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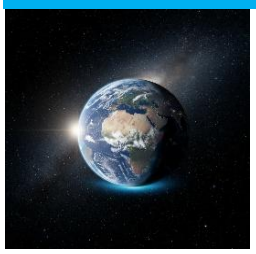

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SGLT2 Inhibitors in Heart Failure with Coexisting Chronic Kidney Disease

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ABSTRACT

Background. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have evolved from their origins as antihyperglycemic agents to become a cornerstone of cardiorenal therapy. The high prevalence of coexisting heart failure (HF) and chronic kidney disease (CKD) creates a complex clinical syndrome where traditional glucose-centric management is insufficient.

Aim. To provide an exhaustive narrative scientific review of the clinical, molecular, and guideline-driven evidence for SGLT2 inhibitors in patients with concurrent heart failure and chronic kidney disease, emphasizing outcomes that transcend glycemic control.

Material and methods. A narrative literature review was conducted using PubMed/MEDLINE, Embase, and the Cochrane Library for articles published between January 2015 and January 2026. Keywords included "SGLT2 inhibitors", "heart failure", "chronic kidney disease", "eGFR", "albuminuria", and "cardiorenal syndrome".

Results. Large-scale randomized controlled trials (DAPA-HF, EMPEROR-Reduced, DAPA-CKD, and EMPA-KIDNEY) and recent meta-analyses like SMART-C (2025) demonstrate that SGLT2 inhibitors reduce cardiovascular death and heart failure hospitalizations by approximately 25%, while slowing renal progression by 30-40% across various eGFR and albuminuria strata. These benefits are mediated through the restoration of tubuloglomerular feedback, metabolic switching toward oxygen-efficient ketone bodies, and direct anti-inflammatory pathways.

Conclusions. SGLT2 inhibitors are foundational therapies for the cardiorenal axis. Their use is now recommended down to an eGFR of 20 mL/min/1.73 m², with benefits extending into advanced CKD stages. Clinicians must integrate these agents early in the disease course to maximize organ preservation and survival.

Key words: SGLT2 inhibitors, heart failure, chronic kidney disease, cardiorenal protection, eGFR dip, empagliflozin, dapagliflozin.

Introduction

The evolution of sodium-glucose cotransporter 2 (SGLT2) inhibitors from specialized diabetic medications to broad-spectrum cardiorenal protective agents represents one of the most significant pharmacological breakthroughs of the 21st century. Originally identified through the study of phlorizin—a natural dihydrochalcone glycoside discovered in 1835 in the root bark of apple trees—early researchers noted its ability to induce glycosuria.[1] However, the therapeutic potential of phlorizin was limited by poor bioavailability and non-selective inhibition of both SGLT1 and SGLT2.[1] It was only with the development of C-glucoside analogs that modern gliflozins achieved the metabolic stability and selectivity required for human clinical use.[1]

The modern history of SGLT2 inhibitors was catalyzed by an unexpected regulatory shift. In 2008, following concerns regarding the cardiovascular safety of rosiglitazone, the United States Food and Drug Administration (FDA) mandated that all new antihyperglycemic therapies undergo rigorous cardiovascular outcome trials (CVOTs) to prove they did not increase major adverse cardiovascular events.[3] The first of these trials, EMPA-REG OUTCOME, published in 2015, did more than prove safety; it demonstrated a profound 35% reduction in hospitalizations for heart failure and a 38% reduction in cardiovascular death among patients with type 2 diabetes mellitus (T2DM).[3] These results signaled that SGLT2 inhibitors were influencing pathophysiological pathways far removed from simple glycemic control.

Heart failure (HF) and chronic kidney disease (CKD) are inherently linked through what is commonly described as cardiorenal syndrome. In this bidirectional pathological state, the impairment of one organ leads to the injury or dysfunction of the other.[5] Approximately 40% to 50% of patients with heart failure also exhibit an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m², a threshold that signifies the presence of CKD.[5] This coexistence is not merely coincidental but is driven by shared risk factors such as hypertension, atherosclerosis, and metabolic syndrome, as well as systemic pathways including neurohumoral activation, oxidative stress, and chronic inflammation.[8] Once both diseases are present, the prognosis for the patient deteriorates rapidly, with each condition serving as a powerful independent predictor of mortality and hospitalization.[5]

