

Review

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[Inderjeet Singh Bharaj](#)^{*}, [Karen Purewal](#), Juzer Munaim, [Ajit Singh Brar](#), [Aayushi Kacheria](#), [Austin Simister](#), [Umabalan Thirupathy](#), [Palak Gupta](#), Jasraj Singh Kahlon, Ei Ei Thwe, [Samer Ibrahim](#), Valerie Martinez Vargas, [Krishnaswami Vijayaraghavan](#)^{*}

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Review

New Advances in Cardiovascular Drugs: In Memory of Professor Akira Endo

Inderjeet Bharaj ^{1,*}, Karen Purewal ¹, Juzer Munaim ¹, Ajit Brar ², Aayushi Kacheria ¹, Austin Simister ¹, Thirupathy Umabalam ³, Palak Gupta ⁴, Jasraj Kahlon ¹, Ei Ei Thwe ⁵, Samer Ibrahim ⁵, Valerie Martinez Vargas ⁶ and Krishnaswami Vijayaraghavan ^{7,*}

- ¹ Abrazo Health Network Internal Medicine Residency Program, Grendale, Arizona, USA
- ² Michigan State University Internal Medicine Residency Program at Hurley Medical Center, Flint, Michigan, USA
- ³ Saint Vincent Hospital Internal Medicine Residency Program, Worcester, Massachusetts, USA
- ⁴ Midwestern University Internal Medicine Residency Program at Verde Valley Medical Center, Cottonwood, Arizona, USA
- ⁵ Abrazo Health Network Cardiovascular Disease Fellowship Program, Phoenix, Arizona, USA
- ⁶ University of Arizona Endocrinology, Diabetes and Metabolism Fellowship Program, Tucson, Arizona, USA
- ⁷ University of Arizona College of Medicine, Phoenix, Arizona, USA
- * Correspondence: inderjeetbharaj@gmail.com (I.B.); kvijaymd@gmail.com (K.V.)

Abstract

Background/Objectives: Cardiovascular-kidney-metabolic (CKM) syndrome encompasses interconnected cardiovascular, renal, and metabolic disorders that contribute significantly to global morbidity and mortality. This review aims to synthesize current therapeutic strategies and evaluate emerging treatments that address the multifactorial pathophysiology of CKM syndrome, with a focus on novel pharmacological targets and the role of artificial intelligence (AI) in personalized care. **Methods:** A comprehensive narrative literature review was conducted using PubMed, Scopus, and Google Scholar. Studies were selected based on relevance to CKM syndrome's pathophysiology, diagnostic criteria, and treatment modalities, including trials on SGLT2 inhibitors, GLP-1 receptor agonists, finerenone, and RNA-based therapies. The review also included analysis of clinical trials investigating agents targeting lipoprotein(a), MASLD, and inflammatory pathways. Inclusion and exclusion criteria ensured focus on CKM-relevant mechanisms and therapeutic outcomes. **Results:** SGLT2 inhibitors and GLP-1 receptor agonists demonstrated consistent efficacy in reducing major adverse cardiovascular events, improving renal outcomes, and aiding in glycemic and weight control. Finerenone showed benefit in CKD patients with type 2 diabetes, particularly in reducing inflammation and fibrosis. Emerging therapies—including RNA-based agents, TR β agonists, and immunomodulators—offer promise in targeting specific metabolic and inflammatory pathways. AI applications were found useful in enhancing CKM risk stratification, biomarker integration, and clinical decision-making. **Conclusions:** Therapeutic strategies for CKM syndrome have evolved with evidence-based support for integrated pharmacologic and technological interventions. Continued research on precision medicine, guided by AI and novel biomarkers, holds potential to further optimize CKM management and patient outcomes.

Keywords: cardiometabolic syndrome; chronic kidney disease; SGLT2 inhibitors; glucagon-like-peptide-1 receptor agonists; finerenone

1. Introduction

Cardiovascular-kidney-metabolic (CKM) syndrome represents a complex interplay of cardiovascular, renal, and metabolic disorders that significantly affect global health. These interconnected conditions are prevalent globally, with cardiovascular diseases (CVD) being the

leading cause of death in the United States and the co-occurrence of diabetes and kidney impairment compounding health risks for millions.[1] The rising incidence of obesity and metabolic disorders has exacerbated this crisis, highlighting the necessity for a comprehensive understanding of CKM disease and the therapeutic approaches to manage it effectively[2]. The pathophysiology of CKM disease is complex, driven by shared mechanisms such as hyperglycemia, oxidative stress, chronic inflammation, and neurohormonal activation, which contribute to a cycle of worsening renal and cardiovascular function[3]. This syndrome encompasses a spectrum of conditions including hypertension, diabetes, obesity, chronic kidney disease, and cardiovascular diseases, which often coexist and exacerbate one another[4].

A comprehensive approach to managing cardiometabolic kidney (CKM) disease incorporates a variety of pharmacological strategies aimed at slowing disease progression and reducing cardiovascular (CV) risk. The therapeutic interventions of well known risk factors for CKM include sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and non-steroidal selective mineralocorticoid receptor antagonists, like Finrenone. These medications are rapidly changing the armamentarium available to clinicians to address CKM and can be implemented in a varied set of clinical scenarios to mitigate overall progression of disease. Additionally, the risk factors for CKM continue to be further elucidated and newer therapeutic targets are being uncovered. Clinical data associated with metabolic dysfunction-associated steatotic liver disease (MASLD) as well as Lipoprotein-a (Lp(a)) have been linked to the development of worsening metabolic disease and clinical outcomes[5,6]. Novel technologies involving liver-specific TR β agonists, RNA-based therapies, such as Antisense Oligonucleotides (ASOs) and Small Interfering RNAs (siRNA) in addition to Interleukin 6 blockers, Cholesteryl ester transfer protein (CETP) inhibitors, and angiopoietin-like 3 (ANGPTL3) are undergoing clinical trials and have the ability to drastically change the treatment options for CKM in the coming years. Finally, the current explosion of artificial intelligence has the potential to synthesize a patient's multitude of biomarkers, help forecast disease progression and potentially help individualize therapies.

This paper aims to bring awareness to the current fund of knowledge regarding known therapies in the treatment of CKM and help understand their mechanisms. Furthermore, we strive to discuss the importance of new therapeutic targets and the associated therapies that are showing promise in current clinical trials. The advancement in biomedical and artificial intelligence technology will play an important role in the future treatment of CKM.

2. Search Strategy

A comprehensive narrative literature review was conducted to evaluate the pathogenesis of cardiovascular-kidney-metabolic (CKM) syndrome using major databases, including PubMed, Scopus, and Google Scholar. The search employed a combination of keywords such as "Metabolic associated steatotic liver disease," "non fibrotic Metabolic associated steatohepatitis," "Nonalcoholic fatty liver disease," "Metabolic syndrome," "Cardiovascular disease," "Heart failure", "Cardiorenal syndrome," "Cardiometabolic syndrome," "Chronic kidney disease", and "antifibrotic therapies," "goal directed medical therapy," along with Boolean operators (AND, OR) and Medical Subject Headings (MeSH) terms to refine results and ensure relevance.

