

TZD Risks May Trump Benefits in Older Patients

BY MARY ANN MOON
Contributing Writer

Thiazolidinediones, primarily rosiglitazone, were associated with a significant increase in the risk of congestive heart failure, myocardial infarction, and mortality in a large study of older patients with diabetes.

"The magnitude of harm observed in our study may be sufficient to outweigh any potential benefits associated with TZDs in an

older, higher-risk population," study investigators reported in JAMA.

Most of the evidence implicating thiazolidinediones in cardiovascular problems has been collected in clinical trials, which usually exclude patients older than 65. Dr. Lorraine L. Lipscombe of the University of Toronto and her associates conducted a retrospective study of 159,026 diabetes patients aged 66 and older who resided in Ontario and received oral hypoglycemic drugs between 2002 and 2005.

The mean subject age was 75, and median follow-up was just under 4 years. During that time, approximately 8% (nearly 12,500) of the study subjects were hospitalized for congestive heart failure (CHF) and 8% for acute myocardial infarction (MI), while 19% (more than 30,000) died.

Compared with other oral diabetes therapies, thiazolidinediones, either alone or in combination regimens, were associated with significantly higher risks for CHF, MI, and all-cause mortality.

Further analysis showed that most of the association was limited to rosiglitazone. However, the study may have been underpowered to detect adverse effects linked to pioglitazone because of the relatively few subjects who received that agent.

The association between thiazolidinediones and adverse cardiac effects remained robust after the data were adjusted to account for various prognostic factors, and was independent of subjects' baseline cardiovascular risk and duration of diabetes. The results suggest that the drawbacks of TZD treatment may outweigh the benefits, even in patients who don't have evidence of cardiovascular disease, the investigators said.

"Our findings argue against current labeling of TZDs that warns against use only in persons at high risk of CHF, as we did not identify any subgroup of older diabetes patients who may be protected from the adverse effects of TZDs," Dr. Lipscombe and her associates said (JAMA 2007;298:2634-43).

(Since this study was conducted, a warning has been added to rosiglitazone sold

in the United States advising patients that a meta-analysis of 42 clinical studies "showed [rosiglitazone] to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction." It also notes that three other studies "have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.")

This is the first study to assess TZD-related outcomes in an entire population of older people with diabetes. "While there have been previous attempts to evaluate the association between TZDs and CHF in real-world settings, prior studies were either small in sample size, composed of lower-risk diabetes populations, or insufficiently adjusted for case-mix," the authors noted.

Dr. David Alter, one of the study's coauthors, disclosed that he is a consultant to INTERVENT Canada and a limited partner in PrevCan. No other disclosures were reported. The study was funded by the Ontario Ministry of Health and Long-Term Care.

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