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When and how to initiate SGLT2i in CKD

I'm going to be talking about when and how to initiate SGLT2 inhibitor therapy in patients with chronic kidney disease. We now have 13 outcome trials that have looked at SGLT2 inhibitors and their clinical impact, and three of these studies have reported kidney outcomes in patients with chronic kidney disease, the CREDENCE trial, the DAPA-CKD study, and the EMPA-KIDNEY study.

Now, these trials all differ somewhat and I've summarized the differences in this slide. CREDENCE recruited just patients with type 2 diabetes and kidney disease, DAPA-CKD and EMPA-KIDNEY, on the other hand, recruited patients who had chronic kidney disease but did not necessarily have type 2 diabetes. The eGFR range in these studies was somewhat different, ranging from a lower limit of 30 in CREDENCE down to a lower limit of 20 in the EMPA-KIDNEY study. The albuminuria ranges were slightly different in the EMPA-KIDNEY study. The EMPA-KIDNEY study recruited patients who had eGFRs of less than 45 with no albuminuria. If the eGFR was greater than 45, patients needed to have albuminuria, and the other two studies only recruited albuminuric patients. Of course, the test drug was different in the different studies.

I'm going to illustrate which patients I feel should be treated with these drugs by using some case studies. I'm going to draw on those three trials I've just mentioned to work out the best option for these patients. Here, we have a 68-year-old white male. He has type 2 diabetes. He's had it for 10 years. He's overweight. He has early diabetic retinopathy, so he's probably got nephropathy. He's on metformin and gliclazide. He's got a high blood pressure treated with ramipril. He's on atorvastatin to reduce his cardiovascular risk. He comes up for his annual review and his blood pressure is too high. He has an estimated GFR of 52 ml per minute. A year ago, it was 58, so his kidney function is declining, and his albuminuria is getting worse with a urinary albumin creatinine ratio of 672 milligram per millimole, almost double from the previous year. His glucose control is not good with an HbA1c of 72 millimole per mole or 8.7%. Now, this patient would have got into the CREDENCE trial which he would have been eligible for the CREDENCE trial based on this information. I would argue that canagliflozin may be a good option in this particular patient. By starting him on canagliflozin, we may reduce the exposure to his risk factors, but we are also in the longer term providing kidney protection.

Let's just look at some data from the CREDENCE study. This is the effect of study drug and placebo on hemoglobin A1c concentrations during the duration of the trial. You'll see that in those patients, in the trial randomized to canagliflozin, there was a reduction in HbA1c of 0.25% time averaged over the duration of the study. A useful reduction in HbA1c, and likewise, a reduction in systolic blood pressure, this is an average reduction of 3.3 mmHg throughout the duration of the study. By putting him on canagliflozin, we're going to be tackling his risk factors, but most importantly, we know from this trial that by treating him with canagliflozin, we reduce his cardiovascular risk and reduce his risk of reaching end-stage kidney disease.

Is there a downside and what should we be worried about in this man? This is my first practical points for nephrologists prescribing SGLT2 inhibitors, and this is the problem of ketoacidosis. What I show here are the ketoacidosis rates in the three studies that I've described showing in both CREDENCE and in EMPA-KIDNEY, an excess of ketoacidosis events. That's the number of events and the percentage of patients compared to patients who went into the trial and are randomized to placebo, and you'll see that we didn't see this in the DAPA-CKD study. There is an increased risk of ketoacidosis, certainly with two of these drugs. Now, how can we avoid this? We should avoid SGLT2 inhibitors in patients with type 1 diabetes, that is something we should leave to our colleagues in diabetology. We should avoid reducing the insulin dose when we start the SGLT2 inhibitors. I should add that SGLT2 inhibitors do not cause

hypoglycemia. We should be aware of the fact that these patients can develop ketoacidosis without high blood sugar levels, euglycemic ketoacidosis. That's because they excrete the glucose in their urine. If these patients become unwell, we should think about testing for ketones and think of the possibility of ketoacidosis.

Just moving to the guidelines, these are kidney disease, improving global outcomes. International guidelines just updated on the management of patients with the combination of type 2 diabetes and chronic kidney disease. You'll see this pyramid of care with lifestyle interventions at the bottom, and then on the first level of the pyramid, the first line therapies for these patients, Metformin, SGLT2 inhibitors have now appeared there along with RAS blockade and statin therapy. These new drugs, the SGLT2 inhibitors are now up there as first-line therapy for diabetic patients with chronic kidney disease.

Let me move on to our second case. This is a Chinese male with IgA nephropathy. We know this because he had a kidney biopsy 10 years ago after developing hematuria. He does not have diabetes and he does not have cardiovascular disease. He initially responded to some steroid therapy, but this has now been discontinued and he finds himself on ramipril and amlodipine. His eGFR is 43 and declining and his UACR is 98 and increasing. He has worsening kidney function. Now, this patient would've probably got into the DAPA-CKD trial and the EMPA-kidney trial even though he doesn't have type 2 diabetes because both of these trials recruited patients with non-diabetic kidney disease. I would argue that dapagliflozin might be a good option for this patient. This is the primary outcome in the DAPA-CKD study in a group of 270 patients who were randomized into the trial with a diagnosis of IgA nephropathy. Most of these patients were not diabetic. You see here a 71% reduction in the risk of this composite primary outcome. DAPA would be a good drug for this patient with IgA nephropathy.

