Finerenone: A New Anchor in Cardiorenal Care – A Comprehensive Review

Finerenona: Uma Nova Âncora no Tratamento Cardiorrenal – Uma Revisão Abrangente

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Abstract

Type 2 diabetes mellitus (T2DM) is a global pandemic with growing prevalence. T2DM significantly contributes to chronic kidney disease (CKD) and cardiovascular disease (CVD). This intricate relationship involves the mineralocorticoid receptor (MR) system, exacerbating inflammation and fibrosis in the heart, kidneys, and blood vessels.
Finerenone, a third-generation non-steroidal MR antagonist, shows promise by selectively inhibiting MR without significant affinity for other receptors. The ARTS program's phase 2 trials confirm finerenone's safety and efficacy in heart failure, CKD and estimated glomerular filtration rate without a significant increase in potassium serum concentration.
In the phase III FIDELIO-DKD trial, finerenone significantly improved kidney outcomes, reducing the risk of kidney failure, sustained decrease in estimated glomerular filtration rate, or death from renal causes. The FIGARO-DKD trial revealed a lower risk of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure with finerenone. The FIDELITY analysis, pooling FIDELIO-DKD and FIGARO-DKD data, affirms a significant reduction in composite cardiovascular and kidney outcomes with finerenone. This evidence earns finerenone a class I recommendation in the 2023 European Society of Cardiology Guidelines.
In conclusion, finerenone emerges as a valuable therapeutic option, supported by robust clinical evidence, for preventing cardiovascular and renal events in patients with type 2 diabetes mellitus and chronic kidney disease. Future prospects include exploring finerenone's potential in heart failure, especially in patients who are intolerant to traditional MR antagonists. We aim to review the evidence of finerenone benefits in cardiorenal care in patients with T2DM.

Keywords: Type 2 diabetes mellitus; chronic kidney disease; cardiovascular disease; mineralocorticoid receptor system; finerenone; FIDELIO-DKD trial; FIGARO-DKD trial; FIDELITY analysis

Resumo

A diabetes *mellitus* do tipo 2 (DMT2) é um problema global de prevalência crescente. A DMT2 contribui significativamente para o desenvolvimento de doença renal crónica (DRC) e doença cardiovascular (DCV). Esta relação envolve a ativação do receptor mineralocorticóide (RM), que contribui para o desenvolvimento de inflamação e fibrose cardíaca, renal e vascular.
A finerenona, um novo antagonista do não-esteróide do RM inibe selectivamente o RM, sem afinidade para outros receptores. Os ensaios clínicos de fase II do programa ARTS demonstraram a segurança e a eficácia da finerenona na insuficiência cardíaca (IC) e DRC, sem aumentar significativamente os valores séricos de potássio.
No ensaio clínico de fase III FIDELIO-DKD, a finerenona melhorou significativamente os *outcomes* renais, reduzindo o composto de risco de lesão renal aguda, declínio mantido da taxa de filtração glomerular estimada ou morte por causas renais. O ensaio FIGARO-DKD mostrou que a finerenona diminui o risco de morte por causa CV, enfarte agudo do miocárdio, acidente vascular cerebral ou internamento por IC. A análises FIDELITY, agregando os dados dos ensaios FIDELIO-DKD e FIGARO-DKD confirmou os benefícios CV e renais da finerenona nos doentes com DRC e DMT2. Consequentemente, as *guidelines* da Sociedade Europeia de Cardiologia de 2023 reconheceram à finerenona uma recomendação de classe I nestes doentes.
Em conclusão, a finerenona emerge como uma opção terapêutica para a prevenção de eventos CV e renais em doentes com DRC e DMT2. Perspectivas futuras incluem esclarecer potenciais benefícios da finerenona em doentes com IC, em particular doentes intolerantes aos antagonistas do RM convencionais. O nosso objetivo com o presente artigo é fazer uma revisão alargada da evidência da utilização da finerenona em doentes com DMT2 e DRC.

