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Review

Cardiovascular–Kidney–Metabolic Syndrome: From Disease Interplay to Therapeutic Advances

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Abstract

Cardiovascular–Kidney–Metabolic (CKM) syndrome, a term introduced by the American Heart Association (AHA) in 2023, reflects the growing recognition of how metabolic dysfunction drives multi-organ pathology through interconnected pathways. This review examines the pathophysiological mechanisms underlying CKM syndrome and evaluates emerging therapeutic strategies. CKM syndrome is driven by the interplay of insulin resistance, chronic inflammation and oxidative stress, activation of the renin–angiotensin–aldosterone system. These mechanisms converge to promote fibrosis, insulin resistance, and end-organ damage across the cardiovascular and renal systems. Therapeutic advances include Sodium–Glucose Cotransporter 2 inhibitors, which demonstrate consistent cardiorenal benefits across heart failure phenotypes and chronic kidney disease. Glucagon-like peptide-1 receptor agonists, including semaglutide and the dual GIP/GLP-1 agonist, tirzepatide, achieve substantial weight reduction and improve cardiovascular, renal, and hepatic outcomes in selected study populations. Non-steroidal mineralocorticoid receptor antagonists, particularly finerenone, offer cardiorenal protection with an improved safety profile, while aldosterone synthase inhibitors represent a promising frontier. The pathophysiological processes involved in CKM also generate a distinct atherogenic dyslipidaemic phenotype, which means effective lipid management has the potential to reduce residual cardiovascular and renal risk in patients with CKM syndrome. Novel potassium binders may also be part of CKM syndrome treatment strategies to reduce hyperkalaemia risk. Despite these advances, questions remain regarding the optimal combination strategies in CKM syndrome. There are also no studies designed to assess treatment efficacy in groups stratified according to the CKM syndrome framework. Future research should prioritise mechanistic studies and large-scale trials evaluating long-term outcomes across the full CKM spectrum.

Keywords: cardiovascular–kidney–metabolic syndrome; SGLT2 inhibitors; GLP-1 receptor agonists; mineralocorticoid receptor antagonists; inflammation

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1. Introduction

Cardiovascular–Kidney–Metabolic (CKM) syndrome, a term first coined in 2023 by the American Heart Association (AHA), reflects the increasing awareness of the relationship between poor metabolic health and the associated downstream organ effects [1]. It recognises the close, interconnected pathophysiology underlying CKM health and the need for further investigation on the topic [1]. Amongst the many overlapping pathophysiological mechanisms in CKM syndrome, the core mechanisms include inflammation, renin–angiotensin–aldosterone system (RAAS) overactivation and insulin resistance. We

will discuss these mechanisms' relationship with CKM syndrome with a focus on the available clinical evidence.

Besides that, the AHA provides a staging construct of five categories stratified according to both risk factors and management strategies for CKM syndrome [1]. The AHA classified those without CKM risk factors as stage 0; individuals with overweight/obesity, or with impaired glucose tolerance/prediabetes, or both are classified as stage 1; and individuals with either chronic kidney disease (CKD) or metabolic risk factors including hypertriglyceridemia, hypertension, diabetes and metabolic syndrome are considered stage 2. Those with subclinical cardiovascular disease (CVD), determined through abnormalities in cardiovascular structure, function or cardiac biomarkers in the absence of symptoms, with the background of excess adiposity, impaired glucose tolerance/prediabetes, metabolic risk factors, or CKD, are stage 3. Stage 4 represents individuals who have progressed to clinical CVD, which can be further subcategorised into those without kidney failure (4a) and those with kidney failure (4b) [1]. Table 1 shows these five stages, with therapeutic strategies that will be discussed later.

It is now increasingly recognised that metabolic dysfunction-associated steatotic liver disease (MASLD) is an important contributor within this interconnected spectrum, representing a new component of the broader CKM syndrome, now labelled as the cardio–kidney–liver metabolic (CKLM) syndrome [3].

Importantly, there have been recent strides made in the pharmacological strategy of managing CKM syndrome with the evidence-based use of Sodium–Glucose Cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RAs). For instance, SGLT2i have shown consistent cardiorenal benefits across heart failure phenotypes and chronic kidney disease. Recent evidence highlights the potential of GLP-1RAs and non-steroidal mineralocorticoid receptor antagonists (ns-MRAs) such as finerenone to deliver cardiovascular and renal benefits across cardio–kidney–metabolic (CKM) syndrome, while also improving metabolic liver disease, including MASLD/Metabolic Dysfunction-Associated Steatohepatitis (MASH).

In this review article, we aim to discuss the possible underlying pathophysiology of CKM syndrome that helps to direct its therapeutic options and the clinical evidence supporting the use of these therapies. We will also discuss other potential therapies for the future, including tirzepatide, a dual receptor agonist for glucagon-like peptide-1 (GLP-1)/glucose-dependent insulinotropic polypeptide (GIP), which demonstrated a more potent weight-loss ability compared to GLP-1RAs and aldosterone synthase inhibitors (ASIs), a class of novel anti-hypertensives. But significant knowledge gaps persist, as the clinical evidence for pharmacological treatments in advanced CKM stages is lacking, due to the common involvement of multi-organ impairment, which is a characteristic that trial populations often do not have. There is also uncertainty about the overall efficacy and safety of combination therapies in CKM syndrome.

Table 1. The clinical manifestations and the principles of management at each stage. Referenced from AHA/ACC/ADA/ASN 2026 guideline on CKM syndrome [2].

Stage	Metabolic Features	Renal Features	Cardiovascular Features	Principles of Management
0—no risk factors	Normal body mass index and waist circumference. Normal blood pressure, lipid profile and non-diabetic	No CKD	No CVD (clinical and subclinical)	Primordial prevention to prevent CKM risk factors development, especially to avoid development of excess adipose tissue or prediabetes
1—excess adiposity or IGT/prediabetes	Overweight/obesity, abdominal obesity, or IGT/prediabetes, without presence of other metabolic risk factors	No CKD	No CVD (clinical and subclinical)	Lifestyle modification and weight loss to prevent development of additional metabolic risk factors
2—metabolic risk factors and/or CKD	Hypertriglyceridemia, HTN, metabolic syndrome or diabetes	Moderate-to-high risk CKD per KDIGO risk categorisation and/or metabolic features	No CVD (clinical and subclinical)	Lifestyle modification and addition of pharmacological therapies to prevent CVD development and decline in kidney function
3—subclinical CVD	Hypertriglyceridemia, HTN, metabolic syndrome or diabetes	CKD stage G1-G3 with subclinical CVD OR CKD G4/G5/very high-risk per KDIGO risk categorisation	Subclinical ASCVD or HF with background of relevant metabolic features or CKD Subclinical ASCVD–coronary artery calcification principally diagnosed as Coronary artery calcium with Agatston score ≥ 100 Subclinical HF—elevated cardiac biomarkers (NT-proBNP ≥ 125 pg mL−1, hs-cTnT ≥ 14 ng L−1 for women and ≥22 ng L−1 for men, hs-cTnI ≥ 10 ng L−1 for women, and ≥12 ngL−1 for men) or by echocardiographic parameters OR Very high CVD risk prediction—relevant CKD stage (G4/G5/very high-risk) or 10-y CVD risk ≥ 20% using PREVENT-CVD	Greater focus on lifestyle modification and pharmacological therapies to reduce risk of short-term clinical events with aim of greater absolute risk reduction

Table 1. *Cont.*

Stage	Metabolic Features	Renal Features	Cardiovascular Features	Principles of Management
4—Clinical CVD (consisting of G4a and G4b)	Hypertriglyceridemia, HTN, metabolic syndrome or diabetes	CKD + CVD G4a—no kidney failure G4b—kidney failure (CKD G5)	Clinical CVD—CHD, HF, stroke, PAD, Afib with background of relevant metabolic features or CKD	Optimisation of secondary prevention strategies of CVD in the background of CKM risk factors

Abbreviations: angiotensin-converting enzyme inhibitor (ACEi); Atrial Fibrillation (Afib); angiotensin receptor-neprilysin inhibitor (ARNI); Angiotensin II receptor blocker (ARB); atherosclerotic cardiovascular disease (ASCVD); chronic kidney disease (CKD); cardiovascular disease (CVD); glucagon-like peptide-1 receptor agonist (GLP-1RA); heart failure (HF); hypertension (HTN); impaired glucose tolerance (IGT); kidney disease: Improving Global Outcomes (KDIGO); metabolic dysfunction-associated steatotic liver disease (MASLD); mineralocorticoid receptor antagonist (MRA); non-steroidal MRA (nsMRA); N-terminal pro-brain natriuretic peptide (NT-proBNP); Peripheral Arterial Disease (PAD); Sodium–Glucose Cotransporter 2 inhibitors (SGLT2i); Type 2 diabetes mellitus (T2DM); Urine Albumin–Creatinine Ratio (UACR).

2. Epidemiology

Obesity and type II diabetes mellitus (T2DM) are increasingly prevalent in the global population, turning into a "global epidemic" as we gradually adopt a more sedentary lifestyle. Between 1990 and 2022, the global age-standardised prevalence of obesity increased from 4.8% to 14.0% for adult men and 8.8% to 18.5% for adult women [4]. Of greater concern, children and adolescents experienced a more dramatic increase, with the age-standardised obesity prevalence rate more than quadrupling over the same period [4]. Further, 529 million people globally were estimated to have T2DM in 2021 and this is expected to more than double to 1.31 billion by 2050 [5].

In terms of the prevalence of CKM, a study of 231,590,853 individuals living in the USA found that older-aged patients tended to have higher stages of the CKM syndrome [6]. In the 20–44-year-old age group, 17.3% were stage 0, 37.6% were stage 1, 43.2% % were stage 2, 0.2% were stage 3, and 1.7% were stage 4. In the 45 to 64 years old group, 5.4% were stage 0, 21.0% were stage 1, 63.8% were stage 2, 1.2% were stage 3, and 8.6% were stage 4. In the 65 years and older age group, 1.8% were stage 0, 8.4% were stage 1, 39.0% were stage 2, 24.6% were stage 3, and 26.2% were stage 4 [6]. The 20 to 44, 45 to 64, and 65 or greater years old groups consisted, respectively, of 104,113,793, 82,640,261, and 44,836,799 individuals [6].

3. Pathophysiology

The pathophysiology of CKM syndrome is clearly multi-faceted, but the underlying mechanisms are likely to be similar regardless of the organs implicated in CKM syndrome. Obesity can be viewed as an upstream driver of CKM syndrome such that excess adiposity initiates a self-reinforcing network of insulin resistance, inflammation, oxidative stress, neurohormonal activation and metabolic toxicity that progressively affects the heart, kidneys and liver (see Figure 1 below).

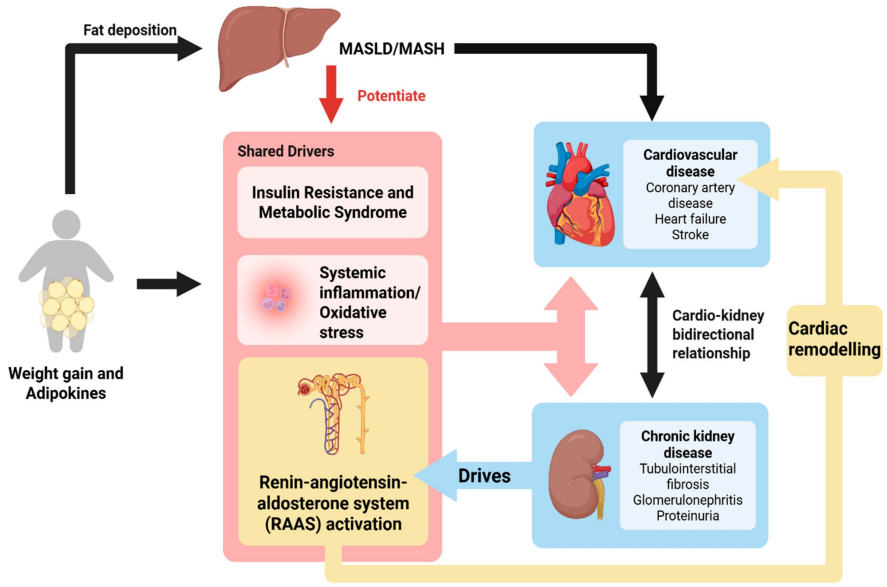


Figure 1. Pathophysiological interplay of CKM syndrome. This figure illustrates cardio-renal organ dysfunction driven by the shared mechanism of systemic inflammation/oxidative stress, renin–angiotensin–aldosterone system activation, insulin resistance and metabolic syndrome. (Created in BioRender. Ho, T. F. (2026) https://BioRender.com/wvo1a3z.) Abbreviations: metabolic dysfunction-associated steatotic liver disease (MASLD); Metabolic Dysfunction-Associated Steatohepatitis (MASH).