Inclusion criteria encompassed studies, review articles, and meta-analyses focusing on the relationship between MASLD, MASH, NASH, NAFLD, Metabolic syndrome and Cardiovascular disease (CVD), Chronic kidney disease (CKD), diagnostic approaches, treatment modalities, and articles exploring the pathophysiological mechanisms linking cardiorenal and metabolic syndrome. Exclusion criteria included non-English publications, studies unrelated to metabolic syndrome, studies focusing solely on non-cardiac manifestations of metabolic syndrome and chronic kidney disease, conference abstracts, editorials, and opinion pieces.

The study selection process involved title and abstract screening to assess relevance, followed by full-text review to confirm alignment with study objectives. Data were systematically extracted using a predefined framework, and findings were summarized qualitatively, focusing on key themes

such as pathophysiology, the impact of cardiovascular-kidney-metabolic (CKM) syndrome, morbidity and mortality, therapeutic targets and emerging research gaps and opportunities.

3. Current and Emerging Therapeutics

Current and emerging therapeutics for cardiovascular-kidney-metabolic (CKM) syndrome target the complex interplay between cardiovascular, renal, and metabolic disorders. Established treatments include SGLT2 inhibitors, GLP-1 receptor agonists, and mineralocorticoid receptor antagonists like finerenone, which have demonstrated benefits in reducing cardiovascular events, slowing CKD progression, and improving metabolic parameters. Emerging therapies focus on novel targets such as Lipoprotein(a), inflammatory pathways, and hepatic fat accumulation. RNA-based therapies like antisense oligonucleotides and small interfering RNAs show promise in modulating gene expression related to lipid metabolism. Additionally, artificial intelligence is increasingly being leveraged to enhance risk prediction, treatment selection, and personalized management strategies in CKM syndrome.

3.1. Sodium Glucose Co-Transport 2 Inhibitors:

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors were originally developed for the management of type II diabetes mellitus. However, their use has now expanded into the cardiorenal and metabolic fields. This expansion is due to the growing recognition of the interconnections between diabetes, cardiovascular disease, and chronic kidney disease (CKD). SGLT2 inhibitors provide cardiorenal protection through multiple, interrelated mechanisms that extend beyond glycemic control. The primary renal mechanism is the restoration of tubuloglomerular feedback via increased sodium delivery to the macula densa, leading to afferent arteriolar vasoconstriction, reduced intraglomerular pressure, and mitigation of hyperfiltration injury[7,8]. This effect is central to nephroprotection and is consistently highlighted in both clinical trials and mechanistic studies[9]. SGLT2 inhibitors also induce osmotic diuresis and natriuresis, resulting in plasma volume contraction, lower blood pressure, and reduced cardiac preload and afterload, which are key contributors to heart failure benefit[10]. Anti-inflammatory, antifibrotic, and antioxidative effects—mediated by reduced macrophage activation, decreased pro-inflammatory cytokines, and improved mitochondrial function—further contribute to both cardiac and renal protection[11,12].

Initial studies evaluating cardiovascular outcomes include DAPA-HF which found dapagliflozin resulted in a 26% reduction in the composite endpoint of cardiovascular death or heart failure hospitalization compared to placebo[13]. The EMPEROR-Reduced trial further exemplified the benefits of SGLT2 inhibitors as there was a 25% lower combined risk of cardiovascular death or heart failure hospitalization in patients receiving empagliflozin vs placebo[14]. The American Heart Association and the American College of Cardiology both recognize these multifactorial mechanisms as the basis for the cardiorenal benefits observed in large outcome trials[15]. In fact, SGLT2 inhibitors are now an essential component of goal directed medical therapy (GDMT) in the treatment of heart failure with reduced ejection fraction (HFrEF)[16]. The EMPEROR-preserved trial found that empagliflozin reduced the risk of the primary endpoint of cardiovascular death or hospitalization for heart failure by 21% in patients with heart failure and a preserved ejection fraction (HFpEF)[17]. This finding was consistent amongst generally all subgroups; including those with or without diabetes[17]. Ultimately, these findings have allowed for SGLT2 inhibitors to become a key player in the treatment of HFrEF/HFpEF. In addition, a meta-analysis of 11 trials involving SGLT2 inhibitors, which assessed rates of major adverse cardiovascular events (MACE), ultimately determined that the observed reduction in cardiovascular mortality is primarily attributable to a decrease in deaths related to heart failure and sudden cardiac death[18]. Notably, the observed reduction in cardiovascular-related mortality was evident among patients exhibiting some degree of albuminuria, as these individuals experienced twice the event rate compared to those without albuminuria. This observation underscores the necessity to further investigate albuminuria in conjunction with the therapeutic benefits of SGLT2 inhibitors in the management of chronic kidney disease (CKD)[18].

Albuminuria has been found to be an independent risk factor for cardiovascular events, kidney failure, and death[19]. The CREDENCE trial evaluated the role of SGLT2 inhibitors, more specifically Canagliflozin, in patients with diabetic CKD. They found that canagliflozin reduced the risk of kidney failure by 30% in this population[19]. The role of SGLT2 inhibitors were further expanded as evidence supported their role in patients without diabetes mellitus and more advanced CKD. The DAPA-CKD trial showed a reduced risk of the primary endpoint of sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular when compared to placebo[20]. This study broadened the treatment population as the benefits of dapagliflozin were noted independent of diabetes mellitus. The study included 14.5% participants that had an eGFR less than 30 which was a contrast to the CREDENCE trial which had included a cut off of eGFR of 30[19,20]. The role of SGLT2 inhibitors in advanced CKD was further solidified as the EMPA-KIDNEY trial enrolled members with an eGFR as low as 20[21]. This study also included a population with a wide range of levels of albuminuria with 48.3% with a urinary albumin to creatinine (UACR) less than 300. This group was also found to have a reduction in progression of CKD in comparison with placebo[21]. This underscores the significance of SGLT2 inhibitors in managing various stages of CKD.

In summary, SGLT2 inhibitors are a cornerstone therapy for CKM syndrome, providing integrated cardiovascular, renal, and metabolic protection as endorsed by the American Heart Association, American Diabetes Association, and KDIGO. Their benefits extend beyond glycemic control and include reduction in progression of CKD, hospitalization for heart failure, major adverse cardiovascular events, and all-cause mortality, with efficacy demonstrated in patients both with and without diabetes. [Figure 1]

