

Do TZDs increase the risk of heart failure for patients with diabetes?

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EVIDENCE-BASED ANSWER

Patients with diabetes who take thiazolidinediones (TZDs) have a higher incidence of congestive heart failure (CHF) than those who do not; the incidence of CHF is similar with the use of pioglitazone (Actos), troglitazone (Rezulin), or rosiglitazone (Avandia) (strength of recommendation [SOR]: **B**, based on a large retrospective cohort study). However, patients on regimens that include

pioglitazone but not insulin have lower rates of CHF than those taking insulin but not pioglitazone (SOR: **B**, based on a retrospective cohort study). Still, patients starting any TZD should be warned of the possibility of CHF and should be monitored for its development. TZDs are contraindicated for patients with class III and IV CHF (SOR: **C**, based on expert opinion).

CLINICAL COMMENTARY

Consider stopping TZDs for patients developing edema or CHF

Improved glycemic control decreases the risk of end organ damage and heart failure in patients with diabetes. Thiazolidinediones are very useful drugs, particularly for patients with marked insulin resistance and hyperlipidemia. However, they do precipitate edema and heart failure. The edema can be severe enough to lead to discontinuation

of the drug, and the risk of heart failure limits the population in which they can be used. They can be used safely in some cardiac patients but, as noted in the article, they should be avoided or used with caution in patients with CHF. Patients taking a TZD who subsequently develop edema should be carefully evaluated for CHF.

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■ Evidence summary

A retrospective cohort study of health insurance claims compared the incidence of CHF among 5441 patients with diabetes who had taken TZDs (rosiglitazone, troglitazone, or pioglitazone) vs 28,103 who had not. Patients were allowed other oral agents and insulin, and they were followed for up to 6 years. The TZD group had more patients on insulin and with pre-existing comorbidities. Based on Kaplan-Meier estimates, which control for censored information, the incidence of new heart failure at 40 months was 8.2% in the TZD group and 5.3% in the non-TZD group (number needed to harm [NNH]=34.5). Using a multivariate analysis that controlled for the coadministration of insulin, the hazard

ratio for TZD use was 1.76 (95% confidence interval [CI], 1.43–2.17).¹ The incidence of CHF was 3.24% in the troglitazone group (n=1665), 2.39% in the rosiglitazone group (n=1882), and 1.63% in the pioglitazone group (n=1347). The difference in these rates is not statistically significant. Of the 28,103 patients not on a TZD, 1.41% developed heart failure. Individual agents were not compared with placebo.

A manufacturer-sponsored study that combined data from 4 separate unpublished randomized controlled trials compared the incidence of CHF at 1 year for patients treated with pioglitazone (as monotherapy and in combination with other oral agents) with those treated only with other oral agents.

Cardiac failure was noted in 12 of 1857 in the pioglitazone group vs 10 of 1856 subjects in the non-pioglitazone groups (not statistically significant). The paper did not comment on how the patients were recruited, how outcomes were measured, or why the 4 original studies were not published.²

Another manufacturer-sponsored retrospective cohort study of pioglitazone analyzed insurance claims data to compare the incidence of CHF among 1668 adult patients taking pioglitazone (and possibly other medications, but not insulin) vs 1668 adult patients taking insulin (and possibly other medications, but not a TZD). The 2 groups were matched in terms of comorbid conditions, but statistical analysis did not take disease severity into account. The incidence of CHF was 2% of pioglitazone users compared with 4% of patients using insulin (NNH for insulin=50). In addition, CHF-related hospitalizations were 0.7% for CHF in the pioglitazone group vs 2.5% in the insulin group (NNH for insulin=55). Both of these findings are statistically significant.³

Recommendations from others

The American Diabetes Association/American Heart Association recommends that patients be evaluated for heart disease or heart failure before starting TZD therapy and monitored for symptoms thereafter. Patients who are at risk for developing CHF, who already have New York Heart Association class I or II CHF, or who take insulin should begin TZD therapy with low doses that are titrated up gradually. The US Food and Drug Administration has not approved TZDs for patients with class III or IV CHF, as there are no studies in these populations.⁴

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FAST TRACK

TZDs are useful for patients with marked insulin resistance, but they do precipitate edema and heart failure