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Review Article

Cardiorenal Syndrome and Emerging Therapeutic Strategies: The Role of SGLT2 Inhibitors and Finerenone

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Abstract

Cardiorenal syndrome is associated with high morbidity and mortality and is characterized by bidirectional interactions between cardiac and renal dysfunction. The advent of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and the nonsteroidal mineralocorticoid receptor antagonist finerenone has substantially changed the therapeutic landscape. Combination therapy with SGLT2i and finerenone may provide additional benefits through complementary mechanisms, representing a potential paradigm shift in the management of cardiorenal syndrome. In this review, we examine the pathophysiological pathways that characterize cardiorenal syndrome, clinical data from major randomized controlled trials, and the rationale for the concomitant use of these two drug classes. SGLT2 inhibitors significantly reduce hospitalization for heart failure, slow renal function decline, and provide benefits in both heart failure with reduced ejection fraction and heart failure with preserved ejection fraction, irrespective of diabetes status. Finerenone has been shown to reduce the risk of cardiovascular events and chronic kidney disease progression in patients with type 2 diabetes and chronic kidney disease, with a more favorable safety profile than steroidal mineralocorticoid receptor antagonists. Emerging evidence suggests that combination therapy may reduce hospitalizations for heart failure and slow renal disease progression beyond the effects of either monotherapy. However, implementation of these therapeutic options requires careful patient selection, ongoing monitoring of renal function and electrolytes, and close collaboration between cardiologists and nephrologists.

Introduction

Cardiorenal syndrome (CRS) is a complex disorder of the heart and kidneys in which acute or chronic dysfunction in one organ can induce acute or persistent dysfunction in the other. Through diverse hemodynamic, neurohormonal, and inflammatory mechanisms, CRS reflects the bidirectional interaction between the cardiovascular and renal systems. Based on the primary organ affected and the timing of clinical manifestation, Ronco *et al*.[1] proposed a classification in 2008 that divides CRS into five subtypes. Type 1 (acute CRS) is defined as acute deterioration in cardiac function leading to acute kidney injury. Type 2 (chronic CRS) is associated with chronic heart failure progressing to chronic kidney disease (CKD). Type 3 (acute renocardiac syndrome) describes acute kidney injury causing rapid cardiac dysfunction, whereas type 4 (chronic renocardiac syndrome) includes CKD exacerbating chronic heart disease. Type 5, or secondary CRS, includes systemic diseases, such as sepsis or diabetes mellitus, that simultaneously compromise both cardiac and renal function.[2]

Epidemiology and clinical burden

With population aging and the increasing prevalence of comorbidities, including type 2 diabetes mellitus, obesity, and hypertension, the incidence of CRS is rising globally. Epidemiological studies indicate that 40–60% of patients with heart failure also have CKD, and cardiac dysfunction affects more than 50% of people with advanced CKD.[3,4] In patients with established CRS, the coexistence of these conditions increases the risk of death, with 5-year mortality rates exceeding 50%.[5] Heart failure is a major cause of hospitalization in industrialized nations, with annual healthcare expenditures exceeding $30 billion in the United States.[6] Worsen-

Keywords: Cardiorenal syndrome; SGLT2 inhibitors; Finerenone; Heart failure; Chronic kidney disease; Type 2 diabetes mellitus; Mineralocorticoid receptor antagonist.

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ing renal function during recovery from acute heart failure is associated with longer hospital stays, greater need for intensive care, and substantially increased short- and long-term mortality.[7]

Cardiovascular-kidney-metabolic (CKM) syndrome

Expanding the scope of conventional CRS, the American Heart Association recently introduced the concept of cardiovascular-kidney-metabolic (CKM) syndrome to encompass metabolic factors, including obesity, type 2 diabetes mellitus, and metabolic liver dysfunction.[8] This new pathophysiological entity recognizes that the relationships among the heart, kidneys, and metabolism are not merely comorbidities but several manifestations of a shared disease process defined by insulin resistance, chronic inflammation, oxidative stress, and neurohormonal activation. The clinical relevance of CKM syndrome is substantial because it enables early identification of high-risk patients through a stepwise approach (stages 0–4), allowing targeted therapies before the onset of overt cardiovascular or renal disease. Stage 0 denotes the absence of risk factors, whereas stage 4 denotes established cardiovascular disease with CKD.[9] This framework underscores the need for treatment approaches that target several organ systems simultaneously rather than relying solely on conventional organ-specific strategies. It also supports the use of combination treatments aimed at shared pathophysiological pathways in the cardiac, renal, and metabolic systems, making sodium-glucose cotransporter 2 inhibitors (SGLT2i) and finerenone especially relevant for these patients.[10]

