

SGLT2 Inhibitors in Heart Failure and Chronic Kidney Disease: Expanding Therapeutic Horizons Beyond Glycemic Control

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Abstract

Heart failure (HF) and chronic kidney disease (CKD) are closely related clinical diseases that significantly increase morbidity and death worldwide. The co-occurrence of both conditions is frequently referred to as the “cardio-renal syndrome,” in which the failure of one organ hastens the decline of the other. The original purpose of sodium–glucose cotransporter-2 (SGLT2) inhibitors was to treat type 2 diabetic mellitus (T2DM) by reducing blood sugar levels. Nevertheless, new data from several sizable randomized controlled studies has shown that these medications have important protective effects on the heart and kidneys that are not dependent on glucose control. The growing therapeutic use of SGLT2 inhibitors in the treatment of chronic renal disease and heart failure is highlighted in this study. Evidence from seminal clinical trials, including DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DAPA-CKD, and CREDENCE, is presented to demonstrate their capacity to lower cardiovascular mortality, halt the progression of renal impairment, and reduce hospitalizations for heart failure. A summary is also provided of the possible mechanisms that underlie these advantages such as natriuresis, decreased intraglomerular pressure, enhanced myocardial energy consumption, and anti-inflammatory actions. Regardless of whether diabetes is present or not, the available data generally supports the use of SGLT2 inhibitors as cornerstone treatments for patients with heart failure and chronic renal disease.

Keywords: SGLT2 inhibitors, heart failure, chronic kidney disease, cardio-renal protection, dapagliflozin

INTRODUCTION

Two of the biggest global public health issues are heart failure and chronic renal disease. Cardio-renal syndrome, a bidirectional interaction between the heart and kidneys, makes it more difficult to make treatment decisions and track the course of the disease. Patients with HF frequently develop CKD, and conversely, CKD greatly raises the risk of HF, hospitalization, and death.

For decades, results in CKD and HF remained less than ideal despite advancements in medication. The introduction of SGLT2 inhibitors has significantly changed the management of heart failure and chronic kidney disease [1, 2]. These medications demonstrated significant reductions in heart failure hospitalization, kidney disease progression, and cardiovascular death in large clinical trials [1, 3, 4].

The mechanistic pathways through which SGLT2 inhibitors provide cardio-renal protection are illustrated in Figure 1.

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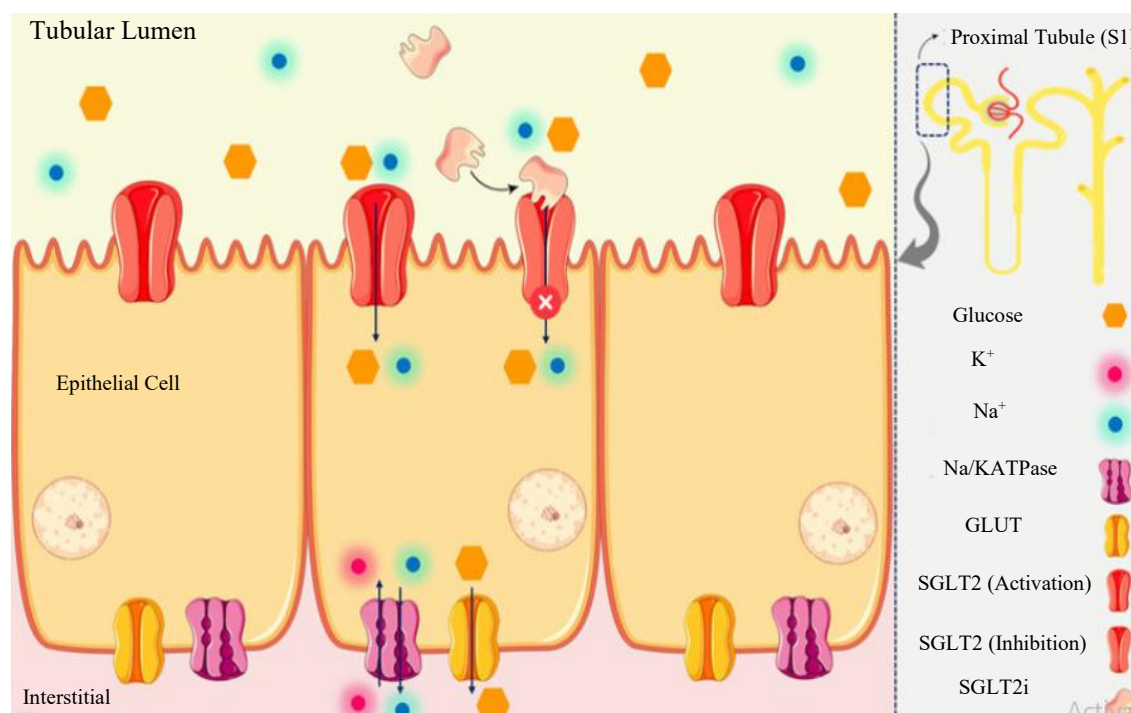


