Metformin Cut Deaths in Patients at Risk for CVD

BY MICHELE G. SULLIVAN

FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN DIABETES ASSOCIATION

ORLANDO — Metformin use was associated with a significant decrease in the risk of all-cause death among diabetic patients at risk for cardiovascular events.

The subanalysis of the Reduction of Atherothrombosis for Continued Health (REACH) Registry found that subjects with type 2 diabetes who took metformin were 24% less likely to die from all-cause mortality over 2 years than were those who did not take the drug. The association remained significant even after researchers controlled for age and gender, and after factoring in a number of baseline characteristics that varied significantly between the groups.

"Given the diversity of the 44 countries and widely different practice settings involved in the registry, we think these data are highly relevant," Dr. Ronan Roussel said at the annual meeting of the American Diabetes Association. While perhaps not sufficient to make practice recommendations, he did say the results are strong enough to prompt clinical trials, especially when viewed in the context of the growing body of evidence about metformin's cardioprotective effects.

The REACH Registry was established to track outcomes in patients with atherothrombosis or atherothrombotic risk factors. Almost 70,000 patients were enrolled. They were either symptomatic, with documented cardiovascular, coronary artery or peripheral artery disease; or asymptomatic with at least three risk factors for atherothrombosis. Of this group, 19,699 had type 2 diabetes and 2-year outcomes data. Dr. Roussel of the Groupe Hospitalier Bichat-Claude Bernard, Paris, and his colleagues compared those who were taking metformin at baseline with those who were not. Metformin was taken by 40% of the patients.

VITALS

Major Finding: Patients with type 2 diabetes and cardiovascular risk factors who took metformin had a 24% decrease in the risk of death over a 2-year period.

Data Source: A subanalysis of the international REACH Registry, focusing on 19,699 patients with type 2 diabetes.

Disclosures: The registry is sponsored by Sanofi-Aventis, Bristol-Myers Squibb, and the Waksman Foundation, Tokyo. Dr. Roussel disclosed that he has received research support or consulting fees from Sanofi-Aventis, Servier Laboratories, Roche, Eli Lilly & Co., Novo Nordisk Inc., Medtronic Inc., and LifeScan Inc.

There were some significant baseline differences between the groups, Dr. Roussel noted. Patients taking metformin were significantly younger (67 vs. 69 years), had a higher average fasting blood glucose (138 vs. 131 mg/dL), and higher systolic blood pressure (138 vs. 136 mm Hg). Prior arterial disease was present in 80% of those taking metformin and 75% of those not. Metformin users were also taking significantly more cardiovascular drugs, including aspirin (74% vs. 69%), statins (75% vs. 67%), and angiotensin-converting enzyme inhibitors (54% vs. 49%).

Over the 2-year follow-up period, there were 1,270 deaths. After researchers adjusted for gender and age only, metformin was associated with a 33% reduction in the risk of all-cause death. A Kaplan-Meier analysis showed that the mortality trajectories began to separate early, with a significant difference appearing around 6 months.

After adjustment for the other factors, the mortality difference still remained significant in favor of metformin use, with a 24% risk reduction in all-cause death.

In an age analysis, with subjects split into groups 40-65 years, 65-80 years, and older than 80 years, the risk reductions were significant for the youngest group (37%), and the middle group (23%). The oldest subjects did not have a survival advantage with the drug.

Metformin also improved the odds of survival in patients with existing congestive heart failure, conferring a significant 31% reduction in the risk of death.

While renal insufficiency is considered a contraindication to metformin use, Dr. Roussel noted that REACH subjects with moderately impaired renal function appeared to benefit from the drug. Those with a glomerular filtration rate of 30-60 mL/min had a significant 36% reduction in the risk of death; those with a GFR of less than 30 mL/min or greater than 60 mL/min did not gain a significant survival advantage.

Subjects who were taking insulin as well as metformin benefited more than did those who were taking metformin alone (hazard ratio 0.64 vs. 0.80). ■

Investigational Insulin Analogue Effective, Safe in Early Trials

BY MIRIAM E. TUCKER

FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN DIABETES ASSOCIATION

ORLANDO — A novel investigational ultra–long-acting insulin analogue produced glycemic control similar to insulin glargine when injected once daily or three times weekly, with better postdinner control.

The analogue, insulin degludec, forms soluble multihexamer depots after subcutaneous injection, resulting in a longer duration of action than any available insulin analogue. Novo Nordisk is developing two formulations, one of degludec alone and the other a 70/30 combination with the short-acting insulin aspart. There is no 70/30 formulation on the market that includes a basal insulin, Dr. Bernard Zinman said in an interview.

