Drug Combo Trumps Rosuvastatin in Cutting LDL

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COPENHAGEN — A combination of ezetimibe and simvastatin provides additional lipid-modifying benefits, compared with rosuvastatin monotherapy in patients with type 2 diabetes or with metabolic syndrome without diabetes, Dr. Alberico L. Catapano said at the annual meeting of the European Association for the Study of Diabetes.

"Overall, ezetimibe/simvastatin, a single-tablet, dual-cholesterol inhibitor, offers an effective and well-tolerated lipid-modifying option for the treatment of hypercholesterolemia in patients with type 2 diabetes and metabolic syndrome," said Dr. Catapano, of the department of pharmacological sciences at the University of Milan.

In a post hoc analysis of data from a multicenter, double-blind, randomized, parallel-group, 6-week study sponsored by Merck & Co., 375 patients with type 2 diabetes, 840 with metabolic syndrome but without diabetes, 1,722 with neither condition, and 22 who could not be placed in a category because of missing data were randomized to one of six treatment groups: ezetimibe/simvastatin (E/S) in doses of 10 mg/20 mg (respectively), 10 mg/40 mg, or 10 mg/80 mg; or rosuvastatin (R) in doses of 10, 20, or 40 mg. All had hypercholesterolemia, defined as an LDL cholesterol level of 145-249 mg/dL (3.7-6.4 mmol/L) with triglycerides at or below 350 mg/dL (4 mmol/L).

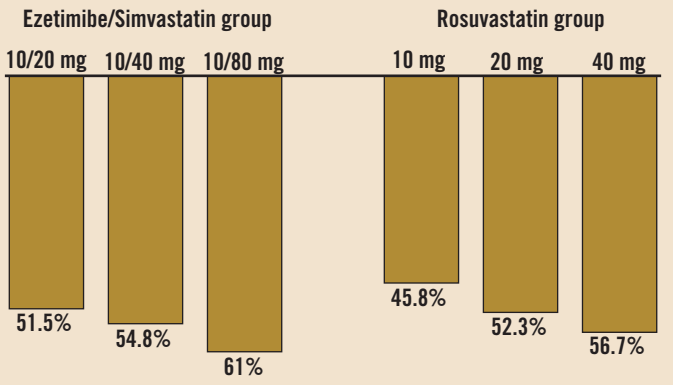
Among the cohort of 2,959 patients, significant reductions in LDL cholesterol from baseline were seen among the E/S group at the usual starting, next highest, and maximum dosing levels. (See chart.)

Across all doses, the difference in LDL-cholesterol reduction between E/S and R was significant for the whole cohort (55.8% vs. 51.6%). LDL-cholesterol lowering was also greater with E/S in patients with type 2 diabetes (58.5% vs. 54.2%), nondiabetics with metabolic syndrome (55% vs. 51.8%), and those with neither (55.6% vs. 51%).

Overall, 95.3% of the E/S group, compared with 92.1% of the R group, attained the LDL cholesterol goals of less than 100 mg/dL (2.6 mmol/L) for the diabetics, 130 mg/dL (3.4 mmol/L) for the nondiabetics with metabolic syndrome, or 160 mg/dL (4.1 mmol/L) for the group with neither. A total of 88.2% of the E/S patients vs. 81.9% of the R patients achieved an LDL-cholesterol level of less than 100 mg/dL (2.6 mmol/L), whereas 45.3% vs. 29.5% reached an LDL-cholesterol level of less than 70 mg/dL (1.8 mmol/L). All of these differences were significant, he said. Reductions in total cholesterol, non-HDL cholesterol, apolipoprotein B, and triglycerides were also significantly greater with E/S, whereas there were no significant differences between the two treatments in HDL cholesterol, or high-sensitivity C-reactive protein.

Both drugs were well tolerated, with similar rates of drug-related adverse events (8.1% E/S vs. 7.4% R) and discontinuations because of adverse events (2.2% for both drugs). Proteinuria was higher at baseline in the R group and in those with diabetes. ■

Greater Reductions in LDL-Cholesterol Level With E/S In Type 2 Diabetes and Metabolic Syndrome Patients



Note: Based on a study of 2,959 patients.
Source: Dr. Catapano

ELSEVIER GLOBAL MEDICAL NEWS

Post-MI Mortality Dip Bigger With New Sulfonylureas

COPENHAGEN — Newer-generation sulfonylureas appear to be associated with lower post–myocardial infarction mortality in diabetic patients than are the older-generation agents, Dr. Henriette Thisted reported at the annual meeting of the European Association for the Study of Diabetes.

Sulfonylureas can block the adenosine triphosphate–sensitive potassium channels in the heart, thereby inhibiting the myoprotective effects of ischemic preconditioning. However, recent data suggest only glibenclamide inhibits this protection, whereas newer sulfonylureas, such as gliclazide and glimepiride, do not. The clinical implications of these differences are still unclear because data are sparse, said Dr. Thisted, of the department of clinical epidemiology at Aarhus (Denmark) University Hospital.

