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Review Article

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How to Enhance Cardiorenal Benefits in Patients With Chronic Heart Failure?

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ABSTRACT

Chronic heart failure (CHF) is frequently complicated by chronic kidney disease (CKD), a comorbidity that profoundly influences disease progression, therapeutic decision-making, and clinical outcomes. The management of CHF in patients with advanced CKD presents substantial challenges, often requiring dose adjustments or even discontinuation of standard therapies. Effective therapeutic strategies must prioritize cardiorenal protection during the early stages of disease progression. Recent advancements in pharmacotherapy, including angiotensin receptor-neprilysin inhibitors, sodium-glucose cotransporter 2 inhibitors, non-steroidal mineralocorticoid receptor antagonists, and glucagon-like peptide-1 receptor agonists, have demonstrated remarkable dual cardiorenal protective effects. These therapies not only reduce the risk of de novo heart failure in high-risk populations and improve clinical outcomes in CHF patients, but also slow the progression of renal dysfunction by targeting critical pathophysiological processes, such as glomerular hyperfiltration, inflammation, ischemia, and endothelial dysfunction. Although transient declines in estimated glomerular filtration rate may occur upon initiating these agents, renal function typically stabilizes over time, facilitating sustained clinical benefits, particularly in patients with diabetes mellitus, albuminuric CKD, and CHF. This review focuses on the latest advancements in heart failure pharmacotherapy, emphasizing the cardiorenal protective mechanisms and clinical efficacy of novel therapeutic agents. It underscores the importance of bridging knowledge gaps and personalizing therapy to enhance cardiorenal benefits avoiding adverse effects.

Keywords: Cardiology; Cardio-renal syndrome; Randomized controlled trial; Cardiovascular diseases; Heart failure

INTRODUCTION

The cascade of hemodynamic fluctuations and compensatory neurohormonal activation in chronic heart failure (CHF) drives cardiac remodeling, hypoperfusion, and systemic congestion, ultimately resulting in the development of multi-organ dysfunction, with renal failure being particularly prevalent.[1] In Japan, chronic kidney disease (CKD) is present in approximately 60-80% of all heart failure cases.[2,3] This high prevalence reflects shared risk factors such as hypertension, obesity, and diabetes mellitus, as well as the complex bidirectional interactions

between the heart and kidneys mediated by cytokines and hemodynamic changes—a phenomenon often described as cardiorenal and cardiorenal-anemia syndrome.[4,5]

The cornerstone of heart failure management remains the timely initiation and optimal up-titration of evidence-based pharmacological therapies, which has substantially improved outcomes with the advent of novel agents in recent years.[6-8] However, renal function serves as a critical determinant in tailoring heart failure treatments, necessitating dose adjustments or discontinuation of essential medications.[9] Renal impairment not only serves as a valuable prognostic marker in CHF patients, but also presents a significant challenge in the management of advanced CHF, particularly concerning indication of left ventricular assist devices and heart transplantation.[10-13] Chronic and irreversible renal impairment adversely affects long-term outcomes, complicating overall prognosis for these patients.

To improve long-term outcomes in CHF patients, effective therapeutic strategies must focus on cardiorenal protection during the early stages of disease progression. While many heart failure therapies unintentionally exhibit renoprotective effects, advancing our understanding of renal pathophysiology and transitioning toward precision medicines may become increasingly essential in the future. This review focuses on the latest advancements in heart failure pharmacotherapy, with a particular emphasis on strategies aimed at preserving renal function and improving outcomes in high-risk populations.

RENAL FUNCTION AND ASSESSMENT IN HEART FAILURE

The nephron: structural and functional dynamics in renal physiology

The nephron, composed of the glomerulus and associated tubule, represents the kidney's fundamental structural and functional unit, with each kidney containing approximately one million nephrons. The glomerulus and renal tubule perform distinct yet interdependent roles essential for renal function (**Figure 1A**). As the kidney's primary filtration unit, the glomerulus filters over 100 L of primary urine daily, removing fluid and solutes from the bloodstream. Subsequently, the renal tubules reabsorb essential substances to maintain homeostasis. Blood enters the glomerulus via afferent arterioles, where a portion is filtered to form primary urine, while the remainder exits through efferent arterioles. These efferent arterioles supply oxygen and nutrients to the renal tubules, ensuring their metabolic activity.[14]

To regulate filtration volume in the glomerulus, the nephron utilizes autoregulation of the afferent and efferent arterioles, allowing adaptation to hemodynamic fluctuations and compensating for nephron loss. This autoregulatory process is mediated by the tubule-glomerular feedback (TGF) mechanism, in which the macula densa—located in the distal tubule—monitors the delivery of sodium chloride and modulates arteriolar resistance to maintain filtration and intravascular volume.[15]

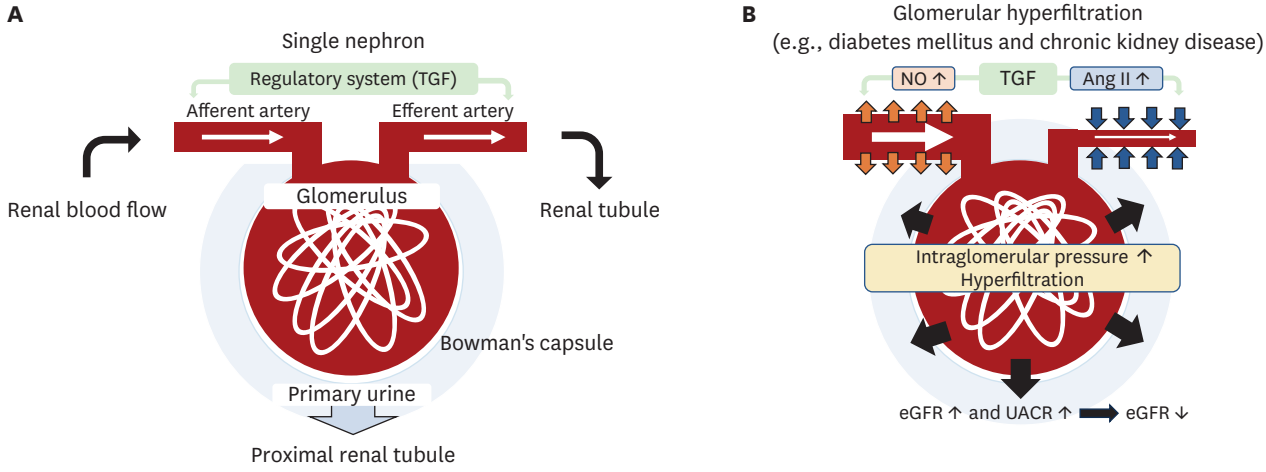

Figure 1. Structure and function of the nephron. (A) The nephron consists of the glomerulus and renal tubule, serving as the kidney's primary filtration unit. The glomerulus filters primary urine, while the renal tubules reabsorb essential substances to maintain homeostasis. Blood enters through afferent arterioles, with filtered plasma forming primary urine, and exits via efferent arterioles, which also supply oxygen and nutrients to the tubules. (B) The nephron regulates filtration through autoregulation of the afferent and efferent arterioles via TGF mechanism, adapting to hemodynamic changes and compensating for nephron loss. Dysregulated filtration leads to glomerular hypertension, albuminuria, tubular overload, and ultimately end-stage renal disease.
TGF = tubule-glomerular feedback; NO = nitric oxide; Ang II = angiotensin II; eGFR = estimated glomerular filtration rate; UACR = urinary albumin to creatinine ratio.

How to evaluate renal function in patients with acute heart failure

Acute and significant reductions in renal blood flow and filtration pressure that exceed the autoregulatory capacity of the TGF mechanism can transiently decrease filtration volume, resulting in reduction urine output.[16] Insufficient perfusion of the renal tubules may further lead to acute renal tubular necrosis or interstitial nephritis. These changes increase Bowman's capsule pressure and reduce trans-glomerular pressure gradient, accompanied by renal congestion and elevated intra-abdominal pressure, which further compromise urine production.[17]

Despite these acute insults, the glomerular structure generally remains intact. In contrast, the renal tubules, consisting of highly regenerative epithelial cells, typically recover within 2–4 weeks after acute necrosis.[18,19] These dynamic alterations complicate the precise assessment of "true" renal function during the acute phase of heart failure.[20-22] Consequently, clinical trials evaluating renal function and prognosis in acute heart failure require careful interpretation.[23-25] This complexity has partially contributed to inconsistent findings and the emergence of phenomena such as "pseudo-worsening renal function."[26]

How to evaluate renal function in patients with CHF

In contrast to acute heart failure, glomerular and renal tubulointerstitial markers serve as well-established prognostic indicators of long-term prognosis in patients with CHF.[3,27-30] Among these, glomerular markers such as estimated glomerular filtration rate (eGFR) and urinary albumin to creatinine ratio (UACR) are widely recognized as independent and robust predictors of renal, cardiovascular (CV), and overall prognosis. The Kidney Disease: Improving Global Outcomes (KDIGO) heat map, stratified by eGFR and UACR, has been an effective tool for risk stratification. As shown in **Figure 2**, recent large randomized controlled trials in heart failure therapies have been mapped onto the KDIGO framework to demonstrate their relevance.