Need for new therapeutic approaches

Although understanding of CRS pathophysiology has continued to improve, its treatment remains complex, and conventional medical approaches have important limitations. Because of the increased risk of hyperkalemia and worsening renal function, renin-angiotensin-aldosterone system (RAAS) inhibitors, the mainstay of heart failure treatment, may be underused or poorly tolerated in patients with advanced CKD.[11] Although loop diuretics are essential for congestion management, they can promote diuretic resistance and compensatory neurohormonal activation, which perpetuate the vicious cycle of CRS.[12] In this context, SGLT2i have marked a turning point in the treatment of type 2 diabetes and CKD after many years without major therapeutic advances, providing cardiovascular and renal benefits that extend beyond glycemic control. By inhibiting the renal reuptake of sodium and glucose in the proximal tubule, they induce glucosuria and osmotic diuresis, lower glomerular hyperfiltration and glomerular capillary pressure, and exert anti-inflammatory and metabolic effects.[13]

At the same time, the development of finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist (MRA), has opened new therapeutic options for diabetic kidney disease. Owing to its improved selectivity and lower risk of hyperkalemia and androgenic effects, finerenone has a more favorable safety profile than conventional steroidal antagonists, such as spironolactone. The FIDELIO-DKD and FIGARO-DKD trials showed that, in patients with type 2 diabetes and albuminuric CKD, finerenone significantly reduces the risk of renal disease progression and cardiovascular events, even when added to optimized RAAS inhibitor therapy.[14] In this setting, SGLT2i and finerenone represent a paradigm shift by providing pharmacological therapies with proven protective effects on both organs. Combining these two drug classes may target multiple pathophysiological pathways simultaneously and provide a more comprehensive strategy for cardiorenal protection. Therefore, this review aims to examine the pathophysiological pathways that characterize cardiorenal syndrome, synthesize the clinical data from major randomized controlled trials, and evaluate the rationale for the concomitant use of SGLT2 inhibitors and finerenone as a comprehensive therapeutic strategy.

Pathophysiology of cardiorenal syndrome

Hemodynamic mechanisms

A series of hemodynamic interactions between the heart and kidneys defines the pathophysiology of CRS. Initially, the main mechanism was thought to be reduced cardiac output leading to renal hypoperfusion. Recent data, however, have shown that elevated central venous pressure and renal venous congestion are equally important, if not more important, contributors to renal dysfunction.[15] Increased renal venous pressure raises renal interstitial pressure, impairing glomerular filtration and tubular function through tubular compression and a reduced transrenal perfusion gradient.[2] Systemic venous congestion, which can be assessed by point-of-care ultrasonography using the venous excess ultrasound system, is an independent indicator of worsening renal function and adverse outcomes in patients with CRS.[16] In addition, elevated intra-abdominal pressure, which is common in patients with ascites or obesity, can exacerbate renal venous constriction and reduce renal blood flow.[17]

Neurohormonal activation

Activation of the sympathetic nervous system and the RAAS is central to the development of CRS. Reduced renal blood flow stimulates juxtaglomerular cells to release renin, initiating a cascade that leads to the formation of angiotensin II and aldosterone. Angiotensin II causes vasoconstriction, particularly at the efferent arteriole, increasing intraglomerular pressure, reducing glomerular filtration, and promoting renal fibrosis through stimulation of profibrotic mediators such as transforming growth factor beta 1 (TGF-β1).[18,19] Beyond its effects on tubular sodium reabsorption, aldosterone directly damages the myocardium and kidneys by promoting interstitial fibrosis, inflammation, and endothelial dysfunction. Sympathetic overactivation promotes renal vasoconstriction, increases tubular sodium reabsorption, stimulates renin release, and promotes cardiac arrhythmias.[20] Together, these neurohormonal systems create a self-perpetuating vicious cycle that aggravates cardiorenal failure.

Inflammation and oxidative stress

Oxidative stress and systemic inflammation are well-recognized drivers of CRS development. In patients with CRS, pro-inflammatory cytokines, including interleukin-6, tumor necrosis factor alpha, and interleukin-1β, are increased and contribute to progressive endothelial dysfunction, leukocyte activation, and fibrotic processes in the heart and kidneys. The regional inflammatory state is sustained by macrophage and T-lymphocyte infiltration into the myocardium and renal parenchyma, accelerating maladaptive tissue remodeling.[21] Oxidative stress, characterized by excessive production of reactive oxygen species (ROS) and reduced availability of endogenous antioxidants such as glutathione, directly damages cells through lipid peroxidation, protein oxidation, and DNA damage. In experimental models of CRS, mitochondrial dysfunction, with decreased adenosine triphosphate production and increased ROS generation, has been identified as a major mechanism of cardiomyocyte and renal tubular cell damage.[22]