3.1. Inflammation

Obesity is recognised as a state of low-grade chronic inflammation, reflected by the increased circulating inflammatory cytokines such as tumour necrosis factor-α (TNF- α), interleukin-6 (IL-6) and C-reactive protein (CRP) reported in human studies [7]. Besides classical inflammatory cytokines, there are specific cytokines secreted by adipose tissues, such as leptin and adiponectin, that can influence the inflammatory pathways as well [8].

These inflammatory cytokines are thought to mediate many of the organ dysfunction found in CKM syndrome [1]. The role of inflammation in atherogenesis pathophysiology has been well-described [9]. Moreover, it is believed that inflammation contributes to HF development of all phenotypes, especially heart failure with preserved ejection fraction (HFpEF) [10,11]. It is also thought that obesity-related inflammation contributes to the pathogenesis of CKD and T2DM [12,13]. It is worth noting that much of the above understanding of the role of inflammation in CKD pathophysiology is derived from pre-clinical animal studies and association studies [14–19]. Inflammatory cytokines are implicated in several molecular mechanisms that may contribute to, but are not limited to, the development of insulin resistance through IκB kinase (IKK)-mediated serine phosphorylation of insulin receptor substrate 1 (IRS-1) or insulin receptor (IR), impaired myocardial contractility and harmful ventricular remodelling, and renal tubulointerstitial fibrosis through upregulation of MYC target genes [20–22].

In terms of supportive evidence from clinical trials, there have been a number. The CANTOS trial tested the effect of the Interleukin-1β (IL-1β) antibody, canakinumab, on 3-point major adverse cardiovascular events (3P-MACE) in patients with previous myocardial infarction and high-sensitivity C-reactive protein (hsCRP) ≥ 2.0 mg L^{-1}, despite optimal secondary prevention [23]. The trial reported a significant reduction in the primary clinical outcome of 3P-MACE [HR = 0.85 (95% CI 0.74–0.98); $p = 0.021$] for those receiving 150 mg of canakinumab every 3 months compared to placebo [23]. In terms of CKM, this cardioprotection extended to those with CKD [24]. Further analysis of the CANTOS trial found dose-dependent reduction in heart HF outcomes as well; unadjusted HR for hospitalisation for heart failure (HHF) are 1.04 (95% CI 0.79–1.36), 0.86 (95% CI 0.65–1.13), and 0.76 (95% CI 0.57–1.01) for those receiving 50 mg, 150 mg, and 300 mg, respectively, when compared to placebo [25].

Further supportive evidence for inflammation in CKM has come from the studies exploring the potential benefits of colchicine, an anti-inflammatory primarily mediated through tubulin disruption, which targets populations with significant atherosclerosis disease burden [26–28]. COLCOT trial recruited those with myocardial infarction within 30 days and the LoDoCo2 trial recruited those with chronic coronary disease. Both trials compared low-dose colchicine to placebo to assess the primary endpoint of atherosclerotic major adverse cardiovascular events (MACE) [26,27]. COLCOT trial reported HR = 0.77 [(95%CI 0.6–0.96); $p = 0.02$] and LoDoCo2 reported HR = 0.69 [(95% CI 0.57–0.83); $p < 0.001$] [26,27]. However, the more recent CLEAR trial assessing those who had previous significant myocardial infarction and underwent percutaneous coronary intervention found no significant reduction in atherosclerotic MACE when comparing colchicine to placebo [HR = 0.99 (95% CI, 0.85–1.16); $p = 0.93$] [29].

IL-6 has also emerged as an inflammatory cytokine of interest, as it has been associated with atherosclerotic cardiovascular disease (ASCVD) risk in studies and is suggested to cause coronary heart disease development in a Mendelian randomisation analysis [30–33]. Despite convincing evidence that suggests an inhibition of IL-6 will lead to lowered ASCVD risk, ziltevikimab, an IL-6 ligand antibody, in the topline results of the ZEUS trial, which recruited patients with known ASCVD, CKD and hsCRP ≥ 2.0 mg L^{-1}, did not show a reduction in 3P-MACE [HR = 0.99, 95% CI 0.88–1.11] [34,35]. At this time, there is intense

debate about these findings, and reasons that have been suggested include that the selection of trial population hsCRP ≥ 2 mg L^{-1} alone may not capture those with predominantly IL-6 inflammation [36].

Evidence from meta-analysis further highlights the inconsistency of treatment effect. A meta-analysis evaluating different randomised trials of anti-inflammatory therapy compared to placebo in secondary prevention of myocardial infarction found a significant reduction in the primary endpoint of MACE [37]. In contrast, a separate meta-analysis on multiple classes of anti-inflammatory therapy trials did not find clear evidence supporting use in the CKD population to reduce the risk of MACE or decline in kidney function [38].

Overall, it does appear that systemic inflammation in obesity contributes to much of the downstream organ damage found in CKM syndrome. However, single targeted anti-inflammatory therapy alone is unlikely to yield sufficient cardiorenal benefits we are looking for in the management of CKM syndrome, stemming from the complexity of multiple overlapping inflammatory pathways.

3.2. Renin–Angiotensin–Aldosterone System (RAAS)

Further mechanisms of interest in CKM syndrome include RAAS overactivation; the molecular pathways involved are thought to cause oxidative damage, local inflammation and fibrosis in both the heart and kidneys [39]. There is an association between RAAS activity and obesity, reported by multiple observational studies in humans, where weight loss results in a reduction in RAAS activity [40]. The cardiorenal dysfunction caused by RAAS is thought to be mediated by the pro-inflammatory and pro-fibrotic effects of both angiotensin II (Ang II) and aldosterone [41–44]. In terms of supportive evidence from clinical trials, clinical outcome trials have consistently demonstrated cardiorenal benefits through RAAS blockade [45–51]. In addition, RAAS blockade is found to decrease the incidence of T2DM [52].

That said, it is not entirely clear why RAAS blockade was shown to be less effective in HFpEF when compared to heart failure with reduced ejection fraction (HFrEF) clinical trials [53–56]. The difference in response in terms of HF phenotype is a subject of much research and discussion. For consideration is the heterogeneous nature of HFpEF [57,58]. Furthermore, the PARAGON-HF trial strengthens the argument that HFpEF is a highly heterogeneous clinical syndrome, as sex seems to be a modifier of treatment effect [59]. Reanalysis of the TOPCAT trial found that mineralocorticoid receptor antagonists (MRAs) may offer cardioprotection in HFpEF, and recent trials on nsMRAs have further supported this observation, which we covered in the therapeutics section below [60].

3.3. Insulin Resistance

The association between obesity and insulin resistance is well-established [61]. It is thought that obesity-related inflammation may contribute to insulin resistance and T2DM [20]. The molecular pathophysiology of diabetes involves increased oxidative stress from increased polyol pathway flux, the formation of advanced glycation end-products (AGEs), protein kinase C activation and increased flux of the hexosamine pathway [62].

Insulin resistance is one of the core pathophysiological mechanisms in CKM syndrome; it is also associated with increased risk of adverse cardiovascular outcomes and kidney dysfunction [63,64]. Therefore, thiazolidinedione, a direct insulin sensitiser, should theoretically ameliorate cardiorenal disease progression in insulin resistance. There is evidence that thiazolidinedione may reduce urinary albumin excretion in T2DM but insufficient proof on the benefits surrounding clinical renal endpoints [65–67]. Furthermore, available evidence does not clearly support its use in ASCVD risk reduction [68,69]. In fact, there are

concerns over increased myocardial infarction risk with rosiglitazone specifically, on top of the known increased risk of HF for all thiazolidinediones [69,70].

Metformin is also an insulin sensitiser, but there are still doubts about its cardiovascular benefits in T2DM despite findings from UKPDS34, as a meta-analysis of randomised trials demonstrated no significant benefits for ASCVD [71,72]. But, contrasting the safety risk of thiazolidinediones in HF patients, metformin appears to show a significant reduction in mortality in those with T2DM and HF in observational studies, and a meta-analysis looking at the HFpEF population group also came to a similar conclusion [73–75]. However, it has been presented at the European Society of Cardiology (ESC) Congress 2026 that the topline results of the Met-HeFT trial did not show improvement in the primary composite outcome of death, worsening heart failure (wHF), acute myocardial infarction or stroke [HR = 1.10 (95% CI 0.84–1.42); $p = 0.48$] for the HFrEF population with diabetes, pre-diabetes or at high risk for diabetes [76]. In terms of potential effects on kidneys, large-scale observational studies appear to support the use of metformin in T2DM for renoprotection, while the evidence in randomised controlled trials is lacking [77–79].

We have summarised the core pathophysiological mechanisms in Figure 1. Nevertheless, gaps remain in the management of HFpEF. More importantly, pharmaceutical treatment for cardiorenal outcomes is not as forthcoming in the diabetic population. But recent advances in pharmaceuticals, especially anti-diabetics, have drastically expanded the available treatment options for those with HFpEF and diabetics with significant cardiorenal dysfunction. These new medications are, to an extent, theorised to modify the core pathophysiological mechanisms in CKM syndrome, thereby conferring significant clinical benefits.

4. Therapeutics

In this section, we will discuss the various therapeutic strategies that have shown promise in combating CKM syndrome.

4.1. Sodium–Glucose Co-Transporter 2 Inhibitors

The SGLT2i drug class has made a great impact on patients identified as having CKM. SGLT2i, commonly known as '-flozins', were originally developed to improve blood sugar control in patients with Type 2 diabetes by inhibiting glucose reabsorption in proximal convoluted tubules of nephrons. The paradigm shift for SGLT2i began with the landmark EMPA-REG outcome trial, published in 2015, a dedicated cardiovascular outcomes trial that demonstrated reduction of 3P-MACE in T2DM patients with established CVD [HR = 0.86 (95.02% CI 0.74–0.99); $p = 0.04$ for superiority], treated with empagliflozin 10 mg once a day [80].

The EMPA-REG outcome trail unexpectedly revealed a profound 35% reduction in HF hospitalisations that prompted a programme of research on the use of SGLT2i in patients with heart failure (HF) that included both HF subtypes of HFrEF and HFpEF randomised controlled trials such as DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved subsequently showed both HFrEF and HFpEF patients benefitting from SGLT2i therapy, regardless of the presence or absence of T2DM, primarily driven by a reduced risk in hospitalisation for HF, a component of the primary composite outcome, with Table 2 showing the respective trials primary outcome results [81–83]. A meta-analysis performed by Zelniker et al. (2019) including 34322 T2DM patients in randomised controlled trials investigating SGLT2i found a reduction in the risk for the composite of cardiovascular death or hospitalisation for HF for patients with a history of HF [HR = 0.71 (95% CI 0.61–0.84); $p < 0.0001$] or without [HR = 0.79 (95% CI 0.71–0.88); $p < 0.0001$] [84]. That being said, the evidence for use in primary prevention and secondary prevention in myocardial infarction is mixed at

best, as demonstrated through meta-analyses of randomised controlled trials performed by Zelniker et. al. (2019) in the T2DM population and Patel et al. (2024) in T2DM with high risks of ASCVD, established HF or CKD [84,85]. But the impact of discovery on SGLT2i cardioprotective effect in HFpEF patients cannot be understated, as EMPEROR-PRESERVED trial demonstrated a significant reduction in the risk of primary composite outcome (death from cardiovascular causes or hospitalisation for HF) in HFpEF patients with ejection fraction > 40% [HR = 0.79 (95% CI 0.69–0.90); $p < 0.001$], primarily driven by reduction in hospitalisation for HF [HR = 0.71 (95% CI 0.60–0.83)] [83].

