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When to start using SGLT2i in HFrEF? Initiating guideline-recommended treatment options

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CHAPTER ONE

Announcer:
When to start using SGLT2 inhibitors in heart failure with reduced ejection fraction? Initiating guideline-recommended treatment options.

In the first episode of this educational series, Professor John McMurray talks about barriers and concerns regarding initiating guideline-recommended therapies in patients with heart failure.

Dr. McMurray:
Hello. I'm John McMurray from the University of Glasgow. And today I'm going to talk about the clinical challenges we face in initiating guideline recommended therapy in heart failure.

So these are my disclosures.

Now there are many barriers and challenges to implementing new treatments in patients with heart failure and I've broken them down into this slide into the barriers faced by physicians, barriers faced by patients, economic barriers and barriers related to the health care system.

I clearly can't talk about all of these today and what I'm going to focus on, firstly are concerns related to tolerability, because those are shared by physicians and patients.

And the three main concerns with most heart failure treatments are about blood pressure being too low, about worsening kidney function, and about hyperkalemia. Often these are more imagined than real and we'll come back to that. And then for the treatments that we're talking about today, SGLT2 inhibitors. There's a very specific concern which is about ketoacidosis.

So let's look first of all at blood pressure and concern about causing hypotension. Well, this isn't something to worry about with SGLT2 inhibitors. Because in fact, the average decrease in blood pressure with these drugs is very small. Here in the DAPA-HF trial, you can see that the average decline in systolic blood pressure was about 2.5 mmHg.

Now, in fact, the interesting thing is that, if you look carefully at the figure here, you can see that the patients who started with the lowest systolic blood pressure, shown in the lilac color, people with a systolic blood pressure of less than 110 mmHg, they actually had a smaller decline in blood pressure than patients who had a higher starting blood pressure. So it's a small reduction overall, and people who have got a lower blood pressure to start with tend to get even smaller reductions.

What about kidney function? Clearly, this is a very big problem in patients with heart failure. We all know how common renal

dysfunction is in our patients with heart failure. But again, there really isn't a concern with SGLT2 inhibitors. Here you can see the decline in eGFR over time in the DAPA-HF trial. What I've done is, I've broken out the patients into four eGFR categories. You can see at the top people with a relatively normal eGFR, and at the bottom people with an eGFR below 45 ml/min/1.73m2 and the overall average decline in GFR was only 3 ml/min/1.73m2 . And as you can see, the decline in patients who started with a low eGFR was, if anything, smaller. And in fact, if you focus in on the around 700 patients that we had with an eGFR between 30 and 45 ml/min/1.73m2, you can see that the average reduction in GFR was only 2.4 ml/min/1.73m2, and very few patients had a substantial decline in eGFR. And only 5 patients, 0.2%, had an eGFR decline to 20 ml/min/1.73m2 or less. So again really nothing to be concerned about with respect to kidney function.

But this is maybe the most important slide I'm going to show you in this presentation. It looks complicated but it really isn't. So along the bottom of the slide, you see various definitions of a decrease in eGFR. There are two bars for placebo. Placebo is shown in blue. There are two bars for SGLT2 inhibitor treatment, dapagliflozin is shown in red. And you can see that in patients receiving placebo who had a decline in eGFR, so that's shown by the hatched bar, you can see that those patients did worse than patients who had no decline in eGFR, who had no worsening renal function. Those are shown by the solid blue bars. Now, contrast that with the patients receiving dapagliflozin, the patients who had a decline in eGFR, who had worsening renal function, so they're shown by the red hatched bars, They had, if anything, a better outcome than those demonstrating no change in eGFR. So a completely different pattern between SGLT2 inhibitor treated patients and placebo treated patients, If you have a decline in the eGFR early after starting placebo that predicts a bad outcome. On the other hand, if you've an early decline in eGFR, with an SGLT2 inhibitor, as you can see, your outcome is not worse, in fact, it tends to be better. So, even the small declines in eGFR that we do see in some people who receive an SGLT2 inhibitor don't matter. In fact, if anything, they predict that those patients are going to have a better outcome. And of course, you've got to remember that in the long term, these drugs slow the rate of decline in eGFR. So, after that initial dip in eGFR, as you can see the rate of subsequent decrease in eGFR over time is actually significantly less in patients getting SGLT2 inhibitor than patients getting placebo.