Figure 1. Mechanistic pathways of SGLT2 inhibitors in cardio-renal protection.

This publication seeks to carefully assess the rising relevance of SGLT2 inhibitors in HF and CKD, emphasizing evidence beyond diabetes control. The focus is on discovering how these drugs affect disease development, enhance clinical outcomes, and contribute to present therapy guidelines [5–10].

The interaction between the heart and kidneys in the cardio-renal continuum and the therapeutic targets of SGLT2 inhibitors are shown in Figure 2.

METHODOLOGY

Design of the Study

The organized narrative review and secondary analysis of seminal randomized controlled trials (RCTs), observational studies, and meta-analyses of SGLT2 inhibitors in populations with heart failure and chronic kidney disease (CKD) form the basis of this work. The methodology follows concepts of evidence synthesis extensively applied in clinical pharmacology and outcomes research [11–15].

Data Source

Data were extracted from:

- Major phase III and IV randomized controlled trials.
- Trials of cardiovascular and renal outcomes.
- Subgroup analyses focused on HF traits and CKD phases.
- Real-world observational studies.
- Consensus statements and international clinical guidelines.

Study Population

The populations included in the trials studied comprised:

- Individuals suffering from reduced ejection fraction heart failure (HFrEF).
- Patients with heart failure with preserved ejection fraction (HFpEF).
- Patients with CKD with and without diabetes.
- Wide age ranges, including senior citizens.

