Diabetes drugs may benefit all heart failure patients

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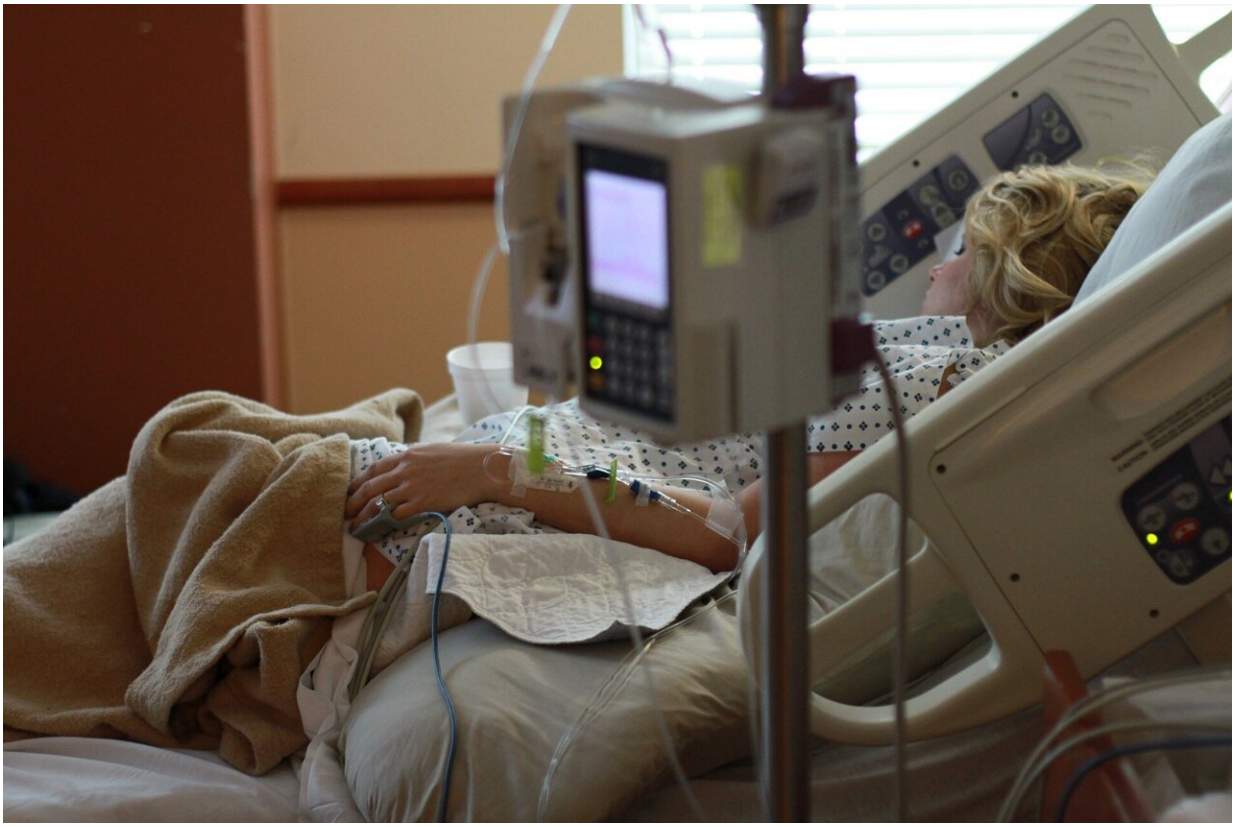

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Researchers from Brigham and Women's Hospital, a founding member of the Mass General Brigham healthcare system, presented new evidence that drugs originally developed to treat type 2 diabetes may benefit a

wide range of patients with heart failure. At a Hot Line session Saturday at the ESC Congress 2022 in Barcelona, and in simultaneous publications in the *New England Journal of Medicine* and *The Lancet*, physician-scientists from the Brigham, in collaboration with a team from University of Glasgow, presented late-breaking research from the largest trial to date of heart failure patients with mildly reduced or preserved ejection fraction. They showed that dapagliflozin, which had previously been shown to benefit patients with heart failure with reduced ejection fraction, is likely to also reduce cardiovascular death and hospitalization for patients with mildly reduced or preserved ejection fraction—a population of millions of patients who have had limited therapeutic options. A meta-analysis that included two clinical trials further strengthened the evidence that this class of drugs may provide protection for a wide range of heart failure patients.

