

REVIEW

Targeting Heart Disease in Cardiovascular–Kidney–Metabolic Syndrome: A Review of Novel Therapeutic Approaches with Prognostic and Quality-of-Life Impact

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Abstract: Cardiovascular-kidney-metabolic (CKM) syndrome describes the complex, bidirectional interplay among cardiovascular, renal, and metabolic dysfunctions, where impairment in one system accelerates decline in the others. This interconnected pathophysiology significantly elevates the risk and progression of heart disease, particularly heart failure, through mechanisms involving insulin resistance, systemic inflammation, neurohormonal activation, and endothelial dysfunction. In this context, therapeutic strategies targeting heart disease must address the multifaceted drivers of CKM. Recent advances highlight the need for an integrated, patient-centered approach that combines lifestyle interventions with pharmacological treatments tailored to individual cardiovascular risk. While foundational therapies such as RAAS inhibitors and statins remain essential, novel agents now offer additional prognostic and quality-of-life benefits. SGLT2 inhibitors have emerged as a cornerstone therapy, improving outcomes in heart failure with both preserved and reduced ejection fraction, independent of glycemic control. GLP-1 receptor agonists and dual GLP-1/GIP agonists like tirzepatide demonstrate cardiometabolic and renal protection, while finerenone shows promise in diabetic kidney disease and several heart failure phenotypes. These therapies not only target glycemic control but also reduce cardiovascular mortality, hospitalizations, and renal decline. Optimizing cardiovascular outcomes in CKM syndrome requires early, multifactorial therapeutic intervention, informed by evolving evidence and a deeper understanding of the heart–kidney–metabolism axis.

Keywords: heart failure, diabetes mellitus, obesity, chronic kidney disease, GLP-1 receptor agonists, SGLT2 inhibitors, mineralocorticoid-receptor antagonists, finerenone, cardiovascular-kidney-metabolic syndrome

INTRODUCTION

Heart disease is frequently observed in patients with CKM syndrome. There is a pathophysiological interplay between the cardiovascular, renal, and metabolic systems, where dysfunction in one organ can exacerbate impairment in others, which substantially increases the risk of developing heart failure. Patients with CKM syndrome usually present with overlapping conditions as type 2 diabetes, chronic kidney disease, and atherosclerotic cardiovascular disease, all of which contribute to functional and structural cardiac dysfunction.

Heart disease and cardiovascular mortality represent the main drivers of prognosis in all CKM syndrome comorbidities. Hence, special consideration should be directed toward understanding pathophysiological mechanisms through which all these metabolic risk factors converge toward cardiovascular impairment. Additionally, emphasis should be placed on the early and appropriate initiation of the right medication for the right patient, tailored to the estimated individual risk, particularly concerning the novel drug classes that have demonstrated beneficial effects across all components of the CKM syndrome: GLP1 receptor agonists, SGLT2 inhibitors, and the non-steroidal mineralocorticoid receptor antagonist finerenone.

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This review emphasises the role of the heart in the CKM spectrum, with particular interest in the therapeutic implications.

GLP-1 RECEPTOR AGONISTS

GLP-1 (glucagon-like peptide-1) is a natural hormone mainly released by intestinal L enteroendocrine cells residing in the distal jejunum, ileum, and colon, as a result to oral glucose intake. GLP-1 is classified as an incretin hormone because it stimulates insulin release from beta pancreatic cells, inhibits the release of glucagon and, along with that, hepatic glucose output, and reduces the rate of gastric emptying and promotes satiety by central appetite suppression. GLP-1 has a very short half-life of approximately 2 minutes, being quickly cleaved by dipeptidyl peptidase IV (DPP-4), a widely expressed enzyme, thereby limiting the strong insulin secretagogue effect of this hormone [1–3].

Owing to the very short half-life, the molecule of GLP-1 is not suitable for an adequate therapeutic agent. Nevertheless, researchers developed molecules capable of being adequate therapeutic agents: inhibitors of DPP-4, which are capable of prolonging the effects of natural GLP-1, and molecules that represent long-acting GLP-1 receptor agonists [1].

Apart from pancreas, GLP-1 receptors are expressed on various types of cells throughout the body and the finding of this widespread localization of receptors led to studies that demonstrated multiple effects beyond the well-known incretin actions, the so-called “pleiotropic effects”: in central nervous system, being involved in the regulation of appetite, in the cardiovascular system, being expressed both in cardiomyocytes and vascular cells, in the musculoskeletal system, gastrointestinal tract, regulating the motility or secretion, interfering in the gut-brain axis, in adipose tissue influencing fat metabolism through interaction with leptin, in kidneys at multiple levels (arterial and arteriolar smooth cells, glomerulus, juxtaglomerular cells, proximal tubule), modulating renal function both directly by altering glomerular hemodynamics and indirectly through less known direct interactions between gastrointestinal system and kidneys known as gut-renal axis [3–7]. Even in beta pancreatic cells, besides altering insulin or glucagon levels, the stimulation of GLP-1R could enhance beta-cell proliferation, inhibit apoptotic pathways, and induce expansion of islet mass [4].

Considering that diabetes mellitus and obesity serve as risk factors in the context of cardiovascular diseases, the effects of GLP-1 receptor agonists on the cardiovascular system are, to a considerable extent, mediated through modulation of these metabolic conditions.

Regarding their role as antidiabetic medications, all GLP-1RAs proved effective in glycemic control by reliably reducing fasting plasma glucose and HbA1c (up to a reduction of 56.2 mg/dl FPG levels and 2.1% for HbA1c levels, respectively) [8].