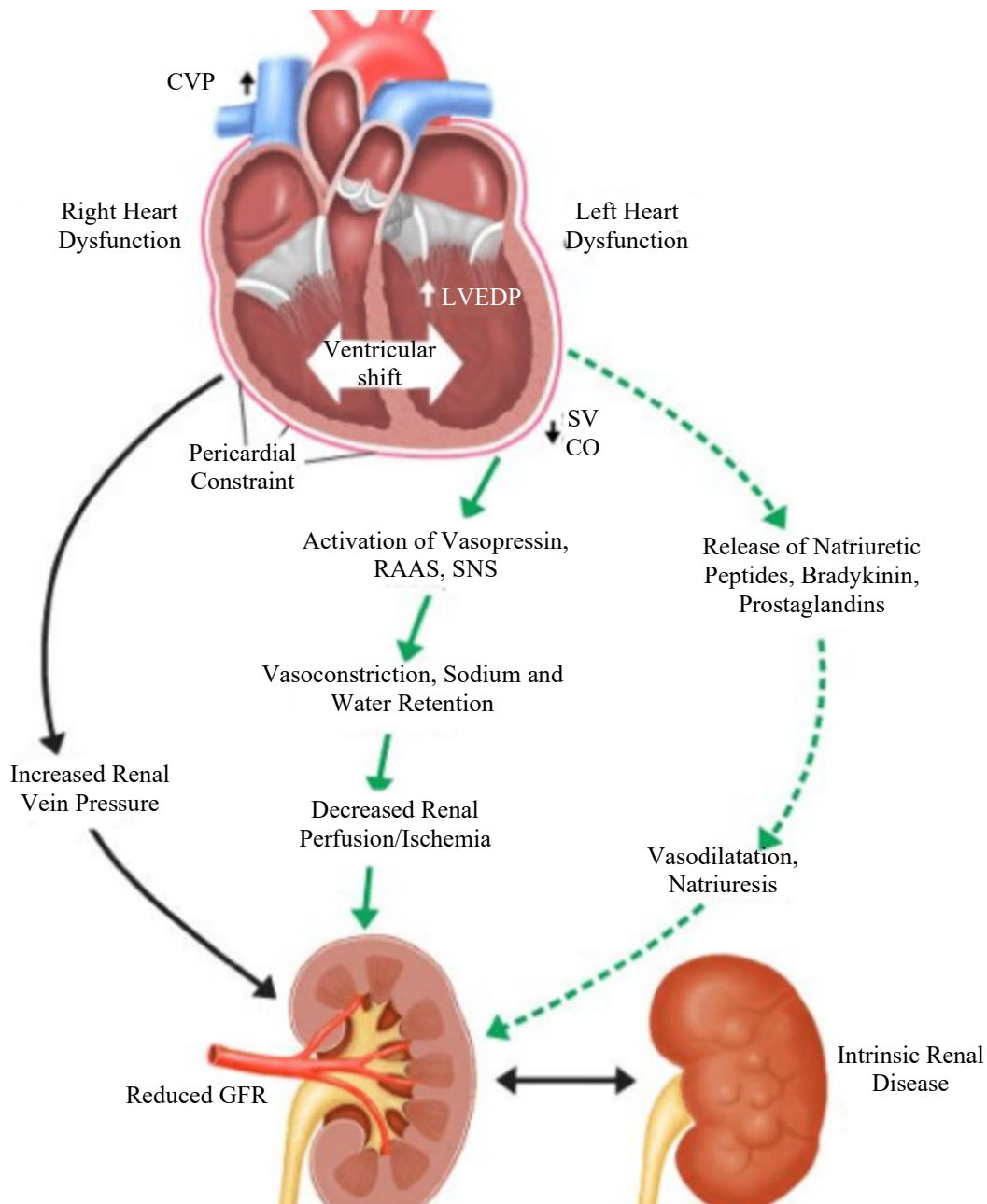


Figure 2. Cardio-renal continuum and sites of action.

DATA ANALYSIS

Statistical Methods

Relative risk reductions (RRRs), confidence intervals (CIs), and hazard ratios (HRs) were used to assess data from large trials. This publication discusses time-to-event analyses that were often used in the original investigations, including Kaplan–Meier curves and Cox proportional hazards models.

Analysis of Subgroups

Subgroup analyses were performed in the original trials based on:

- Presence or absence of diabetes.
- Initial renal function.
- HF phenotype (HFpEF vs. HFrEF).
- Sex and age.

DETAILED ANALYSIS OF RESULTS

Trail-wise Expanded Evidence Synthesis.

DAPA-HF Trial (Dapagliflozin)

Regardless of their diabetes status, 4,744 patients with heart failure with a reduced ejection fraction ($\leq 40\%$) were enrolled in the multicenter, randomized, double-blind, placebo-controlled DAPA-HF trial. Dapagliflozin indicated a significant reduction in the composite endpoint of worsening heart failure or cardiovascular death.

Crucially, the treatment improvement appeared early and persisted throughout the follow-up period. Subgroup analyses established Dapagliflozin as a disease-modifying treatment rather than a glucose-dependent intervention by confirming consistent efficacy across age groups, baseline renal function categories, and diabetic status [1].

Empagliflozin EMPEROR-Reduced Trial

Empagliflozin was assessed in individuals with more severe HFrEF and a greater burden of renal impairment in the EMPEROR-Reduced trial. Empagliflozin slowed the annual rate of eGFR decline and considerably decreased the probability of heart failure hospitalization. Since patients with severe heart failure frequently experience rapid renal deterioration, which limits therapy options, these findings were clinically significant [2].

EMPEROR-Preserved Trial

By showing improvement in heart failure with preserved ejection fraction – a population that has hitherto lacked effective therapies – the EMPEROR-Preserved study represented a significant therapeutic milestone. Empagliflozin addressed a long-standing unmet therapeutic need by considerably lowering the composite of cardiovascular death or hospitalization for heart failure, mostly due to decreases in hospitalization rates [3].

