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Review article

PLEIOTROPIC EFFECTS OF SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS (GLIFLOZINS) BEYOND DIABETES MELLITUS: EVOLUTION OF VIEWS ON CARDIO- AND NEPHROPROTECTION

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Abstract: Sodium-glucose cotransporter 2 (SGLT2) inhibitors were developed for type 2 diabetes mellitus but now have an established role in heart failure and chronic kidney disease, including in patients without diabetes. This narrative review critically integrates outcome trials, human mechanistic studies, proteomics, and contemporary guidelines. Dapagliflozin and empagliflozin improve trial-specific composite outcomes across a broad range of left ventricular ejection fractions and kidney function. These clinical benefits are more firmly established than the contribution of individual molecular pathways. Renal hemodynamic effects and stimulation of erythropoiesis have human experimental support, whereas direct myocardial sodium-hydrogen exchanger inhibition and metabolic reprogramming remain incompletely resolved. EMPEROR proteomic studies provide translational support for coordinated changes in autophagy, iron handling, and cellular stress responses, without establishing causal mediation. Sotagliflozin is considered separately because it inhibits both SGLT1 and SGLT2; its pivotal trials enrolled patients with type 2 diabetes and do not directly establish efficacy in people without diabetes. We propose an evidence-to-indication framework that distinguishes demonstrated clinical efficacy, supportive human biology, and exploratory mechanisms. This synthesis positions gliflozins as complementary components of cardiovascular and kidney care, rather than as uniquely pleiotropic drugs or interchangeable agents for every indication. The 2026 European Society of Cardiology guidelines and the 2024 KDIGO guideline are integrated with the original trial populations. Limitations include selective literature coverage, heterogeneous endpoints, and incomplete mechanistic validation. Treatment selection should follow the patient's disease phenotype and the evidence for the individual agent.

Keywords: SGLT2 inhibitors, gliflozins, sotagliflozin, heart failure, chronic kidney disease, proteomics, cardioprotection, nephroprotection.

INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, or gliflozins, reduce proximal tubular glucose and sodium reabsorption. Their development as glucose-lowering agents preceded recognition of their cardiovascular and kidney benefits (1). In EMPA-REG OUTCOME, empagliflozin reduced cardiovascular mortality by 38% and hospitalization for heart failure by 35% in patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease; these were distinct outcomes rather than a single combined effect (2).

Subsequent trials moved the field beyond diabetes. DAPA-HF and EMPEROR-Reduced studied heart failure (HF) with left ventricular ejection fraction (LVEF) ≤ 40%, whereas EMPEROR-Preserved and DELIVER enrolled patients with LVEF > 40% (3-6). DAPA-CKD and EMPA-KIDNEY established benefits in chronic kidney disease (CKD), including in participants without diabetes (7, 8). Efficacy in non-diabetic populations shows that improvement in hyperglycemia is not a prerequisite for benefit; it does not identify a single causal mechanism.

Pleiotropy is not unique to gliflozins. Established cardiovascular therapies also influence hemodynamic, neurohumoral, and remodeling pathways, and effective treatment commonly combines complementary drug classes (9). This review presents a critical framework linking the strength of mechanistic evidence to

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the populations and outcomes actually studied. We distinguish clinical efficacy from biological plausibility, assess the separate evidence for dual SGLT1/2 inhibition, and place these findings within the evolution from the 2023 ESC focused update to the 2026 ESC HF and cardiovascular disease–CKD guidelines and KDIGO 2024 (10-13).

REVIEW APPROACH AND SCOPE

This narrative review and critical evidence synthesis used targeted searches of indexed biomedical records and publisher websites for the named outcome trials, sotagliflozin, EMPEROR proteomics, and contested mechanistic claims. Guideline statements were checked against ESC and KDIGO publications and official supporting materials available on 21 September 2026. Primary trial reports and human mechanistic studies were prioritized; reviews were used for pharmacological context and hypothesis development. Trial names, populations, endpoint definitions, effect estimates, and bibliographic identifiers were cross-checked. No pooled effect was calculated, and no formal risk-of-bias grading was performed. The tables preserve original eligibility thresholds and trial-specific endpoints rather than harmonizing unlike outcomes.