Let's move on to our third patient. This is an Asian female. She's 73 years old. She has cardiovascular disease, but she's not diabetic and she's not overweight. She's had a prior myocardial infarction that's left her with some heart failure, but she has a preserved ejection fraction. On ultrasound, she has small kidneys suggesting an ischemic nephropathy. She has a bit of ankle oedema. She's on amlodipine, furosemide, and atorvastatin, and there's a worry that she's got peripheral vascular disease to go with her atherosclerotic coronary artery disease. She has an eGFR of 28 falling from 32 and she has no albumin in her urine with a UACR of less than 3 milligram per millimole.

Now, I think the benefits of an SGLT2 inhibitor are possibly less obvious in this patient. Although this patient may well have qualified for the EMPA-kidney study, which recruited patients with low levels of eGFR below 45 who did not have albuminuria. We might offer her empagliflozin, but let's look in a little bit more at the data. This is the primary outcome from the EMPA-kidney study stratified by the baseline eGFR, and you'll see here that patients with an eGFR of less than 30, like our lady, still gain benefit from study medication. Let's look at the study population stratified by baseline urinary albumin creatinine ratio, and this is in milligram per gram. For our patient, with a starting uACR of less than 3 milligram per millimole or 30 milligram per gram, we see a less obvious benefit. You'll see here that the P-value is significant, meaning that these values are statistically significantly different. There's heterogeneity here when we look at baseline albuminuria. I think this makes a decision about starting an SGLT2i in this lady a little bit more difficult. We do know that in these patients with lower levels of albuminuria, there was still a slowing of the rate of decline of eGFR in those randomized to empagliflozin compared to placebo. There's also a slight safety worry here. As I said, there was a concern this lady may have peripheral vascular disease. We saw in the EMPA-KIDNEY study an increased rate of lower limb amputation in patients randomized to empagliflozin. We've seen this in other SGLT2 inhibitor studies in the past. This problem has not gone away. I think we need to be cautious in patients who have peripheral vascular disease or who are at high risk of lower limb amputation as a result of their peripheral vascular disease.

This brings me onto another issue I wanted to discuss, which was the acute drop in eGFR when we start patients on SGLT2 inhibitors. Here are data from the DAPA-CKD study that nicely illustrates the acute drop in eGFR that we see when we start these drugs. Notice that after this acute drop, patients randomized to dapagliflozin progressed at a slower rate than those randomized to placebo with a crossover at 12 months.

This brings us onto my second practical issue for nephrologists is dealing with this acute drop in eGFR, which we've seen in all of these studies. Let's remember that it's a small reduction. We see it with ACEs and ARBs, which we know are renal protective therapies. We believe it's a result of a hemodynamic change in the kidney which we see with ACEIs, ARBs, and SGLT2s, we believe. There's no increased risk of acute kidney injury in these trials of SGLT2 inhibitors, which is hugely reassuring. Again, as I've explained, although there's an acute drop, there's a longer-term benefit in terms of slowing eGFR decline subsequently. If this acute drop is large, and by large, I mean greater than 30%, we probably need to investigate this patient in a little bit more detail for renovascular disease and other problems.

The other issue here is that this lady is on furosemide, and I think we should be careful starting SGLT2 inhibitors in patients who are on loop diuretics. That's because the SGLT2 inhibitors also have a diuretic effect. This is just some of the safety data from the DAPA-CKD

study showing that patients who were on diuretics at the start of the study had a higher rate of serious adverse events than those who were not on diuretics. These patients are more prone to the side effects and adverse effects of these drugs, and I think we should remember that.

This is my third practical point. If you've got a patient who you believe is at risk of volume depletion or who is already volume depleted, think carefully before starting SGLT2 inhibitors, and treat these drugs as sick-day rule drugs. Suspend these drugs when the patient is at high risk of dehydration and suspend these drugs, for example, when a patient has diarrhea and vomiting as you would an ACE or ARB or a non-steroidal anti-inflammatory drug.

That leads me with my conclusions. These drugs, SGLT2 inhibitors improve both kidney and cardiovascular outcomes in a broad range of patients with chronic kidney disease, both with and without type 2 diabetes. The CREDENCE, DAPA-CKD, and EMPA-KIDNEY studies have shown that very clearly. These benefits seem to persist down to low levels of eGFR down to 20 in the EMPA-KIDNEY study. The benefits in patients with lower levels of albuminuria or no albuminuria are not quite so clear. The safety profile appears favorable. Despite this early reduction in eGFR. There's no increased risk of acute kidney injury. We need to be cautious in patients prone to dehydration and those on diuretics. Remember these problems of ketoacidosis and lower limb amputation, and avoid these drugs in patients with type 1 diabetes and in frail and elderly patients likely to suffer from dehydration. Finally, you might want to warn your patients of the risk of genital fungal infections which has been seen in all of these studies and whilst a nuisance is readily treatable.

Thank you very much for listening to me. I hope that was of value to you.