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Non-Steroidal Mineralocorticoid Receptor Antagonists: A Paradigm Shift in the Management of Diabetic Nephropathy

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Abstract
Background: Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease worldwide. The management of DKD relies on controlling glycemia and blood pressure levels, as well as reducing proteinuria. While the traditional renin-angiotensin-aldosterone system inhibitors (RAASi) and the recently approved type 2 Na^+/glucose co-transporter inhibitors (SGLT2i) have significantly improved patient outcomes, residual risks remain unaddressed. ***Summary:*** This review explores (1) the mechanisms of action of finerenone, a novel non-steroidal mineralocorticoid receptor antagonist (ns-MRA), (2) the evidence of finerenone-induced kidney protection in clinical trials, and (3) the comparative advantages over conventional MRAs. The potential synergy between finerenone and SGLT2i is also addressed, alongside research perspectives and practical considerations for implementation in clinical practice. ***Key Messages:*** Finerenone has emerged as a breakthrough therapy in the management of DKD, demonstrating robust nephro- and cardio-protective effects.

Introduction

Chronic kidney disease (CKD) affects approximately 10% of the population, equating to nearly 700 million people worldwide, with diabetic kidney disease (DKD) accounting for approximately half of these cases. DKD not only contributes to kidney failure but also significantly increases the risk of cardiovascular complications, making it a major public health concern [1]. For decades, the management of DKD has relied on controlling glycemia and blood pressure (BP) levels, as well as reducing proteinuria by therapies targeting the renin-angiotensin-aldosterone system (RAAS). While angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have proven their efficacy, they failed to fully prevent DKD progression. More recently, the advent of type 2 Na^+/Glucose co-transporter inhibitors (SGLT2i) has revolutionized the management of DKD and CKD, offering significant renal and cardiovascular protection improvement in association with RAAS inhibitors (RAASi) [2]. However, residual risks remain unaddressed.

The need for additional therapies targeting inflammatory and fibrotic pathways has driven the development of novel agents, including finerenone [3, 4]. This review summarizes the multifaceted role of finerenone, which has been mostly validated against DKD progression in

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several clinical trials. We also explore the broader implications of finerenone in CKD management and cardiovascular medicine.

Pathophysiological Insights of Finerenone in DKD

Pathophysiology of DKD

DKD is characterized by progressive damage to glomeruli, tubules, and interstitial tissue of the kidney. Chronic hyperglycemia is the central driver of kidney injury, triggering a cascade of oxidative stress, inflammation, and fibrotic remodeling. These processes are mediated by pathways such as the activation of the RAAS, advanced glycation end-product accumulation, and dysregulated immune responses. The mineralocorticoid receptor (MR), a key component of the RAAS, plays a central role in these pathological processes. When activated, MR drives sodium retention, thereby favoring hypertension (HTN) and pro-inflammatory signaling. Over time, this leads to structural and functional deterioration of the kidneys, manifesting as albuminuria and decline of the glomerular filtration rate (GFR). While angiotensin-converting enzyme inhibitors and angiotensin receptor blockers mitigate these effects by reducing angiotensin II activity, they do not directly inhibit MR. This gap has prompted research about MR antagonists (MRAs), which eventually target the final downstream effector of the RAAS [5–7].

Mineralocorticoid Receptor

The MR is a member of the nuclear receptor superfamily, activated by steroid hormones such as aldosterone and, under certain conditions, cortisol and corticosterone. The MR is expressed in many tissues/cell types, including the kidney, heart, immune cells, and fibroblasts [8]. In the kidney, the physiological role of aldosterone is to increase sodium (Na^+) reabsorption and potassium (K^+) excretion. Hence, MR over-activation causes Na^+ retention, HTN, glomerulosclerosis and proteinuria, with renal fibrosis and GFR decline [9] (Fig. 1). In the heart, MR over-activation induces cardiomyocyte hypertrophy, oxidative stress and apoptosis, with progressive cardiac fibrosis [6] (Fig. 1). These pathophysiological considerations highlight the MR as a critical pathogenic mediator of cardiorenal dysfunctions. Therefore, MRAs have been tested in patients with heart and kidney diseases. Historically, this class of drugs was limited to steroid-based agents, like spironolactone and eplerenone, which demonstrated robust clinical efficacy in heart failure (HF) and resistant HTN. Their impact on proteinuria and GFR preservation remains debated. Furthermore, the use of spironolactone or eplerenone in the clinical routine is often limited by significant adverse effects, including hormonal disturbances (with painful gynecomastia in men and dysmenorrhea in women) and hyperkalemia. Consequently, non-steroidal MRAs (ns-MRA) have been recently developed, including finerenone [6, 7].