Table 2. Major trials of SGLT2 inhibitors evaluating cardiovascular and renal outcomes.

Trial [Drugs] Reference	Summary of Characteristics of Selected Trial Population	Primary Outcome	Effect Size (HR or Mean Difference), *p*-Value	CKM Syndrome Phenotype
EMPA-REG Outcome [EMPAGLIFLOZIN] [80]	T2DM with either 7% ≤ HbA1c ≤ 10% whom are on background therapy OR 7% ≤ HbA1c ≤ 10 for drug-naive patients BMI ≤ 45 kg m^{-2} eGFR ≥ 30 mL min^{-1} (1·73 m^2)$^{-1}$ Established ASCVD	Composite of CV death, non-fatal myocardial infarction (excluding silent myocardial infarction) and non-fatal stroke between placebo and empagliflozin group	HR 0.86 (95.02% CI 0.74–0.99), $p = 0.04$ for superiority	ASCVD + T2DM
DAPA-HF [DA-PAGLIFLOZIN] [81]	HF EF ≤ 40% with NYHA II, III, IV and specific elevated NT-proBNP criteria eGFR ≥30 mL min^{-1} (1·73 m^2)$^{-1}$ Exclude acute decompensated HF within 4 weeks of enrollment Exclude HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy or uncorrected primary valvular disease	Composite of CV death, HHF or urgent visit with intravenous therapy for HF between placebo and dapagliflozin group	HR 0.74 (95% CI 0.65–0.85), $p < 0.001$	HFrEF
EMPEROR-Reduced [EM-PAGLIFLOZIN] [82]	HF EF ≤ 40% of NYHA II, III, IV with increased risk of serious HF event; for EF > 30%, patient required: specific elevated NT-proBNP criteria OR history of HHF within the previous 12 months. For EF ≤ 30%, NT-proBNP ≥ 600 pg mL^{-1}	Composite of adjudicated CV death or HHF, analysed as the time to the first event between placebo and empagliflozin group	HR 0.75 (95% CI 0.65–0.86), $p < 0.001$	HFrEF
DAPA-CKD [DA-PAGLIFLOZIN] [86]	25 ≤ eGFR ≤ 75 mL min^{-1} (1·73 m^2)$^{-1}$ 200 mg g^{-1} ≤ UACR ≤ 5000 mg g^{-1} Maximum tolerable dose of ACEi or ARB ≥ 4 weeks if not medically contraindicated	First occurrence of KDP1 ** or CV death between placebo and dapagliflozin group	HR 0.61 (95% CI 0.51–0.72), $p < 0.001$	CKD
EMPEROR-Preserved [EM-PAGLIFLOZIN] [83]	HF EF > 40% with NYHA II, III, IV and specific elevated NT-proBNP criteria	Composite of adjudicated CV death or HHF, analysed as the time to the first event between placebo and empagliflozin group	HR 0.79 (95% CI 0.69–0.90), $p < 0.001$	HFpEF

Table 2. *Cont.*

Trial [Drugs] Reference	Summary of Characteristics of Selected Trial Population	Primary Outcome	Effect Size (HR or Mean Difference), *p*-Value	CKM Syndrome Phenotype
EMPA-KIDNEY [EMPAGLIFLOZIN] [87]	Regardless of level of albuminuria, $20 \leq$ eGFR < 45 mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$ OR $45 \leq$ eGFR < 90 mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$ if UACR ≥ 200 mg g^{-1} Clinically appropriate doses of ACEi or ARB unless it is either not tolerated or not indicated	First occurrence of KDP2 † or CV death between placebo and empagliflozin group	HR 0.72 (95% CI 0.64–0.82), $p < 0.001$	CKD

** KDP1 in DAPA-CKD trial is defined as any of the following: a decline of ≥50% in the estimated GFR (confirmed by a second serum creatinine measurement after ≥28 days), the onset of end-stage kidney disease (defined as maintenance dialysis for ≥28 days, kidney transplantation, or an estimated GFR of <15 mL per minute per 1.73 m^2, confirmed by a second measurement after ≥28 days), or death from renal causes. † KDP2 in EMPA-KIDNEY trial is defined as any of the following: progression of kidney disease, which means end-stage kidney disease (ESKD; the initiation of maintenance dialysis or receipt of a kidney transplant), a sustained decrease in the eGFR to less than 10 mL per minute per 1.73 m^2, a sustained decrease from baseline in the eGFR of at least 40%, or death from renal causes. Abbreviation: angiotensin-converting enzyme inhibitor (ACEi); Atrial Fibrillation (Afib); Angiotensin II receptor blocker (ARB); Atherosclerotic Cardiovascular Disease (ASCVD); body mass index (BMI); chronic kidney disease (CKD); confidence interval (CI); cardiovascular (CV); ejection fraction (EF); estimated glomerular filtration rate (eGFR); heart failure (HF); Heart Failure with Preserved Ejection Fraction (HFpEF); Heart Failure with Reduced Ejection Fraction (HFrEF); Hospitalisation for Heart failure (HHF); Hazard Ratio (HR); serum potassium level (K); *p*-value (*p*); Type 2 diabetes mellitus (T2DM).

Recognising the haemodynamic, anti-inflammatory and metabolic protection observed with the nephrons, research with SGLT2i expanded into nephrology. Major clinical trials like DAPA-CKD and EMPA-KIDNEY found SGLT2i administration in CKD patients, with or without T2DM, attenuated renal function decline [86,87]. Both trials found a reduction in the primary composite renal outcome of 39% [HR = 0.61 (95% CI 0.51–0.72); $p < 0.001$] and 28% [HR = 0.72 (95% CI 0.64–0.82); $p < 0.001$] with dapagliflozin and empagliflozin use, respectively [86,87].

Meta-analyses of randomised controlled trials performed by Mavrakanas et al. (2023) and Usman et al. (2023) have concluded that SGLT2i confers cardiorenal benefits in patients with varying key clinical manifestations of CKM syndrome, including T2DM, CKD and HF, regardless of ejection fraction [88,89]. This clinical evidence helped to underpin clinical practice guidelines to recommend SGLT2i as primary organ-protective agents that delay the progression of chronic kidney disease (CKD) and end-stage renal disease, completely transforming standard care guidelines for both cardiovascular and renal health [1].

This extraordinary cardio-renal protection of SGLT2i extends beyond simple glucose control and is a subject of much research globally. The mechanisms underpinning the therapeutic benefits of SGLT2i are likely to be multifaceted. In contrast with many anti-diabetic agents, it does not influence endogenous insulin or incretin pathways [90]. SGLT2i cardiorenal benefits appear to be independent of glycaemic control, suggesting other underlying mechanisms at play. Findings may even suggest that cardioprotective effects of SGLT2i are not dependent on the presence of Sodium–Glucose Co-Transporter 2 (SGLT2) protein [91].

It was initially widely thought that SGLT2i confers benefits in HF through increased osmotic diuresis [92]. In theory, inhibition of SGLT2 protein would lead to glucosuria and natriuresis, thus facilitating diuresis. However, a review of multiple randomised controlled trials in HF patients on SGLT2i suggests it does not produce significant natriuresis [93]. Furthermore, Packer (2023) noted that many randomised controlled trials, despite report-

ing an improvement in Kansas City Cardiomyopathy Questionnaire scores, showed no improvement in the physical signs that are suggestive of fluid overload such as oedema, ascites or pleural effusion [93]. Therefore, it is possible that SGLT2i cardiorenal benefit is not entirely mediated through diuresis.

SGLT2i-induced ketogenesis is suggested to account for the observed cardiorenal benefit [94]. However, studies showing raised β-hydroxybutyrate levels secondary to SGLT2i observe diminished or no increase in the non-diabetic subgroup compared to the T2DM subgroup [95]. This suggests that there are other mechanisms at play because studies such as a meta-analysis conducted by Usman et al. (2023) show homogeneous cardioprotective effects in HF patients with or without T2DM [89,95]. Moreover, ketogenesis is less marked in HFpEF than in HFrEF and is thus unable to explain the uniform benefit seen in both HFpEF and HFrEF; only a minority of HF patients achieve ß-hydroxybutyrate levels greater than 500 μM, and it is also unclear what level of ketogenesis is therapeutic [96]. Instead, it was suggested that ketogenesis is a biomarker for nutrient deprivation, which induces autophagy that contributes to cardiorenal protection [97].

Supporting evidence is provided when the disruption of specific autophagic pathways blocks the action of SGLT2i in reducing oxidative stress, improve mitochondrial homeostasis, ameliorate inflammation and fibrosis [97]. The importance of the AMP-activated Protein Kinase/Mechanistic Target of Rapamycin Complex 1 autophagy pathway was highlighted when inhibition of the pathway negates empagliflozin's effects on cardiac remodelling in HFpEF [98]. The same study also shows the effect of empagliflozin in counteracting the effect of Ang II and palmitate on autophagy in rat myocardium [98]. The same study also shows the effect of empagliflozin in counteracting the effect of Ang II and palmitate on autophagy in rat myocardium [98]. Similarly, glomerular autophagy is reactivated in db/db mice by administering empagliflozin, demonstrating the SGLT2i's ability to induce autophagy [99]. By promoting autophagy, it allows for the preservation of organ function via attenuation of oxidative stress, preserves cell and mitochondrial viability, and inhibits inflammation [97,100].

4.2. Glucagon-like Peptide-1 Receptor Agonist (GLP-1RA) and Glucose-Dependent Insulinotropic Polypeptide Receptor Agonist

Following the foundational success of SGLT2i, the GLP-1RA drug class is emerging as a transformative class for combating CKM syndrome and potentially MASH. Arguably, GLP-1RAs are targeting the central metabolic driver that initiates the CKM syndrome, as discussed above.

The GLP-1RA, semaglutide, was evaluated as a weight-reducing agent in the STEP Programme that included the STEP 1 trial that found overweight individuals with weight-related comorbidity or obese individuals experienced significant weight loss with weekly semaglutide injections [101]. In the STEP 1 trial, 86.4% of those on semaglutide achieved the primary endpoint of 5% loss in body weight or more compared to just 31.5% of the placebo group, $p < 0.001$ [101].

Then, in the SUSTAIN-6 trial, semaglutide was evaluated at doses for use in T2DM with established CVD. It demonstrated a 26% relative risk reduction in 3-point major adverse cardiovascular events (MACE) [102]. This is followed by the landmark SELECT trial demonstrating a reduction in 3-P MACE for non-diabetic overweight or obese patients with established CVD [HR = 0.80 (95% CI 0.72–0.90); $p < 0.001$] when using semaglutide in comparison to placebo [103]. On the other hand, Lee et al. conducted a meta-analysis including 10 trials with 71,351 participants on a variety of GLP-1RAs, finding a reduction in MACEs by 14% [HR = 0.86 (95% CI 0.81–0.90); $I^2 = 27.6\%$] in T2DM patients, demonstrating clear cardiovascular benefit [104]. The results of the SOUL trial also introduced the role of

oral semaglutide within the CKM framework. The results of the SOUL trial also introduced the role of oral semaglutide within the CKM framework. The SOUL trial evaluated oral semaglutide in 9650 high-risk adults with T2DM and an increased atherosclerotic cardiovascular risk profile; it showed that oral semaglutide achieved a 14% relative risk reduction [HR = 0.86 (95% CI 0.77–0.96); $p = 0.006$] in 3-point MACE [105]. A key finding from SOUL was that the cardiovascular benefits of oral semaglutide were completely independent of concomitant SGLT2i use; this might support a dual therapy strategy for advanced CKM syndrome [105]. All these trials highlighted semaglutide's ability to reduce ASCVD events in high-risk population groups, and the trials' details are expanded in Table 3.

Then, the FLOW trial proved that semaglutide confers renoprotective effects as well in diabetic patients by showing a reduction in the primary clinical outcome of major kidney disease events [HR = 0.76 (95% CI 0.66–0.88); $p = 0.0003$] [106]. Badve et al. (2025) conducted a meta-analysis of 11 trials and found that patients with T2DM benefited from a risk reduction of 18% in composite kidney outcome [HR = 0.82 (95% CI 0.73–0.93); $I^2 = 26{\cdot}41\%$] when using GLP-1RA in comparison to placebo [107].

