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What is the evidence of SGLT2i in CKD?

Dear colleagues, my name is Hiddo Heerspink. I'm a clinical trialist. I'm based in Groningen and today I'm going to tell you that SGLT2 inhibitors are a foundational therapy for patients with chronic kidney disease.

My disclosures are listed here. I work with various pharmaceutical companies to develop new drugs for patients with chronic kidney disease.

We know that the number of incident cases of kidney failure continues to rise. This has been shown, for example, in the United States, where we can see that both in patients with and without diabetes, the number of patients who require kidney transplantation or dialysis continues to increase. That is associated with a continuous increase in the cost for dialysis and expenditures for chronic kidney disease. For example, Medicare expenditures, as shown on the left, have continuously increased over time. This is not because the expenditures per patient have increased, because they have stabilized as you can see on the right, but this is because there are more and more patients ending up in kidney failure.

Fortunately, we have new drugs available for the treatment of chronic kidney disease to delay the time to dialysis. Four large clinical kidney outcome trials have demonstrated that SGLT2 inhibitors reduce the risk of dialysis or kidney transplantation. First, the CREDENCE trial, only in patients with type 2 diabetes and chronic kidney disease, which is followed by DAPA-CKD, as shown in the bottom left, which included a population of patients with chronic kidney disease with and without type 2 diabetes, and then in SCORED and EMPA-KIDNEY as shown on the right. All these four trials have consistently demonstrated that SGLT2 inhibitors reduce the risk of kidney failure by 30% to 40%, so very solid evidence.

Although SGLT2 inhibitors were developed for the treatment of type 2 diabetes, the benefit of these agents to reduce the risk of kidney failure is consistent in patients with and without Type 2 diabetes. This is a very nice meta-analysis of all cardiovascular kidney outcome trials with SGLT2 inhibitors that clearly demonstrate that there is no difference in the efficacy of SGLT2 inhibitors to reduce kidney failure in patients with diabetes or without diabetes, as shown here in this forest plot.

What about the efficacy of these drugs by the type of kidney disease? In the kidney outcome trials, there were patients enrolled with diabetic nephropathy, ischemic or hypertensive kidney disease, glomerular disease, or when the type of kidney disease was other. What we can appreciate when we look at all these four kidney outcome trials, that the efficacy, again, of SGLT2 inhibitors to reduce kidney failure or a halting of kidney function is consistent irrespective of the type of kidney disease. This tells us that we can initiate these drugs in a very broad population of patients with chronic kidney disease.

So far, we have looked at the efficacy of these drugs on chronic kidney disease, but these drugs also reduce the risk of acute kidney injury. Again, a very nice meta-analysis published in the Lancet, in November 22, demonstrated that across all the SGLT2 trials, the risk of acute kidney injury is significantly reduced with consistent effects in patients with diabetes and without diabetes.

Although kidney failure is the most obvious outcome for patients with chronic kidney disease, we also know that these patients are at higher risk of cardiovascular complications. We know that SGLT2 inhibitors reduce the risk of heart failure, but, perhaps, what is not so well known is that unplanned hospital admissions are frequently occurring in patients with chronic kidney disease. When we look, for example, at the DAPA-CKD trial as shown in the Kaplan-Meier curve on the left, and we look at the number of unplanned hospital

admissions over three years of follow-up, we see that 40% of patients are hospitalized. Importantly with dapagliflozin, the SGLT2 inhibitor, this risk is reduced by 16%. Also, when we look at all hospitalizations or deaths, as shown on the right, you can see that the risk is significantly reduced by 21% with dapagliflozin, compared to placebo.

But hospitalizations are not the only complication of chronic kidney disease. Other complications like hyperkalemia, anemia, are also frequently occurring. When we look at the trials of SGLT2 inhibitors, for example, in DAPA-CKD, we see on the left that patients without anemia at baseline had a significantly reduced risk for developing anemia when they were assigned to dapagliflozin treatment. Among patients with anemia, correction of anemia occurred more frequently in those patients assigned to dapagliflozin, compared to placebo.

So these drugs have many beneficial effects on other complications of chronic kidney disease. That means that we should use them and use them in clinical practice on top of ACE inhibitors or angiotensin receptor blockers.

Now, when we look at the trials and we compare the efficacy of this combination with ACE inhibitors and SGLT2 inhibitors in patients with non-diabetic kidney disease, here in this slide, we see that if we would initiate this combination RAAS inhibition plus SGLT2 inhibition in a patient who's 50 years of age, as shown on the left. You can see that you can delay dialysis by eight years, and that is clinically meaningful. When you would initiate this combination in a patient who's aged 60 years, you can delay dialysis by four years. Again, a very profound effect.

That brings me to my summary. SGLT2 inhibitors slow the progression of chronic kidney disease. They reduce the risk of kidney failure, acute kidney injury, in patients with chronic kidney disease. These benefits are present, regardless of diabetes status or the type of kidney disease. Screening for chronic kidney disease and appropriate intervention is now a key management goal for all patients with chronic kidney disease. We have the tools to reduce the risk. It's now up to us to identify patients with chronic kidney disease by screening and monitoring of albuminuria and GFR, and then you have to implement these findings in your clinical practice.

Thank you very much.