The standard of care for these patients has historically focused on angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and mineralocorticoid receptor antagonists (MRAs). While effective, these therapies often face challenges in patients with coexisting CKD, as fluctuations in renal function and the risk of hyperkalemia frequently limit their up-titration.[10] SGLT2 inhibitors have emerged as a unique class that not only provides direct benefits to both organs but also acts as an "enabler" for other therapies by stabilizing potassium levels and reducing the risk of acute kidney injury.[10]

This review intends to provide a deep, expert-level analysis of the state of knowledge regarding SGLT2 inhibitors in the coexisting populations of heart failure and chronic kidney disease. It explores the landmark clinical trials that have redefined treatment protocols, the complex molecular mechanisms through which these drugs exert their effects, and the latest 2024-2026 guidelines that recommend their use across the entire spectrum of renal and cardiac dysfunction.

Research materials and methods

The evidence synthesized in this narrative review was gathered through a rigorous literature search strategy designed to capture the transition from early cardiovascular outcome trials to the most contemporary meta-analyses and clinical guidelines available as of early 2026. The objective was to identify peer-reviewed articles that specifically addressed the efficacy, safety, and mechanisms of SGLT2 inhibitors in patients where heart failure and chronic kidney disease overlap.

A structured search was performed across PubMed/MEDLINE, Embase (Ovid), and the Cochrane Library. The search period was restricted to articles published between January 1, 2015, and January 9, 2026, ensuring the inclusion of landmark trials such as DAPA-HF, EMPEROR-Reduced, DAPA-CKD, and EMPA-KIDNEY, as well as the 2025 SMART-C meta-analysis results.[14]

The following search strings and Boolean combinations were utilized:

- ("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "SGLT2 inhibitors" OR "gliflozins" OR "empagliflozin" OR "dapagliflozin" OR "canagliflozin" OR "sotagliflozin")
- AND ("Heart Failure"[Mesh] OR "HFpEF" OR "HFrEF" OR "congestive heart failure")
- AND ("Renal Insufficiency, Chronic"[Mesh] OR "CKD" OR "chronic kidney disease" OR "kidney failure")
- AND ("eGFR" OR "albuminuria" OR "proteinuria" OR "cardiorenal syndrome")

The initial search yielded over 1,500 records. Screening was conducted by reviewing titles and abstracts for relevance to the primary topic of SGLT2 inhibition in coexisting cardiorenal disease. Eligible publications included randomized controlled trials (RCTs), systematic reviews, large-scale meta-analyses, and official clinical practice guidelines from organizations such as the European Society of Cardiology (ESC), the American Heart Association (AHA), and Kidney Disease: Improving Global Outcomes (KDIGO).[14]

Priority was given to studies reporting hard endpoints, including cardiovascular death, hospitalization for heart failure, doubling of serum creatinine, or a sustained 40-50% decline in eGFR.[5] Furthermore, mechanistic studies exploring molecular pathways such as tubuloglomerular feedback, ketogenesis, and inflammatory cytokine modulation were included to provide a comprehensive understanding of the "pleiotropic" effects often cited in the literature.[21, 47] Non-peer-reviewed literature, conference abstracts without full datasets, and purely animal studies without clear clinical translational value were excluded from the final analysis.[14]

Results:

Clinical Evidence in Heart Failure with Reduced Ejection Fraction (HFrEF)

The treatment of HFrEF, defined by a left ventricular ejection fraction (LVEF) of ≤40%, has been revolutionized by two primary trials that established SGLT2 inhibitors as an essential component of quadruple therapy alongside ARNi/ACEi/ARB, beta-blockers, and MRAs.[18]

The DAPA-HF trial (Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure) was a pioneering study that enrolled 4,744 patients with chronic HFrEF, regardless of their diabetes status. Patients were randomized to receive dapagliflozin 10 mg once daily or placebo in addition to recommended background therapy.[4] The primary composite outcome—worsening heart failure (hospitalization or an urgent visit requiring intravenous therapy) or cardiovascular death—occurred in 16.3% of the dapagliflozin group compared to 21.2% in the placebo group.[4] This represented a 26% relative risk reduction (HR 0.74; 95% CI 0.65–0.85; $P < 0.001$). Crucially, the benefit was consistent in patients with an eGFR as low as 30 mL/min/1.73 m², and the trial demonstrated that dapagliflozin slowed the rate of eGFR decline compared to placebo.[5]

