REUE | Review Article

Sodium-glucose co-transporter 2 inhibitors: their role in heart failure management in Emergency Departments

Pere Llorens[1,2]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are effective in patients with heart failure across the ejection fraction (EF) spectrum. These drugs have been shown to reduce admissions for heart failure and emergency department visits. They also reduce arrhythmias and lower cardiovascular and all-cause mortality. Current evidence suggests that SGLT2 inhibitors should be prescribed early in heart failure regardless of the patient's EF or the presence or not of diabetes mellitus. This review discusses the benefits of SGLT2 inhibitors in heart failure with reduced, slightly reduced, or preserved EF, given that these drugs clearly lower morbidity and mortality when started early. Available evidence supports their use in acute or chronic heart failure. Tolerance is good and there is no need for titration.

Keywords: Heart failure. Sodium-glucose co-transporter 2 (SGLT2) inhibitor. Emergency health services.

Uso precoz de los inhibidores del cotransportador de sodio-glucosa tipo 2 (iSGLT2) en pacientes con insuficiencia cardiaca atendidos en urgencias

Los inhibidores del cotransportador de sodio-glucosa (iSGLT2) son eficaces en la insuficiencia cardiaca (IC) con cualquier rango de la fracción de eyección (FE). Han demostrado reducción de ingresos por IC, arritmias, visitas a urgencias, mortalidad cardiovascular y mortalidad por otras causas. La evidencia actual indica que los iSGLT2 deben ser iniciados de forma precoz en los pacientes con IC independientemente de su FE o de la presencia o no de diabetes mellitus (DM). En este trabajo revisamos los beneficios de los iSGLT2 tanto en la IC con FE reducida, con FE ligeramente reducida y conservada, quedando patente que los efectos de reducción de la morbimortalidad se inician de forma precoz tras su Introduction. En conjunto, la evidencia actual apoya su uso tanto en IC aguda y crónica iniciado desde urgencias, con buena tolerancia y sin necesidad de titulación.

Palabras clave: Insuficiencia cardiaca. iSGLT2, inhibidor del cotransportador sodio-glucosa tipo 2. Servicios de urgencias.

Introduction

Heart failure (HF) is a complex clinical syndrome resulting from structural or functional cardiac abnormalities. It is characterized by progressive symptoms leading to emergency department visits and frequent hospitalizations, deterioration in quality of life, and a high mortality rate. It represents the leading cause of hospitalization among patients over 65 years of age. HF accounts for 2% of Spain's annual healthcare expenditure, and hospitalizations are responsible for 75–85% of that cost, with a high economic impact.[1]

Most HF decompensations are evaluated in emergency departments (EDs), and it is estimated that approximately 25% of patients are discharged directly from these care areas.[2]

The goals of medical treatment for HF are to reduce all-cause and cardiovascular mortality, decrease hospitalizations and ED visits, improve functional capacity and quality of life, and prevent or delay deterioration of cardiac function—that is, to modify the temporal progression of HF.[3]

Several clinical trials have shown that treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, or mineralocorticoid receptor antagonists significantly reduces morbidity and mortality in patients with HF with reduced ejection fraction (HFrEF). In recent years, other therapeutic targets involved in HF pathogenesis have been identified, and treatments have been developed accordingly. Among these, sacubitril-valsartan stands out, having demonstrated a benefit in morbidity and mortality (PARADIGM-HF Trial) in patients with HFrEF.[4]

Author Affiliations: [1]Servicio de Urgencias, Unidad de Estancia Corta y Hospitalización a Domicilio, Hospital Doctor Balmis de Alicante, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Universidad Miguel Hernández, Alicante, Spain. [2]Coordinador de Grupo de Trabajo de Insuficiencia Cardiaca Aguda de la Sociedad Española de Urgencias y Emergencias (Grupo ICA-SEMES).
Corresponding Author: Pere Llorens. Servicio de Urgencias Generales. Hospital General Dr. Balmis de Alicante. C/ Pintor Baeza, 12. 03010 Alicante, Spain.
E-mail: llorens_ped@gva.es
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Another therapeutic innovation is sodium–glucose cotransporter-2 (SGLT2) inhibitors (SGLT2i). In individuals with type 2 diabetes mellitus, they showed a reduction in HF hospitalizations. Studies of SGLT2i (dapagliflozin, empagliflozin, and sotagliflozin) in patients with HF—regardless of metabolic profile—have demonstrated their benefit and clinical utility.[5]

