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**The non-steroidal mineralocorticoid receptor antagonist finerenone is a novel therapeutic option for patients with type 2 diabetes and chronic kidney disease**

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## **Abstract**

Despite strong preclinical data supporting the use of mineralocorticoid receptor antagonists (MRAs) to provide cardiorenal protection in rodent models of diabetes, the clinical evidence of their utility in treating chronic kidney disease (CKD) has been limited. Two major clinical trials (FIDELIO-DKD and FIGARO-DKD) including more than 13,000 patients with albuminuric CKD and type 2 diabetes randomized to placebo or finerenone (MRA) have recently provided exciting results showing a significant risk reduction for kidney and cardiovascular outcomes. In this review, we will summarize the major findings of these trials, together with post-hoc and pooled analyses that have allowed evaluation of the efficacy and safety of finerenone across the spectrum of CKD, revealing significant protective effects of finerenone against kidney failure, new-onset atrial fibrillation or flutter, new-onset heart failure, cardiovascular death, and first and total heart-failure hospitalizations. Moreover, we will discuss the current evidence that supports the combined use of MRAs with sodium glucose co-transporter-2 inhibitors, either by providing an additive cardiorenal benefit and/or by decreasing the risk of hyperkalemia. Although the mechanisms of protection by finerenone have only been partially explored in patients, rodent studies have shed light on its anti-inflammatory and anti-fibrotic effects in models of kidney disease, which is one of the main drivers for testing the efficacy of finerenone in non-diabetic CKD patients in the ongoing FIND-CKD trial.

Chronic kidney disease (CKD) is a growing health problem, with an estimated global prevalence of 11% and affecting approximately 850 million patients.(1) Type-2 diabetes (T2D) is the main cause of CKD and is associated with increased cardiovascular morbidity.(2, 3) Current therapeutic options to limit CKD progression and the development of cardiovascular disease in patients with T2D include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), and, more recently, sodium–glucose co-transporter 2 inhibitors (SGLT2i).(4-9) SGLT2i have revolutionized the renal and cardiovascular prognosis of proteinuric CKD patients, limiting the progression of renal dysfunction and proteinuria, as well as the cardiovascular impact associated with CKD in T2D, and has been rapidly introduced as standard of care treatment. However, despite the introduction of these therapeutics, an important residual risk of CKD progression and cardiovascular complications remains among CKD patients with/without T2D, thus motivating the search for other therapeutic options.(10)

Several preclinical studies have supported the use of mineralocorticoid receptor antagonists (MRAs) as a therapeutic option to slow CKD progression in T2D due to its anti-proteinuric, anti-inflammatory, and anti-fibrotic effects (For a review, see Barrera-Chimal et al.(11)). These anti-inflammatory and anti-fibrotic mechanisms are yet to be explored in the clinical setting. Spironolactone and eplerenone are steroidal MRAs that are used for hypertension and heart failure treatment. (12-14) Their clinical use has been limited by concerns of hyperkalemia events among patients with reduced renal function and under RAS treatment. Over the last decade, several novel non-steroidal MRAs have been developed, including finerenone, thus allowing the testing of mineralocorticoid receptor (MR) antagonism safety and efficacy in large populations of patients with CKD.(12, 13) The main differences between steroidal and non-steroidal MRAs include a differential tissue penetration and distribution, shorter half-life and absence of metabolites (for finerenone), and differential modulation of gene expression due to specific binding of transcriptional co-repressors for non-steroidal versus steroidal MRAs. (12-15). Here, we will review recent evidence of finerenone as a novel therapeutic option to slow CKD progression and provide cardiovascular protection in patients with T2D and CKD.

### **Preclinical data**

Preclinical data support direct anti-fibrotic and anti-inflammatory effects of finerenone in cardiorenal protection in the presence or absence of diabetes. In cardiorenal injury induced by deoxycorticosterone acetate-salt challenge in rats, finerenone treatment prevented cardiac and renal hypertrophy, proteinuria, and structural injury, which was associated with the reduction of the mRNA levels of some fibrosis and inflammatory markers including plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein-1, osteopontin and matrix metalloproteinase-2.(16) Finerenone also showed anti-fibrotic capabilities by directly affecting the effector cells of fibrosis, myofibroblasts. With no effects on systemic blood pressure, finerenone dose-dependently decreased pathological myofibroblast accumulation and collagen deposition as well as renal PAI-1 and NKD2 expression in rat models of progressive kidney fibrosis.(17) This is in agreement with several studies showing profibrotic roles of MR/aldosterone via increasing the expression of remodeling factors in the kidney such as TGF- $\beta$ , collagens, connective tissue growth factor, and PAI-1.(18-20) These changes could be a direct effect of MR activation on fibroblasts in which it has been shown *in vitro* that aldosterone stimulation leads to an upregulation of collagen synthesis (I, III and IV), fibronectin and osteopontin. (21-25).