Mechanisms of Action of Finerenone

Finerenone is a ns-MRA with unique pharmacodynamic and pharmacokinetic properties. The non-steroidal structure of finerenone is related to that of dihydropyridines and influences its interaction with specific amino acids in the MR ligand-binding domain. The physico-chemical properties of finerenone may improve its penetration and distribution in both cardiac and renal tissues. By binding selectively to the MR and blocking the action of aldosterone, finerenone inhibits pro-inflammatory and pro-fibrotic pathways, without the off-target effects observed with steroidal MRAs like spironolactone.

Clinical Trial Evidence of Finerenone in DKD

The first two major trials about finerenone are the FIDELIO-DKD [10] and the FIGARO-DKD [11] trials, which were subsequently fused into the prespecified FIDELITY analysis [12]. More recently, the FINEARTS-HF trial assessed the effects of finerenone in patients with symptomatic HF, 40.5% of whom had type 2 diabetes mellitus (T2DM) [13].

The FIDELIO-DKD Trial (Finerenone in Reducing Kidney Failure and Disease Progression in DKD)

The FIDELIO-DKD trial was the first large-scale study to evaluate the renal benefits of finerenone in patients with T2DM with CKD. This phase III trial enrolled over 5,600 participants, with a median follow-up of 2.6 years. Of important note: all patients were already on optimized RAAS blockade. The primary outcome was a composite of end-stage kidney disease, sustained estimated GFR (eGFR) decline of ≥40%, or renal death. Finerenone significantly reduced the incidence of these events compared to placebo, with a hazard ratio (HR) of 0.82 (p = 0.001). Secondary analyses revealed consistent reduction in albuminuria, a key biomarker of nephroprotection. The frequency of adverse events was similar between finerenone and placebo, except for the incidence of hyperkalemia-related discontinuation of the trial regimen, which was higher in the finerenone-exposed group (2.3% and 0.9%, respectively) [10, 14].

