

A Comprehensive Review on the Cardioprotective and Nephroprotective Effects of Semaglutide, and Its Therapeutic Efficacy and Mechanisms in Cardiorenal Syndrome

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Abstract: Semaglutide (SEM), a GLP-1 receptor agonist (GLP-1RA), is commonly used to manage blood glucose and weight in type 2 diabetes mellitus patients (T2DM). Research indicates that SEM protects the kidneys and heart by slowing estimated glomerular filtration rate (eGFR) decline, reducing proteinuria, enhancing cardiac outcomes, and lowering cardiovascular risk. These benefits are linked to various mechanisms, including reduced oxidative stress and inflammation, anti-fibrotic effects, modulation of metabolism, inhibition of apoptosis, suppression of ferroptosis, and improved mitochondrial function for energy regulation. However, some studies have also found that SEM may potentially lead to renal impairment or even promote the progression of cardiorenal syndrome (CRS). Due to conflicting results, more animal studies and large-scale clinical trials are needed to understand SEM's effects on CRS and its side effects, aiding in personalized treatment strategies. This review summarizes the functions and mechanisms of SEM in CRS, and highlights current research limitations and proposed directions for future studies.

Keywords: semaglutide, cardiorenal syndrome, GLP-1RA, cardiovascular outcomes

Introduction

Cardiorenal syndrome (CRS) involves heart or kidney dysfunction causing damage to the other organ. CRS is classified into five subtypes based on its pathological origin and clinical progression: Type 1 is characterized by acute kidney injury (AKI) resulting from acute cardiac dysfunction; Type 2 involves chronic kidney disease (CKD) arising from chronic cardiac dysfunction; Acute cardiac dysfunction induced by AKI defines type 3; Type 4 involves chronic cardiac impairment due to the progression of CKD; and Type 5 is characterized by the concurrent occurrence of cardiac and renal damage due to systemic conditions such as sepsis.^{1,2} In clinical practice, CRS is associated with high prevalence and mortality rates: a large clinical study found CRS prevalence at 0.40% in the general population, rising to 2.3% in type 2 diabetes patients.³ Research shows 60% of acute decompensated heart failure (HF) patients also have CKD, a major mortality risk. An acute estimated glomerular filtration rate (eGFR) decline occurs in 20–30% of patients,⁴ straining healthcare systems and emphasizing the need for early detection and intervention. Thus, developing new treatments offering cardiorenal protection with good safety is crucial in cardiovascular and renal disease research.

Semaglutide (SEM), a GLP-1 receptor agonist (GLP-1RA), shows promise for treating CRS due to its protective effects on the heart and kidneys. Numerous clinical studies reveal that SEM enhances cardiac function, reduces HF hospitalizations, and lowers cardiovascular mortality.^{5,6} Recent large-scale studies have further indicated that SEM also



provides distinct renal benefits, effectively slowing the progression of CKD, improving eGFR, and reducing the risk of major cardiovascular events in high-risk populations.^{7–9} Animal experiments confirm these findings, implying that SEM's positive effects are linked to its anti-inflammatory and anti-apoptotic actions, metabolic reprogramming, and better mitochondrial efficiency.^{10,11} Additionally, SEM helps manage type 2 diabetes mellitus (T2DM) by activating the GLP-1 receptor, which boosts insulin secretion and suppresses glucagon, improving glycemic control and reducing metabolic risks linked to cardiorenal diseases.^{12,13} Simultaneously, SEM is more effective than liraglutide for weight loss,^{14,15} renal protection in patients with T2DM,¹⁶ glycemic control, and cardiovascular outcomes.¹⁷ Importantly, SEM can be used regardless of renal function.¹⁸ In contrast, drugs like finerenone, angiotensin receptor-neprilysin inhibitors (ARNI), and angiotensin-converting enzyme inhibitors (ACEI), which are often used for cardiorenal protection, are restricted by renal function, especially in advanced kidney disease. Therefore, SEM offers distinct advantages for managing CRS and T2DM.

Recognizing SEM's cardiorenal benefits, it's crucial to consider its potential adverse effects, including impaired renal function,¹⁹ diabetic retinopathy progression,²⁰ thyroid tumors,²¹ and psychiatric symptoms like depression,²² which raise concerns about its clinical safety. Thus, this article systematically searched databases, including PubMed, Science Direct, Google Scholar, and Web of Science to review the role and mechanisms of SEM in different subtypes of CRS, as well as its potential adverse effects. The aim is to provide theoretical and practical guidance for the therapeutic application of SEM in CRS.

The Mechanisms Underlying the Cardioprotective and Nephroprotective Effects of SEM

Research indicates that SEM's cardioprotective benefits stem from enhancing heart structure and function, reducing inflammation, oxidative stress, and fibrosis, and regulating energy metabolism. It also offers renoprotective effects by slowing renal dysfunction, managing tubular and glomerular functions, and decreasing oxidative stress and inflammation. Tables 1 and 2 summarize clinical and basic research on SEM's cardiorenal protection.

Table 1 Clinical Investigations on the Cardiorenal Protective Effects of SEM

Organ	Number of Participants	Major Findings	References
Heart	17604 patients were randomly assigned to receive semaglutide (n=8803) or placebo (n=8801).	Compared with placebo, Semaglutide 2.4 mg reduced the incidence of major adverse cardiovascular events and a composite heart failure endpoint in patients with atherosclerotic cardiovascular disease and overweight or obesity.	Deanfield, J. et al, 2024 ⁵
Heart	A total of 136 obese patients with T2D and chronic HF were included in this study.	In obese patients with type 2 diabetes and heart failure, Semaglutide improves cardiac function and reduces heart failure-related emergency department visits, heart failure hospitalizations, and all-cause hospitalizations.	Pérez-Belmonte, L. M. et al, 2022 ⁶
Heart	Among the 3533 participants who underwent randomization (1767 in the semaglutide group and 1766 in the placebo group)	In patients with type 2 diabetes and chronic kidney disease, Semaglutide lowers the risk of clinically important kidney outcomes and cardiovascular mortality.	Perkovic, V. et al, 2024 ⁹
Heart	Among the 9650 participants who underwent randomization (4825 in the semaglutide group and 4825 in the placebo group)	In patients with type 2 diabetes and coronary artery disease, chronic kidney disease, or both, Semaglutide reduces the risk of major adverse cardiovascular events without increasing the incidence of serious adverse events.	McGuire, D. K. et al, 2025 ⁸
Heart	In total, 3533 participants were randomly assigned to semaglutide or placebo.	Semaglutide significantly reduces the risk of cardiovascular death, myocardial infarction, or stroke in patients with type 2 diabetes.	Mahaffey, K. W. et al, 2025 ⁷

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Table 1 (Continued).

