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Understanding Dapagliflozin: Examining Its Use in Chronic Kidney Disease

Dr. Buse:
Regardless of whether a patient has diabetes, those with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. It's been unclear if a treatment for Type 2 diabetes, like dapagliflozin, would benefit these patients. That is, until the DAPA-CKD trial finally gave us that long-awaited answer, and what that answer is, and how it fits into the overall landscape of SGLT2 inhibitors for patients with and without diabetes is what we'll be discussing today. Welcome to Diabetes Discourse on ReachMD. I'm Dr. John Buse, and joining me to discuss his latest research on the use of dapagliflozin in patients with chronic kidney disease is Dr. David Wheeler, a professor of kidney medicine at University College London in the United Kingdom, and an honorary consultant nephrologist at the Royal Free London NHS Foundation Trust. Dr. Wheeler, thanks for being here today.

Dr. Wheeler:
Well, thank you very much for inviting me. It's an honor.

Dr. Buse:
Well, let's start off, Dr. Wheeler, could you give us the top-line results of the DAPA-CKD study?

Dr. Wheeler:
Yes, of course. So the DAPA-CKD trial recruited, around about 4,000 patients with chronic kidney disease. Some of these patients had diabetes, and some of them didn't. They were recruited on the basis of their glomerular filtration rate, and on the basis of the amount of albumin in the urine. And as I say, we included patients in this trial who had chronic kidney disease that was not due to diabetes, and this is probably the most novel feature of the trial, is a study of dapagliflozin, which is, of course, a diabetes agent in patients with chronic kidney disease who do not have Type 2 diabetes. The top-line result was that randomization of these patients to dapagliflozin compared to placebo, resulted in reductions in both adverse kidney outcomes, and adverse cardiovascular outcomes. So, our primary outcome in the trial was a composite of kidney – progression of kidney disease and cardiovascular events. And we demonstrated a reduction in this primary outcome.

Dr. Buse:
Outstanding. You also had benefits in mortality, if I remember. Is that correct?

Dr. Wheeler:
Yeah, so I guess to go into a little bit more detail on the endpoints, our primary endpoint was a composite of kidney disease, progression, and death due to either cardiovascular causes or kidney causes. We then had a number of secondary outcomes, including, an outcome that was just kidney endpoints. It was a reduction in EGFR by greater than 50%. It was reaching end stage kidney disease, or needing dialysis, and that was our first secondary outcome, and we saw a reduction in that outcome, in the patients who were randomized to dapagliflozin. We had another secondary outcome, which was cardiovascular death or hospitalization for heart failure, and we saw a reduction in that outcome. And our third secondary outcome was actually all-cause mortality, and we were able to show a reduction in all-cause mortality in those participants randomized to dapagliflozin, compared to placebo, during the study.

Dr. Buse:
So, were the outcomes different, dapagliflozin versus placebo, in those people with and without Type 2 diabetes?

Dr. Wheeler:
They were remarkably consistent, actually, and I think that was one thing we were quite surprised about. It didn't seem to matter what

the underlying cause of kidney disease was, whether it was diabetic nephropathy or glomerular disease or ischemic nephropathy or hypertensive nephropathy. The benefit was still seen with dapagliflozin, regardless of the underlying cause of the chronic kidney disease. And we've done a statistical analysis that shows there was really no difference between the diabetic and the non-diabetic patients in the study.

Dr. Buse:
Outstanding. So this is not dapagliflozin's first big study, so there are also outcome studies in heart failure, and patients at high risk for cardiovascular disease. How does this DAPA-CKD study fit in the totality of those dapagliflozin studies?

Dr. Wheeler:
So these drugs, the FGLT2s, have all been subjected to these large cardiovascular outcome trials, and these were mandated by the regulators because of concerns we've had before with diabetic drugs that have come to market and then shown some safety signals. So from those initial trials, which were done in diabetic patients, we picked up a few kidney signals actually, even in those studies. And of course, most of those patients didn't have kidney disease, or had very early kidney disease. But the worsened positive kidney signals, even in the DECLARE TIMI 51 study, which was the cardiovascular outcome safety trial of dapagliflozin, so that was, interesting and supported us doing a trial in more advanced chronic kidney disease, so the DAPA-CKD study recruited patients with estimated GFRs between 25 and 75 ml/minute, all of whom had albuminuria. So they were in a much more advanced stage of chronic kidney disease, and in a higher risk group. And then looking at the DAPA-HF study, this was a study in patients with heart failure that was completed, before the DAPA-CKD study. And of course, many of these patients with heart failure also had chronic kidney disease. And the trends in that trial are – in terms of progression of kidney disease are similar to the trends we've seen in the other studies, although the kidney outcome in the DAPA-HF trial, didn't reach statistical significance. But the same patterns were there in the DAPA-HF study. So I think if you put all these data together, you've got patients with Type 2 diabetes and early chronic kidney disease, you've got patients with heart failure, some of whom have diabetes and some don't, we've now got patients with more advanced chronic kidney disease, some of whom, have heart failure. And the effect of DAPA is pretty consistent across these populations.