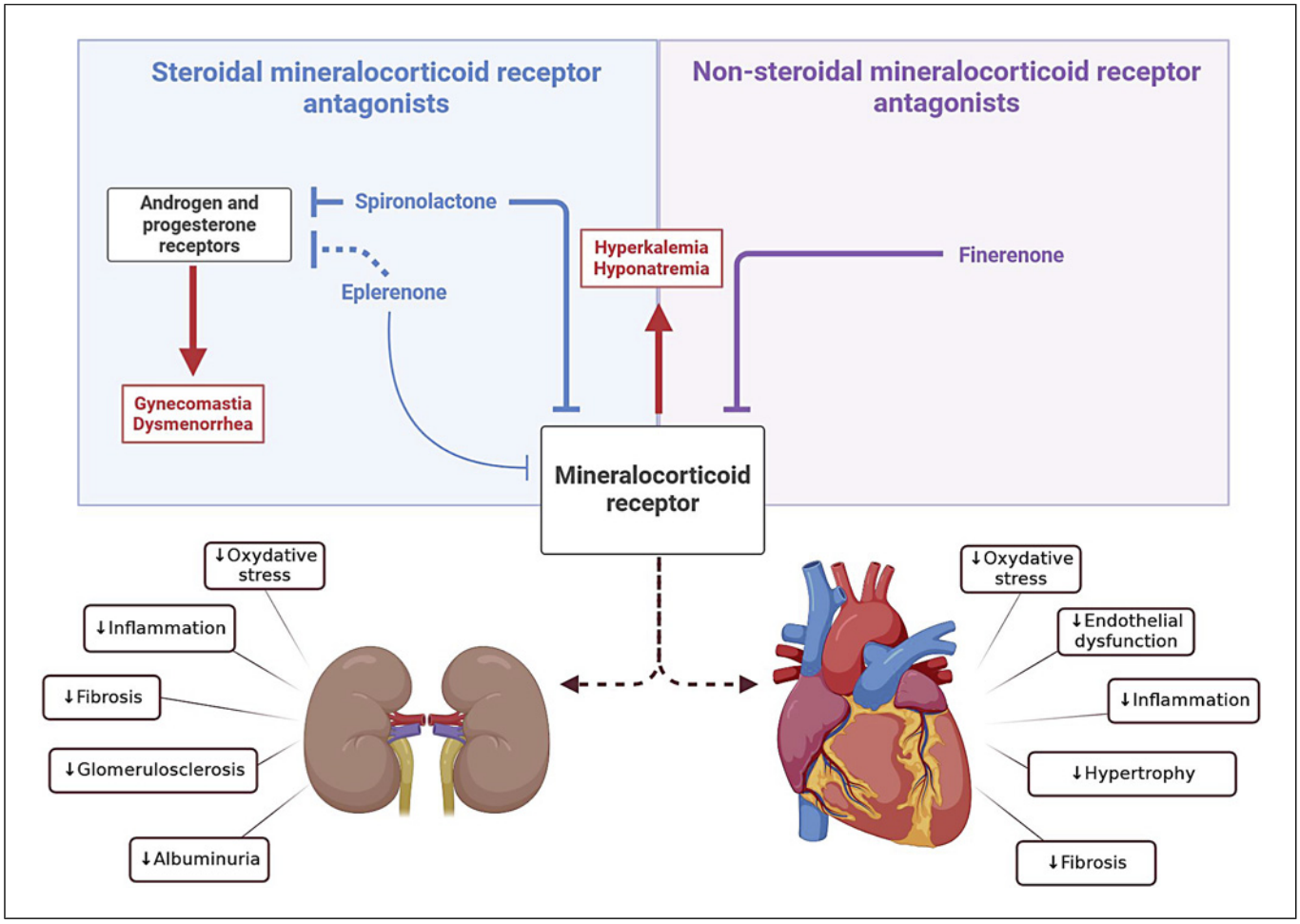

Fig. 1. Putative mechanisms of renal and cardiovascular protective effects of mineralocorticoid receptor antagonists (MRAs). Adapted from Girerd et al. [7].

The FIGARO-DKD Trial (Finerenone in Reducing Cardiovascular Mortality and Morbidity in DKD)

The FIGARO-DKD trial focused on cardiovascular outcomes in 7,437 patients with both CKD and T2DM. After a median follow-up of 3.4 years, finerenone reduced the risk of major adverse cardiovascular events, including myocardial infarction, stroke, and HF hospitalization compared to placebo with a HR of 0.87 (p = 0.03). The benefit was mainly driven by a lower incidence of hospitalization for HF. Importantly, these benefits were observed across diverse subgroups, including patients with and without pre-existing HF. This highlights finerenone potential to address the cardiorenal continuum – a critical consideration in DKD. As for the FIDELIO-DKD trial, the overall frequency of adverse events did not differ substantially between groups, except for the higher incidence of hyperkalemia-related discontinuation of the trial regimen in the finerenone-exposed group (1.2%) compared to placebo (0.4%) [11, 14].

The FIDELITY Analysis (the Finerenone in CKD and T2DM: Combined FIDELIO-DKD and FIGARO-DKD Trial Programme Analysis)

Since the populations in both the FIDELIO-DKD and FIGARO-DKD trials were relatively similar and had complementary primary and secondary endpoints, a combined prespecified analysis was conducted under the acronym FIDELITY [12]. Overall, the cardiovascular composite outcome occurred in 12.7% of patients receiving finerenone and 14.4% of patients receiving placebo (HR: 0.86; p = 0.0018). Similarly, the renal composite outcome was observed in 5.5% of patients on finerenone and 7.1% of patients on placebo (HR: 0.77; p = 0.0002).

These findings confirm that finerenone is an effective complementary option to standard baseline therapy (including RAASi) for cardiorenal protection in individuals with T2DM and moderate-to-severe CKD. The incidence of treatment-emergent adverse events was similar between the finerenone and placebo groups. Hyperkalemia-related adverse events were more frequent with finerenone (14.0% vs. 6.9%), but these events were not fatal and rarely led to treatment discontinuation or hospitalization. Other adverse events, such as hypokalemia, renal-related adverse events, including acute kidney injury, and gynecomastia, occurred infrequently in both groups [4, 12].

The FINEARTS-HF Trial (Finerenone and Nutrition Evaluation in HF and Renal Function Study-HF)

The FINEARTS-HF trial was recently published and focused on the effects of finerenone in over 6,000 patients with symptomatic HF with a preserved or mildly reduced ejection fraction (HFpEF or HFmrEF). T2DM was present in 40.5% of the cohort. After a median follow-up of 32 months, finerenone significantly reduced the primary composite outcome of cardiovascular mortality and HF-related events (worsening or urgent hospitalization) compared to placebo (HR: 0.84; $p = 0.007$). No significant effect was observed on renal outcomes, most likely due to the population's preserved kidney function (mean eGFR 61.9 ± 19.4 mL/min/1.73 m^2 in the finerenone group *versus* 62.3 ± 20 mL/min/1.73 m^2 in the placebo group at baseline). Hyperkalemia was more frequent with finerenone compared to placebo (17% vs. 8%) [4, 13].

