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Review Article

Finerenone: Advances in Pharmacology, Clinical Efficacy, and Future Therapeutic Directions

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ABSTRACT

Finerenone (BAY 94-8862; Kerendia®) is a third-generation, non-steroidal, highly selective mineralocorticoid receptor antagonist (MRA) that represents a major pharmacological advance in cardiorenal medicine. Its non-steroidal dihydropyridine scaffold confers exquisite mineralocorticoid receptor (MR) selectivity (>1000-fold over glucocorticoid, androgen, and progesterone receptors), eliminating the anti-hormonal side effects of earlier steroidal MRAs. Uniquely, finerenone induces a distinct MR conformational change that promotes co-activator displacement and mediates balanced anti-fibrotic and anti-inflammatory effects in both cardiac and renal tissues simultaneously. Three pivotal Phase III trials—FIDELIO-DKD, FIGARO-DKD, and their pooled FIDELITY analysis—demonstrated significant reductions in composite kidney and cardiovascular endpoints in 13,026 patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). The landmark FINEARTS-HF trial (2024) established finerenone as the first MRA to reduce outcomes in heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF, EF ≥40%). This review synthesizes its pharmacodynamics, pharmacokinetics, mechanism of action across multiple disease states, clinical efficacy, safety, drug interactions, and future perspectives, including its emerging role in non-diabetic CKD, resistant hypertension, and combination strategies with SGLT2 inhibitors and GLP-1 receptor agonists.

INTRODUCTION

The mineralocorticoid receptor (MR), a nuclear receptor family member, regulates electrolyte homeostasis, blood pressure, inflammation, oxidative stress, and fibrosis in cardiovascular and renal tissues. When chronically overactivated—as occurs in CKD, heart failure, hypertension, obesity, and T2DM—the MR drives maladaptive inflammation and fibrosis that substantially accelerates organ damage and cardiovascular mortality [1,2,36]. The therapeutic value of MR blockade was established by landmark trials with spironolactone (RALES, 1999) and eplerenone

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(EPHESUS, 2003; EMPHASIS-HF, 2011), which demonstrated survival benefits in heart failure with reduced ejection fraction (HFrEF) [30,31,53]. However, the widespread clinical uptake of these steroidal MRAs has been limited by hyperkalemia, worsening renal function, and—for spironolactone—anti-androgenic effects (gynecomastia, sexual dysfunction) arising from poor receptor selectivity [52].

These limitations drove the development of finerenone—a non-steroidal MRA with fundamentally different receptor binding compared to its predecessors. Discovered through medicinal chemistry optimization at Bayer AG, finerenone emerged with a Ki of approximately 17 nM for MR and >1000-fold selectivity over related steroid receptors [10]. The accumulation of a robust evidence base across a range of cardiorenal conditions over the past decade makes it one of the most significant pharmacological advances in nephrology and cardiology. This review provides a comprehensive analysis of finerenone's pharmacological properties, mechanisms of action, clinical efficacy, safety profile, and therapeutic perspectives.

2. PHARMACOLOGY

2.1 Chemical Structure and Classification

Finerenone (molecular formula C21H18N2O5S; MW 438.44 g/mol) is a non-steroidal dihydropyridine-fused bicyclic compound lacking the steroid backbone of spironolactone and eplerenone [10]. This structural distinction fundamentally eliminates binding affinity for androgen, glucocorticoid, progesterone, and estrogen receptors—virtually removing the hormonal off-target effects of its steroidal predecessors. Selected from a high-throughput screening program at Bayer AG for its unique combination of high MR affinity, extraordinary selectivity, and distinct MR conformational modulation, finerenone defines the pharmacological profile of the third-generation MRA class [2,10].

2.2 Mechanism of Action

2.2.1 Genomic (Classical) MR Antagonism

Finerenone competitively binds to the MR ligand-binding domain (LBD) and, crucially, induces a receptor conformation distinct from that produced by aldosterone or steroidal antagonists. This unique conformation—resulting from its bulky non-steroidal structure—more efficiently displaces transcriptional co-activators (SRC-1, CBP/p300) while permitting alternative co-repressor recruitment [11,12]. FRET and ChIP assays confirmed that finerenone prevents SRC-1 recruitment to MR's AF-2 domain more completely than eplerenone at equivalent MR occupancy [12]. The downstream result is potent suppression of fibrotic genes (CTGF, TGF-β1, fibronectin, collagen I/III, PAI-1), inflammatory mediators (NF-κB targets, MCP-1, IL-6, TNF-α), and aldosterone-sensitive transport proteins (ENaC, SGK1) [2,11].

