

Trial Results Sink Homocysteine's Role in CVD

BY MITCHEL L. ZOLER

Philadelphia Bureau

ATLANTA — The homocysteine hypothesis for secondary prevention of cardiovascular disease appears to be dead.

Reports in March from two large, separate intervention trials failed to show any benefit from supplements of folic acid and B vitamins in patients with proven vascular disease, even though the supplements cut serum levels of homo-

cysteine by the goal of about 25%.

"We achieved what we set out to do and have to conclude that supplements with folic acid and B vitamins do not reduce cardiovascular events in high-risk populations with established vascular disease," Dr. Eva M. Lonn said at the annual meeting of the American College of Cardiology.

The trial, led by Dr. Lonn of the Heart Outcomes Prevention Evaluation (HOPE) 2 study, involved more than 5,500 patients aged 55 or older with vascular dis-

ease or diabetes who were randomized to either a daily folic acid and B vitamin supplement or placebo. The results were presented at the meeting and were simultaneously released in a paper on the Internet (<http://content.nejm.org/cgi/reprint/NEJMoa060900.pdf>).

The second study, the Norwegian Vitamin (NORVIT) trial, randomized more than 3,700 patients soon after a myocardial infarction to a similar supplement or placebo. Results were first reported last

September at the annual meeting of the European Society of Cardiology and were released online along with the HOPE 2 paper (<http://content.nejm.org/cgi/reprint/NEJMoa055227.pdf>).

Both studies were done to test a theory that had become entrenched based on findings from several retrospective and observational studies in the past 25 years. Those studies provided "ample support for the association of mild hyperhomocysteinemia with an elevated risk of atherothrombosis," wrote Dr. Joseph Loscalzo, chairman of the department of medicine at Brigham and Women's Hospital in Boston, in an editorial that accompanied the two reports (<http://content.nejm.org/cgi/reprint/NEJMe068060.pdf>).

"We may have overestimated the strength of the association between homocysteine and cardiovascular risk in retrospective and cross-sectional studies. We can't always fully adjust for confounding and reverse causality," said Dr. Lonn, a professor of medicine and cardiology at McMaster University,

Hamilton, Ont.

Supplements of folic acid and B vitamins lower serum homocysteine, but they do not reduce CV events in populations with established vascular disease.

The new findings "address a really important public health issue and will have an impact on practice," said Dr. Christopher B. Granger, director of the cardiac care unit at Duke University in Durham, N.C.

The HOPE 2 study enrolled 5,522 patients with a history of vascular disease or diabetes and additional risk factors for atherosclerosis; they were randomized to placebo or a single pill daily containing 2.5 mg folic acid, 50 mg vitamin B₆, and 1 mg vitamin B₁₂. After an average of 5 years, the rate of cardiovascular death, nonfatal MI, or nonfatal stroke—the primary end point—was 18.8% in patients taking the supplement and 19.8% in the controls, a nonsignificant difference. Significantly fewer patients taking the supplement had strokes, compared with the control group (4.0% compared with 5.3%), but the importance of this isolated benefit was discounted by Dr. Lonn because it came in the context of an otherwise neutral trial.

The NORVIT study enrolled 3,749 patients within 7 days after an MI. Patients were randomized to one of four daily regimens: 0.8 mg folic acid, 40 mg vitamin B₆, and 0.4 mg vitamin B₁₂; 0.8 mg folic acid and 0.4 mg vitamin B₁₂; 40 mg vitamin B₆; or placebo.

After an average follow-up of 3 years, treatment with folic acid in combination with vitamin B₁₂, with or without vitamin B₆, did not significantly reduce the primary end point—the combined rate of sudden coronary death, fatal and nonfatal MI, and fatal and nonfatal stroke. In fact, there was a trend toward an increased rate of events among patients taking B vitamins, especially in the subgroup taking folic acid and vitamins B₆ and B₁₂. ■

1. Raskin P, Allen E, Hollander P, et al, for the INITIATE Study Group. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care*. 2005;28:260-265. 2. Garber AJ, Wahlen J, Wahl T, et al. Attainment of glycemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (the 1-2-3 study). *Diabetes Obes Metab*. 2006;8:58-66. 3. Boehm BO, Home PD, Behrend C, Kamp NM, Lindholm A. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients. *Diabet Med*. 2002;19:393-399. 4. Boehm BO, Vaz JA, Brøndsted L, Home PD. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. *Eur J Intern Med*. 2004;15:496-502. 5. Weyer C, Heise T, Heinemann L. Insulin aspart in a 30/70 premixed formulation. Pharmacodynamic properties of a rapid-acting insulin analog in stable mixture. *Diabetes Care*. 1997;20:1612-1614. 6. Niskanen L, Jensen LE, Råstam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. *Clin Ther*. 2004;26:531-540.

NovoLog[®] Mix 70/30
70% insulin aspart protamine suspension and 30% insulin aspart injection, (rDNA origin)

Mealtime and in-between time

BRIEF SUMMARY. PLEASE CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

NovoLog Mix 70/30 is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

CONTRAINDICATIONS

NovoLog Mix 70/30 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog Mix 70/30 or one of its excipients.

WARNINGS

Because NovoLog Mix 70/30 has peak pharmacodynamic activity one hour after injection, it should be administered with meals.

NovoLog Mix 70/30 should not be administered intravenously.

NovoLog Mix 70/30 is not to be used in insulin infusion pumps.

NovoLog Mix 70/30 should not be mixed with any other insulin product.