The FINE-HEART Pooled Analysis (Finerenone in HF and CKD with T2DM: FINE-HEART Pooled Analysis of Cardiovascular, Kidney, and Mortality Outcomes)

A recent pooled analysis of data from FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF, known as FINE-HEART, included 18,991 participants with a median follow-up of 2.9 years. The primary outcome, i.e., cardiovascular mortality, occurred in 421 (4.4%) patients receiving finerenone and 471 (5.0%) patients on placebo (HR: 0.89; $p = 0.076$). All-cause mortality was significantly reduced in the finerenone group (1,042 deaths, 11.0%) compared to placebo (1,136 deaths, 12.0%) (HR: 0.91; $p = 0.027$). Finerenone also significantly lowered the composite renal endpoint (sustained reduction in eGFR by at least 50%, eGFR <15 mL/min/1.73 m^2, end-stage kidney disease, or renal death) (HR: 0.80; $p < 0.001$). While the reduction in cardiovascular mortality did not reach statistical significance, the FINE-HEART pooled analysis further demonstrated the benefits of finerenone across the other major cardiovascular and renal outcomes [15].

Comparison of Finerenone with the Traditional Steroid-Based MRAs

Steroidal MRAs, like spironolactone and eplerenone, have been used for many years in various conditions, including HF and resistant HTN. Spironolactone has demonstrated significant nephro-protective effects in various clinical and experimental studies [16–18], except in the SPIREN trial focusing on kidney transplant recipients [19]. Spironolactone effectively lowers proteinuria when added to standard RAASi, without substantial impacts on BP in normotensive patients. However, spironolactone is a non-selective MRA, which also interacts with androgen and progesterone receptors, causing gynecomastia and dysmenorrhea, respectively. Moreover, concerns over hyperkalemia have tempered the widespread use of spironolactone, particularly in individuals with advanced CKD or those at high risk for electrolyte imbalances [6, 8, 20]. By contrast, spironolactone remains the recommended fourth-line agent for the treatment of resistant HTN in patients with an eGFR above 30 mL/min/1.73 m^2, as outlined in the 2023 European Society of Hypertension [21] and 2024 European Society of Cardiology [22] guidelines.

Spironolactone and eplerenone are both steroidal MRAs, but they differ in receptor selectivity and side effect profiles (Table 1). Eplerenone is more MR-selective than spironolactone, resulting in fewer hormonal side effects. However, eplerenone is generally considered less potent in reducing proteinuria and aldosterone-induced fibrosis. Both agents carry a risk of hyperkalemia, but this risk is slightly lower with eplerenone due to its shorter half-life and milder potassium-sparing effects. Consequently, eplerenone may be preferred for patients requiring long-term therapy with fewer endocrine side effects, while spironolactone remains a potent option in settings where its tolerability can be managed [6].

Finerenone offers a safer and more targeted alternative to steroidal MRA mainly because of its non-steroidal structure and its higher MR specificity. The risk of hyperkalemia associated with finerenone is currently considered "manageable." Real-life studies will provide more insight into drug-induced hyperkalemia since clinical trials only selected patients with baseline potassium ≤4.8 mmol/L [14]. The better tissue distribution of finerenone between heart and kidney, which contrasts with the predominant renal accumulation of eplerenone and spironolactone, may explain

Table 1. Steroidal and ns-MRAs

	Spironolactone	Eplerenone	Finerenone	Esaxerenone	Apararenone	Ocedurenone (KBP-5074)	Balcinrenone (AZD9977)
Structural properties	Steroidal	Steroidal	Non-steroidal	Non-steroidal	Non-steroidal	Non-steroidal	Non-steroidal MR modulator
Selectivity to MR	+	++	+++	+++	+++	+++	++
Potency to MR	+++	+	+++	+++	++	++	++
Hormonal side effects	+++	+	–	–	–	–	–
Effect on BP	+++	++	–	+++	++	++	++
Hyperkalemia	+++	++	+	++	+	+	+
Indications	HTN, HF, primary aldosteronism, cirrhosis	In replacement of spironolactone when the patient is intolerant	2024: DKD	HTN (approved in Japan)	Ongoing trials in DKD and HF	Further trials still needed	Further trials still needed

