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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Uncovering the Results of the DELIVER Trial

Dr. Butler:
Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction, otherwise known as the DELIVER trial, was designed to assess whether SGLT2 inhibitors are effective in patients with higher left ventricular ejection fraction. And now that the study results are in, we are taking a look at the findings and what they mean for our patients.

You're listening to *Heart Matters* on ReachMD. I am Dr. Javed Butler, and joining me today to discuss the DELIVER trial is lead author, Dr. Scott Solomon, who is also the Director of the Clinical Trials Outcomes Center and the Edward D. Frohlich Distinguished Chair at Harvard Medical School.

Dr. Solomon, welcome to the program.

Dr. Solomon:
Javed, great to be here. Thanks.

Dr. Butler:
So let's start off with some background on the DELIVER trial. Can you tell us some of the considerations that you had in mind when you were designing the trial?

Dr. Solomon:
Sure. So DELIVER was the largest and broadest inclusion criteria of all trials in heart failure with mildly reduced and preserved ejection fraction, and the design of DELIVER was influenced by all the experience we had for many years before us with heart failure with mildly reduced and preserved ejection fraction trials, including the TOPCAT trial and the CHARM-Preserved trial, and most recently the PARAGON-Heart Failure trial. We decided to enroll patients with signs and symptoms of heart failure, ejection fraction of greater than 40 percent, and we specifically allowed inclusion in this trial of patients who had heart failure who had previously had an ejection fraction of up to 40 percent but whose ejection fraction had improved to over 40 percent by the time of enrollment, and that was one of the things that was different from some of the other trials. The majority of patients enrolled were ambulatory, but some of these patients were either hospitalized or recently hospitalized, and otherwise it's very similar to the EMPEROR-Preserved trial, which of course, you know so well. But this was really designed as the sister trial to the DAPA-HF trial, which was the study of dapagliflozin in patients with heart failure with reduced ejection fraction.

Dr. Butler:
So that's really fascinating. Can you tell us what were the results of the trial?

Dr. Solomon:
So overall, DELIVER saw an 18 percent reduction in the primary endpoint, which was a composite of cardiovascular death or worsening

heart failure. Worsening heart failure consisted of either a heart failure hospitalization or an urgent heart failure visit, and this was driven primarily by the reduction in worsening heart failure. We saw a 12 percent nonsignificant reduction in cardiovascular death. Overall, these results were very similar to what we had seen a year earlier with the EMPEROR-Preserved trial.

One of the more important aspects of this study was that we had obviously known from prior trials, including the PARAGON, TOPCAT, and CHARM, that when we gave neurohormonal agents, ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, and even sacubitril/valsartan, we saw some degree of attenuation of benefit as ejection fraction went up into the normal range. There was at least a hint that, that might have been the case also with EMPEROR-Preserved, although we know that overall, the results of EMPEROR-Preserved suggested that there was no heterogeneity with ejection fraction, but there was clearly, at least reported some possible attenuation. I'm using the word, "possible" because we now believe it might have been the play of chance, possible attenuation at the high end of ejection fraction, so we were obviously very concerned about that. We in fact, were so concerned about it that we had a dual primary endpoint in DELIVER where we actually ascribed some alpha to the patients who had ejection fraction below 60 percent so that we could potentially win just with the group with an EF of under 60 percent.

It turns out it didn't matter because we saw the same degree of benefit in the higher ejection fraction group over 60 percent with no hint of attenuation across the ejection fraction spectrum, and I think that really helps us understand that SGLT2 inhibitors as a class probably work throughout the ejection fraction spectrum, which is different from many of the other agents that we've tested in heart failure with mildly reduced and preserved ejection fraction.

Dr. Butler:
That's really important. Can you expand a little bit more on the two groups that we talked about in the design, those that were hospitalized or recently hospitalized and those with improved and even recovered numerically, even if they have the syndrome of heart failure and really improved ejection fractions, as well?

Dr. Solomon:
Yeah. So the recently hospitalized patients, as we would expect, had a higher overall event rate but their benefit was very similar to the overall group, in fact maybe slightly better from a point estimate, so they derived benefit from dapagliflozin in the study. In addition, we ended up enrolling 18 percent of our patients, so over 1,100 patients with heart failure and with improved ejection fraction, and in these patients, we also saw a significant reduction in the composite endpoint. Interestingly, and I think maybe hypothesis-generating, we saw a pretty profound reduction in cardiovascular death in that group. It's a subgroup of course, so we have to be relatively careful about interpreting the overall results, but certainly, it looks like the benefit is at least as good in that group as in patients who have heart failure with ejection fraction consistently over 40 percent.