Organ	Number of Participants	Major Findings	References
Heart	3743 participants had a history of Heart failure with mildly reduced or preserved ejection fraction (1914 assigned to semaglutide and 1829 assigned to placebo).	In patients with heart failure with mildly reduced or preserved ejection fraction, Semaglutide reduced the risk of the combined endpoint of cardiovascular death or worsening heart failure events, and worsening heart failure events alone.	Kosiborod, M.N. et al, 2024 ²³
Heart	A total of 22,937 patients with overweight or obesity were enrolled, with 12,200 in the semaglutide group and 10,737 in the control group.	Semaglutide reduces the risk of AF, sinus node dysfunction, acute myocardial infarction, and angina pectoris in patients with overweight or obesity.	Wu, R. et al, 2025 ²⁴
Heart	292 participants in the semaglutide group and 291 in the placebo group completed the trial.	Semaglutide effectively reduces body weight and alleviates heart failure symptoms in patients with type 2 diabetes and obesity-related heart failure.	Kosiborod, M.N. et al, 2024 ²⁵
Kidney	A total of 28 patients with diabetic kidney disease were enrolled, including 15 in the control group and 13 in the semaglutide group.	Semaglutide alleviates renal injury in diabetic patients and mice by inhibiting ferroptosis.	Tian, S. et al, 2025 ¹¹
Kidney	A total of 8,803 patients were randomized to semaglutide 2.4 mg and 8,801 to placebo.	Semaglutide reduces the major composite renal endpoint (including renal death, initiation of chronic kidney replacement therapy, etc.) in obese patients with cardiovascular disease.	Colhoun, H. M. et al, 2024 ²⁶
Kidney	A total of 12 637 patients were included in the pooled analysis with 6316 patients in the combined semaglutide/liraglutide group and 6321 patients in the combined placebo group.	Semaglutide demonstrates nephroprotective effects in type 2 diabetic patients, manifested as a reduction in proteinuria and a slowed decline in eGFR.	Shaman, A.M. et al, 2022 ¹⁶
Kidney	125 participants were screened, of whom 101 were randomized to semaglutide (n = 51) or placebo (n = 50).	Semaglutide treatment for 24 weeks resulted in a clinically meaningful reduction in albuminuria in patients with overweight/obesity and non-diabetic chronic kidney disease.	Apperloo, E. M. et al, 2025 ²⁷

Table 2 Basic Research on the Cardiorenal Protective Effects of SEM

Organ	Animal Models	Major Findings	References
Heart	Diabetic cardiomyopathy	Semaglutide directly protects cardiomyocytes from high-glucose injury in db/db mice by promoting AMPK-dependent ATP production and enhancing ULK1-mediated mitophagy.	Tian, M.Y. et al, 2025 ¹⁰
Heart	Obese mouse models	Semaglutide improves obesity-associated cardiac injury through the reduction of inflammation and oxidative stress.	Pan, X. et al, 2024 ²⁸
Heart	Diabetic cardiomyopathy	Semaglutide ameliorates cardiac dysfunction in diabetic mice, concomitantly with reduced cardiac remodeling and mitochondrial injury, by mitigating inflammation, cardiomyocyte apoptosis, and oxidative stress.	Lin, K. et al, 2025 ²⁹
Heart	Exercise-induced myocardial injury	In exercise-induced cardiomyopathy, Semaglutide exerts a cardioprotective effect by activating the AMPK pathway, enhancing autophagy, and reducing ROS and inflammation.	Li, Q. et al, 2020 ³⁰
Heart	Myocardial ischemia/reperfusion injury.	Semaglutide inhibits ischemia/reperfusion-induced cardiomyocyte apoptosis by activating the PKG/PKC ϵ /ERK1/2 pathway.	Zhu, Q. et al, 2023 ³¹
Heart	Transverse aortic constriction	Semaglutide ameliorates cardiac hypertrophy by improving cardiac mitophagy and thereby suppressing NLRP3 inflammasome activation.	He, W. et al, 2024 ³²
Heart	Myocardial infarction	Semaglutide ameliorates cardiac fibrosis and metabolic dysregulation in post-myocardial infarction rats by modulating glucose, lipid, and organic acid metabolism.	Yan, H. et al, 2024 ³³
Heart	Coronary artery disease	Semaglutide improves contractile function, increases myocardial perfusion, and reduces both interstitial and perivascular fibrosis in the chronically ischemic heart.	Stone, C. et al, 2025 ³⁴

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Table 2 (Continued).

Organ	Animal Models	Major Findings	References
Heart	Transverse aortic constriction	Semaglutide improves cardiac energy metabolism and alleviates Transverse aortic constriction-induced cardiac remodeling and mitochondrial injury.	Ma, Y.L. et al, 2024 ³⁵
Heart	Sepsis-induced myocardial dysfunction	Semaglutide attenuates sepsis-induced myocardial injury by inducing cardiac autophagy.	Zhang, W. and J. Zhang, 2023 ³⁶
Heart	Diet-induced obesity model	Semaglutide attenuates lipotoxicity-induced cardiac injury by inhibiting Slc27a2 expression.	Pan, X. et al, 2025 ³⁷
Heart	Myocardial ischemia/reperfusion injury.	Semaglutide ameliorates myocardial ischemia-reperfusion injury by suppressing S100A9 expression and inhibiting cardiomyocyte ferroptosis through activation of the PKC signaling pathway.	Liu, Y. et al, 2025 ³⁸
Kidney	Diabetic kidney disease	Semaglutide alleviates renal injury in diabetic patients and mice by inhibiting ferroptosis.	Tian, S. et al, 2025 ¹¹
Kidney	Kidney ischemia/reperfusion injury.	Semaglutide mediates renoprotection in renal ischemia-reperfusion injury through modulation of inflammatory response and oxidative pathways by targeting the PI3K/AKT signaling pathway.	Tiba, A.T., H. Qassam, and N.R. Hadi, 2023 ³⁹

Cardioprotective Mechanisms of SEM

SEM Exerts Cardioprotective Effects Through Anti-Inflammatory and Anti-Oxidative Stress Mechanisms

SEM is extensively used for type 2 diabetes treatment and is gaining attention for its cardiovascular protection benefits. As demonstrated in a previous clinical study, SEM can reduce the risk of cardiovascular death and worsening in patients with HF.²³ The specific mechanisms may be related to SEM's abilities to alleviate inflammatory responses, preserve mitochondrial function, mitigate oxidative stress, and inhibit cellular apoptosis.^{28–31,40} The NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) inflammasome is linked to cardiac injuries like myocardial ischemia and fibrosis.^{41–43} A study by He et al³² demonstrated that SEM can ameliorate impaired mitophagy induced by transverse aortic constriction (TAC) and suppress NLRP3 inflammasome activation, thereby attenuating cardiac hypertrophy. This finding uncovers the link between SEM and the NLRP3 pathway, emphasizing its strong anti-inflammatory effects. Further validation in a diabetic model demonstrated that SEM treatment attenuates inflammation-induced cardiac injury by upregulating RKIP expression and suppressing the TBK1/NF- κ B signaling pathway. These effects were evidenced by improved cardiac function and reduced myocardial injury biomarkers,²⁹ providing a theoretical foundation for expanding the clinical applications of SEM.

