CARDIOLOGY

Cite as: Archiv EuroMedica. 2026. 16; 4. DOI 10.35630/2026/16/Iss.4.10

Received 26 July 2026;
Accepted 27 August 2026;
Published 28 August 2026

COMBINING SGLT2 INHIBITORS AND FINERENONE IN CARDIOVASCULAR-KIDNEY-METABOLIC (CKM) SYNDROME: A CLINICAL UPDATE

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ABSTRACT

Background

Patients with chronic kidney disease (CKD), particularly those with type 2 diabetes (T2D) and albuminuria, remain at substantial risk of kidney disease progression and cardiovascular complications despite established therapy. SGLT2 inhibitors and finerenone act through distinct and potentially complementary mechanisms.

Aims

To evaluate the mechanisms, clinical effects, and safety of combined SGLT2 inhibitor and finerenone therapy in patients with CKD, particularly those with T2D and albuminuria, and to consider these findings within the broader cardiovascular kidney metabolic (CKM) framework.

Materials and Methods

A narrative review was conducted using PubMed, Scopus, and Web of Science. Publications available up to June 2026 were considered. The search focused on SGLT2 inhibitors, finerenone, CKD, heart failure, eGFR, albuminuria, and cardiorenal syndrome. After removal of duplicates and application of eligibility criteria, 44 publications were retained for qualitative synthesis.

Results

SGLT2 inhibitors primarily affect glomerular hemodynamics, natriuresis, and metabolic pathways, whereas finerenone modulates mineralocorticoid receptor mediated inflammatory and fibrotic pathways. The CONFIDENCE trial showed that simultaneous initiation of finerenone and empagliflozin produced a greater reduction in UACR than either monotherapy over 180 days. Meta analytic and observational data suggest potential additional benefits for MAKE, ESRD, some cardiovascular outcomes, and all cause mortality, although these findings vary according to comparator and study design. Hyperkalemia risk may be lower than with finerenone monotherapy but remains higher than with SGLT2 inhibitor monotherapy in some comparisons. An early decline in eGFR was observed, whereas acute kidney injury and symptomatic hypotension were uncommon.

Conclusions

Combined SGLT2 inhibitor and finerenone therapy is a promising option for carefully selected patients with CKD, T2D, and albuminuria. The strongest randomized evidence concerns reduction in albuminuria, whereas evidence for long term kidney and cardiovascular outcomes and mortality remains limited. Hyperkalemia risk is not eliminated, and regular monitoring of serum potassium and kidney function remains necessary. Extrapolation to the broader CKM population and to patients with heart failure requires further investigation.

Keywords: cardiovascular-kidney-metabolic syndrome; chronic kidney disease; type 2 diabetes; albuminuria; finerenone; SGLT2 inhibitors; hyperkalemia.

INTRODUCTION

Coexisting conditions of heart failure and chronic kidney disease sets one of main challenges for modern cardiovascular medicine. Epidemiological data clearly indicate that more than 40–50% of patients diagnosed with heart failure (HF) present with impaired renal function. This large patient cohort has a poorer prognosis than patients with isolated HF or chronic kidney disease (CKD). The relative difference in mortality rates may be reaching up to 50% [1]. On the other hand, individuals with CKD have higher risk of hospitalization from HF, cardiovascular events and death. The hazard ratio increases inversely with the estimated glomerular filtration rate (GFR) [2]. The heart and kidneys operate in a tight symbiotic relationship. The pathophysiological relationship between these organs is bidirectional and synergistic[3]. Dysfunction in one accelerates damage or progression of existing condition in the other. It happens through hemodynamic mechanisms such as venous congestion and reduced perfusion, overactivation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system as well as chronic inflammation and fibrosis [4,5,6]. Cardiorenal syndrome refers specifically to the bidirectional interaction between cardiac and kidney dysfunction. CKM syndrome is a broader concept that additionally incorporates metabolic risk factors and encompasses patients across different stages of cardiovascular and kidney disease.

Recognizing how closely they are connected, the American Heart Association recently grouped them under a single framework called Cardiovascular-Kidney-Metabolic (CKM) syndrome [7,8]. By definition, this syndrome is a systemic illness where meta-

bolic risk factors, kidney disease, and heart conditions interact, leading to multi-organ damage and poor clinical outcomes. This new approach covers both individuals who are at risk of heart problems due to metabolic or kidney issues, and patients who already have heart disease caused by these conditions. Additionally, the development and severity of CKM syndrome are heavily shaped by social, economic, and environmental factors that pose challenges in lifestyle changes and proper self-care for patients.[9] For the purposes of this review, the clinical focus is narrowed to patients with chronic kidney disease, particularly those with type 2 diabetes and albuminuria, because most available evidence on combined SGLT2 inhibitor and finerenone therapy is derived from this population.

CKM syndrome involves interconnected hemodynamic, metabolic, inflammatory, and fibrotic pathways that contribute to cardiovascular and kidney disease progression [7]. Management therefore requires consideration of multiple mechanisms involved in both cardiovascular and kidney injury. Despite established therapies, patients with chronic kidney disease, particularly those with type 2 diabetes and albuminuria, remain at substantial residual risk of kidney disease progression and cardiovascular events [10].

SGLT2 inhibitors provide renal and cardiovascular protection through effects on glomerular hemodynamics, natriuresis, volume regulation, and metabolic pathways. Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, blocks mineralocorticoid receptor overactivation and modulates proinflammatory and profibrotic signaling. However, finerenone increases the risk of hyperkalemia, particularly in patients with impaired kidney function, and therefore requires serum potassium monitoring [11,12]. The different and potentially complementary actions of SGLT2 inhibitors and finerenone provide a rationale for evaluating their combined use.