Lastly, semaglutide was shown to lead to the resolution of steatohepatitis without worsening of fibrosis in 62.9% of MASH patients, 28.7% [estimated difference = 28.7 (95% CI 21.1–36.2); $p < 0.001$] higher than the placebo group in part 1 of the ESSENCE trial [108]. Similarly, 36.8% of MASH patients had a reduction in liver fibrosis without worsening of steatohepatitis, 14.4% [estimated difference = 14.4 (95% CI 7.5–21.3); $p < 0.001$] higher than those in the placebo group [108]. That said, part 2 of the ESSENCE trial, the clinical events study, is still ongoing to further assess whether the positive histological transformation can be translated to tangible clinical benefits [108]. Table 3 summarises a few major trials of GLP-1RA, with results on cardiovascular, kidney, metabolic and hepatic outcomes.

Table 3. Major trials of GLP-1 receptor agonists evaluating cardiovascular, renal, and metabolic outcomes.

Trial [Drugs] Reference	Summary of Characteristics of Selected Trial Population	Primary Outcome	Effect Size (HR or Mean Difference), *p*-Value	CKM Syndrome Phenotype
SUSTAIN-6 [SEMAGLUTIDE] [102]	Either: 1. Age ≥ 50 years with established CVD, HF (NYHA II, III, IV) or CKD ≥ stage 3 OR 2. Age ≥ 60 years with ≥1 cardiovascular risk factor T2DM with HbA1c ≥ 7%	3P-MACE * between placebo and semaglutide group	HR 0.74 (95% CI 0.58–0.95), $p < 0.001$ for non-inferiority	ASCVD + T2DM
STEP 1 [SEMAGLUTIDE] [101]	≥1 self-reported unsuccessful dietary efforts to lose weight Either a BMI ≥ 30 OR ≥ 27 kg m^{-2} with ≥1 weight-related coexisting conditions (i.e., HTN, dyslipidaemia, obstructive sleep apnoea, or CVD). Exclude HbA1c ≥ 6.5%	Percentage change in body weight from baseline to week 68 and achievement of reduction in body weight ≥ 5% from baseline to week 68 between placebo and semaglutide group	Mean change in body weight: Estimated treatment difference of −12.4% (95% CI −13.4 to −11.5), $p < 0.001$ Body weight reduction ≥ 5%: 86.4% of semaglutide group against 31.5% of placebo group, $p < 0.001$	Obesity

Table 3. *Cont.*

Trial [Drugs] Reference	Summary of Characteristics of Selected Trial Population	Primary Outcome	Effect Size (HR or Mean Difference), *p*-Value	CKM Syndrome Phenotype
STEP-HFpEF [SEMAGLUTIDE] [109]	HF EF ≥ 45% with NYHA II, III, IV BMI ≥ 30 kg m^{-2} KCCQ clinical summary score < 90 Able to perform the 6 min walk test at screening with a minimum distance of 100 metres At least one of the following: elevated left ventricular filling pressures, elevated natriuretic peptide levels plus echocardiographic abnormalities, HHF in the 12 months before screening with either ongoing treatment with diuretics or echocardiographic abnormalities. Exclude HbA1c ≥ 6.5%	Change from baseline to week 52 in the KCCQ-CSS and the percentage change in body weight between placebo and semaglutide group [patient-reported outcome]	Estimated difference in change in KCCQ-CSS: 7.8 (95% CI 4.8–10.9), $p < 0.001$. Estimated difference in percentage change in body weight: −10.7% (95% CI −11.9 to −9.4), $p < 0.001$	Obesity + HFpEF
SELECT [SEMAGLUTIDE] [103]	Age ≥ 45 years BMI ≥ 27 kg m^{-2} Established CVD Exclude T2DM or HbA1c ≥ 6.5%	3P-MACE * between placebo and semaglutide group	HR 0.80 (95% CI 0.72–0.90), $p < 0.001$	ASCVD + Obesity
STEP-HFpEF DM [SEMAGLUTIDE] [110]	HF EF ≥ 45% with NYHA II, III and IV BMI ≥ 30 kg m^{-2} T2DM with HbA1c ≤ 10% At least one of the following: elevated left ventricular filling pressures, elevated natriuretic peptide levels plus echocardiographic abnormalities, HHF within 12 months before screening plus echocardiographic abnormalities or ongoing treatment with diuretics	Change from baseline to week 52 in the KCCQ-CSS and percentage change in body weight between placebo and semaglutide group [patient-reported outcome]	Estimated difference in change in KCCQ-CSS: 7.3 (95% CI 4.1–10.4), $p < 0.001$. Estimated difference in percentage change in body weight: −6.4% (95% CI −7.6 to −5.2), $p < 0.001$	Obesity + T2DM + HFpEF
FLOW [SEMAGLUTIDE] [106]	T2DM with HbA1c ≤ 10% CKD defined as 25 ≤ eGFR ≤ 75 mL min^{-1} (1·73 m^2)$^{-1}$ with 300 mg g^{-1} < UACR < 5000 mg g^{-1} if eGFR ≥ 50 mL min^{-1} (1·73 m^2)$^{-1}$ OR 100 mg g^{-1} < UACR < 5000 mg g^{-1} if eGFR < 50 mL min^{-1} (1·73 m^2)$^{-1}$	Composite renal outcome ** between placebo and semaglutide group	HR 0.76 (95% CI 0.66–0.88), $p = 0.0003$	CKD + T2DM
SOUL [SEMAGLUTIDE] [105]	Age ≥ 50 years T2DM with 6.5% ≤ HbA1c ≤ 10% At least one of the following: coronary artery disease, CVD, symptomatic PAD or CKD [eGFR < 60 mL min^{-1} (1·73 m^2)$^{-1}$]	3P-MACE * between placebo and semaglutide group	HR 0.86 (95% CI 0.77–0.96), $p = 0.006$	ASCVD + T2DM

Table 3. *Cont.*

Trial [Drugs] Reference	Summary of Characteristics of Selected Trial Population	Primary Outcome	Effect Size (HR or Mean Difference), *p*-Value	CKM Syndrome Phenotype
ESSENCE—PART 1 [SEMAGLUTIDE] [108]	Histologically documented steatohepatitis and liver fibrosis of stage 2 or 3 NAS of ≥4	Resolution of steatohepatitis with no worsening of liver fibrosis and reduction in liver fibrosis with no worsening of steatohepatitis between placebo and semaglutide group [surrogate marker for long-term hepatic outcomes]	Resolution of steatohepatitis: ED 28.7% (95% CI 21.1–36.2); reduction in liver fibrosis: ED 14.4% (95% CI 7.5–21.3). Both p <0.001	MASLD

* 3P-MACE in SUSTAIN-6, SELECT, and SOUL trials is defined as the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. However, SUSTAIN-6 specifies the inclusion of silent myocardial infarction, but SELECT and SOUL do not. ** Composite renal outcome in FLOW trial is defined as a composite of onset of kidney failure (initiation of long-term dialysis, kidney transplantation, or a reduction in the eGFR to <15 mL per minute per 1.73 m^2 sustained for ≥28 days), a sustained (for >28 days) 50% or greater reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes. Abbreviation: Atherosclerotic Cardiovascular Disease (ASCVD); body mass index (BMI); body weight (BW); confidence interval (CI); Chronic Kidney Disease (CKD); cardiovascular disease (CVD); estimated difference (ED); ejection fraction (EF); estimated glomerular filtration rate (eGFR); Haemoglobin A1c (HbA1c); heart failure (HF); heart failure with preserved ejection fraction (HFpEF); Hospitalisation for Heart Failure (HHF); Hazard Ratio (HR); hypertension (HTN); Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS); Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD); Non-alcoholic fatty liver disease activity score (NAS); New York Heart Association Functional Classification (NYHA); *p*-value (*p*); Peripheral Arterial Disease (PAD); Type 2 diabetes mellitus (T2DM); Urine Albumin–Creatinine Ratio (UACR).

Following semaglutide, tirzapetide showed a stronger weight loss effect with an estimated treatment difference of −6.5% [estimated treatment difference = −6.5 percentage points (95% CI −8.1 to −4.9); $p < 0.001$] in obese patients when compared to semaglutide in the SURMOUNT-5 trial [111]. In SURPASS CVOT, tirzepatide was found to have a non-inferior but not superior cardiovascular benefit and safety profile when compared to dulaglutide, with 12.2% of the tirzepatide group experiencing the primary cardiovascular endpoint compared to 13.1% in the dulaglutide group [HR = 0.92 (95.3% CI 0.83–1.01); $p = 0.003$ for non-inferiority] [112].

GLP-1RA is also beginning to show therapeutic benefits in patients with HF, especially in HFpEF. Combined with the more recent SUMMIT trial with tirzapetide that showed a reduction in cardiovascular death or HF deterioration by 38% [HR = 0.62 (95% CI 0.41–0.95); $p = 0.026$] in obese participants with HFpEF receiving tirzapetide compared to those on placebo [113]. Table 4 further expanded on major trials of tirzapetide. Despite that, it is noteworthy that the efficacy of GLP-1RAs in HFrEF remains uncertain. This uncertainty stems from a lack of large clinical trials of GLP-1RAs in patients with HFrEF.

Table 4. Major trials of tirzepatide evaluating weight reduction and cardiometabolic outcomes.

Trial [Drug s] Reference	Summary of Characteristics of Selected Trial Population	Primary Outcome	Effect Size (HR or Mean Difference), *p*-Value	CKM Syndrome Phenotype
SURMOUNT-1 [TIRZEPATIDE] [114]	BMI ≥ 30 kg m^{-2} OR BMI ≥ 27 kg m^{-2} with at least one weight-related complication (e.g., HTN, dyslipidaemia, obstructive sleep apnoea, or CVD) Reported ≥ 1 unsuccessful dietary effort to lose weight Exclude Diabetes Mellitus	Percentage change in body weight from baseline to week 72 between tirzepatide and placebo group	Mean change in body weight: −15.0% (95% CI −15.9 to −14.2, 5 mg dose), −19.5% (95% CI −20.4 to −18.5, 10 mg dose), −20.9% (95% CI −21.8 to −19.9, 15 mg dose) vs. placebo −3.1% (95% CI −4.3 to −1.9), $p < 0.001$ for all comparisons against placebo	Obesity
SUMMIT [TIRZEPATIDE] [113]	Age ≥ 40 years HF EF ≥ 50% with NYHA II, III, IV BMI ≥ 30 kg m^{-2} KCCQ-CSS ≤ 80 Able to perform the 6 min walk test at screening with a distance of 100 metres to 425 metres At least one of the following: elevated NTpro-BNP, left atrial enlargement or elevated filling pressures at rest or during exercises HF decompensation within 12 months before baseline or have eGFR < 70 mL min^{-1} (1·73 m^2)$^{-1}$ HbA1c < 9.5% and exclude uncontrolled diabetes	A composite of adjudicated death from CV causes or a worsening HF event and the change at 52 weeks in KCCQ-CSS between tirzepatide and placebo group	Death from CV causes or worsening HF event: HR 0.62 (95% CI 0.41–0.95), $p = 0.026$ Between-group median difference in increase in KCCQ-CSS: 6.9 (95% CI 3.3–10.6), $p < 0.001$	HFpEF + Obesity
SURMOUNT-5 [TIRZEPATIDE] [111]	BMI ≥ 30 kg m^{-2} OR BMI ≥ 27 kg m^{-2} with at least one prespecified obesity-related complication (HTN, dyslipidaemia, obstructive sleep apnoea, or CVD) Exclude Diabetes Mellitus	Percentage change in body weight from baseline to week 72 between tirzepatide and semaglutide group	Estimated treatment difference: –6.5% (95% CI −8.1 to −4.9), $p < 0.001$.	Obesity
SURPASS-CVOT [TIRZEPATIDE] [112]	Age ≥ 40 years T2DM with 7.0% ≤ HbA1c ≤ 10.5% BMI ≥ 25 kg m^{-2} Established ASCVD	Composite of death from cardiovascular causes, myocardial infarction, or stroke between tirzepatide and dulaglutide group	HR 0.92 (95.3% CI 0.83–1.01), $p = 0.003$ for non-inferiority, $p = 0.09$ for superiority	ASCVD + T2DM + Overweight

Abbreviation: Atherosclerotic Cardiovascular Disease (ASCVD); body mass index (BMI); body weight (BW); confidence interval (CI); cardiovascular disease (CVD); ejection fraction (EF); estimated glomerular filtration rate (eGFR); Haemoglobin A1c (HbA1c); heart failure (HF); heart failure with Preserved Ejection Fraction (HFpEF); hypertension (HTN); Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS); N-terminal pro-brain natriuretic peptide (NT-proBNP); New York Heart Association Functional Classification (NYHA); *p*-value (*p*); Type 2 diabetes mellitus (T2DM).