MR, mineralocorticoid receptor; HTN, hypertension; CKD, chronic kidney disease; DKD, diabetic kidney disease; HFpEF, heart failure with preserved ejection fraction. Adapted from Kintscher et al. [6].

the robust cardioprotection observed with finerenone. An additional explanation for the enhanced antifibrotic effects of finerenone lies in its unique binding behavior to the MR, which facilitates the selective recruitment of MR cofactors and the modulation of target genes [23]. This specific mechanism allows finerenone to suppress pro-fibrotic genes more effectively than eplerenone or spironolactone, resulting in a significantly stronger antifibrotic effect in the left ventricle [6]. Finerenone has also shown more potent anti-inflammatory and antifibrotic effects on the kidney in rodent models than eplerenone [8]. However, studies have shown that finerenone does not have a significant effect on BP in patients with CKD or HF, particularly when compared to spironolactone or eplerenone. This lack of a pronounced BP-lowering effect differentiates finerenone from other agents that target the RAAS [10, 11] (Table 1). Direct long-term comparisons between finerenone and spironolactone or eplerenone in patients are unfortunately unlikely to be conducted.

Synergy between Finerenone and SGLT2iisglt2i

The development and FDA/EMA approval of SGLT2i has transformed the management of DKD. These agents reduce intra-glomerular pressure, improve glycemic control, and attenuate inflammation, thereby offering robust nephroprotection. Finerenone and SGLT2i may have complementary effects. Indeed, while SGLT2i primarily targets hemodynamic and metabolic pathways, finerenone addresses inflammatory and fibrotic mechanisms. Combining these therapies could provide additive benefits, as indicated by subgroup analyses from the FIDELIO-DKD and FIGARO-DKD trials [24, 25]. Furthermore, SGLT2i favors K^+ urinary loss, which may facilitate the management of MRA-induced hyperkalemia, as found with eplerenone in the ROTATE3 study [26]. When comparing patients with or without SGLT2i use at baseline in FIDELIO-DKD, fewer hyperkalemia events were found with finerenone in the SGLT2i group (8.1%) compared to patients non-exposed to SGLT2i (18.7%) [25]. In the FIDELITY analysis, patients treated with SGLT2i at baseline showed a lower incidence of hyperkalemia than those without SGLT2i at baseline (10.3% vs. 14.3%, respectively) [24]. Ongoing studies are exploring this combination [9, 22, 25, 26]. Of important reminder, patients recruited in the finerenone clinical trials were all on optimized RAAS blockade.

International Guidelines about the Use of Finerenone in Patients with T2DM

Given the positive results regarding the cardiorenal protection of finerenone in T2DM patients with CKD, the 2022 KDIGO nephrology guidelines recommend adding a ns-

MRA like finerenone to RAASi in high-risk T2DM patients with CKD progression and cardiovascular complications, particularly those with microalbuminuria >30 mg/g creatinine [27]. In cardiology, the 2023 ESC guidelines recommend finerenone for T2DM patients with CKD, in combination with a RAASi [28]. In diabetology, American and European scientific societies have similarly placed finerenone at the forefront of cardiorenal protection, as part of their 2022 guidelines [4, 29].

Implementing finerenone in clinical practice requires careful patient selection and monitoring. Its safety profile necessitates regular assessment of serum K^+ levels, particularly in patients with advanced CKD or concomitant RAAS blockade. The combination of finerenone with a SGLT2i or potassium-binders may help better control the potential hyperkalemia [14]. Dosing recommendations for finerenone are based on the patient's eGFR: patients with eGFR ≤60 mL/min/1.73 m^2 should start with a lower dose of 10 mg, which can be titrated to 20 mg based on potassium tolerance. This tailored approach minimizes the risk of hyperkalemia while maximizing therapeutic efficacy. The introduction of finerenone is generally recommended in patients with eGFR ≥25 mL/min/1.73 m^2 and finerenone should be discontinued if the eGFR falls below 15 mL/min/1.73 m^2 as there is limited evidence regarding its safety and efficacy in this severe stage of kidney dysfunction [27]. Treatment suspension during dehydration, sepsis, or major surgery should be recommended, as for RAASi and SGLT2i [14].