Regarding inflammation, several studies have characterized the pro-inflammatory effects of aldosterone-MR activation in the kidney. This includes the upregulation of NLRP3 inflammasome activity and production of IL-1 $\beta$  and IL-18 (26), production of IL-17 by T<sub>H</sub>17 T cells, and IL-23 by dendritic cells, reduction of regulatory T cells, (27, 28) and promoting the polarization of macrophages to a classical pro-inflammatory phenotype while reducing the polarization towards anti-inflammatory macrophages (29). The latter was shown to be an important mechanism for preventing kidney fibrosis and CKD progression by finerenone in rodent models of ischemic renal injury.(30) Finerenone prevented CKD progression following an ischemic acute kidney injury episode; mice or rats treated with finerenone and that had undergone renal ischemia/reperfusion injury were protected against chronic kidney tubulointerstitial fibrosis and dysfunction.(30, 31) Knocking-out the MR in myeloid cells showed that the MR in macrophages is a key contributor to the early inflammatory response following ischemic AKI, and its subsequent effects of renal injury and transition to CKD.(30) Finerenone modulated macrophage polarization by increasing interleukin-4 receptor signaling in macrophages and increasing the expression of anti-inflammatory genes.(30) Further studies have shown that in response to a pro-inflammatory stimulus, the MR

signals through c-Jun amino-terminal kinase (JNK) and the proto-oncogene c-FOS phosphorylation in macrophages.(32, 33) In addition, MR activation in macrophages can also lead to tissue inflammation effects that are independent of MR transcriptional activity. (33, 34). Whether similar mechanisms contribute to the cardiorenal protective effects of finerenone in CKD with T2D remains to be explored.

Another mechanism activated by aldosterone/MR leading to harmful effects in the kidney is oxidative stress. Aldosterone administration in rodents upregulates the expression of NADPH oxidase subunits, NADPH oxidase activity and ROS generation in the kidney.(35) (36) Increased ROS generation leads to adverse effects such as DNA oxidative damage as evidenced by increased levels of 8-oxodG in the kidney.(37) In rodent models of ischemic acute kidney injury, finerenone prevented acute tubular lesions and renal dysfunction through a mechanism involving a decrease in renal oxidative stress and vascular smooth muscle cell MR inhibition.(31, 38) Following renal ischemia, an increased in Rac1 activity and ROS generation induced a sulfenic acid modification in the endothelin B receptor which lead to a reduction in endothelial nitric oxide synthase activation and nitric oxide generation, thus perpetuating the hypoperfusion-ischemic cycle. (31, 38) The deletion of MR in smooth muscle cells prevented these alterations. (38). In a rat model of metabolic syndrome, long-term finerenone administration reduced diastolic dysfunction and reduced left ventricular hypertrophy and collagen accumulation. Moreover, an antiproteinuric effect was also noted.(39) A shorter-term analysis of the effects of finerenone in this rat model found improved cardiac tissue perfusion, less oxidative stress, and increased plasma nitrite levels, effects that were associated with improved LV hemodynamic parameters.(39) Similarly, in a mouse model of CKD induced by subtotal nephrectomy, finerenone treatment started four weeks after nephrectomy and continued up to 10 weeks prevented diastolic dysfunction and changes in the level of proteins responsible for calcium management in cardiomyocytes (Calmodulin kinase II and phospholamban), without affecting CKD severity, thus showing the potential of finerenone to improve cardiac complications during CKD.(40) In the Munich Wistar Frömter (MWF) rat, which mimics CKD progression, finerenone administration reduced proteinuria by 40% and attenuated vascular dysfunction by promoting increased phosphorylation of eNOS and reduced oxidative stress through a reduction in Mn- and Cu/Zn-superoxide dismutase levels.(41) Therefore, finerenone might improve the cardiovascular health by maintaining a redox balance, endothelial function and vascular contractility.