A recent clinical trial revealed that SEM improves cardiovascular outcomes by enhancing vascular endothelial function and reducing inflammation, independent of weight loss.⁴⁴ In an obesity-related cardiac injury model, its anti-inflammatory effect was confirmed. SEM significantly reduced body weight in obese mice while simultaneously downregulating the expression of inflammation- and oxidative stress-related genes (such as S100A8, S100A9, and Cxcl2) in neutrophils, thereby mitigating cardiac injury.^{28,45} Clinical studies indicate that SEM's anti-inflammatory properties may prevent atrial fibrosis and alleviate atrial fibrillation symptoms in obese individuals.²⁴ When used with antihypertensive and lipid-lowering drugs, SEM lowered high-sensitivity C-reactive protein by 37.8%.⁴⁶ These findings support SEM's potential use in treating heart injuries from inflammation.

SEM Mitigates Myocardial Ischemia-Reperfusion Injury (MIRI)

In addition, SEM has demonstrated protective effects against myocardial injury caused by acute myocardial infarction (AMI), coronary artery perfusion, and ischemia-reperfusion injury.^{33,38} The mechanisms primarily include alleviating cellular injury, modulating metabolism and vascular function, and inhibiting apoptosis, among others. For example, in animal models of AMI, SEM not only significantly alleviated myocardial cell edema, necrosis, and fibrous tissue hyperplasia but also effectively reduced residual risks post-infarction by modulating energy metabolism, lowering blood glucose, lipid levels, and body weight.^{33,47} In Yorkshire swine with myocardial ischemia, SEM treatment markedly enhanced the activation and expression of AMPK, AKT, and eNOS, improved vascular diastolic function, and increased coronary perfusion in ischemic

areas.³⁴ Previous studies have confirmed that the AMPK/AKT/eNOS signaling pathway plays a critical role in regulating vasodilation and promoting angiogenesis,^{28,48} which may be one of the key mechanisms through which SEM alleviates myocardial ischemia. Additionally, SEM exerts cardioprotective effects by inhibiting ferroptosis³⁸ and activating the PKG/PKC ϵ /ERK1/2 signaling pathway,³¹ thereby reducing cellular apoptosis and decreasing infarct size. Meanwhile, subsequent clinical studies have further confirmed that the combined use of GLP-1RA (such as SEM) and SGLT-2 inhibitors after PCI can increase myocardial salvage during the peri-infarction period,⁴⁹ highlighting its potential clinical application value. Clinical studies indicate that SEM significantly lowers the risk of myocardial infarction and heart failure more than sitagliptin and shows a numerical advantage over tirzepatide in reducing major adverse cardiovascular events (MACE).⁵⁰

Therefore, based on the current research, we posit that SEM can exert protective effects in myocardial infarction and MIRI. However, the specific role of SEM in the long-term prognosis of AMI warrants further clinical investigation for confirmation.

Evidence for SEM's Improvement of Cardiometabolic Function

Another significant mechanism through which SEM enhances cardiovascular health is by improving cardiac metabolic function. Myocardial injury is primarily associated with mitochondrial damage and disorders of glucose and lipid metabolism, leading to the accumulation of toxic lipids.^{51–53} For example, SEM can improve mitochondrial function through the PI3K/AKT/CREB5/NR4A1 axis, thereby alleviating TAC-induced myocardial injury.³⁵ Slc27a2 is associated with HF of metabolic origin.⁵⁴ Recent studies show that SEM can lower Slc27a2 expression and reduce cardiac injury by enhancing lipid metabolism and reducing lipid buildup in heart cells. While Slc27a2 levels are higher in the blood of obese individuals,³⁷ confirmation in human heart tissue is lacking due to ethical constraints. Despite this, the research strongly supports SEM's cardioprotective effects in obesity. Studies by Yan et al³³ and Stone et al³⁴ further demonstrated, in models of AMI and chronic cardiac injury, respectively, that SEM modulates glucose and lipid metabolism to optimize myocardial energy utilization. Therefore, the mitochondrial protective and metabolic regulatory effects of SEM underscore its potential therapeutic value in both acute and chronic cardiac injury, presenting promising avenues for future cardiovascular disease treatment.

In conclusion, SEM alleviates cardiac injury through various mechanisms, including anti-inflammatory and anti-apoptotic pathways, as well as enhanced vascular function and maintaining mitochondrial structure and function to regulate glucose and lipid metabolism in cardiomyocytes. Early clinical studies indicate its protective role in ischemic myocardium, offering new strategies for myocardial infarction and reperfusion injury treatment. However, most evidence comes from animal studies, with limited clinical research, particularly in acute myocardial injury cases. Thus, high-quality clinical trials are urgently needed to confirm these findings.

Nephroprotective Mechanisms of SEM

The nephroprotective effects of SEM, particularly in patients with CKD, have garnered significant attention in recent years. Studies indicate that long-term administration of SEM can delay the progression of CKD through multiple mechanisms, including attenuating the decline in eGFR, reducing proteinuria, and alleviating renal fibrosis.^{16,26,27}

SEM Alleviates Renal Injury in CRS: Insights from Mechanisms, Preclinical and Clinical Evidence

Despite limited direct investigation, existing data indicate that SEM's renoprotection may operate through a proposed mechanism that entails mitigating renal fibrosis and inflammation, thereby lowering proteinuria and ultimately resulting in improved renal function—effects that have received preliminary confirmation in clinical research. Initially, SEM was confirmed to have nephroprotective properties in experimental models of CKD. Researchers such as Tian et al⁵⁵ showed that the GLP-1 RA liraglutide can reduce renal fibrosis in CKD animal models by inhibiting the TGF- β 1/Smad3 and ERK1/2 pathways, thus decreasing extracellular matrix secretion and deposition. Based on this mechanism, it is hypothesized that SEM may exert similar effects. Our team's investigations have shown that in a rodent model of unilateral ureteral obstruction (UO), SEM improves renal injury and fibrosis by modulating tubulo-glomerular signaling, as indicated by lower creatinine levels and preserved renal structure. In models of renal ischemia-reperfusion injury, SEM reduced the release of inflammatory mediators through activation of the PI3K/Akt signaling pathway, leading to

decreased serum creatinine and blood urea nitrogen levels, as well as significant suppression of inflammatory and oxidative stress markers such as TNF- α , IL-6, and F2-isoprostane.³⁹ Thus, it is suggested that SEM's renoprotection may be linked to its anti-inflammatory and anti-fibrotic properties. A clinical study has shown that, compared with placebo, GLP-1RA can significantly reduce mortality, MACE, and major adverse kidney events (MAKE) in patients with T2DM and AKI.⁵⁶ The mechanisms may be related to its anti-inflammatory,⁵⁷ blood pressure, and lipid-regulating effects.⁵⁸ Given that the most common causes of AKI are sepsis and CRS,^{56,59} and based on the etiology of AKI as well as the therapeutic effects and mechanisms of GLP-1RA, it is reasonable to speculate that SEM may play an important role in the treatment of AKI and holds great potential in the management of CRS1 and CRS5.

