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Finerenone and Its Role in Diabetic Kidney Disease State of the Art

Raad Sarabia Maria[1*], Daza-Arnedo Rodrigo[2], Rico-Fontalvo Jorge[2], Aguilar-Salcedo Nataly[2], Alfaro Mercedes[2], Navas-Torrejano Diana[2], Cardona-Blanco Maria X[2], Uparella-Gulfo Isabela[2], and Abuabara-Franco Emilio[2]

[1]Department of Internal Medicine, University of Sinu, Cartagena, Colombia

[2]Department of Nephrology, Annamalai University, Annamalainagar, Tamil Nadu

[*]**Corresponding Author:** Raad-Sarabia Maria, Department of Internal Medicine, University of Sinu, Cartagena, Colombia, Tel: 3014566340; E-mail: mariraad22@gmail.com

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Abstract

Diabetic kidney disease represents the leading cause of end-stage kidney disease and its presence directly impacts cardiovascular risk and mortality in individuals with diabetes mellitus. Since albuminuria is the main marker of DKD, its reduction has been established in recent years as one of the therapeutic objectives to impact the evolution of the disease. Finerenone, a mineralocorticoid receptor antagonist, has been described in several recent studies as a drug whose mechanism of action could contribute to reducing the progression of DKD, reducing the deterioration of eGFR and albuminuria with an adequate profile of safety in patients with all stages of kidney disease.

Keywords: Finerenone; Diabetic kidney disease; Mineralocorticoid antagonist

Introduction

Type 2 diabetes mellitus (T2D) is one of the main public health problems in Latin America. According to the International Diabetes Federation, for the year 2019 around 32 million cases of diabetic patients were reported in Central and South America with an estimated average prevalence of 9.4% and a projection of more than 49 million cases in the year 2045 [1]. Persistent hyperglycemia and genetic predisposition promote microvascular damage that compromises target organs such as the kidney, eyes, and central nervous system. One of the most frequent complications presented by diabetic patients is Diabetic Kidney Disease (RDD), a pathology whose incidence has doubled in the last decade, mainly due to the increase in the number of cases of patients suffering from DMT2 [2].

DKD is the leading cause of end-stage kidney disease worldwide; approximately half of patients with T2DM and up to a third of patients with T1DM will develop chronic kidney disease which is characterized by a decrease in estimated glomerular filtration rate and/or an increase in albuminuria. The standard treatment for diabetic kidney disease is made up of a set of actions aimed at the proper management of its etiology, such as adequate glycemic control and the control of other risk factors such as overweight, blood pressure, dyslipidemia and reduction in consumption of alcohol and tobacco; Within the pharmacological strategies, there is an arsenal of medications that seek to regulate the renin-angiotensin-aldosterone system in order to reduce the changes at the glomerular level that lead to the deterioration of the glomerular filtration rate and progression of albuminuria. Despite adequate treatment, a non-negligible percentage of patients with diabetic kidney disease progress to terminal stages requiring renal replacement therapy if they do not die early from cardiovascular causes, so it is important to search for an effective multimodal therapy that reduces the risk of progression of residual diabetic kidney disease.

In this article, an initial review of diabetic kidney disease and its pathophysiology is made, emphasizing the importance of the renin-angiotensin-aldosterone system to subsequently review the usefulness of finerenone as a new therapy in kidney disease.

Diabetic kidney disease

Diabetic kidne y disease is a micr o v ascular complication of Diabetes Mellitus that is characterized by the presence of impaired renal function to the exclusion of other causes of chronic kidney disease. According to the latest guidelines of the American Diabetes Association, the diagnosis is based on the findings of a decreased eGFR<60 ml/min/1.73 m^2 and/or urinary albumin excretion, determined by an Albuminuria-Creatinuria Index (UACR by increased ≥ 30 mg/g for more than 3 months, however, due to high biological variability between measurements in urinary albumin excretion, two of three UACR samples collected within a 3-6 months must be abnormal before a patient is considered to have high albuminuria [3,4].

Renal biopsy is the cornerstone for the diagnosis of diabetic nephropathy, however, it is only carried out in specific circumstances such as cases of rapid decrease in GFR, the presence of active urinary sediment, signs and symptoms of other diseases systemic, rapidly progressive albuminuria, nephrotic range proteinuria and/or absence of diabetic

retinopathy [5]; in the rest of the cases, the deterioration of the glomerular filtration rate and the presence of significant albuminuria are enough to establish the diagnosis of the disease.

Pathophysiology of ERD

Persistent hyperglycemia is the main trigger of DKD; the interaction between high levels of intracellular glucose and free amino groups of proteins, lipids, and nucleic acids results in the formation of advanced glycation end products (AGEs) that induce many of the pathogenic changes in the development of DKD [6].