So the things to take home about changes in eGFR with SGLT2 inhibitors. Is that overall the change is small, that the decline probably reaches the minimum at about two weeks after starting treatment and partially reverses thereafter, it's not associated with a worse outcome in patients getting a SGTL2 inhibitor and in the long run, these drugs slow the rate of decline in eGFR.

Now, what about hyperkalemia. Clearly a concern with particularly drugs inhibiting the renin-angiotensin-aldosterone system. Well again, this is not something we need to be worried about with SGLT2 inhibitors. You can see that, in fact, the incidence of serious hyperkalemia, that's a potassium of 6 mmol/l or above. You can see that that risk was actually significantly less in patients getting a SGLT2 inhibitor than in patients getting placebo. And in fact that benefit was most marked in patients receiving concomitant, mineralocorticoid receptor antagonist treatment, MRA therapy. So again, potentially very useful synergy between these drugs. Hopefully SGLT2 inhibitors, helping us avoid hyperkalemia in patients getting MRAs.

So lastly, there's a very specific concern about ketoacidosis in patients getting SGLT2 inhibitors. But in fact again, this concern is perhaps over-exaggerated, because if you look at the trials, and you can see them all summarized in this slide, the incidence of ketoacidosis is extremely low overall, and really isn't significantly different in the SGLT2 inhibitor group compared to the placebo group.So it does happen occasionally, but it doesn't happen commonly. And to give you some perspective on that, at the bottom of the slide, you see the risk of angioedema with ACE inhibitors and with Sacubitril/Valsartan, and again the perspective here is that the risk of ketoacidosis with an SGLT2 inhibitor, is probably even less than the risk of angioedema with an ACE inhibitor or Sacubitril/Valsartan.

So, I'm now going to switch to one final topic, and that's looking at another type of barrier or challenge and that, of course, relates to physicians and what physicians think. And this is about workloads, something called inertia and something called nihilism. So, let's start with inertia, inertia means our human tendency to do nothing, to really not change things as sort of our passiveness or inactiveness. And clinical inertia is a really big problem for our patients and is indeed one of the major barriers to implementing any new treatment. These are examples of things that I'm sure you've heard your colleagues say, maybe you've even thought them yourself. These are the sort of reasons that we give ourselves for not implementing new therapy, but they're completely false. So the idea that patients are stable, is false. You can see here in the PARADIGM-HF trial, these patients with generally mild symptoms, very well treated. If you look at the Sacubitril/Valsartan arm, you can see that those patients had a very high event rate over about three years of follow-up. And in fact, if we looked at our expanded composite endpoint, looking at all forms of worsening heart failure, you can see that that risk in the Sacubitril/Valsartan group shown in the right-hand panel of this slide was about 30% at three years of follow-up. So even patients with so-called mild symptoms, who are extremely well treated have a very high event rate. So they're not stable, they need more treatments.

And if you don't believe those data, then look at what the patients themselves are telling us. If you look at the two bars, to the left of this figure, you can see placebo treated patients in DAPA-HF reporting a five or greater point change in their KCCQ Total Symptom score. These are the patients reporting a decrease, that's a deterioration. And you can see in the placebo group that proportion was 33% at

eight months. There are 33% of our patients when they fill in that questionnaire, tell us that they've deteriorated within just eight months of being randomized in this trial. And yet again, these were extremely well-treated patients with generally mild symptoms.So they're not stable, they do deteriorate.

It's never too late to introduce a new treatment. Even as long as five years after diagnosis in well-treated patients, who seem to be doing well in conventional therapy. You can reduce risk further with a SGLT2 inhibitor.