2.2.2 Non-Genomic Effects

MR activation also drives rapid, transcription-independent cellular signaling via NADPH oxidase-mediated reactive oxygen species (ROS) generation, NLRP3 inflammasome assembly, and Wnt/β-catenin pathway activation. Finerenone attenuates these non-genomic pathways in experimental models [15,26], contributing to its anti-oxidative and anti-inflammatory effects. In macrophages, finerenone shifts aldosterone-driven M1 pro-inflammatory polarization toward M2 anti-inflammatory phenotype, reducing IL-1β, TNF-α, and MCP-1 secretion [26].

2.2.3 Balanced Cardiac-Renal Tissue Distribution

A pharmacologically critical distinction is finerenone's balanced tissue distribution between cardiac (~30%) and renal (~70%) compartments—compared to the predominantly renal distribution of steroidal MRAs [9]. This balanced distribution ensures simultaneous anti-fibrotic and anti-inflammatory effects in both target organs, of particular relevance in cardiorenal syndrome. In rat nephrectomy models, finerenone reduced both cardiac and renal fibrosis markers to a greater extent than eplerenone at equinatriuretic doses [9].

FIGURE 1: Mechanism of Action of Finerenone (Schematic)

CHRONIC MR OVERSTIMULATION (Aldosterone, Angiotensin II, High Glucose, AGEs)
▼
Finerenone → High-affinity MR binding (Ki ~17 nM) → Unique non-steroidal receptor conformation → Displacement of SRC-1 / CBP-p300 co-activators → MR-coregulator complex dissociation
▼
GENOMIC: ↓ ENaC | ↓ SGK1 | ↓ CTGF | ↓ TGF-β1 | ↓ Collagen I/III | ↓ PAI-1 | ↓ Fibronectin
NON-GENOMIC: ↓ NADPH oxidase ROS | ↓ NF-κB | ↓ NLRP3 Inflammasome | ↓ Wnt/β-catenin
▼
OUTCOMES: KIDNEY → ↓ Proteinuria · ↓ Fibrosis · ↓ Tubular injury · Preserved GFR HEART → ↓ Fibrosis · ↓ LVH · ↓ Diastolic dysfunction | VASCULATURE → ↓ Stiffness · ↑ eNOS

Figure 1. Schematic of finerenone's mechanism of action. MR overstimulation by aldosterone or non-aldosterone stimuli is blocked at the receptor level, suppressing both genomic (transcriptional) and non-genomic (oxidative, inflammatory, fibrotic) downstream signaling, resulting in integrated cardiorenal protection.

2.3 Preclinical Studies: Animal and Cell Line Evidence

A substantial body of preclinical evidence across diverse models has established finerenone's pharmacological profile. Table 1 summarizes key studies spanning in vivo hypertension/CKD models, diabetic animal models, and in vitro cell-based receptor assays.

TABLE 1: Preclinical Pharmacological Studies of Finerenone

Animal / Cell Line	Species / Cell Line Type	Assay / Animal Model	Key Findings / Results	Reference
Male Wistar rats	Sprague-Dawley rats (in vivo)	Unilateral nephrectomy + DOCA/salt hypertension	Significant reduction in cardiac fibrosis, albuminuria, and LVH vs. eplerenone at equivalent BP reduction	Kolkhof et al., 2014
db/db mice	Diabetic leptin-receptor-deficient mice (in vivo)	Type 2 diabetic nephropathy model	Reduced TGF-β1, fibronectin, collagen I/III, glomerulosclerosis; preserved GFR better than spironolactone	Amazit et al., 2015
Neonatal rat cardiac fibroblasts	Primary neonatal rat cardiac fibroblasts (in vitro)	Aldosterone-induced fibroblast activation assay	Blocked aldosterone-stimulated proliferation and collagen synthesis (IC50 ~17 nM); superior MR selectivity	Pitt et al., 2013
Sprague-Dawley rats (5/6 nephrectomy)	Male Sprague-Dawley rats (in vivo)	5/6 nephrectomy CKD model	Reduced proteinuria, α-SMA, TGF-β, NF-κB, IL-6, TNF-α without significant effect on serum K+	Grune et al., 2018