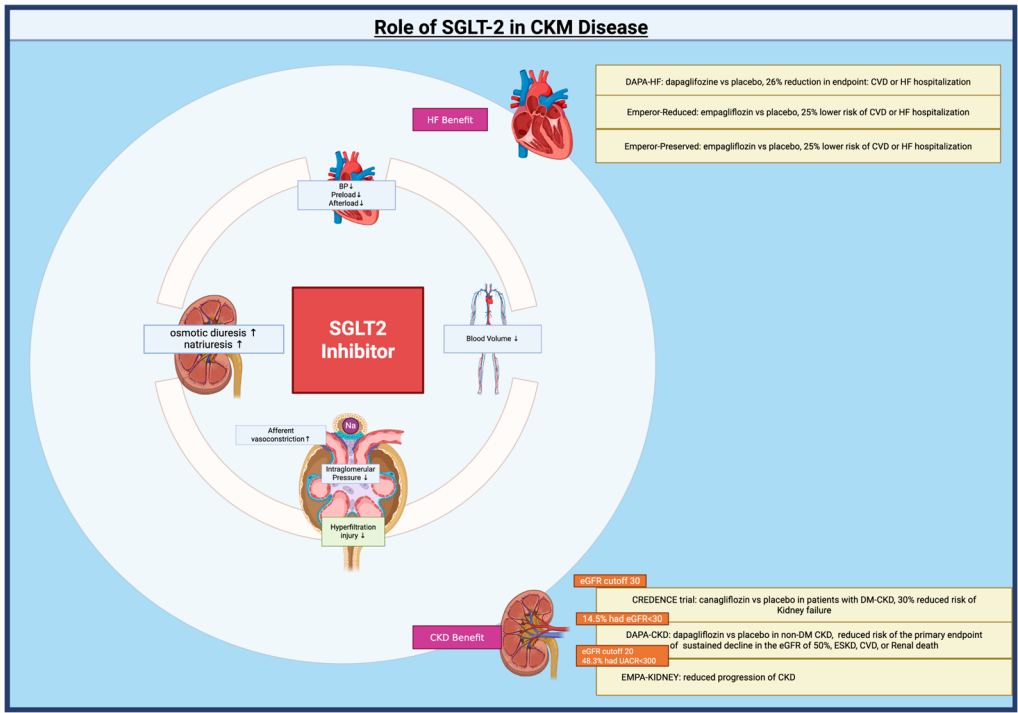


Figure 1. Legend: CKD: Chronic Kidney Disease, CVD: Cardiovascular Death, HF: Heart Failure, MACE: Major adverse cardiovascular events, T2DM: Type 2 Diabetes Mellitus.

3.2. Glucagon-like-Peptide-1 Receptor Agonists:

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) play a central role in the management of CKM syndrome, particularly in patients with type 2 diabetes, obesity, and/or chronic kidney disease (CKD). GLP-1RA were initially developed for treatment of type 2 diabetes. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend GLP-

1 RAs as a preferred first injectable therapy before insulin in most patients with T2D who require intensification beyond oral agents, due to their efficacy in lowering HbA1c, low risk of hypoglycemia, and favorable effects on weight[22,23]. These pharmacological agents effectively manage glycemic levels, facilitate weight reduction, and have been shown to substantially decrease major adverse cardiovascular events (MACE) and all-cause mortality in high-risk cohorts, particularly individuals with CKD and established atherosclerotic cardiovascular disease (ASCVD)[24,25].

GLP-1 RAs are recommended as adjunctive therapy for adults with type 2 diabetes, overweight or obesity, and metabolic dysfunction–associated steatotic liver disease (MASLD), particularly when metabolic dysfunction–associated steatohepatitis (MASH) or high risk for liver fibrosis is present[26]. Multiple phase II and phase III trials have highlighted the efficacy of GLP-1RAs in reducing hepatic fat content and liver histological inflammation and fibrosis among MASLD patients[27–29]. Mechanistically, GLP-1 RAs exert their hepatic benefits primarily through indirect pathways, including weight reduction, improved insulin sensitivity, and decreased systemic inflammation, rather than direct action on hepatocytes. These agents also improve cardiovascular and renal outcomes, which is particularly relevant given the high cardiometabolic risk in MASLD/MASH[30,31]. Despite these advances, no GLP-1 RA is currently approved specifically for MASLD or MASH, and regulatory approval is pending further outcome data.

GLP-1RAs are now approved as adjunctive therapy in adults with T2D and chronic kidney disease (CKD) to improve glycemic control and potentially slow progression of kidney disease, with preference for agents with demonstrated cardiorenal benefit (liraglutide, semaglutide, dulaglutide)[25]. GLP-1RAs demonstrate a decrease in albuminuria and decline in estimated glomerular filtration rate (eGFR), with benefits observed even in patients with reduced eGFR (<60 mL/min/1.73 m²) in patients with T2D and CKD. A clinical trial focusing on diabetes management in patients with CKD indicates that GLP-1 receptor agonists reduce the likelihood of experiencing a composite endpoint related to kidney function deterioration including macroalbuminuria, eGFR decline, progression to kidney failure, or death from kidney disease[25]. A meta-analysis of randomized controlled trials in patients with chronic kidney disease treated with glucagon-like peptide-1 receptor agonists provided evidence of this, demonstrating improved renal and cardiovascular outcomes, as well as enhanced survival[32].

Clinical guidelines highlight the substantial cardiovascular benefits of GLP-1RAs proving particularly valuable for patients with chronic kidney disease (CKD). These agents have demonstrated a robust capacity to reduce major adverse cardiovascular events (MACE) and all-cause mortality, making them a key consideration in managing this vulnerable population[22,23]. Beyond cardiovascular outcomes, GLP-1RAs exhibit several additional properties that contribute to their renoprotective effects. Their anti-inflammatory and antioxidant actions mitigate cellular damage and oxidative stress, while their natriuretic properties promote sodium excretion, aiding in fluid balance[33]. Moreover, these drugs have been shown to reduce hyperfiltration, a maladaptive process that can accelerate kidney damage, and to downregulate receptors for advanced glycation end products (RAGE), thereby reducing inflammation triggered by these molecules[34]. Taken together, these multifaceted mechanisms position GLP-1 receptor agonists as compelling therapeutic options for individuals with CKD, offering both cardiovascular protection and direct renoprotective benefits.

GLP-1 RAs are recommended as pharmacologic options for the management of obesity, particularly semaglutide and liraglutide, by the American Gastroenterological Association[35]. GLP-1 RAs exert their weight-lowering effects primarily through central appetite suppression, delayed gastric emptying, and modulation of energy intake, with additional benefits on glycemic control, blood pressure, and lipid profiles[36]. Building on these recommendations, robust clinical trials and meta-analytic data further clarify the role of GLP-1 receptor agonists as effective agents for weight loss in adults with obesity, regardless of diabetes status. Randomized controlled trials and systematic reviews consistently demonstrate that GLP-1 RAs, particularly semaglutide (2.4 mg once weekly, subcutaneous) and liraglutide (3.0 mg once daily, subcutaneous), produce clinically meaningful reductions in body weight, with semaglutide achieving mean weight loss of 9–16% and liraglutide

4–7% over 1 year, and a substantial proportion of patients achieving ≥10% weight loss. These effects are superior to those of first-generation anti-obesity drugs and lifestyle modification alone[37].

