

WHI Shows Unopposed Estrogen Is Risk Neutral

BY MARY ANN MOON

FROM JAMA

The most recent findings from the Women's Health Initiative study of short-term unopposed estrogen therapy suggest that after 10 years, the treatment neither increases nor decreases risks for coronary heart disease, deep vein thrombosis, stroke, hip fracture, colorectal cancer, or total mortality.

This portion of the WHI study was halted early when interim analysis in 2004 showed an increased risk of stroke in women taking conjugated equine estrogens (CEE) compared with those taking placebo. "All previous reports of this trial were limited to outcomes occurring during the intervention phase. [Now] we report data on postintervention outcomes through a mean of 10.7 years of follow-up," said Andrea Z. LaCroix,

vein thrombosis, and pulmonary embolism that had been noted during the intervention phase did not persist during extended follow-up. In addition, active treatment, which had showed no effect on CHD risks during the intervention, continued to show no effect on CHD risks. For all cardiovascular events, the cumulative hazard ratio was 2.26% with active treatment and 2.12% with placebo. Colorectal cancer incidence did not

differ between women who received CEE and those who received placebo during the intervention phase, and this lack of effect persisted during extended follow-up.

Hip fracture risk had been reduced with CEE therapy during the intervention phase, but this benefit did not persist during the extended follow-up. Numerically, hip fracture incidence was slightly higher in the CEE group than in the placebo group.

Total mortality risk remained similar between the two study groups both during the intervention and during extended follow-up.

Only one benefit of CEE therapy that was seen during the intervention phase persisted in the extended follow-up and became statistically significant: Breast cancer incidence was 0.27% with active treatment and 0.35% with placebo. These results differ from those of the

VITALS

Major Finding: The short-term increase in risks of stroke, DVT, and pulmonary embolism did not persist over the long term after unopposed estrogen therapy; the equivalent risks of CHD, colorectal cancer, and total mortality did persist; the reduction in hip fracture risk did not persist; and the reduction in breast cancer risk did persist.

Data Source: Extended (10-year) follow-up of approximately 78% of subjects who participated in the Women's Health Initiative-Estrogen Alone trial (3,778 postmenopausal women who took conjugated equine estrogen and 3,867 who took matching placebo for a median of 6 years).

Disclosures: The WHI was funded by the National Heart, Lung, and Blood Institute; the National Institutes of Health; and the U.S. Department of Health and Human Services. Wyeth Ayerst donated the study drugs. Dr. LaCroix reported ties to Warner Chilcott, Sanofi-Aventis, Amgen, and Pfizer. Her associates reported ties to numerous other industry sources.

Ph.D., of Fred Hutchinson Cancer Research Center, Seattle, and her associates (JAMA 2011;305:1305-14).

In the estrogen-only portion of the WHI study, 10,739 postmenopausal women who had undergone hysterectomy had been randomly assigned to receive either CEE or placebo. They were followed during this intervention phase for a median of 6 years, but the median "adherent time" – the interval during which the women actually took more than 80% of their study pills – was only 3.5 years because more than half stopped taking the pills even before the early halt of the trial.

Approximately 78% of the surviving study subjects (3,778 who took CEE and 3,867 who took placebo) agreed to participate in the extended follow-up reported here.

The increased risks of stroke, deep

In addition to diet and exercise to improve glycemic

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*saxagliptin

Indication and Important Limitations of Use

KOMBIGLYZE XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

KOMBIGLYZE XR should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

KOMBIGLYZE XR has not been studied in combination with insulin.

Important Safety Information

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, KOMBIGLYZE XR should be discontinued and the patient hospitalized immediately.

[See Warnings and Precautions]

Contraindications

- Renal impairment (e.g., serum creatinine levels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women, or abnormal creatinine clearance)
- Hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis
- KOMBIGLYZE XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials because use of such products may result in acute alteration of renal function.