Obesity is strongly associated with the development of T2DM as excessive adipose tissue, particularly visceral fat, contributes to insulin resistance [9]. The central downregulation of appetite, accompanied by slowing the gastric evacuation, which induces a feeling of fullness, facilitates the reduction of overall calorie intake and the maintenance of a favorable long-term energy balance [3]. Large meta-analyses of the available RCTs proved that GLP-1 RA are effective in inducing weight loss and a reduction in the body mass index and in the waist circumference [8,10].

Conversely, an increasing body of evidence suggests that GLP-1RAs exert direct beneficial effects on various components of the cardiovascular system, independently of their impact on glycemic regulation and weight control.

As far as cardiomyocytes are concerned, the presence and the exact extent of GLP-1R expression are unclear, corroborated by limited evidence regarding the cellular localization of GLP-1R protein [11]. However, in cellular and animal models, besides metabolic effects, which could indirectly improve cardiac function, there is evidence that GLP-1 could restore crucial signaling pathways that could be altered by external stressors [7]. For example, GLP-1 could ameliorate the extent of ischemia-reperfusion injury by activating specific signaling pathways and inhibiting cardiomyocyte apoptosis [3]. Moreover, GLP-1 signaling is involved in reducing hyperglycemia-induced apoptosis of the cardiomyocytes by optimizing the signaling pathways from the sarcoplasmic reticulum and in lowering the extracellular matrix remodeling [12].

There is also important evidence that GLP-1 receptor stimulation influences various pathogenic mechanisms that are involved in atherogenesis. First of all, GLP-1 can mitigate endothelial dysfunction by inducing NOS-mediated vasodilation and by limiting the formation of advanced glycosylation end-products [3,13]. Additionally, GLP-1 is involved in improving lipid metabolism at several levels: with respect to gene expression, it downregulates genes of lipogenic enzymes and upregulates genes of lipolytic enzymes, reduces lipotoxicity by lowering lipid peroxidation, stimulates fatty acid oxygenation, inhibits HMG-CoA reductase and lowers cholesterol levels, ameliorates hepatic steatosis, lowers serum triglyceride levels and even reduces intestinal lipid absorption [3,14]. There are also described effects of enhanced cholesterol efflux from foam cells or suppression of foam cell formation [13]. Even an anti-inflammatory pathway is proposed with the downregulation of genes involved in inflammation and oxidative stress. Moreover, GLP-1 promotes an atherosclerotic plaque remodeling towards stabilization by reduction of matrix metalloproteinases (MMP), proteolytic enzymes involved in weakening of plaque fibrous caps and in increasing the risk of rupture [3,13].

GLP-1RA proved effects of blood pressure reduction both in preclinical and clinical studies, by as much as 6 mmHg (as it was found in DURATION-1 trial) [11,15]. There are several mechanisms possibly involved in this effect: the capacity of GLP-1RA to counteract the sympathetic nervous system hyperactivation, both at the central and peripheral nervous system level, the improvement in the endothelial function and therefore in vasodilation, and the possible effect on renal tubular mechanisms by increased natriuresis, which

was observed in experimental models of hypertension [16,17]. The effect of lowering blood pressure was consistent throughout the entire spectrum of renal function, from normal to severely reduced [18].

Diabetes affected individuals are at high risk of chronic kidney disease (CKD) (as many as 40% diabetic patients develop chronic kidney disease), diabetic nephropathy representing the leading cause of chronic kidney disease worldwide. However, in the CKD population, cardiovascular events constitute the primary contributor to mortality, due to enhanced atherosclerosis, arterial and valvular calcification, and amplification of myocardial fibrosis [19]. There is a clear rationale that reducing both the risk and progression of chronic kidney disease could play a pivotal role in decreasing the burden of cardiovascular complications in diabetic patients.

Apart from indirect beneficial effects of glycemic control, weight loss and blood pressure reduction upon renal function, there are described direct effects: increased natriuresis and diuresis, at least partially explained by inhibiting sodium-hydrogen exchanger 3 in proximal tubular cells, anti-inflammatory effects by inhibition of cytokine production and chemotactic recruitment of inflammatory cells, free-radical scavenging effects and direct glomerular hemodynamic effects [5,17,19].

Another pathophysiological mechanism seemingly targeted by this therapeutic class is the modulation of the renin–angiotensin–aldosterone system, as there was been proven that GLP-1RA could induce a decrease in plasma levels of renin and angiotensin II. The effect of lowering the activity of this system could contribute to the effect of lowering blood pressure, the enhanced natriuresis, and could influence glomerular hemodynamics by vasodilation of the efferent arteriole and reduction of glomerular capillary pressure [18].

Beyond the pathophysiological effects demonstrated at the experimental level, the clinically relevant renoprotective effects include the reduction of albuminuria and, as evidenced by several studies, a reduction in eGFR decline [18,20].

Transitioning from experimental models and pathophysiological mechanisms to clinical evidence, GLP-1RA use in practice is supported by results from representative large-scale cardiovascular outcome trials. These studies have positioned GLP-1 receptor agonists as a distinct class among antidiabetic medications, with benefits that go beyond mere glycemic regulation.

