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# The DELIVER Trial: Dapagliflozin in Heart Failure

**Announcer:**
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**Dr. Greene:**
I'm Dr. Stephen Greene from the Duke Clinical Research Institute, and I'm happy to be discussing dapagliflozin in heart failure with mildly reduced or preserved ejection fraction, the DELIVER trial. The DELIVER trial was presented at the European Society of Cardiology 2022 meeting and was presented by Dr. Scott Solomon from the Brigham and Women's Hospital.

By way of background, there have traditionally been few pharmacologic treatment options for patients with heart failure with mildly reduced or preserved ejection fraction. However, just last year, the SGLT2 inhibitor, empagliflozin, was found to reduce the risk of cardiovascular death or heart failure hospitalization among patients with heart failure with mildly reduced or preserved ejection fraction in the EMPEROR-Preserved trial. However, there still is uncertainty regarding the efficacy of SGLT2 inhibitor therapy in certain subgroups of patients with heart failure with mildly reduced or preserved ejection fraction. These groups include those with ejection fractions in the higher end of the EF spectrum, including those above 60% ejection fraction, as well as patients who are initiated on SGLT2 inhibitor therapy during or soon after hospitalization, as well as patients who had a previously reduced ejection fraction but have had subsequent improvement in their ejection fraction.

In that context, the DELIVER trial was a randomized, double-blind, placebo-controlled trial testing the hypothesis that dapagliflozin would reduce cardiovascular death or worsening heart failure in patients with heart failure with mildly reduced or preserved ejection fraction. The eligibility criteria for the DELIVER trial are on this slide. Patients who were eligible were 40 years of age or older, had NYHA class II through IV heart failure symptoms, and had ejection fraction of greater than 40%. Patients who were eligible were then randomized to dapagliflozin 10 milligrams once daily or matching placebo, and median follow-up time was 2.3 years. Shown here are the baseline characteristics in the DELIVER trial, and you see that they were well-balanced between groups.

There were more than 6,200 patients total enrolled in the trial. And as you can see, looking at these patients, the mean age was 72, 44% of patients were female, and the mean ejection fraction was 54%, and 70% of patients had ejection fractions below 60%. 18% of patients in DELIVER had a previous ejection fraction of 40% or less, then it's subsequently improved. Looking here on this slide, we see that patient had elevations in natriuretic peptides. Also, over 50% had a history of atrial fibrillation, and 42% had atrial fibrillation at time of enrollment. About half the patients had an eGFR less than 60. Looking at medical therapy, you can see that loop diuretic use was common in this population, whereas sacubitril-valsartan was used in about 4 to 5% of patients, and more than 40% of patients were on a mineralocorticoid receptor antagonist.

This slide shows the primary results of the DELIVER trial. The primary endpoint was the composite of cardiovascular death or worsening heart failure. And you see that there were 512 primary events in the dapagliflozin group and 610 primary events in the placebo group. This translated to an 18% relative risk reduction and favoring dapagliflozin. That produced a highly statistically significant

P-value and a Number Needed to Treat over the course of the trial of 32. This slide shows the components of the primary endpoint. And you see on the left, there was a 21% significant reduction in risk of worsening heart failure and on the right, a 12% non-significant reduction in cardiovascular death. There was remarkable consistency in the primary endpoint across subgroups in DELIVER. As you can see with respect to ejection fraction, there was no evidence of heterogeneity, and dapagliflozin was just as effective among patients with very high ejection fraction as among those with lower ejection fraction. Similarly, patients benefited from dapagliflozin just as much among those who are hospitalized or recently hospitalized for heart failure. And lastly, finally, among patients with improved ejection fraction, in other words, patients who formally had a reduced ejection fraction less than or equal to 40% but it's subsequently improved, those patients benefited just as much with dapagliflozin as other patients in the trial.

Looking now at patient-reported quality of life in DELIVER, this was assessed via the KCCQ Total Symptom Score. And that from baseline to eight months, patients with receiving dapagliflozin had greater improvements in quality of life. The mean placebo-corrected change was 2.4 at eight months between groups. Also, looking at a responder analysis of patients and their likelihood of clinical benefit with active therapy, patients with dapagliflozin were more likely to report a clinically meaningful improvement in quality of life and were less likely to report clinically meaningful deterioration compared with placebo.

Looking at adverse events, in serious adverse events, there was remarkable safety and tolerability with dapagliflozin compared with placebo which is very consistent with what we've seen in other SGLT2 inhibitor trials. Looking at total serious adverse events, there were numerically more serious adverse events among patients receiving placebo. And you look at similar patterns for the other adverse events on this slide.

At the same session as the primary DELIVER results were presented, there was also a presentation of a meta-analysis pooling trials, the DELIVER trial with the prior heart failure with mildly reduced or preserved ejection fraction trial and for Preserved. This meta-analysis of these two, heart failure with preserved or mildly reduced ejection fraction trials, was presented by Dr. Muthu Vaduganathan from the Brigham and Women's Hospital. Looking at this pooled analysis of DELIVER and EMPEROR-Preserved, we saw that there was a 20% relative risk reduction on this primary endpoint for cardiovascular death or heart failure hospitalization with remarkable consistency and robustness between the two trials. Looking at the components of this endpoint, cardiovascular death on the bottom left saw 12% relative risk reduction with SGLT2 inhibitor therapy compared with placebo that achieved borderline statistical significance P-value of .052, whereas hospitalization for heart failure also is highly statistically significant, 26% relative risk reduction consistency between the two trials.

Looking at this meta-analysis of patients with mildly reduced or preserved ejection fraction receiving SGLT2 inhibitor therapy, again, consistency across the ejection fraction spectrum between EMPEROR-Preserved and DELIVER. One of the patients had an ejection fraction of 41 to 49%, 50 to 59%, or greater than or equal to 60%. Remarkable benefits on the primary endpoint with SGLT2 inhibitor therapy compared with placebo for each of these risk, each of these ejection fraction strata, highly statistically significant results.

So, in conclusion, based on this new data from DELIVER and the meta-analysis of heart failure with mildly reduced or preserved ejection fraction receiving SGLT2 inhibitor therapy, we now know that dapagliflozin reduced the risk of the primary composite outcome of cardiovascular death or worsening heart failure. These findings in the DELIVER trial were consistent across prespecified subgroups, including those defined according to ejection fraction, and we saw there was no attenuation of treatment effect in the highest ejection fraction subgroup. Dapagliflozin was also as effective in patients with recent heart failure hospitalization, and among those with a prior reduced ejection fraction had subsequently improved. Serious adverse events and adverse events leading to discontinuation were similar between dapagliflozin and placebo. And also, the simultaneously-presented, comprehensive meta-analysis among patients with heart failure with mildly reduced or preserved ejection fraction confirmed robust benefits of SGLT2 inhibitor therapy in this population, including among those patients with the highest ejection fractions, greater than or equal to 60%. We now know based on this data from DELIVER and the prior data among patients with heart failure with reduced, mildly reduced, and preserved ejection fraction, the totality of evidence now clearly supports prioritizing the use of SGLT2 inhibitor therapy in all patients with heart failure, irrespective of patient's phenotype or care setting. Thank you very much for your attention.

**Announcer:**
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