Table 1. Key pathophysiological mechanisms of cardiorenal syndrome

Mechanism	Pathway/mediators	Cardiac effects	Renal effects	Therapeutic targets
Hemodynamic	↑ CVP, ↓ CO, congestion	Reduced coronary filling, ↑ wall stress	Renal venous compression, ↓ GFR, tubular ischemia	Diuretics, ultrafiltration, SGLT2i
Neurohormonal	RAAS, SNS, ADH	Ventricular remodeling, hypertrophy, fibrosis	Vasoconstriction, Na+ retention, interstitial fibrosis	ACEi/ARB, MRA, finerenone, beta-blockers
Inflammatory	IL-6, TNF-α, IL-1β, NF-κB	Leukocyte infiltration, myocardial dysfunction	Tubular damage, glomerulosclerosis	SGLT2i, finerenone, anti-cytokine therapies
Oxidative stress	ROS, ↓ NO, NADPH oxidase	Mitochondrial dysfunction, cardiomyocyte apoptosis	Proximal tubular damage, proteinuria	SGLT2 inhibitors, finerenone, NAC, Nrf2 activators
Fibrosis	TGF-β1, CTGF, Galectin-3, PDGF	Interstitial fibrosis, ventricular stiffness	Tubulointerstitial fibrosis, glomerulosclerosis	Finerenone, SGLT2 inhibitors, Anti-TGF-β
Endothelial dysfunction	↓ NO, ↑ Endothelin-1, Glycocalyx degradation	Coronary microvascular dysfunction	Impaired autoregulation, glomerular permeability	SGLT2 inhibitors, finerenone, endothelin antagonists
Metabolic	Insulin resistance, ↑ FFA, dyslipidemia	Impaired myocardial energy metabolism	Tubular lipid accumulation, lipotoxicity	SGLT2 inhibitors, GLP-1-RA, glycemic control

↑, increased; ↓, decreased. ACEi, angiotensin-converting enzyme inhibitors; ADH, antidiuretic hormone; ARB, angiotensin receptor blockers; CO, cardiac output; CTGF, connective tissue growth factor; CVP, central venous pressure; FFA, free fatty acids; GFR, glomerular filtration rate; GLP-1 RA, GLP-1 receptor agonists; MRA, mineralocorticoid receptor antagonist; NAC, N-acetylcysteine; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; PDGF, platelet-derived growth factor; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system; TGF-β, transforming growth factor beta.

The interplay between inflammation and oxidative stress creates a profibrotic environment that promotes extracellular matrix deposition and progression to organ failure.

Fibrosis and endothelial dysfunction

Fibrosis is a common final pathway of cardiac and renal damage in CRS. In the heart, interstitial and perivascular fibrosis increases ventricular stiffness, contributes to diastolic dysfunction, and increases arrhythmic risk. In the kidney, glomerular and tubulointerstitial fibrosis leads to progressive loss of functioning nephrons and declining renal function. Major profibrotic mediators include TGF-β1, connective tissue growth factor (CTGF), galectin-3, and extracellular matrix proteins such as fibronectin and collagen.[23] Transcriptomic and proteomic analyses have identified shared molecular signatures of fibrosis in both organs, suggesting common pathogenetic pathways that may be therapeutic targets. Endothelial dysfunction, characterized by reduced nitric oxide (NO) bioavailability, increased endothelin-1 production, and abnormal vascular permeability, accompanies the development of fibrosis. In CRS, degradation of the endothelial glycocalyx, a glycosaminoglycan-rich layer covering the luminal endothelial surface, increases vascular permeability, fluid leakage into the interstitium, and edema formation.[24]

Biomarkers in cardiorenal syndrome

The identification of specific biomarkers reflecting underlying pathophysiological processes has improved the diagnosis and monitoring of CRS. Cardiac biomarkers include N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP), which reflect hemodynamic stress and congestion; high-sensitivity troponins, which indicate myocardial injury; and newer markers, such as soluble ST2 and galectin-3, which reflect fibrosis and inflammation.[25] Among renal biomarkers, cystatin C provides a more accurate assessment of glomerular filtration rate (GFR) than creatinine, independent of muscle mass, and is therefore particularly useful in frail or sarcopenic patients. Markers of tubular injury, including neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, and N-acetyl-β-D-glucosaminidase, allow early detection of structural kidney damage before functional deterioration becomes apparent. The U.S. Food and Drug Administration-approved NephroCheck test, which combines TIMP-2 and IGFBP7, can stratify the risk of impending acute kidney injury up to 24 hours before creatinine increases.[26]

These biomarkers help distinguish structural kidney injury from hemodynamic or functional kidney injury, thereby informing therapeutic decisions during diuretic treatment. Integration of cardiac and renal biomarkers can provide a comprehensive assessment of CRS severity and prognosis; elevated levels of both NT-proBNP and markers of tubular injury identify patients at higher risk for disease progression. The main pathophysiological processes of CRS and their corresponding therapeutic targets are summarized in Table 1.

