Giornale Italiano di Nefrologia

From Congestion to Cardiorenal Protection: The New Therapeutic Balance Between SGLT2 Inhibitors and Loop Diuretics in Heart Failure

In depth review

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ABSTRACT

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have redefined the therapeutic landscape of heart failure (HF), both with reduced (HFrEF) and preserved (HFpEF) ejection fraction. Historically, treatment has relied on diuretics to relieve congestion, with limited prognostic impact and dose-related adverse effects. SGLT2i, originally developed for type 2 diabetes mellitus, have demonstrated in randomized trials a significant reduction in hospitalizations and cardiovascular mortality, with benefits extending to non-diabetic patients.

SGLT2 inhibitorsTheir mechanism combines moderate osmotic natriuresis, selective reduction of extracellular volume, renal protection, and minimal neurohormonal activation. In contrast to loop diuretics, which induce rapid volume depletion and RAAS activation, SGLT2i stabilize sodium-water balance without significant hemodynamic compromise. In clinical practice, their combination with diuretics requires careful titration to prevent hypovolemia, hypotension, and renal dysfunction, especially in frail elderly patients.

Evidence suggests that SGLT2i may reduce chronic diuretic requirements, improve renal function, and provide additional cardiovascular protection. These findings support their early and integrated use, positioning SGLT2i as a cornerstone in the contemporary management of heart failure.

KEYWORDS: SGLT2 inhibitors, diuretics, heart failure, cardiorenal protection, osmotic natriuresis, combination therapy

Introduction

For many years, the management of patients with heart failure with preserved ejection fraction (HFpEF) was based on symptomatic approaches, primarily focused on reducing congestion and controlling comorbidities, in the absence of pharmacological options able to significantly modify prognosis. Guidelines recommended empirical treatments (diuretics, beta-blockers, RAAS antagonists), but with limited or inconclusive evidence in patients with HFpEF or mildly reduced ejection fraction (HFmrEF) [1].

The paradigm shifted with the introduction of sodium-glucose cotransporter-2 inhibitors (SGLT2i), particularly dapagliflozin and empagliflozin, which have demonstrated significant benefits in this population, regardless of diabetes status (Table 1). Randomized controlled trials such as EMPEROR-Preserved and DELIVER documented a reduction in the composite risk of heart failure hospitalizations and cardiovascular mortality, in addition to improvements in quality of life, functional status (assessed by KCCQ), and slowing of renal function decline [2].

In the DAPA-HF trial (n = 4744), dapagliflozin significantly reduced the risk of the composite endpoint of cardiovascular death or worsening HF compared with placebo (HR 0.74; 95% CI 0.65–0.85), with benefits consistent in patients with and without type 2 diabetes [3, 4]. Similarly, the EMPEROR-Reduced trial (n = 3730) demonstrated that empagliflozin reduced the primary composite outcome of CV death or HF hospitalization (HR 0.75; 95% CI 0.65–0.86), with additional slowing of the decline in renal function [5].

Beyond chronic HFrEF, evidence also extends to patients with recent acute decompensation. The SOLOIST-WHF trial (n = 1222) evaluated sotagliflozin, a dual SGLT1/2 inhibitor, in patients with type 2 diabetes and recent worsening HF requiring hospitalization or intravenous therapy. Sotagliflozin significantly reduced the risk of the composite of total CV deaths, hospitalizations, and urgent visits for HF (HR 0.67; 95% CI 0.52–0.85), with consistent benefits across EF categories [6].

Despite these favorable clinical results, the pathophysiological mechanisms through which SGLT2i exert their effects remain under investigation. Leading hypotheses include:
• moderate and selective reduction of intravascular volume via osmotic natriuresis without significant neurohormonal activation;
• improvement in ventricular filling pressures and reduction of pulmonary congestion;
• attenuation of glomerular hyperfiltration, resulting in renal protection;
• stimulation of erythropoiesis mediated by increased erythropoietin and improved tissue oxygenation;
• activation of metabolic pathways mimicking a state of energy restriction, with increased ketone body production and improved mitochondrial efficiency [2, 7].

A surrogate marker frequently observed in clinical trials is the increase in hematocrit and hemoglobin concentration, reflecting both selective diuretic effect (with hemoconcentration) and stimulation of renal erythropoiesis. Post hoc analyses from the EMPA-REG OUTCOME trial suggested that the increase in hematocrit may represent one of the main mediators of empagliflozin's effect on reducing cardiovascular risk [8, 9].

