Review: Thiazolidinediones increase congestive heart failure but not cardiovascular deaths in prediabetes or type 2 diabetes

Lago RM, Singh PP, Nesto RW. **Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials.** Lancet. 2007;370:1129-36.

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

QUESTION

In patients with prediabetes or type 2 diabetes, do thiazolidinediones (TZDs) increase the risk for congestive heart failure (CHF) and cardiovascular death?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, Database of Abstracts of Reviews of Effects, and Cochrane Library (1998 to March 2007); hand searches of professional association databases (European Society of Cardiology, American Heart Association, American College of Cardiology, and American Diabetes Association); and reference lists of relevant articles.

Study selection and assessment: English-language, randomized, double-blind, controlled trials (RCTs) of TZDs that reported risk estimates or frequency data for CHF and cardiovascular death. 7 RCTs (n = 20 191, mean age 59 y, 67% men) met the selection criteria: 5 used rosiglitazone (n = 14 491), and 2 used pioglitazone (n = 5700). Study quality assessment included evaluation of selection bias, detection bias, and attrition bias (loss to follow-up).

Outcomes: CHF (investigator-reported or adjudicated CHF requiring hospitalization) and cardiovascular death.

MAIN RESULTS

Meta-analysis of all 7 trials showed that TZDs increased rates of CHF more than placebo or alternative treatment at a mean follow-up of 29.7 months; the groups did not differ for cardiovascular death (Table). Results were consistent for trials of rosiglitazone or pioglitazone (Table).

CONCLUSION

In patients with prediabetes or type 2 diabetes, thiazolidinediones increase the risk for congestive heart failure but not cardiovascular death.

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Thiazolidinediones (TZDs) vs placebo or alternative treatment in patients with prediabetes or type 2 diabetes*

Outcomes at a mean 29.7 mo	Number of trials (n)	Treatment	Weighted event rates	RRI (95% CI)	NNH (CI)
CHF	7 (20 191)	TZDs	2.3% vs 1.3%	72% (21 to 142)	107 (55 to 367)
	5 (14 491)	Rosiglitazone	0.9% vs 0.4%	118% (44 to 232)	212 (108 to 569)
	2 (5700)	Pioglitazone	5.1% vs 3.9%	32% (4 to 68)	81 (38 to 642)
CV death	2 (5700)	Pioglitazone	0.5% vs 0.5%	1% (–49 to 101)	Not significant
				RRR (CI)	NNT
	7 (20 191)	TZDs	0.7% vs 0.7%	7% (–29 to 33)	Not significant
	5 (14 491)	Rosiglitazone	0.7% vs 0.8%	9% (–32 to 37)	Not significant

*CHF = congestive heart failure; CV = cardiovascular; other abbreviations defined in Glossary. RRI, RRR, NNH, NNT, and CI calculated from data in article based on a random-effects model.

COMMENTARY

The meta-analysis by Lago and colleagues is the latest to evaluate benefits and harms of TZDs. The results corroborate previous analyses (1, 2) and show that, as a class, TZDs cause or worsen heart failure. Although the absolute increase in heart failure seems small (number needed to harm = 107), many patients with dysglycemia have other risk factors for heart failure (in addition to diabetes), including older age, hypertension, and coronary or valvular heart disease.

The meta-analysis found no effect of TZDs on cardiovascular mortality; however, caution is advised in interpreting these results. Some limitations should be noted: the small number and short duration of included trials, low event rates, variable (or lack of) adjudication of predefined events, lack of individual patient-level data, and publication bias. Collectively, these limitations preclude quantification of precise event rates, and we must await results of event-driven studies, such as the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) trial.

Given that the treatment groups of most of the TZD trials had 0.5% to 1% absolute improvements in hemoglobin A_{1c} compared with controls, one wonders where all of the expected benefits have gone. Instead, there are adverse events, trends toward harms, and few clinical benefits. Treatments should not only improve glycemia but improve health by preventing macrovascular complications, bettering quality of life, and reducing mortality. Although TZDs lower hemoglobin A_{1c} levels, their clinical benefits have not been borne out. Other options for glucose lowering exist, and these are supported by long-term safety and clinical efficacy data (3). Until better evidence is available, the increased rates of heart failure suggest that TZDs be relegated to second- or third-line agents in those few patients with diabetes who are at low risk for cardiac events or heart failure.

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