There are 8 cardiovascular outcomes randomized controlled trials (CVOTs) for 7 different GLP-1RA (lixisenatide, liraglutide, semaglutide s.c., oral semaglutide, exenatide, albiglutide, dulaglutide, efglenatide) which included type 2 diabetic patients with high cardiovascular risk or previous cardiovascular disease. Four different GLP-1RAs, namely liraglutide, semaglutide s.c., dulaglutide, and efglenatide, proved efficient in reducing a composite end-point of major adverse cardiac events MACE (comprising cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke)[21]. However, analyzing the hazard ratio for individual components of MACE, there is a clear heterogeneity between these molecules. A meta-analysis which included all 8 RCTs, comprising a total of 60.080 patients (72.4% having established cardiovascular disease), concluded that GLP-1RA class reduce MACE by 14% (HR = 0.86, 95% CI 0.79–0.94, P = 0.006), with significant effects on the risk of cardiovascular death by 13% (P = 0.016) and nonfatal stroke by 16% (P = 0.007) [22]. Another meta-analysis, which included the same RCTs but ELIXA (the RCT examining lixisenatide), because lixisenatide is a short-acting agent that raised concerns regarding the lack of sustained GLP-1 inhibition in patients, GLP-1 RA proved effective in reducing MACE by 14% (HR 0.86 [95% CI 0.80–0.93]; p<0.0001), cardiovascular death by 13% (HR 0.87 [0.80–0.94]; p=0.0010), stroke by 17% (0.83 [0.76–0.92; p=0.0002], and, in addition to the other meta-analysis, myocardial infarction by 10% (0.90 [0.83–0.98]; p=0.020) [23]. Additionally, both meta-analyses proved a significant 12% reduction in all-cause mortality [22,23].

Table 1: Major CVOTs of GLP-1RA [21] (Although promising results, albiglutide was withdrawn from the market by the manufacturer due to commercial reasons)

TRIAL	ELIXA	LEADER	SUSTAIN-6	EXSCEL	Harmony Outcomes	REWIND	PIONEER-6	AMPLITUDE-O	SELECT
DRUG	<i>Lixisenatide</i>	<i>Liraglutide</i>	<i>Semaglutide s.c.</i>	<i>Exenatide</i>	<i>Albiglutide</i>	<i>Dulaglutide</i>	<i>Semaglutide oral</i>	<i>Efglenatide</i>	<i>Semaglutide s.c.</i>
POPULATION	T2DM	T2DM	T2DM	T2DM	T2DM	T2DM	T2DM	T2DM	BMI>27 kg/m ²
MACE HR (95% CI)	1.02** (0.89–1.17)	0.87 (0.78–0.97)	0.74 (0.58–0.95)	0.91 (0.83–1.00)	0.78 (0.68–0.90)	0.88 (0.79–0.99)	0.79 (0.57–1.11)	0.73 (0.58–0.92)	0.80 (0.72–0.90)
CV DEATH HR (95% CI)	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.93 (0.73–1.19)	0.91 (0.78–1.06)	0.49 (0.27–0.92)	0.72 (0.50–1.03)	0.85 (0.71–1.01)
MI HR (95% CI)	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.75 (0.61–0.90)	0.96 (0.79–1.15)	1.18 (0.73–1.90)	0.78 (0.55–1.10)	0.72 (0.61–0.85)
STROKE HR (95% CI)	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	0.86 (0.66–1.14)	0.76 (0.61–0.95)	0.74 (0.35–1.57)	0.80 (0.48–1.31)	0.93 (0.74–1.15)

Taking into account the various pleiotropic effects of GLP-1, there has emerged the hypothetical idea of using GLP-1RA in individuals without diabetes. In 2023, the results of the SELECT trial were published, a randomized controlled trial that included overweight patients (BMI > 27 kg/m²) with a history of cardiovascular disease but without diabetes. Subcutaneous semaglutide proved efficient, compared to placebo, in reducing MACE by 20% (HR 0.80 [0.72 to 0.90]; p < 0.001), mainly driven by a statistically significant reduction of myocardial infarction risk by 28% [24].

These solid results, from large, reputable RCTs, have been translated into guideline recommendations. According to the 2024 ESC Guidelines for the management of chronic coronary syndromes and the 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes, GLP-1RAs have a class I (level of evidence A) recommendation in patients with diabetes mellitus type 2 and history of atherosclerotic cardiovascular disease to reduce incident MACE [25,26]. This recommendation stands regardless of the baseline or target HbA1c or any other antidiabetic medications the patient may be taking. Additionally, consistent with the SELECT trial, the 2024 ESC Guidelines for the management of chronic coronary syndromes (CCS) included a IIa (level of evidence B) recommendation for the utilization of subcutaneous semaglutide in overweight (BMI > 27 kg/m²) CCS patients to mitigate the risk of cardiovascular mortality and myocardial infarction [24,25].

As far as kidney outcomes are concerned, there is an RCT specifically designed to assess renal endpoints. The FLOW trial included 3533 patients with type 2 diabetes mellitus and CKD (defined as eGFR 50-75 ml/min/1.73m² and macroalbuminuria UACR >300 mg/g or eGFR 25-50 ml/min/1.73m² and albuminuria UACR >100 mg/g) and compared subcutaneous semaglutide with placebo. The results showed that subcutaneous semaglutide reduced the risk of a primary outcome (defined as a composite of major renal adverse events comprising new onset of kidney failure, a reduction of eGFR of at least 50% from baseline, or death from kidney or cardiovascular-related causes) with 24% (HR 0.76; [0.66 to 0.88]; p = 0.0003) [27]. There is also some evidence toward improving kidney outcomes emerging from the pivotal CVOTs of GLP-1RA and from the meta-analyses which assessed them, but with a lower degree of statistical power as the conclusions are derived from secondary outcomes or exploratory assessments, and the renal benefits were demonstrated through the reduction in the progression of albuminuria, with fewer effects observed on hard end-points [21].

