

# Dapagliflozin Lowers Glucose by Raising Glycosuria

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SAN FRANCISCO — A novel investigational agent that suppresses resorption of glucose in the kidney improved glycemic control in a 12-week trial of 389 treatment-naïve patients with type 2 diabetes.

Bristol-Myers Squibb Co.'s dapagliflozin selectively inhibits the renal sodium-glucose cotransporter 2 (SGLT2), which is the primary transporter of glucose in the kidney, while avoiding the intestinal glucose transporter SGLT1. The inhibition of SGLT2 modulates resorption of glucose in the proximal tubule, which results in excretion of glucose into the urine.

Previous studies have shown that SGLT2 inhibition reduces blood glucose independently of insulin secretion or action and also results in urinary loss of calories, Dr. James F. List said at the annual scientific sessions of the American Diabetes Association.

Dr. List, associate director of global clinical research for Bristol-Myers Squibb Co., Princeton, N.J., presented results from the phase IIb dose-ranging study of dapagliflozin. After a 2-week placebo lead-in phase, the patients were randomized in equal ratios to either once-daily dapagliflozin in doses of 2.5, 5, 10, 20, and 50 mg, metformin (750 mg titrated to 1,500 mg), or placebo for 12 weeks. The 389 patients had a mean age of about 55 years, a mean weight of 89 kg, and a mean body mass index of 31 kg/m<sup>2</sup>. Half of the subjects were female.

Mean hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) values ranged from 7.7% to 8.0% in all treatment arms and were similar to the median HbA<sub>1c</sub> in all groups except the 20-mg arm, which had a median HbA<sub>1c</sub> of 7.4%. Mean fasting plasma glucose (FPG) was about 150 mg/dL in all the treatment arms. At baseline, glycosuria levels ranged from 6 g in 24 hours to 11g/24 hours.

Reduction in HbA<sub>1c</sub> at 12 weeks, the primary end point, was significant in all dapagliflozin dose groups, ranging from 0.55 percentage points in the 20-mg group to 0.90 in the 50-mg group. Reductions in HbA<sub>1c</sub> were 0.71 with 2.5 mg and 0.72 with 5.0 mg, similar to the 0.73 seen with metformin. The placebo group, in contrast, had a reduction of only 0.18. Dose-dependent drops in FPG were similarly significant in all of the dapagliflozin treatment arms, from 16.2 mg/dL in the 2.5-mg treatment group, to 21.1 mg/dL in the 10-mg arm, to 30.5 mg/dL in the group receiving 50 mg dapagliflozin. Reductions in FPG averaged 18.0 mg/dL with metformin and just 5.8 mg/dL with placebo.

Changes in postprandial glucose, assessed by 75-g 3-hour oral glucose tolerance test, also were significant with all doses of dapagliflozin, compared with placebo. However, unlike FPG, those reductions showed no clear dose-dependency, Dr. List said.

The normalized 24-hour urinary glucose:creatinine ratio ranged from 31.72 g/g creatinine at the 2.5-mg dose to 64.75 g/g creatinine for the 20-mg dose, also significant and dose-dependent. There were no changes in those ratios for either metformin or placebo.

The nonnormalized values, expressed as total urinary glucose in 24 hours at week 12, ranged from 51.8 g/day with the lowest dose to a high of 85 g/day with the 20-mg dose (the 50-mg value was similar), compared with baseline values of 5.8-10.9 g/day. That degree of glycosuria translates to a loss of 208-340 calories/day, Dr. List noted.

Changes in weight ranged from 2.5 kg with the 5-mg

dapagliflozin dose to 3.4 kg for both the 20-mg and 50-mg doses, compared with 1.7 kg and 1.2 kg with metformin and placebo, respectively. There were no significant changes in serum sodium, potassium, calcium, or urinary calcium, and no changes in renal function assessed by serum creatinine and by measured 24-hour creatinine clearance.

Adverse events were evenly distributed among the study arms, with 63% of the dapagliflozin groups reporting at least one event of any kind, compared with 68% of the metformin patients and 54% with placebo. There were no deaths, and a total of five serious events that were evenly distributed among the dose arms. Discontinuations due to adverse events were also similar between groups, with no particular event standing out, he said.

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Hypoglycemia (defined as a confirmed glucose value of 50 mg/dL or below) was not increased in the dapagliflozin groups, in which it ranged from 6%-10%, compared with 9% in the metformin group and 4% with placebo. Rates of urinary tract infections—a concern because of the possibility that the excess urinary glucose could serve as a growth medium for microorganisms—were 5%-12% with dapagliflozin, compared with 9% and 6% for metformin and placebo, respectively.

