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. 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 other 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 patients 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.

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 significantly more cardio-vascular 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 clinical insufficiency is considered a contraindication to metformin, 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 much 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, and possibly fewer hypoglycemia.

The subanalysis of the international REACH Registry focusing on 19,699 patients with 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.

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

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 patients were insulin injections 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 A1c (HbA1c) of 8.7%, mean FPG of 184 mg/dL, and mean body mass index of 29.5 kg/m². After 16 weeks, reduction in HbA1c from baseline was similar 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 Profile 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 inadequate 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.

Data from 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. Patients had a mean age of 59 years, HbA1c of 8.5%, and FPG of 209 mg/dL. After 16 weeks, mean HbA1c decreased from baseline in both treatment groups, by 1.31 percentage points with IDegAsp and by 1.29 with insulin glargine. HbA1c values were comparable: 7.0% for IDegAsp and 7.1% for insulin glargine. The proportions achieving HbA1c 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 (37 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 (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. Zinman’s and Dr. Heise’s institution receive research funding from manufacturers of diabetes-related products. Dr. Zinman has financial ties with Glaxo-SmithKline, Merck, Amylin Pharmaceutical Inc., Boehringer Ingelheim Pharmaceuticals Inc., Eli Lilly and Co., and Medtronic Minimed. Dr. Heise serves on an advisory panel for Novo Nordisk.