However, the careful interpretation of these markers is essential, as their levels may reflect not only glomerular dysfunction but also by tubular damage, particularly in patients with advanced CKD.[31]

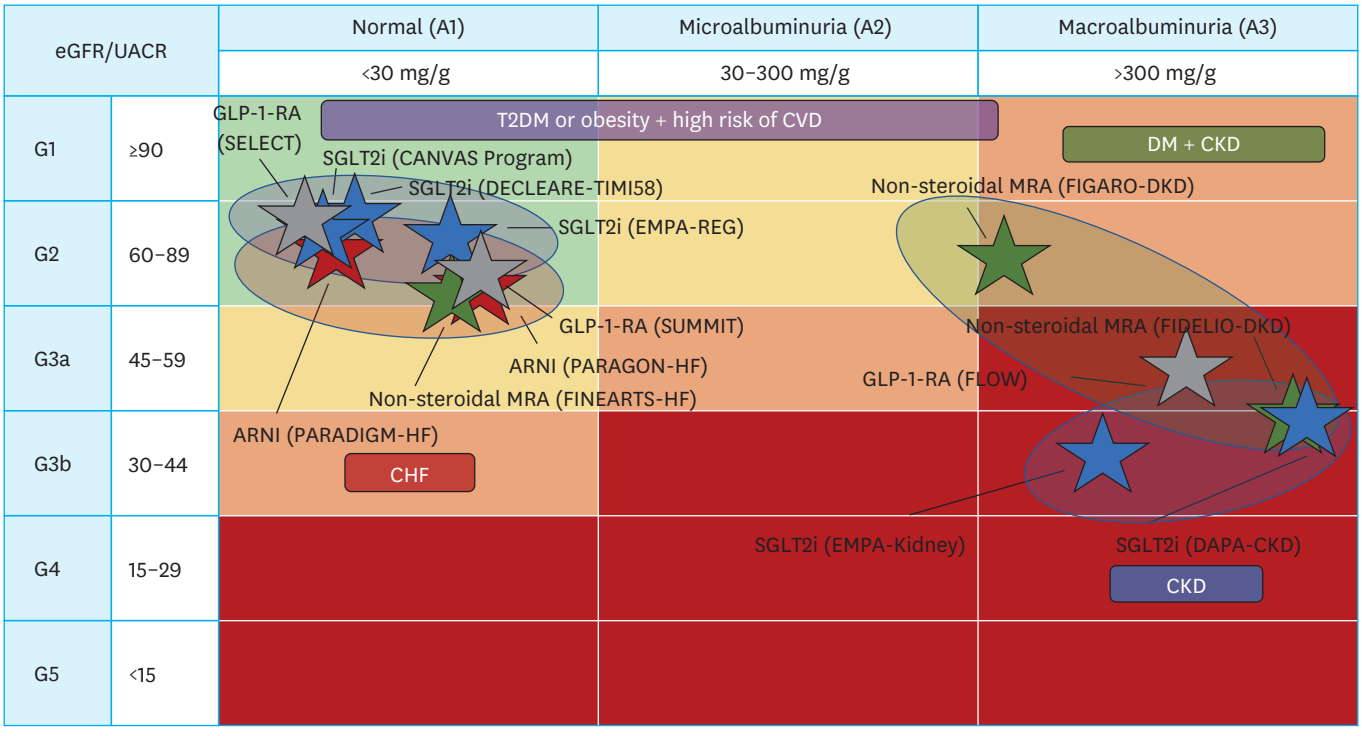

Figure 2. Included randomized controlled trials for evaluating cardiorenal protection evidence on the Kidney Disease: Improving Global Outcomes heat map.
eGFR = estimated glomerular filtration rate; UACR = urinary albumin to creatinine ratio; GLP-1-RA = glucagon-like peptide-1 receptor agonist; T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; DM = diabetes mellitus; CKD = chronic kidney disease; SGLT2i = sodium-glucose cotransporter 2 inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; CHF = chronic heart failure.

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RENAL FUNCTION DETERIORATION IN CHF: INSIGHTS INTO THE GLOMERULAR HYPERFILTRATION THEORY

In patients with CHF, the progression of renal dysfunction—encompassing glomerular, tubular, and interstitial injury—results from a complex interplay of mechanisms extending beyond hemodynamic disturbances, including ischemia, inflammation, metabolic disturbances, and hypoxia driven by neurohormonal activation.[4]

The glomerular hyperfiltration theory is a well-recognized concept, describing a condition where the dysregulation of glomerular filtration results in glomerular hypertension, excessive filtration, albuminuria and proximal tubular overload, ultimately causing end-stage renal disease (ESRD) (**Figure 1B**).[32] Diabetes mellitus is a primary cause of glomerular hyperfiltration, mediated by upregulation of sodium-glucose cotransporters (SGLT) 1 and 2, which reduce sodium delivery to the macula densa.[15] This disruption activates the TGF mechanism, increasing intraglomerular pressure and exacerbating hyperfiltration. In diabetic nephropathy, hyperfiltration typically manifests early, as a transient increase in eGFR, which is subsequently followed by the onset of albuminuria and/or a progressive decline in eGFR, eventually progressing to ESRD as nephron damage accumulates.[33,34]

In CKD, the loss of nephron triggers compensatory hyperfiltration and albuminuria in the remaining functional glomeruli to preserve overall glomerular filtration rate (GFR). However, once nephron loss surpasses approximately half a million nephrons, these compensatory mechanisms become insufficient, resulting in a measurable decline in GFR.[35]

Although evidence on glomerular hyperfiltration in CHF remains limited, it may play a pivotal role in the progression of renal impairment in this complicated clinical context.[36,37] The activation of the renin-angiotensin-aldosterone system (RAAS), a hallmark of heart failure, increases angiotensin II levels, causing efferent arteriole constriction and potentially promoting glomerular hyperfiltration.[38]

RENAL SURROGATE MARKERS IN GLOMERULAR HYPERFILTRATION CONDITIONS AND CHF: PROGNOSTIC AND THERAPEUTIC PERSPECTIVES

Diabetic nephropathy and CKD—which are hallmark conditions of glomerular hyperfiltration—underscore the prognostic and therapeutic value of renal surrogate markers such as the eGFR slope and UACR.[39] As depicted in **Figure 3A**, eGFR naturally declines by approximately 1 mL/min/1.73 m^2 annually with aging in healthy individuals. However, this decline can accelerate substantially in type 2 diabetes mellitus and CKD, as an annual eGFR decline of 3 to 4 mL/min/1.73 m^2. Importantly, an improvement of 0.75 mL/min/1.73 m^2 annually in the eGFR slope has been associated with a 22% reduction in renal event risk.[39,40] Similarly, a 50% reduction in UACR has been associated with an approximately 30% reduction in the risk of progression to ESRD.[41]

In CHF patients, reduced eGFR is frequently associated with diminished renal blood flow, reflecting impaired cardiac output. Interventions, such as cardiac resynchronization therapy and left ventricular assist devices, can temporarily improve eGFR by enhancing cardiac output.[42-44] However, recent large-scale trials have reinforced the utility of changes in the eGFR slope and UACR as robust and reliable surrogate markers in CHF populations.[37,45-48] Observational studies indicate that CHF patients experience an annual eGFR decline of 2 to 3 mL/min/1.73 m^2, with the prevalence of rapid progression—defined as a decrease of ≥5 mL/min/1.73 m^2 annually—being significantly higher in patients with CHF compared to those without CHF (22% vs. 9%).[49] The most pronounced declines typically occur during the periods surrounding heart failure exacerbation, although the precise mechanisms driving these acute changes remain unclear.[50]

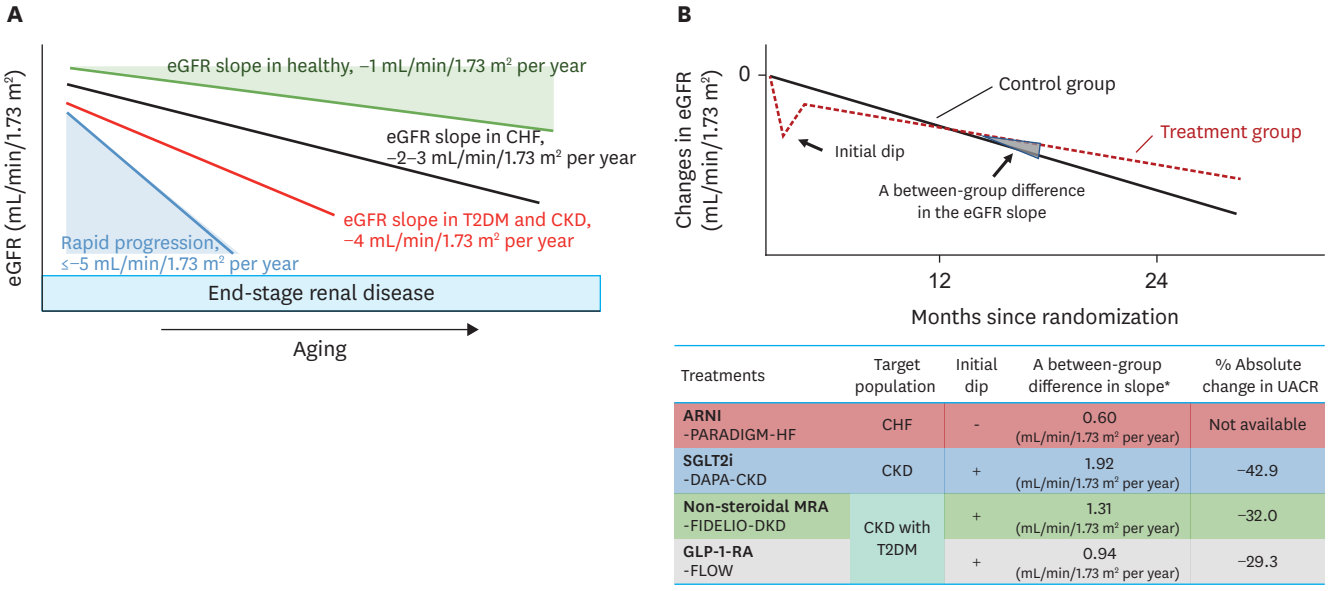
These markers, which have long been established in glomerular hyperfiltration conditions, are now being increasingly recognized as essential tools in guiding and monitoring therapeutic strategies for CHF patients.[37] Leveraging these surrogate markers may facilitate earlier and more precise treatment adjustments, potentially improving outcomes across the heart failure spectrum, from pre-CHF and advanced CHF.[39,40,51]

HEART FAILURE PHARMACOTHERAPY: DUAL IMPACT ON CARDIAC AND RENAL OUTCOMES

Renin-angiotensin system (RAS) inhibitors and angiotensin receptor-neprilysin inhibitor (ARNI)

Evidence of cardioprotection from clinical trials

RAS inhibitors, blocking neurohormonal activation, are cornerstone therapies for heart failure management. Their efficacy was first established in the landmark CONSENSUS trial in 1987, and a robust body of evidence has since reinforced their role in both primary and secondary prevention, particularly in patients with



Treatments	Target population	Initial dip	A between-group difference in slope*	% Absolute change in UACR
ARNI -PARADIGM-HF	CHF	-	0.60 (mL/min/1.73 m² per year)	Not available
SGLT2i -DAPA-CKD	CKD	+	1.92 (mL/min/1.73 m² per year)	−42.9
Non-steroidal MRA -FIDELIO-DKD	CKD with T2DM	+	1.31 (mL/min/1.73 m² per year)	−32.0
GLP-1-RA -FLOW		+	0.94 (mL/min/1.73 m² per year)	−29.3