Now, I just want to finish by saying something about this concept of therapeutic nihilism. And what do I mean by that? Well these are examples of sometimes again you hear your colleagues say or maybe you even think them yourself. My patient is too old, or too frail or has too many other medical problems to do anything further. And again, that's completely wrong. And here you can see the effect of dapagliflozin compared to placebo according to frailty. And along the x-axis of this slide is a Frailty Index, the higher that index, the more frail patients are. And what you can see is that the hazard ratio is consistently below one, in other words, demonstrating benefit of an SGLT2 inhibitor and that's true, even in the most frail patients. So these drugs that we're talking about today are beneficial, even in frail, elderly, morbid patients. And in fact, if you look at quality of life, which may be the most important thing for these older frailer patients, you can see that actually the greatest benefit from SGLT2 inhibition is in the patients who are most frail at baseline.

So the last thing just to briefly touch on, but I'm not going to go through in detail, is that of course there are other challenges and barriers related to the healthcare system. And one of them is the fragmented follow-up, that patients often receive, concerns about monitoring patients during follow-up.

And again all of these concerns emphasize the difference between SGLT2 inhibitors and other therapies. There is no need for dose titration. I've already explained that monitoring needs to be minimal. Maybe one check of kidney function, and all the other benefits of these treatments are obtained along with outstanding tolerability.

Thank you very much.

Announcer:
Thank you for listening! Also, listen to the next episode of this series, in which Professor Carolyn Lam talks about effects of SGLT2 inhibitors in heart failure across the spectrum of left ventricle ejection fraction and reviews current guideline treatment recommendations.

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CHAPTER TWO

Announcer:
When to start using SGLT2 inhibitors in heart failure with reduced ejection fraction? Initiating guideline-recommended treatment options.

In the second episode of this educational series, Professor Carolyn Lam talks about effects of SGLT2 inhibitors in heart failure across the spectrum of left ventricle ejection fraction and reviews current guideline treatment recommendations.

Dr. Lam:
Thank you for the privilege of talking about the benefits and evolving insights on SGLT2 inhibitors across the spectrum of left ventricular ejection fraction in heart failure. The question is, can we set priorities?

Well, first of all, let's talk about heart failure across the spectrum of left ventricular ejection fraction. The ESC 2021 guidelines, which are very consistent with the universal definition, as well as the American 2022 guidelines, all classify heart failure by ejection fraction into these three main bins. We have heart failure with reduced ejection fraction with an EF less than 40 percent, less than or equal to 40 percent. We have heart failure with preserved ejection fraction or HFpEF of ejection fraction, 50 percent and above. And then those in between now called heart failure with mildly reduced ejection fraction.

So, let's start with perhaps the most obvious. HFrEF: the SGLT2 inhibitors are undoubtedly beneficial in this group of patients. In fact, they have become one of the four foundational therapies for patients with HFrEF. And these are based on the landmark data from the DAPA-HF and EMPEROR-Reduced trials. And you can see here the meta-analysis of their primary endpoints of heart failure hospitalization or events and cardiovascular death where you see a robust 25 percent relative risk reduction. And if we look at the components of the primary endpoint, again, remarkable consistency with especially marked reduction in heart failure hospitalizations. Now, please remember that, the benefits of these therapies are realized very quickly and these are data from DAPA-HF, where you see there's a significant benefit already shown at 28 days from initiation. In fact, look at that hazards ratio, it's almost half, which means we would double the risk of worsened health status or heart failure hospitalization or cardiovascular death, if we delay initiation.

Now, what about heart failure with a higher ejection fraction? Let's just talk about anything above 40% now and that was the population studied in the EMPEROR-Preserved trial of empagliflozin versus placebo in these patients. Now, of course, we are all celebrating that it

was the first robustly positive outcomes trial in these patients with the primary composite of first heart failure hospitalization or cardiovascular death robustly reduced by empagliflozin. And this was mainly driven by a reduction in heart failure hospitalization.