It is also important to note that adding finerenone to the standard of care for patients with T2DM and CKD has been demonstrated to improve quality-adjusted life years and cost-effectiveness (based on studies conducted in the USA, the Netherlands, and the UK). This approach offers significant health benefits while remaining economically viable across these countries [30–32].

Future Directions about the Use of Finerenone

While current evidence mostly supports the benefits of finerenone in patients with T2DM, its potential applications in non-diabetic CKD and HF warrant further exploration. Ongoing trials are investigating its efficacy in these populations, as well as its role in combination regimens with SGLT2i and other emerging therapies. Additionally, real-world studies will be crucial in validating the findings of clinical trials and addressing gaps in knowledge, such as the long-term impact of finerenone on quality of life and healthcare utilization [6].

The CONFIDENCE study includes individuals with T2DM and CKD who are already being treated with SGLT2i. The study consists of 3 arms: one with empagliflozin alone; another one with finerenone alone; and a third one combining both drugs for at least 6 months. The primary outcome is a relative change from baseline in albuminuria among the three groups. Secondary outcomes will further characterize efficacy and safety, including changes in eGFR and incident hyperkalemia [4, 33]. The first results are expected in 2025 [34].

The FINE-REAL study is an international, non-interventional "real-world" study that reports a wide range of clinical and biological data from patients receiving finerenone in routine medical practice. The effectiveness and safety of finerenone are the primary outcomes examined in this study [35]. Preliminary results were recently reported from the American cohort: after a median follow-up of 7 months, 93.3% of the 504 participants were on uninterrupted finerenone therapy. Hyperkalemia was observed in 5% of patients, but none of the cases were considered severe enough to require urgent intervention [4, 36].

The extensive MOONRAKER program investigates the utility of finerenone in over 15,000 patients with HF. It includes several complementary studies to the previously mentioned FINEARTS-HF trial [13]: REDEFINE-HF will collect data on hospitalizations in patients with HF and an ejection fraction of ≥40% (similar to FINEARTS-HF but in a real-world settings). FINALITY-HF will provide results in patients with HF who have not previously received a MRA, while CONFIRMATION-HF will focus on hospitalizations in patients with HF (regardless of the ejection fraction) already treated by SGLT2i, making it a complementary study to CONFIDENCE (with a focus on HF rather than CKD) [4, 37].

The FIND-CKD study aims to evaluate the efficacy and safety of finerenone in adults with CKD of non-diabetic origin. This Phase 3 trial investigates its impact on kidney function decline and cardiorenal outcomes compared to a placebo, focusing on patients receiving maximum tolerated doses of RAASi [38].

Finally, the FIONA study focuses on children with CKD and proteinuria [39] and FINE-ONE investigates the use of finerenone in patients with type 1 DM with CKD [40]. Depending on the results, the use of finerenone may expand to non-diabetic CKD and/or HF populations with T2DM.

Emerging ns-MRAs

While finerenone has received significant attention as a pioneering ns-MRA [10, 11], other agents in this class are under development. Some of these "new" ns-MRAs seem

to have a significant impact on BP contrasting with finerenone, which could represent an alternative to spironolactone or eplerenone in resistant HTN, frequently associated with CKD [6]. Esaxerenone has been approved in Japan for the treatment of HTN and is being studied for its potential nephro-protective effects in CKD. This agent has demonstrated efficacy in reducing proteinuria in T2DM and BP in hypertensive patients with a tolerable safety profile [6, 41–43]. Apararenone is currently undergoing clinical trials for DKD and HF [6, 44]. Ocedurenone (or KBP-5074) has demonstrated efficacy in reducing systolic BP (with an insignificant trend for albuminuria), even in patients with advanced CKD but the phase III CLARION-CKD conducted in patients with uncontrolled HTN and advanced CKD was terminated early because it met the prespecified futility criteria [6, 45]. Balcinrenone (or AZD9977), a MR modulator studied in patients with HF and renal impairment, showed a favorable safety profile in phase 1b but did not demonstrate significant albuminuria reduction when combined with dapagliflozin in the phase 2b MIRACLE trial. Based on these observations (limited to a small sample size), early study termination was decided [6, 43, 46–48].

Conclusion

ns-MRAs, particularly finerenone, represent a paradigm shift in the management of patients with T2DM, offering a novel approach to cardiorenal protection by anti-inflammatory and antifibrotic properties. It has a rather favorable safety profile on top of RAASi and its potential synergy with SGLT2i position finerenone at the cornerstone of future CKD and HF treatment strategies.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.H. and F.J.: review of the literature and writing of the manuscript.

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