DAPA-CKD Trial

Dapagliflozin was evaluated in patients with stages 2–4 chronic kidney disease, both with and without diabetes, in the DAPA-CKD experiment. The trial's extraordinary efficacy led to its early termination. Dapagliflozin importance as a renal-protective drug independent of glycemic management was reinforced by its considerable reduction of all-cause mortality, prolonged fall in eGFR, and progression to end-stage kidney disease [4].

Trial of Credence

Canagliflozin's effectiveness in treating diabetic kidney disease was conclusively demonstrated by the CREDENCE trial. SGLT2 inhibition was shown to be a key component in the treatment of diabetic nephropathy, since treatment led to notable decreases in heart failure hospitalization, cardiovascular events, and renal failure.

Effects on Heart Failure

In numerous trials, SGLT2 inhibitors consistently decreased the likelihood of hospitalization for heart failure. Benefits were observed early after initiation and were independent of baseline glycemic state.

The reduction in heart failure hospitalization over time across treatment groups is illustrated using a Kaplan–Meier survival curve (Figure 3).

The effects of SGLT2 inhibitors on heart failure outcomes across major clinical trials are summarized in Table 1.

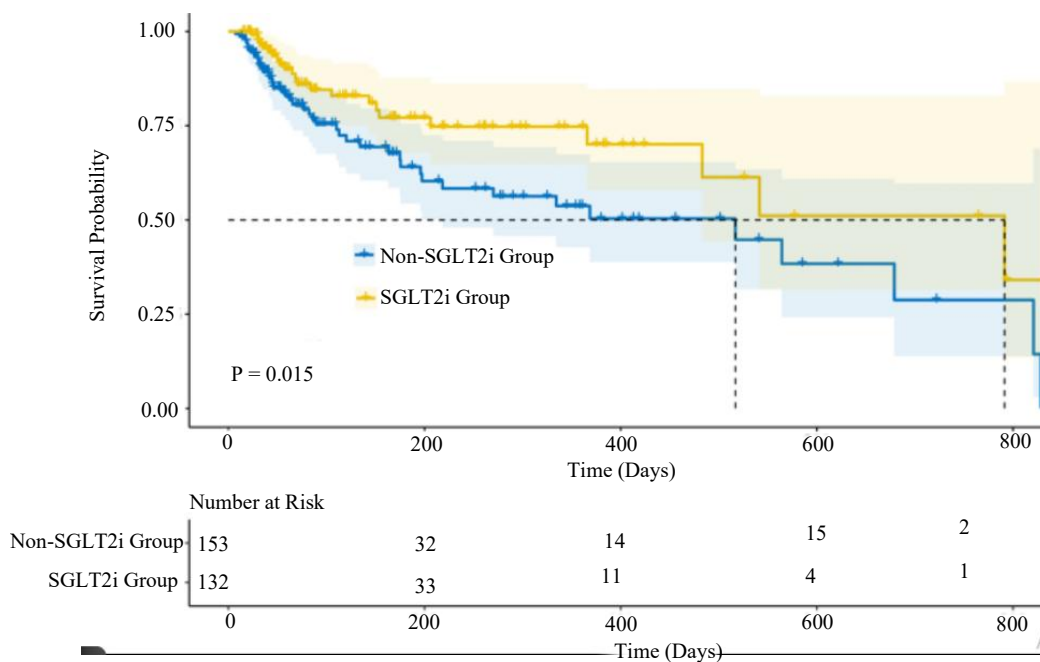


Figure 3. Kaplan–Meier curve – heart failure hospitalization.

Table 1. Effect of SGLT2 inhibitors on heart failure outcomes.

Study (year)	SGLT2 inhibitor	Population	Heart failure type	Primary outcome	Key findings
DAPA-HF (2019)	Dapagliflozin	HFrEF patients with/without T2DM	HFrEF (LVEF ≤40%)	Worsening HF or CV death	26% reduction in composite outcome; significant ↓ HF hospitalizations.
EMPEROR-Reduced (2020)	Empagliflozin	HFrEF patients	HFrEF (LVEF ≤40%)	CV death or HF hospitalization	25% risk reduction; slowed decline in renal function.
EMPEROR-Preserved (2021)	Empagliflozin	HF patients with preserved EF	HFpEF (LVEF >40%)	CV death or HF hospitalization	21% reduction; first therapy showing benefit in HFpEF.
DELIVER (2022)	Dapagliflozin	HF patients across EF spectrum	HFmrEF & HFpEF	Worsening HF or CV death	Significant reduction in HF events regardless of EF.
DECLARE-TIMI 58 (2019)	Dapagliflozin	T2DM with CV risk	HF prevention	HF hospitalization	27% reduction.