So is the story over like that? Well, these are ejection fraction above 40 percent. So who are these patients? Well, there was a subgroup analysis, pre-specified by ejection fraction. And as you can see here it is pretty consistent. And the point estimates are all to the left of one and there was no significant interaction by ejection fraction. However, if you squint a bit, perhaps it's looking like, it's slanting. To address this issue the authors actually did a focused analysis in patients with ejection fraction of 50 percent or above. So, what we call HFpEF as I've reviewed before. And indeed, even if analyzed in this restricted population, you would find a robust reduction in the primary endpoint as shown here, 17 percent reduced risk of the composite of cardiovascular death or heart failure hospitalization. But put this together with this pooled analysis across EMPEROR-Reduced and EMPEROR-Preserved, where if you look across the ejection fraction spectrum, and if you look at the y-axis and realize that, if it falls below one, it says benefit, but as it approaches the one there could be attenuation of benefit and this was the suggestion in this analysis here, that could be attenuation of the benefit of heart failure hospitalization in those with an ejection fraction of 65 percent or above. But the field is still trying to grapple with this, because if you were to analyze now these data with ejection fraction as a continuous variable, we see a line that pretty much stays under the line of unity. But as you can see there appears to be a bit of a slant, with perhaps more benefit with a lower ejection fraction. But again, no significant interaction.

What we really need, of course, is more data. And you will soon hear about the DELIVER trial, which we already know, read out as positive. But what we really need to understand is, is there a difference across the higher ejection fraction range? We will soon find out.

In the meantime, the guidelines are thankfully quite consistent. And here are the foundational medications that I've represented on each row: HFrEF, HFmrEF and HFpEF and in each row split into the ESC 2021 guidelines and the American 2022 guidelines.

Very easy to remember for HFrEF, definitely class 1 recommendations for these medications, including the SGLT2 inhibitors. Now, where it differs is the SGLT2 inhibitors in those above 40% and because the American guidelines were published after the EMPEROR-Preserved study, you can see that this has been upgraded to a 2a across that entire spectrum,but no mention in the ESC 2021 guidelines which were published before EMPEROR-Preserved.

Does the story end there? Definitely not. Remember the question is, can we prioritize? It is a Class 1 recommendation by both ESC and the American guidelines that in patients with heart failure and diabetes Type 2, SGLT2 inhibitors are indicated. So remember if the patient has diabetes, you should be using an SGLT2 inhibitor. Another class 1 guidelines consistent recommendation, consistent in European and American guidelines, is in a patient who has been hospitalized, that we should be really optimizing their therapy before discharge.

Now remember those two groups and why do we say that? Well, this is a trial, not quite of SGLT2 inhibitors alone, but of the SGLT 1 and 2 inhibitor, sotagliflozin, in those patients with recent heart failure hospitalizations, but all of whom had type 2 diabetes and as you can see, there was a robust reduction in the primary endpoint of total cardiovascular deaths, HF hospitalizations or urgent heart failure visits. Now this trial had to be prematurely terminated, because of covid and so on, but still very intriguing suggestion that in these hospitalized patients whether your ejection fraction is below or above 50%, you do benefit.

The EMPULSE trial is another study that addresses this group of patients at high risk with a recent heart failure hospitalization, in fact, the initiation of the SGLT2 inhibitor during hospitalization, was related to benefit to the patient as quantified by a hierarchical endpoint and quantified by the win ratio.

And finally, another reason we treat our patients, is importantly to make them feel better. And in this very remarkable study called PRESERVED-HF. Dapagliflozin was initiated in patients with heart failure and preserved ejection fraction and compared to placebo, it significantly improved the primary outcome of KCCQ clinical summary score. This was a quite remarkable improvement. And in fact in a responder analysis, many more patients felt better and fewer patients felt worse when they received dapagliflozin then placebo. And this is not only for the clinical summary score, but also for the other components of KCCQ shown here. And finally importantly, although it was a secondary endpoint, dapagliflozin also improved six-minute walk distance.

And so, SGLT2 inhibitors in the spectrum of ejection fraction in heart failure, can we set priorities? I would say that as we await to DELIVER results, we have the class 2A recommendations for those with heart failure and ejection fraction above 40%. But regardless of ejection fraction, don't forget to treat these patients if they have diabetes, if they are hospitalized and at high risk and perhaps if they have impaired quality of life, the SGLT2 Inhibitors are something we may consider. And finally, I think with the DELIVER study, we will be able to finally answer the question of: is it mainly restricted to those with an ejection fraction of perhaps less than 65 percent?