The EMPEROR-Reduced trial (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) followed, randomizing 3,730 patients to empagliflozin 10 mg or placebo. This trial targeted a population with more advanced heart failure, evidenced by lower mean LVEF (27% vs. 31% in DAPA-HF) and higher median NT-proBNP levels

(approximately 1900 pg/mL vs. 1430 pg/mL).[20] Despite the increased severity, empagliflozin reduced the primary composite outcome of cardiovascular death or hospitalization for heart failure by 25% (HR 0.75; 95% CI 0.65–0.86; P < 0.0001).[3]

A comparison of the HFrEF trial results reveals a remarkable consistency in efficacy despite differences in patient risk profiles.

Table 1. Comparison of clinical and renal outcomes between Dapagliflozin (DAPA-HF) and Empagliflozin (EMPEROR-Reduced) trials

Trial Feature	**DAPA-HF (Dapagliflozin)**	**EMPEROR-Reduced (Empagliflozin)**
Participants	4,744	3,730
Median NT-proBNP	1,437 pg/mL	1,907 pg/mL
Mean LVEF	31.1%	27.2%
Primary Outcome HR	0.74 (0.65–0.85)	0.75 (0.65–0.86)
Total HHF Reduction	30%	30%
Renal Outcome HR	0.71 (0.44–1.16)*	0.50 (0.32–0.77)
eGFR Slope Difference	+1.76 mL/min/yr	+1.73 mL/min/yr

**Renal outcome definition differed; DAPA-HF was not powered for this endpoint.*

Source: [5, 27]

In the EMPEROR-Reduced trial, the renoprotective benefit was particularly striking. The drug slowed the progressive decline in kidney function by 1.73 mL/min/1.73 m² per year compared with the placebo.[27] This benefit was observed regardless of the baseline presence of CKD, confirming that SGLT2 inhibitors provide a safety net for renal function even in patients whose primary clinical presentation is advanced heart failure.[10]

Evidence in Heart Failure with Mildly Reduced and Preserved Ejection Fraction (HFpEF)

HFpEF (LVEF ≥50%) and HFmrEF (LVEF 41–49%) have historically lacked effective therapies that improve hard clinical outcomes. This therapeutic vacuum was addressed by the EMPEROR-Preserved and DELIVER trials, which demonstrated that SGLT2 inhibitors are the

first class of drugs to reliably reduce the risk of heart failure hospitalization across the entire spectrum of ejection fraction.[10]

EMPEROR-Preserved randomized 5,988 patients with heart failure and an LVEF of more than 40%. The trial showed that empagliflozin reduced the primary composite outcome of cardiovascular death or hospitalization for heart failure by 21% (HR 0.79; 95% CI 0.69–0.90).[10] This reduction was primarily driven by a 29% lower risk of hospitalization for heart failure. Similar to the HFrEF trials, the effect was consistent across subgroups with and without diabetes and across a wide range of baseline eGFR values.[10]

The DELIVER study evaluated dapagliflozin in 6,263 patients with HF and an LVEF >40%. The primary endpoint occurred in 16.4% of the dapagliflozin group and 19.5% of the placebo group, reflecting an 18% reduction (HR 0.82; 95% CI 0.73–0.92; $P < 0.001$).[15] A pooled meta-analysis of DAPA-HF and DELIVER demonstrated a significant reduction in both cardiovascular and all-cause mortality, reinforcing the essential role of SGLT2 inhibitors in comprehensive heart failure management regardless of the pumping capacity of the heart.[2]

An interesting observation in the HFpEF trials was the impact on patient-reported outcomes. Both trials utilized the Kansas City Cardiomyopathy Questionnaire (KCCQ) to measure symptoms and physical limitations. Patients on SGLT2 inhibitors showed early and sustained improvements in KCCQ total symptom scores, suggesting that these drugs not only prevent major clinical events but also significantly enhance the daily quality of life for patients with HF and CKD.[10]

Dedicated Renal Outcome Trials and the 2025 SMART-C Meta-Analysis

While heart failure trials consistently showed renal benefits as secondary endpoints, the CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials were designed specifically to evaluate SGLT2 inhibitors as primary therapies for chronic kidney disease.[26, 45]

