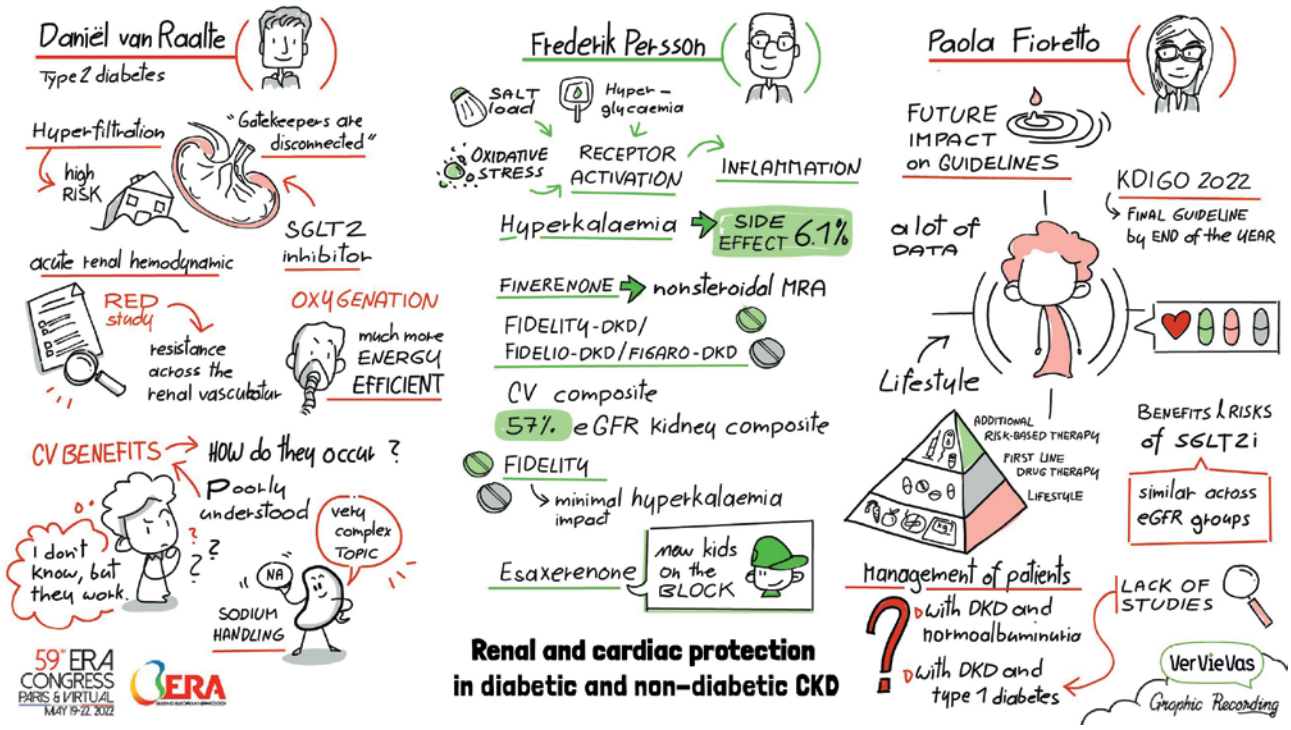
Symposium 4.1
Renal and cardiac protection in diabetic and non-diabetic CKD



SGLT2 inhibitors: from bench to bedside for patients with cardiorenal disease

Daniël van Raalte, Netherlands

The strong connection between chronic kidney disease and cardiovascular disease poses a need for an approach that simultaneously addresses these issues. Sodium-glucose cotransporter-2 (SGLT2) inhibitors were initially introduced as glucose-lowering agents. Nevertheless, it was soon discovered that these drugs have immense kidney protective properties.

The renoprotective mechanism of SGLT2 inhibitors is still not completely unraveled, but clinical trials show an initial acute dip in GFR and its subsequent stabilization compared to the placebo groups. Upon cessation of treatment, the GFR values quickly return to the baseline, proving the kidney hemodynamic effect of SGLT2 inhibitors.