RELEVANCE

Patients with chronic kidney disease, particularly those with type 2 diabetes and albuminuria, remain at high risk of kidney disease progression and cardiovascular complications despite established treatment. Finerenone provides additional kidney and cardiovascular protection in patients with chronic kidney disease and type 2 diabetes, but its use requires careful monitoring of serum potassium. It is therefore clinically important to determine whether combining finerenone with an SGLT2 inhibitor provides additional kidney and cardiovascular benefit while maintaining an acceptable safety profile.

Novelty

Recent evidence from 2025 and 2026, including the CONFIDENCE trial and subsequent comparative studies, provides new data on the simultaneous use of SGLT2 inhibitors and finerenone. These studies permit a more direct assessment of the effects and safety of combination therapy compared with either treatment used alone.

Research Gap

Although the benefits of SGLT2 inhibitors and finerenone as individual therapies are well established, randomized evidence on their simultaneous use remains limited and is concentrated mainly in patients with chronic kidney disease, type 2 diabetes, and albuminuria. The magnitude of additional benefit of combination therapy, its effects on kidney and cardiovascular outcomes, and its safety, particularly with respect to hyperkalemia, therefore require careful evaluation.

AIM

The aim of this narrative review is to evaluate the mechanisms, clinical effects, and safety of combined treatment with SGLT2 inhibitors and finerenone in patients with chronic kidney disease, particularly those with type 2 diabetes and albuminuria, and to consider these findings within the broader CKM framework.

The objectives were:

1. To describe the renal and cardiovascular mechanisms of SGLT2 inhibitors and finerenone.
2. To evaluate the available evidence on albuminuria, kidney outcomes, cardiovascular outcomes, and mortality with combination therapy compared with either treatment alone.
3. To assess the safety of combined therapy, particularly hyperkalemia, changes in eGFR, acute kidney injury, and hypotension.

MATERIALS AND METHODS

This article is a narrative review based on publications identified in PubMed, Scopus, and Web of Science. The search primarily considered publications from the preceding

10 years and included literature available up to June 2026. The search terms included “SGLT2 inhibitors”, “finerenone”, “heart failure”, “chronic kidney disease”, “eGFR”, “albuminuria”, and “cardiorenal syndrome”.

Eligible publications included randomized controlled trials, prospective and retrospective clinical cohort studies, observational studies, systematic reviews, clinical practice guidelines, and relevant experimental studies. The search was restricted to English language publications. Publications older than 10 years were generally excluded. However, older studies were included when they provided key or foundational evidence on mechanisms or basic concepts relevant to the pathophysiology and management of cardiovascular kidney metabolic syndrome that was not adequately covered by more recent publications. Case reports, conference abstracts, non peer reviewed articles, duplicate publications, correspondence lacking original data, publications without clear data on the interventions, and studies not relevant to the main subject of the review were excluded.

The initial database search yielded 189 records. After removal of duplicate entries and application of the eligibility criteria, 44 publications were retained for qualitative synthesis, including 40 publications from the preceding 10 years and 4 earlier publications included as key or foundational sources.

As this work represents a narrative review, no formal protocol registration, standardized risk of bias assessment, or independent duplicate screening procedures were applied. The methodology was intended to provide a structured and transparent overview of the available clinical evidence rather than a quantitative synthesis.

RESULTS

SGLT2 inhibitors mechanism

At the clinical level, the hemodynamic benefits of SGLT2 inhibitors are well documented in human trials. In the kidneys, these agents restore tubuloglomerular feedback by increasing sodium delivery to the macula densa, which induces afferent arteriolar vasoconstriction, mitigates intraglomerular hypertension, and halts progressive hyperfiltration-related renal decline [13,14,15]. Concurrently, mild osmotic diuresis and natriuresis selectively clear interstitial fluid, effectively reducing cardiac preload without inducing intravascular volume depletion or compensatory sympathetic overactiva-

tion [16]. In patients with heart failure, irrespective of diabetes status, randomized clinical trials such as the EMPA-TROPISM study have demonstrated that SGLT2 inhibition leads to favorable left ventricular reverse remodeling, reduced cavitary volumes, and enhanced cardiac efficiency [17].

Beyond these validated hemodynamic outcomes, several metabolic and molecular pathways have been hypothesized based on translational and laboratory models. The "thrifty substrate hypothesis" posits that SGLT2 inhibitors induce a metabolic switch toward beta- hydroxybutyrate utilization [18]. Mechanistically, this substrate utilization has been associated with improved cardiac energetics and attenuated oxidative stress, potentially mitigating mitochondrial dysfunction and supporting ATP synthesis in the failing myocardium [19]. On a macro-level, large animal models of non-diabetic heart failure have demonstrated that this fuel conversion directly enhances overall cardiac efficiency and reduces myocardial oxygen consumption[20].