Overall, GLP-1 receptor agonists are generally preferred in CKM syndrome when weight loss, glycemic control, and ASCVD risk reduction are primary goals,are now established as a cornerstone pharmacologic therapy for obesity management, with demonstrated efficacy for weight loss, metabolic improvement, and potential cardiovascular benefit, as supported by multiple high-quality studies and consensus from major professional societies[22,38,39]. [Figure 2]

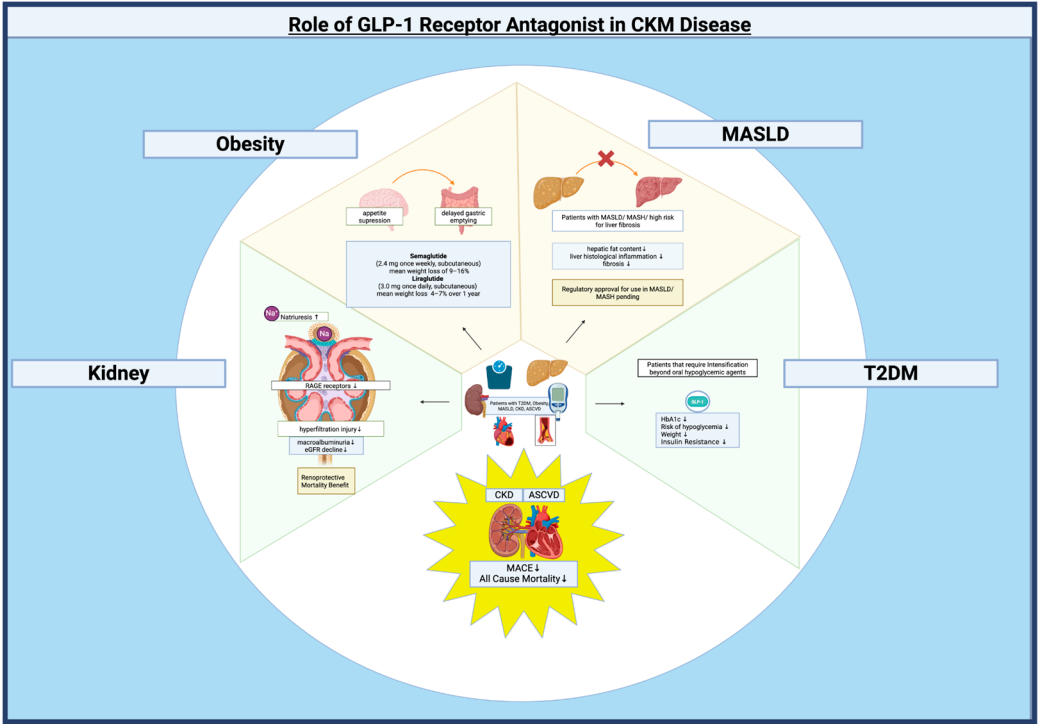


Figure 2. Legend: ASCVD:atherosclerotic cardiovascular disease , CKD: Chronic Kidney Disease, CVD: Cardiovascular Death, MACE: Major adverse cardiovascular events, MASLD: metabolic dysfunction–associated steatotic liver disease, MASH: metabolic dysfunction–associated steatohepatitis, T2DM: Type 2 Diabetes Mellitus.

3.3. Mineralocorticoid Receptor Antagonist:

Finerenone is a nonsteroidal, selective antagonist of the mineralocorticoid receptor (MR). Its mechanism of action involves competitively blocking the binding of aldosterone and cortisol to the MR, thereby inhibiting MR-mediated gene transcription[40]. Finerenone exhibits high potency and selectivity for the MR, with minimal affinity for androgen, progesterone, estrogen, or glucocorticoid receptors, distinguishing it from steroidal MRAs such as spironolactone and eplerenone. Compared to these agents, finerenone demonstrates a more balanced tissue distribution between the heart and kidney and exerts more potent anti-inflammatory and anti-fibrotic effects, with a lower risk of hyperkalemia and hormonal side effects[41]. This blockade occurs in both epithelial tissues (such as the kidney, where it reduces sodium reabsorption) and non epithelial tissues (including the heart and vasculature), leading to reduced inflammation and fibrosis which are the key drivers of cardiorenal disease progression in chronic kidney disease (CKD) and type 2 diabetes[42].

The over activation of the mineralocorticoid receptor has been implicated in end organ damage primarily through promotion of inflammation and fibrosis on top of known sodium retention leading to hypertension[43]. There is well established data on the role of mineralocorticoid receptor benefits in the treatment of HFrEF but use has been limited by side effects such as hyperkalemia and acute kidney injury; especially seen in patients with concomitant advanced CKD[43]. Finerenone through its selective binding to these receptors results in a more targeted approach compared to steroidal

MRAs, potentially leading to fewer side effects while maintaining efficacy[41]. A few key trials have highlighted both cardiovascular and renal outcomes in patients with T2DM. The FIDELIO-DKD trial looked at the primary outcome of kidney failure, a decrease in baseline eGFR by at least 40%, or death from renal causes and a secondary outcome of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure[44]. Barkis et al.[44] found there was a statistically significant decrease in both primary and secondary outcomes in those treated with Finerenone compared with placebo. The FIGARIO-DKD trial published the following year showed Finerenone reduced the risk of hospitalization for heart failure (HHF) and other cardiovascular events. The study included patients with stage 1-4 CKD, including those with moderately increased albuminuria[45].

Finerenone provides benefit in heart failure primarily by reducing the risk of worsening heart failure events and cardiovascular death in patients with heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF)[46,47]. In the FINEARTS-HF trial, finerenone, significantly lowered the rate of a composite outcome of total worsening heart failure events (including first and recurrent unplanned hospitalizations or urgent visits for heart failure) and death from cardiovascular causes compared to placebo (rate ratio 0.84; 95% CI, 0.74–0.95; P=0.007) over a median follow-up of 32 months[46]. The benefit was consistent across all prespecified subgroups, and the reduction in events was observed for both components of the primary outcome. Finerenone also led to a modest improvement in patient-reported health status, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score, but did not significantly improve NYHA functional class or kidney composite outcomes in this population[48].

While finerenone has shown promise in the management of HFmrEF and HFpEF, it does not have an established benefit in HFrEF. The pivotal clinical trials of finerenone, including FIDELIO-DKD and FIGARO-DKD, specifically excluded patients with symptomatic HFrEF, and the observed cardiovascular benefit, including reduction in heart failure hospitalizations, was demonstrated in patients with chronic kidney disease and type 2 diabetes, not in those with established HFrEF[49]. Ongoing and future trials may clarify the role of finerenone in HFrEF, but as of now, finerenone should not be considered a substitute for established MRAs in HFrEF[40].