In preclinical models of direct cardiac injury with different mechanistic etiologies, finerenone has shown beneficial effects. Supporting an anti-fibrotic mechanism, it was observed in a mouse model of cardiac-specific overexpression of the Rac1 GTPase that finerenone administration prevented myocardial fibrosis and the upregulation of mRNA levels of several fibrotic markers in the left ventricle.(42) Moreover, finerenone prevented left atrial dilatation and fibrosis.(42) Similarly, two months after myocardial infarction in mice, finerenone treated animals showed reduced interstitial fibrosis and improved left ventricular compliance.(43) In rats with chronic cardiac failure induced by coronary artery ligation, finerenone improved systolic and diastolic left ventricular function.(16) In mice with pressure-induced cardiac hypertrophy by TAC, finerenone reduced LV wall thickening.(44) Finally, in ovariectomized mice, finerenone improved diastolic dysfunction, with preserved ejection fraction, and prevented impairment in the relaxation of coronary arteries and exercise capacity.(45) Altogether, these experimental studies show that finerenone provides cardiac protection despite the absence of CKD and/or high glucose. This provides a rationale for testing the efficacy of finerenone in cardiovascular outcomes in non-CKD and non-diabetic patients with CKD.

### **Clinical trials using finerenone in diabetic CKD patients**

#### **Finerenone in Reducing Kidney Failure and Disease progression in Diabetic Kidney Disease (FIDELIO-DKD)**

FIDELIO-DKD was the first phase 3 trial to evaluate the effect of a non-steroidal MRA (finerenone) on cardiorenal outcomes among patients with T2D and advanced CKD.(46) The study included 5,734 patients with a urine albumin-creatinine ratio (uACR, mg/g) of 30 to < 300 and an estimated glomerular filtration rate (eGFR) from 25 to < 60 mL/min/1.73 m<sup>2</sup> with diabetic retinopathy, or an uACR of 300 to 5,000 and an eGFR of 25 to < 75 mL/min/1.73 m<sup>2</sup>. Potassium levels at recruitment had to be ≤ 4.8 mmol/L. The patients received optimized standard of care with RAS inhibitors (ACEi or ARB) to the maximum tolerated dose. Finerenone reduced the primary composite outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline or death from renal causes by 18% (HR: 0.82, 95%CI 0.73 – 0.93, p=0.001), while the secondary composite cardiovascular outcome was reduced by 14%

(HR: 0.86, 95%CI 0.75 – 0.99, p=0.03). Besides the increased serum potassium levels (discussed below), a similar rate of adverse events was observed in both groups.(46)

In a prespecified analysis of the cardiovascular outcomes according to the history of atherosclerotic cardiovascular disease, which included 45.9% of the patients in FIDELIO-DKD that presented CVD at baseline, the risk reduction in the cardiovascular composite outcome observed in finerenone randomized patients was found to occur independently from pre-existing cardiovascular disease (p-value for interaction= 0.85).(47) In support of a cardiovascular benefit of finerenone use for patients with CKD and T2D, a pre-specified outcome analysis of patients from the FIDELIO-DKD trial found that finerenone reduced the risk of new-onset atrial fibrillation or flutter by 29% (HR: 0.71, 95%CI: 0.53 – 0.94, p=0.016). Moreover, preexisting atrial fibrillation or flutter did not affect the effect of finerenone on the primary and secondary composite outcomes (p-values for interactions= 0.16 and 0.85, respectively).(48) The efficacy of finerenone to reduce the renal and cardiovascular outcomes was independent of baseline HbA1c levels and insulin treatment (p-values for interaction are 0.41 and 0.56 for renal outcomes or 0.70 and 0.33 for cardiovascular outcomes).(49) In addition, finerenone prevented the renal and cardiovascular outcomes regardless of baseline heart failure (p-values for interaction= 0.33 and 0.89).(50)

### **Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD)**

A second trial for finerenone focused on cardiovascular events as the primary outcome. In FIGARO-DKD, 7,437 patients with CKD and T2D were randomized to finerenone or placebo,(51) which included albuminuric patients with a less severe reduction in renal function as compared to FIDELIO-DKD. The eligibility for FIGARO-DKD included patients with a uACR of 30 to < 300 and eGFR from 25 to 90 mL/min/1.73 m<sup>2</sup> or a uACR of 300 to 5,000 and eGFR > 60 mL/min/1.73 m<sup>2</sup>. Finerenone reduced the occurrence of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure by 13% (HR: 0.87, 95%CI: 0.76 – 0.98, p=0.03).(51) The incidence of the first secondary outcome in FIGARO-DKD (a composite of kidney failure, a sustained decrease of at least 40% from baseline in the eGFR, or death from renal causes), was not significantly different in finerenone versus placebo (HR: 0.87, 95%CI: 0.76 – 1.01, p =0.069). (51, 52) When analyzing the composite outcome that