However, the direct contribution of ketone oxidation to long-term clinical outcomes in humans requires further investigation. In preclinical models, SGLT2 inhibitors appear to simulate a low-nutrient state, promoting the activation of AMP-activated protein kinase (AMPK) and sirtuin-1 (SIRT1) alongside the inhibition of mammalian target of rapamycin (mTOR) [21,22]. This signaling cascade stimulates lysosomal autophagy and mitophagy, which facilitates the clearance of dysfunctional organelles and attenuates excessive generation of reactive oxygen species (ROS). The use of autophagy inhibitors or silencing of SIRT1/AMPK genes in rodents abolished the protective effect of flosins on the heart and kidneys, confirming a cause-and-effect relationship [21,22]. In animal models of cardiac remodeling, SGLT2 inhibitor administration has been shown to attenuate the activation of nuclear factor - κB (NF-κB) and the NLRP3 inflammasome complex [23]. In these in vivo systems, suppression of these inflammatory cascades was associated with a reduction in downstream pro-inflammatory signaling and a limitation of adverse fibrotic cardiac remodeling [23].

Finerenone (nsMRA) mechanism

Mineralocorticoid receptors (MRs) are widely distributed throughout the body, including the brain, lungs, colon, liver, and skeletal muscle. However, their predominant physiological activity is centered in the renal and cardiovascular systems, where they regulate sodium, potassium, and fluid homeostasis [24]. Pathological overactivation of MRs is clinically associated with mineralocorticoid-sensitive hypertension, progressive renal injury, and adverse ventricular remodeling in chronic heart failure [25].

Finerenone, a selective non-steroidal mineralocorticoid receptor antagonist (nsMRA), confers proven cardiorenal protection evidenced by phase III trials such as FIGARO-DKD [26,27]; however, it concurrently increases the incidence of hyperkalemia when compared to placebo, especially in patients with an elevated baseline risk for this adverse event [10].

Beyond these well-documented clinical outcomes, translational and preclinical investigations have delineated several underlying pathophysiological mechanisms. At the cellular level, MR hyperactivation is proposed to promote the generation of reactive oxygen species (ROS), driving persistent inflammation, tissue scarring, glomerular hyperfiltration, and glomerulosclerosis [25]. Furthermore, in vitro and molecular models suggest that MR stimulation directly induces vascular smooth muscle cell proliferation and arterial stiffness via the MR–VEGFR1 pathway, while podocyte dysfunction and progressive renal damage are linked to MR–Rac1 crosstalk [25,28]. Furthermore, evidence from humanized mouse models demonstrates that activation of the renin–angiotensin–aldosterone axis drives T-cell and macrophage infiltration into target organs, exacerbating local inflammation and tissue damage [28]. Consistently, endothelial cell–specific MR knockdown in animal models attenuates renal inflammation and fibrosis by suppressing pro-inflammatory macrophage differentiation and downregulating fibrogenic gene expression [29].

The principal mechanisms of SGLT2 inhibitors and finerenone, together with their potential complementary effects on renal function, potassium homeostasis, and cardiovascular outcomes, are summarized in Table 1.

Table 1. Mechanisms of SGLT2 Inhibitors and Finerenone and Their Potential Complementary Effects

FEATURE / MECHANISM	SGLT2 INHIBITORS	FINERENONE (NSMRA)	POTENTIAL COMPLEMENTARY EFFECTS
Primary mechanism	Restores tubuloglomerular feedback, induces osmotic diuresis, optimizes cardiac fuel utilization (beta hydroxybutyrate) [13–18]	Nonsteroidally blocks overactivated mineralocorticoid receptors (MR) in the heart and kidneys [24,25]	Hemodynamic optimization combined with anti inflammatory and anti fibrotic effects [13–18,24,25]
Renal function	Reduces intraglomerular pressure, restores macula densa feedback, and mitigates hyperfiltration driven decline [13–15]	Inhibits glomerular hypertrophy, podocyte injury, glomerulosclerosis, and interstitial fibrosis associated with MR overactivation [24,25,28,29]	Potential complementary renal protection through hemodynamic effects and suppression of MR mediated inflammatory and fibrotic pathways [13–15,24,25,28,29]
Potassium (K+) homeostasis	Enhances distal sodium delivery and promotes urinary potassium excretion [36]	Increases the risk of potassium retention and hyperkalemia through MR blockade [35]	SGLT2i therapy may partially attenuate finerenone associated hyperkalemia, although hyperkalemia risk is not eliminated [32–34]
Cardiovascular outcomes	Decreases cardiac preload and may improve left ventricular remodeling and cardiac efficiency [17,20,23]	Reduces cardiovascular risk and heart failure related outcomes in patients with CKD and T2D [26,27]	Potential complementary cardiovascular protection through distinct hemodynamic and MR mediated pathways [17,20,23,26,27]

Clinical evidence for the SGLT2i and finerenone combination

To directly test the benefits of combining finerenone with a sodium-glucose cotransporter 2 inhibitor, researchers launched the CONFIDENCE trial (COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with CKD and type 2 diabetes using a UACR Endpoint). This international, multicenter phase 2 trial compared three treatment strategies in patients with chronic kidney disease and type 2 diabetes (T2D). In the final trial, 818 participants were randomized, and the main analysis included 800 participants with CKD and T2D and a UACR ≥100 to <5000 mg/g [32]. Participants were randomly assigned to three treatment groups for a 180 day treatment period: a combination therapy group receiving finerenone and empagliflozin, and two monotherapy groups receiving either agent with a matching placebo. The primary objective was to determine whether simultaneous initiation of finerenone and empagliflozin resulted in a greater reduction in the urine albumin-to-creatinine ratio (UACR) after 180 days than either monotherapy. Additionally, the study monitored safety outcomes, focusing on early changes in the estimated glomerular filtration rate (eGFR) and the frequency of hyperkalemia [30].