Nevertheless, GLP-1RA primary effect is to potentiate insulin secretion by pancreatic beta cells; this action is regulated by circulating glucose concentration, thus reducing the risk of hypoglycaemia from their use [115,116]. The benefit is not limited to the insulinotropic activity; it serves a protective role for pancreatic beta cells, promotes beta-cell proliferation and inhibits beta-cell apoptosis [115,116]. Of note, it also enhances beta cells' ability to detect and respond to glucose [116].

Besides insulinotropic activity, GLP-1RA induces weight loss by neuromodulation; it increases satiety and reduces hunger by binding to the GLP-1 receptors in the nucleus tractus solitarii and area postrema in the brainstem [117]. It also binds to the paraventricular nucleus and lateral hypothalamus to disrupt energy homeostasis and hunger regulation [117]. Furthermore, GLP-1RA lessens rewarding feelings derived from food or substance use by inhibiting dopamine secretion in the mesolimbic reward pathway [117]. Additionally, GLP-1RA can inhibit gut motility, which delays gastric emptying, thus suppressing appetite [118,119]. However, it must be noted that weight loss alone may not explain the benefits of GLP-1RA, as an analysis of the ESSENCE trial proves in the context of MASH [120].

GLP-1RA can suppress NF-κB activity, thereby inhibiting pro-inflammatory cytokine production and inducing anti-inflammatory effects; this may be one of the mechanisms involved [121]. Other mechanisms not involving traditional inflammatory cytokines include the reduction in leptin secretion, thus negating its metabolic effect while promoting the secretion of anti-inflammatory adiponectin [122]. GLP-1RA was also shown to inhibit atherosclerosis progression via anti-inflammatory properties independent of plasma cholesterol and body weight reduction, leading to atherosclerotic plaques that are more stable [123,124]. GLP-1RAs' anti-inflammatory properties help in alleviating kidney inflammation and fibrosis in the context of diabetic kidney disease [125].

Overall, the exact mechanisms of cardiorenal benefits in GLP-1RAs remain unknown. Potentially, they simultaneously treat visceral obesity, which is the metabolic origin of CKM and therefore protect the downstream target organ damage through reduction in inflammation, insulin resistance, and improvement in lipid processing. There may be local effects by removing the mechanical and inflammatory load on the heart and kidneys as well.

Like GLP-1, GIP stimulates insulin secretion, but this effect is diminished in severe hyperglycaemia [126,127]. Nevertheless, tirzapetide, a dual GIP/GLP-1 receptor agonist, was developed so that the GLP-1 characteristic can act synergistically with GIP to introduce a stronger glucose-dependent insulinotropic action [126–129]. The synergistic effect stems from GLP-1s' ability to restore GIP's insulinotropic effect by improving glycaemic control, on top of their similar downstream effects [129]. Of note, tirzapetide's GLP-1RA action causes less GLP-1 receptor desensitisation compared to the endogenous variant; thus, tirzapetide exhibits a stronger insulinotropic property [128].

Similar to GLP-1, GIP exerts anti-apoptotic effects on pancreatic beta cells and promotes beta-cell proliferation [127,128]. GIP also affects the central nervous system, causing weight loss through reduced food intake by suppressing appetite [130]. However, GIP does not influence gut motility; thus, it does not delay gastric emptying [118].

One distinct mechanism that GIP does not share with GLP-1 is its action on adipocytes. GIP promotes healthy expansion of white adipose tissue through adipogenesis; this form of fat expansion alongside reduced ectopic fat deposition can counterbalance the negative metabolic impact in obesity [127,129,131,132]. This expansion is also associated with increased capacity of adipose tissue to store lipids, thereby ameliorating lipotoxicity [127,129,132]. It is also thought that GIP has a direct insulin-sensitising effect on adipocytes, besides indirect effects derived from weight loss, thus further improving adipocytes' glucose uptake capacity [127,129,132].

The addition of GIP action in tirzapetide leads to greater reduction in hepatic lipid deposition and ameliorates hepatic inflammation in Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) [133]. GIP and GLP-1 share the same mechanism in promoting adiponectin expression and secretion [127,132].

4.3. Aldosterone-Target Therapy

There is increasing interest in targeting aldosterone in CKM as a strategy for preventing multi-organ damage in CKM. Obesity and metabolic stress trigger obesity-induced aldosterone excess. Further, in later stages of CKM, HF e and progressive renal disease act as reciprocal accelerators of one another, with RASS and aldosterone excess serving as a bridge between them. Targeting aldosterone could be vital because upstream therapies may be insufficient; this includes the 'aldosterone breakthrough' phenomenon. Standard CKM therapies like angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARBs) inhibit aldosterone levels initially, but, over months, aldosterone levels can rebound. A proportion of 10% to 53% of those taking ACEi or ARB experience aldosterone breakthrough, thus blunting the cardiorenal benefits offered by ACEi or ARB [134,135]. In addition, one-fifth of treatment-resistant hypertensive individuals have primary aldosteronism, highlighting the importance of mineralocorticoid receptor (MR) blockade therapy [136].

The main mechanism of action of MRAs is the prevention of sodium retention and regulation of blood pressure, but their antihypertensive effects alone cannot explain the beneficial impacts they have on the heart and kidney. It is believed that the cardiorenal benefit is mediated through MRA anti-inflammatory and anti-fibrotic effects [137].

The role of steroidal MRAs in the management of both hypertension and HFrEF is well established. The importance of steroidal MRAs in HFrEF cannot be overstated, as it is a core, guideline-recommended therapy. However, steroidal MRA use may be limited in CKM syndrome due to hyperkalaemia risk in advanced CKD [138]. The concern is partly addressed when it was shown that finerenone, an nsMRA, causes a lower rate of hyperkalaemia compared to spironolactone [5.3% for finerenone, 12.7% for spironolactone; $p = 0.048$] in a study on heart failure patients with CKD [139]. This may be due to its pharmacokinetic distribution being more equal between the heart and kidneys compared to its steroidal counterpart [140]. Since both eplerenone and spironolactone concentrate more in the kidneys, this explains how finerenone may contribute to a lower incidence of hyperkalaemia and may be more beneficial for the heart [140]. Interestingly, the CONFIDENCE trial targeting a population with T2DM and CKD found that combination therapy of finerenone and empagliflozin caused a greater reduction in urinary Albumin-to-Creatinine Ratio (UACR) compared to either finerenone or empagliflozin used alone [141]. However, it has to be acknowledged that the CONFIDENCE trial assessed change in albuminuria, a surrogate endpoint, and did not directly measure the effects on clinical kidney disease progression when using combination therapy [141].

Of note, secondary analysis of the CONFIDENCE trial concluded that combination therapy of finerenone and empagliflozin did not significantly reduce hyperkalaemia risk when compared to finerenone alone, and the incidence of hyperkalaemia on combination therapy or finerenone alone was higher than empagliflozin alone [142]. This was despite the initial observation of a lower frequency of hyperkalaemia, reported by site investigators or the central laboratory, in patients on combination therapy compared to finerenone alone in the CONFIDENCE trial, even though the increase in the mean serum potassium level was similar between both groups [141].

On the topic of heart failure, the TOPCAT study found no significant differences between spironolactone and placebo in the primary outcome of composite of death from

cardiovascular causes, aborted cardiac arrest and hospitalisation for HFpEF population [HR = 0.89 (95% CI 0.77–1.04); $p = 0.14$], but the regional difference in primary outcomes between the Americas and Russia/Georgia must be acknowledged [56,60]. Whereas, FINEARTS-HF has certainly demonstrated that its nsMRA counterpart, finerenone, is able to reduce the primary composite outcome of total number of wHF events and cardiovascular deaths [RR = 0.84 (95% CI 0.74–0.95); $p = 0.007$] in HFpEF and heart failure with mildly reduced ejection fraction population, the specific outcome of decrease in cardiovascular-associated mortality is not statistically significant [143]. On the other hand, FIEDELIO-DKD demonstrated renoprotective properties in T2DM patients, demonstrating that finerenone is better at improving primary composite renal outcomes than placebo [HR = 0.82 (95% CI 0.73–0.93); $p = 0.001$] [144].

Nevertheless, it is undeniable that finerenone still imposes hyperkalaemia risk, thereby partially limiting its use, and available trial evidence does not support use if eGFR is below 25 mL min^{-1} (1.73 m^2)$^{-1}$. Thus, balcinrenone, a partial MRA, was developed to address the risk of hyperkalaemia while retaining cardiorenal benefit [145]. On that note, MIRO-CKD, a randomised, active-controlled, double-blind, phase 2b clinical trial assessing UACR change in CKD patients, still found a minor increased incidence of laboratory-defined hyperkalaemia when comparing patients on balcinrenone plus dapagliflozin against those on dapagliflozin alone [146]. However, the same study acknowledged that a significant portion of the trial population carries a high risk of hyperkalaemia and will typically not be included in other MRA trials [146]. To accurately assess the risk of hyperkalaemia when using balcinrenone, further trials comparing its use to other MRAs may be helpful. Furthermore, BalanceD-HF, an ongoing phase 3 trial, may aid us in evaluating its cardiovascular benefits in patients with both HF and poor kidney function [147]. The potential of balcinrenone remains to be seen as we wait for more clinical data. Table 5 lists major trials on finerenone and balcinrenone, including the BalanceD-HF trial, including the BalanceD-HF trial, which is an ongoing phase III trial.

Table 5. Major trials of MRA evaluating cardiovascular and renal outcomes in chronic kidney disease and heart failure.