Inflammation and oxidative stress are also involved in the pathophysiological model of DKD, increasing fibrosis and glomerulosclerosis with increased expression of proinflammatory factors such as monocyte chemoattractant protein-1 (MCP-1), osteopontin (OPN) and transforming growth factor ß (TGF-ß), in addition, there is an overexpression of the mineralocorticoid receptor and greater aldosterone signaling, which increases the inflammatory factor NF-κB, causing the stimulation of growth factors necessary for the differentiation and proliferation of fibroblasts and mesangial and tubular epithelial cells in the kidney; Additionally, aldosterone also induces the synthesis of profibrotic cytokines and causes oxidative stress in the kidney, leading to impaired GFR and increased proteinuria [7].

Therapeutic strategies in DRD

The treatment of DRD is based on preventing its progression and halting the deterioration of GFR and albuminuria, for which the importance of changes in lifestyle must be taken into account initially, with an emphasis on the control of risk factors. And, secondly, the use of pharmacological strategies that prevent progression and damage at the kidney level.

Maintaining adequate glycemic control is crucial for the control of DKD and different studies have shown that achieving glucose goals reduces the occurrence of microvascular complications, including DKD; Within the pivotal studies, the Diabetes Control and Complications Trial (DCCT) study demonstrated a 39% reduction in the rate of grade I albuminuria and a 54% reduction in grade II albuminuria with a goal of Glycated Hemoglobin (HbA1c) <6% *vs*. 9% in DM1 without diabetic kidney disease [8], while the UKPDS study showed that intensive glycemic control significantly reduces microvascular complications in type 2 diabetics [9].

Regarding pharmacological management, the blockade of the Renin-Angiotensin-Aldosterone System (RAAS) is one of the pillars of the management of diabetic kidney disease and its effect is mainly explained by the decrease in intraglomerular pressure with an impact on the decrease in hyperfiltration injury and albuminuria, the latter being one of the main objectives of treatment.

ACE inhibitors or ARBs are the first-line drugs for the treatment of arterial hypertension in patients with diabetes with eGFR<60 ml/min/1.73 m2 and UACR ≥ 300 mg/g due to their benefits in the prevention of DRD progression and its antiproteinuric effect; Clinical trials have demonstrated the efficacy of RAAS blockade treatment beginning in 1993 with the Collaborative study group in patients with T1DM [10] where captopril decreased the doubling of serum creatinine by 43%. In patients with T2DM, the IDNT studies with irbersartan versus amlodipine [11] and RENAAL [12] with losartan compared with placebo reduced the progression of kidney disease by 20%.

In the setting of lower levels of albuminuria (30-299 mg/g), treatment with ACE inhibitors or ARBs has been shown to reduce progression to more advanced albuminuria (≥ 300 mg/g) and cardiovascular events, but not progression to end-stage kidney disease.

Regarding the most recent drugs for the treatment of DM2, the use of SGLT2 inhibitors has demonstrated its cardioprotective and renoprotective effect independent of its effect in the control of hyperglycemia with results demonstrated in different trials such as EMPAREG with empagliflozin [13] which managed to reduce the residual risk (RR) for the development of nephropathy by 39% and the risk of creatinine doubling by 44%.

Similarly, the CANVAS study [14] with canagliflozin reduced the progression of albuminuria by 27% and decreased the outcome of renal compound in 40%, while the CREDENCE study (2019) with canagliflozin, in 4401 patients with T2DM, UACR ≥ 300 mg/g and mean eGFR of 56 ml/min/1.73 m2 with mean albuminuria of more than 900 mg/day,Evaluated as the main outcome the cardiorenal compound of: kidney failure, doubling of serum creatinine and kidney or cardiovascular death stopped early due to demonstrated efficacy with a 32% risk reduction for the development of end-stage kidney disease versus the control group [15].

Based on the above evidence, it is concluded that this group of drugs reduces the risk of worsening kidney disease, progression of microalbuminuria, death from cardiovascular causes and increases the time to development of end-stage kidney disease [16].

Regarding GLP1 analogs, their impact on slowing DRD progression has also been postulated, independent of their effect on hyperglycemia, in the leader studies with liraglutide, rewind with dulaglutide and the study sustain-6 with semaglutide showed a decrease in the risk of developing macroalbuminuria, progression to renal failure, a 30% decrease in GFR, and death from renal causes Table 1 [17-19].

Table 1: Clinical trials of various drugs in DRD.