With regard to heart failure, the aforementioned meta-analyses reported a 10% risk reduction of heart failure hospitalizations, but this result was driven only by the reduction reported in the AMPLITUDE-O trial, which investigated efpeglenatide [21–23]. As a result, this outcome could not be generalized as a class effect.

2 clinical trials specifically investigated GLP-1RA in HFrEF patients: FIGHT and LIVE. Neither of the two trials demonstrated the beneficial effects of GLP-1 receptor agonists in patients with HFrEF. Notably, the LIVE trial even raised concerns regarding a potential trend toward an increased risk of mortality, ventricular arrhythmias, and atrial fibrillation [21,28]. In terms of HFpEF, two complementary RCTs were published, which investigated subcutaneous semaglutide in obese patients (BMI > 30 kg/m²) without DM (STEP-HFpEF) and with DM (STEP-HFpEF DM). In both trials, there are reported similar results: significant reductions in primary end-points such as a reduction of 7.8 points in Kansas City Cardiomyopathy Questionnaire (KCCQ) (95% CI [4.8 to 10.9]; P < 0.001) in STEP-HFpEF and a reduction of 7.3 points in KCCQ in STEP-HFpEF DM (95% CI [4.1 to 10.4]; P < 0.001) and an average of 10.7% reduction in body weight (95% CI [-11.9 to -9.4]; P < 0.001) in STEP-HFpEF and 6.4% reduction in body weight (95% CI [-7.6 to -5.2]; P < 0.001) in STEP-HFpEF DM. There are also reported significant results concerning secondary end-points, such as an average improvement of 20.3 m at 6-minute walk distance (95% CI [8.6 to 32.1]; P < 0.001) in STEP-HFpEF and 14.3 m (95% CI [3.7 to 24.9]; P = 0.008) in STEP-HFpEF DM, respectively. Essentially, these two trials proved that semaglutide improves symptoms and exercise capacity in obese HFpEF patients with or without type 2 DM, but neither study was powered enough to evaluate the influence on hard clinical events, such as heart failure-related hospitalizations or urgent hospital visits [29,30]. It has been suggested that the clear weight reduction effect had a major contribution to the improvement of symptoms and exercise capacity in these patients [21].

Tirzepatide has recently emerged as a new star in the GLP-1 modulation field, being the latest discovered molecule in this class. More specifically, tirzepatide is a dual agonist that acts both on the receptors of GLP-1 and the receptors of GIP (glucose-dependent insulinotropic polypeptide). GIP represents another incretin hormone, naturally released by K-cells of the upper small intestine. Tirzepatide was validated as an effective antidiabetic medication (up to 2.4% reduction in HbA1c), as proved in the series of trials SURPASS 1-5, when tirzepatide was subsequently compared to placebo, or to active comparators, such as semaglutide, to which it was shown to be non-inferior or insulin degludec, to which it was shown to be superior in terms of glycemic control [31]. In terms of weight management, in SURMOUNT 1-4 clinical trials, tirzepatide proved a potent effect, with a mean weight loss of up to 26% [32]. In a recent network meta-analysis, compared to GLP-1 RA, tirzepatide proved higher efficacy in terms of glycemic control and weight control, probably owing to the dual incretin action [8].

Besides direct effects in the metabolic pathway, the SUMMIT trial yielded noteworthy findings in both the cardiovascular and, to some extent, the renal pathways of CKM syndrome. It included 731 obese patients (BMI over 30 kg/m²) with HFpEF (LVEF of at least 50%), regardless of their diabetes status, who were randomized to receive either tirzepatide or placebo. The trial yielded positive results with regard to the both primary end-points: first one representing a composite end-point formed by death from cardiovascular causes or a worsening heart failure event (hazard ratio, 0.62; 95% confidence interval [CI], 0.41 to 0.95; P = 0.026), a result mainly driven by a reduction in worsening heart-failure events (hazard ratio, 0.54; 95% CI, 0.34 to 0.85), and the second one a reduction in KCCQ score, with a between-group difference at the end of the study of 6.9 (95% CI [3.3 to 10.6]; P < 0.001). There was no difference in

cardiovascular death [33]. Therefore, for the first time, the SUMMIT trial offered evidence derived from an RCT that influencing metabolic pathways with tirzepatide, regardless of diabetes diagnosis, we could influence hard cardiovascular end-points.

An interesting, recently published subanalysis of the SUMMIT trial found that the beneficial effects of tirzepatide upon worsening heart failure events or various metrics pertaining to functional capacity or quality of life are not influenced by the presence or absence of CKD, namely, eGFR does not seem to influence the effects on major adverse heart failure outcomes. In a head-to-head comparison pertaining to the primary composite end-point of death from cardiovascular causes or a worsening heart failure event, tirzepatide showed a larger absolute risk reduction in the CKD group (preventing 3.6 primary endpoint events for 100 patients treated for 1 year) compared to the group without CKD (preventing 1.6 primary endpoint events for 100 patients treated for 1 year). This may probably be an effect at least partially explained by the larger global risk of heart failure events in CKD patients. Moreover, tirzepatide seems to significantly ameliorate glomerular function at 52 weeks (+2.9 [95% CI: 0.9-4.9]; $P = 0.004$), an effect which proved constant throughout the broad spectrum of baseline eGFR (between 15 ml/min/1.73 m² and 70 ml/min/1.73m²), as well as UACR at 24 weeks (-25%; 95% CI: -35.5% to -12.7%; $P < 0.001$) [34].