The DAPA-CKD trial included 4,304 patients with an eGFR of 25 to 75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio (UACR) of 200 to 5000 mg/g. The trial was stopped early because of overwhelming efficacy. Dapagliflozin reduced the risk of a composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes by 39% (HR 0.61; 95% CI 0.51–0.72).[26]

The EMPA-KIDNEY trial further expanded the evidence by including a broader patient population, including those with lower levels of albuminuria and an eGFR as low as 20

mL/min/1.73 m². Among 6,609 participants, empagliflozin reduced the primary outcome of kidney disease progression or cardiovascular death by 28% (HR 0.72; 95% CI 0.64–0.82).[15]
In 2025, the SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium (SMART-C) published a comprehensive meta-analysis of 10 large trials involving 70,361 participants.[16] This study provides the definitive data on the efficacy of SGLT2 inhibitors across the spectrum of kidney function and albuminuria.

Table 2. Subgroup Analysis of Hazard Ratios for Chronic Kidney Disease Progression According to Baseline eGFR, Albuminuria, and Diabetes Status

Subgroup Category	**Hazard Ratio (HR) for CKD Progression**	**95% Confidence Interval (CI)**
Baseline eGFR Subgroups		
≥60 mL/min/1.73 m²	0.61	0.52–0.71
45 to <60	0.57	0.47–0.70
30 to <45	0.64	0.54–0.75
<30 (Stage 4)	0.71	0.60–0.83
Albuminuria (UACR) Subgroups		
≤30 mg/g	0.58	0.44–0.76
>30–300 mg/g	0.74	0.57–0.96
>300 mg/g	0.57	0.52–0.64
Diabetes Status		
With Diabetes	0.62	0.56–0.69
Without Diabetes	0.64	0.55–0.73

Source: [16]

The SMART-C analysis confirmed that SGLT2 inhibitors reduced the risk of CKD progression regardless of the presence of diabetes or the initial level of kidney function. Most remarkably,

the analysis showed that even patients with stage 4 CKD (eGFR < 30 mL/min/1.73 m²) or those with minimal albuminuria derived significant kidney-protective benefits.[16] This has profound implications for clinical practice, supporting the routine use of SGLT2 inhibitors across the full spectrum of CKD severity.[31]

Molecular and Physiological Mechanisms of Protection

The benefits of SGLT2 inhibitors are "pleiotropic", meaning they act through multiple integrated pathways that extend beyond blood sugar reduction. To understand their success in coexisting HF and CKD, it is essential to explore these granular mechanisms.

Tubuloglomerular Feedback and Glomerular Hemodynamics

In states of chronic hyperglycemia or early heart failure, the kidney undergoes maladaptive changes. High levels of filtered glucose lead to the upregulation of SGLT2 in the proximal tubule. This increases the reabsorption of both glucose and sodium, resulting in a decrease in the delivery of sodium to the macula densa in the distal tubule.[21] The juxtaglomerular apparatus interprets this reduced sodium delivery as a signal of low effective circulating volume, triggering a feedback loop that causes the vasodilation of the afferent arteriole. This leads to glomerular hyperfiltration and increased intraglomerular pressure, which eventually causes structural damage to the nephrons.[23]

SGLT2 inhibitors reverse this process. By blocking sodium and glucose reabsorption in the proximal tubule, they increase the delivery of sodium to the macula densa. This restores tubuloglomerular feedback (TGF), inducing vasoconstriction of the afferent arteriole.[12] This reduces intraglomerular pressure and "off-loads" the kidney. This hemodynamic mechanism explains the characteristic initial "dip" in eGFR observed after the initiation of SGLT2 inhibitors—a transient, reversible decline that signifies a reduction in the mechanical stress on the glomerular filtration barrier.[10]

Metabolic Reprogramming and the "Thrifty Ketone" Hypothesis

SGLT2 inhibitors induce a unique metabolic state by promoting glycosuria. This loss of calories leads to a shift in energy substrate utilization away from glucose and toward fatty acid oxidation and ketogenesis.[8] The increased levels of ketone bodies, specifically beta-hydroxybutyrate, provide an alternative, more oxygen-efficient energy source for the heart and kidneys. Ketones require less oxygen per unit of ATP produced compared to fatty acids, which

is particularly beneficial in the context of the hypoxic environment seen in failing hearts and kidneys.[9]

