New drug fails to improve diabetes-related heart failure

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One of the first studies to attempt to treat early-stage heart failure in patients with Type 2 diabetes did not meet its primary endpoint, but a preplanned subgroup analysis found a statistically significant effect of treatment in patients who were not taking SGLT2 inhibitors or GLP-1 RAs, which are antidiabetic medications that also have benefits for the heart. The research was presented at the American College of Cardiology's Annual Scientific Session.

A decline in exercise ability is a hallmark of progression to overt heart failure. The international ARISE-HF trial was designed to test the effectiveness of the investigational drug AT-001 at stabilizing exercise capacity in patients with diabetic cardiomyopathy.

The study's primary endpoint was the difference in the maximum amount of oxygen each patient could take in (peak VO2) between the placebo group and the group receiving a higher dose AT-001 in the time from an initial exercise test at study entry and then 15 months later.

"Although our primary endpoint fell short of statistical significance, there are encouraging signals in these results that increase enthusiasm to evaluate effects of AT-001 on diabetic cardiomyopathy further," said James Januzzi, MD, Hutter Family Professor of Medicine at Harvard Medical School, a cardiologist at Massachusetts General Hospital, director of Heart Failure Trials at the Baim Institute for Clinical Research and the study's lead author.

"These results also speak to the importance of continuing to focus on earlier recognition of heart failure risk in patients with diabetes and on initiating treatment before the condition has progressed to overt heart failure."

Diabetic cardiomyopathy is a disease in which chronically high levels of blood glucose (hyperglycemia) damage the heart muscle, leading to heart failure over time. What distinguishes diabetic cardiomyopathy from other forms of heart disease is that people with the condition generally don't have coronary artery disease, heart valve disease, or other causes of heart failure, Januzzi said.

It's estimated that about 1 in 5 people with diabetes have diabetic cardiomyopathy, although they may not be aware of it because, initially, the condition has no symptoms.

AT-001 works by preventing an enzyme, aldose reductase, from breaking down glucose into another type of sugar, called sorbitol, that can damage heart tissue by causing the heart muscle to stiffen and heart function to deteriorate over time. No approved treatments currently exist that target the underlying changes that lead to diabetic cardiomyopathy and its progression to overt heart failure, Januzzi said.

The ARISE-HF trial enrolled 691 patients (median age 67 years), of whom half were women, at 62 sites around the world. Patients had had Type 2 diabetes for an average of 14 years. Although they had no symptoms of heart failure or blockages in arteries carrying blood to the heart, they all had structural heart disease or abnormal cardiac biomarkers that classified them as having "pre-heart failure," putting them at high risk for developing overt symptoms of the diagnosis.

At study entry, 38% of the patients were taking sodium-glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1 RAs), medications for diabetes that have been shown to have beneficial effects on heart disease, including reducing heart failure, heart attacks, and strokes.

Patients were randomly assigned to receive twice-daily doses of either

1,000 mg or 1,500 mg of AT-001 or a placebo. At study entry and again 15 months later, every patient underwent a cardiopulmonary exercise test, which measures levels of oxygen and carbon dioxide in the blood and the amount of air the lungs can take in.

Patients' median peak VO2—the maximum amount of oxygen they could take in—at study entry was 15.7, Januzzi said, which is well below the average of about 27 for a man aged 65 years or over and about 23 for a woman in the same age group.

"Their dramatically reduced peak VO2 is indicative of a highly impaired population with a high likelihood of progression to symptomatic heart failure," Januzzi said.

Secondary endpoints included changes in patients' overall level of physical activity and in their perception of their symptoms and quality of life. The researchers also conducted a preplanned subgroup analysis comparing outcomes for patients who were or were not on SGLT2 inhibitors or GLP-1 RAs at baseline.

At 15 months, in the primary comparison of patients treated with the higher dose of AT-001 with patients in the placebo group, those in the AT-001 group saw no worsening in peak VO2, whereas those in the placebo group saw a statistically significant reduction. The average difference in peak VO2 between the two groups was 0.3, which was not statistically significant, Januzzi said. Results for the secondary endpoints also did not reach statistical significance.

However, in the preplanned subgroup analysis looking only at patients who were or were not taking SGLT2 inhibitors or GLP-1RAs, the average difference in peak VO2 between the AT-001 group and the placebo group was 0.64, which was both statistically and clinically significant, Januzzi said.

"This is an exploratory finding, but the level of difference in peak VO2 might translate to an increased ability to do everyday activities with less effort," he said.

The original plan for the study had included an option to treat patients for an additional 12 months, for a total of 27 months of follow-up, Januzzi said. However, the study launched shortly before the onset of the COVID-19 pandemic, which led to recruitment delays. As a result, the sponsor decided to terminate the study at the 15-month time point.

"We will never know whether longer treatment duration would have resulted in more patients—possibly including those taking medications with benefits for the heart—achieving improvements in peak VO2," Januzzi said.

Another possible study limitation, Januzzi said, is that all the enrolled patients had well-controlled blood glucose levels, which had been a requirement for study approval by the U.S. Food and Drug Administration.

"It may be that, although our patients had early-stage diabetic cardioyopathy, because their blood glucose was so well controlled, the condition was progressing very slowly," he said.

Overall, Januzzi said, the study "has demonstrated the tolerability and safety of a highly potent agent with potential applications in a wide range of complications of diabetes."

Provided by American College of Cardiology