Although we have a very probable class effect of GLP-1RA in reducing MACE and unique evidence for tirzepatide in influencing hard end-points in HFpEF, currently, there is no direct evidence from RCTs that the dual GLP-1R/GIPR agonist reduces MACE. There exists an ongoing trial (SURPASS-CVOT) which currently evaluates the effect of tirzepatide in comparison to dulaglutide on MACE in patients with type 2 diabetes mellitus.

In general, GLP-1RAs are considered relatively well-tolerated medications, and evidence derived from clinical trials supports their effectiveness. However, there are described side effects such as hypersensitivity reactions (including, in rare cases, anaphylactic shock), a hypothetical enhanced risk of C-cell thyroid neoplasm (based on animal studies and theoretical risk), gastrointestinal adverse effects (such as nausea or vomiting, especially during initiation or dose escalation, increased ileus risk), an increased risk of cholelithiasis, cholecystitis and pancreatitis, and concerns of increased pancreatic cancer risk emerging from observational studies. Generally, gastrointestinal adverse effects are the most common and the most frequent cause of drug discontinuation [35].

SGLT2 INHIBITORS

SGLT2 inhibitors were created to target the SGLT2 transporter, a protein mainly located in the first segment of the proximal convoluted tubule, which is responsible for the absorption of 90-97% of the filtered glucose. The reabsorption of one molecule of glucose is coupled with one sodium ion, the latter being transported along the transmembrane concentration gradient created by the Na/K ATP-ase pump [36]. The residual glucose that escapes reabsorption is transported via SGLT1, which is located in the more distal parts of the proximal convoluted tubule. In case of SGLT2 blockage, SGLT1 could partially compensate for its effects, with only 50-60% of the filtered glucose excreted in the urine [37]. Although SGLT2 is mainly located in the kidney, it is also found in the brain, liver, thyroid, and striated muscle [36,37].

The development of SGLT2 inhibitors was inspired by phlorizin, a naturally occurring compound known to be a SGLT2 inhibitor, with the therapeutic objective of promoting natriuresis and glycosuria in order to obtain glycemic control [37]. In the context of efforts to preserve the biologically active properties of phlorizin, while also improving its oral bioavailability and stability, a series of novel molecules were developed: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. Moreover, a dual inhibitor that blocks both SGLT1/SGLT2, namely sotagliflozin, was approved, which adds the effect of delaying intestinal glucose absorption by inhibiting SGLT1 at this level [37,38]. All molecules share very attractive pharmacologic properties: optimal oral absorption, once-daily administration as a result of the long half-life, metabolism occurring primarily in the liver, reduced renal clearance, and absence of clinically significant drug interactions [37].

Throughout studies, SGLT2 inhibitors have shown only modest effectiveness with regard to glycemic control, with reductions in HbA1c levels within the range of 0.5-1% [36,39]. Despite continuous glycosuria, inhibition of SGLT2 reduces insulin release and increases glucagon levels, which stimulates gluconeogenesis besides activation of lipolysis and lipid oxidation [40]. Similar to GLP-1 receptor agonists, and constituting an important observation for the largely overweight type 2 diabetes population, it was observed that SGLT2 inhibitors also exert a weight-reducing effect. This effect was observed to be approximately 2 to 4 kg, a consistent and durable reduction documented across all studies and for all molecules. To refer to specific figures, the inhibition of glucose reabsorption at the nephron level causes a loss of 75 g of glucose per day, which means nearly 300 kcal per day. It would be expected that a yearly weight loss of 10 kg, which is much more than was noted in clinical studies [40]. There are proposed mechanisms for this discrepancy between theory and practice, and the most prominent one is compensatory hyperphagia induced by a reduction in leptin, a hormone released by adipose tissue which inhibits appetite at a central level [40,41].

After the finding that rosiglitazone, a thiazolidinedione, is associated with an increased risk of adverse cardiovascular events, the scientific community requested that the new SGLT2i need to undergo cardiovascular outcome trials in order to prove their safety, similar to the aforementioned GLP-1RA.

The EMPA-REG OUTCOME trial tested empagliflozin in over 7000 patients with established cardiovascular disease and proved that this SGLT2i is associated with a significant 14% (HR 0.86; 95% confidence interval [CI], 0.74–0.99; $p=0.04$) reduction in the risk of major

adverse cardiovascular events, a 32% reduction of all-cause mortality (HR, 0.68; 95% CI, 0.57–0.82; $p<0.001$), and a 35% reduction of HF hospitalization risk (HR, 0.65; 95% CI, 0.50–0.85; $p=0.002$) [42,43]. Similarly, the DECLARE TIMI trial, for dapagliflozin, showed non-inferiority to placebo with respect to MACE ($p<0.001$) and a reduction with 17% of the risk for cardiovascular death or hospitalization for heart failure (HR, 0.83; 95% CI, 0.73–0.95; $p=0.005$) [42,44]. The CANVAS trial, for canagliflozin, showed a reduction with 14% of the combined risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (HR, 0.86; 95% CI, 0.75 to 0.97; $P<0.001$ for noninferiority; $P=0.02$ for superiority) [42,45]. Ultimately, the VERTIS trial, which studied ertugliflozin, found a significant reduction in the risk of heart failure hospitalizations [42]. Based on these preliminary studies, the ESC guidelines for the management of heart failure mention a class I indication for the utilization of SGLT2i in diabetic patients at high risk for CV events to reduce the risk of hospitalization for heart failure events, MACE, end-stage renal dysfunction, or cardiovascular death [46].

These initial trials prompted the conduction of future dedicated trials in order to establish a potential role of SGLT2i in the management of heart failure patients.

