Results from the ACCORD Lipid Study

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study (NCT00000620) does not support the use of combination fibrate and statin therapy compared with statin therapy alone to reduce cardiovascular (CV) risk in high-risk patients with type 2 diabetes mellitus (DM). However, subgroup analyses suggest a treatment interaction that is associated with combination therapy and gender and a possible interaction between combination therapy and severe dyslipidemia.

Henry N. Ginsberg, MD, Columbia University, New York, NY, discussed findings from the ACCORD Lipid Study. The lipid substudy was a randomized, placebo-controlled, double-blind trial that included 5518 participants with stable type 2 DM for >3 months who were at high risk for cardiovascular disease (CVD) events (defined as clinical or subclinical disease or having ≥2 risk factors in addition to type 2 DM; Table 1). All patients were taking simvastatin 20 to 40 mg/day and were randomized to receive either fenofibrate 54 to 160 mg/day (based on estimated glomerular filtration rate) or placebo. The mean follow-up was 4.7 years.

Table 1. Additional Inclusion Criteria for the ACCORD Lipid Study.

Age
≥40 years with history of clinical CVD
≥55 years for all other participants
Lipid Profile
~ Low-Density Lipoprotein (LDL) Cholesterol 60 to 180 mg/dL
~ High-Density Lipoprotein (HDL) Cholesterol
<55 mg/dL for women/blacks
<50 mg/dL for all other participants
~ Triglycerides
<400 mg/dL if on lipid therapy
<750 mg/dL for all other participants

The primary outcome was the first occurrence of a major CV event (defined as nonfatal myocardial infarction [MI], nonfatal stroke, or CV death). Secondary outcomes included the individual components of the primary outcome, an expanded macrovascular outcome (defined as a combination of the primary outcome plus revascularization or hospitalization for congestive heart failure), major coronary disease events (defined as a combination of a fatal coronary event, a nonfatal MI, or unstable angina), hospitalization or death due to heart failure, all stroke, and death from any cause.

There was no significant difference between fenofibrate and placebo for the primary outcome or the prespecified secondary outcomes. The most common adverse event was severe muscle aches/pains, which was similar in both groups regardless of creatine kinase level (40% for both groups). Elevations of creatine kinase were unusual and not different between the two treatment groups. Other serious adverse events were uncommon. Both groups demonstrated increased serum creatinine levels over the course of the study, but the incidence of elevated creatinine was 50% to 100% higher in the fenofibrate group. In contrast to the increases in creatinine in the fenofibrate group, the incidence of both micro- and macroproteinuria was lower in participants who were treated with fenofibrate.

There was evidence of an interaction between gender and fenofibrate + simvastatin combination therapy, suggesting a potential harm for women (9.1% event rate over five years for the fenofibrate group vs a 6.6% event rate over five years for the placebo group) and potential benefit for men (11.2% for fenofibrate vs 13.3% for placebo) with regard to the primary outcome of major CV events (p=0.01 for interaction). When patients with both low HDL levels (≤34 mg/dL) and high triglyceride levels (≥204 mg/dL) were compared with all other participants, a weak heterogeneity was observed, but this interaction did not reach statistical significance (p=0.057 for interaction). However, there was a suggestion of benefit in the subgroup with severe dyslipidemia (12.37% for fenofibrate vs 17.32% for placebo); there was no benefit of fenofibrate in all other participants (10.11% for fenofibrate vs 10.11% for placebo).

While the primary endpoint was not achieved in the ACCORD Lipid study, the interactions that were noted during the subgroup analyses merit further investigation. Whether or not there are gender-specific differences in benefit that are associated with fenofibrate combination therapy has not been established. Additionally, the nonsignificant interaction that was detected in those with significant dyslipidemia requires clarification.

Further Reading: The ACCORD Study. Group *N Engl J Med*. 2010; published online ahead of print.