Study	Follow-up	Characteristics of base limea	Intervention	Comparison	Main findings
diabetes mellitus type I					
Collaborative Study Group(1993) N=409	36	36 sCr. 1.3 mg/dL HbAlc 11.8% Albuminuria: 2.5 g/d	Captopril	Placebo	Captopril time to double sCr by 43%
Diabetes mellitus type#					
DNT(2001) N=1715	31	sCr. 1.3 mg/dL Albuminuria: 2.9 g/d	Irbesartan	Amlodipine, placebo	Irbesartan risk of doubling sCr. death or progression of renal failure in 20% compared to placebo and 23% compared to amodipine
RENAAL (2001) N=1513	41	sCr. 1.9 mg/dL HbA1c:8.4% Albuminuria: 1.2 g/d	Losartan	Placebo	Losartan risk of doubling sCr. death or progression to kidney failure
EMPAREG (2015) N=7020	37	GFR: 82 mL/min/ 1.73 m^2 40% with mycoomacrealbuminuria	Empagificzin	Placebo	Empaglificzin risk of incidence or worsening of netopathy, progression of macroalbuminuria, doubling of the time to renal failure
CANWAS (2017) N=10142	43	GFR: 82 mL/min/ 1.73 m^2 UACR 12.3 mg/g	Canaglifiozin	Placebo	Canagliflozin albuminuria progression and risk of reduced eGFR, kidney failure, or death from kidney disease
CREDENCE (2019) N=4401	31	MbA1c:83% UACR: 923 mg/9	Canaglifiozin	Placebo	Canaglifiozin risk of doubling sCr. kidney failure death from renal cardiovascular causes
LEADER (2016) N=9340	45	GFR:80 mL/min/ 1.73 m^2 HbA1c 8.7% 37% with micro/ macroalbuminuria	Liraglutide	Placebo	Liraglutide risk of new-onset persistent macroalbuminuria, SCr duplication, kidney failure, death from kidney causes
REWIND (2019) N=9901	65	GFR: HbAlc 7.3% 35% with micro/ macroalbuminuria	Dulagiutide	Placebo	Dulaglutide risk of new macroalbuminuria, decrease in GFR by 30% kidney failure

Mineralcorticoid Antagonist and Its Role in Drd

The Renin-Angiotensin-Aldosterone System (RAAS) is regulated by renin secretion from the granular zone of the juxtaglomerular apparatus, which is triggered by three main physiological pathways:

- Sympathetic stimulation of the β1 receptors of the juxtaglomerular apparatus,
- Reduction of the delivery of sodium to the distal convoluted tubule detected by the macula densa
- A reduced perfusion pressure in the kidney detected by the baroreceptors of the afferent arterioles.

Renin secretion is inhibited by the release of BNP and NT-proBNP from cardiac tissue in response to distention of the cardiac chambers with increased blood volume. The enzymatic effect of renin produces cleavage of angiotensinogen to Angiotensin I (ATI) which in turn is converted to Angiotensin II (ATII) by ACE produced by endothelial cells in the lungs and kidney. AT II stimulates 2 different transmembrane G-protein coupled receptors, thus regulating the glomerular filtration rate and sodium excretion through vasoconstriction of the afferent and efferent arterioles, the release of aldosterone from the adrenal cortex, the release of epinephrine and ADH resulting in increased sodium reabsorption, potassium excretion, elevation of hydrostatic pressure to increase GFR, reabsorption from the collecting ducts, and increased circulating volume.

Aldosterone acts directly on Na/K/ATP-ase pumps on the basolateral membrane of kidney principal cells [20], however, mineralocorticoid receptors (MR) are present in multiple tissues, including smooth muscle cells, vascular and endothelial cells, cardiomyocytes, fibroblasts, kidney (mesangial cells and podocytes), adipocytes, macrophages and brain (hypothalamus), activating remodeling in response to inflammation and damage. This wide distribution explains why aldosterone exerts multiple cardiac, vascular, and renal effects including endothelial dysfunction, vasoconstriction, natriuresis, K^+ retention, sympathetic activation, adverse cardiovascular (hypertrophy, fibrosis), and renal (glomerular and tubular sclerosis) remodeling and oxidative stress; it increases vascular stress, stiffness and exerts proarrhythmic, proinflammatory and prothrombotic effects Figure 1 [21].

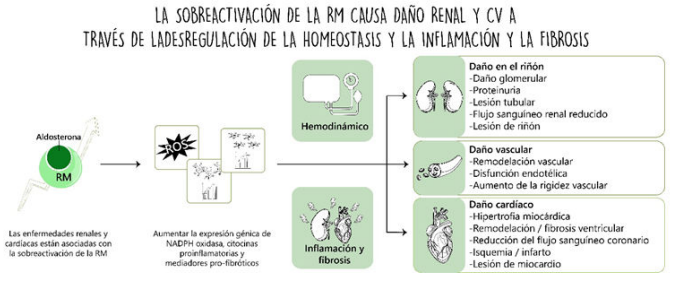

Figure 1: Roll the RM and ERD.

Mineralocorticoid receptor antagonists (MRAs) directly block the receptor, inactivating the action of aldosterone and preventing the genomic and non-genomic response from interacting with the receptor, thus decreasing the degree of inflammation and remodeling in the heart and kidney.