The combination of SGLT2i with conventional diuretics (e.g., furosemide) is common in clinical practice, particularly in patients with more congestive phenotypes. However, such an association requires careful volume status assessment, as natriuretic effects may be additive, increasing the risk of dehydration, hypotension, and renal function deterioration, especially in elderly and frail patients. In such cases, a re-evaluation of diuretic dosing may be necessary when initiating SGLT2i therapy.

Overall, SGLT2i are redefining the role of diuretics in heart failure, shifting the therapeutic target

from mere fluid removal to optimization of hemodynamic, metabolic, and renal balance. Their early and systematic use, even in patients without hyperglycemia, is now a cornerstone strategy for the integrated management of chronic heart failure across the entire spectrum of ejection fraction.

Trial	N. of patients	Population	Mean eGFR (ml/min/1.73m²)	% with eGFR >60	Main Outcome
DAPA-HF (2019)	4744	HFrEF (LVEF ≤40%), con/senza T2D	~66	~70%	↓ CV death/HHF
EMPEROR-Reduced (2020)	3730	HFrEF (LVEF ≤40%), con/senza T2D	~62	~63%	↓ CV death/HHF; ↓ eGFR decline
EMPEROR-Preserved (2021)	5988	HFpEF/HFmrEF (LVEF >40%)	~61	~60%	↓ HHF; benefit independent of diabetes
DELIVER (2022)	6263	HFpEF/HFmrEF (LVEF >40%)	~61	~65%	↓ HHF/CV death
SOLOIST-WHF (2021)	1222	Recent WHF hospitalization, T2D only	~58	~55%	↓ CV death/HHF/urgent visits

Table 1. Key randomized trials of SGLT2 inhibitors in heart failure.

Loop diuretics: essential drugs but with a clinical cost

Loop diuretics, such as furosemide, torasemide, and bumetanide, remain an irreplaceable cornerstone in the treatment of heart failure with signs of volume overload. They act by blocking the sodium-potassium-chloride cotransporter (NKCC2) in the thick ascending limb of the loop of Henle, inducing powerful natriuresis and consequently reducing ventricular filling pressures and both systemic and pulmonary congestion [10].

However, chronic use is associated with several clinical drawbacks. Massive inhibition of sodium reabsorption stimulates marked neurohormonal activation, increasing renin, angiotensin II, aldosterone, norepinephrine, and vasopressin levels. Over time, this can offset the therapeutic effect, leading to diuretic resistance and worsening clinical outcomes [11, 12] (Table 2). In addition, loop diuretics can cause hypovolemia, hypotension, acute kidney injury, and electrolyte disturbances (hypokalemia, hypomagnesemia, hyponatremia), thereby increasing the risk of arrhythmias and mortality [13].

For these reasons, international guidelines recommend using the lowest effective dose to achieve symptomatic control of congestion, avoiding chronic and unnecessary escalation [1]. The clinical goal is not complete elimination of edema, but achieving a functional and tolerable balance for the patient.

In this context, SGLT2i are emerging as physiological modulators of sodium-water balance. Unlike loop diuretics, they act upstream in the proximal tubule, promoting a milder and more sustained osmotic natriuresis without significant neurohormonal activation [2]. This “gentler” but continuous mechanism enables therapeutic synergy with loop diuretics and, in some cases, allows for a reduction in loop diuretic dose.

In the DAPA-HF and EMPEROR-Preserved trials, the addition of SGLT2i avoided the need for diuretic dose escalation in clinically stable patients and, in selected subgroups, even allowed for a dose reduction over time [2, 6]. Furthermore, despite additive natriuretic effects, the incidence of adverse events related to volume depletion, such as symptomatic hypotension, renal dysfunction, and dehydration, was lower in SGLT2i-treated groups than in placebo [14].

This “diuretic-sparing effect,” combined with greater hemodynamic stability, gives SGLT2i a unique

therapeutic profile, justifying their early and integrated use in heart failure management, particularly in patients at risk of iatrogenic complications from conventional diuretics.