The published baseline characteristics of the CONFIDENCE cohort confirm that the enrolled population represents high-risk individuals with advanced cardiorenal risk. The participants had a mean age of 66,5 years and presented with moderate glycemic con-

trol, indicated by a mean HbA1c of 7,3%. Notably, the cohort presented with significant renal impairment, demonstrated by a mean baseline eGFR of 54,2 mL/min/1.73 m^2 and severe macroalbuminuria, indicated by a median baseline UACR of 583,44 mg/g. Additionally 28% of the population had pre-existing atherosclerotic cardiovascular disease, including 4% with established heart failure, establishing this group as a highly relevant model for evaluating aggressive, dual-mechanism cardioprotective and renoprotective therapies[31]. Regarding efficacy and safety across the spectrum of kidney disease, the CONFIDENCE trial showed that starting finerenone and empagliflozin together reduces albuminuria more effectively than either monotherapy alone. This superior efficacy was visible as early as 14 days after randomization and lasted through day 180. Powerful relative UACR reductions occurred across all KDIGO risk categories, reaching-61.7% in the low/moderate-risk group, -60.7% in the high-risk group, and -52.4% in the very high-risk group. Additionally, a significantly larger percentage of patients in the combination therapy arm achieved a clinically meaningful reduction in UACR of more than 30% compared to those on single-drug regimens.

From a safety point of view, although serum potassium levels increased in both the finerenone and combination groups, the risk of treatment-emergent hyperkalemia adverse events was consistently lower with dual therapy than with finerenone monotherapy. Early, transient declines in estimated glomerular filtration rate (a >30% eGFR dip at day 30) were more common in the low/moderate-risk subgroup (12.1%) than in the very high-risk population (4.4%). Both nsMRAs and SGLT2 inhibitors independently induced early hemodynamic drops in eGFR, co-initiating these agents produced an additive transient acute eGFR drop. However, investigator-reported acute kidney injury remained infrequent ≤ 3% across all cohorts. Finally, while dual therapy led to early blood pressure reductions, symptomatic hypotension was exceedingly rare, occurring in only two patients within the very high-risk group[32].

Separate from short-term RCT evidence, data regarding hard clinical endpoints have been evaluated in meta-analyses and retrospective cohort studies, with outcomes depending directly on the specific comparator drug used. Providing further high-level evidence, a systematic review and meta-analysis by Chen-Fu Wen and colleagues evaluated the efficacy and safety of combining SGLT2 inhibitors with finerenone in patients with chronic kidney disease (CKD). In total, this meta-analysis included eight studies with a combined population of 1,580 patients. The results showed that combination therapy significantly improved survival, reducing all-cause mortality specifically when compared to finerenone monotherapy (OR = 0.58; 95% CI: 0.36–0.93). Dual therapy also lowered the risks of major adverse cardiovascular events (MACE) (OR = 0.70; 95%

CI: 0.51–0.97) and major adverse kidney events (MAKE) (OR = 0.63; 95% CI: 0.44–0.89) when compared to finerenone alone. Furthermore, the combination achieved a 10% greater reduction in the urinary albumin-creatinine ratio (UACR) than finerenone monotherapy (mean difference = 0.10; 95% CI: 0.00–0.19; p = 0.045). Nonetheless, when evaluated against SGLT2 inhibitor monotherapy, combination therapy conferred no significant reduction in composite renal endpoints relative to SGLT2 inhibitor monotherapy, while being associated with an increased incidence of hyperkalemia (OR = 3.00; 95% CI: 2.50–3.61). Ultimately, the authors concluded that combining finerenone with an SGLT2i may improve survival and reduce cardiorenal risks compared to finerenone monotherapy in patients with diabetic CKD, supporting careful consideration of this dual therapy, particularly in high-risk populations[33].

Distinct from these pooled findings, real world observational data were provided by a 2025 retrospective study by Min-Hsiang Chuang and colleagues, which compared combination therapy with either SGLT2i or finerenone monotherapy in relation to kidney, cardiovascular, and mortality outcomes in patients with CKD. This retrospective cohort study used data from the TriNetX database and included 47,743 adults with CKD. Combination therapy was associated with a lower risk of major adverse kidney events (MAKE) than either monotherapy. Specifically, combination therapy was associated with a lower risk of MAKE compared with finerenone alone (adjusted hazard ratio [aHR] = 0.20; 95% CI: 0.09–0.45) and SGLT2i alone (aHR = 0.44; 95% CI: 0.22–0.89).

Patients on both drugs also had a much lower risk of developing end-stage renal disease (ESRD) and a lower rate of all cause mortality compared to monotherapies. Crucially, the risk of major adverse cardiovascular events (MACE) was similar between all groups, with no significant difference observed. In terms of safety, taking both medications together led to a higher risk of hyperkalemia compared to taking an SGLT2i alone (aHR = 1.36; 95% CI: 1.08–1.71). This finding highlights that while the combination offers powerful benefits for the kidneys, doctors still need to check serum potassium levels regularly in everyday clinical practice[34].

Potassium homeostasis

Nonsteroidal MRAs such as finerenone inherently carry a risk of inducing hyperkalemia [35]. Concomitant use of SGLT2 inhibitors may partially attenuate this complication. From a mechanistic standpoint, SGLT2 inhibitors enhance distal nephron sodium delivery and promote osmotic diuresis, which subsequently accelerates urinary potassium

excretion. In clinical trials, SGLT2 inhibitors lowered the incidence of severe hyperkalemia without increasing the risk of hypokalemia in patients with type 2 diabetes and high cardiovascular risk or CKD [36]. However, the overall risk profile depends critically on the comparator. Combination therapy carries a significantly higher risk of hyperkalemia compared with SGLT2 inhibitor monotherapy alone, as demonstrated in both pooled meta analyses and real world cohort studies. Therefore, the combination does not eliminate electrolyte risk and requires routine serum potassium monitoring, particularly in patients with advanced chronic kidney disease [33,34].