ARMs are classified as selective or non-selective depending on their chemical composition; the former are non-steroidal, while the latter contain a steroid ring in their composition. First-generation non-selective MRAs (spironolactone) are used to inhibit mineralocorticoid effects; however, due to their steroid composition, they also inhibit the effects of androgens such as testosterone and dihydrotestosterone, leading to the development of gynecomastia, breast tenderness, and feminization, hence spironolactone It is also used in the management of acne and polycystic ovary syndrome. MRAs also have extensive evidence in the management of cardiovascular diseases, such as in the field of heart failure with reduced LVEF, refractory hypertension, hyperaldosteronism, ascites secondary to cirrhosis, and hypokalemia.

Due to their mechanism of action, MRAs have been proposed as therapeutic agents in patients with albuminuria, mainly those with urinary albumin excretion >1 gram/day. Different clinical trials and meta-analyses evaluating spironolactone objectify the reduction of proteinuria and progression of diabetic kidney disease. However, the effect of spironolactone on albuminuria is variable, with decreases of 15% to 60% in studies that ranged from 4 to 52 weeks in duration. It should also be remembered that this drug is not selective for MR and, therefore, its use is limited by sexual side effects [22].

On the other hand, eplerenone is a more selective steroidal MRA, with minimal affinity for progesterone and androgen receptors, which reduce adverse effects, related to the gonadal axis; however, it has 20 to 40 times less potency than eplerenone, spironolactone [23].

Clinical trials evaluating renal outcomes in patients with DKD and MRA use are generally limited to small, short-term studies in which a high rate of side effects such as hyperkalemia, gynecomastia, and other sex hormone-related side effects such as was described above. Given the side effects of non-selective MRAs, strategies have currently been pursued to design more selective MRAs with the aim of improving the relationship between efficacy and safety. Some new-generation ARMs are non-steroidal and their structure is based on a main dihydropyridine chain with no activity on L-type calcium channels at the muscle level. Of these drugs, finerenone has shown encouraging results in phase III clinical trials and it has been positioned in recent years as a probable drug to obtain the maximum therapeutic benefit in DRD.

Pharmacology and pharmacodynamics of finerenone

There is increasing evidence showing how overactivation of the mineralocorticoid receptor leads to inflammation and fibrosis, a key process in the development and progression of kidney disease, which in turn is associated with increased cardiovascular risk. Finerenone is a novel selective non-steroidal mineralocorticoid receptor antagonist with a high affinity for the receptor leading to a reduction in inflammation and fibrosis in various animal models. Likewise, Phase II studies have been

carried out to evaluate finerenone in the reduction of albuminuria and association with adverse events, finding that this medication has a very good safety profile, with less production of hyperkalemia compared to spironolactone.

Mechanism of action: Spironolactone and eplerenone are competitive antagonists that bind to the ligand-binding domain, preventing mineralocorticoid receptors from adopting the active conformation and rendering them transcriptionally inactive, i.e., producing "passive" antagonism, however these 2 drugs are unable to stabilize the (H12) helix in the activation domain at the C-terminus of the receptor and unable to prevent the (H12) helix from adopting the agonist conformation, this explains the partial agonist activity of non-selective ARMs and adverse effects associated with its intake [23].

Finerenone, whose molecular formula is C21H22N4O, is a highly selective, potent, bulky, nonsteroidal antagonist that binds strongly to the RM by acting as a passive antagonist by docking to the ligand-binding domain of the RM with a different accommodation compared to Steroidal ARMs, leading to the formation of a helix 12 bulge in domain 2 at the C-terminus of the mineralocorticoid receptor. This bulge forms an unstable mineralocorticoid receptor-ligand complex unable to recruit transcriptional factors, changing the stability, nuclear translocation, and activation of the mineralocorticoid receptor, leading to rapid mineralocorticoid receptor degradation. Thus, finerenone decreases nuclear accumulation of mineralocorticoid receptors more effectively than spironolactone, inhibits recruitment of mineralocorticoid receptors to DNA target sequences, and suppresses recycling of mineralocorticoid receptors [22].

Finerenone has been shown *in vitro* to reduce aldosterone-induced smooth muscle cell proliferation in a dose-dependent manner. In a preclinical model of hypertension in non-uninephrectomized rats, finerenone at a dose of 1 mg/kg significantly decreased cardiac and renal hypertrophy, glomerular and tubulointerstitial damage, pro-BNP levels, and the expression of several biomarker genes for remodeling and renal profibrotics (PAI 1, MCP-1, osteopontin, MMP-2) compared with placebo, without lowering blood pressure. Finerenone binds to alpha-1 acid glycoproteins, is metabolized by CYP3A4 (90%) and CYP2C8 (10%), and renal elimination accounts for only 0.57% of unchanged drug even in individuals with renal insufficiency [22,24]. The reduced renal accumulation and minimal renal clearance suggest that finerenone may have more favorable safety than other mineralocorticoid receptor antagonists in patients with renal insufficienc Table 2.