Under physiological conditions, most of the glucose filtered in the glomerulus is reabsorbed by the SGLT1 and SGLT2 cotransporters. SGLT2 transporters are mainly expressed in the kidney and are responsible for 90% of filtered glucose reabsorption. Therefore, SGLT2 inhibition leads to glucosuria and natriuresis, the magnitude of which depends on circulating glucose concentration and kidney function, decreasing in patients without hyperglycemia and with a glomerular filtration rate (GFR) < 45 mL/min.[6]

It has also been observed that adding SGLT2i to loop diuretics provides osmotic diuresis, minimizes electrolyte disturbances, and avoids activation of the sympathetic nervous system and the renin–angiotensin system.[7]

SGLT2i are associated with a mild, reversible, and transient decrease in GFR due to afferent glomerular arteriolar vasoconstriction. This results in reduced albuminuria and decreased glomerular hyperfiltration, leading to better long-term renal preservation.[8]

Furthermore, SGLT2-related glucosuria improves glycemic control and reduces body mass through caloric loss. A slight decrease in blood pressure and plasma uric acid levels is also observed. Additionally, endothelial function improves, and various neuromodulatory effects have been described.[9]

A general overview of the mechanism and site of action of SGLT2i is shown in Figure 1.

SGLT2i are essential drugs in the daily clinical management of HF, as they have been shown to reduce HF admissions, ED visits, arrhythmias, cardiovascular mortality, and all-cause mortality—independently of systolic function, degree of renal insufficiency, and the presence of diabetes mellitus (DM).[7]

SGLT2i have been proven effective in HF across all ejection-fraction ranges: < 40% (HF with reduced EF, HFrEF), 40–50% (HF with mildly reduced EF, HFmrEF), and > 50% (HF with preserved EF, HFpEF). Although some trials included patients with acute heart failure (AHF), most studies included patients with stable chronic HF; however, this should not prevent their prescription from the ED. Current evidence indicates that SGLT2i should be initiated across the full spectrum of EF and renal function in patients with HF—with or without diabetes—from any care setting and as early as possible.[10,11]

In this document, we review the benefits of SGLT2i across the full HF spectrum and offer several recommendations to guide emergency physicians in initiating and maintaining SGLT2 inhibitor therapy from the ED.

SGLT2i and HFrEF

Two major clinical trials conducted in patients with HFrEF, the EMPEROR-Reduced[11] and the DAPA-HF,[12] provided evidence of the main benefits associated with the use of SGLT2i in this patient profile. Both the EMPEROR-Reduced and the DAPA-HF tirals included patients with HFrEF, regardless of the presence of DM. The benefit for the primary endpoint (cardiovascular-CV death, HF hospitalization, and urgent visit) was nearly identical in both trials: DAPA-HF: hazard ratio (HR), 0.74, 95% CI, 0.65–0.85; EMPEROR-Reduced: HR, 0.75; 95% CI, 0.65–0.86. In DAPA-HF, all components of the primary endpoint were significantly reduced, whereas in the EMPEROR-Reduced, the benefit was mainly due to a reduction in HF hospitalizations. However, a subsequent meta-analysis of both trials did not show any significant heterogeneity in the reduction of combined primary-endpoint events.[13] The 2 trials served as the basis for defining Class IA recommendations in major international HF management guidelines.