Figure 3. Renal surrogate markers. (A) The eGFR slope in type 2 diabetes mellitus, chronic kidney disease, and chronic heart failure; (B) the eGFR slope, UACR, and novel heart failure therapies. (A) The eGFR slope, indicating the rate of eGFR decline, serves as a reliable surrogate endpoint for kidney disease progression and an efficacy indicator of heart failure therapies. In healthy aging, eGFR declines by ~1 mL/min/1.73 m² annually, while steeper declines of 3–4 mL/min/1.73 m² occur in T2DM and CKD due to glomerular hyperfiltration. CHF patients exhibit an intermediate decline of 2–3 mL/min/1.73 m² annually. (B) Trials of SGLT2i, non-steroidal MRAs, and GLP-1-RAs have shown a less pronounced eGFR decline and significant reductions in UACR, with a transient eGFR decline ("initial dip"). In contrast, ARNI preserves eGFR without inducing UACR reduction or an initial dip.
eGFR = estimated glomerular filtration rate; CHF = chronic heart failure; T2DM = type 2 diabetes mellitus; CKD = chronic kidney disease; UACR = urinary albumin to creatinine ratio; ARNI = angiotensin receptor-neprilysin inhibitor; SGLT2i = sodium-glucose cotransporter 2 inhibitor; MRA = mineralocorticoid receptor antagonist; GLP-1-RA = glucagon-like peptide-1 receptor agonist.
*The between-group difference in eGFR slope was evaluated from baseline in the PARADIGM-HF trial, from week 2 in the DAPA-CKD trial, and from week 12 in the FIDELIO-DKD and FLOW trials, accounting for the exclusion of the initial dip effect.

myocardial infarction and heart failure with reduced ejection fraction (HFrEF).[52-60]

Sacubitril/valsartan, an ARNI, has emerged as a highly effective cardioprotective agent with multifaced mechanisms of action.[61] Beyond its blockade of the RAAS, ARNI exerts additional benefits by inhibiting hormone-degrading pathways that regulate the levels of atrial and brain natriuretic peptides (ANP/BNP), thereby enhancing cardiorenal protection.[62] The PROVE-HF trial, conducted in patients with HFrEF, demonstrated that ARNI significantly reduced N-terminal-proBNP levels while increasing in ANP levels, underscoring its sustained therapeutic benefits.[63]

The PARADIGM-HF trial established ARNI's superiority over RAS inhibitors in reducing all-cause mortality and heart failure-related hospitalizations in HFrEF patients (**Table 1** and **Figure 4**).[64] In contrast, the PARAGON-HF trial did not demonstrate significant benefits in patients with heart failure with preserved ejection fraction (HFpEF).[65] However, an integrated analysis of these trials further underscored the broad efficacy of ARNI across heart failure phenotypes, particularly in patients with left ventricular ejection fraction (LVEF) <57%, with pronounced benefits observed in female patients.[45,66]

Despite its broad efficacy, ARNI failed to demonstrate superiority over ramipril in preventing heart failure in post-acute myocardial infarction patients with LVEF ≤40%, highlighting its limitations in this specific clinical context.[67]

Evidence of renoprotection from clinical trials

RAS inhibitors are well-established therapies with proven renoprotective effects, particularly in patients with diabetes. Their efficacy was first demonstrated in the late 20th century, showing significant reductions in urinary albumin excretion and the progression of renal dysfunction.[68]

RAS inhibitors provide their protective effects primary by lowering intraglomerular pressure, thereby preserving long-term renal function. Landmark trials, such as the COLLABORATIVE and RENAAL trials, have reported significant risk reductions in renal events, with captopril achieving 50% and losartan achieving 16% among diabetic populations.[69,70]

Recent pooled analyses of the PARADIGM-HF and PARAGON-HF trials underscore the superior renoprotective effects of ARNI compared to traditional RAS inhibitors in patients with CHF. ARNI reduced the post hoc renal composite outcome— >50% eGFR

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Table 1. Summary of included randomized controlled trials for evaluating cardiorenal protection evidence

Source	Trial participants	Mean age (years)	Key inclusion criteria	Proportion with diabetes mellitus (%)	Proportion with chronic heart failure (%)	Proportion with history of myocardial infarction (%)	Proportion with eGFR <60 mL/min/1.73 m^2 (%)	Proportion with albuminuria (%)[†]	Proportion with RAS inhibitors (%)	Proportion with beta blockers (%)	Proportion with diuretics (%)	Primary and renal outcomes (event rates in treatment and control groups)
Angiotensin receptor-neprilysin inhibitor												
Chronic heart failure												
PARADIGM-HF, 2014 (LCZ 696 400 mg)	8,442	64	1. HFrEF, 2. Age ≥50years with signs and symptoms of HF (NYHA functional class II–IV), LVEF <35% (40%), and increased NT-proBNP or BNP levels, 3. eGFR ≥30 mL/min/1.73 m^2.	34	100	43	37	Microalbuminuria and macroalbuminuria 24%	99	93	80	1. A composite of CV death or a first HHF (21.8% and 26.5%). 2. A sustained ≥50% reduction in the eGFR, progression to ESRD, or death from renal causes (2.2% and 2.6%).[*]
PARAGON-HF, 2019 (sacubitril/valsartan 400 mg)	4,822	73	1. HFpEF, 2. Age ≥50years with signs and symptoms of HF (NYHA functional class II–IV), LVEF ≥45%, increased NT-proBNP levels, and evidence of SHD (increased left atrial size or left ventricular hypertrophy), 3. eGFR ≥30 mL/min/1.73 m^2.	43	100	23	47	NA	85	80	96	1. A composite of total (first and recurrent) HHF and CV death (37.1% and 42.2%). 2. A sustained ≥50% reduction in the eGFR, progression to ESRD, or death from renal causes (1.4% and 2.7%).
Sodium-glucose cotransporter 2 inhibitors												
Type 2 diabetes mellitus at high risk of atherosclerotic cardiovascular disease												
EMPA-REG, 2015 (empagliflozin 10 mg or 25 mg)	7,020	64	1. Type 2 diabetes, 2. Age ≥18 years and history of coronary, cerebral, or peripheral vascular disease, 3. eGFR ≥30 mL/min/1.73 m^2.	100	10	47	26	Microalbuminuria 29%, macroalbuminuria 11%	81	65	43	1. A composite of CV death, nonfatal myocardial infarction, or nonfatal stroke (10.5% and 12.1%). 2. A doubling of serum creatinine, the need for RRT, or death from renal causes (1.7% and 3.1%).
CANVAS Program, 2017 (canagliflozin 100 or 300 mg)	10,142	63	1. Type 2 diabetes, 2. Age ≥30 years and history of coronary, cerebral, or peripheral vascular disease; or age ≥50 years with at least two CV risk factors, 3. eGFR ≥30 mL/min/1.73 m^2.	100	14	NA	20	Microalbuminuria 23%, macroalbuminuria 8%	80	54	44	1. A composite of CV death, nonfatal myocardial infarction, or nonfatal stroke (NA). 2. A sustained ≥40% reduction in the eGFR, the need for RRT, or death from renal causes (NA).
DECLEARE-TIMI58, 2019 (dapagliflozin 10 mg)	17,160	64	1. Type 2 diabetes, 2. Age ≥40 years and history of coronary, cerebral, or peripheral vascular disease; or age ≥55 years in men or ≥60 years in women with at least one CV risk factor, 3. CCr ≥60 mL/min.	100	10	21	7	Microalbuminuria 23%, macroalbuminuria 7%	77	46	39	1. A composite of CV death, myocardial infarction, or ischemic stroke (4.9% and 5.8%). 2. A sustained ≥40% reduction in the eGFR, progression to ESRD, or death from renal causes (4.3% and 5.6%).

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Chronic heart failure												
DAPA-HF, 2019 (dapagliflozin 10 mg)	4,744	66	1. HFrEF, 2. Age ≥18years with signs and symptoms of HF (NYHA functional class II–IV), LVEF ≤40%, and increased NT-proBNP or BNP levels, 3. eGFR ≥30 mL/min/1.73 m^2.	42	100	44	41	NA	95	96	93	1. A composite of WHF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death (16.3% and 21.2%). 2. A sustained ≥50% reduction in the eGFR, progression to ESRD (defined as eGFR <15 mL/min/1.73m^2, sustained dialysis, or renal transplantation), or death from renal causes (1.2% and 1.6%).
EMPEROR-Reduced, 2020 (empagliflozin 10 mg)	3,730	67	1. HFrEF, 2. Age ≥18years with signs and symptoms of HF (NYHA functional class II–IV), LVEF ≤40%, and increased NT-proBNP or BNP levels (with specific adjustment), 3. eGFR ≥20 mL/min/1.73 m^2.	50	100	NA	48	Microalbuminuria 33%, macroalbuminuria 11%	89	95	NA	1. A composite of CV death or HHF (19.4% and 21.2%). 2. A sustained ≥40% reduction in the eGFR, progression to ESRD (defined as eGFR <10 (15) mL/min/1.73m^2, sustained dialysis, or renal transplantation), or death from renal causes (1.6% and 3.1%).
Emperor-preserved, 2021 (empagliflozin 10 mg)	5,988	72	1. HFmrEF and HFpEF, 2. Age ≥18years with signs and symptoms of HF (NYHA functional class II–IV), LVEF ≥40%, and increased NT-proBNP or BNP levels, 3. eGFR ≥20 mL/min/1.73 m^2.	49	100	29	50	Microalbuminuria 31%, macroalbuminuria 10%	81	86	86	1. A composite of CV death or HHF (13.8% and 17.1%). 2. A sustained ≥40% reduction in the eGFR, progression to ESRD (defined as eGFR <10 (15) mL/min/1.73m^2, sustained dialysis, or renal transplantation), or death from renal causes (3.6% and 3.7%).
DELIVER, 2022 (dapagliflozin 10 mg)	6,263	72	1. HFmrEF, HFpEF, and HFimpEF, 2. Age ≥18years with signs and symptoms of HF (NYHA functional class II–IV), LVEF >40%, and increased NT-proBNP or BNP levels and evidence of SHD (increased left atrial size or left ventricular hypertrophy), 3. eGFR ≥25 mL/min/1.73 m^2.	45	100	26	50	NA	72	76	72	1. A composite of WHF (either an unplanned HHF or an urgent visit for HF) or CV death. (16.4% and 19.5%) 2. A sustained ≥50% reduction in the eGFR, progression to ESRD, or death from renal causes (2.3% and 2.5%).