Furthermore, this metabolic shift activates nutrient-sensing pathways such as SIRT1 and HIF-2alpha. These pathways promote autophagy—a cellular "cleanup" process that removes damaged mitochondria (mitophagy) and protein aggregates—thereby improving cellular quality control and reducing oxidative stress.[21]

Modulation of Sodium-Hydrogen Exchangers (NHE)

Another critical mechanism involves the indirect inhibition of the sodium-hydrogen exchangers NHE1 (in the heart) and NHE3 (in the kidney). In patients with heart failure, NHE1 is often overactive, leading to increased intracellular sodium and calcium, which promotes oxidative stress and cellular injury.[8] SGLT2 inhibitors have been shown to bind to and inhibit NHE1, which reduces the toxic accumulation of intracellular calcium in cardiomyocytes, thereby improving diastolic function and reducing the risk of arrhythmias.[22]

In the kidney, NHE3 inhibition at the proximal tubule works synergistically with SGLT2 inhibition to promote natriuresis. This leads to a reduction in interstitial edema and renal congestion without the compensatory activation of the sympathetic nervous system that is often seen with traditional loop diuretics.[21]

Anti-inflammatory and Anti-fibrotic Effects

SGLT2 inhibitors exhibit significant anti-inflammatory properties that are crucial for limiting organ damage in chronic cardiorenal syndrome. They have been shown to inhibit the NLRP3 inflammasome, a multi-protein complex that triggers the release of pro-inflammatory cytokines such as IL-1beta and IL-18.[35] By suppressing this inflammatory cascade, SGLT2 inhibitors reduce vascular and myocardial stiffness and slow the progression of renal interstitial fibrosis[9].

Table 3. Multi-level mechanisms underlying the cardioprotective and renoprotective effects of SGLT2 inhibitors

Mechanism Category	Cardiac Effect	Renal Effect
Hemodynamic	Reduced preload (diuresis) and afterload (BP drop)	Reduced intraglomerular pressure (TGF restoration)
Metabolic	Fuel switch to ketones; improved mitochondrial efficiency	Reduced tubular workload; enhanced oxygen delivery
Cellular	Autophagy/Mitophagy activation; NHE1 inhibition	Autophagy induction; NHE3 inhibition; reduced hypoxia
Neurohumoral	Sympathoinhibition; reduced RAS activation	Attenuated RAS activation; local oxygen sensing (HIF)
Structural	Reduced fibrosis and adverse remodeling	Inhibited interstitial fibrosis and podocyte loss

Source: [21,48]

Evidence in Special Populations: The Elderly and Acute Hospitalization

The versatility of SGLT2 inhibitors has led to their investigation in populations that were previously considered "high risk" for these agents.

Older Adults (≥ 65 and ≥ 75 years)

Concerns about volume depletion, dehydration, and urinary tract infections initially caused hesitancy in prescribing SGLT2 inhibitors to the elderly. However, a 2025 systematic review and meta-analysis of RCTs specifically focusing on adults ≥ 65 years with cardiovascular disease provided robust evidence for their use.[14]

The study found that in this older population, SGLT2 inhibitors significantly reduced the risk of the primary composite outcome of HHF, urgent HF visits, and cardiovascular death (HR 0.75; 95% CI 0.67–0.83). The benefits remained significant even in the subgroup ≥ 75 years (HR 0.71; 95% CI 0.57–0.88). While the risk of genital infections was elevated (RR 3.18), the overall risk of serious adverse events was actually lower in those treated with SGLT2 inhibitors

(RR 0.92).[14] This suggests that the survival and organ-protection benefits far outweigh the risks of easily managed local infections in older adults.

Initiation During Acute Heart Failure (AHF)

The timing of SGLT2 inhibitor initiation has also been a subject of intense study. The EMPULSE and DICTATE-AHF trials evaluated the safety and efficacy of starting these drugs during the early phase of hospitalization for acute heart failure.[10]

The EMPULSE trial demonstrated that starting empagliflozin at a median of 3 days post-admission led to a "clinical benefit" (a composite of death, heart failure events, and KCCQ score improvement) within 90 days. The DICTATE-AHF trial showed that dapagliflozin could be safely started on the first day of hospitalization, leading to enhanced diuresis and a reduction in the duration of intravenous loop diuretic use.[10] These results advocate for the "early and widespread" use of SGLT2 inhibitors as part of guideline-directed therapy, starting even before the patient leaves the hospital.[10]

Safety and Tolerability Profile in Cardiorenal Disease

While SGLT2 inhibitors are generally well-tolerated, specific risks must be managed to ensure patient safety and adherence.