Table 2: Pharmacokinetics and pharmacodynamics of ARM.

ARM STEROIDS			**ESPLERENONE**
Preclinical data	**SPIRONOLACTONE**	**ESPLERENONE**	
Structural properties	Structural properties	properties Flat (steroidal)	Bulky (non-steroidal)
Potency at MR	High	Moderate	High
Selectivity to MR	Low	Moderate	High
Recruitment of cofactors	Recruitment of partial agonist cofactor	Recruitment of partial agonist cofactors	Inverse agonist (i.e., inhibits cofactor binding)
CNS penetration	Yes	Yes	No based on preclinical data
Sexual side effects	Yes (gynecomastia)	Less than spironolactone	No signal in phase II studies
Hyperkalaemia	Yes	Yes	Moderately increased
Tissue distribution	Kidney>heart (at least 6 times)	Kidney>heart (~ 3 times)	Balanced kidney-heart (1:1)

Effects of finerenone on potassium

Data from phase II trials with finerenone in patients with heart failure and T2DM have shown that it has a low impact on potassium levels and that its use is not limited by lower glomerular filtration rates. The reason for the minimal effects of finerenone on serum potassium levels is unknown; however, it could be related to a different model of interaction with the mineralocorticoid receptor with less recruitment of cofactors, short plasma half-life and a more uniform tissue distribution. Between kidneys and heart, unlike eplerenone and spironolactone, which are concentrated in greater amounts in the kidneys [23,25]

The ARTS (Mineralocorticoid Receptor antagonist tolerability study) clinical program that included more than 2000 patients, designed to evaluate the safety and efficacy of finerenone in patients with T2DM and diabetic kidney disease with or without heart failure, showed that finerenone was associated with less occurrence of hyperkalemia (defined by K>5.6 mEq/l) compared

to spironolactone with similar effectiveness in reducing NT pro-BNP and UACR levels in patients with chronic heart failure [26].

In the ARTS-HF (ARTS -Heart Failure) phase IIb trial in patients hospitalized in the last 7 days for decompensated heart failure, finerenone reduced NT proBNP levels similar to eplerenone and with greater reduction in outcomes such as death from any cause, hospitalization for cardiovascular causes, heart failure decompensation compared to eplerenone with less increase in potassium levels (K>5.6 mEq/l) [27]. Finally, in the ARTS-DN (ARTS Diabetic Nephropathy) study of 823 patients with T2DM and albuminuria (UACR >30 mg/g) under treatment with ACE inhibitors or ARBs, the safety of finerenone administration in doses of 20 mg was evaluated, finding a dose-dependent reduction in albuminuria of 25-38% compared to placebo at 90 days with minimal effect on potassium (hyperkalemia 2.1% *vs* 0%) and on blood pressure Figures without documenting changes in Hba1c with finerenone Figure 2 [28].

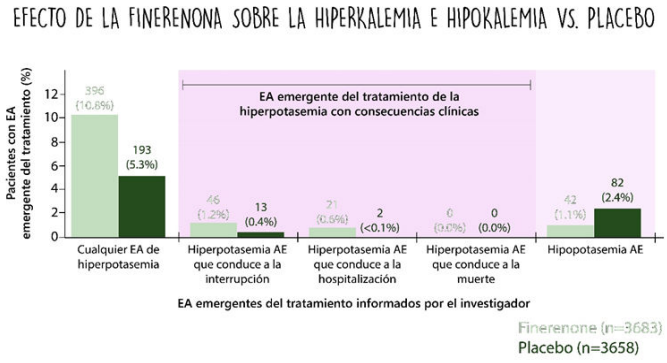

Figure 2: Effects of finer none on potassium levels in the ARTS-DN clinical trial.

Evidence for Finerenone in DKD: Fidelio-DKD and Figaro-DKD

The FIDELIO-DKD and FIGARO-DKD trials constitute 2 large phase III, multicenter, international, double-blind, randomized, placebo-controlled clinical studies (Fidelio n=5674 and FIGARO n=7354) that sought to evaluate the efficacy and safety of finerenone in reducing the progression of kidney disease and major cardiovascular events in patients with diabetic kidney disease and T2DM.

Eligible patients in the FIDELIO and FIGARO studies consisted of adults older than 18 years with T2DM and diabetic kidney disease treated with a maximum tolerated dose of ACE inhibitors or ARBs and potassium levels less than 4.8 mmol/L. Diabetic kidney disease was defined by either of the following 2 criteria:

- Moderate, persistent albuminuria (UACR 30 to <300 mg/g) or CKD-EPI GFR 25 to 60 ml/min/1.73 m) and history of diabetic nephropathy.
- Severe persistent albuminuria (UACR 300 to 5000 mg/g) and an eGFR between 25 and 75 ml/min/1.73 m [29].