SGLT2i in HFmrEF and HFpEF

The EMPEROR-Preserved trial[14] specifically evaluated the effect of SGLT2i in patients with LVEF ≥ 40%. The effect of empagliflozin on the combined endpoint of CV death or HF hospitalization was assessed in 5,988 patients with NYHA class II–IV HF and LVEF ≥ 40%. The reduction in the primary endpoints was nearly identical to that ob-

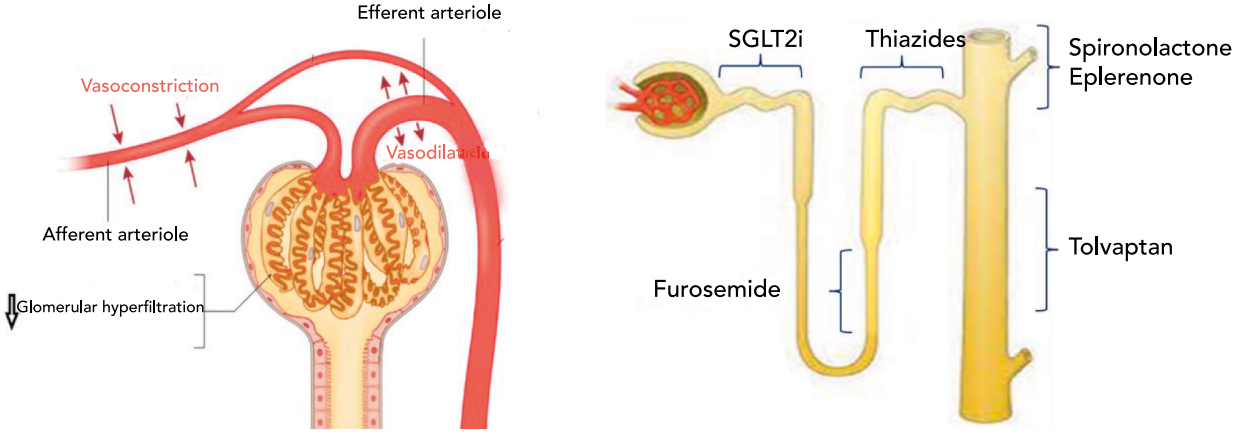

Figure 1. Mechanism of action of SGLT2i at the renal level and localization of their effects in relation to different types of diuretics.

Table 1. Demographic and history/consumption characteristics

Characteristics	EMPEROR-Reduced[11]	EMPEROR-Preserved[14]	EMPA-RESPONSE-AHF[17]	EMPULSE[18]	DAPA-HF[12]	DELIVER[15]	SOLOIST-WHF[19]
iSGLT2	Empaglifozina	Empagliflozina	Empaglifozina	Empaglifozina	Dapaglifozina	Dapagliflozin	Sotagliflozina
Number of patients	3,730	5,988	80	530	4,744	6,263	1,222
Year of publication	2020	2021	2020	2022	2019	2022	2021
Inclusion criteria	LVEF ≤ 40% NYHA class II–IV	LVEF > 40% NYHA II–IV	Any LVEF Signs of congestion NT-proBNP ≥ 1,400 pg/mL IV diuretics Start within first 24 h after admission	Any LVEF De novo HF or decompensated chronic HF NT-proBNP ≥ 1,600 pg/mL IV diuretics Start between days 1–5 of admission	NYHA II–IV LVEF ≤ 45%	LVEF > 40% NYHA II–IV Outpatients or hospitalized	Any LVEF T2DM Decompensated HF on chronic diuretic therapy Start if hemodynamically stable within 3 days before hospital discharge
Glomerular filtration	eGFR ≥ 20 mL/min	eGFR ≥ 20 mL/min	eGFR ≥ 20 mL/min	eGFR ≥ 20 mL/min	eGFR ≥ 30 mL/min	eGFR ≥ 25 mL/min	eGFR ≥ 30 mL/min End-stage HF
Combined favorable effects	CV death All-cause mortality HF hospitalization	CV death HF hospitalization	HF hospitalization Worsening in-hospital HF 60-day mortality Increased diuresis No adverse BP or renal effects	All-cause mortality HF event counts, time to first HF event KCCQ changes	HF worsening CV death	CV death HF worsening	CV death HF hospitalization ED visits

CV: cardiovascular; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; HF: heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire total symptom score; NYHA: New York Heart Association; BP: blood pressure.

served in HFrEF (HR, 0.79, 95% CI, 0.69–0.90; $P < .001$) and was mainly related to a lower risk of HF hospitalization in the empagliflozin group (similar to the EMPEROR-Reduced). Notably, this was the first trial in HFpEF to demonstrate unequivocally positive results.

