Healio

Review of CV outcome trials for diabetes drugs shows neutral or positive results

BOSTON — At the Cardiometabolic Health Conference, **Jay S. Skyler, MD, MACP,** from the division of endocrinology, diabetes and metabolism and the Diabetes Research Institute at University of Miami Miller School of Medicine, presented an update on CV outcome trials of diabetes drugs.

"An FDA guidance was what made these trials come about," Skyler said. "New drugs for diabetes needed to demonstrate they did not increase CVD risk. The way they decided to do that, a little bit arbitrarily, was that upper bound of the two-sided 95% CI from the point estimate of drug vs. control needed to be less than 1.8 for initial approval, and less than 1.3 to be on the market."

Jay S. Skyler

Here are the seven completed trials that he discussed.

SAVOR-TIMI 53

In SAVOR-TIMI 53, 16,492 patients with type 2 diabetes and previous CVD diagnosis were assigned the dipeptidyl-peptidase IV inhibitor saxagliptin (Onglyza, AstraZeneca/Bristol-Myers Squibb) or placebo in addition to the usual care and compared over a median of 2.1 years for first occurrence of CVD death, nonfatal MI or nonfatal stroke.

There was no difference between the groups in the primary endpoint (HR = 1.00; 95% CI, 0.89-1.12), but those assigned saxagliptin were more likely to be hospitalized for HF (3.5% vs. 2.8%; HR = 1.27; 95% CI, 1.07-1.51), Skyler said.

"That raised all sorts of eyebrows," he said. "One of the things demonstrated was that there were biomarkers that predicted HF," including high-sensitivity troponin and N-terminal pro-B natriuretic peptide.

EXAMINE

In 5,380 patients with diabetes diagnosed with ACS 15 to 90 days before randomization, the impact of adding alogliptin (Nesina, Takeda Pharmaceuticals), a DPP-IV inhibitor, or placebo to existing care was evaluated. The primary outcome was CVD death, nonfatal MI or nonfatal stroke, and median follow-up was 1.5 years.

Researchers found no difference in the primary endpoint (HR = 0.96; upper boundary of the one-sided repeated confidence interval, 1.16; *P* < .001 for noninferiority) or in CV death or all-cause mortality. There was no HF signal as seen with saxagliptin.

TECOS

The TECOS trial included 14,671 patients aged 50 years or older with type 2 diabetes and documented vascular disease. Participants were randomly assigned to receive the DPP-IV inhibitor sitagliptin (Januvia, Merck) or placebo on top of ongoing care. Serving as the primary outcome was a composite of CV death, nonfatal MI, nonfatal stroke and hospitalization for unstable angina. Median follow-up was 3 years.

The arms did not differ in the primary endpoint (HR = 0.98; 95% CI, 0.89-1.08) or in all-cause mortality, the primary endpoint minus angina, or hospitalization for HF, Skyler said.

“All three of these showed no benefit, but no increased risk by the standard endpoints,” he said.

ELIXA

This study of lixisenatide (Lyxumia, Sanofi), a glucagon-like peptide-1 receptor agonist, vs. placebo on top of ongoing care in 6,068 patients with diabetes and recent ACS compared the regimens in CV death, nonfatal MI, nonfatal stroke and hospitalization for unstable angina. Median follow-up was 2.1 years.

The investigators did not find a difference in the primary outcome (HR = 1.01; 95% CI, 0.89-1.17), CV mortality, HF hospitalization or all-cause mortality, according to Skyler.

“The caveat is that the patients had to have ACS 5 days to 12 weeks before enrollment,” he said. “That population is going to have more events more quickly, because we know they have coronary disease already. That’s an important factor when we try to analyze these studies.”

EMPA-REG OUTCOME

The EMPA-REG OUTCOME trial evaluated whether 7,020 patients with diabetes and established CVD would differ in CVD death, nonfatal MI or nonfatal stroke when assigned the SGLT2 inhibitor empagliflozin (Jardiance, Boehringer Ingelheim) or placebo in addition to usual care. Patients were followed for an average of 3.1 years.

Empagliflozin was the first diabetes drug to show a CV benefit, Skyler said. Those assigned empagliflozin were at reduced risk for the primary endpoint vs. placebo (HR = 0.86; 95% CI, 0.74-0.99), driven by CV death (HR = 0.62; 95% CI, 0.49-0.77). The empagliflozin group also had lower risk for HF hospitalization and all-cause mortality.

“The curves diverged right from the get-go,” he said. “Those were dramatic outcomes, particularly for CV death. There was a divergence of components of the primary endpoint.”

LEADER

Patients with type 2 diabetes and aged 50 or older who had prior CVD or aged 60 and older at high risk for CVD were assigned liraglutide (Victoza, Novo Nordisk), a GLP-1 receptor agonist, or placebo in addition to ongoing care and followed for a median of 3.8 years to determine differences in CVD death, nonfatal MI and nonfatal stroke.

Among the 9,340 patients, those assigned liraglutide were at reduced risk for the primary outcome (HR = 0.87; 95% CI, 0.78-0.97). Skyler said the liraglutide group also had less risk for CV death; the primary endpoint plus coronary revascularization, hospitalization for unstable angina or HF hospitalization; and all-cause mortality. There was no difference in HF hospitalization, he said.

“Unlike what we saw with EMPA-REG, the curves don’t start to diverge until after 12 months for the primary outcome,” he said.

SUSTAIN-6

The SUSTAIN-6 trial studied patients with diabetes aged 50 or older who had prior CVD or aged 60 and older at high risk for CVD. Researchers assigned 3,297 patients to the investigational GLP-1 receptor agonist semaglutide (Novo Nordisk) or placebo in addition to the usual care. Median follow-up for the trial, designed as a pre-approval study, was 2.1 years.

The primary outcome of CV death, nonfatal MI or nonfatal stroke was lower in the semaglutide group (HR = 0.74; 95% CI, 0.58-0.95), driven by a reduction in nonfatal stroke (HR = 0.61; 95% CI, 0.38-0.99). Differences in the other components of the primary endpoint were not statistically significant, and the same was true for all-cause mortality, Skyler said.

“It was a bit of a surprise” that 254 events was enough to show a difference, he said. “It’s a little odd, in my view, in the way the outcomes came about” since CV death, a major factor in the other two positive trials, was not one here.

“There needs to be a lot more analysis at a patient level looking for issues that might help us understand these [outcomes],” he said. “I expect that to be forthcoming.” – *by Erik Swain*

Reference:

Skyler JS. Update on Cardiovascular Outcome Trials in Diabetes. Presented at: Cardiometabolic Health Congress; Oct. 5-8, 2016; Boston.

Disclosure: Skyler reports financial relationships with multiple pharmaceutical companies.