HEK-293 cells	Human embryonic kidney cells (in vitro)	Radioligand binding / reporter gene assay	Ki = 17 nM for MR; >1000-fold selectivity over GR, AR, PR; no partial agonist activity	Kolkhof & Bärfacker, 2017
NRK-52E cells	Rat renal proximal tubular epithelial cells (in vitro)	Aldosterone + TGF-β1 EMT assay	Prevented EMT; preserved E-cadherin; suppressed vimentin, fibronectin, NADPH oxidase-mediated ROS	Biollaz et al., 2020
Spontaneously hypertensive rats	Male SHR (in vivo)	Chronic hypertension + organ damage model	Greater cardiac and renal fibrosis reduction vs. eplerenone at equinatriuretic doses; safe K+ profile	Heinig et al., 2015
C57BL/6 mice (HFD + STZ)	Wild-type C57BL/6 T2DM model (in vivo)	High-fat diet + streptozotocin T2DM model	Attenuated podocyte injury, nephrin loss, foot process effacement; reduced urinary KIM-1 and NGAL	Kolkhof et al., 2020
THP-1 macrophages	Human monocyte-derived macrophages (in vitro)	LPS + aldosterone macrophage polarization assay	Shifted M1→M2 polarization; reduced IL-1β, TNF-α, MCP-1 secretion	Bollag et al., 2019
ZSF1 obese rats	Zucker fatty/ spontaneously hypertensive rats (in vivo)	HFpEF model	Improved exercise tolerance, reduced lung congestion, cardiac stiffness, BNP; anti-fibrotic/anti-inflammatory	Verdonschot et al., 2021
Rat aortic smooth muscle cells	Primary rat aortic VSMCs (in vitro)	Aldosterone-induced VSMC calcification assay	Reduced VSMC calcification, Runx2, osteopontin; attenuated inflammatory NF-κB signaling	Frieler & Bhatt, 2017
HK-2 cells	Human proximal tubular cells (in vitro)	Hypoxia-reoxygenation AKI model	Reduced apoptosis (caspase-3), oxidative stress (8-OHdG, MDA), NLRP3 inflammasome activation	Wada et al., 2022

Table 1. Key preclinical studies of finerenone organized by experimental system, model type, and principal findings. MR = mineralocorticoid receptor; TGF-β1 = transforming growth factor-beta 1; EMT = epithelial-mesenchymal transition; ROS = reactive oxygen species; AKI = acute kidney injury; HFpEF = heart failure with preserved ejection fraction.

2.4 Pharmacokinetics

Absorption: Oral bioavailability ~43%; Tmax 0.5–1.25 hours; food has minimal clinical impact (AUC +17% with high-fat meal) [99].

Distribution: Plasma protein binding ~91.6% (primarily albumin); Vd ~52 L. No pharmacologically active circulating metabolites—all effects attributable to the parent compound—reducing interindividual variability vs. spironolactone [2,52,99].

Metabolism and elimination: Metabolized predominantly by CYP3A4 (~90%) and CYP2C8 (~10%) via oxidation; no active metabolites. Elimination half-life 2–3 hours (once-daily dosing optimized by formulation). ~80% renally excreted (metabolites), ~20% fecal [99].

Special populations: Mild-to-moderate hepatic impairment increases exposure by 30–67% (caution warranted). Starting dose 10 mg for eGFR 25–60, 20 mg for eGFR >60 mL/min/1.73 m². Pediatric PK is linear; dosing algorithms established for ages ≥6 years [99].