The key clinical evidence on the efficacy and safety of combined SGLT2 inhibitor and finerenone therapy is summarized in Table 2.

Table 2. Summary of Key Clinical Evidence Supporting SGLT2i and Finerenone Combination Therapy

STUDY & DESIGN	STUDY POPULATION & INTERVENTIONS	KEY EFFICACY FINDINGS	SAFETY & TOLERABILITY OUTCOMES
CONFIDENCE Trial [32] (Phase 2 RCT)	n = 818 adults with CKD and T2D, UACR 100 to <5000 mg/g (median UACR 583.44 mg/g), the main analysis included 800 patients. Dual therapy (Finerenone + Empagliflozin) vs. Monotherapy (Finerenone or Empagliflozin)	Dual therapy achieved significantly greater relative UACR reduction at day 180 (-52,4% - 61,7%) across KDIGO risk category: Combination therapy produced a 29% greater reduction in UACR vs. Finerenone alone: UACR reduction at day 180 (-34,3% - 48,1%) across KDIGO risk category. Combination therapy produced a 32% greater reduction in UACR vs. Empagliflozin alone: UACR reduction at day 180 (-28,1% - 38,3%) across KDIGO risk category. A significantly higher proportion of patients achieved a >30% UACR reduction with dual therapy vs. either monotherapy alone.	Dual therapy was associated with lower hyperkalemia rates compared with finerenone monotherapy. Both nsMRA and SGLT2i induce an early, hemodynamically mediated reduction in eGFR; their simultaneous initiation resulted in an additive acute "eGFR dip" (>30% dip occurred in 12.1% of low/moderate-risk vs. 4.4% of very high-risk patients), which was transient and not associated with increased AKI. AKI infrequent (≤ 3%)
Wen et al. [33] (Meta-Analysis)	8 studies, n = 1,580 patients with CKD. SGLT2i + Finerenone vs. Finerenone monotherapy or SGLT2i monotherapy	Combination vs. Finerenone Monotherapy: Reduced risk of all-cause mortality (OR = 0.58; 95% CI: 0.36–0.93, p = 0.02). Reduced risk of MACE (OR = 0.70; 95% CI: 0.51–0.97, p = 0.03). Reduced risk of MAKE (OR = 0.63; 95% CI: 0.44–0.89, p < 0.01). Additional significant UACR reduction (~10% greater decline, p = 0.045). Combination vs. SGLT2i Monotherapy: no significant difference in risk of all-cause mortality was observed (OR = 0.73; 95% CI 0.47-1.13; p = 0.16). risk of MACE: the difference was not statistically significant (OR = 0.77; 95% CI: 0.55–1.08; p = 0.14). risk of MAKE: No significant difference was observed (OR = 0.87; 95% CI: 0.58–1.31; p = 0.51).	Compared to SGLT2i monotherapy, combination therapy was associated with a higher risk of hyperkalemia (OR = 3.00; 95% CI: 2.50–3.61; p < 0.01). There was no significant difference in the risk of hyperkalemia between the combination and finerenone alone.

Chuang et al. [34] (Retrospective Cohort)	n = 47,743 adults with CKD (TriNetX database). Dual therapy vs. SGLT2i monotherapy or Finerenone monotherapy	Risk of MAKE: Dual therapy was associated with a significantly lower risk compared to finerenone alone (aHR = 0.20; 95% CI: 0.09–0.45) and vs. SGLT2i alone (aHR = 0.44; 95% CI: 0.22–0.89). all-cause mortality were lower in the combined group compared with finerenone monotherapy (aHR 0.31; 95% CI 0.12–0.82; P =0 .013) or SGLT2i monotherapy (aHR 0.41; 95% CI 0.17–0.96; P =0 .035). Risk of MACE: No significant risk difference was observed between combination therapy and finerenone monotherapy (aHR 0.77; 95% CI 0.27–2.26; P =0 .640) or SGLT2i monotherapy (aHR 0.66; 95% CI 0.27–1.61; P =0 .362).	Compared to SGLT2i monotherapy, combination therapy was associated with a higher risk of hyperkalemia (aHR = 1.36; 95% CI: 1.08–1.71)

DISCUSSION

In patients with chronic kidney disease, particularly those with type 2 diabetes and albuminuria, SGLT2 inhibitors and finerenone have distinct and potentially complementary mechanisms of kidney and cardiovascular protection. Finerenone has been shown to reduce kidney and cardiovascular risk in patients with CKD and type 2 diabetes, including the risk of heart failure hospitalization [10,26,27,37]. The ARTS-HF trial was designed to compare finerenone with eplerenone in patients with worsening chronic heart failure and diabetes and/or CKD [38]. However, finerenone should not be considered a replacement for conventional steroidal MRAs in the standard treatment of HFrEF. The available evidence supports evaluating finerenone and SGLT2 inhibitors as combination therapy primarily in patients with diabetic CKD rather than as a modification of standard HFrEF therapy. Although finerenone increases the risk of hyperkalemia, concomitant treatment with an SGLT2 inhibitor may attenuate this risk compared with finerenone monotherapy [32]. Nevertheless, hyperkalemia risk is not eliminated, and regular monitoring of serum potassium and kidney function remains necessary during combined treatment.