Trial [Drugs] Reference	Summary of Characteristics of Selected Trial Population	Primary Outcome	Effect Size (HR/RR or Mean Difference), *p*-Value	CKM Syndrome Phenotype
FIDELIO-DKD [FINERENONE] [144]	T2DM (exclude HbA1c > 12%) Either criterion: (a) CKD [25 ≤ eGFR ≤ 60 mL min^{-1} (1·73 m^2)$^{-1}$] with 30 mg g^{-1} < UACR < 300 mg g^{-1} and history of diabetic retinopathy (b) CKD [25 ≤ eGFR ≤ 75 mL min^{-1} (1·73 m^2)$^{-1}$] with 300 mg g^{-1} < UACR < 5000 mg g^{-1} K ≤ 4.8 mmol L^{-1} at screening Treated with maximally tolerated dose of ACEi, ARB or both ≥4 weeks Exclude HFrEF with NYHA (II, III and IV)	Composite renal outcome * between placebo and finerenone group	HR 0.82 (95% CI 0.73–0.93), $p = 0.001$	CKD + T2DM

Table 5. *Cont.*

Trial [Drugs] Reference	Summary of Characteristics of Selected Trial Population	Primary Outcome	Effect Size (HR/RR or Mean Difference), *p*-Value	CKM Syndrome Phenotype
FIGARO-DKD [FINERENONE] [148]	T2DM (exclude HbA1c > 12%) Either criterion: (a) CKD [25 ≤ eGFR ≤ 90 mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$] with 30 mg g^{-1} ≤ UACR < 300 mg g^{-1} and history of diabetic retinopathy (b) CKD [60 ≤ eGFR mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$] with 300 mg g^{-1} ≤ UACR ≤ 5000 mg g^{-1} K ≤ 4.8 mmol L^{-1} at screening Pre-treated with maximally tolerated doses of ACEi or ARB Exclude HFrEF with NYHA (II, III and IV)	Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for HF between placebo and finerenone group	HR 0.87 (95% CI 0.76–0.98), $p = 0.03$	CKD + T2DM
MIRACLE [BALCINRENONE & DAPAGLIFLOZIN] [149]	HF EF < 60% with NYHA functional class II–IV and a specific elevated NT-proBNP criteria CKD [30 ≤ eGFR ≤ 60 mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$] 30 mg g^{-1} < UACR < 3000 mg g^{-1} 3.5 < K ≤ 5 mmol L^{-1} Exclude HbA1c > 10% Exclude HF secondary to pericardial disease, congenital heart disease or clinically significant uncorrected primary cardiac valvular disease or planned cardiac valve repair/replacement, cardiomyopathies, decompensated HF Exclude high-output HF (e.g., due to hyperthyroidism or Paget's disease)	Relative change in UACR from baseline to week 12, comparing the use of balcinrenone/dapagliflozin to dapagliflozin/placebo [Surrogate marker for long-term renal outcomes]	The addition of balcinrenone, regardless of dose, to dapagliflozin does not cause a greater reduction in UACR for patients with both HF and CKD across doses of 15 mg, 50 mg and 150 mg balcinrenone	HF + CKD
FINEARTS-HF [FINERENONE] [143]	Age ≥ 40 years HF EF ≥ 40% with NYHA II, III, IV and specific elevated NT-proBNP criteria	Composite of CV death or total wHF events between placebo and finerenone group	RR 0.84 (95% CI 0.74–0.95), $p = 0.007$	HFpEF
MIRO-CKD [BALCINRENONE & DAPAGLIFLOZIN] [146]	CKD [25 ≤ eGFR ≤ 60 mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$] with 100 mg g^{-1} < UACR ≤ 5000 mg g^{-1} and 3.5 < K ≤ 5 mmol L^{-1} Stable RAAS inhibitor treatment ≥ 4 weeks before screening, but Participants who cannot tolerate or are not treated with RAAS inhibitors can also participate in the study Exclude uncontrolled T2DM	Relative change in UACR from baseline to Week 12, comparing balcinrenone & dapagliflozin against dapagliflozin & placebo [Surrogate marker for long-term renal outcomes]	UACR difference with combination therapy: −32.8% (90% CI −42.0 to −22.1, $p < 0.0001$) for 40 mg balcinrenone; −22.8% (90% CI −33.3 to −10.7, $p = 0.0038$) for 15 mg balcinrenone	CKD

Table 5. *Cont.*

Trial [Drugs] Reference	Summary of Characteristics of Selected Trial Population	Primary Outcome	Effect Size (HR/RR or Mean Difference), *p*-Value	CKM Syndrome Phenotype
CONFIDENCE [EMPAGLIFLOZIN & FINERENONE] [141]	T2DM with HbA1c < 11% CKD [30 ≤ eGFR ≤ 90 mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$] 100 mg g^{-1} ≤ UACR ≤ 5000 mg g^{-1} Treated with maximally tolerated dose of ACEi or ARB ≥ 1 month at screening	Relative change in the log-transformed mean UACR from baseline to 180 days between finerenone & placebo, empagliflozin & placebo and finerenone & empagliflozin [Surrogate marker for long-term renal outcomes]	least-squares mean ratio of the difference in the change from baseline with combination therapy: 0.68; 95% CI, 0.59 to 0.79; $p < 0.001$ compared to empagliflozin alone; 0.71; 95% CL, 0.61 to 0.82; $p < 0.001$ compared to finerenone alone	CKD + T2DM
BalanceD-HF [BALCINRENONE & DAPAGLIFLOZIN] [147]	HF with NYHA II, III, IV and a specific elevated NT-proBNP criteria recent HF event within 6 months (hospitalisation or urgent visit) 20 ≤ eGFR < 60 mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$ K ≤ 5.0 mmol L^{-1}	A composite of first occurrence of CV death, HF event with hospitalisation or HF event without hospitalisation, comparing between balcinrenone & dapagliflozin and empagliflozin and placebo	Ongoing phase III trial	HF + CKD

* Composite renal outcome in FIDELIO-DKD is defined as kidney failure, a sustained decrease of at least 40% in the eGFR from baseline over a period of at least 4 weeks, or death from renal causes. Abbreviation: angiotensin-converting enzyme inhibitor (ACEi); Angiotensin II receptor blocker (ARB); cardiovascular (CV); confidence interval (CI); chronic kidney disease (CKD); ejection fraction (EF); estimated glomerular filtration rate (eGFR); Haemoglobin A1c (HbA1c); heart failure (HF); heart failure with reduced ejection fraction (HFrEF); Hazard Ratio (HR); serum potassium level (K); N-terminal pro-brain natriuretic peptide (NT-proBNP); New York Heart Association Functional Classification (NYHA); *p*-value (*p*); Rate Ratio (RR); Type 2 diabetes mellitus (T2DM); Urine Albumin-to-Creatinine Ratio (UACR); Urine Protein–Creatinine Ratio (UPCR); first or recurrent unplanned hospitalisation or urgent visit for heart failure (wHF).

Overall, MRAs will no doubt remain as one of the pillars in the clinical management of CKM syndrome, with clinical evidence strongly supporting steroidal MRA use in HFrEF and non-steroidal MRA in HFpEF, respectively. Steroidal mineralocorticoid receptor antagonists (sMRAs) use in CKD has been limited due to insufficient clinical evidence to suggest benefits on clinical kidney outcomes, and a substantially increased risk of hyperkalaemia, especially when using ACEi or ARB, based on population studies [150,151]. nsMRA serves as an alternative due to lower hyperkalaemia risk and clinical evidence to support use in diabetic patients with CKD as previously discussed. Nonetheless, sMRA and nsMRA use remain contraindicated in patients with high baseline serum potassium of ≥5.0 mmol L^{-1}.

However, there is increasing interest in inhibiting MR-mediated effects by reducing aldosterone synthesis using ASIs. This is due to MRAs' limitation in overcoming the compensated increase in circulatory aldosterone level and the MR-independent effects of aldosterone [152].

The ASIs with the most advanced clinical data now include baxdrostat. BaxHTN is a phase 3, double-blind, randomised, placebo-controlled trial that recruited 794 patients with uncontrolled or resistant hypertension [153]. At week 12, it demonstrated estimated blood pressure decreases of 8.7 mm Hg (95% CI −11.5 to −5.8; $p < 0.001$) and 9.8 mm Hg

(95% CI −12.6 to −7.0; $p < 0.001$) with 1 mg baxdrostat and 2 mg baxdrostat, respectively, in comparison to placebo [153]. Similarly, Bax24 finds the least-squares mean placebo-corrected treatment difference in ambulatory blood pressure to be −14.0 mm Hg (95% CI −17.2 to −10.8; $p < 0.0001$) with the use of baxdrostat in patients with resistant hypertension at week 12 [154]. Despite that, hyperkalaemia remains a potential adverse event, as 11.1% of patients in BaxHTN and 12% of patients in Bax24 have serum potassium concentration of >5.5 mmol L^{-1} with use of 2 mg baxdrostat [153,154]. In short, ASI will be a welcome addition to the group of pharmacological therapies available for the treatment of CKM syndrome, in view of its effectiveness at treating resistant hypertension. Of interest, there are ongoing trials to explore the use of ASI beyond just the control of blood pressure, such as BaxDuo Prevent-HF and BaxDuo-Baltic [155,156]. A summary of completed and ongoing trials of ASI can be found in Table 6.

Table 6. Major trials involving ASI evaluating hypertension, cardiovascular and renal outcomes.

Trial [Drugs] Reference	Summary of Characteristics of Selected Trial Population	Primary Outcome	Effect Size, *p*-Value	CKM Syndrome Phenotype
Advance-HTN [LORUNDROSTAT] [157]	Receiving 2–5 stable doses of antihypertensive medications 140 mm Hg < SBP < 180 mm Hg and 65 mm Hg < diastolic BP < 110 mm Hg OR 90 mm Hg < diastolic BP < 110 mm Hg regardless of SBP Exclude K > 5 mmol L^{-1} Exclude HbA1c > 9% Exclude eGFR < 45 mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$	Change in 24 h average SBP from baseline to week 12 between lorundrostat against placebo	Placebo-adjusted change: For 50 mg, −7.9 mmHg (97.5% CI −13.3 to −2.6), $p = 0.001$ For dose-adjustment group *: −6.5 mmHg (97.5% CI −11.8 to −1.2), $p = 0.006$	HTN
Launch-HTN [LORUNDROSTAT] [158]	Receiving two to five stable doses of antihypertensive medications 135 mm Hg ≤ SBP ≤ 180 mm Hg and 65 mm Hg ≤ diastolic BP ≤ 110 mm Hg OR 90 mm Hg ≤ diastolic BP ≤ 110 mm Hg regardless of SBP BMI ≥ 18 kg m^{-2} Exclude K > 5 mmol L^{-1} Exclude eGFR < 45 mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$	Change in automated office SBP at week 6 between losartan and placebo	Least-squares between-group mean difference: −9.1 mmHg (95% CI, −13.3 to −4.9); $p < 0.001$	HTN
BaxHTN [BAXDROSTAT] [153]	140 mm Hg ≤ mean seated SBP < 170 mm Hg despite maximally tolerated dose of ≥2 medications (uncontrolled hypertension) OR ≥3 antihypertensive medications (resistant hypertension), including diuretics for ≥4 weeks eGFR ≥ 45 mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$ 3.5 mmol L^{-1} ≤ K < 5 mmol L^{-1}	Change in seated SBP from baseline to week 12 for 1 mg baxdrostat group and 2 mg baxdrostat group against placebo group	Placebo-corrected difference: −8.7 mmHg (95% CI −11.5 to −5.8) with 1 mg, −9.8 mmHg (95% CI −12.6 to −7.0) with 2 mg; $p < 0.001$ for both	HTN
Bax24 [BAXDROSTAT] [154]	140 mm Hg ≤ mean seated SBP < 170 mm Hg despite maximally tolerated dose of ≥3 antihypertensive medications, including diuretics for ≥4 weeks eGFR ≥ 45 mL min^{-1} $(1{\cdot}73\ m^2)^{-1}$ 3.5 ≤ K < 5 mmol L^{-1}	Change in 24 h ambulatory SBP from baseline to week 12 between placebo and baxdrostat group	Placebo-corrected difference: −14.0 (95% CI –17.2 to −10.8); $p < 0.0001$	HTN