GENERAL PHARMACOLOGY AND MECHANISM OF ACTION OF SGLT2 INHIBITORS

SGLT2 accounts for most filtered glucose reabsorption in the early proximal tubule. Its inhibition produces glucosuria and alters sodium handling; the glucose-lowering effect depends on kidney function and the filtered glucose load. Because these agents do not directly stimulate insulin secretion, their intrinsic hypoglycemia risk is low, although concomitant insulin or sulfonylureas can increase that risk. Differences in selectivity exist within the class and should not be used alone to predict clinical superiority (1).

Sotagliflozin requires separate consideration. In addition to renal SGLT2 inhibition, it inhibits SGLT1, including intestinal glucose transport. Its pharmacology and pivotal clinical evidence therefore differ from those of predominantly selective SGLT2 inhibitors. The pivotal SOLOIST-WHF and SCORED trials evaluated sotagliflozin in patients with T2DM and recent worsening HF or CKD, respectively (14).

HEMODYNAMIC AND NEUROHUMORAL PLEIOTROPIC MECHANISMS

Reduced proximal sodium reabsorption increases sodium delivery to the macula densa and modifies tubuloglomerular feedback. Lower intraglomerular pressure provides a plausible explanation for the early fall in filtration followed by longer-term kidney protection. The vascular response is context dependent: the randomized RED study in metformin-treated T2DM supported post-glomerular vasodilation rather than a universal model of afferent arteriolar constriction (15). Thus, one fixed arteriolar mechanism should not be assumed across diabetes types and CKD phenotypes.

Human studies also illustrate the distinction between a physiological response and a clinical endpoint. In DIAMOND, 53 participants with non-diabetic proteinuric CKD received dapagliflozin and placebo in a crossover design. Six weeks of dapagliflozin produced a reversible decline in measured GFR but did not significantly reduce proteinuria (16). Short-term surrogate responses vary and do not negate the longer-term outcome evidence.

Osmotic diuresis, transient natriuresis, and modest blood pressure reductions can reduce cardiac loading conditions. Their magnitude varies with volume status, kidney function, and background treatment (1). The effects on the renin–angiotensin–aldosterone system (RAAS) are context dependent, and the absence of tachycardia does not establish direct sympathetic inhibition. The relative contributions of volume redistribution and neurohumoral adaptation to outcome benefits remain uncertain.

Notes on changes: Added serial commas in lists for consistency. No other changes were necessary.

CELLULAR AND MOLECULAR MECHANISMS OF CARDIOPROTECTION

Direct inhibition of myocardial sodium-hydrogen exchanger 1 (NHE1) is a proposed, contested mechanism. Empagliflozin inhibited exchanger activity in isolated human atrial cardiomyocytes in one experimental study (17). Another investigation found no inhibition of NHE1 or reduction of intracellular sodium under its experimental conditions (18). These differences in preparations and assays preclude describing NHE1 inhibition as an established explanation for clinical benefit.

Changes in substrate availability, nutrient-sensing pathways, and autophagy are biologically plausible. However, the ketone-fuel hypothesis remains unproven in human HF. In the randomized EMPA-VISION trial, 72 participants with reduced or preserved LVEF received empagliflozin or placebo for 12 weeks; myocardial phosphocreatine-to-ATP ratios were not improved (19). This finding does not exclude all metabolic effects, but it argues against treating improved

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myocardial energetics as a demonstrated universal mediator.

Empagliflozin reduced inflammation-associated oxidative stress in cultured human endothelial cells (20). Nutrient-deprivation signaling, AMPK/mTOR regulation, and enhanced autophagic flux remain candidate links between SGLT2 inhibition and cellular adaptation (21). Evidence for antioxidative and antifibrotic effects is primarily experimental. Reduced circulating biomarkers or favorable pathway signatures cannot by themselves establish reversal of human myocardial fibrosis or demonstrate that a particular pathway mediates fewer clinical events.

