# Fracture Risk Spikes With Thiazolidinediones

BY ROBERT FINN

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Rosiglitazone and pioglitazone are both associated with an increased risk of fracture in postmenopausal women with type 2 diabetes, according to a matched case-control study that used data from the Translating Research into Action for Diabetes trial.

After controlling for age, sex, race/ethnicity, body mass index, and health plan, Dori Bilik of the University of Michigan, Ann Arbor, and colleagues, found that both of the thiazolidinediones (TZDs) were associated with a 71% increase in the risk of fracture for women aged 50 and older.

TRIAD enrolled 11,927 patients with diabetes in 2000-2001. All of the patients were at least aged 18 years and in managed care for at least 18 months before the baseline patient survey.

"Our study shows that increased fracture risk is associated with higher TZD dose, but no difference between rosiglitazone and pioglitazone is apparent, suggesting a class effect of TZDs on fracture risk," said senior author Dr. William Herman of the University of Michigan Ann Arbor, in a press release.

Higher TZD doses were associated with a statistically significant 42% increase in the odds of fractures for women age 50 and older, but not for women under 50 or for men (J. Clin. Endocrinol. Metab. 2010; doi:10.1210/jc2009-2638).

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**Table 1: Treatment –emergent adverse events in pooled clinical trials up to 28 weeks duration in adults with type 1 diabetes (adverse events with frequency ≥ 5%) (continued)**

| | LANTUS, % (n=1257) | NPH, % (n=1070) |
|---|---|---|
| Accidental injury | 5.7 | 6.4 |
| Headache | 5.5 | 4.7 |

*Body System not Specified

**Table 2: Treatment –emergent adverse events in pooled clinical trials up to 1 year duration in adults with type 2 diabetes (adverse events with frequency ≥ 5%)**

| | LANTUS, % (n=849) | NPH, % (n=714) |
|---|---|---|
| Upper respiratory tract infection | 11.4 | 13.3 |
| Infection* | 10.4 | 11.6 |
| Retinal vascular disorder | 5.8 | 7.4 |

*Body System not Specified

**Table 3: Treatment –emergent adverse events in a 5-year trial of adults with type 2 diabetes (adverse events with frequency ≥ 10%)**

| | LANTUS, % (n=514) | NPH, % (n=503) |
|---|---|---|
| Upper respiratory tract infection | 29.0 | 33.6 |
| Edema peripheral | 20.0 | 22.7 |
| Hypertension | 19.6 | 18.9 |
| Influenza | 18.7 | 19.5 |
| Sinusitis | 18.5 | 17.9 |
| Cataract | 18.1 | 15.9 |
| Bronchitis | 15.2 | 14.1 |
| Arthralgia | 14.2 | 16.1 |
| Pain in extremity | 13.0 | 13.1 |
| Back pain | 12.8 | 12.3 |
| Cough | 12.1 | 7.4 |
| Urinary tract infection | 10.7 | 10.1 |
| Diarrhea | 10.7 | 10.3 |
| Depression | 10.5 | 9.7 |
| Headache | 10.3 | 9.3 |

**Table 4: Treatment –emergent adverse events in a 28-week clinical trial of children and adolescents with type 1 diabetes (adverse events with frequency ≥ 5%)**

| | LANTUS, % (n=174) | NPH, % (n=175) |
|---|---|---|
| Infection* | 13.8 | 17.7 |
| Upper respiratory tract infection | 13.8 | 16.0 |
| Pharyngitis | 7.5 | 8.6 |
| Rhinitis | 5.2 | 5.1 |

*Body System not Specified

• *Severe Hypoglycemia*

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LANTUS *[See Warnings and Precautions (5.3)]*. Tables 5 and 6 summarize the incidence of severe hypoglycemia in the LANTUS individual clinical trials. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL (≤56 mg/dL in the 5-year



trial) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

The rates of severe symptomatic hypoglycemia in the LANTUS clinical trials (see Section 14 in the full prescribing information for a description of the study designs) were comparable for all treatment regimens (see Tables 5 and 6). In the pediatric phase 3 clinical trial, children and adolescents with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adult trials with type 1 diabetes. (see Table 5) *[See Clinical Studies (14) in the full prescribing information].*

**Table 5: Severe Symptomatic Hypoglycemia in Patients with Type 1 Diabetes**

| | Study A Type 1 Diabetes Adults 28 weeks In combination with regular insulin | | Study B Type 1 Diabetes Adults 28 weeks In combination with regular insulin | | Study C Type 1 Diabetes Adults 16 weeks In combination with insulin lispro | | Study D Type 1 Diabetes Pediatrics 26 weeks In combination with regular insulin | |
|---|---|---|---|---|---|---|---|---|
| | LANTUS | NPH | LANTUS | NPH | LANTUS | NPH | LANTUS | NPH |
| Percent of patients (n/total N) | 10.6 (31/292) | 15.0 (44/293) | 8.7 (23/264) | 10.4 (28/270) | 6.5 (20/310) | 5.2 (16/309) | 23.0 (40/174) | 28.6 (50/175) |

**Table 6: Severe Symptomatic Hypoglycemia in Patients with Type 2 Diabetes**

| | Study E Type 2 Diabetes Adults 52 weeks In combination with oral agents | | Study F Type 2 Diabetes Adults 28 weeks In combination with regular insulin | | Study G Type 2 Diabetes Adults 5 years In combination with regular insulin | |
|---|---|---|---|---|---|---|
| | LANTUS | NPH | LANTUS | NPH | LANTUS | NPH |
| Percent of patients (n/total N) | 1.7 (5/289) | 1.1 (3/281) | 0.4 (1/259) | 2.3 (6/259) | 7.8 (40/513) | 11.9 (60/504) |

• *Retinopathy*

Retinopathy was evaluated in the LANTUS clinical studies by analysis of reported retinal adverse events and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH insulin treatment groups were similar for patients with type 1 and type 2 diabetes.

LANTUS was compared to NPH insulin in a 5-year randomized clinical trial that evaluated the progression of retinopathy as assessed with fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Scale (ETDRS). Patients had type 2 diabetes (mean age 55 yrs) with no (86%) or mild (14%) retinopathy at baseline. Mean baseline HbA1c was 8.4%. The primary outcome was progression by 3 or more steps on the ETDRS scale at study endpoint. Patients with pre-specified post-baseline eye procedures (pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy, local photocoagulation for new vessels, and vitrectomy for diabetic retinopathy) were also considered as 3-step progressors regardless of actual change in ETDRS score from baseline. Retinopathy graders were blinded to treatment group assignment. The results for the primary endpoint are shown in Table 7 for both the per-protocol and Intent-to-Treat populations, and indicate similarity of Lantus to NPH in the progression of diabetic retinopathy as assessed by this outcome.

**Table 7. Number (%) of patients with 3 or more step progression on ETDRS scale at endpoint**

| | Lantus (%) | NPH (%) | Difference*,† (SE) | 95% CI for difference |
|---|---|---|---|---|
| **Per-protocol** | 53/374 (14.2%) | 57/363 (15.7%) | -2.0% (2.6%) | -7.0% to +3.1% |
| **Intent-to-Treat** | 63/502 (12.5%) | 71/487 (14.6%) | - 2.1% (2.1%) | -6.3% to +2.1% |

*Difference = Lantus – NPH

†using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata (cutoff 9.0%) as the classified independent variables, and with binomial distribution and identity link function