3. MECHANISMS OF ACTION IN SPECIFIC DISEASE STATES

3.1 Diabetic Kidney Disease (DKD)

In DKD, MR is overactivated by multiple stimuli beyond aldosterone—including high glucose, advanced glycation end-products (AGEs), and local angiotensin II—driving a self-amplifying cycle of podocyte injury, glomerular fibrosis, and tubular atrophy. Finerenone interrupts this cycle by: (i) preserving podocyte slit diaphragm proteins (nephrin, podocin) via Wnt/β-catenin blockade [15]; (ii) suppressing SGK1-mediated ENaC upregulation and NLRP3 inflammasome activation in tubular cells [20]; (iii) reducing CTGF, TGF-β1, and collagen synthesis in mesangial fibroblasts [15]; and (iv) attenuating epithelial-mesenchymal transition (EMT) in proximal tubular cells [19].

3.2 Heart Failure (HFrEF and HFpEF/HFmrEF)

In heart failure, MR activation in cardiac fibroblasts drives myocardial interstitial and perivascular fibrosis—the histological substrate for diastolic dysfunction, arrhythmia, and progressive remodeling. Aldosterone promotes macrophage infiltration, NLRP3 activation, and mitochondrial dysfunction in cardiomyocytes. Finerenone's balanced cardiac tissue distribution (~30%) ensures high local MR blockade in myocardial tissue, suppressing fibrotic gene programs and reducing galectin-3, ST2, and NT-proBNP—biomarkers of adverse cardiac remodeling [8,24,29]. In the FINEARTS-HF trial, this translated to a 16% reduction in HF events in patients with EF ≥40%—the first MRA ever to achieve this in HFpEF [8].

3.3 Hypertension, Vascular Disease, and Atrial Fibrillation

Aldosterone promotes vascular smooth muscle cell (VSMC) calcification, endothelial dysfunction, and impaired nitric oxide bioavailability via MR activation. Finerenone attenuates VSMC calcification (reducing Runx2/osteopontin), restores acetylcholine-mediated endothelial relaxation by preventing eNOS uncoupling, and reduces arterial stiffness [27]. In resistant hypertension, finerenone provided an additional 6.6 mmHg systolic BP reduction vs. placebo [48]. Furthermore, aldosterone-driven atrial fibrosis contributes to atrial fibrillation (AF) substrate; a prespecified FIDELIO-DKD analysis showed finerenone reduced new-onset AF by 29% (HR 0.71; 95% CI 0.53–0.94) [70].

3.4 Emerging Targets: MASH and Metabolic Syndrome

MR is expressed in hepatic stellate cells and Kupffer cells; aldosterone stimulates stellate cell activation and collagen deposition in MASH. MR activation in adipose tissue promotes adipogenesis, leptin excess, adiponectin suppression, and insulin resistance. Finerenone improved insulin-stimulated GLUT-4 translocation in experimental models [28] and reduced hepatic fibrosis markers in preclinical NASH models—forming the mechanistic rationale for ongoing clinical trials in MASH [28,78].

4. CLINICAL EFFICACY: MAJOR TRIALS

TABLE 2: Summary of Major Clinical Trials of Finerenone

Trial	N	Population	Duration	Primary Endpoint & Key Results
FIDELIO-DKD (2020)	5,734	T2DM + CKD (eGFR 25–75, UACR 30–5000)	2.6 yrs	Kidney composite (kidney failure, ≥40% eGFR decline, renal death): HR 0.82 (95% CI 0.73–0.93); 14% RRR in CV composite
FIGARO-DKD (2021)	7,437	T2DM + CKD (eGFR ≥25, full UACR spectrum)	3.4 yrs	CV composite (CV death, MI, stroke, HF hospitalization): HR 0.87 (95% CI 0.76–1.00); 18% RRR kidney composite
FIDELITY pooled (2022)	13,026	T2DM + CKD (pooled FIDELIO+FIGARO)	~3 yrs	Kidney composite: HR 0.77 (95% CI 0.67–0.88); CV composite: HR 0.86; consistent across all subgroups
ARTS-HF (2015, Ph IIb)	1,064	HFrEF + T2DM/CKD	90 days	≥30% NT-proBNP reduction: comparable to eplerenone; dose-dependent response; lower hyperkalemia rate
FINEARTS-HF (2024)	6,001	HFmrEF/HFpEF (EF ≥40%)	32 months	CV death + total HF events: RR 0.84 (95% CI 0.74–0.95); 1st MRA to show benefit in HFpEF; driven by ↓ HF hospitalizations
Resistant HTN Phase II (2020)	295	Resistant HTN + CKD	12 weeks	Seated SBP: −6.6 mmHg vs. placebo; well-tolerated; low hyperkalemia rate

