

# TZD Use in Heart Failure: Not That Bad After All?

BY PATRICE WENDLING  
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TORONTO — A retrospective analysis has shown no adverse effects of thiazolidinediones on clinical outcomes in heart failure patients with diabetes.

In fact, thiazolidinedione (TZD) use was associated with reductions in all-cause hospitalizations, heart failure hospitalizations, and total hospital days. The reduction in hospital days also was noted in patients treated with TZD plus insulin.

These findings challenge current recommendations against the use of TZDs in heart failure that are based on concerns regarding fluid retention, particularly when used in combination with insulin. To date, there have been no trials assessing the impact of TZD therapy on heart failure outcomes.

"These findings support the concept that perhaps the non-hypoglycemic cardiovascular effects of TZDs may have favorable clinical impact in heart failure patients," investigator John S. Golden, M.D., said during a poster presentation at the annual meeting of the Heart Failure Society of America.

Ultimately, clinical trials will determine the specific effects of TZDs in heart failure, and the

extent to which an observational study can be extrapolated to a larger population.

"I can't tell you on the basis of this study that it is something we ought to be doing as a therapeutic intervention at this point," said Dr. Golden of Mid-Atlantic Permanente Medical Group, Fairfax, Va. "I'm certainly not putting that much stock in hospital day reductions

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based on a small study like this. But, again, it lends some clinical support to the biochemical mechanisms supporting not only the safety, but efficacy, of TZDs in this population."

Consecutively, 97 diabetic patients were referred to the heart failure treatment program at Mid-Atlantic with left ventricular ejection fractions of 35% or less and New York Heart Association (NYHA) class II-IV; 37% were treated with a TZD and 15% received a TZD plus insulin.

Patients treated with TZD and those not treated with the drug were well matched with regard to baseline left ventricular ejection fraction, glycosylated hemoglobin, and NYHA class. All patients were treated with ACE inhibitors or angiotensin receptor blockers, and 97% received  $\beta$ -blockers.

Clinical outcomes were measured at 1 year evaluating TZD use both alone and in combination with insulin.

Improvements in ejection fractions did not differ significantly between patients treated with TZDs and those who were not. Patients treated with a TZD, compared with those not treated, had significantly reduced all-cause hospitalizations per patient (0.19 vs. 0.71), heart failure hospitalizations per patient (0.03 vs. 0.16), and total hospital days (0.67 vs. 2.72), he said.

In the subpopulation treated with TZD plus insulin, there was a significant reduction in total hospital days per patient (0.07 vs. 2.30), compared with those not on the combination therapy. There was a trend toward increased diuretic usage in the TZD plus insulin group (69.3 mg vs. 45.5 mg furosemide/day). This was not seen in patients treated with TZD alone. ■

# Drug Watch System Misses Hypoglycemic Events

BY MIRIAM E. TUCKER  
Senior Writer

A new national active surveillance system designed to detect adverse drug events is very good at picking up true cases, but not particularly sensitive—especially when it comes to detecting hypoglycemia due to diabetes medications and bleeding associated with anticoagulants, the Centers for Disease Control and Prevention reported.

In 2003, the CDC collaborated with the Consumer Product Safety Commission and the Food and Drug Administration in developing the National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project. Because adverse drug events (ADEs) are often more difficult to identify than other injuries, the CDC conducted an independent chart review in a sample of six NEISS-CADES hospitals, representing a range of sizes and of ADE reporting rates (0.2%-1.7% of emergency department visits).

Of 4,561 ED visit charts reviewed, a total of 68 ADE cases were identified. The patients had a median age of 57 years and 53% were female. Of the 29 ADE cases that had been reported to NEISS-CADES prior to the chart review, 25 were among the 68 cases detected by the reviewers.

The remaining four were false-positives in which an injury attributed to a drug in the chief complaint section of the chart was not confirmed elsewhere in the chart, the CDC explained (MMWR 2005;54:380-3).

The estimated sensitivity of the NEISS-CADES for ascertaining ADEs was 0.33, while the estimated positive predictive value of a reported ADE to the system was 0.92. The relatively low sensitivity of the system was attributed to the difficulty in detecting hypoglycemia associated with diabetes agents (just 3 of 16 were detected), and of bleeding associated with anticoagulants such as warfarin and heparin (1 of 9 were detected).