Thank you.

Announcer:
Thank you for listening! Also, listen to the next episode of this series, in which Professor Scott Soloman talks about unanswered questions with SGLT2 inhibitors and discusses the study design of the DELIVER trial.

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CHAPTER THREE

Announcer:
When to start using SGLT2 inhibitors in heart failure with reduced ejection fraction? Initiating guideline-recommended treatment options.

In the third and last episode of this educational series, Professor Scott Soloman talks about unanswered questions with SGLT2 inhibitors and discusses the study design of the DELIVER trial.

Dr. Solomon:
Hi. Today, I will be talking about evidence on SGLT2 inhibition. Where we are and what can we expect?

Here are my disclosures.

Well, I think we all know that there are still some unanswered questions. Despite the incredible success of SGLT2 inhibitors. First: "Is the benefit of SGLT2 Inhibitors similar across the full spectrum of ejection fraction in heart failure?" Second: "Are SGLT2 Inhibitors as effective in hospitalized patients and recently hospitalized patients as they are in outpatients?" Third: "Is addition of SGLT2 Inhibitors beneficial to patients with heart failure and "improved" Left Ventricular Ejection Fraction (LVEF)?" In other words, those who had a prior LVEF less than 40%. Fourth: "Can SGLT2 Inhibitors reduce cardiovascular death in patients with heart failure and a Left Ventricular Ejection Fraction greater than 40%?" And finally: "Can SGLT2 Inhibitors improve symptoms in patients with heart failure with mildly reduced and preserved Ejection Fraction?"

Let's first get the elephant in the room out of the way. We all know that the Top Line results of the DELIVER trial were announced last month, DELIVER met its primary endpoint of a composite of cardiovascular death or worsening heart failure in patients with mildly reduced and preserved ejection fraction. I am not going to talk about the results of DELIVER today. So instead I am going to tell you about what we can expect with DELIVER. What the baseline results of DELIVER look like, and what we're hoping to be able to show at an upcoming conference.

So first, let's talk about the design and baseline characteristics of patients in the DELIVER trial. This is the design of DELIVER. In order to get in this trial, patients had to be 40 years of age or older. They had to have New York Heart Association Class 2 to 4 heart failure, a Left Ventricular Ejection Fraction of greater than 40% and evidence of structural heart disease. What I mean by that is either left ventricular hypertrophy (LVH) or left artrial (LA) enlargement. They also had to have evidence of elevation of natriuretic peptide 300 for patients in sinus rhythm and 600 for patients in atrial fibrillation. They could be either ambulatory or hospitalized and they could have had prior Left Ventricular Ejection Fraction less than 40%. This is a group that has been excluded from all other clinical trials in this area. Patients were randomized to either Placebo or Dapagliflozin 10 milligrams once daily.

We ended up randomizing 6263 patients. The primary endpoint with the time to the first composite of cardiovascular death or heart failure event. Meaning either a heart failure hospitalization or an urgent heart failure visit. And this primary endpoint was assessed, both in the full population, everybody. And simultaneously in the patients with an ejection fraction under 60%, we split the alpha between those two groups, secondary end points included, total heart failure events, and cardiovascular death in both populations. Change in KCCQ total symptom score by eight months in the full population. And then cardiovascular death and all-cause mortality. Also in the full population and, of course, we also did a sensitivity analysis looking at COVID-19.

The DELIVER design, compared to other trials, is unique. And the main thing that is unique about DELIVER, is that it is larger. We have more patients with heart failure with mildly reduced and preserved ejection fraction, than any trial thus far. We did require structural heart disease and elevation of natriuretic peptides similar to what we did in the PARAGON study. The LVEF is over 40%. This is lower than in many of the prior trials, but similar to EMPEROR-Preserved and the endpoint was a combination of cardiovascular death, heart failure hospitalization and urgent heart failure visit, which was a little bit different from EMPEROR-Preserved, which did not have urgent heart failure visit in their endpoint.