In the FIGARO study, the eligibility criteria varied considering:

- Severely elevated albuminuria (UACR>300 mg/g) and eGFR>60 ml/min/1.73 m
- eGFR 25-90 ml/min/1.73 m and albuminuria moderately elevated, persistent (UACR<300 mg/g) [30].

Patients were randomly assigned in a 1:1 ratio to receive placebo or oral finerenone at a starting dose of 10 mg once daily in case of eGFR<60 ml/min who would be titrated to 20 mg/day every day. Month as long as potassium levels were less than 4.8 mmol/L; otherwise, the finerenone dose should be maintained/ reduced to 10 mg OD. Those with GFR>60 mL/min at randomization received a dose of 20 mg daily that would be decreased to 10 mg in case of hyperkalemia (K>4.8 mmol/L); at follow-up visits every 4 months until the end of the study (2.6 years and 3.4 years, respectively), finerenone suspension was recommended if potassium levels rose above 5.5 mmol/L.

The primary outcome evaluated in FIDELIO-DKD is a composite of time to renal failure, defined as initiation of renal replacement therapy within 90 days, renal transplantation, or sustained glomerular filtration rate <15 mL/min/1.73 m^2 for at least 4 weeks. In the FIGARO-DKD, the primary and secondary outcomes were the same as in the FIDELIO-DKD; however, other secondary outcomes evaluated were overall mortality, reduction in albuminuria, and hospitalization for any cause.

In the FIDELIO study, it was found that patients treated with finerenone had a lower incidence for the primary renal outcome with a lower occurrence of a decrease in eGFR of at least 40% and a lower rate of death from renal causes than the control group (17.8% *vs.* 21.1% HR 0.82; 95% CI 0.73-0.93; p=0.001) with an NNT of 29 to 3 years to prevent 1 event, additionally the patients in the FIDELIO study had a lower risk of frequency of secondary cardiovascular outcome (13% *vs*. 14.8 HR 0.86; 95% CI, 0.75 to 0.99; p=0.03) with an NNT of 42 to 3 years. Exploratory results showed the association of finerenone with a greater reduction in UACR at 4 months compared to placebo (HR: 0.69; 95% CI, 0.66 to 0.71), a result that was maintained throughout the study. A total of 8.9% of patients in the finerenone group and 11.5% in the placebo group developed a secondary renal endpoint event that included renal failure, >57% sustained decline in GFR, or renal death HR 0.76; CI 0.65 to 0.90.

The incidence of adverse events occurring during the study was similar for both groups, being 31.9% in the finerenone group and 34.3% in the placebo group. Adverse events associated with hyperkalemia were found to be 2 times more frequent with finerenone than with placebo (18.3% *vs.* 9.0%), with a higher rate of discontinuation due to hyperkalemia (K>5.5 mmol/l) in the finerenone group (2.3% *vs.* 0.9%). However, no case of fatal hyperkalemia was reported. The maximum difference was 0.23 mmol/L throughout the study. Regarding blood pressure, HbA1c or weight Figures, no significant change was found with the use of finerenone *vs.* placebo.

In the FIGARO study, the primary cardiovascular composite endpoint (representing the secondary efficacy endpoint in FIDELIO) defined by the incidence of cardiovascular death, nonfatal AMI, nonfatal stroke, or hospitalization for heart failure was significantly lower in the FIDELIO group. Finer none *vs.* placebo (12.4% *vs.* 14.2% HR, 0.87; 95% CI 0.76 to 0.98 p=0.03)

with an NNT of 47. The incidence of ESRD was lower with finerenone and occurred in 32 patients *vs.* 49 in the placebo group (0.9% *vs.* 1.3%, HR 0.64, CI 0.4 to 0.955), the reduction in UACR was also 32% greater in the finerenone group. Regarding adverse events, the incidence was similar in both groups (31.4% *vs.* 33.2%). As in FIDELIO, the incidence of hyperkalemia was higher with finerenone than with placebo (10.8% *vs.* 5.3%), with a difference of 0.16 mmol/L in potassium levels in both groups that remained stable throughout the study. there were no cases of death and few led to treatment discontinuation (1.2% *vs.* 0.4%), gynecomastia was very little reported and similar in both groups. Regarding the impact on blood pressure Figures, SBP was -3.5 mmHg at month 4 and -2.6 mmHg at month 24. The average glycated hemoglobin was similar in both groups throughout the study Figure 3.

