

Bone Hormone May Predict Mortality in HF

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STOCKHOLM – Higher blood levels of the bone hormone osteoprotegerin are linked with a higher long-term risk of death in patients with chronic heart failure, reported Dr. Ragnhild R. Roysland.

The relationship between osteoprotegerin (OPG) and mortality in heart fail-

ure 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 animal studies, low levels of OPG are associated with de-

creased skeletal calcification, osteoporosis, and increased calcification of the major arteries. But 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 HF, Dr. Roysland said at the congress.

The GISSI-HF study was a randomized clinical trial in which 6,975 Italian pa-

tients with chronic heart failure were assigned to rosuvastatin, fish oil, or placebo and followed up for a median of 3.9 years (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% in patients in the highest tertile, with an OPG 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.



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

DR. ROYSLAND

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 HF in clinical practice. There is early evidence that treatments for osteoporosis reduce OPG levels in a non-HF population, but no studies have been done in patients with chronic HF, she said.

Dr. Marco Metra, a member of the ESC congress scientific program committee, said he'd reviewed all the HF studies being presented at the meeting. Two studies in addition to Dr. Roysland's consistently showed that HF 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," said Dr. Metra of the University of Brescia (Italy). ■

Disclosures: Dr. Roysland said she had no financial conflicts.

Hypertriglyceridemia: Patients with fasting serum TG levels above 500 mg/dL were excluded from the diabetes clinical trials. In the phase 3 diabetes trials, 637 (63%) patients had baseline fasting serum TG levels less than 200 mg/dL, 261 (25%) had baseline fasting serum TG levels between 200 and 300 mg/dL, 111 (11%) had baseline fasting serum TG levels between 300 and 500 mg/dL, and 9 (1%) had fasting serum TG levels greater than or equal to 500 mg/dL. The median baseline fasting TG concentration for the study population was 172 mg/dL; the median post-treatment fasting TG was 195 mg/dL in the WELCHOL group and 177 mg/dL in the placebo group. WELCHOL therapy resulted in a median placebo-corrected increase in serum TG of 5% (p=0.22), 22% (p<0.001), and 18% (p<0.001) when added to metformin, insulin and sulfonylureas, respectively [See Warnings and Precautions (5.2) and Clinical Studies (14.2) in the full prescribing information]. In comparison, WELCHOL resulted in a median increase in serum TG of 5% compared to placebo (p=0.42) in a 24-week monotherapy lipid-lowering trial [See Clinical Studies (14.1) in the full prescribing information].

Treatment-emergent fasting TG concentrations \geq 500 mg/dL occurred in 4.1% of WELCHOL-treated patients compared to 2.0% of placebo-treated patients. Among these patients, the TG concentrations with WELCHOL (median 604 mg/dL; interquartile range 538-712 mg/dL) were similar to that observed with placebo (median 644 mg/dL; interquartile range 574-724 mg/dL). Two (0.4%) patients on WELCHOL and 2 (0.4%) patients on placebo developed TG elevations \geq 1000 mg/dL. In all WELCHOL clinical trials, including studies in patients with type 2 diabetes and patients with primary hyperlipidemia, there were no reported cases of acute pancreatitis associated with hypertriglyceridemia. It is unknown whether patients with more uncontrolled, baseline hypertriglyceridemia would have greater increases in serum TG levels with WELCHOL [See Contraindications (4) and Warnings and Precautions (5.2)].

Cardiovascular adverse events: During the diabetes clinical trials, the incidence of patients with treatment-emergent serious adverse events involving the cardiovascular system was 3% (17/566) in the WELCHOL group and 2% (10/562) in the placebo group. These overall rates included disparate events (e.g., myocardial infarction, aortic stenosis, and bradycardia); therefore, the significance of this imbalance is unknown.

Hypoglycemia: Adverse events of hypoglycemia were reported based on the clinical judgment of the blinded investigators and did not require confirmation with fingerstick glucose testing. The overall reported incidence of hypoglycemia was 3.0% in patients treated with WELCHOL and 2.3% in patients treated with placebo. No WELCHOL treated patients developed severe hypoglycemia.

6.2 Post-marketing Experience

The following additional adverse reactions have been identified during post-approval use of WELCHOL. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Drug Interactions with concomitant WELCHOL administration include:

- Increased seizure activity or decreased phenytoin levels in patients receiving phenytoin. Phenytoin should be administered 4 hours prior to WELCHOL.
- Reduced International Normalized Ratio (INR) in patients receiving warfarin therapy. In warfarin-treated patients, INR should be monitored frequently during WELCHOL initiation then periodically thereafter.
- Elevated thyroid-stimulating hormone (TSH) in patients receiving thyroid hormone replacement therapy. Thyroid hormone replacement should be administered 4 hours prior to WELCHOL [See Drug Interactions (7)].

Gastrointestinal Adverse Reactions

Bowel obstruction (in patients with a history of bowel obstruction or resection), dysphagia or esophageal obstruction (occasionally requiring medical intervention), fecal impaction, pancreatitis, abdominal distension, exacerbation of hemorrhoids, and increased transaminases.

