The DELIVER Trial: the Beginning of the End of Ejection Fraction Tyranny

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Abstract

It has been reported at the 2022 European Society of Cardiology Congress that the DELIVER trial has met its primary outcome – a relative reduction of 18% in a composite of worsening heart failure (HF) or cardiovascular death. These results, added to evidence from previously reported pivotal trials with sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with reduced and preserved heart failure (HF), provide compelling evidence of the benefit of SGLT2is across the HF spectrum, irrespective of ejection fraction. New diagnostic algorithms that are quick and easy to implement at the point of care are needed for quick diagnosis and implementation of these drugs. Ejection fraction may come later for proper phenotyping.

Keywords

Heart failure, dapagliflozin, ejection fraction, natriuretic peptides, diagnosis, sodium-glucose cotransporter-2 inhibitors

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'The DELIVER trial has Delivered!', declared consultant cardiologist Theresa McDonagh when she discussed the trial findings at the European Society of Cardiology Congress in Barcelona on 27 August, 2022 with principal investigator Scott Solomon when he presented the results.

The Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial was designed to test the hypothesis that the sodium-glucose cotransporter-2 inhibitors (SGLT2i) dapagliflozin would reduce the risk of worsening heart failure (HF) or cardiovascular (CV) death among patients with a mildly reduced ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF).

The primary outcome was a composite of worsening HF (which was defined as either an unplanned hospitalisation for HF or an urgent visit for HF) or cardiovascular (CV) death, as assessed in a time-to-event analysis. Over a median of 2.3 years, the primary outcome occurred in 512 patients (16.4%) in the dapagliflozin group and in 610 patients (19.5%) in the placebo group (HR 0.82; 95% CI [0.73–0.92]; p<0.001). The main benefit of dapagliflozin in this population was mainly in reducing worsening HF with a non-significant effect on CV death. The benefit was consistent across prespecified subgroups, including those defined according to left ventricular ejection fraction (LVEF), with no attenuation in the highest LVEF group. Dapagliflozin was effective in patients with recent HF hospitalisation and in those with previously reduced LVEF that had improved to over 40%.[1]

DELIVER is the second positive trial using SGLT2is in patients with HFmrEF and HFpEF, together with EMPEROR-Preserved.[2] The two trials share many similarities. First, despite different components of the composite primary endpoint, the relative reduction achieved in primary outcomes were similar: 18% for DELIVER versus 21% for EMPEROR-Preserved. A recent analysis of EMPEROR-Preserved found a 24% reduction in outcomes if an endpoint similar to that of DELIVER was used. Second, in both trials, the principal effect was essentially on reduction of HF hospitalisation, without a meaningful reduction on CV mortality. Third, the population enrolled in both trials had identical age, mean LVEF and estimated glomerular filtration rate (eGFR) and had a similar proportion of patients with LVEF >60%.[3] The new information provided by DELIVER is its efficacy in patients with improved/recovered LVEF and the clear signal of benefit across LVEF categories including LVEF ≥60%. Last, DELIVER's safety data were of no concern, similar to all pivotal clinical trials of HF, without the need for titration nor close monitoring.

These two trials provide compelling evidence of the benefit of using SGLT2i in patients with HFmrEF and HFpEF and add to the already robust evidence in patients with reduced ejection fraction (HfrEF) found in the DAPA-HF and EMPEROR-Reduced trials. Clinical guidelines will have to adapt soon to incorporate these new data, with a more than likely class IA indication for SGLT2i in HFmrEF and HFpEF (it is already class IA for patients with HFrEF).

SGLT2is have emerged as first-line medication (along with diuretics, if necessary) across the HF spectrum, irrespective of LVEF. In terms of clinical practice, this represents a major game changer, particularly in the primary care setting, where echocardiography is not always available or has major delays. With the recent evidence from SGLT2i trials, patients

with signs and symptoms of HF plus positive natriuretic peptide levels should receive an SGLT2i, even before echo data are available. It is the right time to extend the use of natriuretic peptides in primary care (ideally as point-of-care) and in-hospital, to start an SGLT2i (dapagliflozin or empagliflozin) without delay.[4] In summary, after DELIVER, it is clear that waiting to have an LVEF – which may take weeks or months – before initiating a disease-modifying medication in HF is unnecessary and may even be harmful. ❑

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