The available clinical evidence supports a cautious interpretation of the benefits of combined SGLT2 inhibitor and finerenone therapy. The CONFIDENCE trial provides randomized evidence that simultaneous initiation of finerenone and empagliflozin produces a greater reduction in UACR than either treatment alone over 180 days [32]. However, CONFIDENCE was not designed to establish effects on long term kidney out-

comes, MACE, ESRD, or mortality. The trial also showed an early decline in eGFR with combination therapy, whereas acute kidney injury and symptomatic hypotension were uncommon [32]. Evidence for major clinical outcomes comes mainly from the meta analysis by Wen et al. [33] and observational studies by Chuang et al. [34] and Mortada et al. [39]. Compared with finerenone monotherapy, combination therapy was associated with lower risks of several cardiovascular and kidney outcomes, whereas compared with SGLT2 inhibitor monotherapy, benefits were less consistent and the risk of hyperkalemia was higher [33,34]. In Chuang et al., combination therapy was associated with lower risks of MAKE, ESRD, and all cause mortality, while no advantage was observed for MACE [34]. These differences should be considered when assessing the overall benefit and safety of combination therapy and when extrapolating the findings beyond patients with CKD, type 2 diabetes, and albuminuria.

Current clinical guidelines support the use of SGLT2 inhibitors and finerenone in appropriately selected patients with type 2 diabetes and CKD. KDIGO 2022 indicates that a nonsteroidal MRA may be added to RAS inhibition and an SGLT2 inhibitor in eligible patients [40]. ADA recommendations also include SGLT2 inhibitors and nonsteroidal MRAs among treatment options for reducing cardiovascular and kidney risk in appropriate patients with type 2 diabetes and CKD [41]. These recommendations support an individualized approach rather than routine combined therapy in all high risk patients.

Emerging evidence also suggests potential benefit from adding GLP1 receptor agonists to treatment strategies that include SGLT2 inhibitors and finerenone. FIDELITY analyses indicate that the effects of finerenone on UACR, blood pressure, and eGFR were generally maintained across different background therapies [42,43]. However, the number of patients receiving both SGLT2 inhibitors and GLP1 receptor agonists was limited, and background therapies were not randomized. Therefore, triple therapy should currently be regarded as a promising treatment strategy requiring further prospective evaluation rather than as an established synergistic approach with proven benefits on major clinical outcomes [44].

Limitations

This narrative review has several limitations. First, randomized evidence on the simultaneous use of SGLT2 inhibitors and finerenone remains limited. The CONFIDENCE trial had a relatively short follow up period of 180 days and primarily evaluated change in UACR rather than long term kidney, cardiovascular, or mortality outcomes. Second, the available evidence includes studies with different designs, populations, comparators,

and outcome definitions, including retrospective observational analyses, which limits direct comparison between studies. Third, most clinical data on combined therapy are derived from patients with chronic kidney disease, type 2 diabetes, and albuminuria. Therefore, these findings should not be directly generalized to the broader CKM population or to all patients with heart failure. Finally, as this is a narrative review, no formal risk of bias assessment or quantitative synthesis of the included studies was performed.

CONCLUSION

Combined therapy with SGLT2 inhibitors and finerenone in patients with chronic kidney disease, particularly those with type 2 diabetes and albuminuria, is based on distinct and potentially complementary mechanisms of action. SGLT2 inhibitors primarily affect intraglomerular hemodynamics, natriuresis, and metabolic pathways, whereas finerenone blocks pathological mineralocorticoid receptor activation and the associated inflammatory and fibrotic processes.

The most convincing randomized evidence concerns the reduction of albuminuria. In the CONFIDENCE trial, simultaneous initiation of finerenone and empagliflozin resulted in a greater reduction in UACR than either monotherapy. Data on MAKE, ESRD, some cardiovascular outcomes, and all cause mortality suggest potential additional benefits of combination therapy, although these findings are derived mainly from a meta analysis and observational studies and therefore require cautious interpretation.

From a safety perspective, the combination showed generally acceptable tolerability. The risk of hyperkalemia may be lower than with finerenone monotherapy, but it is not eliminated and remains higher than with SGLT2 inhibitor monotherapy in some comparisons. An early decline in eGFR was observed with combination therapy, whereas acute kidney injury and symptomatic hypotension were uncommon. Regular monitoring of serum potassium and kidney function therefore remains necessary during combined treatment.

Overall, the available evidence supports consideration of this combination primarily in carefully selected patients with CKD, type 2 diabetes, and albuminuria. Extrapolation of these findings to the broader CKM population and to patients with heart failure requires further investigation.

DISCLOSURE

Author Contributions

Conceptualization: Przemysław Krukowski, Zuzanna Gąsior. Methodology: Mateusz Zdaniewicz, Adrianna Przedborska. Formal analysis: Michał Stermach, Kacper Ćwiek. Investigation: Michał Maciejowski, Maria Grabowska. Writing – original draft: Zuzanna Gąsior. Writing – review and editing: Przemysław Krukowski. Supervision: Zuzanna Lecyk, Agata Leszek.

All authors have read and agreed to the final version of the manuscript.

Funding

The article did not receive any funding.

Conflict of Interest

The authors declare no conflicts of interest.

Use of Artificial Intelligence

The authors declare that no artificial intelligence tools were used in the generation, writing, editing, or revision of this manuscript. All content was created solely by the authors.