STIMULATION OF ERYTHROPOIESIS AS A COMPONENT OF CARDIORENAL PROTECTION

The rise in hemoglobin and hematocrit during SGLT2 inhibition is not adequately explained by hemoconcentration alone. In a post hoc analysis of the randomized Empire HF trial, which enrolled 190 participants, empagliflozin increased erythropoietin and reduced hepcidin over 12 weeks, supporting increased erythropoiesis and altered iron utilization (22). These findings provide direct human biological evidence, but the fraction of cardiovascular benefit attributable to this pathway remains undetermined. Changes in erythropoietin production, renal cellular signaling, and iron mobilization may interact; a single model in which improved oxygenation simply removes an erythropoietin stimulus is insufficient. Mediation estimates from correlated biomarkers should not be interpreted as experimental proof of causality.

HUMAN PROTEOMICS AS A TRANSLATIONAL BRIDGE

Zannad and colleagues assessed 1,283 circulating proteins in 1,134 participants from EMPEROR-Reduced and EMPEROR-Preserved at baseline, 12 weeks, and 52 weeks. At 12 weeks, 32 proteins met their differential-expression criterion of a change of at least 10% with a false discovery rate below 1%. The affected proteins included erythropoietin, transferrin receptor 1, and insulin-like growth factor-binding protein 1. The investigators linked the pattern to nutrient-deprivation signaling, autophagy, and transmembrane sodium transport (23).

A subsequent validation analysis by Packer and colleagues studied 2,155 proteins in 1,120 other EMPEROR participants. Twenty-five proteins met the prespecified threshold for the largest enrichment, and the biological signatures broadly replicated those in the discovery cohort, including iron mobilization, cellular housekeeping, and mitochondrial pathways (24). This replication strengthens the relevance of coordinated biological responses in treated patients.

Our interpretation is that proteomics supplies a bridge between laboratory observations and outcome

Table 1. *Evidence levels for proposed mechanisms*

Mechanism or signal	Evidence supporting it	Interpretive boundary
Renal hemodynamic adaptation	Human physiological trials, including RED and DIAMOND (15, 16).	Hemodynamic responses vary by phenotype; short-term GFR changes are not clinical outcome estimates.
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Erythropoiesis and iron mobilization	Randomized human exposure with exploratory erythropoietin/hepcidin measurements in Empire HF (22).	Biological response demonstrated; its causal share of outcome benefit remains uncertain.
Autophagy and cellular stress adaptation	EMPEROR discovery and validation proteomics (23, 24).	Reproducible circulating signatures; tissue origin and causal mediation are unresolved.
Direct myocardial NHE1 inhibition	Positive isolated human-cell experiments and negative experimental replication (17, 18).	Conflicting experimental findings; not an established clinical mediator.
Improved myocardial energetics	Plausible substrate hypotheses; neutral randomized EMPA-VISION result (19).	No improvement in PCr/ATP over 12 weeks in this trial; broader metabolic effects are not excluded.
Antioxidative and antifibrotic responses	Experimental endothelial-cell findings and pathway hypotheses (20, 21).	Laboratory or inferred responses do not establish reduced human fibrosis or event mediation.

Evidence categories represent a qualitative synthesis and are not formal GRADE ratings. PCr/ATP, phosphocreatine-to-adenosine triphosphate ratio. Proven outcome efficacy and certainty about its molecular explanation are separate questions.

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trials, not a direct demonstration of intracellular drug targets. Circulating protein concentrations can reflect secretion, tissue turnover, and renal clearance. Pathway annotation is inferential, and randomized drug exposure does not randomize the change in each protein. These studies therefore support mechanistic hypotheses without proving that any individual protein or pathway is necessary or sufficient for clinical benefit. Table 1 distinguishes these evidence levels.

GLIFLOZINS IN HEART FAILURE ACROSS THE EJECTION FRACTION SPECTRUM

DAPA-HF and EMPEROR-Reduced demonstrated benefit on their primary composites in patients with LVEF ≤ 40%, with hazard ratios (HRs) of 0.74 and 0.75, respectively (3, 4). EMPEROR-Preserved and DELIVER extended the evidence to patients with LVEF > 40%, with HRs of 0.79 and 0.82 (5, 6). The designs, populations and absolute results are summarized in Table 2. The inclusion of participants without diabetes is central to the organ-protection concept.

