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Dapagliflozin provides kidney protection even in cases of FSGS kidney disease

The progressive loss of renal function in focal segmental glomerulosclerosis (FSGS) was reduced by half in the DAPA-CKD study.

ABSTRACT: Many patients with the rare kidney disease FSGS require dialysis in the course of the disease, despite anti-inflammatory corticosteroid therapies. The DAPA-CKD study showed a significant benefit in renal outcomes for chronic kidney disease patients with and without diabetes mellitus, following treatment with dapagliflozin, an SGLT-2 (sodium dependent glucose co-transporter 2) inhibitor [1]. A subgroup analysis of the DAPA-CKD study [2] suggests that the beneficial effect of dapagliflozin extends to patients with FSGS.

Focal segmental glomerulosclerosis (FSGS) is a rare form of kidney inflammation (glomerulonephritis) in which the glomeruli become increasingly scarred (sclerotic), leading to progressive loss of kidney function. Dysregulation of the immune system plays a role in pathogenesis, which is why immunosuppressive therapy with glucocorticoids can be successful, alongside supportive therapy (especially blocking of the renin-angiotensin system with ACE inhibitors or angiotensin receptor blockers). Many patients nevertheless require dialysis in the course of the disease. New therapeutic approaches that stabilize or protect kidney function are therefore needed.

In patients with type 2 diabetes, who often have concomitant kidney damage, treatment with an oral antidiabetic agent from the group of SGLT2 inhibitors (gliflozins) results in stabilization of renal function and improvement of clinical (renal and cardiovascular) outcomes. These medications inhibit SGLT-2 (sodium-dependent glucose co-transporter 2) in the proximal renal tubule, thereby increasing urinary glucose excretion. The DAPA-CKD study showed that the SGLT2 inhibitor dapagliflozin markedly reduces the risk of progressive loss of renal function in patients with chronic kidney disease (CKD), both in the presence and in the absence of diabetes mellitus [1].

A pre-specified subgroup analysis specifically investigated safety and efficacy in study patients with FSGS [2]. The trial included 115 participants with FSGS randomized to receive either 10 mg dapagliflozin (n=53) or placebo (n=62) on top of standard treatment. The combined primary endpoint included a $\geq 50\%$ decrease in eGFR, reaching dialysis requirement, or cardiovascular death. In the present analysis, the course of kidney function

(eGFR) was specifically investigated during the median 2.4-year follow-up. The FSGS patients were 53.7 ± 13.9 years old, had a glomerular filtration rate (eGFR) of 41.6 ± 11.6 ml/min/1.73 m² and a median urinary protein excretion of 1553 (758-2257) mg/g.

The results showed that four out of 53 patients on dapagliflozin (7.5%) and nine out of 62 patients on placebo (14.5%) reached the primary endpoint (HR 0.54). In the first two weeks after the start of the study, the familiar phenomenon of initial eGFR decline occurred (eGFR dip of -4.5 ml/min/1.73m² in the dapagliflozin group compared to -0.8 ml/min/1.73m² in the placebo group). Over the remainder of the study, the annual eGFR loss was -1.9 versus -4.2 ml/min/1.73 m². Tolerability and safety of dapagliflozin were good, and discontinuations due to side effects were similar in both groups.

The results of several previous studies have demonstrated that SGLT2 inhibitors improve cardiovascular and kidney outcomes in patients with type 2 diabetes. We know that for dapagliflozin, these benefits extend to patients with heart failure and chronic kidney disease who do not have diabetes. New data from this subgroup analysis suggest that FSGS patients also gain benefit,' said Professor David Wheeler.

'SGLT2 inhibitors offer a promising new therapeutic option in the field of nephrology and are likely to be used more extensively in future, both in diabetic and non-diabetic kidney diseases. Not only do these agents slow progression of kidney disease, but they also reduce the risk of cardiovascular diseases, which are important comorbidities in this patient population.'

[1] Wheeler DC, Stefánsson BV, Jongs N et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol* 2021; 9 (1):22-31

[2] 2479 David Wheeler, London. Effects of Dapagliflozin on major adverse kidney events in patients with focal segmental glomerulosclerosis: a prespecified analysis of the DAPA-CKD trial.

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