Finerenone has a defined role in the management of CKM syndrome, particularly in patients with type 2 diabetes and CKD. In this population, finerenone has been shown to reduce the risk of CKD progression and major adverse cardiovascular events, especially heart failure hospitalizations, when added to maximally tolerated renin-angiotensin system (RAS) blockade (ACE inhibitor or ARB)[4]. The American Diabetes Association and Kidney Disease: Improving Global Outcomes (KDIGO) consensus, as well as the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI), recommend finerenone as an adjunctive, risk-based therapy for patients with T2D, CKD, and albuminuria (UACR >30 mg/g), particularly when residual risk persists despite optimized RAS inhibition and, when possible, SGLT2 inhibitor therapy[25,50]. [Figure 3]

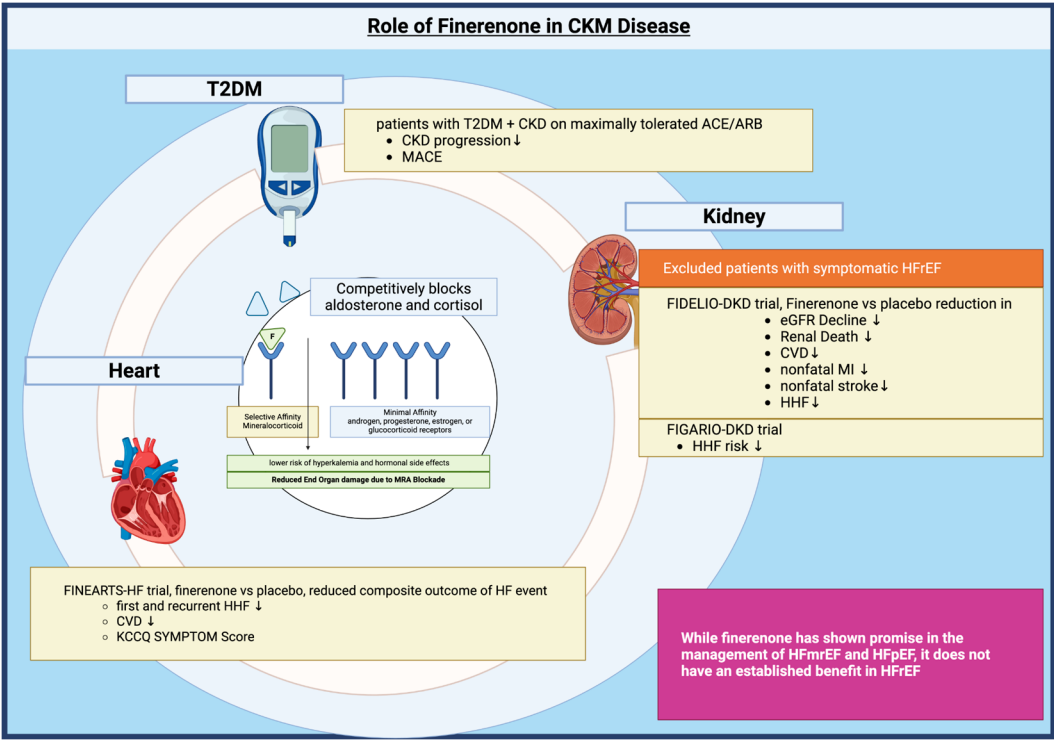


Figure 3. Legend: CKD: Chronic Kidney Disease, CVD: Cardiovascular Death, HFrEF: Hospitalization for Heart Failure, KCCQ: Kansas City Cardiomyopathy Questionnaire, MACE: Major adverse cardiovascular events, MRA: mineralocorticoid receptor antagonist, T2DM: Type 2 Diabetes Mellitus.

3.4. *Thyroid Receptor Beta Agonists:*

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a significant global health concern, affecting over 30% of the adult population[6]. Characterized by the accumulation of fat in the liver due to metabolic dysfunctions such as insulin resistance (IR) and chronic low-grade inflammation, MASLD is associated with a heightened risk of cardiovascular complications[51]. In fact, cardiovascular disease (CVD) is the leading cause of mortality among affected individuals[51]. While MASLD remains a broad category, MASH represents a more severe form, characterized by inflammation, liver damage, and an increased risk of fibrosis, cirrhosis, and liver cancer[52]. The clinical implications of MASLD extend beyond hepatic health, emphasizing the importance of a holistic understanding of its cardiovascular consequences.

Management of MASLD primarily revolves around lifestyle modifications and pharmacological interventions. One promising therapeutic approach involves liver-specific TR β agonists, such as GC-1 (sobetirome), KB-2115 (eprotrirome), and MGL-3196 (resmetirom). Hepatocytes express thyroid hormone receptor beta (THR- β), whose activation by T3 regulates several key metabolic functions, including mitochondrial fatty acid uptake and β -oxidation, mitochondrial biogenesis, upregulation of hepatic LDL receptor expression, and reduction in circulating LDL cholesterol[53]. These agents have shown encouraging results in reducing hepatic steatosis and improving lipid profiles. However, clinical development has encountered setbacks. Phase 2 trials for sobetirome have not yet been conducted, and a phase 3 trial for eprotrirome was discontinued after animal studies revealed cartilage damage in dogs. Additionally, a significant increase in liver enzymes was observed during the study period[53]. Resmetirom has emerged as the first Food and Drug Administration-approved drug for effective management of MASLD[54].

Resmetirom is a selective TR β agonist with 28-fold greater affinity for TR β in the liver. This reduces the creation of new fats, increases the breakdown of fatty acids, and offers benefits against inflammation and scarring[55]. Clinical trials have demonstrated the efficacy of Resmetirom in treating non-cirrhotic MASH with moderate to advanced fibrosis. In a randomized, double-blind Phase 2 trial (NCT02912260), patients with MASH (fibrosis stages F1–F3) received either resmetirom

(80 mg/day, n=78) or placebo (n=38) for 36 weeks. Resmetirom significantly reduced hepatic fat at both 12 and 36 weeks compared with placebo[55]. Following Phase 2 results, MAESTRO-NAFLD-1 phase 3 trial (NCT04197479) was conducted. The MAESTRO-NASH trial (NCT03900429) showed that resmetirom (80 mg and 100 mg) achieved 26% and 30% NASH resolution rates, respectively, versus 10% with placebo, significantly reduced LDL cholesterol, and had mild gastrointestinal side effects. Both 52-week trials were randomized, double-blind, and placebo-controlled[54]. Younossi et al.[56] assessed health-related quality of life (HRQL) in 125 NASH patients treated with resmetirom (n=84) or placebo (n=41) over 36 weeks. Resmetirom significantly improved HRQL scores compared to placebo[56].

Resmetirom demonstrated a favorable safety profile in Phase 3 trials, with mostly mild to moderate gastrointestinal symptoms[6]. Serious adverse event rates were comparable between resmetirom and placebo, and no drug-induced liver injury was reported. Cancer rates, major cardiovascular events, bone fractures, and significant BMD changes were not increased with resmetirom[6]. Resmetirom was approved in the US in 2024 for noncirrhotic NASH with moderate to advanced fibrosis, alongside diet and exercise, based on its safety profile in trials. It reduces liver fat, lowers liver enzyme levels, improves liver fibrogenesis indicators, reduces liver stiffness, and improves cardiovascular profile by lowering serum lipid levels, including LDL cholesterol[57]. Ongoing investigations are assessing the applicability of this drug in pediatric, adolescent, and adult patients diagnosed with cirrhosis. Commercially distributed as Rezdiffra, it is presented in tablet formulations of 60 mg, 80 mg, and 100 mg strengths. The prescribed daily dose is 80 mg for adult individuals weighing below 100 kg and 100 mg for those with a weight of 100 kg or greater[58].

Currently, five ongoing clinical trials are evaluating resmetirom (NCT02912260, NCT04197479, NCT03900429, NCT04951219, NCT04643795)[59]. Further longitudinal investigations and post-marketing surveillance are essential to confirm the long-term safety of resmetirom and to detect any unforeseen off-target effects.