Effects on Chronic Renal Disease

In CKD populations, SGLT2 inhibitors dramatically slowed the progression of renal impairment and lowered the probability of ESKD.

The slowing of kidney function decline with SGLT2 inhibitors is demonstrated by the eGFR slope analysis shown in Figure 4.

Renal outcomes associated with SGLT2 inhibitors in major clinical trials are summarized in Table 2.

Mechanistic Insights

Numerous processes are responsible for the benefits that have been identified, including:

- Decrease in intraglomerular pressure.
- Natriuresis and osmotic diuresis.
- Enhancement of cardiac energetics.
- Reduction in inflammation and oxidative stress.

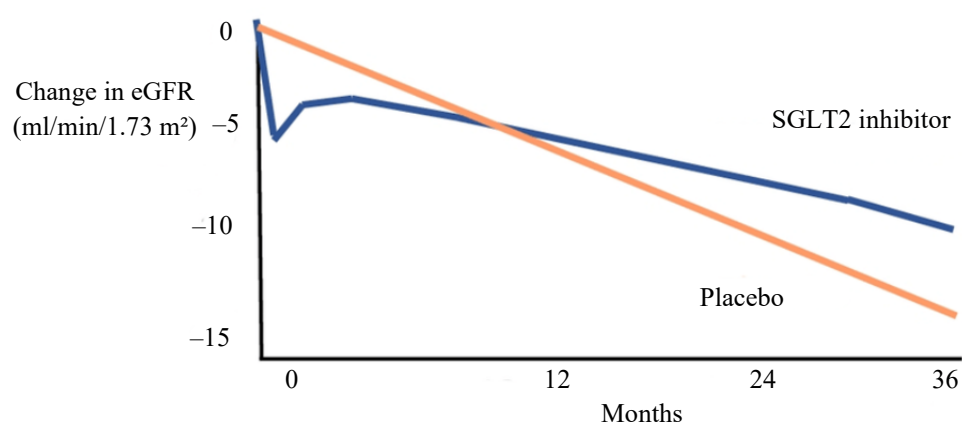


Figure 4. eGFR slope analysis in CKD.

Table 2. Renal outcomes with SGLT2 inhibitors.

Study (Year)	SGLT2 inhibitor	Population	Baseline renal status	Primary renal outcome	Key renal findings
DAPA-CKD (2020)	Dapagliflozin	CKD with/without T2DM	eGFR 25–75 mL/min/1.73 m ²	Sustained ↓ eGFR, ESKD, or renal/CV death	39% risk reduction; significant delay in CKD progression.
EMPA-KIDNEY (2022)	Empagliflozin	Broad CKD population	eGFR ≥20 mL/min/1.73 m ²	Kidney disease progression or CV death	28% reduction; benefit independent of diabetes.
CREDENCE (2019)	Canagliflozin's	T2DM with albuminuric CKD	eGFR 30–90 mL/min/1.73 m ²	ESKD, doubling of serum creatinine, renal/CV death	30% risk reduction; strong nephroprotection.
DECLARE-TIMI 58 (2019)	Dapagliflozin	T2DM with CV risk	Mostly preserved renal function	≥40% eGFR decline or ESKD	Reduced renal composite outcome.
CANVAS Program (2017)	Canagliflozin's	T2DM with CV risk	eGFR ≥30 mL/min/1.73 m ²	Progression of albuminuria	Slowed albuminuria progression and ↓ renal events.
EMPEROR-Reduced (2020)	Empagliflozin	HFrEF patients	Mild–moderate CKD	Rate of eGFR decline	Slower annual eGFR declines vs placebo.
DAPA-HF (2019)	Dapagliflozin	HFrEF patients	Mixed renal function	Worsening renal function	Reduced risk of renal deterioration.