included a sustained decrease in eGFR of at least 57% from baseline, a significant risk reduction was observed (HR= 0.77, 95%CI: 0.60 – 0.99, p= 0.041). (51, 52) Further exploratory analyses showed that a larger effect of finerenone vs. placebo on kidney outcomes is observed in patients with more severe albuminuria (uACR: 300-5000 mg/g) as compared to patients with uACR 30-299 mg/g. (52) This larger effect observed in patients with high albuminuria levels might explain the lack of significant effect on the first secondary outcome in FIGARO-DKD in which patients with less albuminuria were included as compared to the FIDELITY analysis in which a bigger spectrum of patients with low and high albuminuria were included (see below). Of note, the effect of finerenone on uACR reduction, slowing eGFR decline and cardiovascular risk reduction was similar in both albuminuria subgroups. (52)

Importantly, a prespecified analysis from the FIGARO-DKD trial found that finerenone reduced the risk of new-onset heart failure by 32% (HR: 0.68, 95%CI: 0.50 – 0.93, p=0.016), with significant reductions in the risk of cardiovascular death or hospitalization for a first heart failure (18%, p=0.011) and the risk of total hospitalizations for heart failure (30%, p=0.018). Pre-existing heart failure did not modify the effect of finerenone on these outcomes.(53) Since heart failure with preserved ejection fraction (HFpEF) is common in patients with T2D and CKD, it will be interesting to evaluate the effect of finerenone or other non-steroidal MRAs on preventing HFpEF since spironolactone failed to reduce the primary cardiovascular endpoint in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with Aldosterone Antagonist) study.(54) Currently, finerenone is being evaluated in the FINEARTS-HF phase III trial, for its effect on cardiovascular death and heart failure events in patients with HFpEF (NCT04435626). Nevertheless, adding finerenone to the optimized standard of care significantly reduced cardiovascular mortality in patients with T2D and CKD.

### **Combined FIDELIO-DKD and FIGARO-DKD Trial Program Analysis (FIDELITY)**

FIDELITY was a pre-specified pooled-analysis of FIDELIO-DKD and FIGARO-DKD to investigate the efficacy and safety of finerenone across the spectrum of CKD and T2D (CKD stage 1 to 4 and moderate to severe albuminuria), in which 13,171 patients were included for randomization.(55) In this analysis, finerenone was reported to reduce the kidney composite outcome by 23% (HR: 0.77, 95%CI: 0.67-0.88,

p=0.0002), a benefit that was maintained in subgroups according to eGFR and uACR. Moreover, a 20% risk reduction (HR: 0.80, 95%CI: 0.64 – 0.99, p=0.040) in end-stage kidney disease requiring dialysis was observed with finerenone. During the first four months of treatment, a drop in the eGFR was observed in the finerenone-treated group. However, finerenone slowed the decline in the eGFR from month 4 by 1.2 mL/min/1.73 m<sup>2</sup>/year).(55) Blood pressure was slightly reduced in finerenone group at 4 months -3.2 mmHg (SD: 15.0 mmHg) as compared to placebo +0.5 mmHg (SD: 14.6 mmHg).(55)

In the FIDELITY prespecified pooled analysis, finerenone reduced the risk of the composite CV outcome by 14% (HR: 0.86, 95%CI: 0.78-0.95, p=0.018) and the risk for first hospitalization for heart failure by 22% (HR: 0.78, 95%CI: 0.66 – 0.92, p=0.0030), This benefit was maintained in the subgroup analysis by eGFR and uACR.(55)

In summary, FIDELIO-DKD/FIGARO-DKD/FIDELITY showed that finerenone can be used in addition to the standard of care for patients with T2D and proteinuric CKD to improve cardiorenal outcomes, including the slowing of CKD progression and a reduced risk of heart failure.

#### **Adverse events associated with the use of finerenone: the hyperkalemia risk**

Patients with altered renal function are prone to develop increased serum potassium levels, with a risk of life-threatening hyperkalemia. Therefore, it is of utmost importance that a survey be performed for the impact of novel MRAs on serum potassium. A direct comparison of the efficacy and safety of spironolactone and finerenone in patients with heart failure and mild CKD in a phase II trial showed that finerenone at doses 5-10 mg/d was as effective as 25 or 50 mg/d of spironolactone in reducing albuminuria and cardiac stress markers while inducing a significantly smaller increase in serum potassium as compared to spironolactone.(56) In FIDELIO-DKD and FIGARO-DKD, following randomization, serum potassium was monitored by central laboratory quantifications at the visits scheduled at month 1 and 4 and every 4 months along the follow-up. Mild hyperkalemia was defined when potassium was > 5.5 mmol/L and moderate hyperkalemia with potassium levels >6.0 mmol/L. This frequency of potassium monitoring is similar to the KDIGO guidelines recommendations for potassium monitoring in patients with CKD. (57) A post-hoc safety analysis of FIDELIO-DKD found that 4.5% of patients in the finerenone group developed mild hyperkalemia during the 2.6 years of median follow-up versus 1.4% in the placebo