EMPEROR trials combined cardiovascular death with HF hospitalization, whereas DAPA-HF and DELIVER also incorporated urgent HF visits in their worsening-HF definitions. In the higher-LVEF trials, the composite benefit was driven mainly by fewer HF events; neither trial independently established a statistically significant reduction in cardiovascular mortality. Similar subgroup effects support broad applicability, but do not prove identical benefit in every phenotype.

Trial terminology differs from current HF classification. Older trials used HFrEF for LVEF ≤ 40% and HFmrEF for 41–49%. The 2026 ESC guideline uses HFrEF for LVEF < 50% and HFpEF for LVEF ≥ 50% (11). The trial tables report the original numerical eligibility thresholds.

NEPHROPROTECTIVE EFFECTS BEYOND DIABETIC KIDNEY DISEASE

CREDENCE established kidney-outcome benefit for canagliflozin in T2DM with albuminuric CKD on RAAS blockade; its primary composite was reduced by 30% (25). DAPA-CKD broadened the population to CKD with or without diabetes. The overall primary composite, which included cardiovascular death, had HR 0.61 (95% CI 0.51–0.72). The HR of 0.56 concerned a secondary kidney-specific composite excluding cardiovascular death (7). In the prespecified subgroup without diabetes, the primary-composite HR was 0.50 (95% CI 0.35–0.72), with no significant treatment-by-diabetes interaction (26).

Table 2. *Pivotal heart failure trials*

Trial and intervention	Population and median follow-up	Primary endpoint	Main result
DAPA-HF (2019) Dapagliflozin 10 mg daily (3)	n = 4,744; symptomatic HF; LVEF ≤ 40%; with or without T2DM.18.2 months.	First worsening HF event (hospitalization or urgent visit requiring IV therapy) or CV death.	16.3% vs 21.2%;HR 0.74(95% CI 0.65–0.85).
EMPEROR-Reduced (2020) Empagliflozin 10 mg daily (4)	n = 3,730; symptomatic HF; LVEF ≤ 40%; with or without diabetes.16 months.	First HF hospitalization or CV death.	19.4% vs 24.7%;HR 0.75(95% CI 0.65–0.86).
EMPEROR-Preserved (2021)Empagliflozin 10 mg daily (5)	n = 5,988; symptomatic HF; LVEF > 40%; with or without diabetes.26.2 months.	First HF hospitalization or CV death.	13.8% vs 17.1%;HR 0.79(95% CI 0.69–0.90).
DELIVER (2022)Dapagliflozin 10 mg daily (6)	n = 6,263; symptomatic HF; LVEF > 40%; with or without diabetes.2.3 years.	First worsening HF event (unplanned hospitalization or urgent visit) or CV death.	16.4% vs 19.5%;HR 0.82(95% CI 0.73–0.92).
SOLOIST-WHF (2021) Sotagliflozin (14)	n = 1,222; T2DM; recent worsening HF; no LVEF restriction.9 months.	Total CV deaths, HF hospitalizations and urgent HF visits, including recurrent events.	51.0 vs 76.3 events/100 patient-years;HR 0.67(95% CI 0.52–0.85).

*All trials were randomized, double-blind and placebo-controlled, on background care. Values are active treatment versus placebo. Percentages denote participants with a first event; SOLOIST-WHF reports event rates and includes recurrent events. SOLOIST-WHF ended early after funding loss. CV, cardiovascular; IV, intravenous; CI, confidence interval. Trial-specific LVEF thresholds are preserved. The results are not head-to-head comparisons.

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Table 3. *Pivotal trials in chronic kidney disease*