Genital infections occurred in 2%-3% of the dapagliflozin groups, compared with 2% on metformin and none with placebo. Hypotension—a theoretical concern because of the osmotic diuretic effect of the urinary glucose—was seen in one patient on 50 mg dapagliflozin, two metformin patients, and one on placebo.

Dapagliflozin is now in phase III testing. ■

## Roux-En-Y Bypass Helps Obese Meet Type 2 Treatment Goals

BY ALICIA AULT  
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SAN FRANCISCO — Roux-en-Y gastric bypass surgery is effective in helping people with type 2 diabetes meet the American Diabetes Association goals for hemoglobin A<sub>1c</sub>, systolic blood pressure, and LDL cholesterol, according to a retrospective study presented June 16 at the annual meeting of the Endocrine Society.

Dr. Daniel Leslie of the University of Minnesota, Minneapolis, said that his study was the first to report on the effectiveness of Roux-en-Y in meeting treatment goals set by the American Diabetes Association (ADA) in 2004 for the management of type 2 diabetes.

Dr. Leslie and colleagues reviewed all Roux-en-Y gastric bypass procedures conducted at the University of Minnesota between 2001 and 2007. Eighty-five percent of the procedures were done laparoscopically. There were a total of 2,210 consecutive surgeries, and of those patients, 564 had type 2 diabetes.

But only 338 patients had all three measures—HbA<sub>1c</sub>, systolic blood pressure, and LDL cholesterol—available at baseline. Only 169 patients had all three measures available both pre- and postoperatively, Dr. Leslie said.

The average age of the patients was 51 years; 79% (133) were women and 85% (143) were white. The average duration of diabetes was 9 years, although 39% (66) of the group had diabetes for more than 10 years. Patients

were followed for an average of 26 months.

Dr. Leslie estimated that 32% (54) of the patients met the ADA goals after surgery. Only 9.5% (16) of patients had met those goals before gastric bypass. The duration of diabetes was not associated with meeting the goals.

The ADA goals included an HbA<sub>1c</sub> of 7% or less, LDL cholesterol of 100 mg/dL or less, and systolic blood pressure of 130 mm Hg or less.

The HbA<sub>1c</sub> value improved from 7.7% on average to 6.2% after the procedure. Systolic blood pressure dropped from an average of 136 mm Hg to 128 mm Hg. The use of oral antidiabetic medications and insulin dropped dramatically, Dr. Leslie noted. Use of cholesterol-lowering and blood pressure-lowering drugs also fell, but the need for antihypertensives increased after about 24 months, Dr. Leslie said.

The mean body mass index dropped from 49 to 33 kg/m<sup>2</sup> after the surgery.

"Gastric bypass is a useful tool for improving diabetes treatment goals," said Dr. Leslie, although he noted that the study was not controlled. He also said that surgery improved glycemic control the most out of all the parameters measured, but that the procedure should not be used to replace any other modalities aimed at cardiovascular risk factors.

Dr. Leslie disclosed that his surgery division receives grant support from Covidien AG and Ethicon Endo-Surgery Inc., but said that he does not personally receive any industry grants. ■

## Diabetes, Depression Appear to Have Bidirectional Association

Type 2 diabetes and depressive symptoms have a bidirectional association: People with diabetes are at increased risk of developing depressive symptoms, and those with depressive symptoms are at increased risk of developing diabetes, according to a report in the June 18 issue of the *Journal of the American Medical Association*.

These results, from a population-based longitudinal study that followed approximately 5,000 middle-aged subjects for up to 5 years, are the first to demonstrate a bidirectional association between "these two serious long-term diseases," said Dr. Sherita Hill Golden of Johns Hopkins University, Baltimore, and her associates.

The findings suggest that interventions targeting depression may complement diabetes prevention strategies, and that patients who already have diabetes perhaps should be screened for depressive symptoms, the investigators noted (*JAMA* 2008;299:2751-9).

They examined the relationship between diabetes and depression using data from a multicenter longitudinal cohort study of men and women whose mean age was in the 60s and who resided in six U.S. com-

munities. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) scale, a 20-item questionnaire designed to evaluate such symptoms in community populations.

Among subjects who had no depressive symptoms at baseline, those with type 2 diabetes were at significantly higher risk for developing depressive symptoms during follow-up, independent of their body mass index, socioeconomic status, and comorbidities.

It is possible that the psychological stress of managing diabetes may lead to depression, or that the complications and comorbidities of the disease may increase depressive symptoms, Dr. Golden and her associates said.

In addition, subjects who had depressive symptoms at baseline were at modestly increased risk of developing diabetes during follow-up, independent of sociodemographic, economic, and metabolic factors.

The National Heart, Lung, and Blood Institute was a sponsor of this study. Dr. Golden serves on the Merck Clinical Diabetes Advisory Board and has received an unrestricted educational grant from Novo Nordisk in the past.

—Mary Ann Moon