Dr. Buse:
That's outstanding. And your data has already changed guidelines. In the United States, the guidelines are now moving to recommending very strongly that patients with diabetes with estimated GFR down to 25, as opposed to down to 30 from before, and, albumin to creatinine ratios down to 200, as opposed to 300 before – so we've widened the population that now has a strong indication in the United States for using an SGLT2 inhibitor. For those just tuning in, you're listening to Diabetes Discourse on ReachMD. I'm Dr. John Buse, and I'm speaking with Dr. David Wheeler about the use of dapagliflozin in patients with chronic kidney disease. Now Dr. Wheeler, one community that's a bit frozen out from SGLT2 inhibitor therapy in the U.S. is patients with Type 1 diabetes. What's the thinking in Europe regarding SGLT2 inhibitors in patients with diabetes, particularly those with chronic kidney disease or heart failure?

Dr. Wheeler:
Yeah, that's an important question that we really need answers to. We decided to exclude patients with – with Type 2 diabetes from the DAPA-CKD study, I think largely because we were worried about the risk of diabetic ketoacidosis and that's certainly been seen with these drugs in patients with Type 1 diabetes and in studies of patients with Type 2 diabetes. I think the general view in Europe is that we need more evidence in that population, and there is actually another study going on, called the EMPA-KIDNEY study, which as the name suggests, is a study of empagliflozin in patients with chronic kidney disease, and that trial is actively recruiting patients with Type 1 diabetes. And when the results of that study are released in a year or so, I think we'll be able to answer that question about the risk to benefit ratio of SGLT2 inhibitors in patients with Type 1 diabetes.

Dr. Buse:
Great. And you mentioned, the consistency of the story and the broadening populations with benefit for dapagliflozin. But there's fair consistency across the SGLT2 inhibitors as a class, not 100%, but are you a believer that all SGLT2 inhibitors are created equal, and that the differences between trials is related to design and conduct?

Dr. Wheeler:
I guess I tend to stick to the evidence as closely as I can. And you look at the individual trial and the risk to benefit ratio, in an individual trial, and you tend to recommend the drug that was used, in that trial for that particular patient population. I think there has been consistency, generally across the class. Some of the drugs, of course, have SGLT one, inhibitory properties, and that's – means that they have slightly different actions. They may have actions in the gastrointestinal tract, and I think, for those drugs, we may have to be a little bit more cautious, but certainly for the drugs that certainly are widely available in Europe – empagliflozin, dapagliflozin and canagliflozin – there seems to be reasonably consistent data in terms of benefits and risks in the diabetes population, certainly. So I think we'll probably be able to interchange these drugs eventually. But as I say, I'm very much sticking to the evidence at present time, and using the drugs that were studied in the trials in the relevant patient population, because I think that's the safest approach.

Dr. Buse:
Lastly, Dr. Wheeler, if you could give one take home message to our listeners, what would that be?

Dr. Wheeler:
Well, if I was a patient with diabetes, perhaps at an early stage, and my doctor said to me, “Look, you’ve got protein in your urine, you’ve got, you know, you’ve got an early stage of your kidney disease. I’m also worried about your heart, you may be, developing some heart failure.” I might say to my doctor, you know, “Well can you give me a drug that will help those problems?” And in fact, my doctor could give me a drug, that not just treats the diabetes, but also prevents those complications of diabetes, in the longer term. And I would want to be on that drug as a patient. I would want to be prescribed the drug that not only treats the diabetes and brings my blood sugar down, but protects my kidneys and heart from the complications of diabetes in the longer term.

Dr. Buse:
And, for patients with kidney disease, but not diabetes, you know, we have ACE inhibitors, we have a variety of other therapies. Where will the SGLT2 inhibitors fit in there?

Dr. Wheeler:
Well, I think for many of those patients, really, all – all we’ve got is ACE inhibitors. So these are patients with a variety of kidney diseases, as we talked about earlier, who have GFRs, between 25 and 75, they have albuminuria now, proteinuria. We haven’t got a lot to offer those patients, at present, and I think having the SGLT2s will help usoffer those patients more. There may be a few logistic issues, because we’re gonna be asking, nephrologists, perhaps, to prescribe these drugs that traditionally have been used by diabetologists. But you know, many of my primary care, my family doctors say, to me, “Look, we’re prescribing these drugs anyway, so just tell us, which patients to prescribe them in.” And maybe the patient won’t need to come to a specialist to get onto these drugs. We certainly want to get these drugs initiated early, to get the maximum benefit, and we may be working with our primary care physicians to get these drugs into patients at an early stage of their disease. So I think we now have another treatment for chronic kidney disease, which is quite exciting, because we, as nephrologists, want to stop kidney disease progressing and avoid patients needing dialysis, and I think this drug will help us with that.

Dr. Buse:
Outstanding. That’s really a great way to round out our discussion on DAPA-CKD as a trial, and the SGLT2 inhibitors as a class, and I want to thank my guest, Dr. David Wheeler, for joining me today. Dr. Wheeler, it was great having you on the program.

Dr. Wheeler:
Well, thank you very much for inviting me.

Dr. Buse:
I’m Dr. John Buse. To access this and other episodes in our series, visit reachmd.com/diabetesdiscourse, where you can be part of the knowledge. Thanks for listening.