According to Kidney Disease: Improving Global Outcomes (KDIGO) risk stratification analysis, treatment with SEM resulted in a general reduction in KDIGO risk categories. Regardless of baseline CKD severity, patients exhibited a slower decline in eGFR and a reduced rate of increase in urinary albumin-to-creatinine ratio (UACR), indicating significant nephroprotective effects.⁶⁰ Furthermore, this nephroprotective effect was independent of blood pressure, blood glucose, and UACR levels.⁶¹ The SUSTAIN 6 trial was limited to T2DM patients with concomitant cardiovascular disease or risk, excluding a wider spectrum of patients; thus, future research requires finer patient stratification to assess SEM's renoprotection across distinct subgroups.

Animal and clinical studies indicate that SEM's nephroprotective benefits go beyond lowering glucose and weight. In AKI and CKD, SEM may reduce proteinuria, inhibit renal fibrosis, and slow renal dysfunction. However, more research is needed on SEM's role in AKI. Overall, evidence suggests SEM could be a key therapeutic agent for glycemic control and kidney protection.

Mechanisms of SEM in Regulating Tubular and Glomerular Function

The reduction of damage to renal tubules and glomeruli might be another way SEM contributes to mitigating kidney injury. For example, in renal ischemia-reperfusion models, SEM significantly lowers injury scores and improves kidney function³⁹. Furthermore, in chronic conditions like diabetic nephropathy, by inhibiting ferroptosis, SEM ameliorates renal structural damage, including tubular epithelial cell detachment, glomerular hypertrophy, mesangial expansion, and podocyte foot process effacement.¹¹ These effects decrease proteinuria and slow CKD progression, demonstrating SEM's role in mitigating kidney injury through various mechanisms in both AKI and CKD models. Slc27a2 is associated with structural damage, increased proteinuria, and decreased eGFR in diabetic kidney disease (DKD).⁶² As mentioned earlier, SEM can alleviate high-lipid-induced cardiac injury by inhibiting Slc27a2.³⁷ Therefore, SEM may potentially reduce renal structural damage and proteinuria levels while maintaining eGFR in DKD through the inhibition of Slc27a2. Consequently, SEM decreases the incidence of end-stage renal disease, postpones the necessity for renal replacement therapy, enhances patients' quality of life, and alleviates the economic burden on families and healthcare systems associated with long-term dialysis or transplantation.

The Protective Role of SEM in Regulating Purine Metabolism in the Heart and Kidneys

As a GLP-1RA, SEM has been shown to reduce serum uric acid concentrations in diabetic animal models,⁶³ and clinical studies have also observed a certain uric acid-lowering effect.⁶⁴ Chen et al's⁶⁵ metabolomic analysis links SEM's effects to purine metabolism, specifically adenosine and NAD⁺. This finding provides a theoretical basis for related basic and clinical research. Further investigations by our team have demonstrated that in UO-induced CRS4, SEM reduces uric acid production by downregulating xanthine oxidase activity, thereby mitigating cardiac and renal tissue damage. However, a randomized controlled clinical trial conducted by Lennart Tonnejck et al⁶⁶ showed that GLP-1 Ra did not significantly reduce serum uric acid levels in patients. The discrepancy between this clinical outcome and preclinical findings may be attributed to the relatively normal baseline uric acid levels of the enrolled patients, limited sample size, and short follow-up duration.

Hyperuricemia is a key indicator of purine metabolism disorder and is closely associated with an increased risk of cardiovascular diseases and CKD.^{67–69} High serum uric acid levels predict all-cause mortality, major cardiovascular events, and heart failure hospitalizations in patients with heart or kidney problems.^{70,71} Managing uric acid levels is crucial due to its impact on cardiorenal health. The effect of SEM on lowering uric acid is debated, with unclear

mechanisms. Future research should focus on detailed investigations and extensive clinical trials to understand SEM's impact on uric acid metabolism.

SEM May Exert Cardioprotective Effects by Modulating the Gut Microbiota

Dysbiosis of gut microbiota is closely associated with the progression of cardiovascular disease⁷² and the worsening of CKD.⁷³ GLP-1, an enteric peptide, can serve as a prognostic indicator in patients with AMI complicated by cardiogenic shock and is a strong predictor of adverse outcomes in AMI patients.⁷⁴ This suggests a potential close relationship between the heart and the gut. Relevant studies have confirmed that SEM alleviates β -cell dysfunction by modulating the gut microbiota, notably by significantly reducing the abundance of Proteobacteria.⁷⁵ This finding is consistent with our team's experimental results in a CRS4 model. Furthermore, increased levels of Proteobacteria have been observed in patients with HF,^{76,77} and the involvement of Proteobacteria in the production of trimethylamine (TMA) and trimethylamine N-oxide (TMAO) is associated with an elevated risk of CKD and cardiovascular diseases.^{76,78} These findings indicate a link between SEM, gut microbiota, and the heart and kidneys, potentially explaining SEM's cardiorenal protective effects. However, direct proof of SEM's role in cardiorenal protection through gut microbiota is absent, necessitating further animal studies as a future research priority.

Role of SEM in Different Subtypes of CRS

Current research indicates that SEM exhibits protective effects across various types of CRS. The mechanisms may involve its anti-inflammatory, anti-fibrotic properties, and inhibition of ferroptosis and apoptosis, suggesting that SEM could be a potential therapeutic agent for different subtypes of CRS. However, some studies have found that SEM may lead to AKI and even exacerbate the progression of CRS. The following section reviews the research progress on SEM in each subtype of CRS.

