

# Bone Hormone May Predict Mortality in HF

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FROM THE ANNUAL CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY

STOCKHOLM – Higher blood levels of the bone hormone osteoprotegerin are associated with an increased long-term risk of death in patients with chronic heart failure, according to Dr. Ragnhild R. Roysland.

The relationship between osteoprote-

gerin (OPG) and mortality in heart failure is independent of the conventional cardiovascular risk factors, based on a secondary analysis of results of the Italian GISSI-Heart Failure trial.

Osteoprotegerin, a cytokine that's a member of the tumor necrosis factor superfamily, is drawing increasing attention among cardiovascular researchers as a likely key player in what's known as "the calcification paradox." In recent human

studies, increased OPG levels have been linked to a greater atherosclerotic burden; an increased risk of death following acute MI; and now, in GISSI-HF, to increased mortality in the setting of chronic heart failure, Dr. Ragnhild R. Roysland said at the congress.

The GISSI-HF study was a randomized clinical trial in which 6,975 Italian patients with all kinds of chronic heart failure were assigned to rosuvastatin,

fish oil, or placebo and followed up for a median of 3.9 years. The primary results have been published in *Lancet* (2008;372:1223-30;1231-9). Dr. Roysland presented a new substudy involving 1,229 GISSI-HF participants for whom baseline OPG levels were available.

The aim was to see if baseline OPG was predictive of all-cause mortality. This indeed proved to be the case. During follow-up 332 patients died. The mortality rate was 20% in those in the bottom tertile for baseline OPG with a value less than 1,210 ng/L, and more than twice as great at 45% among patients in the highest tertile, with an OPG



**Mortality for patients with high OPG levels, at 45%, was more than twice that in patients with low levels, at 20%.**

DR. ROYSLAND

of at least 1,923 ng/L. Patients with an intermediate-tertile baseline OPG of 1,210-1,922 ng/L split the difference in terms of mortality, said Dr. Roysland of Akershus University Hospital, Lørenskog, Norway.

Treatment assignment in GISSI-HF did not affect OPG levels. However, if a medication could be identified that reduces OPG levels and attenuates the risk associated with high OPG, then OPG could become an important marker to use in managing chronic heart failure in clinical practice.

Dr. Marco Metra commented that as a member of the European Society of Cardiology congress scientific program committee, he'd reviewed all the heart failure studies scheduled for presentation at the meeting.

Two other studies in addition to Dr. Roysland's consistently showed that heart failure patients with high levels of OPG have a poor prognosis.

"We know that patients with heart failure have low levels of vitamin D and increased rates of osteoporosis and bone fractures. So the bone is in some way a target of heart failure," observed Dr. Metra of the University of Brescia (Italy).

Dr. Roysland said she had no financial conflicts. ■

## • *Insulin initiation and intensification of glucose control*

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

### • *Lipodystrophy*

Long-term use of insulin, including LANTUS, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. [See *Dosage and Administration* (2.1)].

### • *Weight gain*

Weight gain can occur with insulin therapy, including LANTUS, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

### • *Peripheral Edema*

Insulin, including LANTUS, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

### • *Allergic Reactions*

#### *Local Allergy*

As with any insulin therapy, patients taking LANTUS may experience injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation. In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

#### *Systemic Allergy*

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LANTUS and may be life threatening.

### • *Antibody production*

All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LANTUS, increases in titers of antibodies to insulin were observed in NPH insulin and insulin glargine treatment groups with similar incidences.

## 6.2 Postmarketing experience

The following adverse reactions have been identified during post-approval use of LANTUS.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of LANTUS [See *Patient Counseling Information* (17) in the full prescribing information]. To avoid medication errors between LANTUS and other insulins, patients should be instructed to always verify the insulin label before each injection.

## 7. DRUG INTERACTIONS

A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of drugs that may increase the blood-glucose-lowering effect of insulins including LANTUS and, therefore, increase the susceptibility to hypoglycemia: oral anti-diabetic products, pramlintide, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of drugs that may reduce the blood-glucose-lowering effect of insulins including LANTUS: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

## 8. USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C: Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m<sup>2</sup>. In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m<sup>2</sup>, were administered during

## LANTUS® (insulin glargine [rDNA origin] injection) solution for subcutaneous injection

organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of LANTUS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

### 8.3 Nursing Mothers

It is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when LANTUS is administered to a nursing woman. Use of LANTUS is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

### 8.4 Pediatric Use

The safety and effectiveness of subcutaneous injections of LANTUS have been established in pediatric patients (age 6 to 15 years) with type 1 diabetes [see *Clinical Studies* (14) in the full prescribing information]. LANTUS has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes. LANTUS has not been studied in pediatric patients with type 2 diabetes.

Based on the results of a study in pediatric patients, the dose recommendation when switching to LANTUS is the same as that described for adults [see *Dosage and Administration* (2.3) and *Clinical Studies* (14) in the full prescribing information]. As in adults, the dosage of LANTUS must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

### 8.5 Geriatric Use

In controlled clinical studies comparing LANTUS to NPH insulin, 593 of 3890 patients (15%) with type 1 and type 2 diabetes were ≥65 years of age and 80 (2%) patients were ≥75 years of age. The only difference in safety or effectiveness in the subpopulation of patients ≥65 years of age compared to the entire study population was a higher incidence of cardiovascular events typically seen in an older population in both LANTUS and NPH insulin-treated patients.

Nevertheless, caution should be exercised when LANTUS is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly [See *Warnings and Precautions* (5.3)].

## 10. OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

Rev. September 2009  
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Bridgewater, NJ 08807  
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