Palavras-chave: Diabetes *Mellitus* tipo 2; doença renal crónica; doença cardiovascular; sistema receptor mineralocorticóide; finerenona; estudo FIDELIO-DKD; estudo FIGARO-DKD; análise FIDELITY

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> INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a growing pandemic affecting over half a billion individuals worldwide. [1] In Portugal, the prevalence of T2DM grew from 11.7% to 13.6% between 2009 and 2018, impacting more than 1.3 million people. [2]

Diabetes accounts for 40% of cases of chronic kidney disease (CKD), making it the leading cause. CKD is characterized by elevated urinary albumin excretion, reduced glomerular filtration rate, or both, significantly heightening the risk of cardiovascular morbidity and mortality. [3] T2DM is also a major risk factor for the development of cardiovascular disease (CVD), the leading cause of mortality and morbidity among T2DM patients. [4] Heart failure (HF) contributes substantially to the CVD burden, with T2DM patients being more than twice as likely to develop HF as those without T2DM. [5]

The close relationship between the heart and the kidney has given rise to the concept of cardiorenal syndrome, [6] where dysfunction in one organ, whether acute or chronic, can trigger dysfunction in the other due to hemodynamic, neurohormonal, and inflammatory interactions.

T2DM is characterized by insulin resistance and impaired glucose handling which generates deleterious mechanisms at molecular, cellular, organ and systemic levels. [7] These include oxidative stress, impaired mitochondrial function, endothelial dysfunction, cardiomyocyte hypertrophy, fibrosis, systolic and diastolic dysfunction, glomerular sclerosis, dyslipidemia, hypertension, inflammation and neurohormonal hyperactivation. In particular, evidence supports a major pathophysiologic role for the overactivation of the mineralocorticoid receptor (MR) system. [8] Although the MR's involvement in blood pressure (BP) regulation and sodium retention is well understood, there is a growing realization that excessive MR activation plays a role in fostering inflammation and fibrosis in the kidneys, blood vessels, and heart, worsening of cardiorenal disease. [9]

In recent years, the first-generation spironolactone and the second-generation eplerenone MR antagonists (MRA) have been class I recommended therapies for patients with HF and CKD. [10] Notwithstanding, MRA remain underutilized in real-world clinical practice due to concerns about side effects. These side effects include hyperkalemia and worsening renal function. In addition, the binding of MRA to androgen and progesterone receptors can lead to gynecomastia and impotence in men, as well as menstrual disturbances in women. [11]

> FINERENONE – PHARMACOLOGY AND PRECLINICAL STUDIES

Finerenone is a third-generation non-steroidal MRA with high potency, selectivity, and affinity for the MR. [12] Finerenone inhibits renal tubular MR-mediated sodium reabsorption and the overactivation of MR. [13] It achieves this by robustly binding to MR in the kidneys, heart, and blood vessels. This 'bulky'-like binding hinders the recruitment of transcriptional cofactors, disrupting the expression of genes associated with hypertrophy, inflammation, and fibrosis. [14] Unlike spironolactone and eplerenone, it has no significant affinity for androgen, estrogen, progesterone, and glucocorticoid receptors. Furthermore, it demonstrates a balanced distribution in the heart and kidneys of mice, in contrast to steroid mineralocorticoid receptor antagonists (MRAs) that are primarily concentrated in renal tissue. [14, 15]

In preclinical studies focusing on cardiorenal injury, finerenone demonstrated protective effects against cardiac remodeling and fibrosis, preserved systolic and diastolic function, mitigated kidney hypertrophy, sclerosis, fibrosis, and proteinuria. [15] The antifibrotic and anti-inflammatory effects of finerenone were superior to those of steroid MRA.

> ARTS – MINERALOCORTICOID RECEPTOR ANTAGONIST TOLERABILITY STUDIES

The MinerAlocorticoid Receptor antagonist Tolerability Study (ARTS) program conducted three phase 2 clinical trials to assess the safety and efficacy of finerenone, comparing it with placebo or spironolactone/eplerenone. [16-18]

The randomized, controlled phase II ARTS trial comprised two parts. In Part A, the safety and tolerability of finerenone were assessed against placebo in 65 patients with heart failure with reduced ejection fraction (HFrEF) and mild CKD (Table I). In Part B, finerenone was compared to placebo or spironolactone in 392 patients with HFrEF and moderate CKD. The safety and tolerability of finerenone were confirmed after the analysis of data from Part A. In Part B, finerenone demonstrated significantly lower increases in serum potassium (0.04 to 0.3 *vs.* 0.45 mmol/L with spironolactone), a lower incidence of hyperkalemia (5.3 *vs.* 12.7% with spironolactone), and a mean variation in estimated glomerular filtration rate (eGFR) of –0.85 to –2.69 *vs.* –6.70 mL/min/1.73 m² with spironolactone over the trial duration." [16]

The randomized, double-blind, placebo-controlled ARTS-Diabetic Nephropathy (ARTS-DN) trial investiga-

Table I - Phase II MinerAlocorticoid Receptor antagonist Tolerability Studies (ARTS).