Warnings and Precautions

- The reported incidence of lactic acidosis in patients receiving metformin is very low (approximately 0.03 cases/1000 patient-years). When it occurs, it is fatal in approximately 50% of cases. Reported cases of lactic acidosis have occurred primarily in diabetic patients with significant renal insufficiency.
- Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis.
- Lactic acidosis risk increases with the degree of renal dysfunction and patient age. The risk may be significantly decreased by use of minimum effective dose of metformin and regular monitoring of renal function. Careful renal monitoring is particularly important in the elderly. KOMBIGLYZE XR should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.
- Withhold KOMBIGLYZE XR in the presence of any condition associated with hypoxemia, dehydration, or sepsis.
- Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal.
- KOMBIGLYZE XR is not recommended in patients with hepatic impairment.
- Metformin may lower vitamin B12 levels. Measure hematological parameters annually.
- Warn patients against excessive alcohol intake.
- KOMBIGLYZE XR should be suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids), and should not be restarted until patient's oral intake has resumed and renal function is normal.
- Use of saxagliptin or metformin with medications known to cause hypoglycemia
 - Saxagliptin: Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia if used in combination with KOMBIGLYZE XR.

Please see adjacent Brief Summary of US Full Prescribing Information including Boxed WARNING about lactic acidosis.

other portion of the WHI trial in which subjects received combined estrogen-plus-progestin. In that study arm, active treatment impeded mammographic accuracy and was associated with significantly higher rates of breast cancer and breast cancer mortality, the researchers noted.

The women's age at commencing treatment showed a significant interaction with outcomes, both in the intervention phase and during extended follow-up. The results suggest there may be greater benefit and safety for women who start CEE in their early 50s, and less benefit with more potential harm for women who are older when they begin treatment. ■

VIEW ON THE NEWS

Findings Don't Agree With the Body of Evidence

“The lack of an adverse effect of unopposed estrogen when used for a short period in the WHI does not counter the larger,” long-standing, corroborated body of evidence that the treatment generally elevates the risk of breast cancer, said Dr. Emily S. Jungheim and Dr. Graham A. Colditz.

One can question whether results in the WHI study population, in

which nearly 70% of the subjects were older than 60 years at baseline, can even be applied to younger women, particularly with regard to breast cancer risk and hormone therapy.

In addition, the duration of CEE use in the WHI remains problematic since the median “adherent time” was 3.5 years. “Thus, the WHI results do not address the bal-

ance of risks and benefits associated with longer term estrogen use,” they said.

DR. JUNGHEIM and DR. COLDITZ are at Washington University, St. Louis. These remarks were taken from their editorial comment accompanying Dr. LaCroix's report (*JAMA* 2011;305:1354-5). They reported no relevant financial disclosures.

control in your adult patients with type 2 diabetes when treatment with both saxagliptin and metformin is appropriate



A dynamic duo

Combining complementary mechanisms
of action of saxagliptin and metformin XR

- Adverse reactions reported in $\geq 5\%$ of patients treated with saxagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (7.7% vs 7.6%), urinary tract infection (6.8% vs 6.1%), and headache (6.5% vs 5.9%).
- Adverse reactions reported in $\geq 5\%$ of treatment-naïve patients treated with coadministered saxagliptin and metformin immediate-release (IR) and more commonly than in patients treated with metformin IR alone were: headache (7.5% vs 5.2%) and nasopharyngitis (6.9% vs 4.0%).

Drug Interactions: Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, limit KOMBIGLYZE XR to 2.5 mg/1000 mg once daily when coadministered with a strong CYP3A4/5 inhibitor (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

Use in Specific Populations

- **Pregnant and Nursing Women:** There are no adequate and well-controlled studies in pregnant women. KOMBIGLYZE XR should be used during pregnancy only if clearly needed. It is not known whether saxagliptin or metformin are secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when KOMBIGLYZE XR is administered to a nursing woman.
- **Pediatric Patients:** Safety and effectiveness of KOMBIGLYZE XR in pediatric patients have not been established.

—Metformin: Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, during concomitant use with other glucose-lowering agents (such as sulfonylureas or insulin), or with use of ethanol. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects.

- Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. KOMBIGLYZE XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours after the procedure and reinstated only after renal function is normal.
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with KOMBIGLYZE XR or any other anti-diabetic drug.

Adverse Reactions

- Adverse reactions reported in $>5\%$ of patients treated with metformin extended-release and more commonly than in patients treated with placebo were: diarrhea (9.6% vs 2.6%) and nausea/vomiting (6.5% vs 1.5%).

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