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog Mix 70/30. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

PRECAUTIONS

General

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of NovoLog Mix 70/30 and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level).

Fixed ratio insulins are typically dosed on a twice daily basis, i.e., before breakfast and supper, with each dose intended to cover two meals or a meal and snack. The dose of insulin required to provide adequate glycemic control for one of the meals may result in hyper- or hypoglycemia for the other meal. The pharmacodynamic profile may also be inadequate for patients (e.g., pregnant women) who require more frequent meals.

Adjustments in insulin dose or insulin type may be needed during illness, emotional stress, and other physiologic stress in addition to changes in meals and exercise.

The pharmacokinetic and pharmacodynamic profiles of all insulins may be altered by the site used for injection and the degree of vascularization of the site. Smoking, temperature, and exercise contribute to variations in blood flow and insulin absorption. These and other factors contribute to inter- and intra-patient variability.

Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

Hypoglycemia - As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog Mix 70/30. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal Impairment - Clinical or pharmacology studies with NovoLog Mix 70/30 in diabetic patients with various degrees of renal impairment have not been conducted. As with other insulins, the requirements for NovoLog Mix 70/30 may be reduced in patients with renal impairment.

Hepatic Impairment - Clinical or pharmacology studies with NovoLog Mix 70/30 in diabetic patients with various degrees of hepatic impairment have not been conducted. As with other insulins, the requirements for NovoLog Mix 70/30 may be reduced in patients with hepatic impairment.

Allergy - Local Reactions - Erythema, swelling, and pruritus at the injection site have been observed with NovoLog Mix 70/30 as with other insulin therapy. Reactions may be related to the insulin molecule, other components in the insulin preparation including protamine and cresol, components in skin cleansing agents, or injection techniques.

Systemic Reactions - Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient.

Antibody production - Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in the 3-month, open-label comparator trial as well as in a long-term extension trial. Changes in cross-reactive antibodies were more common after NovoLog Mix 70/30 than with Novolin[®] 70/30 but these changes did not correlate with change in HbA1c or increase in insulin dose. The clinical significance of these antibodies has not been established. Antibodies did not increase further after long-term exposure (>6 months) to NovoLog Mix 70/30.

Information for patients - Patients should be informed about potential risks and advantages of NovoLog Mix 70/30 therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction for use of injection devices, and proper storage of insulin.

Female patients should be advised to discuss with their physician if they intend to, or if they become, pregnant because information is not available on the use of NovoLog Mix 70/30 during pregnancy or lactation (see PRECAUTIONS, Pregnancy).

Laboratory Tests - The therapeutic response to NovoLog Mix 70/30 should be assessed by measurement of serum or blood glucose and glycosylated hemoglobin.

Drug Interactions - A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring. The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).

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.

In addition, under the influence of sympatholytic medical products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

Mixing of Insulins

NovoLog Mix 70/30 should not be mixed with any other insulin product.

Carcinogenicity, Mutagenicity, Impairment of Fertility Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog Mix 70/30. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog[®], the rapid-acting component of NovoLog Mix 70/30, at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for NovoLog was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and in ex vivo UDS test in rat liver hepatocytes. In fertility studies in male and female rats, NovoLog at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area) had no direct adverse effects on male and female fertility, or on general reproductive performance of animals.

Pregnancy-Teratogenic Effects—Pregnancy Category C

Animal reproduction studies have not been conducted with NovoLog Mix 70/30. However, reproductive toxicology and teratology studies have been performed with NovoLog (the rapid-acting component of NovoLog Mix 70/30) and regular human insulin in rats and rabbits. In these studies, NovoLog was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of NovoLog did not differ from those observed

with subcutaneous regular human insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32-times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area), and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits based on U/body surface area.

It is not known whether NovoLog Mix 70/30 can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or NovoLog in pregnant women. NovoLog Mix 70/30 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers - It is unknown whether NovoLog Mix 70/30 is excreted in human milk as is human insulin. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or NovoLog in lactating women.

Pediatric Use - Safety and effectiveness of NovoLog Mix 70/30 in children have not been established.

Geriatric Use - Clinical studies of NovoLog Mix 70/30 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

ADVERSE REACTIONS

Clinical trials comparing NovoLog Mix 70/30 with Novolin 70/30 did not demonstrate a difference in frequency of adverse events between the two treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as whole: Allergic reactions (see PRECAUTIONS, Allergy).

Skin and Appendages: Local injection site reactions or rash or pruritus, as with other insulin therapies, occurred in 7% of all patients on NovoLog Mix 70/30 and 5% on Novolin 70/30. Rash led to withdrawal of therapy in <1% of patients on either drug (see PRECAUTIONS, Allergy).

Hypoglycemia: see WARNINGS and PRECAUTIONS.

Other: Small elevations in alkaline phosphatase were observed in patients treated in NovoLog controlled clinical trials. There have been no clinical consequences of these laboratory findings.

OVERDOSAGE

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

More detailed information is available on request.

Rx only

Date of issue: November 21, 2005

Manufactured For Novo Nordisk Inc., Princeton, New Jersey 08540
Manufactured By Novo Nordisk A/S, 2880 Bagsvaerd, Denmark
www.novonordisk-us.com

Novolin[®], NovoLog[®], and Novo Nordisk[®] are trademarks of Novo Nordisk A/S.

License under U.S. Patent No. 5,618,913 and Des. 347,894.

© 2005 Novo Nordisk Inc. 126208R December 2005