group.(58) Of note, in FIDELIO-DKD, serum potassium levels at each visit were used to guide the dosing, with a suspension of the drug for those patients presenting mild hyperkalemia until serum potassium was  $\leq 5.0$ . The drug was then reinitiated at 10 mg/day. Thus, even though finerenone is associated with hyperkalemia, systematic potassium monitoring proved to be sufficient to reduce hyperkalemic events with finerenone use and should be considered when implementing the use of finerenone in the daily practice.(58, 59)

In FIGARO-DKD, the incidence of hyperkalemia was higher in the finerenone-treated (8.3%) than placebo (4.6%) group, regardless of heart failure history. Nevertheless, hyperkalemia-related treatment discontinuation was less in the finerenone-treated than placebo group (0.3 vs 0.7%) for those patients with a history of heart failure.(53)

In FIDELITY, hyperkalemia was more frequent in the finerenone arm (14.0%) than in the placebo arm (6.9%).(55) Drug discontinuation due to hyperkalemia for those patients with an eGFR  $< 60$  mL/min/1.73m<sup>2</sup> was 2.4% for the finerenone arm versus 0.8% for the placebo arm and 0.6 versus 0.3% for those patients with an eGFR  $> 60$ mL/min/1.73m<sup>2</sup>.(55) Permanent discontinuation was observed for 1.7% versus 0.6% respectively.(55) In this pooled analysis, 6.7% of the patients were receiving a SGLT2i at baseline and finerenone reduced the CV outcome independently from SGLT2i use.(55)

In conclusion, the use of finerenone by diabetic proteinuric CKD patients under maximum recommended dose of RAS inhibitors is associated with a mild increase in serum potassium levels and a low number of events of clinically relevant hyperkalemia. It should be emphasized, however, that this needs to be confirmed in real-world use. Of note, a retrospective cohort study that analyzed the “real-world” effect of steroidal MRAs in adults with CKD and a GFR  $\geq 10$  and  $< 60$  mL/min per 1.73 m<sup>2</sup> found that MRA use was associated with a 28% reduction in the risk of renal replacement therapy initiation (HR: 0.72, 95%CI: 0.53 - 0.98, p=0.039) after a median follow-up of 5.9 years, while the risk of hyperkalemia was higher for those receiving MRA, although not significant.(60) In addition to potassium monitoring, another strategy to minimize the risk of hyperkalemia would be the co-treatment with new generation potassium binders that have shown to be efficient to prevent hyperkalemia in patients with CKD and under RAAS inhibitors treatment.(61)

### **SGLT2i/MRA: a fruitful combination?**

In recent years, SGLT2 inhibitors have been proven to slow CKD progression and provide cardiovascular benefits for patients with T2D and CKD (for an in-depth review, see Tuttle et al.(62)). Empagliflozin reduced the risk of incident or worsening nephropathy by 44% (HR: 0.61, 95%CI: 0.53 – 0.70, p<0.001) and provided cardiovascular protection towards T2D patients with high cardiovascular risk relative to placebo.(63, 64) Moreover, canagliflozin decreased the risk of a cardiorenal composite outcome by 30% (HR: 0.70, 95%CI: 0.59 – 0.82, p=0.00001) for T2D patients with CKD-albuminuria and had a significant impact in reducing cardiovascular outcomes.(65, 66) In support of the protective effects of SGLT2i being a class effect, dapagliflozin conferred a significant reduction in the risk of renal outcomes for T2D patients.(67) Furthermore, dapagliflozin slowed proteinuric CKD progression, regardless of diabetes status.(7) The mechanisms proposed to be responsible for the cardiorenal protection by SGLT2 inhibitors are associated to a reduction in glomerular hyperfiltration due to the inhibition of the tubuloglomerular feedback and to the prevention of metabolic and inflammatory changes associated to type 2 diabetes and CKD. (68, 69)

### ***Preclinical data supporting the potential add-on benefit of the combination of finerenone and SGLT2 inhibitors for diabetic CKD patients***

