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Novel therapeutic Agents in CKD Management: -SGLT2i, MRA and Others

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Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been the mainstay of treatment for the prevention of kidney failure in patients with CKD over the last 2 decades. However, despite use of these agents, the risk of kidney failure remains high. New therapeutic options to slow progressive loss of kidney function in patients with CKD with and without diabetes have emerged.

Recently, the use of sodium–glucose cotransporter 2 inhibitors (SGLT2is) are strongly recommended for patients with CKD regardless of glycemia since they can reduce the risk of kidney failure and slow the progression of eGFR decline. These benefits were initially demonstrated in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, which recruited patients with type 2 diabetes and CKD. The DAPA-CKD trial and EMPA-KIDNEY trials confirmed and extended these findings by demonstrating that the 39% reduction in risk of the composite kidney end point was similar in patients with CKD with or without type 2 diabetes.

Another class of newer agent is non-steroidal mineralocorticoid receptor antagonist (MRA), finerenone, which is now approved in the United States. Finerenone has greater aldosterone receptor selectivity and affinity compared to steroidal MRA, thus affording a higher potency and a lower risk of hyperkalemia. It can reduce proteinuria in CKD patients. Two large randomized controlled studies have been published on finerenone in T2D on a background of maximal RAS inhibition therapy. In the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease progression in Diabetic Kidney Disease) study, finerenone reduced the relative risks of the primary composite outcome of CKD progression by 18%, and the secondary composite outcome of CV morbidity and mortality by 14%, in T2D with advanced CKD over a median follow-up of 2.6 years.

In addition, glucagon-like peptide-1 receptor agonists (GLP-1RA) have demonstrated in large CV outcome trials to have significant CV and kidney benefits, particularly in patients with established CVD or those who are at high risk. Data on semaglutide (SUSTAIN-6 and PIONEER-6 studies) and dulaglutide (REWIND study) similarly showed CV benefits and reduced risk of albuminuria onset and kidney disease progression. However, there is not yet a trial with a primary endpoint of kidney outcomes for any GLP-1 RA. The ongoing FLOW (Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease) trial should address whether GLP-1 RA can slow the progression of DKD.

Currently, research into potential novel therapeutic targets for DKD is particularly active and brings much anticipation and optimism to this field. New targets for therapeutic intervention include drugs that interfere with the formation and action of AGEs or receptors for AGEs, drugs that target oxidative stress, inflammatory cytokines, or fibrosis. The role of micro-RNAs in the pathogenesis of DKD is an emerging field and may also provide additional novel treatment approaches. Cell therapies targeting intrarenal vascular restitution are in early clinical trials. New insights into the molecular mechanisms that underlie the origin and progression of DKD are emerging from large-scale genetic and molecular studies in experimental models and humans.