Trial and intervention	Population and median follow-up	Primary endpoint	Main result
CREDENCE (2019) Canagliflozin 100 mg daily (25)	n = 4,401; T2DM; eGFR 30 to < 90; UACR > 300–5,000; RAAS blockade.2.62 years.	ESKD, doubling of serum creatinine, or kidney/CV death.	43.2 vs 61.2 events/1,000 patient-years;HR 0.70(0.59–0.82).
DAPA-CKD (2020)Dapagliflozin 10 mg daily (7)	n = 4,304; eGFR 25–75; UACR 200–5,000; with or without T2DM.2.4 years.	Sustained eGFR decline ≥ 50%, ESKD, or kidney/CV death.	9.2% vs 14.5%;HR 0.61(0.51–0.72).
EMPA-KIDNEY (2023)Empagliflozin 10 mg daily (8)	n = 6,609; eGFR 20 to < 45 at any UACR, or 45 to < 90 with UACR ≥ 200; with or without diabetes.2.0 years.	Kidney disease progression (ESKD, sustained eGFR < 10, sustained decline ≥ 40%, or kidney death) or CV death.	13.1% vs 16.9%;HR 0.72(0.64–0.82).
SCORED (2021)Sotagliflozin (14)	n = 10,584; T2DM; eGFR 25–60; CV risk; with or without albuminuria.16 months.	Revised endpoint: total CV deaths, HF hospitalizations and urgent HF visits.	5.6 vs 7.5 events/100 patient-years;HR 0.74(0.63–0.88).

*All trials were randomized, double-blind and placebo-controlled. eGFR is in mL/min/1.73 m² and UACR in mg/g. Results are active treatment versus placebo; intervals are 95% CIs. ESKD, end-stage kidney disease, as defined in each trial. CREDENCE and DAPA-CKD stopped early for efficacy; SCORED stopped after funding loss and revised its endpoint during the trial. SCORED tested a cardiovascular recurrent-event composite, not a primary kidney-failure composite. These results do not establish comparative superiority between agents.

EMPA-KIDNEY enrolled 6,609 participants with eGFR 20 to < 45 mL/min/1.73 m² irrespective of albuminuria, or eGFR 45 to < 90 with urine albumin-to-creatinine ratio (UACR) ≥ 200 mg/g. The primary composite of kidney disease progression or cardiovascular death had HR 0.72 (95% CI 0.64–0.82) (8). This was an overall estimate, not a non-diabetic-only estimate. Kidney disease progression comprised kidney replacement therapy or other trial-defined end-stage kidney disease, sustained eGFR < 10, sustained eGFR decline ≥ 40%, or kidney death. Trial designs, populations and outcomes are summarized in Table 3.

Secondary analyses supported broadly consistent effects across included primary kidney diseases, although individual etiologic subgroups were less precisely estimated (27). Polycystic kidney disease was excluded from EMPA-KIDNEY; the trial therefore cannot establish efficacy in that condition. Evidence in low-albuminuria CKD also requires attention to the endpoint: chronic eGFR slope and event-based composites differ in statistical power and clinical interpretation. These boundaries are essential when translating a broad class concept into individual treatment decisions.

SOTAGLIFLOZIN AND THE DISTINCT EVIDENCE FOR DUAL SGLT1 AND SGLT2 INHIBITION

Sotagliflozin combines renal SGLT2 inhibition with SGLT1 inhibition, which delays intestinal glucose absorption. This provides a mechanistic distinction, but does not establish additional cardiovascular benefit over selective SGLT2 inhibition. SOLOIST-WHF randomized 1,222 patients with T2DM after worsening HF; treatment began before discharge or shortly thereafter. The total-event composite of cardiovascular death, HF hospitalization and urgent HF visits was reduced (HR 0.67, 95% CI 0.52–0.85) (14).

SCORED randomized 10,584 patients with T2DM, CKD and cardiovascular risk. Sotagliflozin reduced its revised primary composite of total cardiovascular deaths, HF hospitalizations and urgent HF visits (HR 0.74, 95% CI 0.63–0.88) (14). The outcome was cardiovascular, not a kidney-failure primary endpoint. Both trials ended early following loss of funding; SCORED's endpoint revision is an additional interpretive consideration.

Both pivotal populations had T2DM. Their results cannot be used as direct evidence for sotagliflozin in non-diabetic HF or CKD, nor can cross-trial comparisons demonstrate superiority over dapagliflozin or empagliflozin. Diarrhea and other adverse events are relevant to its distinct benefit–risk profile. Sotagliflozin therefore has a distinct evidence base defined by the populations and endpoints studied.

OTHER SYSTEMIC EFFECTS AND THEIR CLINICAL BOUNDARIES

Potential benefits beyond HF and CKD remain unevenly established. In a 48-week randomized trial

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involving 154 adults with biopsy-confirmed metabolic dysfunction-associated steatohepatitis, dapagliflozin improved the primary histological endpoint in 53% versus 30% with placebo (28). This provides disease-specific evidence, but does not demonstrate prevention of liver-related mortality or establish a class-wide indication.