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Chronic kidney disease												
DAPA-CKD, 2020 (dapagliflozin 10 mg)	4,304	62	1. CKD with eGFR 25–75 mL/min/1.73 m^2 and UACR 200–5,000 mg/g, 2. Age ≥18 years with stable and maximum tolerated RAS inhibitors, 3. Excluded polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis.	68	11	9.1	90	Microalbuminuria 10%, macronalbuminuria 90%	98	39	44	1. A sustained ≥50% reduction in the eGFR, progression to ESRD or death from renal causes, or CV death (9.2% and 14.5%). 2. A sustained ≥50% reduction in the eGFR, progression to ESRD or death from renal causes (6.6% and 11.3%).
EMPA-KIDNEY, 2022 (empagliflozin 10 mg)	6,609	64	1. CKD with eGFR 20–45 mL/min/1.73 m^2 or eGFR 45–90 mL/min/1.73 m^2 and UACR ≥200 mg/g, 2. Age ≥18 years with appropriate RAS inhibitors, 3. Excluded polycystic kidney disease.	46	10	NA	NA	Microalbuminuria 28%, macroalbuminuria 52%	85	42	43	1. A sustained ≥40% reduction in the eGFR, eGFR <10 mL/min/1.73m^2, progression to ESRD or death from CV causes (13.1% and 16.9%). 2. A sustained ≥40% reduction in the eGFR, eGFR <10 mL/min/1.73m^2, progression to ESRD (11.6% and 15.2%).
Non-steroidal mineralocorticoid receptor antagonists												
Chronic heart failure												
FINEARTS-HF, 2024 (finerenone 40 mg)	6,001	72	1. HFmrEF and HFpEF, 2. Age ≥40years with signs and symptoms of HF (NYHA functional class II–IV) and LVEF ≥40%, increased NT-proBNP or BNP levels, and evidence of SHD (increased left atrial size or left ventricular hypertrophy), 3. eGFR ≥25 mL/min/1.73 m^2.	42	100	17	48	Microalbuminuria 30%, macroalbuminuria 10%	98	85	87	1. A composite of the WHF events (either a hospitalization or an urgent visit for HF) and CV death (36% and 43%). 2. A sustained ≥50% reduction in the eGFR, eGFR <15 mL/min/1.73m^2, or the need for long-term dialysis or kidney transplantation (2.5% and 1.8%).
CKD with type 2 diabetes mellitus												
FIDELIO-DKD, 2020 (finerenone 20 mg)	5,674	66	1. Type 2 diabetes and CKD with eGFR 20–60 mL/min/1.73 m^2 and UACR 30–300 mg/g, or eGFR 25–75 mL/min/1.73 m^2 and UACR 300–5,000 mg/g, 2. Age ≥18 years with RAS inhibitors, 3. Excluded HFrEF.	100	8	14	88	Microalbuminuria 12%, macroalbuminuria 87%	100	52	57	1 and 2. A sustained ≥40% reduction in the eGFR, or death from renal causes (17.8% and 21.1%).

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FIGARO-DKD, 2021 (finerenone 20 mg)	7,352	64	1. Type 2 diabetes and CKD with eGFR 25–90 mL/min/1.73 m² and UACR 30–300 mg/g, or eGFR ≥60 mL/min/1.73 m² and UACR 300–5,000 mg/g, 2. Age ≥18 years with RAS inhibitors, 3. Excluded HFrEF.	100	8	26	38	Microalbuminuria 46%, macroalbuminuria 51%	100	48	47	1. A first occurrence of CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF (12.4% and 14.2%). 2. A sustained ≥57% reduction in the eGFR (equivalent to a doubling of the serum creatinine level), or death from renal causes (9.5% and 10.8%).
Glucagon-like peptide-1 receptor agonists												
Overweight or obesity with atherosclerotic cardiovascular disease (without diabetes mellitus)												
SELECT, 2023 (semaglutide 2.4 mg)	17,604	62	1. BMI of ≥27 kg/m² and history of coronary, cerebral, or peripheral vascular disease, 2. Aged ≥45 years, 3. Excluded ESRD.	0	24	76	11	Microalbuminuria 11%, macroalbuminuria 2%	76	70	33	1. A first occurrence of CV death, nonfatal myocardial infarction, nonfatal stroke (6.5% and 8.0%). 2. A five-component composite of death from renal causes, the need for RRT, eGFR <15 mL/min/1.73m², A sustained ≥50% reduction in the eGFR, or persistent macroalbuminuria (1.8% and 2.2%).
Overweight or obesity with chronic heart failure												
SUMMIT, 2024 (tirzepatide 2.5 mg)	731	65	1. HFpEF and BMI ≥27 kg/m², 2. Age ≥40 years with signs and symptoms of HF (NYHA functional class II–IV) and LVEF ≥50%, increased NT-proBNP or BNP levels, and evidence of SHD, 3. eGFR ≥15 mL/min/1.73 m².	48	100	NA	60	Microalbuminuria 27%, macroalbuminuria 8%	80	70	74	1. A composite of death from any cause or WHF event combined with changes at 52 weeks in the KCCQ-CSS and in the 6-minute walk distance (9.9% and 15.3%). 2. NA.
CKD with type 2 diabetes mellitus												
FLOW, 2024 (semaglutide 1.0 mg)	3,533	67	1. Type 2 diabetes and CKD with eGFR 50–75 mL/min/1.73 m² and UACR 300–5,000 mg/g, or eGFR 25–50 mL/min/1.73 m² and UACR 100–5,000 mg/g, 2. Age ≥18 years with RAS inhibitors. eGFR 25–50 mL/min/1.73 m² and UACR 100–5,000 mg/g, 2. Age ≥18 years with RAS inhibitors.	100	19	23	80	Microalbuminuria 32%, macroalbuminuria 68%	96	52	50	1. A sustained ≥50% reduction in eGFR, progression to ESRD (initiation of long-term dialysis, kidney transplantation, or eGFR <15 mL/min/1.73m²), or death from renal or CV causes (18.7% and 23.2%). 2. A sustained ≥50% reduction in eGFR, progression to ESRD (initiation of long-term dialysis, kidney transplantation, or eGFR <15 mL/min/1.73 m²), or death from renal causes (12.3% and 14.7%).

eGFR = estimated glomerular filtration rate; RAS = renin-angiotensin-system; HFrEF = heart failure with reduced ejection fraction; HF = heart failure; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro B-type natriuretic peptide; BNP = B-type natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; SHD = structural heart disease; CV death = cardiovascular death; HHF = hospitalization for heart failure; ESRD = end-stage renal disease; RRT = renal replacement therapy; NA = not available; CCr = creatinine clearance; WHF = worsening heart failure; HFimpEF = heart failure with improved ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; CKD = chronic kidney disease; UACR = urinary albumin to creatinine ratio; BMI = body mass index; KCCQ-CSS = the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score.

*This represents the modified renal outcome in the integrated analysis of the PARAGON-HF trial.

†Microalbuminuria was defined as UACR 30-300 mg/g and Macroalbuminuria as UACR ≥300 mg/g.

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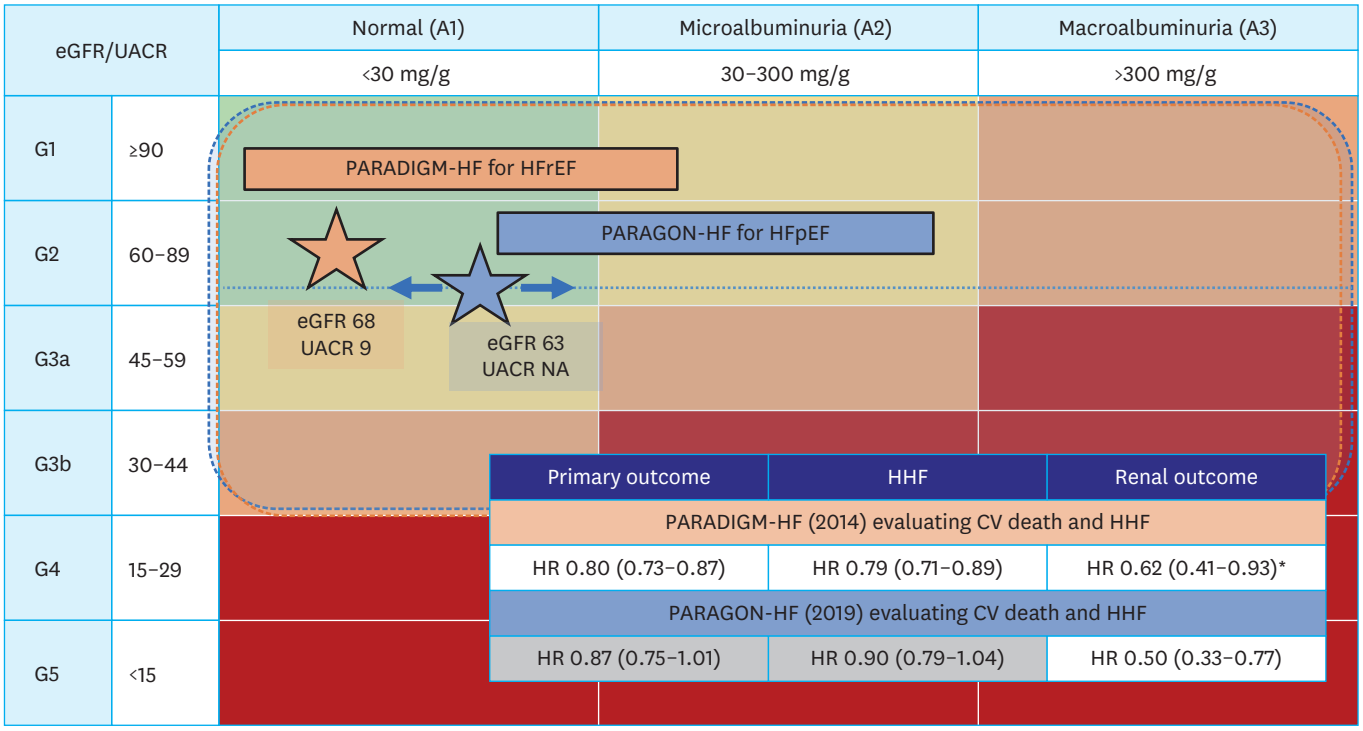

Figure 4. Outcomes of randomized controlled trials with angiotensin receptor-neprilysin inhibitor on the KDIGO heat map. The KDIGO heat map highlights the PARADIGM-HF trial (orange star: mean eGFR: 68 mL/min/1.73 m^2, median UACR: 9 mg/g) and PARAGON-HF trial (blue star: mean eGFR: 63 mL/min/1.73 m^2), with dotted boxes indicating inclusion criteria. Primary outcomes were CV death or first HHF in the PARADIGM-HF trial, and CV death and total HHF in the PARAGON-HF trial. Renal outcomes included a sustained ≥50% eGFR reduction, end-stage renal disease, and death from renal causes in both trials. Treatment effects are presented as HRs (95% confidence interval).
eGFR = estimated glomerular filtration rate; UACR = urinary albumin to creatinine ratio; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; NA = not available; HHF = hospitalization for heart failure; CV death = cardiovascular death; HR = hazard ratio; KDIGO = The Kidney Disease: Improving Global Outcomes.
*This represents the modified renal outcome in the integrated analysis of the PARAGON-HF trial.

decline, ESRD, and renal death—by 44%. Remarkably, in CHF patients with baseline eGFR ranging from 30 to 110 mL/min/1.73 m^2, ARNI consistently achieved about 50% reduction in the risk of composite renal events (**Figure 4**). By promoting mesangial cell and podocyte relaxation and efferent arteriole vasodilation through ANP/BNP-mediated pathways, ARNI enhances eGFR without reducing UACR and prevents the transient eGFR decline ("initial dip") commonly observed with RAS inhibitor initiation (**Figure 3B**).[38,45] However, whether ARNI's limited impact on intraglomerular pressure regulation accounts for its lack of significant UACR reduction remains unclear.