3.5. Lipoprotein-a (Lp(a))

Lipoprotein-a (Lp(a)) is increasingly recognized as a significant risk factor for atherosclerotic cardiovascular disease (ASCVD) and heart failure (HF)[60]. The American Heart Association's recent scientific statement highlights the causal role of elevated Lp(a) in ASCVD, a conclusion supported by extensive observational, genetic, and mechanistic evidence accumulated over decades[60]. Unlike traditional lipids, Lp(a) levels are predominantly genetically determined and remain stable throughout an individual's lifespan, rendering them a promising candidate for early cardiovascular risk stratification[60]. Potential mechanisms linking Lp(a) to heart failure (HF) include its proinflammatory and prothrombotic effects, as well as its role in promoting coronary atherosclerosis[61,62]. Some studies suggest that the relationship between Lp(a) and HF may be partially mediated by myocardial infarction and aortic valve stenosis, although independent pathways are also likely involved[61]. The CASABLANCA study, which assessed patients undergoing coronary angiography, identified a link between elevated Lp(a) and oxidized phospholipids with progression toward symptomatic HF, independent of coronary artery disease (CAD) severity[5]. A meta-analysis of Mendelian randomization studies corroborates that higher genetically predicted Lp(a) levels are significantly associated with an increased risk of HF, suggesting a potential causal relationship[63]. These findings are consistent with other large cohort studies that have identified elevated Lp(a) as a risk factor for both the development of HF and adverse outcomes, including mortality, in individuals with established heart failure with reduced ejection fraction (HFrEF)[61,62].

Notable complexities exist in the relationship between Lp(a) and cardiovascular risk. Research indicates that elevated Lp(a) was predictive of heart failure (HF) and heart failure with preserved ejection fraction (HFpEF) specifically within White participant cohorts, potentially indicative of genetic or environmental factors influencing Lp(a) risk manifestation[64]. Further research is warranted to identify these specific modifiers and elucidate the mechanisms through which they

influence Lp(a)'s impact on HF and HFpEF development in diverse populations. Furthermore, a more pronounced impact of elevated Lp(a) has been observed in individuals with diabetes mellitus[65]. This heightened risk in the diabetic population underscores the critical need for Lp(a) screening within the context of comprehensive cardiovascular risk assessment in these individuals. Identifying individuals with both diabetes and elevated Lp(a) may allow for more targeted and intensified preventive strategies within the CKM framework.

While statin therapy has become a cornerstone in the management of hypercholesterolemia and the subsequent reduction of low-density lipoprotein cholesterol (LDL-C), leading to a significant decrease in the risk of ASCVD) its efficacy does not extend to Lp(a)[66]. Compelling evidence, notably from the landmark JUPITER trial, has revealed that even in individuals receiving effective statin treatment and achieving target LDL-C levels, elevated Lp(a) concentrations continue to pose an independent and significant cardiovascular risk. This finding underscores a critical unmet clinical need for therapeutic interventions specifically designed to target and lower Lp(a) levels[66]. In this context, antisense oligonucleotides (e.g., APO(a)LRx) represent a promising new class of agents, with early-phase clinical trials demonstrating potent, selective reductions in Lp(a) levels with good safety profiles[67]. The future of preventive cardiology and heart failure management may be significantly impacted by these Lp(a)-lowering therapies. If subsequent large-scale clinical trials can definitively establish a direct correlation between the reduction of Lp(a) levels achieved with agents like APO(a)LRx and a tangible decrease in the incidence of heart failure events or a demonstrable improvement in overall survival rates, these targeted treatments would represent a major breakthrough.

The available data strongly indicates that Lipoprotein(a) is not merely a residual risk factor for atherosclerotic cardiovascular disease, but a significant and potentially modifiable factor in the development and progression of heart failure. Routine measurement of Lipoprotein(a) may be justified in clinical practice, particularly for patients with unexplained heart failure, premature atherosclerotic cardiovascular disease, metabolic syndrome, or a family history of early-onset cardiovascular disease. As innovative therapeutic approaches continue to be developed, the identification and targeted treatment of elevated Lipoprotein(a) levels may become a fundamental component of individualized cardiovascular prevention strategies.

3.6. Phase 3 Trial Drugs for CKM Syndrome

New therapies are in the pipeline for Cardio-Kidney-Metabolic (CKM) Syndrome. Contemporary management includes lifestyle modifications and traditional pharmacotherapies. Newer therapies rapidly expanded the options available in the armamentarium against CKM syndrome.

RNA-based therapies, such as Antisense Oligonucleotides (ASOs) and Small Interfering RNAs (siRNA) in addition to Interleukin 6 blockers, Cholesteryl ester transfer protein (CETP) inhibitors, and angiopoietin-like 3 (ANGPTL3) Inhibition, are currently the face of such therapies[68]. RNA-based therapies focus on modulating gene expression or RNA interference. Volanesorsen, an antisense oligonucleotide (ASO), specifically targets hepatic APOC3 mRNA, leading to its cleavage and degradation. This process reduces plasma apolipoprotein C-III levels. Apolipoprotein C-III acts as an inhibitor of lipoprotein lipase (LPL) activity and also impedes an LPL-independent pathway for the clearance of triglyceride-rich lipoproteins. Consequently, reducing apolipoprotein C-III effectively decreases plasma triglycerides, thereby mitigating the risk of pancreatitis in individuals with Familial Chylomicronemia Syndrome (FCS)[69,70]. siRNAs, such as Plozasiran, are double-stranded RNAs that engage with the RNA-induced silencing complex (RISC), leading to the degradation (silencing) of the targeted mRNA[68]. Plozasiran, when used against APOC3 mRNA, achieves the same outcome as Volanesorsen, though it operates through a different mechanism.

Inclisiran is a siRNA that targets the hepatic synthesis of proprotein convertase subtilisin-kexin type 9 (PCSK9), significantly lowering LDL cholesterol levels[71]. As established previously, higher levels of Lipoprotein(a), Lp(a) have an association with increased risk of atherosclerotic

cardiovascular disease[60]. It consists of apolipoprotein B-containing lipoprotein that is covalently bound to apolipoprotein(a). Apolipoprotein(a) gene (LPA) controls the expression of Lp(a). Olpasiran is a siRNA that disrupts the expression of LPA, resulting in lower levels of apolipoprotein(a) synthesis and the final product, Lp(a). Phase III trials are currently underway to assess the effects of MACE reduction with Olpasiran in those with a history of ASCVD and Lp(a) ≥ 200 nmol/L[72].

These novel therapeutic approaches targeting different aspects of cardiovascular disease pathophysiology highlight the ongoing advancements in the field. While Olpasiran focuses on reducing Lp(a) levels, Ziltivekimab addresses the inflammatory component of atherosclerosis, both of which are significant risk factors in cardiovascular disease progression[73]. The fully human monoclonal antibody, Ziltivekimab, targets IL-6 ligand and has been shown to reduce hsCRP, a biomarker of inflammation and thrombosis, in a Phase II trial[73]. Cholesteryl ester transfer protein (CETP) facilitates the transfer of cholesterol from high-density lipoprotein (HDL) particles to low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) particles, thereby increasing the concentration of the latter two. Previous attempts at CETP inhibition had failed until the arrival of Obicetrapib, a CETP inhibitor that has been shown to lower LDL-C effectively in combination with high-intensity statins[74,75].