Here are the baseline characteristics of DELIVER compared with the other HFpEF trials. And I'm not going to go through, of course, all of these numbers. But what you can see here is that DELIVER was remarkably similar to many of the other studies, we had a lower percentage of women in DELIVER as they had in EMPEROR-Preserved than in some of the other trials because our Left Ventricular Ejection Fraction was in fact lower. We had about 70% of patients who are New York Heart Association class 2, 45% of patients with diabetes, 26% of patients were hospitalized within the last 12 months, and we had a subacute population, patients who were either

enrolled in the hospital or hospitalized within 30 days that made up 10% of our patients. And then, as I have said, we allowed patients with an improved LVEF that represented 18% of our population. Our mean LVEF was 54% and our mean NT-proBNP was approximately 1,000.

These patients were on RAAS inhibitors, a very high percentage on ACE inhibitors and ARBs we even had some patients on ARNIs and about 40% of our patients were on MRAs, which is the highest percent of any of the trials on MRAs. The medication use in these patients, you can see in DELIVER and EMPEROR-Preserved. We had the most MRAs of any trial so far And DELIVER really and EMPEROR-Preserved were the only trials that had any use of ARNIs.

Now, we have known that patients who are recently hospitalized seem to have a higher event rate and they also seem to benefit from therapies to a greater extent, than patients who are more chronic when they are enrolled in trials. We saw this in the PARAGON trial and it was also seen in the SOLOIST and SCORED HFpEF cohorts using sotagliflozin. We have enrolled patients in DELIVER who were either in hospital or within 30 days of hospitalization, you can see that the mean age here of these patients was about the same as the other patients there are a couple of other things though that are different, including the fact that they had a higher use of mineralocorticoid receptor antagonist and also they had a higher NT-proBNP.

The other sub group that is going to be very important, is this group of patients with heart failure, with so-called improved LVEF. We used to call this recovered LVEF. This is recently been defined in the guidelines as any patient who had a previous LVEF less than or equal to 40% and a follow-up measurement of greater than 40%. We had 18% of patients in DELIVER. This is what they look like on the right and you can see here that there are some really important differences in this group. They were more likely to be New York Heart Association Class 2, they were less likely to be women. Their mean NT-proBNP was identical. Their ejection fraction was a little bit lower, about five points lower than patients who are not enrolled in this group and there were some important differences in medications. They were more likely to be on the kind of medications that we use for heart failure with reduced ejection fraction.

Well importantly, we've also seen in other trials that as ejection fraction goes up, the benefit of therapies seems to decline. We saw that with candesartan in CHARM, with the mineralocorticoid receptor spironolactone in TOPCA and we saw that with sacubitril/valsartan in the PARADIGM and PARAGON programs. So, in EMPEROR-Preserved although the study was overall positive. There was at least a suggestion on these post hoc analyses of heterogeneity by Left Ventricular Ejection Fraction. As you can see in these two slides. This is a question that is obviously very important and we hope to be able to answer with DELIVER. Why might this be? Because we think that as ejection fraction goes up, the contribution of the cardiac effects, The cardiac benefit of our therapies actually goes down And so, our cardiovascular therapies may not be as effective as ejection fraction goes up. We are going to find that out in DELIVER. We certainly know that patients with heart failure, with reduced and mildly reduced ejection fraction, seem to respond to therapy with many of the drugs that we have currently used for treating heart failure with reduced ejection fraction. I think that the group in the upper area, what we call heart failure with normal ejection fraction, is right now, our discomfort zone and we hope to answer that question with DELIVER, which is the largest and broadest trial in heart failure with mildly reduced and preserved ejection fraction.

As I said, we have two ways we can win in the full population and with the patients who have an ejection fraction under 60%. DELIVER should elucidate whether SGLT2 Inhibition, like other therapies, shows attenuation in patients, with normal left ventricular ejection fraction. DELIVER will further assess benefit of SGLT2 Inhibitors, in hospitalized, or recently hospitalized patients and we will assess the benefit in this group with improved LVEF, a group excluded from other trials.

Stay tuned.

Announcer:
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