Review: Pioglitazone does not reduce risk for mortality or cardiovascular events in type 2 diabetes

Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. **Pioglitazone for type 2 diabetes mellitus.** Cochrane Database Syst Rev. 2006;(4):CD006060.

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

QUESTION

In patients with type 2 diabetes, does pioglitazone reduce cardiovascular events, other adverse events, and mortality or improve health-related quality of life?

METHODS

Data sources: Cochrane Library (issue 3, 2006), MEDLINE, EMBASE/Excerpta Medica (to August 2006), Controlled Clinical Trials, and reference lists.

Study selection and assessment: Randomized controlled trials (RCTs) ≥ 24 weeks in duration that evaluated pioglitazone in adults with type 2 diabetes. 22 RCTs (n = 12 466, mean age range 54 to 64 y) met the selection criteria: pioglitazone vs placebo (4 RCTs) or another oral antidiabetic medication (13 RCTs), or pioglitazone combined with other oral medications or insulin vs another combination of oral medications or insulin (7 RCTs). Assessment of methodological quality included randomization method, allocation concealment, blinding, intention-to-treat analysis, and dropouts.

Outcomes: Mortality, morbidity, adverse events, health-related quality of life, costs, and metabolic control.

MAIN RESULTS

The duration of follow-up was 6 to 12 months in all but 1 RCT. Mortality and major morbidity events were reported by only 1 RCT that compared pioglitazone plus other glucose-lowering drugs with placebo plus other glucose-lowering drugs; mean follow-up was 35 months. Groups did not differ for any individual outcome (Table). Greater increase in weight or body mass index with pioglitazone was reported by 19 of the 22 RCTs. Greater decrease in hemoglobin levels with pioglitazone was reported by all 6 RCTs that evaluated this outcome, including a dose-related decrease in 1 trial that evaluated several doses. Edema occurred more frequently with pioglitazone (Table). No RCT reported on costs or health-related quality of life. Pioglitazone treatment resulted in similar reductions in glycosylated hemoglobin A_{1c} compared with other oral antidiabetic medications.

CONCLUSIONS

Based on 1 randomized trial, pioglitazone does not reduce risk for mortality or cardiovascular events in patients with type 2 diabetes. Some evidence exists that pioglitazone increases risk for such adverse events as weight gain, decrease in hemoglobin level, and edema.

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Pioglitazone vs placebo, other oral medications, or insulin in type 2 diabetes*

Outcomes	Number of trials (*n*)	Weighted event rates		RRR (95% CI)	NNT
		Pioglitazone	Control		
Death	1 (5238)	6.8%	7.1%	3.9% (–17 to 21)	Not significant
Myocardial infarction	1 (5238)	4.6%	5.5%	17% (–6 to 34)	Not significant
Stroke	1 (5238)	3.3%	4.1%	19% (–7 to 39)	Not significant
				RRI (CI)	NNH (CI)
Edema	18 (11 565)	21%	7.4%	186% (114 to 218)	8 (7 to 12)

*Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article using a random-effects model.

COMMENTARY

When does a meta-analysis not add much to the knowledge base about a particular health-related issue? When only 1 of the 22 included trials examined the targeted question: in this case, does pioglitazone affect risk for cardiovascular disease events? That 1 study, PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) (1), lasted 35 months and included patients with diabetes and macrovascular disease at baseline. Although pioglitazone did not lower the risk for the primary endpoints, it did result in a statistically significant, albeit small, 2% absolute risk reduction in a secondary composite endpoint of myocardial infarction, stroke, and all-cause mortality.

Cardiologists have been forced to live with such bewildering findings, with some outcomes significant and others not, as prevention trials have become larger and more complex and additional therapies have added seemingly less and less to proven treatments. Thus, we await confirmation from other clinical trials that fortunately are under way. Trials using surrogate outcomes will compare the effects of pioglitazone with those of a sulfonylurea on carotid intima medial thickness and coronary atheroma volume measured by intravascular ultrasonography. One secondary cardiovascular disease prevention trial is comparing insulin sensitizers with insulin or sulfonylureas, or both, whereas another is comparing pioglitazone with sulfonylureas in patients with diabetes and coronary disease for the prevention of death or a second cardiovascular event.

The meta-analysis by Richter and colleagues confirmed that pioglitazone is as effective as other hypoglycemic therapies in maintaining glucose control, but at the cost of greater weight gain attributable at least in part to increased edema. In addition, PROactive showed an absolute increase of 2% in hospitalization for congestive heart failure with pioglitazone, although mortality from this condition was not increased.

Keep your ears tuned as the benefit–risk story plays out.

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Reference

1. **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.