These renoprotective benefits are likely multifactorial beyond inhibiting glomerular hyperfiltration, encompassing improved renal perfusion, a reduction in CV events, and decreased reliance on loop diuretics.[71,72]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors

Evidence of cardioprotection from clinical trials

Initially developed for the treatment of diabetes, SGLT2 inhibitors have demonstrated substantial CV benefits in patients with type 2 diabetes mellitus, particularly in reducing the risk of hospitalization for heart failure. Meta-analyses indicate that these benefits were predominantly observed in individuals with coexisting atherosclerotic CVD, achieving a 24% reduction in the primary composite outcome of CV death or hospitalization for heart failure (**Table 1** and **Figure 5A**).[73]

Notably, the cardioprotective benefits of SGLT2 inhibitors extend beyond diabetic populations. Landmark clinical trials, including the DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER, have confirmed their efficacy in reducing CV events, particularly hospitalization for heart failure, across a broad spectrum of heart failure phenotypes, including HFpEF, heart failure with mildly reduced ejection fraction (HFmrEF), and HFrEF.[74-77] A meta-analysis among patients with CHF demonstrated a 23% reduction in the primary composite outcome of CV death or hospitalization for heart failure, largely driven by a 28% reduction in heart failure hospitalization.[78] Kaplan-Meier curves from these trials demonstrated rapid therapeutic effects, with benefits evident

within the "first" month of treatment initiation, likely attributable to their osmotic diuretic action.[74-77]

In contrast to conventional heart failure therapies that directly target sympathetic nervous system and RAAS activation, SGLT2 inhibitors exhibit cardioprotective effects through diverse and unique mechanisms. These include intravascular and tissue decongestion via diuretic effects, modulation of myocardial metabolism, activation of sirtuin 1, and upregulation of hypoxia-inducible factor 2α.[79,80] These multifaceted mechanisms underscore the transformative potential of SGLT2 inhibitors in heart failure management.

Evidence of renoprotection from clinical trials

SGLT2 inhibitors exhibit potent renoprotective effects through multiple mechanisms, with the inhibition of the TGF pathway serving as a central role. By increasing sodium delivery to the macula densa—mediated by inhibiting SGLT2 receptors at proximal renal tubules—they suppress nitric oxide release in the afferent arteriole. This cascade lowers intraglomerular pressure, mitigates hyperfiltration, and reduces UACR. Furthermore, by decreasing ATP consumption in the mitochondria-rich proximal renal tubules, SGLT2 inhibitors may alleviate ischemia in the renal cortex and enhance cellular viability.[81,82]

A

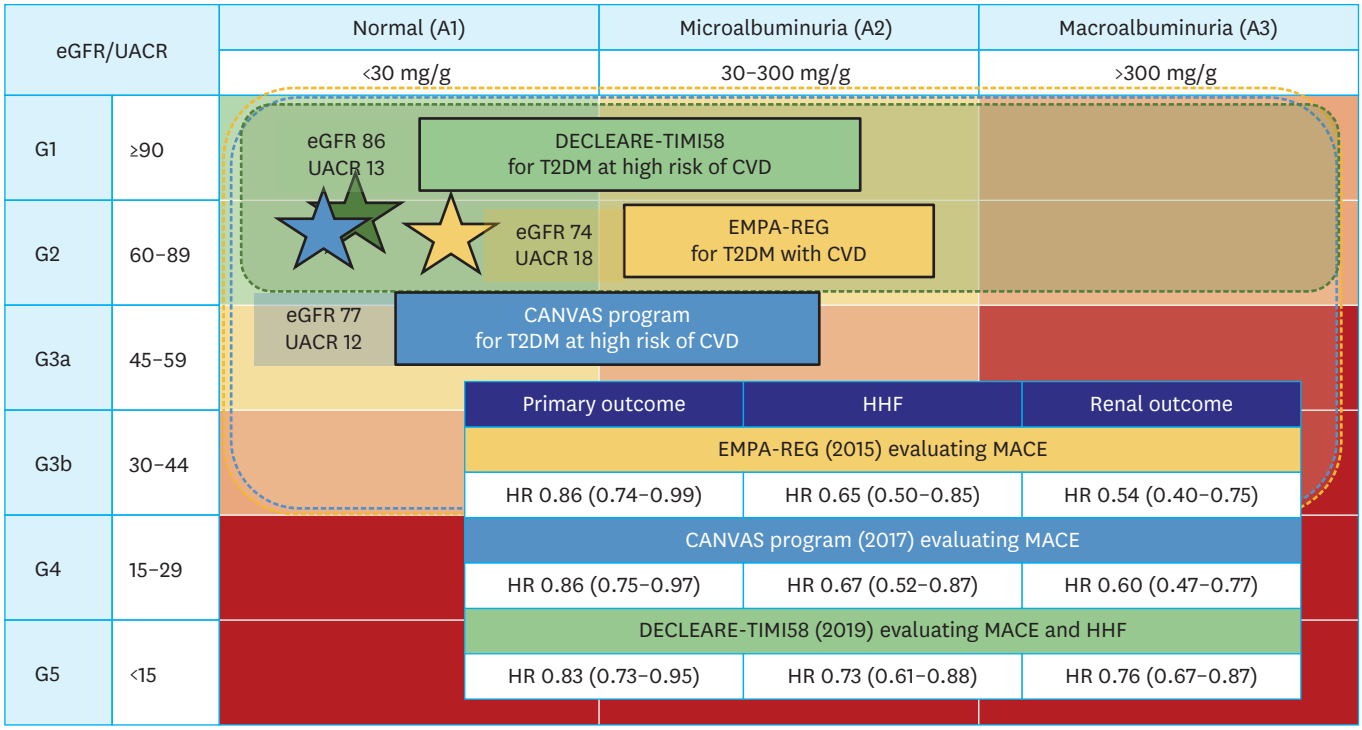

Figure 5. Outcomes of RCTs with SGLT2 inhibitors on the KDIGO heat map: (A) RCTs with SGLT2 inhibitors targeting type 2 diabetes mellitus at high risk of cardiovascular disease; (B) RCTs with SGLT2 inhibitors targeting CKD. (A) The KDIGO heat map highlights the EMPA-REG trial (yellow star: mean eGFR: 74 mL/min/1.73 m^2, median UACR: 18 mg/g), CANVAS program trial (blue star: mean eGFR: 77 mL/min/1.73 m^2, median UACR: 12 mg/g), and DECLEARE-TIMI58 trial (green star: mean eGFR: 86 mL/min/1.73 m^2, median UACR: 13 mg/g), with dotted boxes indicating inclusion criteria. Primary outcomes across all trials included a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke. Renal outcomes included a doubling of serum creatinine, the need for renal replacement therapy, or death from renal causes in the EMPA-REG trial, and a sustained ≥40% reduction in the eGFR, the need for renal replacement therapy, or death from renal causes in the CANVAS program and DECLEARE-TIMI58 trial. Treatment effects are presented as HRs (95% confidence interval). (B) The KDIGO heat map highlights the DAPA-CKD trial (yellow star: mean eGFR: 43 mL/min/1.73 m^2, median UACR: 949 mg/g), and EMPA-KIDNEY trial (purple star: mean eGFR: 38 mL/min/1.73 m^2, median UACR: 412 mg/g), with dotted boxes indicating inclusion criteria. Primary outcomes were a sustained ≥50% reduction in the eGFR, progression to end-stage renal disease or renal or CV death in the DAPA-CKD trial, and a sustained ≥40% reduction in the eGFR, eGFR <10 mL/min/1.73 m^2, end-stage renal disease or death from CV causes in the EMPA-KIDNEY trial. Renal outcomes included a sustained ≥50% reduction in the eGFR, progression to end-stage renal disease or death from renal causes in the DAPA-CKD trial. and a sustained ≥40% reduction in the eGFR, eGFR <10 mL/min/1.73 m^2, or end-stage renal disease in the EMPA-KIDNEY. Treatment effects are presented as HRs (95% confidence interval).
eGFR = estimated glomerular filtration rate; UACR = urinary albumin to creatinine ratio; T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; HHF = hospitalization for heart failure; MACE = major adverse cardiovascular event; GFR = glomerular filtration rate; CV death = cardiovascular death; HR = hazard ratio; CKD = chronic kidney disease; RCT = randomized controlled trial; SGLT2 = sodium-glucose cotransporter 2; KDIGO = The Kidney Disease: Improving Global Outcomes.

