

# Addressing Depression in Diabetic Patients Pays Off

BY NANCY WALSH  
New York Bureau

Older depressed patients with diabetes who were treated in primary care practices using a depression care management program had lower 5-year all-cause mortality than did those treated with usual care, a study has found.

Depression and diabetes are closely linked, with depression being a risk factor

for diabetes while also contributing to poor glucose control as well being associated with micro- and macrovascular complications.

Previous investigations have suggested that depression increases the risk of death among patients with diabetes, but the potential effects of an intervention to modify this risk have not previously been evaluated.

Using data from the randomized PROSPECT (Prevention of Suicide in

Primary Care Elderly: Collaborative Trial) and the National Death Index, Dr. Hillary R. Bogner of the department of family medicine and community health at the University of Pennsylvania, Philadelphia, and colleagues investigated the effects on mortality of a primary care-based intervention in depressed patients with diabetes.

PROSPECT included 20 primary care practices from New York, Philadelphia, and Pittsburgh. Depression care man-

agers worked with 10 of the practices, providing guideline-based treatment recommendations to physicians, helping patients with adherence, and providing follow-up care. Citalopram (Celexa) and interpersonal psychotherapy were provided at no cost.

In the other 10 practices, the primary care physicians were given informational materials and treatment guidelines on geriatric depression, but no specific management recommendations were provided.

The analysis included 584 depressed patients with a mean age of 70.3 years. Among this cohort, 72.3% were women, 69.7% were white, and 21.2% reported a history of diabetes.

After 5 years, 110 patients had died. The mortality rate among depressed patients with diabetes in the intervention group was 68.2/1,000 person-years,

**Depressed patients with diabetes in the intervention group were significantly less likely to have died during the 5-year follow-up period than were those in the usual care group.**

whereas the rate in depressed patients with diabetes in the usual care group was 103.4/1,000 person-years (Diabetes Care, Aug. 23 [Epub ahead of print]).

Depressed patients without diabetes in both groups had similar mortality rates,

with those in the intervention group having a mortality rate of 36/1,000 person-years and those in the usual care group having a rate of 38.2/1,000 patient-years.

After adjusting for multiple factors, which included baseline imbalances in age, gender, education, and number of medical conditions, the investigators found that depressed patients with diabetes in the intervention group were significantly less likely to have died during the 5-year follow-up period than were depressed patients with diabetes in the usual care group. The adjusted hazard ratio was 0.49.

In contrast, depressed patients without diabetes in the intervention group were not at decreased risk, compared with depressed patients without diabetes in the usual care group.

According to the investigators, these findings suggest that "the intervention attenuates the influence of diabetes on mortality risk among older adults with depression."

They concluded that a depression care management intervention can significantly reduce all-cause mortality among depressed patients with diabetes, and that models of care that integrate depression management into the care of diabetes should be developed and more widely implemented.

The investigation was provided funding by the National Institute of Mental Health. ■

**References:** 1. 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(10):1612-1614. 2. 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(2):260-265. 3. Garber AJ, Wahlen J, Wahl T, et al. Attainment of glycaemic 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(1):58-66. 4. Data on file. Novo Nordisk Inc, Princeton, NJ. 5. IMS Health Inc. Q3 2005 IMS formulary focus data, interstudy lives. Valid as of December 2006.

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

**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, floxetine, 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.

© 2006 Novo Nordisk Inc. 126208R1 July 2006