Angiopoietin-like 3 (ANGPTL3) is an inhibitor of lipoprotein lipase and endothelial lipase, resulting in increased concentration of triglycerides and LDL-C. Another fully human monoclonal antibody that inhibits ANGPTL3 has resulted in a significant reduction of LDL-C levels in homozygous familial hypercholesterolemia with a mechanism independent of LDL receptors. Finally, emerging RNA-based therapies now target hypertension, obesity, insulin resistance, cardiac remodeling, cardiomyocyte regeneration, AKI, and diabetic nephropathy[68]. The development of these targeted therapies underscores the importance of addressing multiple pathways in the management of cardiovascular risk, especially in high-risk populations such as those with CKD.

3.7. Role of Artificial Intelligence

The integration of artificial intelligence (AI) in CKM management has the potential to revolutionize patient care by providing personalized treatment plans based on individual risk profiles using large datasets to identify multifaceted patterns. Recent studies show that innovations in AI have further enhanced cardiovascular medicine including drug design, procession therapeutics and personalised inference from clinical trials. A study focusing on a machine learning model for cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) by Zhu H., et al[76] states that AI-driven models can predict risk of CVD in patients with CKD by evaluating electronic health records and recognizing essential predictive factors like age, medical history and biochemical markers that support clinical decision making in CKM disease. While its predictive capability is extremely beneficial considering the high incidence of CVD in CKD patients, AI also plays a role in optimizing management of CKM diseases. Its ability to integrate multisource data sets, to further enable disease risk prediction and population categorization allows streamlined management of multiple independent factors like blood glucose, blood pressure, nutrition, etc which are crucial in patients with CKM diseases.

AI provides comprehensive data-informed evidence that guides clinical decision-making and enhances patient care. These systems can integrate diverse data sources including electronic health records, laboratory results, imaging studies, and even genetic information to create a holistic view of a patient's condition. By applying machine learning algorithms to this comprehensive dataset, AI can identify subtle patterns and risk factors that may not be immediately apparent to human clinicians, potentially leading to earlier interventions and more personalized treatment plans. The American Heart Association's recent recommendations highlight the critical role that AI can play in advancing CKM[77]. By developing and implementing sophisticated predictive algorithms, healthcare providers can more accurately forecast disease progression, treatment responses, and potential complications[77].

Furthermore, AI-powered decision support tools can assist clinicians in navigating complex treatment decisions by providing evidence-based recommendations tailored to individual patient profiles, thus aligning with the growing emphasis on precision medicine in nephrology. Machine learning aids in early intervention through diagnosis of acute kidney injury prior to biochemical changes, identification of modifiable risk factors that cause CKD progression and accurate diagnosis of renal tumors[78].

Therefore, AI can play an increasingly important role in the diagnosis, risk stratification, and management of CKM syndrome. AI models, particularly those using machine learning and deep learning, can integrate multimodal data including clinical, laboratory, imaging, and omics data to improve early detection of metabolic syndrome, chronic kidney disease, and cardiovascular disease, all of which are core components of CKM syndrome[79–81]. Despite these advances, challenges remain regarding data quality, model interpretability, workflow integration, and regulatory oversight, which must be addressed to ensure safe and effective clinical implementation[82,83].

Table 1. Overview of selected publications defining CKM syndrome and major meta-analyses evaluating therapies relevant to CKM components (Cardiovascular Disease, Chronic Kidney Disease, Type 2 Diabetes/Metabolic issue).

Paper Name	Authors*	Year	Study Type	Population Studied	Key Findings	Inclusion Criteria / Indication	Outcome Trial Results (with p-value if available)	Side Effect Profile*
Defining CKM Syndrome								
Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association	AHA (Ndumele CE, et al.)[77]	2023	Presidential Advisory / Scientific Statement	General US population; focus on individuals with/at risk for CVD, CKD, T2D, Obesity.	Defines CKM syndrome as a health disorder linking obesity, diabetes, CKD, and CVD. Proposes staging (0-4) based on risk factors and disease presence. Emphasizes prevention, integrated care, and addressing social determinants of health (SDOH).	N/A (Definition al document)	N/A (Definitional document)	N/A (Recommend s therapies like SGLT2i/GLP-1 RA for appropriate stages)
An Overview of Cardiovascular-Kidney-Metabolic Syndrome	Ferdinand KC et al.[84]	2024	Review	General overview of CKM syndrome patients.	Reinforces CKM definition, staging. Highlights role of excess/dysfunctional adipose tissue, inflammation, oxidative stress. Notes impact of SDOH and additional risk factors (chronic inflammation, family history, sleep/mental health).	N/A (Review)	N/A (Review)	N/A (Review)
Cardiovascular-Kidney-Metabolic (CKM) syndrome: A state-of-the-art review	Sebastian SA et al.[3]	2024	Review	Epidemiological data from NHANES and AHA reports, highlighting prevalence across	CKM syndrome involves interconnected metabolic, cardiovascular, and renal diseases. Key mechanisms include insulin resistance, RAAS activation, oxidative	N/A (Review)	N/A (Review)	1. GLP-1 RA: Primarily causes gastrointestinal issues like nausea,

				different demographics	stress, chronic inflammation, and lipotoxicity. The syndrome progresses through five stages, from no risk factors to symptomatic cardiovascular disease with kidney failure. Management focuses on screening, early intervention, and multidisciplinary care to reduce adverse outcomes.			vomiting, and diarrhea. 2. SGLT2 inhibitors: Increase the risk of genital and urinary tract infections 3. Finerenone: May lead to hyperkalemia
SGLT2 Inhibitor Trials (Meta-Analyses)								
Effects of SGLT2 inhibitors on cardiovascular outcomes in patients with stage 3/4 CKD: A meta-analysis	Li N, et al.[85]	2022	Meta-analysis	11 RCTs; 27,823 patients with stage 3/4 CKD.	SGLT2i significantly reduced primary CV outcomes (CV death/HHF) across stage 3a, 3b, and 4 CKD, irrespective of T2D or HF status.	Patients with stage 3/4 CKD included in RCTs comparing SGLT2i vs placebo.	Reduced primary CV outcome risk by 26% (HR 0.74, 95% CI 0.69–0.80, p<0.001 inferred). Consistent benefit across CKD stages (p interaction = 0.71).	<i>General Class Effects: Genitourinary infections, potential for volume depletion/hypotension, rare risk of DKA.</i>
Effect of SGLT2 Inhibitors on Cardiovascular Outcomes Across Various Patient Populations	Usman, et al.[86]	2023	Meta-analysis	13 RCTs; >90,000 patients with HF, T2D, CKD or combinations.	SGLT2i consistently reduced the composite of first HHF or CV death (~23-24%) across HF, T2D, and CKD populations and combinations. Also reduced CV death (~12-16%) and HHF (~29-32%) separately.	Patients with HF, T2D, or CKD in large RCTs comparing SGLT2i vs placebo.	Reduced HHF/CV Death by ~24% (HR ~0.76-0.77, p<0.001 inferred). Reduced CV Death by ~12-16% (p<0.001 inferred). Reduced HHF by ~29-32% (p<0.001 inferred).	<i>General Class Effects: Genitourinary infections, potential for volume depletion/hypotension, rare risk of DKA.</i>

