Transcript: DELIVER Commentary – Clyde Yancy, MD, FAHA

This is Clyde Yancy, former president of American Heart Association and national spokesperson for the AHA. Delighted to come to you and share with you top line results from the late breaking clinical trial session at ESC 2022.

The data we have available today are going to feel very important to me and to many of you and especially to our patients. It's about heart failure. Particularly heart failure with preserved ejection fraction.

Previously, we acknowledged that we had no definitive therapies that would modify that natural history, but recently data emerged suggesting that the drug class sodium-glucose cotransporter-2 inhibitor might not only be beneficial but might actually change that natural history. Those tentative statements cannot be more declarative.

The release of the important the pack of flows in a heart failure with mild reduced or preserved ejection fraction, studied brilliantly by Scott Solomon’s colleagues really closes the loop on some of the outstanding questions.

This study done in over 6,000 patients with heart failure with either mildly reduced and preserved ejection fraction, was decidedly positive. The composite endpoint was that of worsening heart failure that is an unscheduled visit or an admission for decompensated heart failure or cardiovascular death.

Compared to background with placebo therapy, the study was resoundingly positive.

These results are very important because they clear up some previous questions. First, there was a robust capture of those patients with heart failure with mildly reduced ejection fraction. A new phenotype, and a real phenotype of this condition for which we needed more evidence to suggest we can change that natural history that's in hand now.

Next, we previously had concerns that there was an attenuation of the effect of the SGLT2 inhibitor in patients with ejection fraction beyond 60%. The investigators *a priori* did an analysis of those with EFS greater than 60 versus those less than 60 with enrollment criteria being greater than 40.

So two really important groups, 40 to 60 exclusively and greater than 60, and the results were durable in both groups. This is very important because this is immediately an importantly clinically actionable. The one thing that we still have is the absence of a signal that we can modify cardiovascular death.

But these investigators offered us some insight too. Perhaps we need an even larger denominator than the 6,000-patient study and a longer time when to capture that survival advantage. The other important consideration is that now that we have evidence across the board prevention and treatment in multiple ejection fraction ranges that the SGLT2 inhibitors are very important in the broader scenario of heart failure.

It really begs the question, what are they modifying? We'd like to believe that it's something in the cardiometabolic space. Something beyond human dynamics even something beyond reverse remodeling.

But it's pretty evident that we have an immediate call for more research to undersign biological implications of these very effective therapeutics. Because with that question answered. we can consider additional patient cohorts, additional cardiovascular syndromes that might benefit from exposure to the sodium-glucose cotransporter-2 inhibitors. These drugs might be today's this generation's version of the statin: capable of not only modifying disease but modifying life and that is not hyperbole. It's something worth our consideration.

I must also add that at this same meeting investigators related to this entire drug class -- but particularly to DELIVER -- release important additional analyses, stratified according to presence or absence of atrial fibrillation, a condition that we know exaggerates poor outcomes in the setting of heart failure particularly HFpEF.

Again, the use of the SGLT2 inhibitor was durable, present AF or absent AF. And they also released information looking at the influence of dapagliflozin in the setting of HFpEF according to age groups. And once again, demonstrated durability of the fact.

Finally, where does all of this get us?

We have a new randomized control trial. We have important subgroup analyses already available. We've answered questions that were persisting from previous analyses. We still have a question about mortality.

But where does all of this get us? I think it gets us to this point. We must accept now that based on evidence, the sodium-glucose cotransporter-2 inhibitors really become a new standard of care for patients with heart failure with preserved ejection fraction. And we can include heart failure with mildly reduced ejection fraction as well.

So, the narrative completely changes. We no longer have to be mourning the absence of an effective therapy. Yes, we need to address mortality.

But we know that today, drugs that are available right now, are appropriate and beneficial in a setting of heart failure with preserved ejection fraction. This really is cause for celebration. And these data are clinically actionable as we speak.

Once again, this is Clyde Yancy bringing you top line results from ESC 2022. Thank you for your attention.