SGLT-2 inhibitors show mixed results after heart attack

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While the composite of death and heart failure hospitalizations was not significantly reduced, empagliflozin may help reduce heart failure risks

after a heart attack

Use of the sodium-glucose cotransporter-2 (SGLT-2) inhibitor empagliflozin following a heart attack did not show a significant benefit in reducing overall heart failure hospitalizations or death from any cause, according to a study presented at the American College of Cardiology's Annual Scientific Session. However, researchers said the drug may be helpful in reducing heart failure risks, including hospitalization following a heart attack.

Despite falling short of its primary endpoint, results from the EMPACT-MI trial found that people who took empagliflozin had a significantly lower risk of certain outcomes directly related to heart failure, including first hospitalization for heart failure, total hospitalization for heart failure and a composite of heart failure hospitalization and death from heart failure, without any increased risk of adverse events.

"We found that empagliflozin did not reduce mortality after a heart attack but did reduce the risk of heart failure after a heart attack," said Javed Butler, MD, president of the Baylor Scott and White Research Institute in Dallas, distinguished professor of medicine at the University of Mississippi in Jackson, Mississippi, and the study's lead author.

"To have a 25% to 30% reduction in heart failure hospitalizations is pretty clinically meaningful, but if you put it together with all-cause mortality, it was not a positive study for our primary endpoint."

SGLT-2 inhibitors were initially approved to treat Type 2 diabetes by lowering blood sugar. As evidence has mounted pointing to their benefits in reducing heart failure and other forms of heart disease, researchers have sought to determine whether these drugs could help to prevent heart failure, even in people without diabetes or chronic kidney disease.

A heart attack can damage the heart muscle in ways that sometimes lead to heart failure, a condition in which the heart becomes too weak or too stiff to pump blood throughout the body effectively. The EMPACT-MI trial was designed to determine whether SGLT-2 inhibitors could safely help prevent heart failure and reduce mortality in people with a high risk of heart failure following a heart attack.

The study enrolled 6,522 people treated for acute myocardial infarction at 451 centers in 22 countries. Participants had no history of heart failure but had at least one heart failure risk factor in addition to signs of potential heart dysfunction as indicated by a newly lowered left ventricle ejection fraction to below 45% and/or signs or symptoms of congestion requiring treatment. About 32% had Type 2 diabetes.

On average, participants were 64 years old. Approximately 25% were women, and 84% were White.

Within 14 days of being admitted to the hospital for a heart attack, half of the participants were randomly assigned to receive empagliflozin at a dose of 10 mg daily, while the other half received a placebo. Researchers tracked outcomes for a median of just under 18 months.

The study's primary composite endpoint occurred in 8.2% of those who received empagliflozin and 9.1% of those receiving a placebo, a difference that was not statistically significant. There was also no difference in the rate of death from any cause, which occurred in 5.2% of those receiving empagliflozin and 5.5% of the control group.

All secondary endpoints related specifically to heart failure outcomes were significantly reduced among patients who received empagliflozin.

For example, those receiving empagliflozin were 23% less likely to experience a first heart failure hospitalization and 33% less likely to

experience any heart failure hospitalization—including recurrent hospitalizations—compared with those taking a placebo. The composite rate of total heart failure hospitalizations and death from heart failure was also 31% lower among those receiving empagliflozin.

Among patients who were not taking common heart failure therapies such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor/neprilysin inhibitor (ARNI) at the time of their initial hospital discharge, those taking empagliflozin were significantly less likely to start such therapies within six months compared with those taking a placebo.

"In terms of heart failure outcomes, the data is not only strong, but it's consistent with what we've found over the past 10 years in yet another population," Butler said. "This finding is completely consistent in both direction and magnitude with other studies of SGLT-2 inhibitors in populations with diabetes and chronic kidney disease."

While as a pragmatic trial design to simplify trial procedures and make it easier on both the participants and the sites, the study had limitations that may have influenced the findings, researchers said. For example, because independent reviewers did not adjudicate outcomes, outpatient heart failure events were not formally captured as part of the primary endpoint.

However, researchers said data on outpatient heart failure visits were collected as part of the study protocols for assessing adverse events. An analysis of these events showed outpatient visits for heart failure were substantially lower in participants who received empagliflozin compared with placebo.

Another limitation was the use of all-cause mortality as part of the primary endpoint, which meant that deaths unrelated to heart failure

were included in the endpoint even though the study drug was unlikely to influence them.

There were also some unusual circumstances that may have influenced rates of both hospitalization and death, including the COVID-19 pandemic and conflicts involving Russia, Ukraine, and Israel, all countries that participated in the trial.

Finally, researchers said that the follow-up period may have been too short to capture any difference in mortality related to heart failure fully. Since people who developed heart failure following their heart attack typically did not begin to show heart failure symptoms until a few months later, any reductions in mortality would not be expected to emerge until after that.

"We just did not have long enough follow-up to see whether that heart failure prevention would lead to a benefit in mortality, but it's a reasonable clinical thing to say that if you're preventing heart failure, it's a good thing," Butler said.

This study was simultaneously published online in the *New England Journal of Medicine* at the time of presentation.

More information: Javed Butler et al, Empagliflozin after Acute Myocardial Infarction, *New England Journal of Medicine* (2024). DOI: 10.1056/NEJMoa2314051

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