipients.

If diabetes was diagnosed shortly after rosiglitazone washout (cur-

rently studied in the ongoing DREAM discontinuation trial), rosiglitazone would have delayed the diagnosis of diabetes by lowering glucose levels but not by "true" prevention. Even if "true" prevention is found, however, the potential benefits will need to outweigh the clear downsides (e.g., pill taking, costs, edema, and heart failure) to consider prevention of diabetes with TZDs.

Until evidence of efficacy of early drug use to prevent premature morbidity and mortality associated with the diagnosis of diabetes accrues, patients and clinicians should continue to focus on lifestyle interventions, including dietary and exercise regimens.

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References

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