SGLT2 inhibitors in cardiorenal syndrome

Pleiotropic mechanisms of action

Initially developed to treat type 2 diabetes mellitus, SGLT2i have shown major cardiorenal benefits independent of glycemic control.[27] At the renal level, their main mechanism of action is inhibition of glucose and sodium reabsorption in the proximal convoluted tubule, resulting in glycosuria and natriuresis. However, this direct mechanism does not fully explain the broad cardiovascular and renal benefits observed, suggesting the involvement of additional mechanisms.[28] SGLT2i restore tubuloglomerular feedback by increasing sodium delivery to the macula densa, thereby inducing afferent arteriolar vasoconstriction and reducing intraglomerular pressure.

This paradoxical renoprotective effect causes a small initial decrease in estimated glomerular filtration rate (eGFR), followed by stabilization and a slower long-term decline in renal function. SGLT2i also reduce renal congestion through their diuretic and natriuretic effects without triggering compensatory RAAS activation or depleting intravascular volume.[29] At the cardiac level,

SGLT2i reduce ventricular preload and afterload, improve myocardial energy metabolism by promoting the use of ketone bodies as a preferential substrate, and reduce arterial stiffness and blood pressure. At the systemic level, they modulate inflammation by reducing pro-inflammatory cytokines, decreasing oxidative stress through reduced mitochondrial ROS production, and activating nutrient-deprivation signaling pathways, such as AMP-activated protein kinase and sirtuins, which promote autophagy and cellular protection.[30]

Evidence from major clinical trials in diabetes mellitus

Published in 2015, the EMPA-REG OUTCOME trial marked a turning point in the treatment of type 2 diabetes mellitus with established cardiovascular disease. In enrolled patients, empagliflozin (10 mg or 25 mg once daily) added to conventional therapy reduced the risk of cardiovascular death by 38%, hospitalization for heart failure by 35%, and nephropathy progression by 46% compared with placebo.[31,32] In the CREDENCE trial, canagliflozin 100 mg once daily reduced the risk of the composite renal endpoint (dialysis, renal transplantation, renal death, or sustained decline in GFR) by 30% in patients with type 2 diabetes and albuminuric CKD, all treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at the highest tolerated dose.[33]

The DAPA-CKD study extended these findings by showing that dapagliflozin reduced the risk of worsening renal function or cardiovascular/renal death by 39% in patients with CKD, with similar effects in those with and without diabetes.[34] More recently, the EMPA-KIDNEY study confirmed the efficacy of empagliflozin in a diverse CKD population (eGFR 20–45 mL/min/1.73 m^2 or eGFR 45–90 mL/min/1.73 m^2 with albuminuria), demonstrating a 28% reduction in the risk of renal disease progression or cardiovascular death, with benefits consistent across CKD stages and independent of diabetes status.[35] Long-term follow-up of the EMPA-KIDNEY trial further showed that the cardiorenal benefits of empagliflozin persisted for up to 12 months after treatment cessation, suggesting sustained disease-modifying effects.[36]

Evidence in patients with heart failure

Published in 2019, the DAPA-HF study showed for the first time that, irrespective of diabetes status, the SGLT2i dapagliflozin reduced the risk of cardiovascular death or worsening heart failure by 26% in patients with heart failure with reduced ejection fraction (HFrEF).[37] The EMPEROR-Reduced study confirmed these findings with empagliflozin, showing a 25% reduction in the risk of the primary composite endpoint.[38] The EMPEROR-Preserved and DELIVER trials extended the benefits of SGLT2i to patients with heart failure with preserved ejection fraction (HFpEF), a population for which treatment options have historically been limited.[39,40] Combined analyses of these trials showed consistent benefits of SGLT2i across the ejection fraction spectrum (from < 40% to > 60%), with significant reductions in heart failure hospitalization and cardiovascular death and improvements in quality-of-life measures.[41] In patients hospitalized for acute heart failure, early initiation of SGLT2i has shown an acceptable safety profile and potential benefits in reducing rehospitalization.