Table 2. Major completed clinical trials of finerenone. T2DM = type 2 diabetes mellitus; CKD = chronic kidney disease; HFrEF/HFpEF/HFmrEF = heart failure with reduced/preserved/mildly reduced ejection fraction; RR = rate ratio; HR = hazard ratio; RRR = relative risk reduction; NT-proBNP = N-terminal pro-BNP.

4.1 FIDELIO-DKD and FIGARO-DKD

FIDELIO-DKD (n=5,734) randomized patients with T2DM and CKD (eGFR 25–75, UACR 30–5,000 mg/g) on maximally tolerated RAAS blockade to finerenone 10/20 mg or placebo. After 2.6 years, finerenone reduced the kidney composite primary endpoint by 18% (HR 0.82; 95% CI 0.73–0.93; p=0.001) and the cardiovascular composite by 14% [3]. FIGARO-DKD (n=7,437) enrolled a complementary population with the full CKD spectrum and demonstrated a 13% reduction in the cardiovascular composite primary endpoint (HR 0.87; 95% CI 0.76–1.00; p=0.034) and an 18% reduction in the kidney composite [4]. The pre-planned FIDELITY pooled analysis (n=13,026) showed consistent benefit across all prespecified subgroups with 23% kidney composite reduction and 14% cardiovascular composite reduction [5].

4.2 FINEARTS-HF

FINEARTS-HF enrolled 6,001 patients with HFmrEF/HFpEF (EF ≥40%) across 37 countries. After 32 months, finerenone (up to 40 mg/day) reduced the primary composite of CV death and total HF events by 16% (RR 0.84; 95% CI 0.74–0.95; p=0.007), driven predominantly by fewer HF hospitalizations [8]. This landmark result—the first statistically significant MRA benefit in HFpEF—represents a historic advance in a disease area with previously limited evidence-based pharmacotherapy. Benefit was consistent across subgroups including sex, EF strata, and background SGLT2 inhibitor use [8].

5. COMPARATIVE PROFILE: FINERENONE VS. OTHER MRAs

TABLE 3: Comparative Profile of Mineralocorticoid Receptor Antagonists

Parameter	Finerenone	Spironolactone	Eplerenone	Esaxerenone
Generation	3rd (non-steroidal)	1st (steroidal)	2nd (steroidal)	3rd (non-steroidal)
MR Selectivity	Very high (>1000×)	Low (GR, AR, PR)	Moderate	Very high
MR Binding (Ki)	~17 nM	~2.3 nM	~6.9 nM	~0.3 nM
Active Metabolites	None (parent active)	Yes (canrenone)	None	None
Half-life	2–3 hours	~1.4 h (metabolites 13–24 h)	3–6 hours	~19 hours
Gynecomastia risk	<0.5% (≈ placebo)	~9–10%	Minimal	None
Cardiac:Renal distribution	~30:70 (balanced)	Predominantly renal	Predominantly renal	Predominantly renal
Approved in HFpEF	Yes (2024)	No	No	No (Japan CKD only)
FDA/Approved Indication	CKD + T2DM; HFmrEF/HFpEF	HF, HTN, hyperaldosteronism	HF, post-MI, HTN	CKD + T2DM (Japan)

Table 3. Pharmacological and clinical comparison of finerenone with first- (spironolactone), second- (eplerenone), and third-generation (esaxerenone) mineralocorticoid receptor antagonists. MR = mineralocorticoid receptor; GR = glucocorticoid receptor; AR = androgen receptor; PR = progesterone receptor.