Research Progress on SEM in Type I Cardiorenal Syndrome (CRS1)

CRS1 refers to AKI secondary to acute worsening of cardiac function, with an incidence ranging from 25% to 40%. One clinical study reported an associated mortality rate of 20.5%.^{79,80} Although current research on SEM in CRS1 remains limited, existing studies indicate its protective effects in both acute cardiac and renal injury. In an animal model of myocardial infarction, four-week SEM treatment ameliorated myocardial fibrosis and significantly improved left ventricular ejection fraction (LVEF) after infarction.³³ A clinical study by Filippo Trombara et al⁸¹ demonstrated that diabetic patients on long-term GLP-1RA therapy who experienced AMI had lower rates of in-hospital mortality, acute HF, and AKI. The findings indicate a potentially significant role for GLP-1RAs in CRS1. A recent study demonstrated that the addition of GLP-1RA or sodium-glucose co-transporter-2 inhibitors (SGLT2-i) to treatment regimens after percutaneous coronary intervention (PCI) for AMI resulted in enhanced myocardial salvage during the peri-infarction period compared to SGLT2-i monotherapy.⁴⁹ Despite these findings, the study did not evaluate renal outcomes, leaving the extension of cardioprotective benefits to CRS1 uncertain. While evidence for SEM in treating AKI and CRS1 is limited, GLP-1RAs have been proven to enhance mortality rates and long-term cardiorenal outcomes in T2DM patients with AKI. Given SEM's protective effects in acute cardiac injury, it shows promise for CRS1 treatment. More clinical and animal studies are needed to investigate its mechanisms and efficacy, offering additional treatment options for CRS1.

Recent Advances in SEM for Type 2 Cardiorenal Syndrome (CRS2)

CRS2 is defined as chronic kidney injury resulting from chronic cardiac dysfunction. Previous studies have indicated that nearly half of all patients with chronic HF exhibit some degree of renal impairment, with approximately one-third experiencing moderate to severe renal dysfunction.^{82,83} Current research demonstrates that SEM offers significant advantages in the treatment of patients with chronic HF and CKD, including a reduced incidence of HF, improved exercise tolerance in HF patients, decreased proteinuria, and slowed progression of renal impairment. A network meta-analysis showed that type 2 diabetes patients treated with GLP-1RA experienced an 11% reduction in HF hospitalization risk and a 21% decrease in composite kidney outcomes—primarily consisting of renal function deterioration and the need for renal replacement therapy,⁸⁴ highlighting the therapeutic potential of GLP-1RAs in CRS2. SEM has been shown to

attenuate plaque progression in murine models of atherosclerosis through its anti-inflammatory effects, concurrently reducing systemic inflammatory markers and cardiovascular risk.⁸⁵ In rat models of CRS2, elevated levels of pro-inflammatory cytokines have been observed, which may be closely associated with chronic kidney injury secondary to congestive HF.⁸⁶ The ability of SEM to mitigate systemic inflammatory responses represents one potential mechanism through which it may ameliorate cardiorenal damage in CRS2. In a randomized controlled trial involving patients with T2DM and ASCVD, SEM reduced the number of adverse kidney outcomes compared with placebo. Although not statistically significant, it significantly slowed the decline in eGFR.⁸⁷ Although direct evidence for SEM in the treatment of CRS2 is currently lacking, ongoing research into the pathogenesis of CRS2 and the pharmacological effects of SEM is expected to elucidate its efficacy and detailed mechanisms of action in this specific context.

SEM in Type 3 Cardiorenal Syndrome (CRS3): Current Research Perspectives

CRS3 occurs when AKI leads to acute cardiac dysfunction. The incidence of CRS3 is notably increased in critically ill patients. AKI-induced disturbances in water and electrolyte balance, volume overload, and activation of the sympathetic nervous and renin–angiotensin–aldosterone systems contribute to the development of acute HF and malignant arrhythmias, resulting in varying degrees of cardiac injury.⁸⁸ Recent research indicates that SEM exerts synergistic protective effects on acute cardiac and renal injuries. In models of renal ischemia–reperfusion injury, SEM has been shown to reduce the release of inflammatory mediators, including TNF- α and IL-6, through the PI3K/Akt signaling pathway. This modulation leads to a reduction in renal damage, highlighting SEM's potential efficacy in the treatment of AKI.³⁹ A clinical study by Pan et al⁵⁶ reported significant benefits in diabetic patients with AKI treated with GLP-1RAs, including notable reductions in MACE, major adverse kidney events, and all-cause mortality, indicating concurrent cardiorenal protection. The cardiorenal protective effects of SEM may be attributed to its potent anti-inflammatory properties, which mitigate organ damage, and its ability to ameliorate fluid retention caused by acute renal dysfunction.

However, while SEM demonstrates protective potential, some reports have associated its use with adverse renal outcomes such as AKI and acute interstitial nephritis (AIN).⁸⁹ Case reports have documented elevated serum urea nitrogen and creatinine levels, interstitial inflammation, tubulitis, and tubular injury following SEM use.⁹⁰ In another case, renal biopsy demonstrated focal segmental glomerulosclerosis (FSGS), AIN with mild interstitial fibrosis and tubular atrophy, variable thickening of the glomerular basement membrane lamina densa, and segmental foot process effacement (25%).¹⁹ Therefore, SEM-related AKI has the potential to aggravate the further progression of CRS. However, current evidence suggests that the overall cardiorenal benefits of SEM surpass the risks associated with its rare adverse events. As SEM use increases, monitoring renal function is essential for early detection and management of potential issues, ensuring optimal treatment outcomes. Given the conflicting evidence on SEM use in CRS3, further research is needed to clarify its safety and efficacy, explore its mechanisms in CRS3-related AKI, and confirm its potential for cardiorenal protection.

Advances in SEM for Type 4 Cardiorenal Syndrome (CRS4)

CRS4 describes a condition in which CKD leads to chronic myocardial injury. CKD is recognized as an independent risk factor for cardiovascular disease, not only increasing the incidence of various cardiovascular disorders but also worsening cardiovascular outcomes as eGFR declines.^{91,92} CKD contributes to the accumulation of uremic toxins and impairs vascular endothelial function through mechanisms such as chronic inflammation and oxidative stress, leading to arterial stiffness, increased cardiac load, and relative cardiac hypoperfusion. These pathological changes further promote coronary artery disease, myocardial infarction, and cardiac remodeling, ultimately resulting in life-threatening complications and reduced quality of life.^{93,94} Given that SEM has been shown to ameliorate vascular remodeling in various injury models,^{95–97} it may similarly alleviate CKD-induced endothelial dysfunction and arterial stiffness, thereby mitigating cardiac impairment in CRS4. Current research on the mechanisms by which SEM alleviates CRS4-induced myocardial injury is limited. The anti-inflammatory and nephroprotective effects of SEM are likely among the key mechanisms contributing to its beneficial role in CRS4. During CKD, cardiorenal crosstalk occurs wherein Toll-like receptors, the NLRP3 inflammasome, and other inflammatory pathways are activated, leading to the production of chemokines and subsequent chronic inflammatory damage.⁹⁸ As previously mentioned, SEM can attenuate pressure

overload-induced myocardial hypertrophy mediated by NLRP3 inflammasome activation,³² suggesting that the NLRP3 inflammasome may be one of the targets through which SEM exerts its anti-inflammatory effects and mitigates CRS4-related cardiac injury.