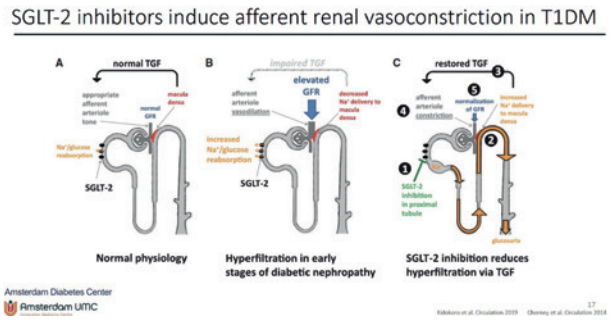


Figure 1.
Postulated tubuloglomerular feedback mechanisms in the normal nephron, early stages of diabetic nephropathy, and after SGLT2 inhibition (from ref. 1)

The study by Cherney et al. on type 1 diabetes (T1D) patients with hyperfiltration proved that SGLT2 inhibitors induced an immense efferent arterial constrictive response, which was suggested to be their renoprotective mechanism. The Amsterdam trial, led by Van Bomel, concluded that similarly to renin-angiotensin-system (RAS) blockers, the SGLT2 inhibitors in people with type 2 diabetes (T2D) provide post-glomerular vasodilation that induces the drop in GFR. A similar trial was

conducted by the German group, led by Ott and Schmieder. It observed a reduction in vascular resistance and concluded that post-glomerular vasodilation is the underlying mechanism of hemodynamic function change in T2D patients.

Another two potentially protective mechanisms are currently being explored, both of which are linked to kidney energy metabolism and oxygen availability. Since the SGLT2 inhibitors shift the metabolism toward the usage of ketones from fatty acids rather than glucose, the research is based on the hypothesis that SGLT2 inhibitors make the kidney more energy efficient by altering the energy metabolism. The central hypothesis of SGLT2 inhibitors' cardiovascular benefits, on the other hand, focuses on hematocrit. SGLT2 inhibitors induce natriuresis and osmotic diuresis, which in turn reduce plasma volume and consequently increase hematocrit. Nevertheless, numerous facts call this hypothesis into question. The DAPASALT trial recently evaluated the effects of dapagliflozin on sodium excretion, 24-h blood pressure, and extracellular, intracellular, and plasma volumes in patients with type 2 diabetes and preserved kidney function. It showed that dapagliflozin reduced blood pressure unrelated to urine sodium excretion during standard sodium intake, suggesting that factors other than natriuresis and volume changes may contribute to the blood-pressure-lowering effects.

Future research into the effects of SGLT2 inhibitors on cardiorenal illness is anticipated to focus on combination therapy involving finerenone, GLP-1 receptor agonists, and endothelin receptor antagonists, with the issue of putting together combined medication guidelines waiting ahead. Another unmet need is the use of SGLT2 inhibitors to protect the kidneys of patients with T1D, with an emphasis on euglycemic diabetic ketoacidosis mitigation strategies.

Novel mineralocorticoid receptors antagonists: an update of mechanisms and recent trials

Frederik Persson, Sweden

The mineralocorticoid receptors (MR) are present in many different tissues, including the kidney. They play a key role in blood pressure regulation and electrolyte homeostasis. By binding either aldosterone or cortisol, and together with a range of different cofactors, MR affect different processes. They are essential for maintaining electrolyte homeostasis, but their overactivation contributes to inflammation and fibrosis that are associated with long-term chronic conditions, such as diabetes or hypertension. Furthermore, the high salt load of the western diet increases the renal MR expression, eventually leading to heart and kidney damage.

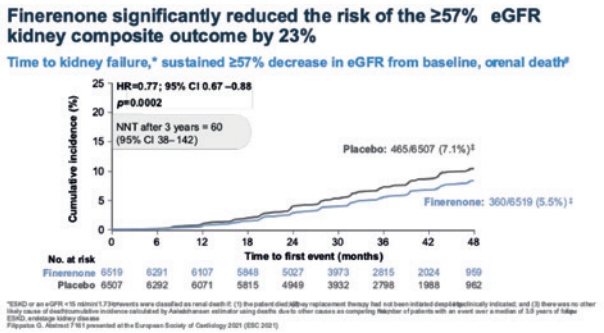


Figure 2.
The impact of finerenone on kidney function

Developing a selective mineralocorticoid antagonist to prevent these effects has been a long-term endeavor. The two already established mineralocorticoid antagonists, spironolactone and eplerenone, still have not shown any hard outcomes for CKD. Some smaller studies analyzing the effect of spironolactone in diabetic nephropathy exhibited positive effects, but they were never included in CKD guidelines. Eplerenone/enalapril in diabetic hypertensive patients with proteinuria showed a significant reduction of albuminuria but was often discontinued due to hyperkalemia, a known side effect of mineralocorticoid antagonists.