Genital Mycotic Infections (GMI)

The most common side effect is a 2- to 4-fold increase in the risk of GMIs due to the presence of glucose in the urine.[12] These infections are more frequent in women and in uncircumcised men. Most cases are mild and can be managed with standard antifungal treatments without the need for drug discontinuation.[12]

Diabetic Ketoacidosis (DKA)

A rare but serious complication is DKA, which often presents with near-normal blood glucose levels (euglycemic DKA).[2] The risk is primarily limited to patients with diabetes. To mitigate this risk, patients should be educated on "sick day rules"—temporarily withholding the medication during times of major surgery, prolonged fasting, or critical illness.[17]

Acute Kidney Injury and the "eGFR Dip"

Observational reports initially suggested an increased risk of AKI. However, comprehensive meta-analyses and data from major trials like CREDENCE have shown that SGLT2 inhibitors actually reduce the risk of serious AKI events.[13] The initial eGFR dip (a 3-10% decline) is a hemodynamic effect, not a sign of tubular injury. In the CREDENCE trial, an initial eGFR dip of > 30% occurred in only 0.5% of patients and was not associated with long-term kidney function loss.[33]

Other Rare Concerns: Amputation and Fournier's Gangrene

Early data from the CANVAS program suggested an increased risk of lower-limb amputations with canagliflozin. However, this finding was not replicated in the subsequent CREDENCE trial or any other large-scale RCT of empagliflozin or dapagliflozin.[12] Similarly, while the FDA has issued warnings about Fournier's gangrene (necrotizing fasciitis of the perineum), the absolute risk is extremely low, and meta-analyses of over 42,000 patients have found no significant difference in the risk of Fournier's gangrene between SGLT2 inhibitors and placebo.[12]

Discussion

The clinical and mechanistic data reviewed here demonstrate that SGLT2 inhibitors represent a paradigm-shifting intervention in the management of coexisting heart failure and chronic kidney disease. The synthesis of this information leads to several higher-order insights regarding current practice and future therapeutic directions.

The Shift to Unified Cardiorenal Management

Historically, heart failure and chronic kidney disease were treated as separate entities, often leading to fragmented care. The evidence from DAPA-HF, EMPEROR-Reduced, and EMPA-KIDNEY suggests that these diseases are so pathophysiologically intertwined that they should be approached with a unified "cardiorenal" strategy.[39] SGLT2 inhibitors act as the ideal bridging therapy. By restoring tubuloglomerular feedback, they protect the kidney while simultaneously reducing the cardiac workload through preload reduction and metabolic optimization.[21]

Furthermore, the 2025 SMART-C meta-analysis results confirm that the benefits of SGLT2 inhibitors are consistent across the entire spectrum of kidney function.[16] This highlights a

critical trend: the move away from using these drugs solely for "diabetic control" toward using them as "organ-protection" agents. The fact that non-diabetic patients with CKD or HF derive similar relative benefits suggests that the underlying mechanisms of cardiorenal protection—hemodynamic stabilization, metabolic shifting, and anti-inflammation—are universal pathological drivers.[21]

Understanding and Communicating the eGFR Dip

One of the greatest barriers to the widespread implementation of SGLT2 inhibitors in patients with CKD is clinician hesitation regarding the "initial eGFR dip".[10] This review clarifies that the dip is not a sign of toxicity but rather a reflection of the restoration of healthy tubuloglomerular feedback. Just as clinicians have learned to tolerate a slight rise in creatinine when starting ACE inhibitors, they must learn that the SGLT2 inhibitor dip is a marker of therapeutic engagement.[33]

The long-term implications are profound. While the treatment group starts with a lower eGFR, the slope of decline is significantly shallower compared to the placebo. Long-term trajectories typically show a "crossover point" around 12 to 18 months, after which the SGLT2 inhibitor group has better-preserved renal function than the control group.[10] Education for both providers and patients is essential to avoid the premature discontinuation of these life-saving medications.