GLP-1 Receptor Agonist Trials (Meta-Analyses)								
Kidney and Cardiovascular Outcomes Among Patients With CKD Receiving GLP-1 Receptor Agonists: A Systematic Review and Meta-Analysis of Randomized Trials	Chen et al.[32]	2024	Meta-analysis	12 RCTs; 17,996 participants with baseline eGFR < 60 mL/min/1.73m2.	GLP-1 RAs significantly reduced composite kidney outcome, risk of >30/40/50% eGFR decline, all-cause mortality, and composite CV outcomes in patients with CKD.	Adults with varying kidney function (incl. CKD eGFR<60) in RCTs comparing GLP-1 RA vs control.	Reduced composite kidney outcome (OR 0.85, 95% CI 0.77-0.94, P=0.001). Reduced all-cause mortality (OR 0.77, 95% CI 0.60-0.98, P=0.03). Reduced composite CV outcomes (OR 0.86, 95% CI 0.74-0.99, P=0.03).	General Class Effects: Gastrointestinal side effects (nausea, vomiting, diarrhea), injection site reactions, rare risk of pancreatitis/thyroid tumors.
Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: a meta-analysis of randomized controlled trials	Badve et al.[87]	2024	Meta-analysis (incl. SELECT trial)	11 RCTs; 85,373 participants (mostly T2D, one trial non-diabetic obesity/CVD).	GLP-1 RAs reduced composite kidney outcome, kidney failure, MACE, and all-cause death in T2D patients. Similar effects when non-diabetic SELECT trial included.	Participants (mostly T2D, one non-diabetic obesity/CV D trial) in large RCTs comparing GLP-1 RA vs placebo.	Reduced composite kidney outcome by 18% (HR 0.82, 95% CI 0.73-0.93). Reduced kidney failure by 16% (HR 0.84, 95% CI 0.72-0.99). Reduced MACE by 13% (HR 0.87, 95% CI 0.81-0.93). Reduced all-cause death by 12% (HR 0.88, 95% CI 0.83-0.93).	Higher treatment discontinuation due to AEs (RR 1.51). No difference in serious AEs vs placebo.

Table 2. The indications, mechanisms of action, outcomes, and adverse effects of phase III drugs for CKM.

Drugs	Phase 3 Trials	Principal investigator	Indication	MOA	Outcome	Adverse effects
Volanesorsen	NCT02211209	Gaudet et al.[58]	Hypertriglyceridemia, Type 2 diabetes mellitus, Familial Chylomicronemia Syndrome (FCS)	ASO targeting ApoC-III	77% decrease in mean triglyceride levels(TG).	Thrombocytopenia and injection site reaction.
Olezarsen	NCT04568434	Stroes et al.[88]	Hypertriglyceridemia, Acute coronary syndrome (ACS), FCS	Gal- NAc3 conjugated ASO targeting ApoC-III	Reduction in the fasting triglyceride level of at least 70% at 6 months.	Abdominal pain, and diarrhea.
Mipomersen	NCT00794664	McGowan et al.[89]	Hypercholesterolemia, Dyslipidemias	Induces ApoB100 degradation	Reduced LDL-C by 36%	Injection site reactions, flu-like symptoms.
Pelacarsen	NCT05305664	Novartis Pharmaceuticals[90]	ACS, Hyperlipoproteinemia	ASO targeting Lp(a)	Pending results	Mild injection site reactions.
Plozasiran	NCT06347016	Arrowhead Pharmaceuticals[91]	Mixed dyslipidemia, Hypertriglyceridemia, FCS	siRNA targeting apoC-III mRNA	Currently recruiting.	Worsening glycemic control, diarrhea, urinary tract infection.
Inclisiran	NCT03399370	Ray KK et al.[92]	Coronary artery disease (CAD), Familial hypercholesterolemia (FHS), ACS	siRNA targeting PCSK9	50% reduction in low density lipoprotein (LDL)	Injection site reactions.
Lepodisiran	NCT06292013	Ferdinand et al.[93]	Cardiovascular disorders (CVD), Metabolic disorders	siRNA targeting ApoA	Currently recruiting.	Injection site reactions, hypersensitivity reactions, hepatobiliary adverse events.
Olpasiran	NCT05581303	UCSD Health[94]	CAD, elevated Lp(a)	siRNA targeting Lp(a)	Pre-recruitment stage	Injection-site reactions
Ziltivekimab	NCT05021835	Ridker et al.[95]	CVD, Chronic kidney disease (CKD)	IL-6 Blocker	Currently recruiting	Injection-site reactions
Obicetrapib	NCT05142722	Ditmarsch et al.[96]	Heterozygous FHS, CAD	CETP Inhibitors	Completed, pending publication of results.	Nausea, urinary tract infection, and headache.
Evinacumab	NCT05611528	Gaudet et al.[97]	Homozygous Familial Hypercholesterolemia	ANGPTL3 Inhibition	47.1% reduction in LDL	Nasopharyngitis, influenza-like illness, headache.

4. Conclusions

CKM syndrome represents a critical intersection of cardiovascular, renal, and metabolic diseases, necessitating an integrated approach to treatment. Current therapies, including SGLT2 inhibitors, GLP-1 receptor agonists, and Finerenone, demonstrate promising advancements in addressing CKM complexities. Additionally, RNA-based therapies and AI-driven healthcare innovations hold potential for personalized disease management. Understanding CKM syndrome’s pathophysiology, risk factors, and evolving therapeutic landscape is essential for improving outcomes and reducing global disease burden. Future research should focus on refining treatment strategies, optimizing multi-organ protection, and leveraging technological advancements to enhance patient care and clinical decision-making in CKM-related diseases.

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Abbreviations

The following abbreviations are used in this manuscript:

ADA	American Diabetes Association
AI	Artificial intelligence
ACEi	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
ASO	Antisense Oligonucleotides
ANGPTL3	angiopoietin-like 3
ASCVD	Atherosclerotic cardiovascular disease
CETP	Cholesteryl ester transfer protein
CKM	Cardiovascular-kidney-metabolic syndrome
CVD	Cardiovascular disease
CKD	Chronic kidney disease
EASD	European Association for the Study of Diabetes
GLP1-RA	Glucagon-like peptide-1 receptor agonists
HFPEF	Heart failure with preserved ejection fraction
HFREF	Heart failure with reduced ejection fraction
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
LDL	Low density lipoprotein
MACE	Major adverse cardiovascular events
MASLD	Metabolic dysfunction-associated steatotic liver disease
PCSK9	Proprotein convertase subtilisin–kexin type 9
RAS	Renin angiotensin system
SGLT2i	Sodium–glucose cotransporter 2 inhibitors
TRβ	Thyroid receptor beta

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