Furthermore, in the CRS4 model induced by UUO, SEM demonstrated efficacy in improving cardiac function, suppressing myocardial apoptosis, and alleviating cardiorenal fibrosis. Separately, a clinical study involving patients with type 2 diabetes and chronic renal failure confirmed that SEM treatment significantly reduced the risk of major kidney outcomes - including renal replacement therapy and death from renal causes - by 24%, and lowered the risk of MACE by 18%.⁹ Moreover, this cardioprotective effect was independent of CKD severity.⁷ These findings collectively indicate the therapeutic potential of SEM for CRS4. Currently available cardiorenal protective agents (such as ARNI, SGLT2i, and finerenone) are often limited by renal function. In contrast, SEM can be used in patients with all stages of renal impairment, including those with end-stage uremia, offering broader clinical applicability.^{18,99} Therefore, SEM holds considerable promise and may provide optimized treatment options for patients with CRS4.

Research Progress on SEM in Type 5 Cardiorenal Syndrome (CRS5)

CRS5 is characterized by concurrent cardiac and renal dysfunction resulting from systemic disorders, such as sepsis, septic shock, diabetes, amyloidosis, and systemic lupus erythematosus. Among these, sepsis is a leading cause of death in CRS5 patients, with an in-hospital mortality rate reaching 100% in severe cases.^{100–103} The pathogenesis of CRS5 may involve systemic inflammatory responses, cytokine dysregulation,¹⁰⁴ and direct cardiac and renal injury mediated by endotoxins and other inflammatory mediators. As demonstrated in a previous clinical study, in patients with diabetes complicated by cardiovascular disease, CKD, or both, treatment with SEM was associated with a lower incidence of new-onset or worsening kidney disease and a significant reduction in cardiovascular mortality.²⁰ Furthermore, SEM also reduces the risk of sepsis, prosthetic joint infections, and hospital readmissions in obese or diabetic patients undergoing joint arthroplasty.^{89,105} In a mouse model of sepsis-induced myocardial dysfunction (SIMD), SEM treatment significantly lowered levels of inflammatory cytokines and cardiac injury markers compared to untreated controls.³⁶ As the primary cause of CRS5, sepsis can be effectively prevented and its associated cardiac injury mitigated by SEM, offering novel insights for the prevention and treatment of CRS5. While the cornerstone of CRS5 prevention remains the treatment of underlying systemic diseases,² SEM may mitigate common predisposing factors, thereby reducing the incidence of CRS5 at its source. However, the mechanisms through which SEM may confer cardiorenal protection in established CRS5 remain unclear; elucidating these mechanisms represents an important direction for future research and could reveal further pharmacological applications of SEM.

Adverse Effects and Management of SEM

SEM is generally well-tolerated, with a safety profile comparable to other GLP-1RA. It has demonstrated both safety and efficacy not only in adult patients but also in children with obesity.^{6,106,107} Despite its favorable overall safety profile, treatment initiation with SEM can lead to certain adverse effects, and longer-term observation is still required to fully characterize its adverse reaction spectrum. Early recognition of these reactions and appropriate management strategies are essential to maximize the clinical benefits of SEM.

Gastrointestinal Symptoms

Gastrointestinal symptoms are among the most common adverse effects of SEM, primarily including nausea, vomiting, and diarrhea during the initial treatment phase. These symptoms are generally transient, occurring mainly in the early stages of treatment and during dose escalation. They are closely related to the administration method and dosage.¹⁰⁸ In most cases, these symptoms resolve spontaneously over time. Strategies such as dietary adjustments, gradual dose titration, careful timing of administration, and minimizing concomitant use of medications with known gastrointestinal side effects can help manage these reactions.

Hypoglycemia

Although hypoglycemia is a well-known adverse effect of glucose-lowering medications, the insulinotropic action of SEM is glucose-dependent, and glucagon secretion remains unimpaired under hypoglycemic conditions. Consequently, SEM is associated with a relatively low risk of hypoglycemia.^{109–111} A meta-analysis further indicated that SEM does not significantly increase the incidence of hypoglycemic events.¹¹² Cases of hypoglycemia in patients using SEM often occur in the context of concomitant use of insulin or other antihyperglycemic agents.¹⁰⁹ Studies suggest that the dosage of concomitant glucose-lowering medications may require reduction or adjustment following SEM initiation.⁶ Regular monitoring of blood glucose levels, patient education regarding recognition of hypoglycemia signs, periodic glycated hemoglobin (HbA1c) testing, and treatment adjustment by specialists based on glycemic profiles are essential to minimize or prevent hypoglycemia.

Cholelithiasis

The formation of gallstones may result from direct effects of SEM on bile secretion, alterations in gallbladder motility, or drug dosage-related factors,¹⁰⁶ though the precise mechanisms remain unclear. Studies have indicated a linear relationship between the rate of weight loss and the risk of cholelithiasis development. Specifically, when obese individuals lose weight at a rate of 1.5 kg/week, the risk of gallstone formation increases significantly.¹¹³ For patients with a history of cholelithiasis or those possessing high-risk factors, regular imaging follow-up is recommended. Additional measures include controlling the dosage, moderating the rate of weight loss, and considering pharmacological prophylaxis when appropriate. In cases where necessary, laparoscopic cholecystectomy may be performed.

Depression

Two case reports have indicated a potential association between SEM and the induction or recurrence of depression. In both cases, depressive symptoms emerged approximately one month after initiating SEM treatment and resolved following drug discontinuation. One of the patients had a prior history of depression.²² Additionally, the European Medicines Agency reviewed approximately 150 reports of self-harm and suicidal ideation among users of liraglutide or SEM. As a result, patients with a history of depression or suicidal ideation were excluded from subsequent clinical trials of SEM.¹¹⁴ However, a fundamental experiment observed opposite results: in a mouse model of type 2 diabetes-associated depression, SEM not only effectively alleviated depression- and anxiety-like behaviors and enhanced cognitive function but also exhibited neuroprotective effects.¹¹⁵ Due to conflicting findings, further research on SEM's role in neuropsychiatric disorders is needed. While psychiatric side effects from SEM are rare, caution is recommended when prescribing it to patients with a history of depression or other psychiatric conditions to prevent symptom relapse or worsening.

Thyroid Tumors

A study by Julien Bezin et al suggested that treatment with GLP-1RAs for 1–3 years may increase the risk of thyroid tumors.²¹ However, a meta-analysis examining the association between SEM and cancer yielded contrasting results.¹¹⁶ Interestingly, a preclinical study even observed an inhibitory effect of SEM on thyroid cancer cells.¹¹⁷ Furthermore, multiple studies have not established a causal relationship between SEM and the development of thyroid tumors.¹¹⁸ Although the association between SEM and thyroid cancer remains controversial, clinical vigilance is still warranted. Physicians are advised to evaluate thyroid function and perform thyroid ultrasonography before initiating SEM therapy to mitigate this potentially serious, though rare, adverse effect.