Class	Main Site of Action	RAAS/Sympathetic Activation	Typical Side Effects	Clinical Notes
Loop Diuretics (furosemide, torasemide, bumetanide)	NKCC2 in the thick ascending limb of the loop of Henle	Marked neurohormonal activation (↑ RAAS, ↑ SNS)	Hypovolemia, hypotension, AKI, hypokalemia, hypomagnesemia, hyponatremia, arrhythmias	Powerful; essential in acute congestion. Chronic high-dose use may lead to resistance
Thiazides (hydrochlorothiazide, metolazone, chlorthalidone)	NCC in the distal convoluted tubule	Moderate RAAS activation	Hyponatremia, hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia	Effective for hypertension; less potent in severe congestion; often used in combination therapy
Mineralocorticoid Receptor Antagonists (MRAs) (spironolattone, eplerenone)	Mineralocorticoid receptor in the collecting duct	Inhibit aldosterone-mediated activation	Hyperkalemia, gynecomastia (spironolactone)	Prognostic benefit in HFrEF; use with caution in CKD
SGLT2i (dapagliflozin, empagliflozin, ecc.)	SGLT2 (+NHE3) in the proximal tubule	Minimal or no neurohormonal activation	Genital mycotic infections, rare euglycemic ketoacidosis, mild initial “dip” in eGFR	Moderate, gentle, and self-limiting osmotic natriuresis; reduce HHF and CKD progression even in non-diabetics

Table 2. Comparative table: site of action, neurohormonal activation and adverse effects of diuretics vs SGLT2i.

Pharmacological differences: diuretics vs SGLT2i

Diuretics are a heterogeneous class of drugs with marked differences in pharmacodynamic and pharmacokinetic profiles. Loop diuretics, such as furosemide, torasemide, and bumetanide, act on the sodium-potassium-chloride cotransporter (NKCC2) in the thick ascending limb of the loop of Henle, inducing potent natriuresis. They display a steep dose-response curve with a well-defined ceiling effect: beyond a certain threshold, further dose increases do not enhance efficacy but only increase toxicity [15].

Thiazide diuretics, which act on the sodium-chloride cotransporter (NCC) in the distal convoluted tubule, have a flatter dose-response curve, implying a smaller gap between the minimum effective dose and the maximum dose [16]. This makes them potentially more predictable in blood pressure management, but less effective in treating severe congestion.

An additional critical aspect of loop diuretics is the variability in oral bioavailability. Furosemide, in particular, exhibits highly variable bioavailability (10–100%) due to differences in intestinal absorption, food interactions, and saturation of active tubular transport [17]. Conversely, torasemide and bumetanide have higher and more consistent bioavailability (>80%), making them preferable in certain clinical settings, especially in patients with impaired gastrointestinal absorption.

Individual response to diuretics is further influenced by genetic and biological factors. Polymorphisms in genes encoding tubular transporters, hepatic metabolism, and active renal transport can significantly affect efficacy and tolerance. Biological sex has also been associated with pharmacokinetic differences, likely due to hormonal influences, lean body mass, and hepatic and renal function [18 –20].

In contrast, SGLT2i display more stable and predictable pharmacokinetic profiles (Table 3). Drugs such as dapagliflozin, empagliflozin, and ertugliflozin have high oral bioavailability (78–90%), long

half-lives (10–13 hours), hepatic metabolism (via UGT1A9 or CYP3A4, depending on the compound), and minimal urinary excretion of the active drug, with low risk of accumulation or direct renal toxicity [21]. These features allow fixed once-daily dosing, regardless of meals, with minimal interindividual variation and low potential for drug-drug interactions.

Beyond the initial natriuretic effect, SGLT2i induce a sustained reduction in body weight over time, initially due to extracellular fluid loss and subsequently attributable to selective reduction in visceral fat mass. This is mediated by metabolic changes such as increased lipolysis, ketogenesis, and improved insulin sensitivity [7, 22].

These differences make SGLT2i particularly suited for long-term management of patients with heart failure or type 2 diabetes, with fewer pharmacokinetic fluctuations, lower risk of electrolyte disturbances, and greater hemodynamic stability compared to conventional diuretics.