Preclinical data are emerging on the potential add-on benefit of the combination of finerenone and SGLT2 inhibitors. A head-to-head comparison of finerenone and empagliflozin in mouse models of unilateral ureteral obstruction and renal ischemia showed finerenone to have direct anti-fibrotic effects that were independent of changes in blood pressure, whereas empagliflozin had no effect on fibrosis, suggesting that the two drugs may lead to enhanced renal protection through different mechanisms.(17) In hypertensive, N( $\omega$ )-nitro-L-arginine methyl ester-treated, renin-transgenic (mRen2)27 rats, a seven-week co-treatment with a low dose of finerenone (1 mg/kg) and empagliflozin (3 mg/ kg) was found to be superior to either of them alone in reducing mortality, proteinuria, plasma creatinine, and cardiac and renal fibrosis, as well as vasculopathy.(70) However, it should be emphasized that this pathological animal model is highly complex and does not mimic diabetic kidney disease but rather hypertensive CKD, precluding a direct translation to the possible benefit in diabetic

CKD patients in the absence of a SGLT2i-MRA combination study in an appropriate preclinical model.

*Clinical data supporting the potential add-on benefit of the combination of finerenone and SGLT2 inhibitors for diabetic CKD patients*

A sub-analysis of the FIGARO-DKD data for the 8.4% of participants who were taking SGLT2i showed that the effect of finerenone in reducing uACR was greater among those patients receiving SGLT2i at baseline (41%) versus finerenone alone (32%). Of note, the HR for the CV endpoint was 0.87 (95%CI 0.76 – 0.98) for the overall population, whereas it was 0.49 (95%CI 0.28 – 0.86) for those with a history of SGLT2i use, which suggests a benefit with combined use.(51) This additive effect of MRA and SGLT2i is supported by a randomized cross-over clinical trial showing that the combination of dapagliflozin plus eplerenone was significantly more effective in reducing uACR (-53% from baseline) as compared to dapagliflozin (-19.6%) or eplerenone (-33.7%) alone over a four week period in patients with CKD. (PMID: 35440501)

Importantly, the use of SGLT2i and diuretics may reduce the risk of hyperkalemia. A post-hoc analysis of the CREDENCE trial showed that canagliflozin reduced the risk of hyperkalemia and the incidence of potassium binder initiation among patients with CKD and T2D on RAAS inhibitor treatment.(71) Therefore, combined treatment with finerenone and an SGLT2i may be beneficial by decreasing the hyperkalemia event rate. In FIDELIO-DKD, 4.6% of the patients were receiving an SGLT2i at baseline and the uACR, as well as renal and cardiovascular outcomes, was reduced by finerenone, irrespective of baseline SGLT2i use.(72) In accordance with the findings from the CREDENCE trial, hyperkalemia occurred less frequently among the finerenone patients who were receiving an SGLT2i (8.1 vs. 18.7%).(72) An analysis of participants in the DAPA-CKD trial, which evaluated the efficacy of dapagliflozin in cardiorenal outcomes among patients with CKD, with or without T2D,(7) found that dapagliflozin had a consistent effect on the renal-specific outcome and hyperkalemia among those receiving an MRA (spironolactone or eplerenone) at baseline.(73)

In the CREDENCE trial, canagliflozin reduced the primary composite cardiorenal outcome by 30% (HR: 0.70, 95%CI, 0.59 - 0.82, p=0.00001).(66) Thus, canagliflozin appears to have had better efficacy in slowing diabetic CKD progression than finerenone in FIDELIO-DKD. However, differences in the inclusion criteria, as

well as the primary outcome definition, between the two trials make a direct comparison difficult. A post-hoc exploratory analysis on patients from the FIDELIO-DKD trial that met the inclusion criteria for CREDENCE was recently performed using the primary cardiorenal endpoint for CREDENCE. A risk reduction of 26% (HR: 0.74, 95%CI: 0.63 – 0.87, p=0.0003) was observed among patients treated with finerenone, while the kidney-specific endpoints, including time to onset of kidney failure, a sustained decrease in eGFR > 57%, or renal death, showed a risk reduction of 31% with finerenone (HR: 0.69, 95%CI: 0.57 – 0.84, p=0.0002) versus 34% (HR: 0.66, 95%CI: 0.53 – 0.81, p<0.001) with canagliflozin. This may indicate that the two drugs have similar efficacy in patients with T2D and CKD, which is important when considering recommendations for guidelines and regulations.(74)

### **Future trials with finerenone**

The FIDELIO-DKD/FIGARO-DKD trials targeted patients with T2D and CKD. Finerenone (KERENDIA<sup>®</sup>) was approved on July 9<sup>th</sup>, 2021, by the FDA and is indicated to reduce the risk of a sustained decline in the eGFR, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with CKD associated with T2D. On December 17<sup>th</sup>, 2021, The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended finerenone for marketing authorization in the European Union. Finerenone (10 mg or 20 mg) is recommended for the treatment of CKD (stage 3 and 4 with albuminuria) associated with T2D in adults.