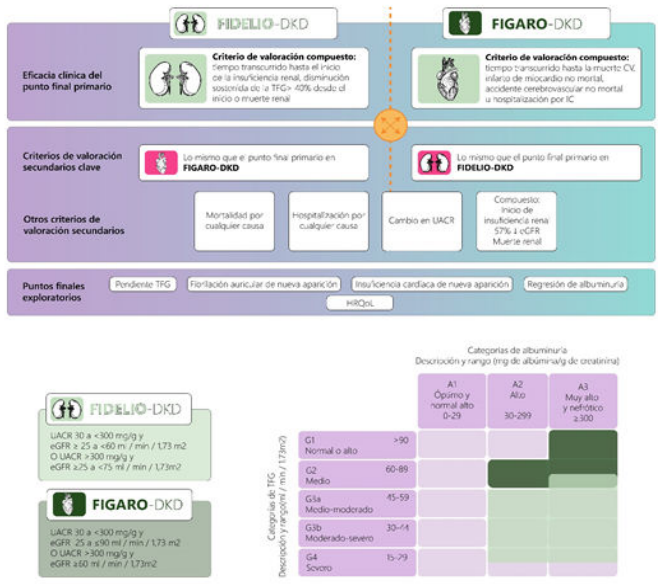

Figure 3: Comparison of clinical data in the FIDELIO-DKD *vs.* FIGARO-DKD trial.

Fidelity

With results not officially published at the time of writing this review, preliminary data from the FIDELITY study were released at the European Society of Cardiology 2021 congress.

FIDELITY is a pre-specified analysis of total data from both the FIDELIO DKD and FIGARO DKD studies those together address 13,717 patients evaluating efficacy outcomes over a 3-year follow-up period. It was observed that the use of finerenone significantly reduced the primary cardiovascular outcome (12.7% *vs.* 14.4%; HR 0.86 [95% CI 0.78-0.95]; p=0.0018) with a number needed to treat (NNT) of 46. For renal outcome, finerenone reduced the risk of a decrease in eGFR ≥ 57% by 23% compared to placebo, with a statistically significant difference between the subgroups analyzed (5.5% *vs.* 7.1%). HR 0.77 [95% CI 0.67-0.88]; p=0.0002) and with an NNT=60, without observing a statistically significant reduction in mortality associated with renal causes. Regarding adverse events and the occurrence of hyperkalemia, the results were similar in both finerenone *vs.* placebo groups, with a frequency of hyperkalemia of 14% for finerenone *vs.* 6.9% (HR 0.86; 95% CI, 0.78-0.95; p=0.0018); hyperkalemia leading to drug discontinuation was 5.5% for finerenone *vs.* 7.1% in the placebo group (HR 0.77; 95% CI, 0.67-0.88; p=0.0002) The risk of cardiovascular events and acute heart failure in diabetic patients increases proportionally with the increase in UACR and the decrease in eGFR<75 ml/min/1.73 m^2. It is noteworthy that the results observed with finerenone were presented in the context of standard medical therapy titrated to maximum tolerated doses with at least one RAAS blocking agent such as ACE inhibitors or ARBs and that some percentage of patients additionally received management with ISGLT2 or GLP1 which allows us to conclude that the use of finerenone in addition to the RAAS blockade allows to reduce the effect of aldosterone escape that may exist in diabetic patients, allowing an even greater reduction in the progression of diabetic kidney disease and albuminuria with adequate impact on the residual risk and a good safety profile including the risk of hyperkalaemia (ACE inhibitors+ARA II 9.2%)

In the FIDELIO-DKD study, finerenone improved renal outcomes in patients with diabetic kidney disease stages 3 and 4 and severe albuminuria, a population at very high cardiovascular risk, while in the FIGARO study it was shown that patients with DKD stages 2 to 4 with moderately elevated albuminuria or DKD stages 1 and 2 with severely elevated albuminuria treated with finerenone have a lower risk of cardiovascular mortality and morbidity.

There is currently limited evidence to support the use of drugs to improve cardiorenal outcomes in patients with less advanced diabetic kidney disease, so this clinical study makes striking contributions in this regard and is an attractive therapeutic option in diabetic kidney disease with persistent albuminuria despite the standard management and also in those patients with eGFR less than 50 ml/min and high risk of hyperkalemia. This is why we consider that finerenone is a drug that, in light of the most recent studies, reduces the risk of progression of diabetic kidney disease, end-stage kidney disease, albuminuria, progression to renal replacement therapy and death from renal causes and which also has a cardiovascular protective effect by reducing the risk of death of cardiovascular origin, non-fatal AMI and hospitalization for heart failure.

Conclusion

The most common microvascular complication of diabetes mellitus is diabetic kidney disease, characterized by impaired eGFR and/or presence of albuminuria (UACR>30 mg/g). Among its main pathophysiological mechanisms, the hyperreactivity of mineralocorticoid receptors and increased activity of the RAAS stand out, leading to a permanent inflammatory state with secretion of transcription factors such as TGF and NF Kb that lead to increased oxidative stress and increased of fibroblast activity causing fibrosis and damage to the glomerular basement membrane. Through measures to control risk factors and control over the RAAS, it has been possible to reduce the progression of DKD in a proportion of patients, however, the residual risk persists with a non-negligible percentage of patients who progress in their kidney disease or present cardiovascular outcomes. With the creation of the new molecule finerenone,

responding to an unmet need in patients with kidney disease and diabetes, phase 2 and phase 3 studies such as FIDELIO DKD and FIGARO DKD and the most recent FIDELITY analysis have succeeded in demonstrating the impact that the use of finerenone has on reducing the progression of DKD, decreasing albuminuria, reducing mortality and cardiovascular risk with an adequate safety profile and less production of hyperkalemia compared to other classic MRAs, which makes it a a safe and effective strategy for use in patients with DKD.