Table 6. *Cont.*

Trial [Drugs] Reference	Summary of Characteristics of Selected Trial Population	Primary Outcome	Effect Size, *p*-Value	CKM Syndrome Phenotype
BaxDuo Prevent-HF [BAXDROSTAT & DAPAGLIFLOZIN] [155]	Age ≥ 40 years Diagnosed with T2DM and requiring treatment Established CVD History of HTN and an SBP ≥ 130 mmHg at screening and ≥120 mmHg at the randomisation visit At least one additional risk factor for HF: Age ≥ 70 years OR UACR > 20 mg g^{-1} OR eGFR < 60 mL min^{-1} (1·73 m^2)$^{-1}$ OR history of CVD, Afib, atrial flutter OR NT-proBNP > 125 ng L^{-1} Exclude eGFR < 30 mL min^{-1} (1·73 m^2)$^{-1}$ Exclude K ≥ 5 mmol L^{-1} Exclude T2DM with HbA1c > 10.5%	A composite of first occurrence of hospitalisation for HF, HF without hospitalisation or CV death between baxdrostat & dapagliflozin against dapagliflozin alone	Ongoing Phase III trial	HF + T2DM
BaxDuo-Baltic [BAXDROSTAT & DAPAGLIFLOZIN] [156]	CKD [30≤ eGFR < 90 mL min^{-1} (1·73 m^2)$^{-1}$] with 200 mg g 1 < UACR < 5000 mg g^{-1} History of HTN and SBP ≥ 130 mm Hg at screening and ≥ 120 mm Hg at randomisation visit Stable and maximally tolerated dose of ACEi or ARB ≥ 4 weeks SBP ≤ 180 mmHg or diastolic BP ≤ 110 mmHg Exclude known hyperkalaemia Exclude HbA1c > 10.5%	Change from baseline in UACR between baxdrostat & dapagliflozin against baxdrostat alone [Surrogate marker for long-term renal outcomes]	Ongoing Phase IIb trial	CKD
BaxDuo- Pacific [BAXDROSTAT & DAPAGLIFLOZIN] [159]	Either one criterion: (a) CKD [30 ≤ eGFR < 60 mL min^{-1} (1·73 m^2)$^{-1}$] with 30 mg g^{-1} ≤ UACR ≤ 5000 mg g^{-1} or 700 mg g^{-1} ≤ UPCR ≤ 7000 mg g^{-1} (b) CKD [60 ≤ eGFR ≤75 mL min^{-1} (1·73 m^2)$^{-1}$] with 500 mg g^{-1} ≤ UACR ≤ 5000 mg g^{-1} or 700 mg g^{-1} ≤ UPCR ≤ 7000 mg g^{-1} History of HTN and SBP ≥ 130 mm Hg at screening and ≥120 mm Hg at randomisation visit Stable and maximally tolerated dose of ACEi or ARB ≥ 4 weeks SBP ≤ 180 mmHg or diastolic BP ≤ 110 mmHg Exclude known hyperkalemia Exclude HbA1c > 10.5%	Composite of the first occurrence of ≥50% sustained decline in eGFR, onset of kidney failure (sustained eGFR < 15 mL min^{-1} (1·73 m^2)$^{-1}$, chronic dialysis, kidney transplant or renal primary cause death) and CV event (CV death, HF with or without hospitalisation) between baxdrostat & dapagliflozin against dapagliflozin alone	Ongoing Phase III trial	CKD

* dose-adjustment group in Advance-HTN refers to the group of participants that receive 50 mg of the dose for the first 4 weeks of treatment, then followed by an increase to 100 mg daily when systolic blood pressure is 130 mm Hg or higher. Abbreviation: Atrial Fibrillation (Afib); blood pressure (BP); confidence interval (CI); cardiovascular (CV); cardiovascular disease (CVD); group of participants that receive 50 mg of dose for the first 6 weeks and increased to 100 mg the subsequent week (dose-adjustment group); Estimated glomerular filtration rate (eGFR); Haemoglobin A1c (HbA1c); heart failure (HF); Hospitalisation for Heart failure (HHF); hypertension (HTN); serum potassium level (K); least-squares mean (LSM); N-terminal pro-brain natriuretic peptide (NT-proBNP); *p*-value (*p*), systolic blood pressure (SBP); Type 2 diabetes mellitus (T2DM); Urine Albumin-to-Creatinine Ratio (UACR).

4.4. Lipid-Lowering Therapy

The importance of lipid-lowering therapies in CKM syndrome cannot be overstated. The drivers of CKM highlighted above, i.e., the interplay of visceral adiposity, insulin resistance, chronic inflammation, oxidative stress, and progressive kidney dysfunction, generate a distinct atherogenic dyslipidaemic phenotype characterised by elevated triglycerides (TG), reduced high-density lipoprotein-cholesterol (HDL-C), increased apolipoprotein B (apoB)-containing lipoproteins, remnant cholesterol (RC) accumulation, small dense low-density lipoprotein (LDL) particles, and frequently elevated lipoprotein(a) [Lp(a)] [160]. Based on a large body of evidence confirming that statins significantly reduce the risk of ASCVD, major global authoritative guidelines, including the Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Guidelines and the American Diabetes Association (ADA) 2024 Guidelines, explicitly recommend the use of statins for both primary and secondary prevention in the majority of patients with CKD [161]. Moreover, while the AHA guidelines reaffirm statins as the cornerstone of therapy, they also recommend PCSK9 inhibitors (PCSK9i), ezetimibe, and bile acid sequestrants for secondary prevention of ASCVD [162]. Furthermore, the current AHA and ESC (European Society of Cardiology) guidelines emphasise risk-based lipid targets, particularly for patients at high or very high cardiovascular risk, such as those with CKD, to guide clinical intensity of therapy beyond simple percentage reductions [162]. Meanwhile, KDIGO suggests exploring potential benefits of fibrates and niacin in patients with CKD [161]. However, these recommendations are not entirely based on RCT evidence, specifically in the CKM population. Overall, the evidence is robust for ASCVD risk reduction with lipid-lowering therapies, thereby cementing their role in CKM syndrome management. There is emerging data that lipid-lowering therapy may be beneficial for renal and HF outcomes [163,164]. Effective lipid management is crucial for CKM syndrome treatment, with the potential to reduce residual cardiovascular and renal risk and improve long-term clinical outcomes. At this time, management requires a multimodal approach tailored to the patient's lipid phenotype and overall cardiovascular risk, incorporating a range of lipid-lowering strategies including statins, ezetimibe, PCSK9i, bempedoic acid, fibrates and icosapent ethyl. We are also mindful of emerging therapies targeting Apolipoprotein C-III, Angiopoietin-like 3, and Lp(a) that may become relevant in patients with CKM syndrome. Clearly, there is a need for future research that may reveal unrecognised cardiorenal benefits associated with novel lipid-modifying therapies, as exemplified by SGLT2i and GLP-1RA.

4.5. Potassium Binder

As mentioned previously, hyperkalaemia risk remains a challenge in CKM syndrome management. This can be attributed to the increasing use of ACEi/ARB with MRA in patients with advanced CKM syndrome, as combining both therapies raises the risk of hyperkalaemia further, and the development of nsMRAs did not resolve the issue. Therefore, novel hyperkalaemia management strategies may include the use of potassium binders such as sodium zirconium cyclosilicate and patiromer.

Sodium zirconium cyclosilicate is assessed in the REALIZE-K trial, which recruited HFrEF patients on either ACEi, ARB or ARNI with hyperkalaemia or increased hyperkalaemia risk [165]. These patients were started or uptitrated on spironolactone in the trial to assess whether sodium zirconium cyclosilicate allows for safe MRA use by controlling the potassium level [165]. About 71% of patients on sodium zirconium cyclosilicate achieved at least 25 mg/day of spironolactone while maintaining normokalaemia and did not require hyperkalaemia rescue therapy for 6 months compared to around 36% of patients on placebo [OR = 4.45 (95% CI 2.89–6.86); $p < 0.001$] [166]. In those with HF and/or CKD, ZORA, an

observational study programme, found that patients are less likely to discontinue RAAS inhibitors when treated with sodium zirconium cyclosilicate as well [167,168].

In the DIAMOND trial, HFrEF patients with hyperkalaemia or high hyperkalaemia risk have their RAAS inhibitor therapy, including MRA, optimised and then given either patiromer or placebo [169]. The between-group difference in adjusted mean change in serum potassium from randomisation to the end of the study in the trial is −0.10 mmol L^{-1} (95% CI −0.13 to −0.07; $p < 0.001$) [169]. In CKD patients who were receiving one or more RAAS inhibitors and had hyperkalaemia, the OPAL-HK trial shows that treatment with patiromer reduces the recurrence of hyperkalaemia compared to placebo [170].

Overall, clinical evidence supports the use of sodium zirconium cyclosilicate or patiromer to mitigate hyperkalaemia risk as a potential management strategy when optimising RAAS inhibitors in CKM syndrome. However, sodium zirconium cyclosilicate use may be limited by a potential increased risk of HF events, and it is unclear if patiromer is less likely to cause HF events compared to sodium zirconium cyclosilicate as well [2,171].

5. Practical Considerations: CKM Syndrome Management

Management of CKM syndrome requires a multimodal approach targeting metabolic dysfunction, renal injury, and cardiovascular disease simultaneously. Interventions include lifestyle modifications, pharmacotherapy, and integrated care pathways, reflecting the syndrome's multisystem pathophysiology (see Table 1).

5.1. Lifestyle and Dietary Interventions

Lifestyle modification is the foundation of CKM management, targeting the metabolic dysfunction and risk factors that drive disease progression. Early and sustained interventions combining healthy nutrition, physical activity, behavioural support, and weight management can reduce body mass index (BMI) and visceral adiposity, improving glycaemic control, albuminuria, and cardiovascular outcomes across the CKM continuum.

5.2. Pharmacologic Therapies

Pharmacologic management of CKM syndrome should address shared pathophysiological pathways while being tailored to the extent of metabolic, renal, and cardiovascular involvement. RAAS inhibitors (ACEi and ARBs) remain central to therapy, reducing blood pressure, slowing CKD progression, and improving cardiac remodelling. MRAs provide additional renal and cardiovascular protection through anti-fibrotic effects.

SGLT2i delivers broad cardiorenal-metabolic benefits, including reduced HHF, preservation of kidney function, improved glycaemic control, and lower albuminuria. GLP-1RA improves glycaemic control, promotes sustained weight loss, reduces cardiovascular risk, and may provide renal protection through favourable metabolic and anti-inflammatory effects. Statins remain essential for ASCVD prevention, while newer lipid-lowering agents may offer further benefit in selected patients.

Given the multisystem nature of CKM syndrome, combination therapy is often required. Combining RAAS inhibitors, SGLT2i, MRA, and GLP-1RA targets complementary mechanisms, providing additive benefits on haemodynamic stress, neurohormonal activation, inflammation, fibrosis, and metabolic dysfunction. Evidence supports enhanced cardiorenal protection with these multi-pillar approaches compared with individual therapies alone. Table 7 expands on the pharmaceutical strategies by describing the different CKM syndrome phenotypes and the recommended treatment.

Table 7. The different CKM syndrome phenotypes with stages and the respective pharmacological treatments, mainly referenced through AHA/ACC/ADA/ASN 2026 guideline on CKM syndrome, supplemented with other guidelines [2,138,171–173].

	Obesity	T2DM	CKD
No other phenotype	**Stage 1 to 3** **First line:** Consider GLP-1RA if <5% weight loss despite lifestyle modification and behavioural change	**Stage 2 to 3** **First line:** Standard glycaemic pharmacotherapy If increased CVD risk, initiate GLP-1RA (prioritise in severe obesity or MASLD) or SGLT2i (prioritised in CKD or pre-HF). Strongly consider addition of metformin to either GLP-1RA or SGLT2i (if not already initiated) if HbA1c > 0.5–1.0% above glycaemic goal	**Stage 2 to 3** **First line:** UACR ≥ 30–199 mg g^{-1}: Recommends ACEi/ARB, consider addition of SGLT2i UACR ≥ 200 mg g^{-1}: Recommends both ACEi/ARB + SGLT2i **Consideration of renal function:** SGLT2i appropriate if eGFR ≥ 20 mL min^{-1} (1·73 m^2)$^{-1}$ ACEi/ARB: Caution if eGFR < 30 mL min^{-1} (1·73 m^2)$^{-1}$ and consider dose reduction or discontinuation if eGFR < 15 mL min^{-1} (1·73 m^2)$^{-1}$
T2DM	**Stage 2 to 3** Similar to management in T2DM phenotype alone	N/A	**Stage 2 to 3** **First line:** Recommends both ACEi/ARB + SGLT2i as first-line (regardless of UACR) **Second line:** If persistent UACR ≥ 30 mg g^{-1}: Recommends add nsMRA OR If persistent UACR ≥ 100 mg g^{-1} AND obese/MASLD: Recommends add GLP-1RA **Third line:** If persistent albuminuria: Consider both GLP1-RA + nsMRA **Consideration of renal function:** SGLT2i appropriate if eGFR ≥ 20 mL min^{-1} (1·73 m^2)$^{-1}$ nsMRA appropriate if eGFR ≥ 25 mL min^{-1} (1·73 m^2)$^{-1}$ ACEi/ARB: Caution if eGFR < 30 mL min^{-1} (1·73 m^2)$^{-1}$ and consider dose reduction or discontinuation if eGFR < 15 mL min^{-1} (1·73 m^2)$^{-1}$ Note—ESC guidelines 2026 recently recommend finerenone to reduce risk of HF (Class I Level A evidence) [171]