However, nonproteinuric DKD and CKD in a non-diabetic setting are still important unmet clinical needs. The FIND-CKD trial is a phase 3 study that will evaluate the efficacy of finerenone on the rate of change in the eGFR slope from baseline to 32 months for more than 1,500 patients with non-diabetic CKD, including hypertension and glomerulonephritis. As in FIDELIO and FIGARO, the patients will receive optimized RAS therapy and will be allocated to placebo or finerenone 10 mg or 20 mg. Results for this trial (NCT05047263) are expected in 2025. In addition, it was recently announced that the safety and efficacy of finerenone in a pediatric population will be evaluated in the FIONA trial, which will be a phase III study that will randomize children and adolescents with CKD and severely elevated proteinuria to finerenone or placebo in addition to the standard of care (ACE inhibitor or ARB) and evaluate its potential to reduce proteinuria from baseline to six months. Finally, an add-on study to

FIGARO-DKD (FIGARO-BM) will evaluate the levels of biomarkers of pathological processes, including inflammation, fibrosis, vascular function, and congestion, among FIGARO-DKD participants to determine their differential behavior between placebo and finerenone-allocated patients and gain mechanistic insights into the beneficial effects of finerenone. (NCT05013008). Indeed, it was recently announced that the CONFIDENCE phase II trial will investigate the potential benefit of combining empagliflozin and finerenone in patients with T2D and CKD. This will be a three-arm study in which patients will be randomized to empagliflozin alone, finerenone alone or a combination group and the primary outcome (uACR reduction from baseline in the combination vs empagliflozin) will be evaluated after 180 days of treatment (NCT05254002).

### **Conclusion**

The past several months have been exciting for the nephrology community due to the results of large clinical trials showing a benefit of SGLT2is and MRAs against cardiorenal outcomes. Finerenone has emerged as a new therapeutic tool to slow CKD progression, reduce albuminuria, and prevent cardiovascular complications in T2D patients with CKD (Figure 1). The FIGARO-DKD trial has shown the power of albuminuria to detect those patients at high risk of heart failure and how finerenone treatment significantly reduced these outcomes. Exciting times are coming and results from future trials are expected to add information on whether finerenone also shows a benefit for non-diabetic CKD patients and its safety and efficacy on pediatric populations (Figure 2). Despite few severe hyperkalemia events in the clinical trials, potassium monitoring is still important for patients receiving finerenone in the “real-world” setting. Other non-steroidal MRAs are in different stages of development including KBP-5074, esaxerenone, apararenone, AZD9977, among others(13, 14). From those, apararenone and esaxerenone have already shown a benefit in reducing UACR in patients with T2D and CKD and future trials are expected. (75-77)

A major challenge will be the uptake and implementation of novel therapeutic options into the daily clinical practice in CKD patients. As an example, despite the clear benefit of MRAs in HF with reduced ejection fraction (HFrEF)(78, 79), MRAs are under-prescribed in these group of patients as evidenced in the CHAMP registry in which it was reported that only a third of the patients with HFrEF are treated with an MRA.

The current preclinical and clinical evidence supporting a benefit from a combination of SGLT2i and MRAs on top of standard of care is scarce but promising, showing a possible synergistic effect of a combinatorial regime and a potassium lowering effect of SGLT2is. Future research is warranted to clarify the effects of MRA co-treatment with other drugs that have proven a benefit in T2D patients with CKD such as SGLT2i or glucagon like peptide-1 receptor agonists (GLP-1RA) (10) and to gain further mechanistic insights on the effects of finerenone (Figure 2).

## **DISCLOSURES**

JB-C and CG have nothing to disclose.