Safety Profile

Numerous extensive clinical trials including individuals with heart failure and chronic renal disease have shown that SGLT2 inhibitors have an overall positive safety profile. Both people with and without diabetes tolerate these medications well. The most frequently reported side effects include moderate urinary tract infections brought on by increased glucose excretion in urine and genital mycotic infections, especially in females. When starting treatment, there may be a brief and slight drop in estimated glomerular filtration rate (eGFR), although this is typically reversible and is followed by long-term renal protection. Particularly in older patients or those taking concurrent diuretics, volume depletion-related problems including hypotension and dehydration may occur and necessitate close observation. When proper patient selection and clinical surveillance are maintained, serious adverse events, such as acute renal injury and diabetic ketoacidosis, are uncommon. In general, the regular therapeutic use of SGLT2 inhibitors in qualified patients with heart failure and chronic renal disease is supported by the consistent safety results across landmark trials.

CONTRIBUTION TO THE STATE OF KNOWLEDGE

By combining good clinical trial data showing that SGLT2 inhibitors provide considerable cardiovascular and renal benefits irrespective of glycemic control, this review substantially

strengthens the body of current evidence. SGLT2 inhibitors, which were once thought of as glucose-lowering medications for type 2 diabetes mellitus, are now well-established as disease-modifying treatments for chronic renal disease and heart failure. By integrating findings from landmark trials, such as DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DAPA-CKD, and CREDENCE, this work clarifies their consistent efficacy across diverse patient populations, including those without diabetes, thereby redefining their therapeutic identity beyond endocrinology.

Additionally, by emphasizing the wide applicability of SGLT2 inhibitors throughout the entire spectrum of heart failure phenotypes and CKD stages, this study increases clinical understanding. A paradigm shift in cardiovascular therapy is represented by the proven improvements in HFrEF, HFpEF, and HFmrEF – areas previously constrained by insufficient therapeutic options. The crucial function of SGLT2 inhibition in cardio-renal protection is further supported by the steady slowing of eGFR decline and decrease in progression to end-stage kidney disease in both diabetic and non-diabetic CKD populations. These findings support the incorporation of SGLT2 inhibitors as basic therapy in contemporary heart failure and CKD management recommendations.

Lastly, by summarizing new knowledge about the cardio-renal protective mechanisms of SGLT2 inhibitors – such as decreased intraglomerular pressure, natriuresis-driven hemodynamic effects, enhanced myocardial energetics, and attenuation of inflammation and oxidative stress – this review adds mechanistic clarity. By integrating molecular pathways with clinical outcomes, our work bridges the gap between pharmacological theory and real-world treatment impact. When taken as a whole, these contributions highlight the revolutionary potential of SGLT2 inhibitors in contemporary medicine and offer a solid body of evidence to help physicians, researchers, and legislators optimize patient care.

SUMMARY AND CONCLUSION

In summary, this review underlines the expanding importance of sodium–glucose cotransporter-2 (SGLT2) inhibitors as cornerstone medicines in the therapy of heart failure and chronic renal disease. These medications dramatically lower heart failure hospitalizations, halt the progression of chronic renal disease, and enhance cardiovascular outcomes in a variety of patient demographics, according to data from numerous large-scale randomized controlled trials. Significantly, these advantages go beyond glycemic control and are seen in both with and without diabetes, highlighting a significant change in the therapeutic paradigm of managing cardio-renal illness.

SGLT2 inhibitors have long-lasting and early protective benefits on both cardiac and renal function, according to the combined results of seminal trials including DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DAPA-CKD, and CREDENCE. Long-standing unmet clinical requirements are addressed by their effectiveness throughout the entire spectrum of heart failure phenotypes, including maintained and modestly diminished ejection fraction, as well as across different stages of chronic kidney disease. Coupled with a favorable safety profile and ease of clinical implementation, SGLT2 inhibitors have emerged as crucial components of guideline-directed medical care.

In summary, SGLT2 inhibitors redefine the conventional limits of diabetes-focused pharmacology and constitute a revolutionary development in contemporary cardio-renal therapies. Their regular usage in suitable individuals with heart failure and chronic renal disease is supported by their pleiotropic mechanisms and reliable therapeutic advantages. Current results clearly confirm SGLT2 inhibitors as fundamental agents in decreasing morbidity, mortality, and quality of life in cardio-renal disease; however, more study and practical evidence will further refine patient selection and long-term outcomes.

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