

# Pioglitazone did not reduce a composite endpoint of macrovascular complications and increased risk for heart failure in type 2 diabetes with macrovascular disease

Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAZone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366:1279-89.

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

## QUESTION

In patients with type 2 diabetes and evidence of macrovascular disease, does pioglitazone reduce all-cause mortality and macrovascular complications?

## METHODS

**Design:** Randomized placebo-controlled trial (PROactive study).

**Allocation:** Concealed.\*

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

**Follow-up period:** Mean 34.5 months.

**Setting:** 321 centers (including communities and hospitals) in 19 European countries.

**Patients:** 5238 patients 35 to 75 years of age (mean age 62 y, 66% men) who had type 2 diabetes, hemoglobin A<sub>1c</sub> level  $\geq$  6.5%, and evidence of extensive macrovascular disease defined by  $\geq$  1 of the following criteria: myocardial infarction (MI), stroke, percutaneous coronary intervention, or coronary artery bypass surgery  $\geq$  6 months previously, acute coronary syndrome  $\geq$  3 months previously, or objective evidence for coronary artery disease or obstructive arterial disease in the leg. Exclusion criteria were type 1 diabetes; taking only insulin; planned coronary or peripheral revascularization;  $\geq$  class II New York Heart Association heart failure; ischemic ulcers, gangrene, or pain at rest in the leg; hemodialysis; or alanine aminotransferase level  $\geq$  2.5 times the upper limit of normal.

**Intervention:** Oral pioglitazone, 15 mg/d for the first month, 30 mg/d for the second month, then 45 mg/d ( $n = 2605$ ), or placebo

( $n = 2633$ ). All patients took their regular glucose-lowering drugs and other medications.

**Outcomes:** Composite endpoint of all-cause mortality, nonfatal MI (including silent MI), stroke, acute coronary syndrome, endovascular or surgical intervention on the coronary or leg arteries, and amputation above the ankle. The preplanned secondary outcomes were the components of the primary endpoint and cardiovascular death. A “main secondary composite” endpoint (not described in the trial registration or methods paper [but stated by authors to have been described in the analysis plan before unblinding]) was defined as all-cause mortality, nonfatal MI, and stroke. “Serious adverse events” (components not specified) and heart failure were also reported. **Patient follow-up:** 99.96% (intention-to-treat analysis).

## MAIN RESULTS

Pioglitazone and placebo groups did not differ for the primary (Table) or the preplanned

secondary endpoints. Pioglitazone-group patients had a lower incidence of the “main secondary” composite endpoint (Table). Groups did not differ for “serious adverse events,” but pioglitazone-group patients had a higher incidence of heart failure (Table).

## CONCLUSIONS

In patients with type 2 diabetes and evidence of macrovascular disease, pioglitazone did not reduce the primary or preplanned secondary composite endpoints. Pioglitazone use reduced a “main secondary” composite endpoint of all-cause mortality, nonfatal MI, and stroke, but increased the incidence of heart failure.

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\*See Glossary.

## Pioglitazone vs placebo for type 2 diabetes and macrovascular events†

| Outcomes at mean 34.5 mo             | Pioglitazone | Placebo | RRR (95% CI)       | NNT (CI)        |
|--------------------------------------|--------------|---------|--------------------|-----------------|
| Primary composite endpoint‡          | 20%          | 22%     | 9.2% (−0.9 to 18)  | Not significant |
| “Main secondary” composite endpoint§ | 12%          | 14%     | 15% (1.9 to 26)    | 49 (27 to 407)  |
| Any serious adverse event            | 46%          | 48%     | 4.6% (−1.1 to 9.9) | Not significant |
|                                      |              |         | RRI (CI)           | NNH (CI)        |
| Heart failure                        | 11%          | 8%      | 40% (22 to 60)     | 23 (16 to 38)   |

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

‡All-cause mortality (4.2% vs 4.6%), nonfatal myocardial infarction (MI) (4.0% vs 4.5%), stroke (2.9% vs 3.6%), acute coronary syndrome (1.6% vs 2.4%), endovascular or surgical intervention on the coronary or leg arteries (6.6% vs 6.0%), and amputation above the ankle (0.3% vs 0.6%). The effect on each of these components was not significant.

§All-cause mortality (5.0% vs 5.4%), nonfatal MI (3.5% vs 4.4%), and stroke (3.1% vs 3.8%).

## COMMENTARY

Clinicians caring for patients with type 2 diabetes either have been enamored with the putative beneficial vascular effects of glitazones, or have considered them expensive, marginally effective glycemic agents that promote weight gain and fluid retention. Should the results of the PROactive trial be considered a triumph for the therapeutic acumen of the former group and another nail in the coffin of atherosclerosis? No. The findings of benefit are far from compelling. Both the primary endpoint and preplanned secondary endpoints were negative.

Furthermore, even taking the most optimistic spin of the authors for the “main secondary” composite endpoint not mentioned in the study design paper (1), the pioglitazone group had approximately 2 cases of heart failure (and 4 cases of edema) for every cardiovascular event prevented and gained an average weight of 4 kg.

The interpretation of the effect of pioglitazone therapy is further complicated by the 0.6% difference in HbA<sub>1c</sub> between the 2 groups. Although glycemic control generally has not been shown to reduce macrovascular events, it is clear that the placebo group did not have adequate glycemic therapy to match that of the active treatment group.

I see this study primarily as a confirmation of concerns about fluid retention and weight gain with glitazones, and not about clear evidence of cardiovascular event reduction (which will have to wait for results from ongoing glitazone trials).

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## Reference

- Charbonnel B, Dormandy J, Erdmann E, et al. *Diabetes Care*. 2004; 27:1647-53.