Lower serum urate is a reproducible pharmacological observation, but it should not be attributed categorically to direct competitive URAT1 inhibition (1). Similarly, potential cognitive benefits remain outside the proven indications discussed here. These exploratory effects do not establish an indication for routine treatment in people without an established cardiovascular, kidney or diabetes indication.

SAFETY AND CLINICAL LIMITATIONS OF APPLICATION

Genital mycotic infection is a recognized adverse effect; it should not be conflated with a uniform increase in all urinary infections. Volume depletion can be relevant in susceptible patients. Hypoglycemia is uncommon without other glucose-lowering therapies, while ketoacidosis is rare but clinically important. Sotagliflozin adds a particular gastrointestinal tolerability consideration, consistent with intestinal SGLT1 inhibition (14). These risks require assessment alongside the individual's volume status, comedications and clinical stability.

An initial eGFR dip is often a reversible hemodynamic response rather than kidney injury. KDIGO 2024 advises temporary interruption during prolonged fasting, surgery or critical illness, and permits continuation below an eGFR of 20 mL/min/1.73 m² after initiation unless treatment is not tolerated or kidney replacement therapy begins (13). Initiation and continuation are separate decisions; reduced glucose-lowering efficacy at low eGFR should not be confused with loss of cardiorenal benefit.

The amputation signal observed with canagliflozin in CANVAS was not reproduced in CREDENCE (25, 29). The observed risk therefore differs by agent and study population. Evidence remains limited for some advanced kidney disease populations, and trial exclusions should be respected when discussing generalizability.

EVOLUTION OF GUIDELINES AND THE PLACE OF GLIFLOZINS IN CURRENT PRACTICE

The 2023 ESC focused update recommended dapagliflozin or empagliflozin for HFmrEF and HFpEF at Class I, level A, and addressed HF prevention in T2DM with CKD (10). This historical step should be distinguished from the earlier 2022 AHA/ACC/HFSA recommendations, which assigned Class IIa to SGLT2 inhibition in the higher-LVEF groups (9).

The 2026 ESC HF guideline recommends dapagliflozin or empagliflozin for symptomatic HF across LVEF categories (Class I, level A). It also recommends in-hospital initiation after stabilization of decompensated HF to improve congestion and quality of life and reduce rehospitalization (Class I, level B1) (11). These recommendations support timely implementation while retaining attention to stability and contraindications.

The 2026 ESC cardiovascular disease–CKD guideline recommends SGLT2 inhibition at eGFR ≥ 20 mL/min/1.73 m² in T2DM with CKD, and in non-diabetic CKD when UACR is ≥ 200 mg/g (both Class I, level A). For non-diabetic CKD with eGFR 20–44 and lower albuminuria, treatment should be considered (Class IIa, level B1). In HF with CKD and eGFR ≥ 20, the recommendation applies irrespective of LVEF (12).

KDIGO 2024 similarly supports treatment in CKD with eGFR ≥ 20 and UACR ≥ 200 mg/g, or HF irrespective of albuminuria (grade 1A), and suggests treatment at eGFR 20–45 with UACR < 200 mg/g (grade 2B) (13). ESC classes and KDIGO grades are distinct grading systems. Eligibility for treatment depends on these clinical criteria.

CLINICAL SYNTHESIS AND INTERPRETATION

We propose an evidence-to-indication framework with three linked questions: Is clinical benefit demonstrated in a comparable population? What level of evidence supports the proposed biological explanation? Does the individual agent have evidence for the indication under consideration? Figure 1 presents this synthesis. The framework integrates outcome evidence, mechanistic support and clinical eligibility.

First, treatment decisions should be anchored to outcome trials. Glucose-independent efficacy supports the use of proven agents in eligible HF and CKD populations, but does not imply that every proposed glucose-independent mechanism is correct. Mechanistic uncertainty is therefore compatible with well-established clinical utility. Conversely, a favorable laboratory pathway does not establish benefit in an untested population.