The further DAPA-HF trial proved to be a pivotal study, which paved the way for the actual large indications of SGLT2i in heart failure with reduced ejection fraction (HFrEF). This trial included 4744 patients with II-IV NYHA class heart failure, with an ejection fraction of less than 40% and proved that dapagliflozin (10 mg single dose) is associated with the reduction of a primary composite outcome of cardiovascular death, HF hospitalizations, and worsening HF (HR, 0.74; 95% CI, 0.65 to 0.85; $P<0.001$), with all components of this composite outcome being positively and significantly influenced. This trial also found that the effect is not influenced by the diabetic status of the patient [42,47].

For empagliflozin, the EMPEROR-Reduced trial showed similar results: a reduced composite outcome of cardiovascular death and HF hospitalizations (HR, 0.75; 95% CI, 0.65–0.86; $p<0.001$), similarly independent of the diabetic status of the patient. In the case of empagliflozin, the effect on the primary outcome was mainly driven by the reduction of the rate of HF hospitalizations, as the reduction of cardiovascular death proved to be non-significant [42,48]. A meta-analysis of these 2 landmark trials found significant reductions in all-cause death (pooled HR 0.87, 95% CI 0.77–0.98; $p=0.018$) and in cardiovascular death (pooled HR 0.86, 0.76–0.98; $p=0.027$) [49].

These findings have been incorporated into guideline recommendations, as both the ESC guidelines and the ACC/AHA guidelines on heart failure mention dapagliflozin and empagliflozin as indicated in all HFrEF patients, irrespective of their diabetic status, to reduce the risk of heart failure-related death or hospitalization (class I level of recommendation A) [46,50].

Encouraged by the positive results in the HFrEF field and taking into account the lack of available medications with prognostic effects in HFpEF, the idea of investigating the efficacy of these medications in this prevalent HF phenotype has emerged. And initial evidence emerged from the SOLOIST-WHF trial, which evaluated the effects of sotagliflozin, the dual SGLT1/SGLT2 inhibitor, initiated soon after an episode of decompensation of heart failure; sotagliflozin proved a lower risk of a primary composite end-point formed by cardiovascular death or hospitalizations and urgent visits for heart failure (HR, 0.67; 95% confidence interval [CI], 0.52 to 0.85; $P<0.001$). The result, suggesting a potential effect of SGLT2i in HFpEF, was that the risk reduction of the primary end-point was consistent across the entire spectrum of ejection fraction [51].

Empagliflozin gained evidence for HFpEF and HFmrEF attributable to the results of the EMPEROR-Preserved trial (which included patients with an ejection fraction above 40%). Empagliflozin 10 mg once daily reduced a composite end-point of worsening heart failure or cardiovascular death (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; $P<0.001$), a result driven by a significant reduction in the risk of worsening heart failure (with no difference in death from cardiovascular causes) [52]. Likewise, in the DELIVER trial (heart failure patients with an ejection fraction above 40%), dapagliflozin 10 mg od reduced the events of a similar primary composite end-point (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; $P<0.001$). Once again, this effect is attributable to the reduction of the worsening heart failure events, without significant effects on cardiovascular mortality [53]. As a result, clinical guidelines have been harmonized and currently recommend empagliflozin and dapagliflozin (unique dose of 10 mg per day) in HFpEF and HFmrEF for the reduction of the risk of HF hospitalization or cardiovascular death (class I recommendation in European guidelines, class IIa recommendation in American guidelines) [50,54].

Important evidence for using SGLT2i in heart failure derives from the EMPULSE trial, in which empagliflozin was initiated in hospitalized acute heart failure after stabilization, regardless of ejection fraction or diabetes status. The primary analysis was a win ratio, being a composite of death, heart failure events, time to first heart failure event, and modifications in KCCQ. Empagliflozin proved a better win ratio, with a statistically significant result (win ratio 1.36, 95% CI 1.09–1.68, $p=0.0054$), with consistent results across the prespecified subgroups [55]. Besides this combination of prognostic and symptomatic benefits, empagliflozin also proved significant results on various indices of decongestion, suggesting that early initiation of empagliflozin in hospitalized acute heart failure patients also has the potential to contribute to an early and sustained decongestion [56].

Regarding the benefits of SGLT2 inhibitors in another acute setting—this time early after myocardial infarction—a recently published meta-analysis concluded that early administration of SGLT2i post-myocardial infarction may be beneficial by reducing the risk of recurrent major adverse cardiovascular events (MACE) or hospitalization for heart failure. However, this meta-analysis did not demonstrate a significant reduction in mortality among these patients [57].

Similar to GLP-1RA, SGLT2i is also an effective medication in chronic kidney disease. Based on findings from early studies on cardiovascular safety, specific trials have been designed to directly assess the potential beneficial effects of SGLT2i in CKD. 4 trials, CREDENCE (for canagliflozin), DAPA-CKD (for dapagliflozin), SCORED (for sotagliflozin), and EMPA-KIDNEY (for empagliflozin) proved that SGLT2i slow the progression of CKD. Whereas for canagliflozin and sotagliflozin, the effects were proven only in T2DM populations, in contrast, for empagliflozin and dapagliflozin, the effects were irrespective of the diabetic status, similar to HF trials. It is important to mention that the recommendation is to initiate dapagliflozin at an eGFR of at least 25 ml/min/1.73m² and empagliflozin at an eGFR of at least 20 ml/min/1.73m², but the administration may continue even if the renal function further deteriorates (this indication derives from the design of the studies and the characteristics of the included patients) [58].