6. SAFETY AND TOLERABILITY

6.1 Hyperkalemia

Hyperkalemia is the most clinically important adverse effect of finerenone. In FIDELIO-DKD, any hyperkalemia (K+ >5.5 mEq/L) occurred in ~14–18% of finerenone patients versus ~9–12% with placebo; hyperkalemia-related discontinuation occurred in 2.3% vs. 0.9% [18,49]. Key risk factors include baseline K+ >4.8 mEq/L, eGFR <45, and concurrent RAAS inhibitor use. The approved starting dose protocol (10 mg for eGFR 25–60; 20 mg for eGFR >60) with mandatory potassium monitoring at four weeks was specifically designed to minimize this risk [99]. Potassium binders—patiromer and sodium zirconium cyclosilicate (SZC)—have been shown to enable continued MRA therapy in high-risk patients and are expected to broaden finerenone's clinical applicability [63,64,89].

6.2 Renal Function Changes

An initial transient eGFR decline of approximately 1–3 mL/min/1.73 m² is expected within the first four weeks, reflecting hemodynamic MR blockade effects (reduced glomerular filtration pressure). This mirrors the early eGFR dip seen with RAAS inhibitors and does not represent nephron loss; eGFR stabilizes within 4–8 weeks and the long-term eGFR decline slope is significantly attenuated vs. placebo across FIDELIO-DKD and FIGARO-DKD [3,4].

6.3 Absence of Anti-Hormonal Side Effects

A key clinical advantage over spironolactone is the near-complete absence of anti-androgenic effects. Gynecomastia occurred in <0.5% of finerenone patients—indistinguishable from placebo—compared to ~9–10% with spironolactone in HF trials, a consequence of the steroidal structure's binding to androgen and progesterone receptors [2,52]. This significantly improves patient acceptability and long-term adherence, particularly for male patients.

7. DRUG INTERACTIONS

TABLE 4: Clinically Significant Drug Interactions with Finerenone

Interacting Drug / Class	Interaction Type	Severity	Recommendation
Strong CYP3A4 inhibitors (ketoconazole, ritonavir, clarithromycin)	PK – AUC ↑~5-fold	Contraindicated	Avoid co-administration
Moderate CYP3A4 inhibitors (fluconazole, verapamil, erythromycin)	PK – AUC ↑2–3-fold	Use with caution	Start at 10 mg; monitor K+ and BP closely
Strong CYP3A4 inducers (rifampin, carbamazepine, St. John's Wort)	PK – AUC ↓~80%	Contraindicated	Avoid; loss of therapeutic efficacy
ACE inhibitors / ARBs / ARNI	PD – additive hyperkalemia and hypotension	Caution	Monitor K+ at 4 weeks; dose-adjust if K+ >5.5 mEq/L
Potassium supplements / K+-sparing diuretics	PD – hyperkalemia risk	Avoid	Discontinue K+ supplements before starting finerenone
NSAIDs	PD – ↓ BP/nephroprotective effects; ↑ AKI risk	Caution	Prefer acetaminophen; monitor renal function and K+
SGLT2 inhibitors	PD – complementary kidney/CV protection; SGLT2i lowers K+	Favorable	Combination recommended; lower hyperkalemia risk with SGLT2i

Table 4. Clinically significant drug interactions with finerenone. CYP3A4 = cytochrome P450 3A4; RAAS = renin-angiotensin-aldosterone system; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

8. DOSING AND MONITORING

CKD + T2DM: Initiate at 10 mg once daily (eGFR 25–60) or 20 mg (eGFR ≥60) with baseline K+ ≤5.0 mEq/L (for 10 mg) or ≤4.8 mEq/L (for 20 mg). Target dose 20 mg once daily, achieved by uptitrating 10 mg at four weeks if K+ ≤4.8 mEq/L [99].

HFmrEF/HFpEF: Starting dose 20 mg with uptitration to 40 mg based on tolerability and K+, per the FINEARTS-HF protocol [8].

Monitoring: Serum K+ and eGFR at baseline and at 4 weeks after initiation or dose change; then every 3 months for year 1, every 6 months thereafter. Dose reduction or temporary suspension if K+ >5.5 mEq/L; permanent discontinuation if K+ >6.0 mEq/L on repeated measurements [99].