Scott Solomon, MD, of the Brigham's Division of Cardiovascular Medicine, presented results from the DELIVER trial, a randomized, placebo-controlled trial of dapagliflozin among patients with heart failure with mildly reduced or preserved ejection fraction, funded by AstraZeneca.

"In the largest and most inclusive trial of heart failure with mildly reduced or preserved ejection fraction, we found that treatment with the SGLT2 inhibitor dapagliflozin can benefit patients across the full spectrum of heart failure," said Solomon. "These findings establish SGLT2 inhibitors as foundational treatment for patients living with heart failure, regardless of ejection fraction, to help prevent hospitalization and morbidity and to extend meaningful survival and improve health-related quality of life. These are the outcomes that matter most to patients and to clinicians—to keep patients feeling well and living longer."

Muthiah Vaduganathan, MD MPH, also of the Brigham's Division of

Cardiovascular Medicine, presented results from a pre-specified meta-analysis of DELIVER and EMPEROR-Preserved, a large-scale clinical trial of empagliflozin, funded by Boehringer Ingelheim and Eli Lilly.

"Our meta-analysis, encompassing more than 12,000 patients, provides a summary of the totality of the evidence and drives home the message that, when it comes to heart failure, this is a therapy for all," said Vaduganathan. "These trials included patients across a broad range of ages, race, functional class, sex and medical histories, but regardless of individual characteristics, they benefited consistently from this treatment."

Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor—a class of drugs that cause the body to excrete sugar in urine. In addition to controlling blood sugar in patients with diabetes, SGLT-2 inhibitors have been shown to provide significant cardiovascular and kidney disease benefits. The DELIVER trial was designed to determine whether dapagliflozin would decrease cardiovascular morbidity and mortality in patients with heart failure with mildly reduced or preserved ejection fraction. The trial was conducted at 353 sites across 20 countries. The trial enrolled patients who were 40 or older and had symptomatic heart failure with an ejection fraction of greater than 40 percent, including mildly reduced ejection fraction and preserved ejection fraction, as well as patients who had previously had reduced ejection fraction that had improved to greater than 40 percent, and in both the outpatient and inpatient setting. More than 6,000 participants were randomized to receive dapagliflozin or placebo and followed for a median of 2.3 years. The primary endpoint was a composite of cardiovascular death or worsening heart failure.

Dapagliflozin significantly reduced the primary composite endpoint by 18 percent. Worsening heart failure occurred in 368 participants (11.8 percent) in the dapagliflozin group compared to 455 participants (14.5

percent) in the placebo group. Cardiovascular death in these groups occurred in 231 (7.4 percent) and 261 (8.3 percent) participants, respectively. Key secondary outcomes were also significantly reduced, including total heart failure hospitalizations and total symptom burden.

The meta-analysis, led by Vaduganathan and colleagues, used data from DELIVER and EMPEROR-Preserved, with a composite of cardiovascular death or first hospitalization for heart failure. The team found that SGLT2 inhibitors reduced the risk of the primary outcome by 20 percent. Effects were consistent across subgroups by age, sex, race, body mass index, systolic blood pressure, history of various medical conditions and more. Vaduganathan and colleagues further incorporated data from additional clinical trials with SGLT2 inhibitors, including those performed with dapagliflozin and empagliflozin in patients with reduced ejection fraction, and in patients from a clinical trial of the SGLT1/2 inhibitor sotagliflozin. The totality of the evidence with all these data suggest that patients across the full spectrum of heart failure benefit from this class of drugs, irrespective of ejection fraction or care setting.

The authors note that the work has some limitations. Less than 5 percent of patients enrolled in DELIVER were Black, the COVID pandemic limited symptom assessment after March 2020, and subgroups in the trial were underpowered. However, findings were consistent across prespecified subgroups.

"There are more than 64 million people worldwide affected by heart failure, half of whom have mildly reduced or preserved ejection fraction ," said Solomon. "Our goal is to rigorously and scientifically evaluate potential treatments so that we can provide the best evidence-based care to help them lead longer, healthier lives."

More information: Muthiah Vaduganathan et al, SGLT-2 inhibitors in

patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials, *The Lancet* (2022). DOI: 10.1016/S0140-6736(22)01429-5

Scott D. Solomon et al, Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction, *New England Journal of Medicine* (2022). DOI: 10.1056/NEJMoa2206286