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## Figure Legends

**Figure 1. Cardiorenal benefits of finerenone in type 2 diabetic patients with chronic kidney disease.** The pooled analysis of the patients included in FIDELIO and FIGARO allowed evaluation of the efficacy of finerenone across the spectrum of CKD severity among patients with an eGFR  $\geq 25$  mL/min/1.73m<sup>2</sup>. At inclusion, potassium levels of the patients had to be  $\leq 4.8$  mmol/L and RAS blockade was optimized to the maximum tolerated. After a median follow-up of three years, finerenone reduced the primary composite renal outcome by 23%, p=0.0002 and the primary composite cardiovascular outcome by 14%, p=0.0018. Hyperkalemia related discontinuation was observed for 0.22% of the patients in the placebo arm and 0.66% of the patients receiving finerenone. Strategies to reduce the risk of hyperkalemia include potassium monitoring, the use of potassium binders, down-titration of the finerenone dose until potassium levels are stabilized, and it has been suggested that co-treatment with SGLT2i reduces the hyperkalemia risk.

**Figure 2. Future directions in clinical research for non-steroidal MRAs.** Future trials are expected to evaluate the efficacy and safety of MRAs to prevent cardiorenal outcomes among patients with non-diabetic CKD and in pediatric population, investigate its mechanisms of action in humans, and elucidate whether a combination with other drugs might have a synergistic effect and potentiate the slowing of CKD progression and reduction in adverse cardiovascular outcomes.

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Figure 1

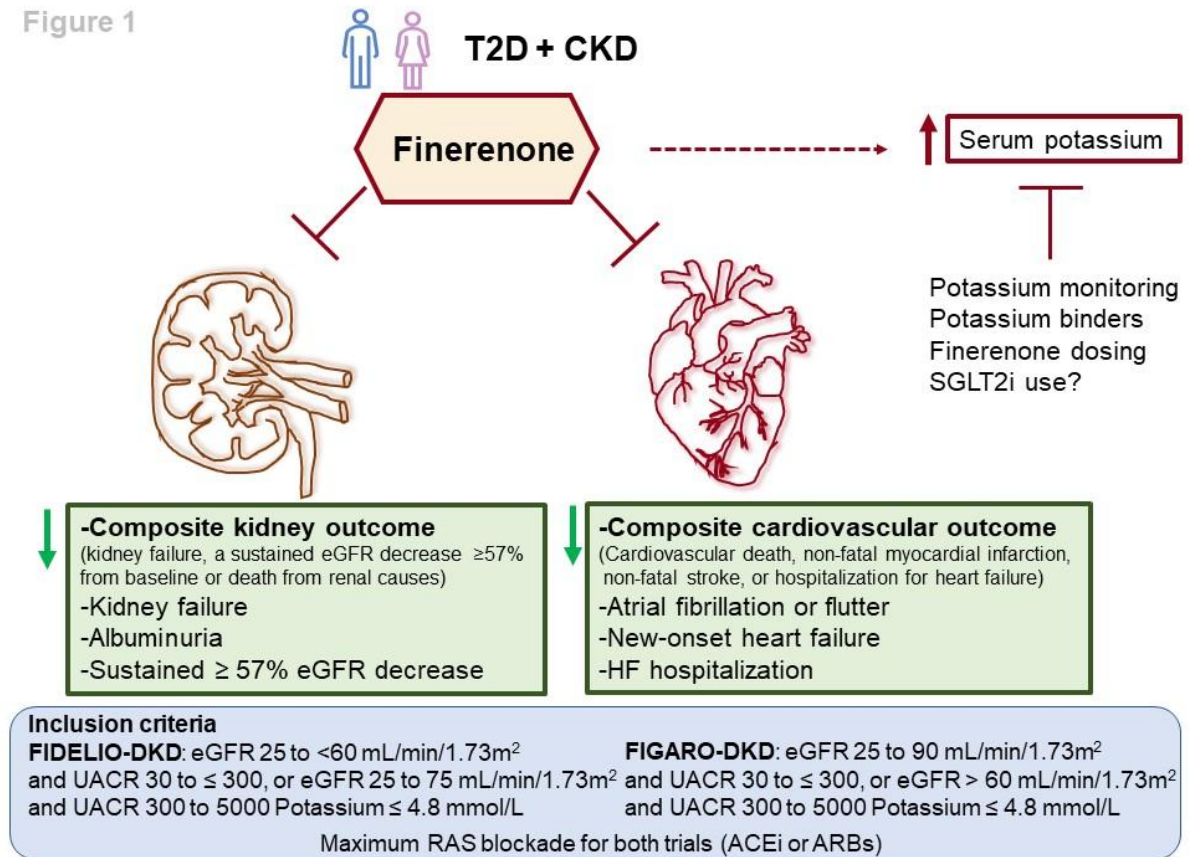


Figure 2

