

Benefits Eclipse Rare Events

Over the many years of placebo-controlled statin trials, physicians have encountered inconsistent reports on the risk of new-onset diabetes with statins.

A recent meta-analysis of statin/placebo trials with 91,140 participants found a 9% increased risk of diabetes with number needed to harm, or cause one case of new-onset diabetes per year, as 1,020.

This new meta-analysis examining the dose-response association, giving the number needed to harm with intensive versus moderate dose statin therapy as 498 per year, with both high-dose simvastatin and atorvastatin associated with this effect.

What is clear from this meta-analysis is that the number needed to treat with higher- versus lower-dose statin to prevent cardiovascular events is 155 per year, which in subanalyses is significant for the more frequent nonfatal MI and coronary revascularizations but not for the fewer cardiovascular deaths and nonfatal strokes. This cardiovascular preventive effect of intensive versus moderate statin dosing was significant for atorvastatin but not for simvastatin. This plus the recent Food and Drug Administration recommendation to no longer increase simvastatin from 40 to 80 mg in those not attaining LDL cholesterol goals but to switch to another statin (see article on p. 11), suggests that use of 80-mg dose simvastatin for intensive statin-lowering therapy will decrease.

Although a mechanism for possible myocyte insensitivity to carbohydrate oxidation with the use of simvastatin has recently been shown (J. Physiol. 2009;587:219-30), thus increasing the probability of this association as causal, nonetheless, the absolute low frequency of new-onset diabetes of 1/500 to 1/1,000 per year, can be used to reassure worried patients that the greater cardiovascular preventive effects of statin therapy significantly outweigh the possible but much smaller risk of diabetes.

DONALD A. SMITH, M.D., M.P.H., is associate professor of medicine at Mount Sinai Medical Center, New York. He has no relevant disclosures.

Diabetes Risk Rises With Statin Dose

BY MARY ANN MOON

FROM JAMA

The risk of developing type 2 diabetes rises with increasing doses of statin therapy, according to the findings of a large meta-analysis.

"Our findings suggest that clinicians should be vigilant for the development of diabetes in patients receiving intensive statin therapy," said Dr. David Preiss of the BHF Glasgow (Scotland) Cardiovas-

cular Research Centre at the University of Glasgow, and his associates.

Several recent studies have suggested that statin therapy may raise the risk of diabetes, and some have indicated that the risk is higher at higher doses of the drugs.

Dr. Preiss and his colleagues conducted a meta-analysis of five large (at least 1,000 subjects each) randomized clinical trials that compared moderate-dose with intensive-dose statin therapy and followed patients for a minimum of 1 year.

These trials were intended to compare cardiovascular outcomes, but they also tracked adverse events, blood glucose levels, and the use of diabetes medications, so cases of new-onset diabetes could be identified.

Overall, 32,752 subjects who did not have diabetes at baseline were followed for a mean of 5 years. During that time 2,749 subjects (8%) developed diabetes.

There were 149 more cases of diabetes among subjects taking intensive statin



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In addition to diet and exercise to improve glycemic

ONCE A DAY
kombiglyze XR
(saxagliptin and metformin HCl
extended-release) tablets

1
ONE DAILY DOSE

The first and only once-a-day metformin XR + DPP-4 inhibitor* combination tablet.

Generally taken once-daily with evening meal; gradually titrate dose to reduce GI side effects associated with metformin. Maximum daily recommended dose is 5 mg saxagliptin and 2000 mg metformin XR that can be taken as two 2.5 mg/1000 mg tablets once a day.

*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.

VITALS

Major Finding: Two additional cases of incident diabetes per 1,000 patient-years developed in subjects taking intensive statin therapy, compared with those taking moderate statin therapy.

Data Source: A meta-analysis of five large randomized controlled trials comparing intensive with moderate statin therapy in 32,752 participants who were followed for a mean of 5 years.

Disclosures: Dr. Preiss' associates reported ties to numerous industry sources.

ditional cases of diabetes per 1,000 patient-years among those receiving intensive-dose therapy (mean 18.9 cases per 1,000 patient-years with high-dose statin treatment vs. 16.9 cases per 1,000 patient-years with moderate-dose therapy), corresponding to a number needed to harm of 498

therapy than in those taking moderate statin therapy, for an odds ratio of 1.1.

"In absolute terms, there were two ad-

ditional cases per year," the investigators said.

This dose-response relation persisted across several subgroups of patients, re-

gardless of age, HDL cholesterol level, body mass index, or fasting plasma glucose level at baseline. The dose-response relation also was comparable between subjects receiving simvastatin and those receiving atorvastatin, Dr. Preiss and his associates said (JAMA 2011;305:2556-64).

However, more intensive statin therapy also provided clear cardiovascular benefits compared with less intensive statin therapy. "When expressed in absolute terms, there was one additional case of diabetes for every 498 patients treated for 1 year, compared with one fewer patient experiencing a cardiovas-

cular event for every 155 patients treated for 1 year," they noted.

"We hypothesize that given that cardiovascular risk from diabetes is modest in the first decade after diagnosis, and as the benefit of statin therapy increases over time and in absolute terms with increasing age, net cardiovascular benefit in high-risk individuals will still strongly favor statin therapy," the investigators said.

The mechanism by which statins raise diabetes risk is not known. The data on subgroups in this meta-analysis do not shed light on the issue since all subgroups were at comparable risk. ■

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%).

ONCE A DAY
kombiglyze XR
(saxagliptin and metformin HCl
extended-release) tablets

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