Table 2: Major CVOTs of SGLT2i [42]

	Type 2 diabetes mellitus	Heart failure	Chronic kidney disease	
Proved effects	In high-risk cardiovascular patients, it reduces the risk of major adverse cardiac events or cardiovascular death. (Besides improved glycemic control and weight loss)	Reduce the risk of heart failure-related death or hospitalization (across the entire ejection fraction spectrum) Improves decongestion in stabilized acute heart failure (empagliflozin)	Mitigate the progressive reduction of eGFR and lower the risk of renal or cardiovascular-related death	
Drugs approved	Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin	Dapagliflozin, empagliflozin	Canagliflozin, Dapagliflozin, Empagliflozin	
Guideline recommendations	Recommended as first-line add-on therapy to metformin, especially in cardiovascular high-risk, heart failure, or CKD patients	Class I recommendation in HFrEF Class I recommendation in ESC guidelines, class IIa recommendation in ACC/AHA guidelines for HFpEF	T2DM and CKD with eGFR>20 ml/min/1.73m ² ACR>200 mg/g (and eGFR>20 ml/min/1.73m ²) ACR<200 mg/g with eGFR 20-45 ml/min/1.73m ² CKD + heart failure	

MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRAs)

It is known that overactivation of the renin-angiotensin-aldosterone system and aldosterone receptors (mineralocorticoid receptors, MR) in particular, has effects beyond salt and water retention and hypertension. MR overactivation is capable of inducing inflammation and fibrosis in various organs, being involved in CKD and CV disease progression, situations in which RAAS is overly activated and aldosterone is in excess [73]. As far as metabolic derangement is involved, diabetes mellitus also induces a state of overactivation of MRs, and in obese patients there was observed a significant aldosterone production from adipose tissue was observed [74,75].

The deleterious effects of excess aldosterone are facilitated by the widespread expression of mineralocorticoid receptors throughout the body, as they are present not only in the kidneys but also in the heart, blood vessels, gastrointestinal tract, adipose tissue, and central nervous system [73].

The first therapeutic options to block MRs were the steroidal agents spironolactone and eplerenone, respectively.

The first results for these agents came from RCTs, which tested them in HFrEF, a common entity in advanced stages of cardio-renal-metabolic syndrome. In RALES trial, conducted in 1999, spironolactone reduced all-cause mortality by 30% (RR, 0.70; 95% CI, 0.60 to 0.82; P<0.001) and the risk of heart failure hospitalization by 35% (RR 0.65; 95% CI, 0.54 to 0.77; P<0.001), besides observed benefits on improvement regarding the symptoms of heart failure [76]. Eplerenone gained evidence from the EMPHASIS-HF trial, which proved a significant reduction of the primary composite endpoint of CV death or heart failure hospitalization (HR, 0.63; 95% CI, 0.54 to 0.74; P<0.001) [77]. Further trials provided evidence for steroidal MRAs, namely eplerenone, early after myocardial infarction. EPHEUS and REMINDER trials found that eplerenone, early initiated after MI, in patients with clinical signs and symptoms of heart failure and an ejection fraction of less than 40% could reduce all-cause mortality, length of hospitalization due to heart failure, ventricular arrhythmias, or the risk for deterioration of ejection fraction [78,79]. The beneficial effects of MR blockade in HFrEF and after myocardial infarction emphasize the important effects of aldosterone in cardiac adverse remodelling.

Regarding the HFmrEF and HFpEF, the available results are not as solid as in HFrEF. In the TOPCAT trial, 3,445 patients with symptomatic heart failure and a left ventricular ejection fraction of ≥45% were randomized to receive either spironolactone or placebo. Although the study narrowly failed to meet its primary composite endpoint (including cardiovascular death, aborted cardiac arrest, and hospitalization for heart failure), its results generated considerable debate [80]. The difference between a significant HR in American cohort (HR, 0.82; 95% CI, 0.69-0.98; p = 0.026) and a non-significant HR in Russian and Georgian cohort (HR, 1.10; 95% CI, 0.79-1.51; interaction p = 0.12) has led to speculation that the apparent neutral results of the TOPCAT trial may be due to issues

with enrollment and drug adherence in the Eastern European cohort [81]. Based on the significant results on American cohort, there is a 2b recommendation in ACC/AHA guidelines on heart failure for steroidal MRA use in HFpEF and HFmrEF [50].

Hypertension in general and resistant hypertension in particular are common entities in chronic kidney patients or in obese, insulin-intolerant, or diabetic patients. Resistant hypertension is associated with a poor prognosis, causing target organ damage. The PATHWAY-2 RCT established spironolactone as a first-line agent in resistant hypertension, on top of maximum tolerated doses of ACEI/ARB, calcium-channel blocker, and thiazide diuretic [82].

The main limitation of steroidal MRAs' use is the risk of hyperkalemia, a risk observed since the early trials and considered relatively significant, particularly in a population with chronic kidney disease. A meta-analysis that included the landmark RCTs of steroidal MRAs proved that the risk of hyperkalemia and the benefits are inversely proportional to the eGFR (with unclear benefits compared to high risk of hyperkalemia in patients with an eGFR<30 ml/min/1.73m²) [83].

Gynecomastia and breast pain are other well-known and relatively frequent adverse effects of spironolactone (with a 10% to 1% ratio observed in the RALES trial) [73].

There is a limitation in the steroidal MRAs' potential for broader cardiorenal protection, given the fact that their widespread use is limited by hormonal adverse effects or, in advanced CKD, by a significant risk of hyperkalemia. Moreover, data regarding the direct effects of steroidal MRAs on slowing CKD are unconvincing. There is a meta-analysis that proposes some benefits on intermediate endpoints such as albuminuria or eGFR slope, albeit at the cost of significant risk of hyperkalemia, worsening renal function, or gynecomastia [84].