	ARTS[17]	ARTS-DN[18]	ARTS-HF[19]
Population	Part A: 65 Pts with HFrEF (≤40%) and mild CKD (eGFR 60 to <90 mL/min/1.73 m²) Part B: 392 Pts with HFrEF and moderate CKD (30 to 60 mL/min/1.73 m²)	823 Pts with T2DM and albuminuria (high [UACR 30 to <300 mg/g] or very high [≥300 mg/g]) receiving at least the minimum recommended dosage of an RAS blocker	1066 Pts with worsening HFrEF (≤40%) and T2DM and/or CKD (eGFR of >30 mL/min/1.73 m² in patients with T2DM and 30-60 mL/min/1.73 m² in patients without T2DM
Study treatments	Part A: Finerenone (2.5, 5 or 10 mg qd) *vs.* Placebo Part B: Finerenone (2.5, 5, or 10 mg q.d., or 5 mg bid) *vs.* Placebo or Spironolactone (25, 50 qd)	Finerenone 1.25, 2.5, 5, 7.5, 10, 15 and 2 mg *vs.* matching placebo	Finerenone 2.5, 5, 7.5, 10 or 15 mg, uptitrated to 5, 10, 15, 20 or 20 mg, respectively, on day 30 *vs.* Eplerenone 25 mg every other day, increased to 25 mg qd on day 30, and to 50 mg qd on day 60
Primary endpoint	Part B: Change in serum potassium	Ratio of UACR at day 90 *vs.* at baseline	Percentage of individuals with a decrease of >30% in plasma NT-proBNP from baseline to day 90
Duration	29±2 days	90 days	90 days

bid: Twice daily; CKD: Chronic kidney disease; T2DM: Type 2 diabetes mellitus; eGFR: estimated glomerular filtration rate; HFrEF: Heart failure with reduced ejection fraction; Pts: Patients; qd: Once daily; RAS: Renin-angiotensin system; UACR: Urinary albumin-to-creatinine ratio.

ted the efficacy and safety of finerenone in 823 patients with T2DM and albuminuria who were receiving either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker (Table I). [17] The group treated with finerenone showed a 21 to 38% reduction in urinary albumin-to-creatinine ratio (UACR) relative to placebo (p = 0.004 to < 0.001). Hyperkalemia leading to discontinuation was not observed in the finerenone 10 mg and placebo groups. However, it occurred in the range of 1.7% to 3.2% in the finerenone 7.5, 15, and 20 mg groups. No significant differences were observed in the incidences of eGFR decrease ≥ 30%, adverse events, and serious adverse events between the finerenone and placebo groups.

The ARTS-Heart Failure (ARTS-HF) trial, a randomized, double-blind study, assessed the efficacy and safety of finerenone compared to eplerenone in 1066 patients with worsening chronic heart failure with reduced ejection fraction (HFrEF). These patients required hospitalization and treatment with intravenous diuretics and had comorbidities such as T2DM and/or CKD (Table I). The exploratory combined endpoint, encompassing death from any cause, cardiovascular hospitalization, or emergency presentation for worsening heart failure, occurred less frequently in all patient groups receiving finerenone greater than 5mg versus eplerenone. The incidence of hyperkalemia (≥ 5.6 mmol/L) was 4.3%, with a balanced distribution among all groups. [18]

> CARDIOVASCULAR AND KIDNEY OUTCOMES OF FINERENONE IN TYPE 2 DIABETES MELLITUS

The phase III outcome trial program for finerenone comprises two twin studies designed to assess its impact on kidney endpoints (FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease - FIDELIO-DKD) [19] and cardiovascular endpoints (FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease – FIGARO-DKD) [20] in patients with T2DM and DKD.

> FIDELIO-DKD

The FIDELIO-DKD trial is a phase 3 study designed to address the substantial cardiovascular and renal risks associated with T2DM and CKD. The trial focused on patients with UACR ratio of 30-300 and an estimated glomerular filtration rate (eGFR) of 25-60ml/min/1.73m², and diabetic retinopathy, or UACR of 300-5000 and an eGFR of 25-75 ml/min/1.73m². All patients received renin–angiotensin system blockade, adjusted to the maximum tolerable dose. Finerenone was evaluated for its impact on kidney outcomes, including a composite of kidney failure, sustained decrease in eGFR, or death from renal causes assessed in a time-to-event analysis. There was also a key secondary outcome of a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Results from the FIDELIO-DKD trial demonstrated that finerenone significantly improved kid-

ney outcomes in the study population. Patients receiving finerenone experienced a lower risk of the primary composite outcome compared to those receiving a placebo (hazard ratio, 0.82; CI, 0.73 to 0.93; P = 0.001). Finerenone also lowered the risk of a key secondary outcomes suggesting that in patients with CKD and T2DM, finerenone may confer kidney and cardiovascular protection (Table II). [20]