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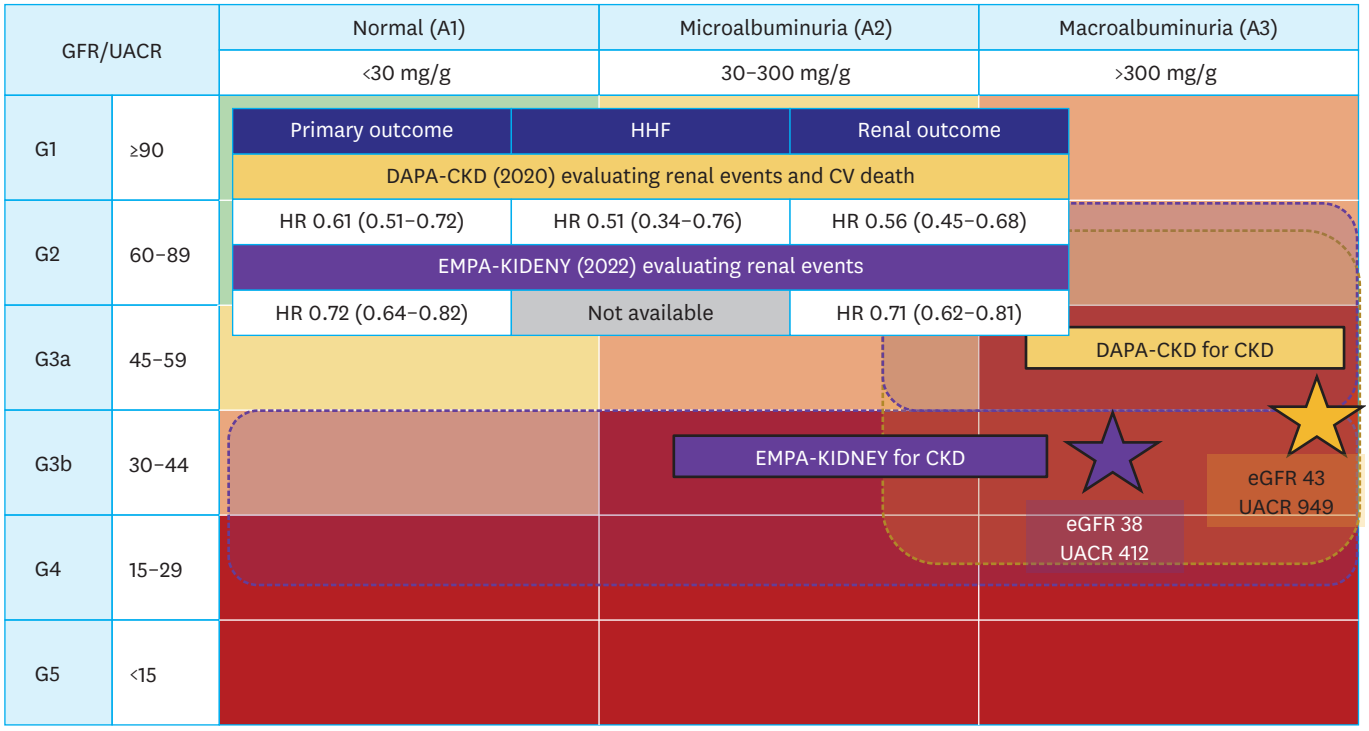

Figure 5. (Continued) Outcomes of RCTs with SGLT2 inhibitors on the KDIGO heat map: (A) RCTs with SGLT2 inhibitors targeting type 2 diabetes mellitus at high risk of cardiovascular disease; (B) RCTs with SGLT2 inhibitors targeting CKD. (A) The KDIGO heat map highlights the EMPA-REG trial (yellow star: mean eGFR: 74 mL/min/1.73 m^2, median UACR: 18 mg/g), CANVAS program trial (blue star: mean eGFR: 77 mL/min/1.73 m^2, median UACR: 12 mg/g), and DECLEARE-TIMI58 trial (green star: mean eGFR: 86 mL/min/1.73 m^2, median UACR: 13 mg/g), with dotted boxes indicating inclusion criteria. Primary outcomes across all trials included a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke. Renal outcomes included a doubling of serum creatinine, the need for renal replacement therapy, or death from renal causes in the EMPA-REG trial, and a sustained ≥40% reduction in the eGFR, the need for renal replacement therapy, or death from renal causes in the CANVAS program and DECLEARE-TIMI58 trial. Treatment effects are presented as HRs (95% confidence interval).
(B) The KDIGO heat map highlights the DAPA-CKD trial (yellow star: mean eGFR: 43 mL/min/1.73 m^2, median UACR: 949 mg/g), and EMPA-KIDNEY trial (purple star: mean eGFR: 38 mL/min/1.73 m^2, median UACR: 412 mg/g), with dotted boxes indicating inclusion criteria. Primary outcomes were a sustained ≥50% reduction in the eGFR, progression to end-stage renal disease or renal or CV death in the DAPA-CKD trial, and a sustained ≥40% reduction in the eGFR, eGFR <10 mL/min/1.73 m^2, end-stage renal disease or death from CV causes in the EMPA-KIDNEY trial. Renal outcomes included a sustained ≥50% reduction in the eGFR, progression to end-stage renal disease or death from renal causes in the DAPA-CKD trial. and a sustained ≥40% reduction in the eGFR, eGFR <10 mL/min/1.73 m^2, or end-stage renal disease in the EMPA-KIDNEY. Treatment effects are presented as HRs (95% confidence interval).
eGFR = estimated glomerular filtration rate; UACR = urinary albumin to creatinine ratio; T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; HHF = hospitalization for heart failure; MACE = major adverse cardiovascular event; GFR = glomerular filtration rate; CV death = cardiovascular death; HR = hazard ratio; CKD = chronic kidney disease; RCT = randomized controlled trial; SGLT2 = sodium-glucose cotransporter 2; KDIGO = The Kidney Disease: Improving Global Outcomes.

As shown in **Table 1** and **Figure 5B**, the DAPA-CKD trial and EMPA-KIDNEY trial, which included CKD patients regardless of diabetes status, demonstrated robust renoprotective effects. The DAPA-CKD trial, which enrolled patients with eGFR 25–75 mL/min/1.73 m^2 and UACR 200–5,000 mg/g, demonstrated an early and substantial 42.9% reduction in UACR, coupled with sustained renal function preservation, despite an initial transient decline in eGFR (**Figure 3B**).[46] Similarly, the EMPA-KIDNEY trial, targeting patients with eGFR 20–45 mL/min/1.73 m^2 or eGFR 45–90 mL/min/1.73 m^2 with UACR >200 mg/g, confirmed robust renoprotective effects, particularly in individuals with high UACR levels.[83] However, a sub-analysis of the EMPA-KIDNEY trial found that patients with UACR <300 mg/g did not show significant reductions on renal events, suggesting that albuminuric CKD remains the primary therapeutic target for SGLT2 inhibitors in preventing future renal complications.

In contrast, the DECLARE-TIMI58 revealed renal benefits even in diabetic patients without elevated UACR, underscoring the broader applicability of SGLT2 inhibitors beyond albuminuric CKD (**Figure 5A**).[84] These findings suggest that mitigation of glomerular hyperfiltration is a central mechanism underlying their renoprotective effects. Furthermore, a meta-analysis of the EMPA-REG, CANVAS Program, and DECLARE-TIMI58 trials revealed consistent reductions in combined renal events, regardless of presence of pre-existing CVD.[73] This reinforces the notions that SGLT2 inhibitors exert a direct renoprotective effects beyond their CV benefits.

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Mineralocorticoid receptor antagonists (MRAs)

Evidence of cardioprotection from clinical trials

Aldosterone influences a wide range of cell types in the heart and kidneys, including endothelial cells, vascular and smooth muscle cells, mesangial cells, podocytes, macrophages, and fibroblasts, thereby promoting pathological processes such as ischemia, inflammation, and fibrosis.[85]

MRAs counteract these effects by inhibiting aldosterone from binding to its receptor, providing significant cardiorenal benefits. Landmark trials of traditional MRAs, such as the RALES and EMPHASIS-HF, have demonstrated significant prognostic improvements in patients with HFrEF receiving beta-blockers and RAS inhibitors.[86,87] In contrast, the TOPCAT trial, which enrolled patients with HFpEF, failed to show significant prognostic benefits.[88] This outcome may partially reflect the inclusion of patients with chronic obstructive pulmonary disease misdiagnosed as HFpEF in outside of America. Furthermore, approximately 30% of patients in the MRA group enrolled in Russia failed to achieve detectable canrenone concentrations, highlighting limitations of the study.[89,90]

Recently, non-steroidal MRAs (e.g., finerenone and esaxerenone) have gained attention for their novel therapeutic potential compared to steroidal MRAs (e.g., spironolactone and eplerenone). Steroidal MRAs bind to mineralocorticoid receptors, translocate into the nucleus, and interact with cofactors, potentially acting as partial agonists that promote the expression of pro-inflammatory and pro-fibrotic genes, albeit small. In contrast, non-steroidal MRAs block cofactor binding without activating these genes, resulting in superior organ-protective effects.[91]

Finerenone, a novel non-steroidal MRA, stands out for its high specificity for mineralocorticoid receptors and balanced distribution to the heart and kidneys. Unlike traditional MRAs, finerenone exerts minimal diuretic effects, resulting in negligible impacts on blood pressure and body weight. These features might lower the risk of hyperkalemia and enhance cardioprotective effects independent of hemodynamic modulation.[91,92]

The FIGARO-DKD trial, which evaluated CV outcomes in patients with diabetic kidney disease (DKD), demonstrated that finerenone significantly reduced major adverse CV events, primarily by lowering heart failure hospitalizations, while having no significant impact on myocardial infarction or stroke (**Table 1** and **Figure 6**).[93] A sub-analysis further demonstrated finerenone reduced the incidence of new-onset heart failure.[94] The FIDELITY pooled analysis of the FIGARO-DKD and FIDELIO-DKD confirmed a 14% reduction in major adverse CV events, partially attributable to fewer treatment discontinuations from hyperkalemia.[95] Interestingly, a pooled analysis of EMPEROR trials suggested that SGLT2 inhibitors may attenuate MRA-induced hyperkalemia, despite not being direct potassium-lowering agents.[96,97]

The FINEARTS-HF trial, which enrolled patients with HFmrEF and HFpEF, demonstrated that finerenone significantly reduced the composite outcomes of CV death and heart failure hospitalizations, primary by decreasing the risk of worsening heart failure (**Table 1** and **Figure 6**).[98]

Evidence of renoprotection from clinical trials

In the FIDELIO-DKD trial, which evaluated renal outcomes in patients with DKD, finerenone demonstrated a significant reduction in UACR by approximately 30% to 40% from baseline, accompanied by an initial dip in eGFR (**Figure 3B**).[47] These findings align with the expert opinion that non-steroidal MRAs exert renoprotective effects, partly by modulating intraglomerular pressure through the regulation of arteriolar resistance and podocyte.[99] The FIDELITY pooled analysis further confirmed the robust renoprotective effects of finerenone in patients with DKD.[95]

Interestingly, a sub-analysis of the FIDELIO-DKD trial did not identify a synergistic effect between finerenone and SGLT2 inhibitors in preventing renal events.[47] In contrast, a sub-analysis of the FIGARO-DKD trial suggested a synergistic effect between these agents in reducing CV events.[93] These findings imply that finerenone may confer more direct cardiac benefits, whereas SGLT2 inhibitors primarily target renal pathways for their protective effects.

The FINEARTS-HF trial, which enrolled patients with HFmrEF and HFpEF, did not demonstrate a significant reduction in renal event risk with finerenone treatment (**Figure 6**).[98] This outcome highlights the need for further investigation into the potential renoprotective benefits of finerenone in patients with CHF.