The novel class of non-steroidal mineralocorticoid receptor antagonists (nsMRAs) has emerged in an effort to overcome these limitations while preserving the beneficial effects of the steroidal MRAs.

Finerenone is the most prominent agent of this pharmacological class, with several advantages over its steroidal counterparts: a comparable potency of MR inhibition but with a much higher selectivity, virtually no sexual side-effects, a more balanced tissue distribution between kidneys and the heart (in comparison with sMRA which are more concentrated at the renal level) and a shorter plasma half-time, which might contribute to a lower risk of hyperkalemia [85,86].

The first RCTs investigating finerenone were FIDELIO-DKD and FIGARO-DKD. FIDELIO-DKD primarily enrolled diabetic patients suffering from advanced CKD with prominent albuminuria, and there was a prespecified primary composite kidney endpoint. FIGARO-DKD enrolled diabetic patients with moderate albuminuria associated with a wider spectrum of CKD and stated a primary composite cardiovascular endpoint [85]. The results from these 2 RCTs and from their pooled analysis (FIDELITY) form the basis for the KDIGO guideline recommendation of finerenone in CKD: in patients with diabetic nephropathy, with an eGFR>25 ml/min/1.73 m² and with an albuminuria >30 mg/g, despite a maximum dose of ACEI/ARB [72]. Apart from reducing the kidney disease progression, finerenone reduced cardiovascular risk (HR 0.86, 95% CI: 0.78-0.95) and the risk of heart failure hospitalization (HR 0.78, 95% CI 0.66-0.92) in diabetic CKD patients [86].

The latter FINEARTS-HF trial provides the first quality results for MRAs (particularly nsMRA, finerenone) in HF with EF above 40%. In this RCT, finerenone reduced the risk of a primary composite endpoint formed by worsening heart failure events and cardiovascular death with 16% (rate ratio, 0.84; 95% confidence interval [CI], 0.74 to 0.95; P=0.007), driven by a significant reduction in worsening heart failure events, similar to SGLT2i results in the same patient population [87]. Compared to the previous ones, FINEHEARTS was a revolutionary trial also by the population included, with approximately 60% not having CKD or diabetes, suggesting that there may be important direct effects on the heart [88].

The recent FINE-HEART meta-analysis allows for the formulation of global conclusions regarding finerenone as far as cardiovascular and renal outcomes are concerned. This meta-analysis included the three RCTs, FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF, encompassing a total of 18991 patients. 12.1% of the included patients concurrently had HF, CKD, and diabetes, the main conditions encompassed in the CKM syndrome. The results indicate that finerenone reduces the risk of heart failure hospitalization (HR: 0.83; 95% CI: 0.75-0.92; P < 0.001) and of a composite kidney outcome, thus delaying CKD progression (HR: 0.80; 95% CI: 0.72-0.90; P < 0.001). Although not succeeding in proving risk reductions in cardiovascular death (HR 0.89; 95% CI: 0.78-1.01; P = 0.076), finerenone seems to reduce the risk of all-cause death (HR: 0.91; 95% CI: 0.84-0.99; P = 0.027) [88].

Currently, the sole recommendation for finerenone within cardiology guidelines is the class IA recommendation in the 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes, in patients with type 2 DM and CKD (UACR>300 mg/g or eGFR 25-60 ml/min/1.73m² and UACR>30 mg/g), in addition to ACE-I or ARB, to reduce the risk of cardiovascular events or kidney failure [26].

This recommendation, similar to those related to SGLT2i or GLP-1RA, empowers all medical doctors involved in the management of CKM syndrome to take proactive measures aimed at improving the prognosis of these patients. It remains to be seen what future heart failure guidelines will unveil regarding nsMRA indications, probably related to future trials that may investigate the effects of finerenone in this population.

CONCLUSION

Management of cardiovascular disease within the cardiorenal metabolic (CKM) syndrome requires a comprehensive, individualized approach, guided by cardiovascular risk stratification. While lifestyle interventions remain foundational, pharmacologic therapy plays a pivotal role in improving prognosis and quality of life.

Standard treatments such as RAAS blockade—with ACE inhibitors, ARBs, and steroidal MRAs—form the therapeutic backbone. However, recent advances support the early initiation of novel agents with proven benefits across all three CKM components.

GLP-1 receptor agonists and dual GLP-1/GIP agonists (e.g., tirzepatide) not only promote glycemic control and weight reduction but also lower the risk of major adverse cardiovascular events and may preserve renal function. SGLT2 inhibitors have demonstrated robust prognostic benefits in heart failure—regardless of ejection fraction—and chronic kidney disease, independent of glycemic status. Finerenone, a non-steroidal mineralocorticoid receptor antagonist, is recommended in diabetic kidney disease with albuminuria and shows emerging evidence of efficacy in HFpEF and HFmrEF, although formal guideline recommendations are still pending.

Optimizing therapeutic strategies with both established and novel agents is essential for altering the course of heart disease in CKM syndrome and addressing its complex, multisystem pathophysiology.

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Authors' contribution

Conceptualization, A.G.F., S.H. and S.M.S.; methodology, M.J.; formal analysis, M.F.; data curation, E.R.; writing—original draft preparation, A.G.F., S.A.P.; writing—review and editing, E.C., R.D.G., M.F., E.R.; visualization, R.D.G.; supervision, S.M.S.; project administration, S.H. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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