

Review: Thiazolidinediones increase risk for heart failure in type 2 diabetes

Singh S, Loke YK, Furberg CD. **Thiazolidinediones and heart failure: A teleo-analysis.** *Diabetes Care.* 2007;30:2148-53.

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

QUESTION

In patients with type 2 diabetes, what is the risk for heart failure (HF) associated with thiazolidinediones (TZDs)?

METHODS

Data sources: MEDLINE (January 2003 to September 2006), EMBASE/Excerpta Medica, Google Scholar, Web of Knowledge, Canadian Drug Reaction Monitoring Program, bibliographies of relevant studies, and manufacturers for unpublished studies. **Study selection and assessment:** Randomized controlled trials (RCTs) in any language comparing TZDs (rosiglitazone [RGZ] or pioglitazone) with placebo for ≥ 6 months in patients with type 2 diabetes and HF; cohort or case-control studies comparing TZDs with other oral antidiabetic drugs (with or without insulin) for new-onset HF; and case reports or case series of all adverse drug reactions (HF and pulmonary edema) with TZDs. {Quality assessment of individual studies was based on the definition of HF

and ascertainment of HF outcomes.}* 3 RCTs ($n = 10\ 731$), 3 retrospective cohort studies ($n = 65\ 717$), 1 case-control study ($n = 1665$), and 214 case reports (median age 67 y, age range 31 to 88 y, based on 162 cases) met the selection criteria.

Outcomes: HF.

MAIN RESULTS

Meta-analysis showed that TZDs increased risk for HF compared with placebo or other drugs (Table). 42 (26%) of 162 case patients with HF were < 60 years of age. In 99 cases,

the median duration for onset of HF was 24 weeks (range 1 to 260 wk) after starting TZD therapy; high or low doses of TZDs did not differ for HF.

CONCLUSION

Thiazolidinediones increase risk for heart failure in patients with type 2 diabetes.

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*Information provided by author.

Thiazolidinediones (TZDs) vs placebo or other oral antidiabetic drugs for heart failure at 3 months to 3.6 year[†]

| Outcome | Number of studies (n) | Comparisons | Weighted event rates | RRI (95% CI) | NNH (CI) |
|---------------|-----------------------|---------------------|----------------------|-------------------|----------------|
| Heart failure | 3‡ (10 731) | TZDs vs placebo | 7.9% vs 3.9% | 101% (7.7 to 264) | 26 (10 to 335) |
| | 4§ (67 382) | TZDs vs other drugs | 11% vs 7.3% | 49% (30 to 70) | 29 (20 to 47) |

†Abbreviations defined in Glossary. RRI, NNH, and CI calculated from control event rates and odds ratios in article using a random-effects model.

‡Randomized controlled trials.

§3 retrospective cohort studies and 1 case-control study.

COMMENTARY

It is well accepted that treatment with TZDs is associated with HF, but the level of risk is uncertain. The meta-analysis by Singh and colleagues is useful for practicing health care professionals because the magnitude of risk is quantified. The review evaluated evidence from RCTs, controlled observational studies, anecdotal case reports, case series, and spontaneous reports in the Canadian Drug Reaction Monitoring Program. A teleo-analysis, which is an analysis that attempts to determine the adverse effects of a drug by collating information from different study designs across all grades of evidence, was reported.

3 RCTs ($n = 10\ 731$) provided numerical information on HF events (2 evaluated RGZ and 1 evaluated pioglitazone). The pooled odds ratio for HF was 2.1 (95% CI 1.08 to 4.08). The moderate heterogeneity around this estimate probably reflects the heterogeneous patient population and variable baseline risk for and definitions of HF. It is known that diabetes, duration of disease, and use of any therapy for diabetes are associated with increased risk for HF. The background incidence of HF in people with diabetes is approximately 1.9% over 2.2 years. The review estimated that the number needed to harm with TZDs would be about 50 over a 2.2-year follow-up period based on an odds ratio of 2.1.

It is important to note that, despite concerns about inconsistent diagnostic criteria for identifying HF among studies, the review showed that HF can occur in the absence of concomitant insulin therapy. HF also occurred within weeks to months after commencement of TZD therapy, at high and low doses, and in patients without a history of HF. The review recommends changes to package inserts for TZD drugs (glitazones).

Since this review, the U.S. Food and Drug Administration (FDA) has updated the black box warning for RGZ, which states that RGZ is not recommended for patients with symptomatic HF and is contraindicated in patients with New York Heart Association classes III and IV HF and in patients who should be monitored for HF (1). The FDA report concludes that data on risk for myocardial ischemia are inconclusive (1). The European Medicines Agency has also finalized its review of the benefits and risks of both RGZ and pioglitazone and concluded that benefits continue to outweigh risks in the approved indications (2). Clearly, further work is needed to define the precise role of TZDs in the management of type 2 diabetes.

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