Glucagon-like peptide-1 (GLP-1) receptor agonists

Evidence of cardioprotection from clinical trials

GLP-1, secreted by L cells in the distal small intestine in response to nutrient intake, binds to GLP-1 receptors on pancreatic beta cell membranes. This interaction increases intracellular cAMP levels, enhancing insulin secretion, delaying gastric emptying, and activating the hypothalamic feeding center, thereby promoting weight loss.[100] While GLP-1 receptor agonists (GLP-1-RAs) are primarily utilized as antidiabetic agents, their CV benefits extend beyond glycemic control and improvements in insulin resistance. Although the precise mechanisms are not fully elucidated, these agents are considered to improve CV outcomes by addressing risk factors such as hypertension and dyslipidemia.[101]

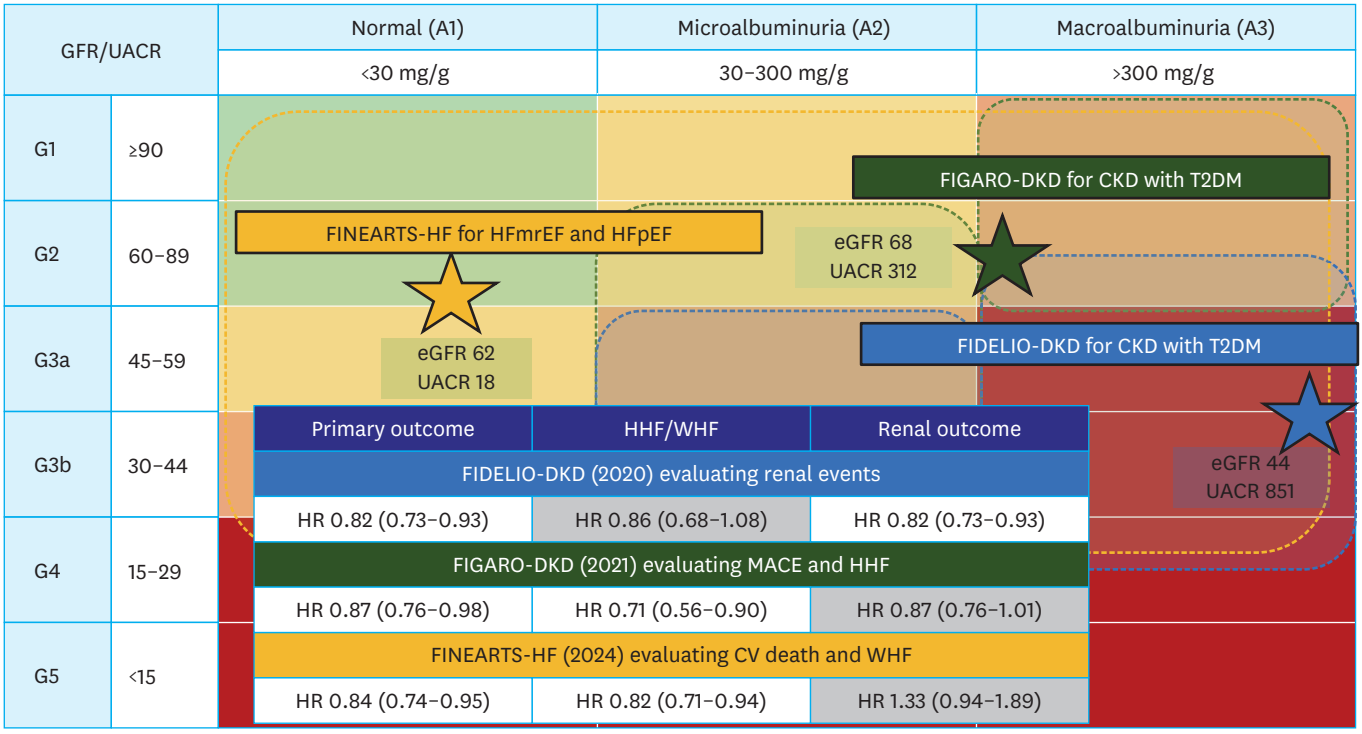

Figure 6. Outcome of randomized controlled trials with non-steroidal mineralocorticoid receptor antagonist on the KDIGO heat map. The KDIGO heat map highlights the FIDELIO-DKD trial (blue star: mean eGFR: 44 mL/min/1.73 m^2, median UACR: 851 mg/g), FIGARO-DKD trial (green star: mean eGFR: 68 mL/min/1.73 m^2, median UACR: 312 mg/g), and FINEARTS-HF trial (yellow star: mean eGFR: 62 mL/min/1.73 m^2, median UACR: 18 mg/g), with dotted boxes indicating inclusion criteria. Primary outcomes included a sustained ≥40% eGFR reduction or renal death in the FIDELIO-DKD trial, CV death, nonfatal myocardial infarction/stroke, or HHF in the FIGARO-DKD trial, and WHF events (either a hospitalization or an urgent visit for HF) or CV death in the FINEARTS-HF trial. Renal outcomes included a sustained ≥57% eGFR reduction (equivalent to a doubling of the serum creatinine level), or renal death in the FIGARO-DKDtrial, a sustained ≥40% eGFR reduction or renal death in the FIDELIO-DKD trial, and a sustained ≥50% eGFR reduction, eGFR <15 mL/min/1.73 m^2, or the need for dialysis or transplantation in the FINEARTS-HF trial. Treatment effects are presented as HRs (95% confidence interval).
GFR = glomerular filtration rate; UACR = urinary albumin to creatinine ratio; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; T2DM = type 2 diabetes mellitus; HHF = hospitalization for heart failure; WHF = worsening heart failure; HR = hazard ratio; MACE = major adverse cardiovascular event; CV death = cardiovascular death; KDIGO = The Kidney Disease: Improving Global Outcomes; HF = heart failure.

The SELECT trial, which targeted obese patients without diabetes mellitus, revealed that a sub-analysis focusing on patients with CHF demonstrated that semaglutide significantly reduced CV events by approximately 35%, with particularly notable benefits observed in patients with HFrEF.[102] Similarly, meta-analyses focusing on HFpEF demonstrated that semaglutide reduced CV death and worsening heart failure events by 31%.[103] The FLOW trial, conducted in patients with DKD, further indicated that semaglutide reduces heart failure events irrespective of baseline HF history and may also prevent de novo heart failure (**Figure 7**).[104] Notably, the SUMMIT trial, which evaluated hard endpoints as primary outcomes, confirmed that trizepatide significantly reduced heart failure events by 38% in obese patients with HFpEF, underscoring its therapeutic potential in this population (**Table 1** and **Figure 7**).[105]

Evidence of renoprotection from clinical trials

Renoprotection effects mediated by GLP-1-RAs likely involves a combination of metabolic, anti-inflammatory, anti-fibrotic, and hemodynamic mechanisms.[106] These agents have demonstrated the ability to enhance urinary sodium excretion by inhibiting sodium reabsorption via the Na+/H+ exchanger in the renal proximal tubules.[107] However, it remains uncertain whether this natriuretic effect contributes to improved glomerular filtration through the TGF mechanism.[108]

The FLOW study was the first clinical trial to specifically evaluate the renoprotective effects of semaglutide in patients with DKD, focusing on renal outcomes designated as the primary endpoint (**Table 1** and **Figure 7**).[48] Semaglutide reduced renal specific events by 21%, accompanied by only a modest initial decline in eGFR, suggesting its potential to preserve renal function without significant adverse effects. Furthermore, a sub-analysis revealed a significant reduced in UACR with GLP-1-RAs, reinforcing their potential role in mitigating kidney damage and slowing disease progression (**Figure 3B**).

