More Evidence for Cardiovascular Benefits from Anti-Diabetes Medications with Release of LEADER Results

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Highlights:
1. Liraglutide reduced the risk for 3-point MACE by 13%
2. Liraglutide reduced the risk of all-cause death by 15%
3. Liraglutide reduced the risk of cardiovascular death by 22%
4. Liraglutide was associated with increases in gastrointestinal adverse events and heart rate

Liraglutide, a glucose lowering drug, has been shown to safely and effectively lower the overall risk of heart attack, stroke or cardiovascular (CV) death among people with type 2 diabetes (T2D) at high risk for cardiovascular disease. Investigators representing the LEADER trial (Liraglutide Effect and Action in Diabetes-Evaluation of Cardiovascular Outcome Results) presented study results at the 76th Scientific Sessions of the American Diabetes Association in New Orleans on June 13, 2016. Liraglutide, a glucagon-like peptide-1 (GLP-1), stimulates post-prandial insulin secretion and acts as an incretin hormone, thus potentiating glucose-stimulated insulin release and suppressing food intake in humans.

LEADER, designed as a regulatory safety trial, included 9,340 adults with T2D at high risk for heart disease randomly assigned to either liraglutide or placebo and followed for an average of 3.8 years. Participants in both arms of the trial were also treated according to the standard of care, using other medications as needed to control their diabetes, high blood pressure, cholesterol levels and risk of complications from diabetes. The primary outcome was time to first occurrence of 3-point MACE (major adverse cardiac event). The MACE measure was comprised of CV death, non-fatal myocardial infarction (MI) and non-fatal stroke. Key secondary outcomes included an expanded composite of CV outcome (CV death, non-fatal MI, non-fatal stroke, coronary revascularization, unstable angina or hospitalization for heart failure) and all cause death.

Patients in the liraglutide arm experienced a 13% reduced risk of time to first occurrence of CV death, non-fatal heart attack or non-fatal stroke, compared to patients assigned to the placebo group. In addition, participants in the liraglutide group had a 22% reduced risk of CV mortality, 15% reduced risk of all-cause mortality and a 22% reduced risk of new evidence of advanced diabetic kidney disease. Adverse outcomes observed among the liraglutide patients were similar to what has been seen in other trials.

The study results, which went beyond the regulatory requirements that launched the trial, leads investigators to ask if this is a class effect or an effect that is unique to the molecule. One of the investigators suggested that the results from a second trial showing good CV outcomes
from a drug in the GLP-1 class will be presented in September at the Annual Meeting of the European Association for the Study of Diabetes (EASD), thereby validating the consideration that this would be a class effect. A similar question has been asked about empagliflozin following the release of the EMPA-REG Outcomes trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) at the at the 51st Annual Meeting of the EASD in Stockholm, in September, 2015. Empagliflozin, a sodium glucose-cotransporter (SGLT)-2 inhibitor blocks the reabsorption of glucose in the kidneys, thereby promoting excretion of excess glucose in the urine and is thought to control glycemia independently of insulin pathways with a low risk of hypoglycemia. As reported here in *Clinical Therapeutics* (LINK), EMPA-REG Outcomes was also initiated as a safety trial but showed important CV outcomes that had been unexpected at the outset.

Investigators suggested that when taking the results of LEADER and EMPA-REG Outcomes together, clinicians may need to think about what the drug of choice will be as an add-on to metformin. Investigators asked a rhetoric question about how the results of these trials explains benefits: is it a modest decrease in glycosylated hemoglobin levels that wanes over time or is it some composite model in which each element is additive? One of the investigators suggested that the outcomes of this and other trials will change the conversation between providers and patients, to go beyond the need to manage hyperglycemia with T2D but to potentially reduce risk for CV disease, kidney disease and death. Another investigator speculated that a plausible mechanism of action for these drugs is atherosclerosis and and the prevention of disease progression of coronary artery disease, and that this is likely to be the focus of more pre-clinical research moving forward.