Second, gliflozins should be considered complementary to other disease-modifying therapies. Shared effects on inflammation, oxidative stress or fibrosis do not imply therapeutic redundancy, and pleiotropy

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does not establish superiority. Gliflozins are not the only effective therapy in higher-LVEF HF: FINE-ARTS-HF demonstrated a reduction in the composite of total worsening-HF events and cardiovascular death with finerenone in patients with LVEF ≥ 40% (30). Comparisons should concern demonstrated outcomes, tolerability and opportunities for complementary treatment.

Third, class-level reasoning must retain agent-level boundaries. Dapagliflozin and empagliflozin have direct outcome evidence in people without diabetes; the pivotal sotagliflozin trials do not. Differences in selectivity, endpoint definitions and trial populations prevent a ranking based on the numerical size of HRs alone. Absolute event rates in Tables 2 and 3 illustrate differences in baseline risk and do not establish comparative superiority.

Future studies should combine longitudinal molecular measurements, prespecified causal analyses and functional validation to test whether proteomic signatures improve treatment selection or monitoring. Until then, mechanistic biomarkers should not substitute for established eligibility criteria.

LIMITATIONS OF THE REVIEW

This narrative synthesis is vulnerable to selection and publication bias because it did not use a registered protocol, exhaustive database search, duplicate screening or formal risk-of-bias assessment. The selected trials establish the main evidence base but do not constitute a complete inventory of all gliflozin studies. Literature and guidelines were checked at a defined time; later publications may alter conclusions.

Clinical trials differed in population, background treatment, follow-up, stopping rules and composite endpoints. Some evaluated first events, whereas SOLOIST-WHF and SCORED evaluated recurrent events. Consequently, effect estimates and absolute differences cannot be compared as if derived from a head-to-head trial. Non-significant interaction tests do not prove identical efficacy across subgroups, and low event counts limit conclusions for individual CKD etiologies or narrowly defined HF phenotypes.

Mechanistic studies vary in species, drug exposure, tissue preparation and duration. Human proteomics adds translational relevance but does not establish tissue-specific causality, and the validation cohort came from the same trial programme rather than an independent treatment programme. Generalization is limited for populations excluded or sparsely represented in pivotal trials, including polycystic kidney disease, dialysis and some transplant settings. Finally, the proposed framework is qualitative and has not been prospectively validated.

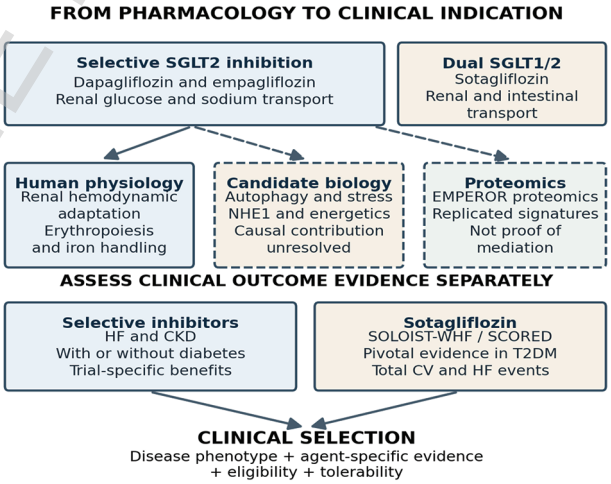
CONCLUSIONS

1. Dapagliflozin and empagliflozin are established components of HF and CKD care in appropriately selected patients, including those without diabetes. Clinical conclusions should retain each trial's population and endpoint definition.

2. Renal hemodynamics, erythropoiesis and coordinated cellular stress responses provide plausible complementary explanations. Direct NHE1 inhibition and improved myocardial energetics remain unresolved, and proteomic signatures support hypotheses rather than prove mediation.

3. Sotagliflozin broadens the pharmacological discussion through dual SGLT1/2 inhibition, but its pivotal T2DM trials should not be extrapolated uncritically to non-diabetic populations or used to infer superiority over selective agents.

4. Our synthesis positions gliflozins within complementary cardiovascular and kidney therapy. The current ESC and KDIGO recommendations, clinical phenotype and agent-specific outcome evidence should guide their place in practice; pleiotropy alone is neither a unique property nor an indication.



