Title: HFA 23: The DELIVER Phase III Trial
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Prof Martin Cowie

"Hello, my name is Martin Cowie, I'm a professor of cardiology. I'm clinical vice president of late stage CVRM, R&D at AstraZeneca.

What was the reasoning behind this trial?

There's a huge unmet need in terms of patient symptoms and mortality for those that have a particular form of heart failure called HFpEF with ejection fractions above 40%.And until we had the evidence from SGLT2inhibitors, there was no therapy that had been shown to improve the outcome for those patients. So, a huge unmet need. Clinicians were desperate to get a therapy that would make a difference for their patients. And that's why we designed the DELIVER trial to specifically get robust evidence for improvement in outcome for patients with that condition.

Please tell us more about the mechanism of action behind dapagliflozin?

Forxiga or dapagliflozin is an SGLT2 inhibitor and it's a very interesting journey in discovering how much this molecule could do for our patients. So, it started out being designed to improve the quality of control of type two diabetes and indeed it does that and it's licensed for that. But then we found out it had a beneficial effect for patients with heart failure and then also chronic kidney disease. So, this molecule has moved and is now very widely beneficial for patients with cardiorenal disease. How does it work? Well, we still don't know all the answers to that question. It certainly affects sodium and fluid balance and the way the body holds on to fluid has effects of the kidney level, but it also has effects on the heart and we're not entirely clear what it's doing, but it's very beneficial and protects people from the development of heart failure or worsening of heart failure. And we think part of that might be a metabolic switch where the heart becomes more efficient at burning fuel. So multiple mechanisms of action all through the SGLT2 receptor, which is largely in the kidney. So complex drug, but very simple evidence of

the benefit across a broad spectrum of patients. Type two diabetes for diabetes control, heart failure patients for preventing cardiovascular death and heart failure worsening, but also in chronic kidney disease as well. So, a real blockbuster and very exciting to watch the story become better known in the last ten years or so.

What was the patient population and study design?

The DELIVER study was specifically designed to demonstrate the value of dapagliflozin or Forxiga in patients with heart failure with preserved ejection fraction. So that means an ejection fraction above 40%.So patients with that could enter the study, they had to have a BNP above a certain level and evidence of structural heart disease. We're very confident this is true heart failure patients going into the study, the end of the day, we had just over 6200 patients, average age was 72 years. We followed them up for an average of2.3 years and what did we show? An 18% reduction in the primary endpoint, which was cardiovascular mortality and heart failure worsening. So very important benefit and what was really striking was it didn't matter what subgroup of patients you looked at, there was benefit of about that level. So very convincing evidence, both EMA and FDA recognized that gave licenses for the use in HFpEF. And, very recently NICE has recognized the value for money and approved its use also for HFpEF in the NHS in England. So, very exciting trial only published in August 2022, already now licensed in the major markets and available for people to prescribe the benefit of their patients with HFpEF.

What were the key results revealed at HFA 23?

So, at HF 2023 in Prague in May 2023,we gave some further data insights from the DELIVER study and there were two major pieces of work. One was about what's the benefit like for patients that have had heart failure for longer. And those patients that have heart failure for longer tend to be older, they tend to have more comorbidity and they have a higher event rate. And many clinicians feel, well, this patient's too old, too sick, got too many problems, they probably won't benefit. And that is not right. When we looked at the data, the relative benefit was the same irrespective of the duration of heart failure. And importantly, the absolute benefit was even greater because their event rate

was higher. So, it's never too late to start Forxiga, dapagliflozin for a patient with heart failure and we're talking about DELIVER. Let's just remember there's also very robust evidence for DAPA HF with low ejection fraction heart failure. So, it's across the whole spectrum of heart failure irrespective of ejection fraction. You will get benefit from this drug and never too late to start. The second piece of work that was presented at Heart Failure 2023 was looking about the level of comorbidity. And in fact, 90% of heart failure patients have at least one other cardiovascular problem and20% have at least three other problems. But it didn't matter how many or how few other comorbidities the patient had; the relative benefit was the same. And once again, as the number of comorbidities mounts, the risk to the patient goes up and the absolute benefit of Forxiga dapagliflozin goes up. So, it doesn't matter how much comorbidity your patient has or how long or short they've had heart failure. This is a drug that should be used and that's recognized in guidelines. Now this is a foundational therapy for patients with heart failure irrespective of ejection fraction.

How should these findings impact practice and future research?

Well, I think the results of DELIVER, but also DAPA HF prior to that have already impacted therapy in day-to-day practice. It's got into all the guidelines now that these are foundational therapy for patients with heart failure irrespective of ejection fraction. And now you will find that if you see somebody who knows anything about heart failure, they will be very keen to make sure that you get put on dapagliflozin as soon as possible so that you get the benefit. And the interesting thing is, in the trials that the evidence became statistically significant within two weeks of starting therapy. So almost immediately, before you've even finished your first month's pack of drug, you'll be getting benefit from using this. So, it's a lot of good practice now by implementing this, so everybody with heart failure can at least have a chance to get on to this life-changing therapy. In terms of research from SGLT2 inhibitors, what a journey it's been from moving from improving the quality of control of type two diabetes into heart failure, irrespective of ejection fraction, and then also into chronic kidney disease with evidence of slowing the decline of renal function and improving hard outcomes for those patients. So, it's already been a huge amount of research in this area. I think we're asking ourselves the question why couldn't we work out that those benefits were there earlier?

And that's a lesson for the future. But also making sure, which is the most important thing is that every patient who could benefit from this therapy gets access to that. So, it's been a very exciting period, and we look to the future as well, where we may well combine dapagliflozin with other drugs where there's a synergistic effect, whether it's in chronic kidney disease, whether it's in heart failure or other disease areas. So, it's a very exciting time in the field for SGLT2 inhibition.

What surprised you about the results of DELIVER?

Well, you know, this whole scientific community was holding its breath. Here was a group of patients with heart failure we knew had a high unmet need, but no therapy had broken through to provide evidence. And we designed DELIVER to give a robust answer to this question. And we were just delighted to sit back and see results of this huge effort by our investigators in the patient community and within AstraZeneca to deliver this robust evidence base. Just persuaded regulators around the world, reimbursement authorities, and more importantly, meant that we can offer patients a new option to make sure that their future is better than it would be. And this is just very surprising, very pleasing, and it shows a point of doing research in this, doing the randomized trials, getting the evidence, and then seeing that move into guidelines and into practice is enormously encouraging for the future."