Specific benefits in cardiorenal syndrome

In 11 randomized controlled trials evaluating SGLT2i in patients with coexisting heart failure and CKD (n = 34,999), SGLT2i consistently reduced hospitalization for heart failure and cardiovascular death by 25–35%, slowed eGFR decline, and were associated with low rates of acute kidney injury.[42] Subgroup analyses confirmed these benefits in CKD stages 2–4 and in patients with heart failure with reduced or preserved ejection fraction. A meta-analysis also showed that SGLT2i provided greater reductions in hospitalization for heart failure and composite renal outcomes than glucagon-like peptide 1 receptor agonists in patients with type 2 diabetes, CKD, and/or cardiovascular disease.[43] In elderly patients (>65 years) with type 2 diabetes complicated by type 2 and 4 CRS, empagliflozin improved glycemic control, renal function (serum creatinine and microalbuminuria), cardiac markers (NT-proBNP and left ventricular ejection fraction), and major adverse cardiovascular events. SGLT2i have also been shown to reduce renal venous congestion on intrarenal ultrasonography, supporting their role in improving renal hemodynamics in CRS.[44]

Finerenone: Nonsteroidal mineralocorticoid receptor antagonist

Pharmacodynamics and selectivity

Compared with conventional steroidal MRAs, such as spironolactone and eplerenone, finerenone is a third-generation nonsteroidal mineralocorticoid receptor antagonist (nsMRA) with distinct pharmacological characteristics. Its nonsteroidal chemical structure, based on a dihydropyridine scaffold, provides improved selectivity for the mineralocorticoid receptor (MR) compared with other steroid receptors, thereby reducing off-target endocrine adverse effects (gynecomastia, menstrual disturbances, and erectile dysfunction) typical of steroidal MRAs. Although its plasma half-life is relatively short (2–3 hours), its tissue effects are prolonged, with preferential distribution to cardiac and renal tissues compared with steroidal MRAs, which tend to accumulate more in renal tissue. Preclinical studies have shown that finerenone is more potent than eplerenone in blocking MR and suppressing MR-mediated gene expression, with a superior MR/other nuclear receptor selectivity profile. At the molecular level, finerenone preferentially regulates the recruitment of transcriptional cofactors into the MR-DNA complex, favoring interaction with co-repressors rather than co-activators, which may explain its stronger anti-inflammatory and antifibrotic effects.[45]

Antifibrotic and anti-inflammatory mechanisms

Through multiple molecular mechanisms, finerenone exerts strong antifibrotic effects in the renal and cardiovascular systems. In preclinical models of non-diabetic CKD, finerenone reduced renal hypertrophy, albuminuria, left ventricular diastolic dysfunction, and cardiac fibrosis, thereby improving cardiac tissue perfusion. Increased activating phosphorylation of endothelial nitric oxide synthase (eNOS) and decreased expression of profibrotic markers, including TGF-β1, CTGF, fibronectin, and collagen, suggest improved endothelial function.[46] In the kidney, finerenone limits tubular dedifferentiation, epithelial-mesenchymal transition, and extracellular matrix accumulation, which characterize the progression of renal fibrosis. Finerenone suppresses the proliferation and activation of cardiac fibroblasts, reduces macrophage infiltration, and regulates macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype.[47] It also reduces nicotinamide adenine dinucleotide phosphate oxidase (NOX2 and NOX4) activity and enhances antioxidant enzyme activity, such as superoxide dismutase, thereby reducing oxidative stress. In experimental models of cardiorenal syndrome, finerenone normalized renal venous congestion parameters, improved renal and cardiac mitochondrial function, and reduced markers of organ damage.[48]

FIDELIO-DKD and FIGARO-DKD trials

In the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) trial, 5,674 patients with type 2 diabetes mellitus and albuminuric CKD were assigned to finerenone 10 or 20 mg or placebo, in addition to standard therapy including renin-angiotensin system inhibitors. Finerenone reduced the risk of the primary composite renal endpoint (renal failure, sustained ≥ 40% decline in GFR, or renal death) by 18% (HR 0.82, 95% CI 0.73–0.93, $P = 0.001$). Secondary cardiovascular outcomes showed a 14% reduction in the risk of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure (HR 0.86, 95% CI 0.75–0.99, $P = 0.03$).[49]

The FIGARO-DKD trial enrolled 7,437 patients with type 2 diabetes mellitus and early CKD or moderate albuminuria and showed a 13% reduction in the risk of the composite cardiovascular endpoint (HR 0.87, 95% CI 0.76–0.98, $P = 0.03$), along with a significant reduction in new-onset heart failure.[50] Both trials showed substantial reductions in albuminuria, with an average 30–40% decrease in the urine albumin/creatinine ratio within four months of treatment initiation. The effect of finerenone on renal function was characterized by an early modest decrease in GFR, attributable to a hemodynamic reduction in intraglomerular pressure, followed by a significant slowing of long-term GFR decline compared with placebo.