REFERENCES

1. Hein AM, Scialla JJ, Sun JL, Greene SJ, Shaw LK, Chiswell K, et al. Estimated Glomerular Filtration Rate Variability in Patients With Heart Failure and Chronic Kidney Disease. J Card Fail. 2021;27(11):1175-1184. https://doi.org/10.1016/j.cardfail.2021.04.016
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-1305. https://doi.org/10.1056/NEJMoa041031
3. Marques M, Cobo M, López-Sánchez P, García-Magallón B, Salazar MLS, López-Ibor JV, et al. Multidisciplinary approach to patients with heart failure and kidney disease:

preliminary experience of an integrated cardiorenal unit. Clin Kidney J. 2023;16(11):2100-2107. https://doi.org/10.1093/ckj/sfad169

4. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J. 2010;31(6):703-711. https://doi.org/10.1093/eurheartj/ehp507
5. Zannad F, Rossignol P. Cardiorenal Syndrome Revisited. Circulation. 2018;138(9):929-944. https://doi.org/10.1161/CIRCULATIONAHA.117.028814
6. Alvi A, Singamala H, Gadde SSV, Javvaji CK. The Intersection of Heart Failure and Chronic Kidney Disease: Challenges in Co-management. Cureus. 2026;18(1):e100993. https://doi.org/10.7759/cureus.100993
7. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, et al. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. Circulation. 2023;148(20):1606-1635. https://doi.org/10.1161/CIR.0000000000001184
8. Rangaswami J, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, et al. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. Circulation. 2019;139(16):e840-e878. https://doi.org/10.1161/CIR.0000000000000664
9. Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, et al. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. Circulation. 2023;148(20):1636-1664. https://doi.org/10.1161/CIR.0000000000001186
10. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. N Engl J Med. 2020;383(23):2219-2229. https://doi.org/10.1056/NEJMoa2025845
11. Secora AM, Shin JI, Qiao Y, Alexander GC, Chang AR, Inker LA, et al. Hyperkalemia and Acute Kidney Injury with Spironolactone Use Among Patients with Heart Failure. Mayo Clin Proc. 2020;95(11):2408-2419. https://doi.org/10.1016/j.mayocp.2020.03.035
12. Agarwal R, Kolkhof P, Bakris G, Bauersachs J, Haller H, Wada T, et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. Eur Heart J. 2021;42(2):152-161. https://doi.org/10.1093/eurheartj/ehaa736
13. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129(5):587-597. https://doi.org/10.1161/CIRCULATIONAHA.113.005081

14. Tang J, Ye L, Yan Q, Zhang X, Wang L. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Water and Sodium Metabolism. Front Pharmacol. 2022;13:800490. https://doi.org/10.3389/fphar.2022.800490

15. Bjornstad P, Greasley PJ, Wheeler DC, Chertow GM, Langkilde AM, Heerspink HJL, et al. The Potential Roles of Osmotic and Nonosmotic Sodium Handling in Mediating the Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Heart Failure. J Card Fail. 2021;27(12):1447-1455. https://doi.org/10.1016/j.cardfail.2021.07.003

16. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes Obes Metab. 2018;20(3):479-487. https://doi.org/10.1111/dom.13126

17. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, Garcia-Ropero A, Mancini D, Pinney S, et al. Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction. J Am Coll Cardiol. 2021;77(3):243-255. https://doi.org/10.1016/j.jacc.2020.11.008

18. Ferrannini E, Mark M, Mayoux E. CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis. Diabetes Care. 2016;39(7):1108-1114. https://doi.org/10.2337/dc16-0330

19. Yurista SR, Nguyen CT, Rosenzweig A, de Boer RA, Westenbrink BD. Ketone bodies for the failing heart: fuels that can fix the engine? Trends Endocrinol Metab. 2021;32(10):814-826. https://doi.org/10.1016/j.tem.2021.07.006

20. Santos-Gallego CG, Requena-Ibanez JA, San Antonio R, Ishikawa K, Watanabe S, Picatoste B, et al. Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics. J Am Coll Cardiol. 2019;73(15):1931-1944. https://doi.org/10.1016/j.jacc.2019.01.056

21. Packer M. SGLT2 Inhibitors Produce Cardiorenal Benefits by Promoting Adaptive Cellular Reprogramming to Induce a State of Fasting Mimicry: A Paradigm Shift in Understanding Their Mechanism of Action. Diabetes Care. 2020;43(3):508-511. https://doi.org/10.2337/dci19-0074

22. Packer M. Critical Reanalysis of the Mechanisms Underlying the Cardiorenal Benefits of SGLT2 Inhibitors and Reaffirmation of the Nutrient Deprivation Signaling/Autophagy Hypothesis. Circulation. 2022;146(18):1383-1405. https://doi.org/10.1161/CIRCULATIONAHA.122.061732

23. Quagliariello V, De Laurentiis M, Rea D, Barbieri A, Monti MG, Carbone A, et al. The SGLT-2 inhibitor empagliflozin improves myocardial strain, reduces cardiac fibrosis and pro-inflammatory cytokines in non-diabetic mice treated with doxorubicin. Cardiovasc Diabetol. 2021;20(1):150. https://doi.org/10.1186/s12933-021-01346-y

24. Lv R, Xu L, Che L, Liu S, Wang Y, Dong B. Cardiovascular-renal protective effect and molecular mechanism of finerenone in type 2 diabetic mellitus. Front Endocrinol (Lausanne). 2023;14:1125693. https://doi.org/10.3389/fendo.2023.1125693