Molecole (Italy)	Dose in major CV/renal trials	SGLT2: SGLT1 selectivity (≈)	Outcome evidence (summary)	Dosing by eGFR and minimum threshold (EU SmPC)	Indications
Dapagliflozin	10 mg qd (DAPA-HF, DELIVER, DAPA-CKD)	≈1200:1	↓ CV death/HF hospitalization in HFrEF/HFpEF; ↓ CKD progression and all-cause mortality, with or without diabetes	Single 10 mg dose; do not initiate if eGFR <25 mL/min; reduced hypoglycemic effect <45	Also for non-diabetic patients (HF, CKD, T2D)
Empagliflozin	10 mg qd (EMPEROR-Reduced/Preserved, EMPA-KIDNEY)	≈2700:1	↓ HF hospitalization and CV mortality in HF; ↓ CKD progression	10 mg qd; initiation not recommended if eGFR <20 mL/min; reduced hypoglycemic effect <45	Also for non-diabetic patients (HF, CKD, T2D)
Canagliflozin	100 mg qd (CREDENCE); 100–300 mg qd (CANVAS)	≈160–200:1	↓ composite renal and CV events in DKD (T2D); ↓ MACE (CANVAS)	100 mg qd; initiation not recommended if eGFR <30 mL/min; indicated only for DKD with T2D	Diabetic patients only (T2D ± DKD)
Ertugliflozin	5–15 mg qd (VERTIS-CV)	≈2000:1	Non-inferior for MACE in T2D; signal for ↓ HF hospitalization (post hoc); no HF/CKD indication	Initiation not recommended if eGFR <60; discontinue if <45; contraindicated <30	Diabetic patients only (T2D)

Table 3. Pharmacological differences: SGLT2 inhibitors available in Italy.

Renal adaptations to SGLT2i and clinical significance: modulation of sodium balance and hemodynamic impact

The human kidney filters the entire plasma volume approximately 30–40 times daily, producing over 170 liters of ultrafiltrate per day. About 99% of this is reabsorbed along the nephron. The proximal tubule, responsible for reabsorbing 60–70% of filtered water and sodium, represents a key physiological hub for fluid-electrolyte balance and is the primary site of SGLT2i action [23, 24].

Initially developed for type 2 diabetes mellitus, SGLT2i exert their natriuretic effects through dual inhibition of the sodium-glucose cotransporter SGLT2 and the sodium-hydrogen exchanger NHE3, both located in the S1-S2 segment of the proximal tubule [23, 25]. This dual mechanism reduces reabsorption of sodium, glucose, and water, producing an osmotic effect that increases diuresis and natriuresis, leading to modest reductions in plasma volume and blood pressure [26]. However, despite blocking up to 20-25% of proximal sodium reabsorption, the clinical impact on volume status is modest and self-limiting. This is attributable to the distal nephron's substantial capacity –

particularly the thick ascending limb of the loop of Henle, distal tubule, and collecting duct – to activate compensatory sodium and water reabsorption mechanisms [27]. These adaptations occur rapidly, effectively preventing marked hypovolemia or dehydration while preserving renal perfusion.

From a hemodynamic perspective, SGLT2i reduce intraglomerular pressure through restoration of tubuloglomerular feedback: increased sodium delivery to the macula densa triggers afferent arteriolar vasoconstriction, thereby reducing glomerular hyperfiltration – a key pathogenic mechanism in diabetic and non-diabetic nephropathies [28, 29]. This effect is entirely distinct from conventional diuretics, such as thiazides or loop diuretics, which produce more marked plasma volume reductions, often associated with symptomatic hypotension, acute kidney injury, RAAS activation, and electrolyte disturbances (hypokalemia, hyponatremia) [10].

Moreover, unlike traditional diuretics, the natriuretic effect of SGLT2i diminishes over time, stabilizing at a new physiological set point without chronic sodium or volume loss. This “plateau” aligns with their safety profile, even in elderly or frail patients, and contributes to their excellent tolerability [30].

Overall, SGLT2i provide a modulated and self-regulating diuretic and natriuretic action compatible with renal and systemic hemodynamic protection. This unique pharmacodynamic profile supports their use not only in diabetic patients but also in those with heart failure or chronic kidney disease, regardless of glycemic status, as confirmed by recent clinical trials (EMPA-REG OUTCOME, DAPA-HF, EMPEROR-Reduced, CREDENCE, DAPA-CKD) [26–30].

Renal function and therapeutic use

Renal function deterioration is one of the main negative prognostic factors in patients with heart failure and is associated with increased risk of mortality, hospitalizations, and functional decline [35]. This condition, known as cardiorenal syndrome, is often exacerbated by chronic, high-dose use of loop diuretics which – although essential for congestion control – can induce renal hypoperfusion, neurohormonal activation, and electrolyte imbalances, further compromising glomerular function [35, 37].

Numerous observational studies and clinical trials have shown a direct correlation between the intensity of diuretic therapy and adverse outcomes, suggesting that diuretics are more a marker of disease severity than a causal determinant, but nonetheless emphasizing the importance of titrating to the lowest effective dose. ESC and ACC/AHA/HFSA guidelines recommend periodic reassessment of diuretic therapy and progressive dose reduction in the setting of clinical stabilization and absence of residual congestion [1, 39].