Retinopathy

The SUSTAIN-6 trial indicated that while SEM improves renal function, it is associated with an increased risk of diabetic retinopathy complications.²⁰ However, a meta-analysis on this topic found no overall correlation between SEM and retinopathy in the unstratified analysis. Yet, subgroup analyses based on age and duration of diabetes revealed a significantly elevated risk of SEM-associated retinopathy in patients with a mean age of ≥ 60 years and a diabetes

duration of ≥ 10 years.¹¹⁹ Additionally, a more rapid reduction in glycated hemoglobin (HbA1c) was correlated with a higher incidence of retinal complications.¹²⁰ These findings provide valuable clinical guidance: caution is advised when prescribing SEM to elderly patients with long-standing diabetes or pre-existing retinopathy. It is recommended to achieve glycemic control gradually, schedule regular ophthalmologic follow-up, and implement early intervention to mitigate potential vision-threatening outcomes.

Renal Adverse Events

In recent years, the expanding clinical use of SEM—driven by its demonstrated efficacy in weight control and cardiorenal protection—has been accompanied by increased reporting of renal adverse events. Farhana Begum et al identified 2,375 renal adverse events associated with GLP-1RA reported to the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) over 12 years, including 17 cases of proteinuria and one case of glomerulonephritis specifically linked to SEM.¹⁹ Mark M. Smits et al proposed that SEM-related renal impairment may be precipitated by dehydration secondary to drug-induced vomiting, diarrhea, and increased urinary sodium excretion.¹⁰⁹ In contrast, Richeek Pradhan and Farhana Begum et al hypothesized that SEM, as a peptide-based therapeutic, may possess immunogenic properties capable of triggering autoimmune-mediated renal injury. Notably, such injury often showed reversibility following drug discontinuation and corticosteroid therapy.^{19,121} Although SEM-related kidney injury is rare compared to its therapeutic benefits, monitoring for renal issues is crucial in clinical practice. If patients experience severe gastrointestinal side effects, dose reduction or discontinuation should be considered, along with managing symptoms and regularly checking kidney function and urinary protein levels. Future research should aim to clarify the mechanisms and risk factors of SEM-related kidney injury to create targeted prevention strategies.

Future Research Directions for SEM in CRS

As SEM's cardiorenal protective effects become clearer, key research areas are emerging to better understand its mechanisms, optimize treatments, and improve patient outcomes. [Table 3](#) summarizes current knowledge gaps and future research directions.

Mechanistic Exploration, Particularly in Animal Models

Future research should continue to utilize animal models to gain deeper insights into the underlying pharmacological mechanisms of SEM. Studies involving transgenic mice or other suitable animal models could help elucidate the specific pathways through which SEM exerts its cardioprotective and nephroprotective effects. Integrating findings from basic research with clinical data will enable a more comprehensive exploration of how SEM interacts with various metabolic,

Table 3 Knowledge Gaps and Studies Needed to Be Performed

Knowledge Gaps	Studies Needed to Be Performed
Specific Mechanisms of Sem in Cardiorenal Syndrome Subtypes	To validate the mechanisms and pathways through which Sem exerts cardiorenal protective effects in different animal models of each subtype.
Association Between the Cardio-renal Protective Effects of Sem and the Gut Microbiota	To investigate relevant bacteria, microbial communities, and gut microbiota-derived metabolites in animal models.
Scarcity of large-scale domestic clinical trials.	It is imperative to conduct domestic multicenter clinical trials that incorporate regional characteristics and dietary patterns, thereby providing evidence for personalized therapy. Furthermore, the safety and efficacy of SEM should be evaluated in large-scale domestic clinical trials.
Safety and Efficacy of Long-Term Sem Treatment	In high-risk populations prone to adverse drug reactions, relevant parameters should be monitored regularly. Large-scale clinical studies should be initiated to track participants' cardiac and renal function, glycemic parameters, and adverse events, alongside conducting long-term follow-up of patients who discontinue treatment.

renal, and cardiac processes in humans, as well as its direct impact on cardiorenal function. Such efforts will provide stronger evidence to support the effective, reliable, and broad application of SEM.

With CRS having five subtypes, it's crucial to study SEM's impact on each. Understanding its varied effects on HF types and renal impairments will help clinicians create tailored treatments. Future research should focus on SEM's mechanisms in each subgroup.

Association Between the Microbiome and SEM

In recent years, the gut microbiota has become a major focus of scientific research. Current studies have shown that microbial-derived metabolites—such as trimethylamine N-oxide (TMAO), N, N, N-trimethyl-5-aminovaleric acid (TMAVA), indoxyl sulfate (IS), indole-3-acetic acid (IAA), and p-cresyl sulfate (PCS)—contribute to cardiac and renal injury by influencing lipid metabolism, inflammation, oxidative stress, and mitochondrial function, thereby promoting reciprocal dysfunction across both organs.¹²² Whether and how the gut microbiota interacts with SEM remains an important open question for future investigation. A study by Duan et al demonstrated that SEM reduces body weight, fat mass, and insulin resistance in mice by increasing the abundance of *Akkermansia*, *Faecalibaculum*, and *Allobaculum*.¹²³ Furthermore, SEM modulates the relative abundance of gut bacteria and reduces food intake,¹²⁴ providing compelling evidence for its role in metabolic regulation via the gut microbiome. However, based on current research findings, it remains unclear whether SEM can exert cardiorenal protective effects by modulating the gut microbiota. The outcomes and underlying mechanisms require further elucidation in future animal studies. Given the influential role of the gut microbiota in the onset and progression of various diseases, the interaction between SEM and the gut microbiome will constitute a key research direction for our team.

Potential for Individualized Treatment Approaches

As research advances, opportunities are emerging to develop personalized treatment plans tailored to individual patient profiles. The creation of algorithms incorporating biomarkers, genetic variations, and metabolic characteristics could assist clinicians in optimizing drug selection, dosing, and combination therapies. Such an approach would aim to enhance therapeutic efficacy while minimizing side effects and reducing the financial burden on patients. Additionally, dynamic monitoring of cardiac and renal function, along with metabolic changes, would allow for treatment adjustments—such as dose modification and combination regimens—based on the evolving pathophysiological state during the disease course. This strategy is especially promising for optimizing management in patients with multiple underlying comorbidities.

Importance of Multicenter Clinical Trials

Multicenter clinical trials are essential for validating outcomes across diverse populations and healthcare settings. Such trials enhance the generalizability of findings by including a broader representation of demographic backgrounds, socioeconomic statuses, and comorbid conditions. This inclusivity helps ensure that the results are widely applicable and effective across varied clinical contexts, ultimately promoting greater health equity in the management of CRS. Furthermore, treatment efficacy and optimal dosing of SEM—both as monotherapy and in combination with other drugs—may vary among CRS subtypes, underlying diseases, and concomitant medications. Large-scale, long-term clinical studies are needed to analyze these variables, clarify therapeutic effects, establish evidence-based dosing strategies, and achieve optimal treatment outcomes. Currently, there is a lack of large-scale clinical studies on SEM within China. Most existing clinical evidence is derived from international data. It is therefore imperative to collect and analyze data specific to the Chinese population—considering factors such as dietary habits, genetic predispositions, and environmental exposures—in order to develop more tailored treatment approaches and conclusively establish its therapeutic efficacy for Chinese patients.