Pooled FIDELITY analysis

Combining individual patient-level data from 13,026 participants in the FIDELIO-DKD and FIGARO-DKD trials, the FIDELITY analysis provides the most comprehensive evidence currently available regarding the efficacy and safety of finerenone. The analysis showed that finerenone reduced hospitalization for heart failure (HR 0.78, 95% CI 0.66–0.92, $P = 0.003$) and composite renal outcomes (HR 0.77, 95% CI 0.67–0.88, $P = 0.0002$) and showed a trend toward lower all-cause mortality (HR 0.89, 95% CI 0.79–1.00, $P = 0.051$). Although the reduction in cardiovascular death did not reach statistical significance in the pooled analysis (HR 0.88, 95% CI 0.76–1.02, $P = 0.092$), the direction of effect was consistently favorable. The benefits of finerenone were consistent across levels of baseline renal function (eGFR < 60 and ≥ 60 mL/min/1.73 m^2) and albuminuria (< 300 and ≥ 300 mg/g), confirming its efficacy across a wide range of renal disease severity. Among Asian patients, who comprised approximately 22% of the FIDELITY population, finerenone showed cardiorenal benefits equal to or greater than those observed in non-Asian patients, with a similar safety profile.[51]

FINEARTS-HF trial: Expansion to HFpEF/HFmrEF

The FINEARTS-HF trial, which evaluated finerenone in patients with heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF; left ventricular ejection fraction ≥ 40%), substantially expanded the evidence base for finerenone. Patients with HFmrEF/HFpEF were randomized to finerenone or placebo, and finerenone reduced the risk of the primary composite endpoint of cardiovascular death and total worsening heart failure events by 16% (rate ratio 0.84, 95% CI 0.74–0.95).[52] The benefit appeared early and was driven mainly by fewer heart failure hospitalizations. A prespecified analysis also showed that finerenone slowed the development of new albuminuric CKD in patients with HFpEF/HFmrEF, suggesting a preventive effect on renal disease progression. The benefits of finerenone were consistent regardless of baseline SGLT2i use, suggesting possible additive effects with combination therapy. In patients with HFpEF/HFmrEF and coexisting CKD or diabetes, finerenone improved cardiac biomarkers (NT-proBNP) and cardiac remodeling, with reductions in left ventricular end-diastolic diameter and improvements in ejection fraction.[53]

Safety profile vs. steroidal MRAs

Finerenone has shown a more favorable safety profile than steroidal MRAs, particularly regarding hyperkalemia and endocrine adverse effects. In the FIDELITY analysis, hyperkalemia (potassium > 5.5 mmol/L) occurred in 14.0% of patients treated with finerenone and 6.9% of those treated with placebo; severe hyperkalemia (> 6.0 mmol/L) occurred in only 1.1% versus 0.2%, and permanent treatment discontinuation due to hyperkalemia was uncommon.[51] Among patients with CKD and type 2 diabetes, real-world comparative research has shown that finerenone is associated with a significantly lower incidence of hyperkalemia than spironolactone (17.2% vs. 26.4%, $P < 0.001$).[54]

In a randomized controlled trial of patients with stage 3b CKD, low-dose spironolactone (25 mg) was often withdrawn because prespecified safety criteria were met; 35.4% of patients discontinued treatment because of reduced GFR, 18.9% because of adverse effects, and 8.0% because of hyperkalemia, without evidence of cardiovascular benefit over conventional treatment.[55] Conversely, in the FIDELIO-DKD and FIGARO-DKD trials, finerenone was better tolerated, with permanent treatment discontinuation rates below 5%. Endocrine adverse effects (gynecomastia and menstrual irregularities) were rare with finerenone (< 1%), reflecting its greater selectivity for MR than for other steroid receptors.[49,50] Compared with finerenone monotherapy, the combination of finerenone and SGLT2i has been shown to further reduce the risk of hyperkalemia, most likely by increasing renal potassium excretion through SGLT2i.[56] Table 2 summarizes the key clinical trials of finerenone.

Combination therapy: SGLT2i + finerenone

Rationale for combination therapy

Based on complementary and potentially synergistic mechanisms of action, the combination of SGLT2i and finerenone represents a promising therapeutic strategy. SGLT2i act mainly through hemodynamic effects (reduced preload and optimized renal perfusion), metabolic effects (improved energy substrate utilization), and modulation of tubuloglomerular feedback, whereas finerenone exerts potent antifibrotic and anti-inflammatory effects through selective MR blockade.[10] This complementarity suggests that combination therapy may provide additive or synergistic benefits beyond monotherapy. In addition, concomitant SGLT2i use may reduce the risk of finerenone-associated hyperkalemia by enhancing renal potassium excretion, thereby improving tolerability and enabling sustained MRA therapy in more patients.[56] Together, these agents form a comprehensive protective approach: SGLT2i target the hemodynamic and metabolic components of CRS, whereas finerenone targets structural remodeling and fibrosis. By reducing preload, optimizing renal perfusion, improving metabolic efficiency, and limiting inflammatory and fibrotic damage, the combination may explain the superior clinical outcomes observed with dual therapy.[57]