Earlier this year, Dr. Thisted and her associates published preliminary findings from a regional Danish hospital database, in which they found a lower rate of MI in patients using gliclazide and glimepiride, compared with those using other sulfonylureas, and a trend toward lower 30-day post-MI mortality in users of gliclazide, compared with users of other sulfonylureas (Am. J. Ther. 2006;13:134-40).

They have now expanded the study nationwide to include 72,913 first-time admissions for MI during 1996-2004 from the Danish National Patient Registry.

The researchers used a national prescription database to identify 3,992 patients as sulfonylurea users, including 2,554 who were taking the "old" sulfonylureas glibenclamide, glipizide, or tolbutamide and 1,438 users of the "new" agents gliclazide or glimepiride.

Those using the older sulfonylureas were older than those using the new agents (73.3 vs. 71.6 years) and had a longer duration of diabetes (14.4% vs. 10.6% had been diagnosed for more than 10 years). They also tended to have more comorbidities.

At 30 days following MI, 24.1% of the old sulfonylurea users had died, compared with 17.9% of the new-agent user group. After adjustment for age, sex, socioeconomic status, diabetes duration, comorbidity index, discharge diagnoses, and use of relevant medications, the new sulfonylurea users still had a 23% lower 30-day mortality rate than did the old-agent users, Dr. Thisted reported.

This apparent advantage in 30-day mortality with new sulfonylureas was also evident during the entire follow-up period, with a mean of 1.68 years: The adjusted mortality rate ratio was 0.78, or a 22% lower risk of death post MI.

For the individual older agents, mortality was 61.7% in the 877 glibenclamide patients, 61.5% of the 436 tolbutamide patients, and 60.9% of the 412 who had been taking glipizide. With the newer agents, 47.9% of the 167 taking gliclazide and 40.7% taking glimepiride died during follow-up. ■

Further Benefit of Pioglitazone Seen in High-Risk Type 2 Patients

COPENHAGEN — Pioglitazone (Actos) demonstrates a beneficial effect on a variety of measures of cardiovascular disease outcome in high-risk patients with type 2 diabetes, speakers said at the annual meeting of the European Association for the Study of Diabetes.

The data come from four subanalyses of the Eli Lilly and Takeda Global Research and Development's PROactive study.

In that study, 5,238 patients with type 2 diabetes and evidence of macrovascular disease were randomized to oral pioglitazone (maximum dose 45 mg/day) or placebo in addition to their other glucose-lowering drugs and other medications.

In a mean follow-up of 34.5 months, pioglitazone nonsignificantly reduced the risk of the composite primary end point of all-cause mortality, nonfatal myocardial infarction (MI), stroke, acute coronary syndrome (ACS), endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle (10% relative risk reduction for experiencing one or more of those events). Pioglitazone significantly reduced the main secondary end point of all-cause mortality, nonfatal MI, and stroke (16% relative risk reduction).

At this year's meeting, Dr. Stuart R. Kupfer, senior medical director of clinical sciences, cardiovascular, at Takeda, in Lincolnshire, Ill., presented statistically significant findings for additional combined end points, including time to all-cause death, nonfatal MI, stroke, or ACS (17% relative risk reduction); cardiovascular (CV) death, MI, stroke, or ACS (18%); cardiovascular death, MI, stroke, or ACS (20%); and fatal or nonfatal MI (22%).

In a second study, presented by Dr. Robert Spanheimer, Takeda's director of diabetes and metabolism, medical and scientific affairs, pioglitazone therapy produced beneficial effects on patient lipid profiles during PROactive, with significantly greater mean decreases in triglycerides and mean increases in HDL cholesterol with pioglitazone, compared with insulin, metformin, and sulfonylurea (each analyzed separately). Triglycerides were reduced by 1.7% from baseline with pioglitazone while increasing 12.5% with placebo. For HDL cholesterol, the increase was 21.3% with pioglitazone vs. 11.3% with placebo. Although LDL cholesterol rose with pioglitazone (12.1% vs. 8.4% with placebo), the overall ratio of LDL-C:HDL-C was significantly improved.

A third analysis, presented in a poster by PROactive lead investigator Dr. John A. Dormandy, compared outcomes between the 984 study subjects who entered the study with a history of prior stroke and the 4,254 without prior stroke.

In those with prior stroke, pioglitazone significantly reduced the risk of recurrent stroke (5.6% vs. 10.2% with placebo), and of the combined end point CV death, MI, or stroke (13.0% vs. 17.7%). There was also a trend of benefit for other combined end points. Pioglitazone had no effect on subsequent strokes among the patients without previous stroke, noted Dr. Dormandy, of St. George's Hospital, London.

Dr. Erland Erdmann, of the University of Cologne, Germany, and chairman of the PROactive executive committee, reported in a poster that there was no significant impact of gender, age (less than 65 years vs. 65 and older), or diabetes duration (less than 5 years vs. 5 years and longer) on the hazard ratios for time to fatal or nonfatal MI, suggesting that "the best estimate for the reduction in risk of recurrent MI for each subgroup is given by that for the entire previous MI cohort." ■