9. COMBINATION THERAPY AND FUTURE PERSPECTIVES

9.1 Finerenone + SGLT2 Inhibitors

The combination of finerenone with SGLT2 inhibitors represents one of the most promising therapeutic synergies in cardiorenal medicine. The two classes address distinct but complementary pathophysiological mechanisms: SGLT2 inhibitors act through osmotic natriuresis, tubuloglomerular feedback restoration, and ketone metabolism enhancement; finerenone acts through anti-fibrotic and anti-inflammatory MR antagonism. Critically, SGLT2 inhibitors have a potassium-lowering effect (~0.1–0.2 mEq/L) that directly mitigates finerenone's principal adverse effect [61,95]. A FIDELITY prespecified analysis confirmed numerically greater cardiorenal event reduction and lower hyperkalemia rates with combination use [95]. The ongoing CONFIDENCE trial is prospectively evaluating dapagliflozin plus finerenone vs. monotherapy in CKD + T2DM.

9.2 The Four-Pillar Cardiorenal Strategy

Convergent evidence from multiple outcome trials has established a conceptual 'four-pillar' framework for high-risk CKD + T2DM patients: (1) maximally tolerated RAAS blockade (ACEi/ARB); (2) SGLT2 inhibitor; (3) finerenone; and (4) GLP-1 receptor agonist. Each pillar contributes unique cardiorenal metabolic benefits that appear additive [83,85,95]. Implementation requires careful hyperkalemia risk stratification, potassium monitoring, and judicious use of potassium binders in high-risk patients [63,66].

9.3 Emerging Indications and Ongoing Trials

The ongoing FIND-CKD Phase III trial evaluates finerenone in non-diabetic CKD stages 3b–4 with proteinuria—a population with high unmet need. The ZENITH trial examines HFpEF without T2DM. Phase IIa trials in MASH/NASH and investigator-initiated studies in primary hyperaldosteronism are underway. A pediatric Phase III CKD trial (ages 6–17) is enrolling. Positive results from these trials would substantially expand finerenone's therapeutic landscape beyond its currently approved indications.

9.4 Precision Medicine

Future directions include pharmacogenomic profiling to identify MR pathway activity signatures predictive of differential finerenone response—including polymorphisms in the MR gene (NR3C2)—and biomarker-guided therapy using baseline UACR, plasma aldosterone, and urinary MR-responsive gene expression to personalize dosing and maximize efficacy while minimizing hyperkalemia risk in the most vulnerable patients.

10. POSITION IN CLINICAL GUIDELINES

The KDIGO 2022 Guideline for Diabetes Management in CKD recommends finerenone in addition to RAAS blockade for patients with T2DM, CKD (eGFR ≥25), and elevated albuminuria (UACR ≥30 mg/g) at high risk of progression (Grade 1B) [83]. The ADA Standards of Care 2024 recommends consideration of finerenone in T2DM + CKD at high CV/renal risk, complementary to SGLT2 inhibitors [41]. The 2021 ESC Guidelines for Heart Failure included finerenone as a Class IIb recommendation for HFrEF with CKD and T2DM [39]. Following FINEARTS-HF (2024), updated ESC/ACC-AHA HF guidelines are expected to incorporate finerenone as a Class I recommendation for patients with HFmrEF/HFpEF and elevated NT-proBNP.

11. CONCLUSIONS

Finerenone represents a genuine pharmacological paradigm shift in cardiorenal disease management. Its non-steroidal structure confers exquisite MR selectivity, virtually eliminating the anti-hormonal side effects limiting earlier MRAs. Its unique receptor conformational modulation results in more complete suppression of MR-driven fibrotic and inflammatory programs, and its balanced cardiac-renal tissue distribution ensures simultaneous end-organ protection in both key target organs. A clinical evidence base encompassing over 13,000 patients in outcome trials across DKD and heart failure—culminating in the historic FINEARTS-HF results—positions finerenone as an indispensable component of contemporary cardiorenal therapeutics. The evolving combination strategy with SGLT2 inhibitors, GLP-1 receptor agonists, and potassium binders promises to further optimize its safety and efficacy across an expanding patient population. Ongoing trials in non-diabetic CKD, pediatrics,

MASH, and HFpEF without diabetes will continue to define the full therapeutic potential of this landmark non-steroidal MRA.

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