In addition, the DELIVER trial,[15] which tested dapagliflozin's effect on the composite endpoint of CV death, HF hospitalization, and urgent HF visit in patients with LVEF ≥ 40%, showed a reduction in HF worsening—defined as unplanned HF hospitalization, urgent HF visit, or CV death (HR, 0.82, 95% CI, 0.73–0.92; $P < .001$). These findings further supported the evidence of a homogeneous effect of SGLT2i across all EF ranges.

Overall, results from trials in both HFrEF and HFpEF indicate that SGLT2i (particularly empagliflozin) are beneficial regardless of LVEF.

A recent meta-analysis of the EMPEROR-Reduced and EMPEROR-Preserved trials, examining empagliflozin across the entire EF spectrum, showed that the benefit on the risk of first HF hospitalization was very similar up to an EF of 64%. These findings further support that the effect of SGLT2i is homogeneous in most patients with HF, regardless of EF.[16]

SGLT2i in AHF

The EMPA-RESPONSE-AHF trial[17] evaluated the effect of empagliflozin in patients with AHF (mean EF 36%) on symptoms, diuretic response, and changes in NT-proBNP levels from baseline to day 4, as well as on the composite endpoint of in-hospital HF worsening, all-cause mortality, and HF hospitalization up to day 60. Despite the small sample size (n = 80), empagliflozin increased diuresis and reduced the combined outcome compared with placebo.

The EMPULSE trial[18] evaluated early initiation of empagliflozin—randomization within 24 hours of admission and administration at a median of 3 days after admission—in AHF across the full EF spectrum (mean EF, 31%), regardless of DM status. Empagliflozin significantly improved the composite endpoint of death, number of HF hospitalizations and/or urgent HF visits and/or unplanned outpatient visits, and time to first HF event, by approximately 30% (Win Ratio, 1.36; 95% CI, 1.09–1.68; $P = .005$).

The SOLOIST-WHF trial[19] evaluated SGLT2 inhibitor initiation during or shortly after a hospitalization for worsening HF in patients with reduced or preserved EF and type 2 DM (mean EF, 35%). Sotagliflozin reduced by approximately 30% the total number of CV deaths, HF hospitalizations, and urgent HF visits compared with placebo (HR, 0.67, 95% CI, 0.52–0.85). Effects on CV death and first HF hospitalization were similar (HR, 0.71, 95% CI, 0.56–0.89).

Results from EMPA-RESPONSE-AHF, EMPULSE, and SOLOIST-WHF indicate that SGLT2i can be safely initiated in patients hospitalized for worsening HF, with benefits comparable to those observed in stable chronic HF. From our perspective, SGLT2i should be started in AHF patients discharged directly from the ED, as these patients are hemodynamically stable, have good oral tolerance without hypovolemia, and have already undergone effective decongestion in a hospital setting.

Table 1 illustrates a comparison of major clinical trials of SGLT2i in HF.