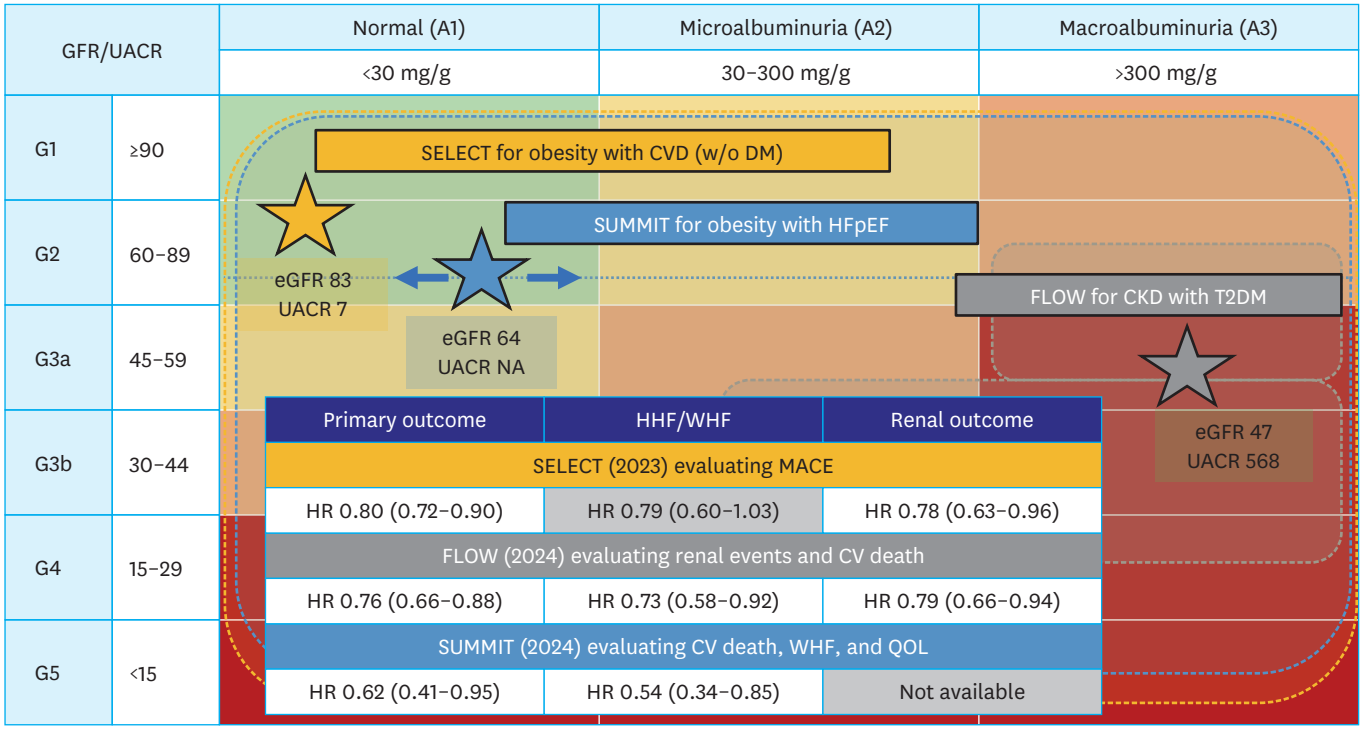

Figure 7. Outcomes of randomized controlled trials with glucagon-like peptide-1 receptor agonists on the KDIGO heat map. The KDIGO heat map highlights the SELECT trial (yellow star: mean eGFR: 83 mL/min/1.73 m^2, median UACR: 7 mg/g), FLOW trial (gray star: mean eGFR: 47 mL/min/1.73 m^2, median UACR: 568 mg/g), and SUMMIT trial (blue star: mean eGFR: 64 mL/min/1.73 m^2), with dotted boxes indicating inclusion criteria. Primary outcomes were a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke in the SELECT trial, a sustained ≥50% eGFR reduction, eGFR <15 mL/min/1.73 m^2, or the need for dialysis/transplantation, or renal or CV death in the FLOW trial, and a composite of death from any cause or WHF event combined with changes at 52 weeks in the the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score and in the 6-minute walk distance in the SUMMIT trial. Renal outcomes included a five-component composite of death from renal causes, the need for dialysis, eGFR <15 mL/min/1.73 m^2, a sustained ≥50% eGFR, or persistent macroalbuminuria in the SELECT trial, a sustained ≥50% eGFR reduction, the need for dialysis/transplantation, eGFR <15 mL/min/1.73 m^2, or death from renal causes in the FLOW trial. Treatment effects are presented as HRs (95% confidence interval).
GFR = glomerular filtration rate; UACR = urinary albumin to creatinine ratio; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; CKD = chronic kidney disease; T2DM = type 2 diabetes mellitus; HHF = hospitalization for heart failure; WHF = worsening heart failure; MACE = major adverse cardiovascular event; HR = hazard ratio; CV death = cardiovascular death; QOL = quality of life; KDIGO = The Kidney Disease: Improving Global Outcomes.

Loop diuretics and tolvaptan

Evidence of cardiorenal protection from clinical trials

Loop diuretics are potent diuretics that effectively relieve intravascular congestion by promoting sodium excretion.[109] However, excessive reduction of intravascular volume could induce hemodynamic instability, manifesting as hypotension, worsening renal function, and increased neurohormonal activation, including elevated aldosterone levels.[110,111] Furthermore, loop diuretics directly inhibit the Na–K–Cl cotransporter NKCC2 at the macula densa, ultimately triggering the RAAS activation.[112] The dose-dependent association between loop diuretic use and adverse clinical outcomes underscores the need to minimize their dosage within an optimized heart failure management framework.[113,114]

Tolvaptan, a selective vasopressin V2 receptor antagonist, promotes free water excretion by targeting aquaporin-2 channels in the renal collecting ducts.[115] The EVEREST trial, the landmark multicenter randomized controlled study, investigated the short- and long-term effects of a 30 mg dose of tolvaptan initiated within 48 hours of hospital admission in patients with acute decompensated heart failure (HFrEF), alongside standard therapy.[116] Although the trial reported no significant differences in all-cause mortality, hospitalization for heart failure, or post-discharge quality of life compared to placebo, these findings require careful interpretation.

Tolvaptan offers unique advantages that may not have been fully captured in the EVEREST trial.[114,117] By increasing intravascular osmolarity through free water clearance, it alleviates systemic congestion without inducing intravascular dehydration, thereby minimizing hemodynamic instability.[118,119] Although tolvaptan does not confer direct renoprotective effects, its capacity to reduce loop diuretic requirements mitigates the risk of renal impairment. Our meta-analysis suggests that even modest reductions

in loop diuretic usage facilitated by tolvaptan are associated with improved renal outcomes and a lower incidence of CV events.[114] Furthermore, our real-world clinical data indicate that tolvaptan use correlate with reduced in-hospital mortality rates compared to conventional diuretic regimens.[120]

PATHWAYS FORWARD IN CARDIORENAL OPTIMIZATION: BRIDGING KNOWLEDGE GAPS AND PERSONALIZING THERAPY

Despite significant advancements in managing CHF, optimizing cardiorenal benefits remain several challenges.

Several critical areas warrant further exploration: 1) Knowledge gaps in advanced CKD: Large-scale clinical trials have traditionally excluded patients with severely reduced eGFR (<25 or 30 mL/min/1.73 m^2), leaving substantial uncertainty about the efficacy and safety of therapies in advanced CKD (**Figure 2**). Expanding research in this population is imperative.[121] 2) The efficacy of heart failure medications and ongoing clinical trials for ESRD patients: The efficacy of heart failure pharmacotherapy in ESRD patients remains uncertain due to the paucity of dedicated clinical trials and conflicting findings in observational studies.[122] However, given the heightened neurohormonal activation in this population, RAS inhibitors and MRAs may provide prognostic benefits.[123] Ongoing clinical trials, including studies on ARNI, MRA, and SGLT2 inhibitors—such as ARNI in Hemodialysis (NCT05498181), ACHIEVE (NCT03020303), and DAPA-HD (NCT05179668)—are expected to generate robust evidence to guide heart failure management in this population. 3) Refinement of renal damage assessment: Current clinical tools for evaluating pathological renal damage lack precision and universal applicability. Developing standardized and sensitive biomarkers or imaging modalities could significantly enhance diagnostic and prognostic accuracy. There is a need for simplified biomarkers that encapsulate the multifaceted pathophysiology of renal dysfunction and provide actionable insights.[124] These could be instrumental in developing precision medicine strategies tailored to individual profiles. 4) Integrating renal function into clinical practice: In real-world setting, declining renal function often limits the use of ARNI, MRA, and SGLT2 inhibitors. Given the risk of rapid renal deterioration or hyperkalemia, some specialists recommend starting at a low dose, with subsequent adjustments or discontinuation if renal function worsens.[125] Conversely, some clinical strategies advocate for the early initiation of dialysis when fluid overload, electrolyte imbalances, and uremic toxin accumulation become unmanageable despite necessary medications. Due to the limited availability of robust evidence, current treatment decisions largely rely on specialist expertise and the clinical judgment of the attending physician. Addressing this gap is essential for optimizing individualized treatment strategies. 5) Mechanistic insights into combination therapies (**Figure 8**): While individual pharmacologic agents exhibit renoprotective effects, the potential synergistic mechanisms among drug combinations, such as ARNI, SGLT2 inhibitors, MRAs, and GLP-1-RAs, remain underexplored.[126] Comprehensive understanding of optimal regimens, particularly with cardioprotective agents, and adjustments in loop diuretic usage is vital to balancing efficacy with safety. To enhance cardiorenal benefits by heart failure pharmacotherapies avoiding adverse effects, optimal combination in each patient profile should be taken into consideration.

CONCLUSION

Most heart failure medications introduced since the 1990s, except for beta-blockers, have demonstrated renoprotective benefits. These agents not only provide significant clinical advantages for CHF patients but also help prevent the onset of heart failure and the progression of renal dysfunction in high-risk populations. To maximize their cardiorenal benefits while minimizing adverse events, careful consideration of combination pharmacotherapies tailored to each patient's profile is essential in the future.

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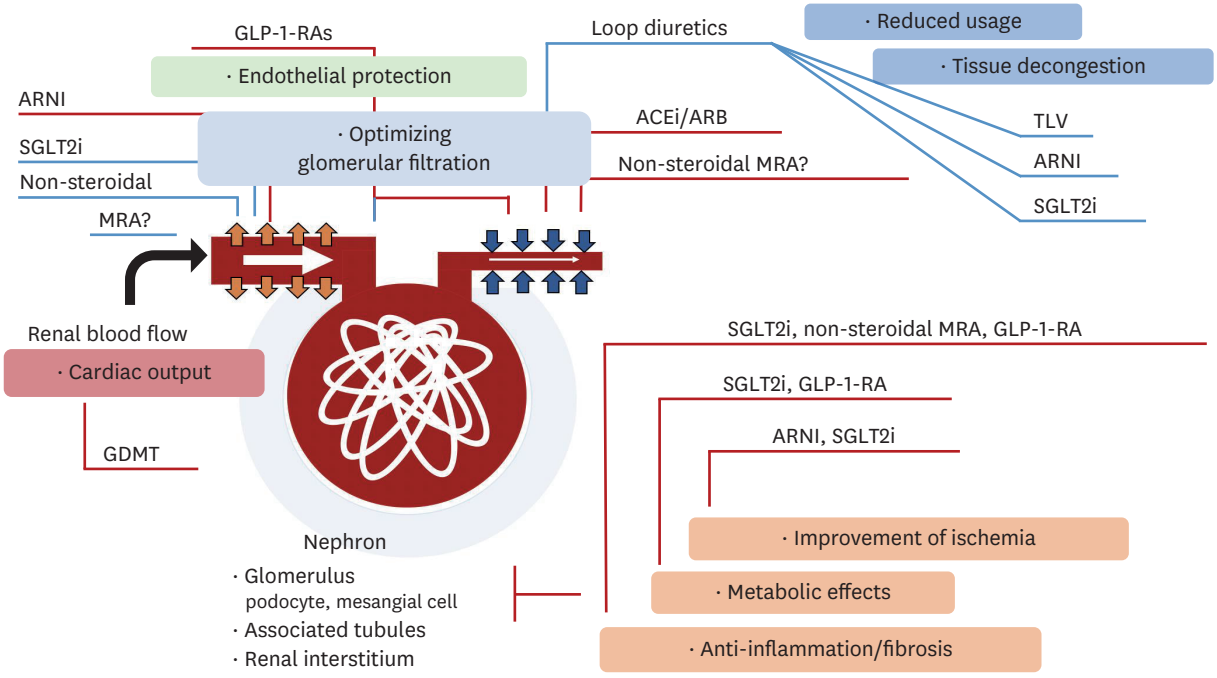

Figure 8. Overview of novel heart failure therapies and renoprotective mechanism.
GLP-1-RA = glucagon-like peptide-1 receptor agonist; ARNI = angiotensin receptor-neprilysin inhibitor; SGLT2i = sodium-glucose cotransporter 2 inhibitor; MRA = mineralocorticoid receptor antagonists; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; TLV = tolvaptan; GDMT = guideline-directed medical therapy.

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Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Kinugawa K; Data curation: Izumida T, Kinugawa K; Formal analysis: Kinugawa K; Investigation: Izumida T; Methodology: Izumida T; Project administration: Kinugawa K; Resources: Izumida T, Kinugawa K; Supervision: Kinugawa K; Validation: Izumida T, Kinugawa K; Visualization: Izumida T, Kinugawa K; Writing - original draft: Izumida T; Writing - review & editing: Izumida T, Kinugawa K.

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