References

1. Castillo GA, Aroca G, Buelvas J, Buitrago AF, Carballo V, et al. (2020) Recommendations for the management of cardiac and renal risk in the patient with type 2 diabetes mellitus. Rev Colomb Cardiol 27:3-22
2. Rico Fontalvo JE (2021) Guía de práctica clínica para la enfermedad renal diabética. Rev Colomb Nefrol 8
3. Microvascular complications and foot care: Standards of medical care in diabetes (2021) Diabetes Care 44:151-167
4. Cheung AK, Chang TI, Cushman WC, Furth SL, Hou FF, et al. (2021) Executive summary of the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int 99:559-569
5. Chaharsooghi SK, Honarvar M, Modarres M (2011) A multi-stage stochastic programming model for dynamic pricing and lead time decisions in multi-class make-to-order firm. Sci Iran 18:711-721
6. Rico Fontalvo JE, Daza Anedo R, Raad Sarabia M, Pájaro Galvis N, et al. (2021) Proteoma urinario en la enfermedad renal diabética. Estado del arte. Rev Colomb Nefrol 8:546-547
7. Patel V, Joharapurkar A, Jain M (2021) Role of mineralocorticoid receptor antagonists in kidney diseases. Dru Devel Res 82:341-363
8. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, et al. (1993) DCCT reseach trial. N Engl J Med 55:3556-3565
9. NA (1999) Intensive Blood-Glucose Control with Sulfonylureas or Insulin Compared with Conventional Treatment and Risk of Complications in Patients with Type 2 Diabetes. Endocrinologist
10. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD (1993) The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 329:1456-1462
11. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, et al. (2001) Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. N Engl J Med 345:851-860
12. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, et al. (2001) Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. N Engl J Med 345:861-869
13. Steiner S (2016) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. Zeitschrift fur Gefassmedizin
14. Mahaffey KW, Neal B, Perkovic V, De Zeeuw D, Fulcher G, et al. (2018) Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation 137:323-334
15. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, et al. (2019) Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 380:2295-2306
16. Jorge R-F, Rodrigo D-A, Maria Ximena C-B, Victor L-M, Emilio A-F, et al. (2020) SGLT2 Inhibitors and nephroprotection in diabetic kidney disease: From mechanisms of action to the latest evidence in the literature. J Clin Nephrol 4: 44-55
17. Marso SP, Daniels GH, Frandsen KB, Kristensen P, Mann JFE, et al. (2016) Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 375:311-322
18. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, et al. (2019) Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 394:121-130
19. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, et al. (2016) Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 375:1834-1844
20. Lytvyn Y, Godoy LC, Scholtes RA, van Raalte DH, Cherney DZ (2019) Mineralocorticoid Antagonism and Diabetic Kidney Disease. Cur Diab Reports 19:1-10
21. Ruilope LM, Tamargo J (2017) Renin–angiotensin system blockade: Finerenone. Nephr et Therap 13:47-53
22. Rico-Mesa JS, White A, Ahmadian-Tehrani A, Anderson AS (2020) Mineralocorticoid Receptor Antagonists: a Comprehensive Review of Finerenone. Curr Cardiol Rep 22:1-1
23. Vodošek Hojs N, Bevc S, Ekart R, Piko N, Petreski T, et al. (2021) Mineralocorticoid receptor antagonists in diabetic kidney disease. Pharmace 14:561-561
24. Stockand JD, Meszaros JG (2003) Aldosterone stimulates proliferation of cardiac fibroblasts by activating Ki-RasA and MAPK1/2 signaling. Am J Physiol - Hear Circ Physiol 39:219-224
25. Erraez S, López-Mesa M, Gómez-Fernández P (2021) Bloqueantes del receptor mineralcorticoide en la enfermedad renal crónica. Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia
26. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, et al. (2013) Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease:A randomized, double-blind trial. Eur Heart J 34:2453-2463
27. Pitt B, Anker SD, Böhm M, Gheorghiade M, Kober L, et al. (2015) Rationale and design of MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF): A randomized study of finerenone vs. eplerenone in patients who have worsening chronic heart failure with diabetes and/or chronic kidney disease. Eur J Heart Fail 17:224-232
28. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, et al. (2019) Design and Baseline Characteristics of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease Trial. Am J Nephrol
29. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, et al. (2020) Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. N Engl J Med
30. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, et al. (2021) Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. N Engl J Med