Finerenone, the new selective nonsteroidal mineralocorticoid antagonist, selectively blocks MR overactivation which contributes to inflammation and fibrosis, leading to kidney and cardiovascular (CV) damage. In the FIDELIO-DKD trial finerenone slowed CKD progression and improved cardiovascular outcomes in patients with CKD and type 2 diabetes. The FIDELITY analysis pooled the data from the FIDELIO-DKD and FIGARO-DKD trials and measured the CV (time to CV death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization due to heart failure) and the renal outcomes (time to kidney failure, sustained ≥57% decrease of eGFR from baseline or renal death). Finerenone significantly reduced the risk of the composite CV outcome by 14%, and the risk of the kidney composite outcome by 23%.

Finerenone showed no effect on HbA1c, no sexual side effects, a modest impact on blood pressure, and increased hyperkalemia but with minimal clinical repercussion. The 438 subjects in the FIDELITY analysis who were on combined therapy with SGLT2 inhibitor and finerenone showed no difference in the renal outcome and no increase in potassium. The combination is approved by the FDA and EMA and has recently been included in the guidelines of the American Diabetes Association (ADA).

The future of exploring finerenone effects lies in two new trials: the CONFIDENCE trial, which studies the combination of finerenone and an

SGLT2 inhibitor – Empagliflozin, and the FIND-CKD trial, looking at the slope of eGFR as the primary outcome in non-diabetic CKD patients. Also, two large outcome trials using the spironolactone in hemodialysis patients, the ALCHEMIST, and the ACHIEVE studies, are currently in the pipeline.

New kidney protective drugs: how do they impact the guidelines

Paola Fioretto, Italy

In the last years, two classes of glucose-lowering agents, the SGLT2 inhibitors and the glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been demonstrated to exhibit cardio and nephroprotective effects. This led to the inclusion of SGLT2i and GLP-1RA in the guidelines of diabetes, nephrology, and cardiology societies.

Since the publication of guidelines from the ADA and the European Association for the Study of Diabetes (ESC/EASD), along with the cardiology and the 2020 KDIGO guidelines for diabetes management in CKD, several very important clinical trials with SGLT2i and finerenone have been published. There are no new completed trials with GLP-1RA but several are expected in the coming years.

The results of the latest studies have been taken into consideration in ADA 2022 Standards of Medical Care, which include several treatment options for patients with T2D and CKD. The KDIGO guidelines underwent a major revision of the clinical data and a draft of the new 2022 version is already prepared and released for public review.

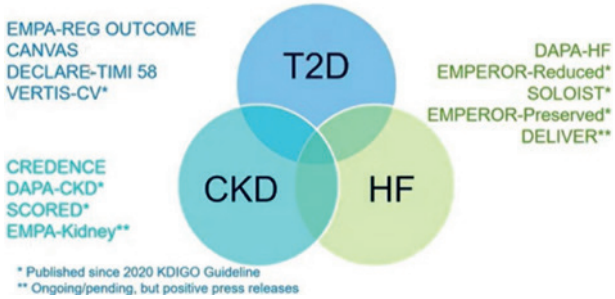


Figure 3.
Major clinical trials of SGLT2 inhibitors

The new KDIGO guidelines suggest that diabetic patients, in general, are to receive RAS blockade and statins, and patients with T2D should be treated with SGLT2 inhibitors and metformin. The major difference from the 2020 KDIGO guidelines is that the eGFR threshold at which SGLT2 inhibitors can be used is lowered to 20mL/min. Patients with T2D who have not achieved individualized glycemic targets or are unable to use metformin and/or SGLT2 inhibitors may receive GLP-1RA, especially if they are also overweight. A non-steroidal MRA with proven kidney or CV benefit is also recommended in T2D patients with an eGFR ≥25mL/min, normal serum potassium, and albumin to creatinine ratio >30mg/g on the maximum tolerated dose of RAS inhibition. If blood pressure is not well controlled, both type 1 and type 2 diabetes patients should be treated with dihydropyridine calcium channel blocker and/or diuretic, and in case of resistant hypertension, steroidal MRA is introduced if eGFR ≥45mL/min.

Nevertheless, there are still some open questions, requiring more data and more studies to be resolved. The first one is how to manage patients with diabetic kidney disease, low eGFR, and normoalbuminuria. The other question is the efficacy and safety of SGLT2i in kidney transplant recipients, and finally the management of T1D patients with diabetic kidney disease. In the last years, clinical trials with SGLT2 inhibitors, and now also with finerenone, have demonstrated that the progression towards end-stage renal disease in patients with T2D can be delayed even further from results achieved with RAS blockade. Thus, if this treatment is applied to patients with T2D and CKD, the trajectory of GFR loss may be changed, to approach what is considered the physiologic loss of GFR associated with aging.

Further readings

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All the speakers reviewed and approved the content.