Dr. Butler:
For those just joining us, you're listening to *Heart Matters* on ReachMD. I am Dr. Javed Butler, and I'm speaking with Dr. Scott Solomon about the results of the DELIVER trial.

Talking about subgroups, did you have any differences in men versus women, in general but more importantly, in terms of ejection fraction and outcomes?

Dr. Solomon:
No. We looked at virtually every subgroup in this study, and we see remarkable consistency. In fact, that word is getting old because every time we look at different subgroups and DELIVER, we see consistency of the treatment effect, so it's true of men and women; it's true of younger versus older; it's true of more frail or less frail; it's true of people who are or not on certain background medications like MRAs, and sacubitril/valsartan was very low in this patient population, so we really can't say much about that. But we will be discussing and presenting data about men and women across the spectrum of ejection fraction at the American Heart Association, so stay tuned for more granular results about men and women, in both the DELIVER and DAPA-HF trials, to be presented there.

Dr. Butler:
Really looking forward to seeing those results. Now, DELIVER trial sort of wraps up the whole SGLT2 heart failure-related trials

between HFrEF, HFpEF. There are certain adjacent population trials ongoing in post MI patients, but your group also did a meta-analysis putting all the heart failure data together. Can you tell our listeners a little bit about the meta-analysis, and what's your overall impression of SGLT2 inhibitors in patients with heart failure?

Dr. Solomon:
Yeah, of course. So we took the opportunity to put together the two trials in heart failure with mildly reduced and preserved ejection fraction, which were DELIVER and EMPEROR-Preserved. As I said, when you harmonize the endpoints in these trials, there's really remarkable consistency in the overall result, so what we saw was a combined hazard ratio of 0.80, so a 20 percent risk reduction, highly statistically significant when you put the two trials together, no evidence of heterogeneity there. When we look at cardiovascular death, we see a 12 percent reduction overall when we harmonize the definition with a P value of 0.052, so that tells you that we are very close to significance for cardiovascular death. It's one of the things that I think we misinterpret when we look at the data from these trials individually. It's not that I don't think that we have any effect on mortality or cardiovascular mortality in these trials. It's that they're not powered to look at cardiovascular death. And so when we put the two trials together, we do see what approaches statistical significance.

If we look at for example, DAPA-HF and DELIVER together, we see a significant reduction in cardiovascular death with no evidence of heterogeneity, so this question, which has really boggled us for a while—Is there a reduction in cardiovascular death?—I think we can say there probably is. It's modest, 12 percent in the two higher ejection fraction trials, but I think it's real. If you then go ahead and look at this even across the ejection fraction spectrum, that hint of attenuation of a benefit as ejection fraction goes up in EMPEROR-Preserved is basically offset by DELIVER, so when you put the data together, you get complete consistency across the EF spectrum. And then, we also put together all of the trials with SGLT2 inhibitors, and of course as you can imagine, there's substantial benefit across heart failure in general, and I think we can now safely assume that at least for SGLT2 inhibitors, heart failure is heart failure. We can for this therapeutic class, stop worrying about ejection fraction. If a patient has heart failure, they probably should be on an SGLT2 inhibitor.

Dr. Butler:
Well both of us have so much interest in this topic that we can probably go on for a very long time, but our time is almost up, so I will give you the last word. Any final thoughts for our listeners?

Dr. Solomon:
The evidence is, I think, pretty definitive there. The question is going to be about implementation and making sure that our patients are on the right therapies. If we don't put our patients on the right therapies, it's like the tree falling in the forest and nobody hearing it, so we have to make sure that we do utilize the best guideline-directed therapies. And I suspect that the guidelines for the use of SGLT2 inhibitors in heart failure with mildly reduced and preserved ejection fraction will get updated at some point in the hopefully near future, and then there'll be enormous incentive to put our patients with heart failure with mildly reduced ejection fraction and preserved ejection fraction on this class of drugs, just like we have been doing in patients with heart failure with reduced ejection fraction.

Dr. Butler:
Well this has been incredibly informative, and there's nothing like talking directly with the researcher who designed and conducted the trial and have that nuanced insight into the matter. So I really want to thank my guest, Dr. Scott Solomon, for sharing all of these insights and findings. Scott, always a pleasure to talk to you. Thank you so much for joining me today.

Dr. Solomon:
Thanks, Javed. It's been a real pleasure.

Dr. Butler:
For ReachMD, I'm Dr. Javed Butler. To access this and other episodes in our series, visit ReachMD.com/HeartMatters where you can Be Part of the Knowledge. Thanks for listening.