*Solid connectors indicate pharmacological or clinical relationships; dashed connectors indicate candidate biological links. The proposed biological pathways have not been established as causal mediators of clinical benefit. Human mechanistic and proteomic evidence is summarized in Table 1; trial populations and endpoints are detailed in Tables 2 and 3 (15, 17-19,22-24).

Figure 1. *Evidence-to-indication framework*

Abbreviations

CKD – chronic kidney disease
HF – heart failure
LVEF – left ventricular ejection fraction
NHE – sodium-hydrogen exchange
RAAS – renin-angiotensin-aldosterone system
SGLT-2 – Sodium-glucose cotransporter 2

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T2DM – type 2 diabetes mellitus
TGF – tubuloglomerular feedback
TGF-β – transforming growth factor β

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Note: The authors state that artificial intelligence was not used as a tool in this study.

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Sažetak

PLEIOTROPNI EFEKTI INHIBITORA SGLT2 (GLIFLOZINA) IZVAN LEČENJA DIJABETES MELITUSA: RAZVOJ SAZNANJA O KARDIOPROTEKTIVNOM I NEFROPROTEKTIVNOM DELOVANJU

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Inhibitori kotransportera natrijuma i glukoze 2 (SGLT2) razvijeni su za lečenje dijabetes melitusa tipa 2, ali danas imaju utvrđeno mesto u lečenju srčane insuficijencije i hronične bolesti bubrega, uključujući i pacijente bez dijabetesa. Ovaj narativni pregledni rad kritički objedinjuje rezultate kliničkih studija, istraživanja mehanizama delovanja sprovedenih na ljudima, proteomskih analiza i savremenih smernica. Dapagliflozin i empagliflozin povoljno utiču na kompozitne ishode definisane u pojedinačnim kliničkim studijama, u širokom rasponu vrednosti ejekcione frakcije leve komore i stepena bubrežne funkcije. Kliničke koristi ovih lekova bolje su dokazane nego uloga pojedinačnih molekularnih puteva u njihovom ostvarivanju. Hemodinamski efekti na bubrege i stimulacija eritropoeze potkrepljeni su eksperimentalnim dokazima dobijenim u istraživanjima na ljudima, dok direktna inhibicija natrijum-vodoničnog izmenjivača u miokardu i metaboličko reprogramiranje još nisu u potpunosti razjašnjeni. Proteomske studije u okviru programa EMPEROR pružaju translacionu potporu postojanju koordinisanih promena u autofagiji, metabolizmu gvožđa i ćelijskim odgovorima na stres, ali ne potvrđuju uzročno-posledičnu ulogu ovih promena u ostvarivanju kliničkih koristi. Sotagliflozin se razmatra zasebno jer inhibira i SGLT1 i SGLT2. U ključne kliničke studije ovog leka bili su uključeni pacijenti sa dijabetes melitusom tipa 2, te te studije ne pružaju neposredne dokaze o njegovoj efikasnosti kod osoba bez dijabetesa. Predlažemo pristup zasnovan na povezivanju naučnih dokaza sa terapijskim indikacijama, pri čemu se razlikuju dokazana klinička efikasnost, biološki mehanizmi potkrepljeni istraživanjima na ljudima i mehanizmi koji su još u fazi ispitivanja. Objedinjeni nalazi ukazuju na to dagliflozini predstavljaju komplementarne lekove u lečenju kardiovaskularnih i bubrežnih bolesti, a ne lekove čija je pleiotropija jedinstvena niti lekove koji se mogu međusobno zamenjivati u svim terapijskim indikacijama. Smernice Evropskog kardiološkog društva iz 2026. godine i smernice KDIGO iz 2024. godine razmatraju se uz uvažavanje populacija pacijenata uključenih u originalne kliničke studije. Ograničenja obuhvataju selektivni prikaz literature, heterogenost ishoda i nepotpunu potvrdu mehanizama delovanja. Izbor terapije treba da se zasniva na fenotipu bolesti kod konkretnog pacijenta i dokazima o efikasnosti pojedinačnog leka.

Ključne reči: inhibitori SGLT2, gliflozini, sotagliflozin, srčana insuficijencija, hronična bolest bubrega, proteomika, kardioprotekcija, nefroprotekcija.

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