Unlike conventional diuretics, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have shown a favorable impact on the course of kidney disease and hemodynamic stability, even in patients with advanced renal impairment. Although their action occurs in the proximal tubule, the mechanism is not strictly dependent on glomerular filtration rate (GFR), and clinical efficacy is preserved even at reduced eGFR levels, although the glucose-lowering effect progressively diminishes [41].

Multiple clinical trials (CREDENCE, DAPA-CKD, EMPA-KIDNEY) have demonstrated that SGLT2i significantly slow the progression of chronic kidney disease, reduce the need for dialysis, and lower hospitalization and mortality from cardiovascular and renal causes, with benefits evident even at eGFR values below 30 mL/min/1.73m² [48]. Recent evidence, including the EMPA-KIDNEY trial, supports safe use of SGLT2i down to an eGFR of 20 mL/min/1.73 m², extending therapeutic indications to patients in the pre-dialysis stage [33, 34].

Furthermore, the initial decline in eGFR observed after SGLT2i initiation represents a predictable hemodynamic response, attributable to the reduction in intraglomerular pressure and restoration of tubuloglomerular feedback. This phenomenon, known as the “transient dip,” stabilizes within weeks and does not predict progressive kidney injury; in fact, it is associated with a slower decline in renal function over the long term [34].

Beyond the expected and generally benign “transient dip,” dedicated analyses suggest that an initial eGFR decline >30% may be associated with worsening renal function in vulnerable subgroups. In the supplementary analyses of EMPEROR-Reduced, a >30% dipping was correlated with adverse renal outcomes, highlighting the importance of identifying and monitoring at-risk patients [51]. In EMPA-REG OUTCOME, baseline diuretic use and higher KDIGO risk were predictive of eGFR dip after SGLT2i initiation, although without attenuating the cardio-renal benefits of treatment [52]. In real-world cohorts, loop diuretics were associated with both a more pronounced dipping and worse composite renal outcomes during SGLT2i therapy, whereas RAAS inhibitors retained a favorable association with long-term outcomes [53]. A large-scale analysis further showed that the presence of dipping does not negate the clinical benefits of SGLT2i, but underscores the need to contextualize this phenomenon within the overall frailty profile of each patient [54].
In clinical practice, particularly in frail elderly patients receiving polypharmacy (especially those on loop diuretics), it is prudent to: (i) re-evaluate the overall loop diuretic dose at SGLT2i initiation; (ii) optimize hydration and reassess potentially nephrotoxic or volume-depleting medications; (iii) recheck serum creatinine/eGFR approximately 30 days after initiation (or earlier in the presence of symptoms or hypotension) and subsequently as clinically indicated; (iv) consider loop diuretic down-titration if signs of volume depletion or significant dipping occur. This approach helps balance, in the context of cardiorenal syndrome, the cardiac and renal prognostic axes, prioritizing the net clinical benefit of treatment rather than optimization of a single domain.

Taken together, these findings position SGLT2i as first-line cardiorenal protective agents in the integrated management of heart failure and chronic kidney disease, including patients with reduced renal function, in whom traditional diuretics may be more unstable and potentially iatrogenic.

Therapeutic implications in the elderly and in clinical practice

In clinical practice, managing diuretic therapy in frail elderly patients or those with multimorbidity requires particular caution. Chronic, non-individualized use of diuretics is frequently associated with adverse events such as fatigue, reduced exercise tolerance, orthostatic hypotension, and acute kidney injury, especially in individuals with impaired physiological reserve and altered extracellular volume homeostasis [36, 50].

These effects are worsened by common prescribing errors, such as the use of diuretics for peripheral edema secondary to calcium channel blocker therapy (e.g., amlodipine), or for fluid retention induced by neuroactive drugs such as gabapentinoids or antipsychotics. When such interventions are not based on an adequate etiopathogenetic evaluation, they constitute typical examples of a prescribing cascade, i.e., a drug prescribed to treat the adverse effects of another medication without addressing the underlying cause [36, 37]. These situations not only expose patients to further side effects but also compromise quality of life and functional independence.

The introduction of SGLT2i into the treatment of heart failure and chronic kidney disease has significantly modified the therapeutic approach in elderly patients. While they exert a mild but physiological natriuretic and diuretic effect, SGLT2i can interact additively with conventional diuretics, increasing the risk of dehydration, hypotension, electrolyte imbalance, and renal function deterioration, particularly in frail and hypovolemic individuals [2, 34].