When those two types of cases were excluded, sensitivity of the NEISS-CADES increased to 0.45. This figure compares favorably with the FDA's Adverse Event Reporting System, a passive surveillance system estimated to capture 1%-38% of serious adverse drug reactions. It is a system which is influenced by factors such as the length of time the drug has been on the market and media attention, the CDC noted.

Due to these findings, NEISS-CADES coders now receive a streamlined ADE flow sheet and are trained to identify unintentional overdoses of diabetes agents and anticoagulants. ■

## Gestational Diabetes Prevalence Almost Doubled in a Decade

BY MIRIAM E. TUCKER  
Senior Writer

Gestational diabetes is on the rise. The finding is not surprising given the dramatic increases in obesity and type 2 diabetes, but few studies have examined trends in gestational diabetes mellitus, reported Dana Dabelea, M.D., of the University of Colorado, Denver, and her associates.

The findings from Kaiser Permanente of Colorado's perinatal database include 36,403 pregnancies among 30,216 initially nondiabetic women who delivered singleton infants from 1994 to 2002 and had been screened at 24-28 weeks by the same protocol: a 1-hour 50-g oral glucose tolerance test, followed by a diagnostic 3-hour 100-g test in those with glucose values of at least 140 mg/dL on the 50-g test (Diabetes Care 2005;28:579-84).

A total of 1,183 pregnancies were complicated by gestational diabetes mellitus (GDM). The prevalence of

GDM almost doubled—from 2.1% in 1994 to 4.1% in 2002. The rate increased by an average of 12% per year during that period.

The rise in GDM occurred in all ethnic groups, from 1.9% to 3.4% in non-Hispanic whites, 2.8% to 5.1% in Hispanics, 2.5% to 4.6% in African Americans, and 6.3% to 8.6% in Asians. However, throughout the study period, the combined prevalence of GDM in women of all the minority ethnic groups was consistently twice that of white women.

When broken down by the mother's birth period, the prevalence of GDM was about 40% higher for each successive birth decade from 1946 to 1990. This finding probably reflects women's exposure to increasing rates with time. Obesity is one of the strongest risk factors for GDM, the researchers said. Even in Colorado, with the lowest estimated prevalence of obesity of any state, obesity among women more than doubled from 1990 to 2001, they noted. ■

## Metabolic Syndrome, Atherosclerosis Flag Cardiovascular Risk in HIV/AIDS

BY DIANA MAHONEY  
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BOSTON — The concurrent presence of metabolic syndrome and subclinical atherosclerosis in HIV infection may help identify individuals at increased risk for cardiovascular disease, a study has shown.

The findings could be used to guide therapy designed to prevent cardiovascular events in people with AIDS or HIV, reported Alexandra Mangili, M.D., in a poster presentation at a conference on retroviruses and opportunistic infections.

In a longitudinal study examining nutritional and metabolic parameters in HIV infection, Dr. Mangili and colleagues at Tufts University in Boston measured common carotid and internal carotid intima-medial thickness (IMT) by B-mode ultrasonography in 327 HIV-infected patients.

Coronary calcium score was also measured by high-resolution ECG-synchronized computed tomography.

The investigators compared these parameters in patients with and without signs of metabolic syndrome, defined as the presence of at least three of the following: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, hypertension, and elevated fasting glucose.

After adjustment for sex, age, race, and smoking, individuals with metabolic syndrome had significantly higher common carotid IMT values than did patients without metabolic syndrome. The metabolic syndrome patients were also more likely to have abnormal coronary calcium scores, but not internal carotid IMT values, Dr. Mangili said at the conference, sponsored by the Foundation for Retro-

virology and Human Health.

CD4 cell counts, viral load values, and use of highly active antiretroviral regimens, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors were similar between patients with and without metabolic syndrome, she noted.

Subclinical carotid and coronary atherosclerosis are independent predictors of adverse cardiac events, and there is increasing evidence that metabolic syndrome is predictive of cardiovascular disease. The association seen in this study population between metabolic syndrome and subclinical atherosclerosis as determined by elevated IMT and coronary calcium adds to the growing body of knowledge linking HIV infection and/or treatment to an increased risk of cardiovascular events, Dr. Mangili said. ■