LEADING EUROPEAN NEPHROLOGY

PRESS RELEASE

Parma, Italy, August 31, 2020

Great news for patients with Chronic Kidney Disease: SGLT2 inhibitors slow disease progression

Two randomized controlled studies show: SGLT2 inhibitors can slow chronic kidney disease (CKD) progression in all patients, not only in diabetics. Results of one study [1] were presented at the virtual ESC Congress 2020 and the results of the other were published in NEJM [2].

ABSTRACT: The CREDENCE trial [3] provided evidence that the SGLT2 inhibitor Canagliflozin slows the progression of CKD in individuals with type 2 diabetes (T2D) and CKD with albuminuria. The Phase III DAPA-CKD trial [1] has now shown that the SGLT2 inhibitor Dapagliflozin can significantly slow CKD progression in all CKD patients, not only in those with diabetes. This breakthrough in kidney disease treatment goes back to an incidental study finding of Professor Christoph Wanner, President of the ERA-EDTA.

---

850 million people worldwide are affected by chronic kidney disease (CKD) – a worrying figure, and one that continues to rise. Treatment options for patients with CKD are multiple and often determined by the aetiology of CKD. So far, RAAS blockade (ACE inhibitors or angiotensin receptor blockers) was one of the most effective therapeutic intervention which has been shown to affect CKD disease progression. Now, SGLT2 inhibitors add significantly to the armentarium and provided another breakthrough in the management of CKD.

The first to realize this potential of SGLT2 inhibitors was Professor Christoph Wanner, co-author of the EMPA-REG OUTCOME trial and President of the ERA-EDTA. Wanner

and his colleagues conducted the EMPA-REG OUTCOME trial [4], the aim of which was to investigate whether the SGLT2 inhibitor Empagliflozin could lower the rate of cardiovascular events in patients with T2D. "It could, but the much more exciting result for me as a nephrologist was an incidental finding of the study, which we analysed and published in a second paper [5]. It seemed that the medication could also slow progression of CKD. At that moment the effect was 'too good to be true' Wanner remembers, but this effect was confirmed in subsequent cardiovascular outcome trials (CVOTs) with other SGLT2 inhibitors [6, 7]. However, the proportion of patients with CKD in these CVOTs, which were conducted among patients with T2D, was relatively low.

At that point, the kidney study program with Canagliflozin was already underway. It was not until 2019 that the CREDENCE trial provided evidence that the SGLT2 inhibitor Canagliflozin could slow CKD progression in patients with T2D and CKD with albuminuria who were already on standard RAAS blockade and baseline glucose lowering therapy [3].

An important link was still missing, however. In about one third of all CKD patients, diabetes is the cause of kidney failure, but what about the other two thirds? Can SGLT2 inhibitors really help these patients, too, and prevent them from reaching end stage kidney disease in need of regular dialysis treatments or renal transplantation?

A new study (DAPA-CKD) was initiated to answer these questions and the results were presented at the virtual ESC Congress. Cardiologists welcomed the prominent treatment originating its effects in the kidney and extending to the heart. The rationale and protocol of the study had been published in Nephrology Dialysis Transplantation, the premier kidney journal in Europe [8], earlier this year. The results were groundbreaking: 4304 patients (67.5% had diabetes) were randomized 1:1 to dapagliflozin or placebo. The primary outcome of worsening of kidney function was a composite of sustained ≥50% eGFR decline, occurrence of end stage kidney disease, or renal or CV death. There were 197 events in the dapagliflozin group and 312 in the placebo group; the HR for the primary endpoint was 0.61 (95% CI, 0.51-0.72; P=0.000000028) resulting in a number needed to treat of 19. The benefit of dapagliflozin on the primary endpoint was consistent in patients with and without T2D. No concerning safety signals were observed.

A study on the SGLT2 inhibitor Empagliflozin in 3730 heart failure patients (EMPEROR-Reduced) with and without T2D was already published the day before, saturday morning 8:30 am Eastern US-Time in "The New England Journal of Medicine" [2]. Although kidney parameters were analyzed as secondary endpoints, the results point in the same direction: The annual rate of decline in the estimated glomerular filtration rate was significantly slower in the empagliflozin group than in

the placebo group (–0.55 vs. –2.28 ml/min/1.73 m^2 per year, P<0.001), and empagliflozin-treated patients had a lower risk of serious kidney outcomes.

"All in all, this is great news for patients with CKD. For years, no new treatment option has proved to be safe and effective, which meant that no new drug could be introduced into clinical practice. We now have a whole new substance class that is obviously very effective. It is quite amazing how often important medical innovations derive from incidental discoveries. We wanted to find a therapy to improve cardiovascular outcomes in individuals with type 2 diabetes and found a long-awaited treatment to slow progression of chronic kidney disease, even in those who do not suffer from type 2 diabetes. It's a bit 'Flemingesque', at the beginning we did not realize the significance of our findings, now we have a kidney drug in hands" Wanner concludes.

[1] Results of the DAPA-CKD trial presented at the ESC congress on Aug 30, 2020
[2] Packer M, Anker SD, Butler J et al. Cardiovascular and renal outcomes with empagliflozin in heart failure (EMPEROR-Reduced). NEJM 2020, https://www.nejm.org/doi/full/10.1056/NEJMoa2022190
[3] Perkovic V, Jardine MJ, Neal B et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy.N Engl J Med 2019;380:2295-2306
[4] Zinman B, Wanner C, Lachin JM et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-2128
[5] Wanner C, Inzucchi SE, Lachin JM et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med 2016;375:323-334
[6] Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-657
[7] Wiviott SD, Raz I, Bonaca MP et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes.N Engl J Med 2019;380:347-357
[8] Heerspink HJL, Stefansson BV, Chertow GM et al. Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. Nephrol Dial Transplant 2020;35:274-282

About ERA-EDTA

With more than 7,000 active members, the ERA-EDTA is one of the biggest nephrology associations worldwide. It leads European nephrology and is one of the most important European medical associations. It organizes annual congresses and other educational and scientific activities. ERA-EDTA also produces guidelines, collects data, and performs epidemiological studies through its Registry. The association supports fellowships and educational/research projects through its committees and working groups. Its publications are NDT, CKJ (Open Access journal), and the online educational journal NDT-Educational.
Website www.era-edta.org