For this reason, combined use of SGLT2i and diuretics requires careful clinical and laboratory monitoring, with possible diuretic dose reduction when starting SGLT2i, especially in the presence of concomitant hypotension or renal function decline.

Despite their generally favorable safety profile, SGLT2i are not without risks. Known adverse effects include an increased risk of genital and urinary tract infections, mainly mycotic, particularly in women, and rare cases of euglycemic ketoacidosis, often associated with metabolic stress (e.g., prolonged fasting, infections, surgery) [36, 37]. Some observational studies and meta-analyses have also suggested a possible increased risk of digital amputations (particularly with canagliflozin) [55] and bone fractures, although these data remain debated and not uniformly confirmed [56].

An additional contribution comes from the EMPA-ELDERLY trial [57], a randomized, double-blind, placebo-controlled study conducted in Japan in patients aged ≥ 65 years with type 2 diabetes, with a follow-up of 52 weeks, designed to assess the efficacy and safety of empagliflozin 10 mg in an elderly population. The trial showed that empagliflozin, compared with placebo, reduced HbA_1c (–0.57%, 95% CI –0.78; –0.36) and body weight (–2.37 kg, 95% CI –3.07; –1.68) without significant loss of muscle mass or handgrip strength. No ketoacidosis or severe volume-depletion events occurred, even in participants ≥ 75 years. Although UTIs were not reported as a leading adverse event, “drug-related adverse events” were more frequent with empagliflozin (24.6% vs 9.4%), underscoring the need for careful monitoring of frail older patients, particularly those predisposed to UTIs.

Therefore, the use of SGLT2i in the geriatric population should be considered within a personalized approach, integrated into a deprescribing model and periodic medication review, aimed at reducing inappropriate polypharmacy and optimizing the risk-benefit profile.

Heart failure and innovative drugs with diuretic effect

A further consideration concerns the role of angiotensin receptor-neprilysin inhibitors (ARNI), particularly sacubitril/valsartan, in the management of heart failure. Beyond their established prognostic benefits, ARNI exert indirect diuretic and natriuretic effects through augmentation of endogenous natriuretic peptides, which promote vasodilation, natriuresis, and inhibition of maladaptive neurohormonal activation [58, 59]. In clinical practice, these effects can contribute to a reduction in loop diuretic requirements, potentially mitigating diuretic-related adverse events in frail or multimorbid patients [60]. Nevertheless, careful monitoring remains essential, as the concomitant use of ARNI and conventional diuretics may still predispose to hypotension, electrolyte disturbances, and renal dysfunction, especially in the elderly population.

Conclusions

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) represent a major breakthrough in the management of heart failure, both with reduced (HFrEF) and preserved (HFpEF) ejection fraction, due to their multifactorial and integrated mechanism of action. In addition to improving clinical symptoms, these agents are associated with significant reductions in cardiovascular mortality, heart failure hospitalizations, and progression of kidney disease, with benefits extending to non-diabetic patients [2].

Unlike conventional diuretics, which act rapidly but forcefully on sodium-water balance, SGLT2i provide a modulated, physiological diuretic action mediated by osmotic natriuresis in the proximal tubule. This mechanism allows selective reduction of extracellular volume while preserving intravascular volume and maintaining renal perfusion, without activating the renin-angiotensin-

aldosterone system (RAAS) or the sympathetic nervous system [2, 39, 61].

This approach translates into superior hemodynamic and renal protection, with lower incidence of adverse events such as dehydration, orthostatic hypotension, and renal function deterioration compared to loop diuretics, particularly in elderly and frail patients [17, 62]. In addition, favorable effects on hematocrit and endothelial function suggest potential benefits on microcirculation and tissue oxygenation [5].

SGLT2i should therefore not be regarded as mere “add-on diuretics” but rather as modulators of volume set-point and cardiovascular homeostasis, capable of targeting deep pathophysiological mechanisms such as glomerular hyperfiltration, low-grade chronic inflammation, mitochondrial dysfunction, and insulin resistance [7–63].

Given the accumulated evidence, early placement of SGLT2i in the integrated therapeutic strategy for heart failure is now recommended by international guidelines, regardless of ejection fraction or diabetes status, making them one of the most revolutionary drug classes in contemporary cardiology and nephrology [1].

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