In a subanalysis of the FIDELIO-DKD trial, examining the impact of concurrent use of sodium-glucose cotransporter-2 inhibitor (SGLT-2i) on the efficacy of finerenone, it was found that among the 4.6% of patients receiving an SGLT-2i at baseline, finerenone significantly reduced UACR from baseline to month 4 with a 25% reduction versus placebo. Also the efficacy of finerenone compared with placebo was consistent for the primary composite kidney outcome and secondary composite CV outcome irrespectively of SGLT-2i use. These findings point that finerenone's benefits may extend to patients with CKD and T2DM who are already on SGLT-2i therapy. [21]

> FIGARO-DKD

The FIGARO-DKD trial included patients with moderately elevated albuminuria (UACR of 30-300) and stage 2 to 4 CKD or severely elevated albuminuria (UACR of 300 to 5000) and stage 1 or 2 CKD. The primary outcome comprised a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, compared to those in the placebo group. Patients assigned to the finerenone group had a significantly lower risk of the primary composite outcome (hazard ratio, 0.87; 95% confidence interval [CI], 0.76 to 0.98; P = 0.03). The reduction in the primary outcome was mainly driven by a lower incidence of hospitalization for heart failure in the finerenone group. Additionally, finerenone consistently reduced the primary outcome across various patient subgroups. The incidence of hyperkalemia-related discontinuation of the trial regimen was as low as 1.2% (Table II). [20]

It should be noted that the trial excluded patients with HFrEF and NYHA class II–IV. Nevertheless, patients with

Table II - Phase III cardiovascular and kidney outcomes trials with finerenone.

	FIDELIO-DKD[20]		FIGARO-DKD[21]	
Population	5734 Pts with T2DM and 1) UACR of 30 to <300 + eGFR of 25 to <60 mL/min/1.73 m² or 2) UACR of 300 to 5000 mg/g + eGFR of 25 to <75 ml/min/1.73 m²		7437 Pts with T2DM and 1) UACR of 30 to <300 + eGFR of 25 to <90 mL/min/1.73 m² or 2) UACR of 300 to 5000 mg/g + eGFR of ³60 ml/min/1.73 m²	
Study treatments	eGFR of 25 to <60: Finerenone 10 20 mg qd eGFR ³60 ml/min/1.73 m²: Finerenone 20 mg qd or matching placebo		eGFR of 25 to <60: Finerenone 10 20 mg qd eGFR ³60 ml/min/1.73 m²: Finerenone 20 mg qd or matching placebo	
Primary endpoint	Composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline over a period of at least 4 weeks, or death from renal causes		Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure	
Duration, median, years	2.6		3.4	
Age, mean, years	65.6		64.1	
Male sex, %	70.2		69.4	
Glycated hemoglobin, mean, %	7.7		7.7	
eGFR, mean, ml/min/1.73	44.3		67.8	
UACR, median, mg/g	852		308	
Number of Pts	5732		7347	
	Finerenone	Placebo	Finerenone	Placebo
Primary endpoint events	504 (17.8%)	600 (21,1%)	458 (12.4%)	519 (14.2%)
HR for primary endpoint	0.82; [CI] 0.73 to 0.93; P=0.001		0.87; [CI], 0.76 to 0.98; P=0.03	
HK-related discontinuation	2,3	0,9	1,2%	0,4%

T2DM: Type 2 diabetes mellitus; eGFR: estimated glomerular filtration rate; Pts: Patients; qd: Once daily; UACR: Urinary albumin-to-creatinine ratio.

asymptomatic HFrEF, HF with mildly reduced ejection fraction (HFmrEF) or HF with preserved ejection fraction (HFpEF) were eligible for enrollment, constituting 7.8% of the included patients. Notably, in the 92.2% of patients without a previous diagnosis of HF, finerenone lead to a 32% reduction in the risk of incident HF. [22] Importantly, the effects of finerenone on the composite of cardiovascular and renal outcomes, including HF hospitalizations were found to be independent of the patients' previous history of HF.