Expanding Guidelines and the Advanced CKD Frontier

The evolution of guidelines from 2021 to 2025 reflects a growing confidence in the safety and efficacy of SGLT2 inhibitors in advanced disease.

Table 4. Key 2024 Guideline Recommendations for SGLT2 Inhibitor Use in CKD, Heart Failure, and Type 2 Diabetes

Organization	Guideline Update	Key SGLT2i Recommendation
KDIGO	2024 Update	Recommended for adults with CKD and eGFR ≥ 20 mL/min/1.73 m² with UACR ≥ 200 mg/g or heart failure.[17]
ESC	2024 Supplement	Class I, Level A for heart failure across the entire LVEF spectrum and for prevention in diabetic CKD.[10]
AHA/ACC	2024 Focused Update	Class I recommendation for symptomatic HFrEF and Class IIa/I for HFpEF/HFmrEF.[19]
ADA	2024/2025 Standards	First-line treatment with metformin for patients with T2D and CKD (eGFR ≥ 20).[19]

Source: [17, 19]

The recent recommendation to initiate therapy down to an eGFR of 20 mL/min/1.73 m² represents a significant expansion of the eligible population.[34] Even more striking is the consensus that once initiated, the medication can and should be continued until the patient starts dialysis, regardless of further eGFR decline.[17] This suggests that the cardioprotective and renoprotective benefits persist even at the very edges of renal viability.

Challenges and Unresolved Questions

Despite the "emphatic win" for SGLT2 inhibitors, some questions remain. The 2025 meta-analysis by Singh et al. and the SMART-C consortium noted that while relative benefits are consistent, absolute benefits are lower in patients with minimal albuminuria.[16] For example, the number needed to treat (NNT) to prevent one case of CKD progression in a non-diabetic patient with UACR < 200 mg/g may be as high as 358, compared to an NNT of only 25 for those withUACR ≥ 200 mg/g.[16] This raises questions about cost-effectiveness in low-risk

populations that will likely be addressed as generic versions of gliflozins become more widely available.

Another emerging controversy involves "lean" CKD patients (BMI < 25). Some evidence suggests that the renal benefits may be attenuated in this group, potentially because their disease is driven more by genetic or inflammatory factors than by the hyperfiltration and sodium retention seen in obesity and diabetes.[26] Dedicated trials are needed for these underrepresented subgroups, including pediatric patients and those with rare glomerulopathies.[39]

Finally, the role of SGLT2 inhibitors in Stage 5 CKD (on dialysis) or in renal transplant recipients remains unclear. While current trials were not designed to include these populations, pilot studies are ongoing to see if the systemic anti-inflammatory and cardiovascular benefits can be realized in the most advanced stages of renal failure.[21]

Conclusions

The transformation of SGLT2 inhibitors from diabetic medications to foundational therapies for the cardiorenal axis is complete. This review has demonstrated that in the high-risk population where heart failure and chronic kidney disease coexist, SGLT2 inhibitors provide an unparalleled level of protection. By reducing cardiovascular death, heart failure hospitalizations, and the progression to end-stage kidney disease, they address the most critical needs of patients suffering from cardiorenal syndrome.

The mechanisms through which these drugs work—restoring tubuloglomerular feedback, optimizing myocardial energy metabolism through ketogenesis, and suppressing systemic inflammation—explain why their benefits are independent of glycemic status and ejection fraction. The clinical evidence from trials like DAPA-HF, EMPEROR-Reduced, DAPA-CKD, and EMPA-KIDNEY, synthesized in the 2025 SMART-C meta-analysis, provides the clearest support to date for their routine use down to an eGFR of 20 mL/min/1.73 m^2.

For clinicians, the primary takeaway is that SGLT2 inhibitors should no longer be viewed as "add-on" therapies for diabetes. They are foundational agents that should be initiated as early as possible in the disease course of heart failure or chronic kidney disease to maximize organ preservation. While safety monitoring for genital infections and "sick day" ketoacidosis is necessary, the overall tolerability and the profound reduction in the risk of serious adverse events like acute kidney injury make them a remarkably safe option even for elderly and advanced-stage patients. As we look toward the next decade of cardiorenal medicine, the integration of SGLT2 inhibitors as a central pillar of therapy is not just recommended; it is essential for improving the survival and quality of life for millions of patients worldwide.

Disclosure

Author's Contribution

Conceptualization: Nikodem Cieleban

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