Long-Term Safety and Efficacy Monitoring

Long-term follow-up studies are urgently needed to evaluate the sustained efficacy and safety of SEM in the context of CRS. Such studies should monitor cardiovascular health, renal function, and potential long-term adverse effects to comprehensively assess the outcomes of prolonged treatment.

Although SEM shows promise in the treatment of CRS, further research is essential to fully realize its therapeutic potential. By elucidating its mechanisms of action, conducting multicenter clinical trials, and advancing personalized treatment strategies, future studies will not only improve patient outcomes but also refine our understanding of this innovative agent. Such investigations are crucial for exploring SEM's pharmacological foundations and evaluating its long-term safety and efficacy across different CRS subtypes.

Conclusion

This article reviews SEM's cardiorenal protective effects and therapeutic strategies for CRS, focusing on mechanisms, clinical evidence, and future prospects. In T2DM, SEM reduces cardiorenal risk factors like blood glucose, blood pressure, and lipids through metabolic regulation. Its anti-inflammatory properties decrease cardiorenal injury and the risk of MACE and MARE. SEM protects the heart by reducing cardiac injury, preserving function, and improving mitochondrial function, energy metabolism, and inhibiting ferroptosis. In kidney disease, SEM prevents inflammatory damage, oxidative stress, fibrosis, and ferroptosis, maintaining renal integrity and slowing disease progression. Figures 1 and 2 illustrate these mechanisms.

While SEM may offer therapeutic benefits for CRS, its side effects, such as thyroid tumors, kidney issues, depression, and retinopathy progression, must be considered. The risk of SEM-induced AKI needs further clinical validation, and alternative

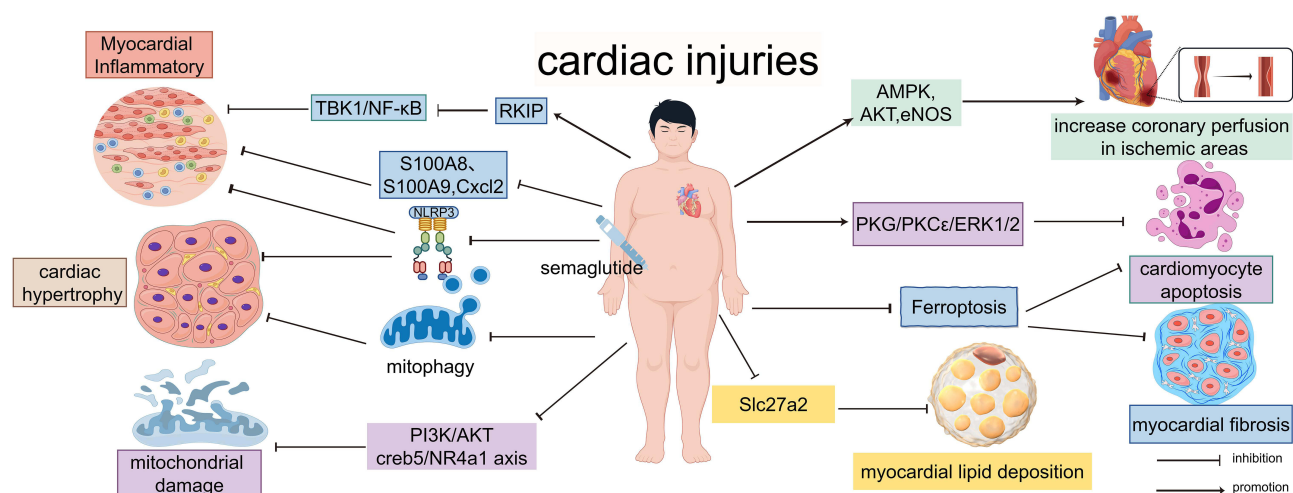


Figure 1 The Cardiac Protective Mechanism of SEM.

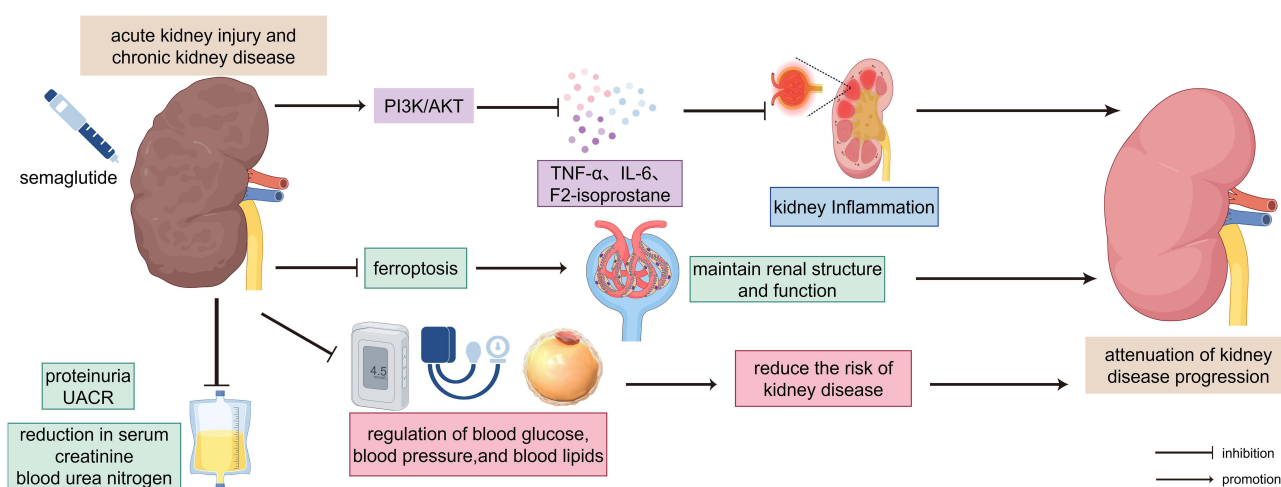


Figure 2 The Renal Protective Mechanism of SEM.

treatments to reverse kidney damage should be actively pursued. Future research should focus on understanding the subtype-specific mechanisms of SEM in different CRS subtypes. Rigorous evaluation of SEM's efficacy and safety in real-world CRS populations is needed through multicenter trials and long-term studies. Clinically, improved monitoring and personalized risk management are crucial for the effective use of SEM. These steps will help integrate SEM into precision therapy for CRS.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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