Evidence from combination clinical trials

The CONFIDENCE trial was the first randomized study to evalu-

Table 2. Key results of finerenone trials

Trial	Population	N	Follow-up	Primary endpoint	HR (95% CI)	*P* value
FIDELIO-DKD	T2D + CKD (eGFR 25–75, UACR 30–5,000)	5,674	2.6 years	Kidney composite (↓40% eGFR, ESKD, kidney failure)	0.82 (0.73–0.93)	0.001
FIGARO-DKD	T2D + CKD (eGFR 25–90, UACR 30–5,000)	7,437	3.4 years	CV composite (CV death, MI, stroke, HHF)	0.87 (0.76–0.98)	0.03
FIDELITY (pooled)	T2D + CKD	13,026	3.0 years	CV death	0.88 (0.76–1.02)	0.092
				All-cause mortality	0.89 (0.79–1.00)	0.051
				HHF	0.78 (0.66–0.92)	0.003
				Kidney composite (↓57% eGFR, ESKD, kidney failure)	0.77 (0.67–0.88)	0.0002
FINEARTS-HF	HFpEF/HFmrEF (LVEF ≥ 40%)	6,001	3.0 years	CV death + total worsening HF events	0.84 (0.74–0.95)	0.007
CONFIDENCE	T2D + CKD (SGLT2i subgroup)	~750	180 days	UACR reduction	–29% vs FIN, –32% vs EMPA	<0.001

↓, decrease/reduction; +, and/plus. CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; ESKD, end-stage renal disease; FIN, finerenone; HF, heart failure; HFpEF/HFmrEF, heart failure with preserved/mildly reduced ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; T2D, type 2 diabetes mellitus; UACR, urine albumin/creatinine ratio.

ate the concurrent effects of finerenone and empagliflozin compared with either monotherapy in patients with CKD and type 2 diabetes. After 180 days, combination therapy resulted in a 29% greater reduction in urinary albumin/creatinine ratio compared with finerenone alone and a 32% greater reduction compared with empagliflozin alone ($P < 0.001$ for both comparisons). Regarding safety, combination treatment was not associated with unexpected adverse events; hyperkalemia, acute kidney injury, and symptomatic hypotension leading to drug withdrawal were uncommon in all groups.[58] Approximately 6.7% of patients in the subgroup analyses of the FIDELIO-DKD and FIGARO-DKD trials were receiving SGLT2i at baseline. These analyses showed that the effects of finerenone on cardiovascular and renal outcomes were consistent regardless of baseline SGLT2i use, supporting potential additive effects of the combination.[49–51] Compared with monotherapy, a meta-analysis of real-world observational studies showed that the combination of SGLT2i and finerenone was associated with greater reductions in all-cause mortality, major adverse cardiovascular events, and major adverse renal events.[57]

Additive benefits in cardiovascular and renal outcomes

Observational studies have shown that combined SGLT2i plus finerenone therapy provides additional protection against major adverse cardiovascular events in patients with heart failure and CKD compared with SGLT2i or finerenone monotherapy. Combination therapy may also reduce hospitalization for heart failure and slow CKD progression more effectively than either monotherapy alone.[57,58] A cost-effectiveness study in the Chinese healthcare system showed that triple therapy with finerenone plus SGLT2i and standard of care was cost-effective, resulting in lifetime cost savings of CNY 102,953 per patient and an additional gain of 0.291 quality-adjusted life-years compared with finerenone plus standard of care.[59] The benefits of combination therapy appear especially evident in high-risk subgroups, including patients with eGFR < 45 mL/min/1.73 m^2, significant albuminuria (urine albumin/creatinine ratio > 300 mg/g), and concomitant diabetes, heart failure, and CKD.[60]

Management of hyperkalemia

Hyperkalemia is a serious adverse effect associated with MR antagonist use, particularly in patients with advanced CKD. SGLT2i increase potassium excretion through several mechanisms, including increased sodium delivery to the distal tubule and collecting duct, where sodium-potassium exchange mediated by the epithelial sodium channel (ENaC) occurs.[61] This effect may partially offset the potassium-retaining action of finerenone, enabling safer use of the combination even in patients at elevated risk of hyperkalemia. Management strategies include frequent monitoring of serum potassium levels (at 1, 4, 8, and 12 weeks after initiation or dose adjustment), dietary potassium restriction, optimization of diuretic therapy, and use of new potassium binders, such as patiromer or sodium zirconium cyclosilicate, when needed.[62,63] Most patients can maintain combination therapy with dose adjustment rules based on serum potassium levels, including temporary discontinuation if K+ is > 5.5 mmol/L and dose reduction if K+ is 5.0–5.5 mmol/L.