Laboratory Abnormalities

Hypertriglyceridemia

7 DRUG INTERACTIONS

Table 4 lists the drugs that have been tested in *in vitro* binding or *in vivo* drug interaction studies with colessevelam and/or drugs with postmarketing reports consistent with potential drug-drug interactions. Orally administered drugs that have not been tested for interaction with colessevelam, especially those with a narrow therapeutic index, should also be administered at least 4 hours prior to WELCHOL. Alternatively, the physician should monitor drug levels of the co-administered drug.

Table 4
Drugs Tested in *In Vitro* Binding or *In Vivo* Drug Interaction Testing or With Post-Marketing Reports

Drugs with a known interaction with colessevelam ^a	cyclosporine ^c , glyburide ^a , levothyroxine ^a , and oral contraceptives containing ethinyl estradiol and norethindrone
Drugs with postmarketing reports consistent with potential drug-drug interactions when coadministered with WELCHOL	phenytoin ^a , warfarin ^b
Drugs that do not interact with colessevelam based on <i>in vitro</i> or <i>in vivo</i> testing	cephalexin, ciprofloxacin, digoxin, warfarin ^b , fenofibrate, lovastatin, metformin, metoprolol, pioglitazone, quinidine, repaglinide, valproic acid, verapamil

^a Should be administered at least 4 hours prior to WELCHOL

^b No significant alteration of warfarin drug levels with warfarin and WELCHOL coadministration in an *in vivo* study which did not evaluate warfarin pharmacodynamics (INR). [See Post-marketing Experience (6.2)]

^c Cyclosporine levels should be monitored and, based on theoretical grounds, cyclosporine should be administered at least 4 hours prior to WELCHOL.

In an *in vivo* drug interaction study, WELCHOL and warfarin coadministration had no effect on warfarin drug levels. This study did not assess the effect of WELCHOL and warfarin coadministration on INR. In postmarketing reports, concomitant use of WELCHOL and warfarin has been associated with reduced INR. Therefore, in patients on warfarin therapy, the INR should be monitored before initiating WELCHOL and frequently enough during early WELCHOL therapy to ensure that no significant alteration in INR occurs. Once the INR is stable, continue to monitor the INR at intervals usually recommended for patients on warfarin. [See Post-marketing Experience (6.2)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of colessevelam use in pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of fetal harm. Requirements for vitamins and other nutrients are increased in pregnancy. However, the effect of colessevelam on the absorption of fat-soluble vitamins has not been studied in pregnant women. This drug should be used during pregnancy only if clearly needed.

In animal reproduction studies, colessevelam revealed no evidence of fetal harm when administered to rats and rabbits at doses 50 and 17 times the maximum human dose, respectively. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

8.3 Nursing Mothers

Colessevelam hydrochloride is not expected to be excreted in human milk because colessevelam hydrochloride is not absorbed systemically from the gastrointestinal tract.

8.4 Pediatric Use

The safety and effectiveness of WELCHOL as monotherapy or in combination with a statin were evaluated in children, 10 to 17 years of age with heFH [See Clinical Studies (14.1) in the full prescribing information]. The adverse reaction profile was similar to that of patients treated with placebo. In this limited controlled study, there were no significant effects on growth, sexual maturation, fat-soluble vitamin levels or clotting factors in the adolescent boys or girls relative to placebo [See Adverse Reactions (6.1)].

Due to tablet size, WELCHOL for Oral Suspension is recommended for use in the pediatric population. Dose adjustments are not required when WELCHOL is administered to children 10 to 17 years of age. WELCHOL has not been studied in children younger than 10 years of age or in pre-menarchal girls.

8.5 Geriatric Use

Primary Hyperlipidemia: Of the 1350 patients enrolled in the hyperlipidemia clinical studies, 349 (26%) were \geq 65 years old, and 58 (4%) were \geq 75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Type 2 Diabetes Mellitus: Of the 1128 patients enrolled in the four diabetes studies, 249 (22%) were \geq 65 years old, and 12 (1%) were \geq 75 years old. In these trials, WELCHOL 3.8 g/day or placebo was added onto background anti-diabetic therapy. No overall differences in safety or effectiveness were observed between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No special considerations or dosage adjustments are recommended when WELCHOL is administered to patients with hepatic impairment.

8.7 Renal Impairment

Type 2 Diabetes Mellitus: Of the 1128 patients enrolled in the four diabetes studies, 696 (62%) had mild renal insufficiency (creatinine clearance [CrCl] 50-80 mL/min), 53 (5%) had moderate renal insufficiency (CrCl 30-50 mL/min), and none had severe renal insufficiency (CrCl <30 mL/min), as estimated from baseline serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation. No overall differences in safety or effectiveness were observed between patients with CrCl <50 mL/min (n=53) and those with a CrCl \geq 50 mL/min (n=1075).

10 OVERDOSAGE

Doses of WELCHOL in excess of 4.5 g/day have not been tested. Because WELCHOL is not absorbed, the risk of systemic toxicity is low. However, excessive doses of WELCHOL may cause more severe local gastrointestinal effects (e.g., constipation) than recommended doses.

Welchol
(colessevelam HCl)

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