At the trial's end, mean daily insulin doses were lower for the analogue than for glargine.

DR. HEISE

Data from two phase II proof-of-concept trials presented at the scientific sessions suggest that insulin degludec provides glucose control comparable to regimens using available basal insulins, with the advantages of fewer injections, better postdinner control, and possibly less hypoglycemia.

Dr. Zinman, professor of medicine and director of the Leadership Sinai Centre for Diabetes at the University of Toronto, reported on a 16-week, open-label, parallel-group, treat-to-target trial in which 245 patients with type 2 diabetes that was inadequately controlled by oral agents were randomized to one of four arms: the 70/30 formulation; a once-daily 55/45 formulation, which has since been discontinued; a three-times-weekly formulation (Monday, Wednesday, and Friday); or insulin glargine. All insulins were injected in the evening and titrated to target a fasting plasma glucose (FPG) of 72-108 mg/dL. All patients also continued taking metformin.

At baseline, the patients had a mean age of 54 years, mean hemoglobin A_{1c} of 8.7%, mean FPG of 184 mg/dL, and mean body mass index of 29.5 kg/m^2.

After 16 weeks, reduction in HbA_{1c} from baseline was similar across treatment arms, with drops of 1.3 percentage points with once-daily insulin degludec, 1.5 points with thrice-weekly degludec, and 1.5 points with insulin glargine. Final mean HbA_{1c} also did not differ between groups, at 7.4% for once-daily degludec, 7.3% for the thrice-weekly version, and 7.2% for insulin glargine. Results for the 55/45 formulation were not reported.

FPG reductions were similar, as were final mean FPG (113, 116, and 115 mg/dL). Mean weekly insulin doses were similar at the end of the trial.

Rates of confirmed hypoglycemia (plasma glucose value of less than 56 mg/dL or requiring assistance) were low and only one severe event was reported (for thrice-weekly degludec). The rate of confirmed hypoglycemia was lower with once-daily degludec than with the thrice-weekly formulation and glargine, but the differences were not statistically significant (0.6, 2.3, 1.1 events per patient-year, respectively).

The proportion of subjects with adverse events did not differ significantly across treatment arms, with no specific patterns or clustering. Most adverse events were mild or moderate in severity, he said.

Dr. Tim Heise, CEO of the Profil Institute for Metabolic Research Ltd., Neuss, Germany, presented the data on the 70/30 degludec-aspart combination (IDegAsp). This 16-week open-label, parallel-group, treat-to-target trial randomized 178 patients who were inadequately controlled on oral agents to receive either once-daily 70/30 IDegAsp, the alternate 55/45 combination, or insulin glargine, all in combination with metformin. (Because the 55/45 combination has been discontinued, reports for that group are not available.)

Both insulins were dosed before dinner and titrated to an FPG target of 72-108 mg/dL. The patients had a mean age of 59 years, HbA_{1c} of 8.5%, and FPG of 209 mg/dL. After 16 weeks, mean HbA_{1c} decreased from baseline in both treatment groups, by 1.31 percentage points with IDegAsp and by 1.29 with insulin glargine. HbA_{1c} values were comparable: 7.0% for IDegAsp and 7.1% for insulin glargine. The proportions achieving HbA_{1c} values of less than 7.0% without confirmed hypoglycemia were 51% for IDegAsp and 50% with glargine, Dr. Heise reported.

The mean increase in plasma glucose at 2 hours after dinner was significantly lower for degludec than for glargine (2 mg/dL for IDegAsp versus 29 mg/dL with glargine), while FPG was similar between groups (122 and 126 mg/dL, respectively). At the trial's end, mean daily insulin doses were lower for IDegAsp than for insulin glargine.

No severe hypoglycemic events were reported. Rates of confirmed hypoglycemia (PG less than 56 mg/dL) were lower for IDegAsp and glargine than for the 55/45 version (1.2, 0.7, and 2.4 events per patient-year, respectively). One confirmed nocturnal hypoglycemic event was reported for IDegAsp in one patient and three events were reported in three patients on insulin glargine. No other adverse events were reported.

This study was funded by Novo Nordisk, which is now proceeding with phase III trials of insulin degludec.

Dr. Zinman's and Dr. Heise's institution receive research funding from manufacturers of diabetes-related products. Dr. Zinman has financial ties with GlaxoSmithKline, Merck, Amylin Pharmaceuticals Inc., Boehringer Ingelheim Pharmaceuticals Inc., Eli Lilly and Co., and Medtronic Minimed. Dr. Heise serves on an advisory panel for Novo Nordisk. ■