25. Barrera-Chimal J, Bonnard B, Jaisser F. Roles of Mineralocorticoid Receptors in Cardiovascular and Cardiorenal Diseases. Annu Rev Physiol. 2022;84:585-610. https://doi.org/10.1146/annurev-physiol-060821-013950

26. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, et al. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. N Engl J Med. 2021;385(24):2252-2263. https://doi.org/10.1056/NEJMoa2110956

27. Filippatos G, Anker SD, Agarwal R, Ruilope LM, Rossing P, Bakris GL, et al. Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial. Circulation. 2022;145(6):437-447. https://doi.org/10.1161/CIRCULATIONAHA.121.057983

28. Ferreira NS, Tostes RC, Paradis P, Schiffrin EL. Aldosterone, Inflammation, Immune System, and Hypertension. Am J Hypertens. 2021;34(1):15-27. https://doi.org/10.1093/ajh/hpaa137

29. Bauersachs J, López-Andrés N. Mineralocorticoid receptor in cardiovascular diseases-Clinical trials and mechanistic insights. Br J Pharmacol. 2022;179(13):3119-3134. https://doi.org/10.1111/bph.15708

30. Green JB, Mottl AK, Bakris G, Heerspink HJL, Mann JFE, McGill JB, et al. Design of the COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint study (CONFIDENCE). Nephrol Dial Transplant. 2023;38(4):894-903. https://doi.org/10.1093/ndt/gfac198

31. Agarwal R, Green JB, Heerspink HJL, Mann JFE, McGill JB, Mottl AK, et al. COmbinatioN effect of FInerenone anD EmpaglifloziN in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint (CONFIDENCE) trial: baseline clinical characteristics. Nephrol Dial Transplant. 2025;40(8):1559-1569. https://doi.org/10.1093/ndt/gfaf022

32. Vaduganathan M, Green JB, Heerspink HJL, Kim SG, Mann JFE, McGill JB, et al. Simultaneous initiation of finerenone and empagliflozin across the spectrum of kidney risk in the CONFIDENCE trial. Nephrol Dial Transplant. 2025;41(1):161-170. https://doi.org/10.1093/ndt/gfaf160

33. Wen CF, Chuang MH, Wu VC, Chen JY. Efficacy of combined sodium-glucose cotransporter 2 inhibitors and finerenone in chronic kidney disease: a systematic review and meta-analysis. Front Pharmacol. 2026;17:1803971. https://doi.org/10.3389/fphar.2026.1803971

34. Chuang MH, Wang HY, Kan WC, Chien CC, Jiang MY, Huang YT, et al. Cardio-kidney outcomes for combined versus monotherapy with finerenone or SGLT2 inhibitors in patients with CKD. Nephrol Dial Transplant. 2025;40(10):1897-1905. https://doi.org/10.1093/ndt/gfaf064

35. Agarwal R, Joseph A, Anker SD, Filippatos G, Rossing P, Ruilope LM, et al. Hyperkalemia Risk with Finerenone: Results from the FIDELIO-DKD Trial. J Am Soc Nephrol. 2022;33(1):225-237. https://doi.org/10.1681/ASN.2021070942

36. Neuen BL, Oshima M, Agarwal R, Arnott C, Cherney DZ, Edwards R, et al. Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Hyperkalemia in People With Type 2 Diabetes: A Meta-Analysis of Individual Participant Data From Randomized, Controlled Trials. Circulation. 2022;145(19):1460-1470. https://doi.org/10.1161/CIRCULATIONAHA.121.057736

37. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023;44(37):3627-3639. https://doi.org/10.1093/eurheartj/ehad195

38. Pitt B, Anker SD, Böhm M, Gheorghiade M, Køber L, Krum H, et al. Rationale and design of MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF): a randomized study of finerenone vs. eplerenone in patients who have worsening chronic heart failure with diabetes and/or chronic kidney disease. Eur J Heart Fail. 2015;17(2):224-232. https://doi.org/10.1002/ejhf.218

39. Mortada I, Lee AW, Sahu A, Nwaogu C, Quach V, Mansour S, et al. Additive Cardiorenal Benefits of Finerenone and SGLT2 Inhibitor Combination Therapy in Diabetic CKD: A Propensity-Matched Real-World Study. Am J Cardiol. 2026;266:92-97. https://doi.org/10.1016/j.amjcard.2026.02.035

40. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022;102(5S):S1-S127. https://doi.org/10.1016/j.kint.2022.06.008

41. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S191-S202. https://doi.org/10.2337/dc23-S011

42. Singh AK, Anker SD, Pitt B, Rossing P, Ruilope LM, Ahlers C, et al. A FIDELITY Analysis on Finerenone With SGLT-2i and GLP-1RA in CKD. Kidney Int Rep. 2025;11(3):103704. https://doi.org/10.1016/j.ekir.2025.10.032

43. Rossing P, Anker SD, Filippatos G, Pitt B, Ruilope LM, Birkenfeld AL, et al. Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Sodium-Glucose

Cotransporter 2 Inhibitor Treatment: The FIDELITY Analysis. Diabetes Care. 2022;45(12):2991-2998. https://doi.org/10.2337/dc22-0294

44. Stougaard EB, Curovic VR, Hansen TW. Combining SGLT2is, GLP1-RAs and nsMRAs in Diabetes: A Scoping Review of Current and Future Perspectives. Diabetes Ther. 2025;16(5):799-811. https://doi.org/10.1007/s13300-025-01726-7

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