> FIDELITY

The FIDELITY analysis was a prespecified pooled examination of FIDELIO-DKD and FIGARO-DKD. [23] It involved 13,026 patients with a median follow-up of 3.0 years, confirming a significant reduction in the composite cardiovascular outcome (including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure) with a hazard ratio of 0.86 compared to placebo. Additionally, the composite kidney outcome (involving kidney failure, a sustained > 57% decrease in estimated glomerular filtration rate, or renal death) was significantly lower in the finerenone group (5.5%) compared to placebo (7.1%) with a hazard ratio of 0.77. Once again, safety outcomes were similar between the finerenone and placebo groups. However, hyperkalemia leading to permanent treatment discontinuation was observed more frequently in patients receiving finerenone (1.7%) compared to those on placebo (0.6%). [23]

> PRESENT USE AND RECOMMENDATIONS

As a corollary to the substantial evidence of its efficacy in reducing cardiovascular and kidney events, finerenone has been recognized with a class I, level of evidence A recommendation in reducing the risk of cardiovascular events, kidney failure, and HF hospitalization in patients with T2DM and CKD by the 2023 European Society of Cardiology Guidelines for the management of cardiovascular disease in patients with T2DM, the 2022 ADA/KDIGO consensus report, the 2022 KDIGO Clinical Practice Guideline for T2DM Management in CKD and the 2022 ADA Standards of Medical Care in T2DM. [24-27] Also, an emphasis in finerenone HF prevention properties in patients with diabetes and CKD is enlightened in the 2023 Focused Update of the European society of Cardiology HF guidelines. [28]

Considering this, one may conclude that CKD treatment in patients T2DM, similarly to what happens in HF, is now based on a three-pillar approach encompassing renin–angiotensin system blockade, SGLT-2i and finerenone (Figure 1). As so, a step wise drug introduction approach is suggested, strict diuretic management is advised and renal function and serum potassium levels monitoring are mandatory.

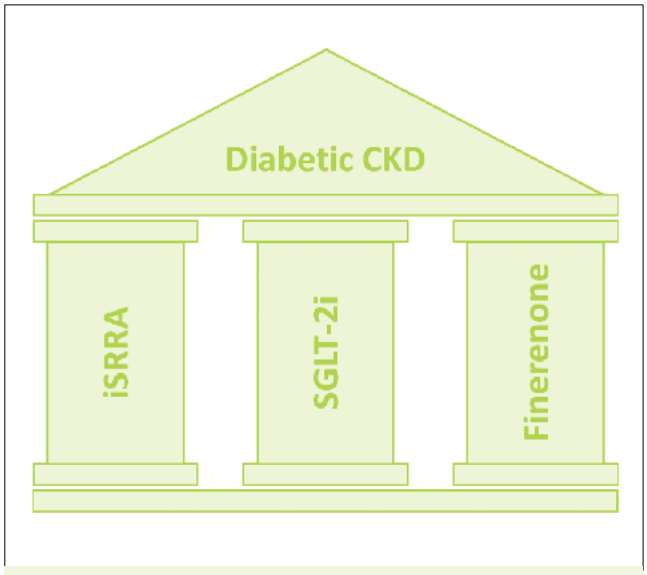

Figure 1 - Pillar approach for Diabetic CKD management.

> FUTURE PROSPECTS

In contrast to its role in CKD due to diabetic kidney disease, evidence for finerenone use in HF is still lacking. The MOONRAKER program aspires to generate valuable evidence in some specific HF scenarios, mainly in patients with HFmrEF or HFpEF or in patients who cannot tolerate spironolactone nor eplerenone. This program will also provide evidence on whether finerenone can potentiate the already established benefits of SGLT-2i in HF – Table 3. <

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Table III - MOONRAKER heart failure clinical trial program. [29]

	FINEHEARTS-HF	REDEFINE-HF	FINALITY-HF
Population	HF (NYHA II-IV) and LVEF ≥ 40%	Hospitalized or recently discharged patients with a decompensated HF and LVEF ≥ 40%	HFrEF patients who are intolerant or ineligible to receive treatment with (sMRA).
Study treatment	FInerenone vs Placebo in addition to SoC	FInerenone vs Placebo in addition to SoC	FInerenone vs Placebo in addition to SoC
Primary endpoint	Composite of CV death and HF events	Composite of first and subsequent HF events and CV death	Time to first occurrence of CV death or HF event.
Recruitment target (number of patients)	5500	5200	2600
Estimated Completion Date	June 2024	April 2026	June 2026

CV - cardiovascular; HF - Heart failure; HFrEF - Heart failure with reduced ejection fraction LVEF - Left ventricle ejection fraction; sMRA- steroidal mineralocorticoid antagonists; SoC - standard of care

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