Clinical applications and recommendations

Identification of candidate patients

Patients with type 2 diabetes and CKD (eGFR ≥ 20 mL/min/1.73 m^2 with albuminuria, defined as urine albumin/creatinine ratio ≥ 30 mg/g), those with heart failure (HFrEF, HFmrEF, or HFpEF) regardless of diabetes status, and those with CKM syndrome at high cardiovascular and renal risk are suitable candidates for SGLT2i and/or finerenone therapy.[64] Guidelines recommend SGLT2i as first-line therapy in patients with HFrEF (Class I, level of evidence A) and in patients with CKD and type 2 diabetes to slow renal disease progression and reduce cardiovascular events.[65,66] In patients with type 2 diabetes and CKD, finerenone is recommended to reduce the risk of CKD progression and cardiovascular events, even under optimized RAAS inhibitor thera-

py.[64] In patients with type 2 diabetes, CKD, and persistent albuminuria despite monotherapy, especially those with concomitant heart failure, combination therapy with SGLT2i and finerenone should be considered.[10]

Timing of initiation and monitoring

SGLT2i can be started early in the course of CKD, down to an eGFR of 20 mL/min/1.73 m^2, and in heart failure, with demonstrated benefits even after stabilization in patients hospitalized for acute heart failure. After optimization of RAAS inhibitor therapy, finerenone should be started at 10 mg/day for patients with an eGFR of 25 to < 60 mL/min/1.73 m^2 and at 20 mg/day for those with an eGFR ≥ 60 mL/min/1.73 m^2. Monitoring requires assessment of renal function and electrolytes at 1, 4, and 12 weeks after treatment initiation, followed by reassessment every three to six months. Both medications may cause an early eGFR decrease of up to 10–15%; unless accompanied by symptoms of acute kidney injury, this does not usually require treatment discontinuation. Blood pressure should be monitored to avoid symptomatic hypotension, particularly in elderly patients and those receiving intensive antihypertensive therapy.[64]

Limitations

Despite the significant therapeutic advancements offered by SGLT2 inhibitors and finerenone in managing cardiorenal syndrome, several limitations must be acknowledged:

- Initial eGFR decline: Both drug classes can induce an early, hemodynamically mediated decrease in estimated glomerular filtration rate (eGFR) of up to 10–15%. Although this is generally expected and does not usually require treatment discontinuation unless accompanied by symptoms of acute kidney injury, it necessitates careful monitoring and may cause clinical hesitancy.
- Hyperkalemia risk: Although finerenone has a more favorable safety profile than traditional steroidal MRA, hyperkalemia remains an important clinical concern, especially in patients with advanced CKD. This requires strict adherence to monitoring protocols and dose adjustment rules based on serum potassium levels.
- Need for long-term combination data: Although early randomized data, such as those from the CONFIDENCE trial, and observational studies of concurrent SGLT2i and finerenone use are promising, comprehensive long-term data from large randomized controlled trials specifically evaluating this combined approach are still evolving. Results from ongoing trials, such as REDEFINE-HF, CONFIRMATION-HF, and FINALITY-HF, will be important for validating the safety, cost-effectiveness, and additive efficacy of this dual therapy across broader and more diverse patient populations.
- Clinical implementation challenges: Safe and effective implementation of these therapeutic options requires continuous monitoring of renal function, electrolytes, and blood pressure and a coordinated, multidisciplinary approach involving cardiologists, nephrologists, and endocrinologists, which may be challenging to implement consistently in real-world practice.

Conclusions

CRS remains a challenging clinical problem associated with high morbidity and mortality. The emergence of SGLT2i and finerenone has changed the therapeutic landscape by providing therapies with proven protective effects on both the heart and kidneys. SGLT2i consistently reduce heart failure hospitalization and slow renal function decline across the spectrum of ejection fractions and CKD stages. Similarly, finerenone reduces cardiovascular events and renal disease progression in patients with type 2 diabetes and CKD, while offering a more favorable safety profile than steroidal MRAs. Importantly, combined finerenone and SGLT2i therapy may provide additive benefits by reducing major adverse cardiovascular events and slowing renal disease progression more effectively than monotherapy alone. Implementing these treatments in clinical practice requires a multidisciplinary approach involving cardiologists, nephrologists, and endocrinologists to monitor renal function, electrolytes, and blood pressure. Ongoing trials, including REDEFINE-HF, CONFIRMATION-HF, and FINALITY-HF, will provide further evidence on combination therapy. In the era of integrated cardiorenal medicine, these advances offer new opportunities to improve outcomes and quality of life in patients with CRS and mark a clear move toward precise, individualized care based on underlying pathogenic mechanisms.

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Conflict of interest

The authors declare no competing interests relevant to the contents of this article.

Author contributions

Conception, literature review, writing, and critical revision of the manuscript (AF, ADS, PS, EB, LP, VB, LD, AB, PP, LDL). All authors read and approved the final version of the manuscript.

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