Hip Fracture Risk Rose at Start of Loop Diuretic

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SAN DIEGO – The risk of hip fracture nearly doubles in the week following a new prescription for a loop diuretic.

In contrast, there is no spike in the risk of hip fracture in the 7 days after a new prescription for other classes of diuretics or for ACE inhibitors, according to an analysis of the Health Improvement Network (THIN) database involving more than 400 U.K. primary care practices.

The short-term jump in risk of hip fracture may be related to the prominent urinary symptoms that often accompany a new prescription for loop diuretics. The resultant rush to the bathroom could increase falls during that initial adjustment period, Dr. Sarah D. Berry speculated.

She reported on 28,703 subjects who experienced a hip fracture and more than 2 million others who did not. She and her coworkers compared the occurrence of new diuretic prescriptions in the 7 days prior to a hip fracture to the occurrence of new diuretic prescriptions in the control period 31-37 days before the fracture.

The adjusted odds ratio of an incident hip fracture was significantly increased by 80% in the 7 days following a new prescription for a loop diuretic. The absolute risk during this week-long window, however, remained low: 2.9 hip fractures per 100,000 new loop diuretic prescriptions, said Dr. Berry of the Hebrew SeniorLife Institute for Aging Research and Beth Israel Deaconess Medical Center, Boston.

Dr. Berry declared having no financial conflicts regarding the study, which was supported by the National Institutes of Health and Hebrew SeniorLife. ■

Pediatric Patients 10 to 17 Years of Age: In an 8-week double-blind, placebo-controlled study boys and post-menarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (heFH) (n=192), were treated with WELCHOL tablets (1.9-3.8 g, daily) or placebo tablets *[See Clinical Studies (14.1) in the full prescribing information]*.

Table 2
Placebo-Controlled Clinical Study of WELCHOL for Primary Hyperlipidemia in heFH Pediatric Patients: Adverse Reactions Reported in ≥2% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality

	Number of Patients (%)	
	WELCHOL N = 129	Placebo N = 65
Nasopharyngitis	8 (6.2)	3 (4.6)
Headache	5 (3.9)	2 (3.1)
Fatigue	5 (3.9)	1 (1.5)
Creatine Phosphokinase Increase	3 (2.3)	0 (0.0)
Rhinitis	3 (2.3)	0 (0.0)
Vomiting	3 (2.3)	1 (1.5)

The reported adverse reactions during the additional 18-week open-label treatment period with WELCHOL 3.8 g per day were similar to those during the double-blind period and included headache (7.6%), nasopharyngitis (5.4%), upper respiratory tract infection (4.9%), influenza (3.8%), and nausea (3.8%) *[See Clinical Studies (14.1) in the full prescribing information]*.

Type 2 Diabetes Mellitus: The safety of WELCHOL in patients with type 2 diabetes mellitus was evaluated in 4 double-blind, 12-26 week, placebo-controlled clinical trials. These trials involved 1128 patients (566 patients on WELCHOL; 562 patients on placebo) with inadequate glycemic control on metformin, sulfonylurea, or insulin when these agents were used alone or in combination with other anti-diabetic agents. Upon completion of the pivotal trials, 492 patients entered a 52-week open-label uncontrolled extension study during which all patients received WELCHOL 3.8 g/day while continuing background treatment with metformin, sulfonylurea, or insulin alone or in combination with other anti-diabetic agents.

A total of 6.7% of WELCHOL-treated patients and 3.2% of placebo-treated patients were discontinued from the diabetes trials due to adverse reactions. This difference was driven mostly by gastrointestinal adverse reactions such as abdominal pain and constipation.

One patient in the pivotal trials discontinued due to body rash and mouth blistering that occurred after the first dose of WELCHOL, which may represent a hypersensitivity reaction to WELCHOL.

Table 3
Placebo-Controlled Clinical Studies of WELCHOL Add-on Combination Therapy with Metformin, Insulin, Sulfonylureas: Adverse Reactions Reported in ≥2% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality

	Number of Patients (%)	
	WELCHOL N = 566	Placebo N = 562
Constipation	49 (8.7)	11 (2.0)
Nasopharyngitis	23 (4.1)	20 (3.6)
Dyspepsia	22 (3.9)	8 (1.4)
Hypoglycemia	17 (3.0)	13 (2.3)
Nausea	17 (3.0)	8 (1.4)
Hypertension	16 (2.8)	9 (1.6)

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 ≥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 ≥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 colesevelam and/or drugs with postmarketing reports consistent with potential drug-drug interactions. Orally administered drugs that have not been tested for interaction with colesevelam, 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 colesevelam	Cyclosporine[c], glyburide[a], levothyroxine[a], and oral contraceptives containing ethinyl estradiol and norethindrone[a]
Drugs with post-marketing reports consistent with potential drug-drug interactions when coadministered with WELCHOL	phenytoin[a], warfarin[b]
Drugs that do not interact with colesevelam based on *in vitro* or *in vivo* 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,