Table 7. *Cont.*

	Obesity	T2DM	CKD
ASCVD	**Stage 4** **First line:** Recommends GLP-1RA	**Stage 4** **First line:** Recommends GLP-1RA (prioritise in severe obesity or MASLD) OR Recommends SGLT2i (prioritise in CKD or pre-HF/HF) Second line: Consider both GLP-1RA and SGLT2i	**Stage 4** Analogous to management recommendations for CKD phenotype alone.
	Standard recommendation for all ASCVD regardless of combined phenotype: Recommends antiplatelet + high-intensity statin, add other lipid-lowering therapy if requires more intensive LDL-C lowering or management of triglyceride		
HFpEF	**Stage 4** **First line:** Recommends SGLT2i + nsMRA/sMRA * + GLP1-RA	**Stage 4** **First line:** Recommends SGL2i + nsMRA/sMRA * **Second line:** Consider adding GLP-1RA if MASLD, ASCVD or CKD with albuminuria (UACR $\geq$ 100 mg g^{-1})	**Stage 4** **First line:** Recommends SGL2i + nsMRA/sMRA * Note—nsMRA if T2DM + CKD with albuminuria (UACR $\geq$ 30 mg g^{-1}) **Consideration of renal function:** SGLT2i appropriate if eGFR $\geq$ 20 mL min^{-1} (1·73 m^2)$^{-1}$ nsMRA appropriate if eGFR $\geq$ 25 mL min^{-1} (1·73 m^2)$^{-1}$
	Additional note ESC 2026 guidelines recently recommended sMRA/nsMRA for HFpEF in symptomatic HF to reduce HHF or CV death (Class I Level A evidence) [171] American College of Cardiology 2026 expert consensus decision pathway recommends nsMRA in HFpEF [172]		
HFrEF	**Stage 4** **First line:** Recommends BB + sMRA + ACEi/ARB/ARNI + SGLT2i		**Stage 4** **First line:** Recommends BB + sMRA + ACEi/ARB/ARNI + SGLT2i **Consideration of renal function:** SGLT2i appropriate if eGFR $\geq$ 20 mL min^{-1} (1·73 m^2)$^{-1}$ sMRA appropriate if eGFR > 30 mL min^{-1} (1·73 m^2)$^{-1}$ [173] ACEi/ARB: Caution if eGFR < 30 mL min^{-1} (1·73 m^2)$^{-1}$ and consider dose reduction or discontinuation if eGFR < 15 mL min^{-1} (1·73 m^2)$^{-1}$ ARNI: Caution if eGFR < 30 mL min^{-1} (1·73 m^2)$^{-1}$

Table 7. *Cont.*

Obesity	T2DM	CKD
General lifestyle modification advice for all CKM syndrome stages and phenotypes		
Avoid tobacco or smoking cessation		
Avoid excessive alcohol intake		
Maintenance of healthy weight. If overweight/obese, aim for at least 5–10% weight loss and maintain weight loss. Strategies include weight loss counselling, self-monitoring of dietary intake with calorie deficit of 500–700 kcal per day.		
≥150 min per week of moderate-intensity aerobic activity for weight loss and functional capacity.		
Mediterranean, pescatarian, and vegetarian diet to reduce cardiometabolic risks. Adoption of a low-sodium diet as well.		

* Recommendation of nsMRA/sMRA use in HFpEF patients as per recent guidelines as described in the additional note section in HFpEF row. Abbreviation: angiotensin-converting enzyme inhibitor (ACEi); Angiotensin II receptor blocker (ARB); angiotensin receptor-neprilysin inhibitor (ARNI); atherosclerotic cardiovascular disease (ASCVD); beta blocker (BB); chronic kidney disease (CKD); cardiovascular (CV); cardiovascular disease (CVD); estimated glomerular filtration rate (eGFR); Glucagon-like peptide-1 receptor agonist (GLP-1RA); European Society of Cardiology (ESC); Haemoglobin A1c (HbA1c); heart failure (HF); Heart Failure with Preserved Ejection Fraction (HFpEF); Heart Failure with Reduced Ejection Fraction (HFrEF); Hospitalisation for Heart Failure (HHF); low-density lipoprotein cholesterol (LDL-C); metabolic dysfunction-associated steatotic liver disease (MASLD); mineralocorticoid receptor antagonist (MRA); non-steroidal mineralocorticoid receptor antagonist (nsMRA); Sodium–Glucose Cotransporter 2 inhibitors (SGLT2i); steroidal mineralocorticoid receptor antagonist (sMRA); Type 2 diabetes mellitus (T2DM); Urine Albumin–Creatinine Ratio (UACR).

Combination regimens are generally well tolerated but require monitoring for serum potassium levels and renal function, particularly when RAAS inhibitors are used in combination with MRAs, as well as volume status in those receiving SGLT2i and gastrointestinal side effects in users of GLP-1RAs. Furthermore, notable potential adverse drug reactions include acute kidney injury and hyperkalaemia associated with RAAS inhibitors and MRAs, urinary tract infections and euglycaemic diabetic ketoacidosis with SGLT2i, and gallbladder diseases with GLP-1RAs.

Patients are more susceptible to adverse drug reactions during acute illnesses, which range from acute decompensated HF and significant dehydration to sepsis or when undergoing major surgery. During these scenarios, SGLT2i should be temporarily withheld to reduce the risk of euglycaemic diabetic ketoacidosis, with frequent blood ketone monitoring. Temporary interruption of MRAs is recommended due to the risk of acute kidney injury, which may also precipitate clinically significant hyperkalaemia. Lastly, continuing GLP-1RA while unwell can worsen dehydration due to gastrointestinal symptoms, which may exacerbate metabolic instability with SGLT2i use and acute kidney injury with MRA use, respectively. These medications should be restarted only when the patient recovers from acute illness and is clinically stable. Normal oral intake and hydration should be achieved before resuming SGLT2i and GLP-1RA, while renal function and potassium should stabilise before restarting MRAs. Therefore, patients should be educated about sick-day rules surrounding the use of SGTL2i, MRA or GLP-1RA, so there will be temporary withdrawal during acute illnesses.

Overall, treatment should be individualised according to patient risk, comorbidities, and treatment tolerability, within a multidisciplinary and integrated model of care.

6. Evidence Gap

The AHA 2023 presidential advisory has defined CKM syndrome and provided a staging framework, but clinical studies have not yet incorporated this framework into study design. Many trials assess clinical outcomes with the background of single-organ dysfunction and occasionally may include certain metabolic risk factors. Few studies were built around multi-organ dysfunction, which can be observed in advanced CKM stages. Future trials should instead enrol participants by CKM stages, rather than focusing on single organ pathology.

There are also many unknowns regarding the overall therapeutic strategies involving multiple drugs of different classes. For one, the optimal sequencing and initiation of these medications remain uncertain in CKM syndrome, especially regarding which medications should be prioritised, and we do not know the ideal time to initiate these treatments. Whether early combination therapy offers significant clinical benefit over a stepwise approach is unknown too. Lastly, the long-term efficacy and, more importantly, safety, of combination therapy in the management of CKM syndrome are not clear.

7. Conclusions

CKM syndrome reflects the close interconnection between metabolic, cardiovascular, and kidney health, underscoring the need for holistic, patient-centred care. Future research should focus on translating growing mechanistic and clinical evidence into effective, evidence-based management strategies. In particular, there is a need for multi-system clinical trials that evaluate interventions across metabolic, renal, and cardiovascular outcomes simultaneously. There is an argument that the future of managing CKM is moving away from treating isolated single organ failures towards early, multi-organ ‘triple’ therapy. Combining SGLT2i, GLP-1RA and the nsMRA could address the metabolic, haemodynamic and structural pillars of the syndrome. Trials such as the CONFIDENCE trial that tested

the simultaneous initiation of finerenone and empagliflozin resulted in a higher efficacy in reducing UACR compared to each drug used alone [141]. Although change in UACR serves as a surrogate clinical marker, we should not extrapolate immediately as an actual clinical benefit. It does suggest that combination therapy, especially a triple therapy of SGLT2i, GLP-1RA, and nsMRA, may potentially have synergistic clinical effects in CKM syndrome, but more clinical studies investigating combination therapies are required to confirm this hypothesis. Whilst adding SGLT2i was shown to not reduce hyperkalaemia risk when used with finerenone, as demonstrated in the secondary analysis of the CONFIDENCE trial, novel potassium binders may be part of CKM syndrome management strategies in the future to address hyperkalaemia risk [142]. Furthermore, as mentioned in the evidence gap subsections, there are still many unknowns when it comes to the therapeutic strategies in CKM syndrome, especially in combination therapies where the long-term efficacy and safety remain unclear.

Overall, longitudinal cohort studies are also essential to better define the natural history of CKM syndrome, identify early predictors of disease progression, and assess the long-term impact of integrated treatment approaches. Clinical studies should also consider stratifying and recruiting patients according to CKM syndrome stages. Furthermore, multicentre and international research collaborations will be critical to generating robust, scalable evidence and accelerating advances in CKM care.

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Abbreviations

Abbreviation	Full Form
3P-MACE	3-Point Major Adverse Cardiovascular Events (composite of death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke)
ACEi	Angiotensin-converting enzyme inhibitors
ADA	American Diabetes Association
Afib	Atrial Fibrillation
AGEs	Advanced Glycation End-products
AHA	American Heart Association
Ang II	Angiotensin II
apo-B	Apolipoprotein B
ARB	Angiotensin-receptor blockers

ARNI	Angiotensin receptor-neprilysin inhibitor
ASCVD	Atherosclerotic Cardiovascular Disease
ASI	Aldosterone Synthase Inhibitor
BB	Beta Blocker
BMI	Body Mass Index
BP	Blood Pressure
BW	Body Weight
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKM	Cardiovascular–Kidney–Metabolic
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular Disease
ED	Estimated difference
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
ER	Endoplasmic Reticulum
ESC	European Society of Cardiology
GIP	Glucose-dependent Insulinotropic Polypeptide
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Haemoglobin A1c
HDL-C	High-density lipoprotein-cholesterol
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HHF	Hospitalisation for Heart Failure
HR	Hazard Ratio
hsCRP	High-sensitivity CRP
IGT	Impaired Glucose Intolerance
IKK	IκB kinase
IKKβ	Inhibitor of nuclear factor kappa B kinase subunit β
IL-1β	Interleukin-1β
IL-6	Interleukin-6
IR	Insulin Receptor
IRS-1	Insulin Receptor Substrate 1
K	Serum Potassium level
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire clinical summary score
KDIGO	Kidney Disease: Improving Global Outcomes
LDL	Low-density lipoprotein
Lp(a)	Lipoprotein(a)
LSM	Least-squares mean
MACE	Major Adverse Cardiovascular Events
MAFLD	Metabolic Dysfunction-Associated Fatty Liver Disease
MASH	Metabolic Dysfunction-Associated Steatohepatitis
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
MRs	Mineralocorticoid Receptors
MRAs	Mineralocorticoid Receptor Antagonists
NAS	Non-alcoholic fatty liver disease activity score
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association Functional Classification
nsMRA	Non-steroidal Mineralocorticoid Receptor Antagonists
p	*p*-value
PAD	Peripheral Arterial Disease

PCSK9	Proprotein convertase subtilisin–kexin type 9
PCSK9i	Proprotein convertase subtilisin–kexin type 9 inhibitor
RAAS	Renin–Angiotensinogen–Aldosterone system
RC	Remnant cholesterol
ROS	Reactive Oxygen Species
RR	Rate Ratio
SBP	Systolic Blood Pressure
siRNA	small interfering RNA
SGLT2	Sodium–Glucose Cotransporter 2
SGLT2i	Sodium–Glucose Cotransporter 2 inhibitors
sMRA	Steroidal Mineralocorticoid Receptor Antagonists
T2DM	Type II Diabetes Mellitus
TG	Triglycerides
TGF-β1	Transforming growth factor-beta1
TNF-α	Tumour Necrosis Factor-α
UACR	Urine Albumin–Creatinine Ratio
UPCR	Urine Protein–Creatinine Ratio
wHF	First or recurrent unplanned hospitalisation or urgent visit for heart failure
WL	Weight Loss

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