TRANSCRIPT: Pooled Analysis of DAPA-HF and DELIVER – Pardeep S. Jhund, MBChB, MSC, PHD

Hello, I'm Pardeep Jhund and I'm here today to give you the results of our presentation from the ESC hotline session of the pooled analysis of the DAPA-HF and DELIVER trials.

In this study, our aim was to examine the effect of dapagliflozin in a pooled data set from DAPA-HF and DELIVER. As you'll be aware in DAPA-HF, we showed that dapagliflozin was of benefit in reducing the risk of cardiovascular death or worsening heart failure events. That's heart failure, hospitalizations, or urgent visits for heart failure in patients with heart failure with reduced ejection fraction.

And you'll also now be aware of the results of the DELIVER trial demonstrating the benefit of dapagliflozin in patients with heart failure, with mildly reduced or preserved ejection fraction, showing a reduction in cardiovascular death or worsening heart failure event.

But what these two trials were not designed to do was look at anything other than their primary composite endpoint. So, they had power to look at the primary composite endpoint but not the components of the endpoint or other key second outcomes, like cardiovascular death alone, or all-cause mortality.

So, before we locked DELIVER, and we made database lock in that, we designed a statistical analysis plan that combined both DAPA-HF and DELIVER to examine the effect of dapagliflozin in a number of key outcomes.

Now, as we were doing this, many of you will be aware of an analysis that was produced by the EMPORER trial investigators which used empagliflozin indicating that there might also be a lack of benefit of empagliflozin in patients with a higher ejection fraction. So we also reviewed our analysis plan and looked at ejection fraction over the continuous spectrum as well as a couple of subgroups that we'd already pre-planned.

So, what we did was we combined DAPA-HF with its just over 4500 patients, along with DELIVER, again with over 6,000 patients. So, in the end, we had a pooled data set of 11,007 patients with heart failure across the entire rejection fraction spectrum. And we looked at a number of different outcomes at which we were unable to look at separately in each of the dataset.

So, we had a hierarchy of outcomes that we wanted to look at, and a hierarchy meant that if we tested the first outcome and it was statistically significant at P less than 0.05, we moved on to the next one.

Now those outcomes were cardiovascular death, then followed by all-cause mortality, then total heart failure hospitalizations, and then followed on by MACE, major adverse cardiovascular events, or cardiovascular death, myocardial infarction, and stroke is a time to first composite.

And what we saw was that we in the patient pooled population using the individual patient level data there was a substantial reduction in the risk of cardiovascular death in the patient's randomized to dapagliflozin. In fact, what we saw was a relative risk reduction of 24%. We also saw a 10% relative risk reduction in all-cause mortality in MACE, cardiovascular death, MI or stroke. And we saw a 29% relative risk reduction in total hospitalizations for heart failure.

Now that was very nice, but what we also wanted to look at was the subgroup, according to LVF. Now we categorized LVF and above and below 40, and then also in a couple of other subgroups, but really the best way to look at this is in a continuous measure, looking at the interaction or between randomized therapy there for dapagliflozin and ejection fraction.

And what we saw is it didn't matter what ejection fraction you had, the benefit of dapagliflozin was consistent over the range of EF. So, it didn't matter if you had low EF or you had higher EF, you still gained benefit from being prescribed dapagliflozin instead of placebo in this pill data set.

So, this was consistent, not only for cardiovascular death, but also all of the other outcomes that I mentioned, so all-cause mortality, total heart failure, hospitalizations, and MACE.

So, we think this has some very important implications for the heart failure community, and indeed patients with heart failure. Our findings would suggest that patients, regardless of the rejection fraction can benefit from dapagliflozin. And that's important for clinicians because as many of you will know, sometimes our patients wait quite a while before being able to get access to investigations where they can have the rejection fraction measured such as echo cardiography.

So, this means that in the patient with clinically diagnosed heart failure, providing have no contraindications to an SGLT2 inhibitor, then it may be possible to start dapagliflozin and get them early access to this drug.

So, thank you very much for listening. And if you would like to find out more details of our analysis, the results are published online simultaneously with the presentation in *Nature Medicine*.