Safety of SGLT2i

In the first few weeks following initiation of SGLT2 inhibitors, a transient and reversible decline in GFR occurs,

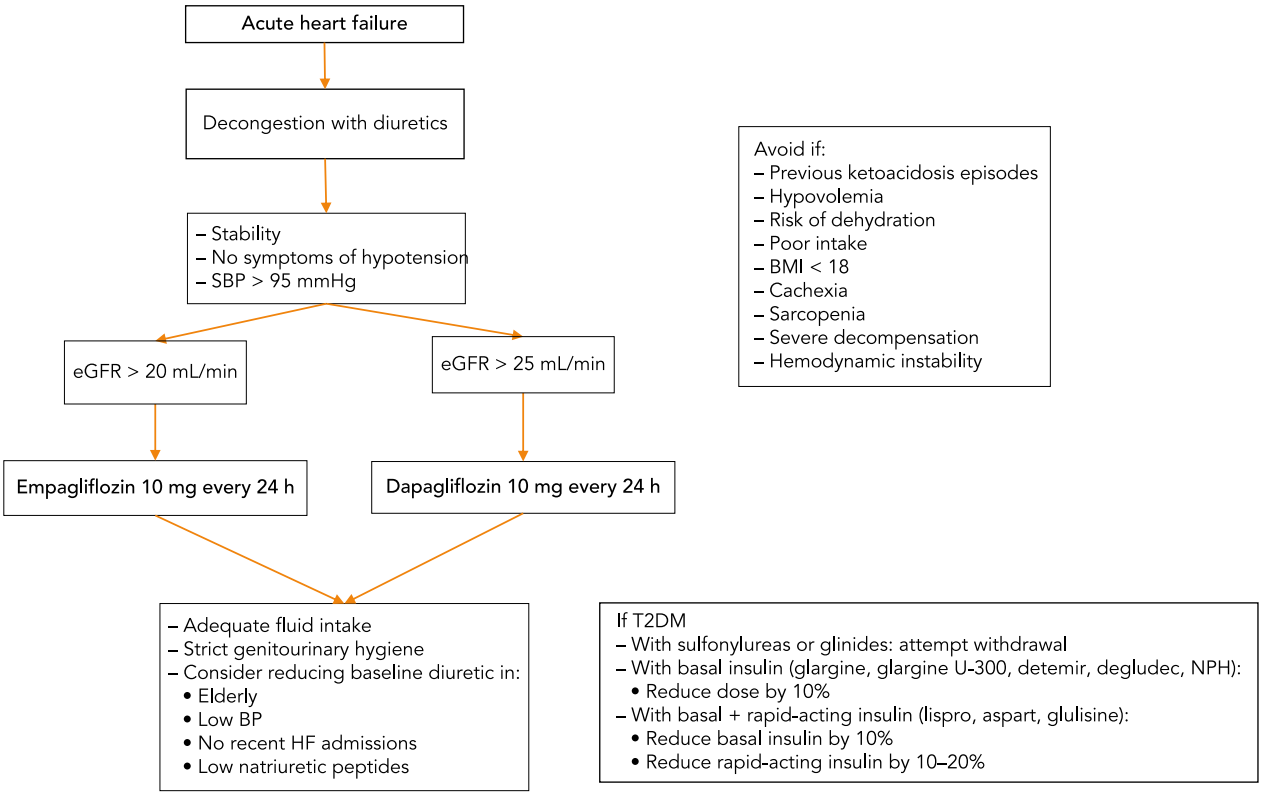

Figure 2. Algorithm for initiating SGLT2i in patients with acute heart failure in emergency departments.
DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HF: heart failure; BMI: body mass index; SBP: systolic blood pressure.

which is not associated with reduced clinical benefit or increased adverse events. Therefore, an initial GFR drop of < 30% should notl ead to discontinuation. Of note, SGLT2 inhibitor efficacy is not diminished by baseline renal dysfunction, considering that HF trials included patients with GFR > 20 mL/min in the case of empagliflozin.20 Rates of adverse events such as hypotension, significant renal worsening, and volume depletion were similar between SGLT2 inhibitor groups and placebo in multiple trials.[11-15]

The main adverse event associated with SGLT2i is urogenital mycotic infection, which is less common in patients without DM. It should be treated systemically and generally does not require drug discontinuation. Strict genital hygiene is advised when starting therapy.

A slightly increased risk of ketoacidosis has been observed; however, the absolute risk increase is low (0.3% per year) and occurs primarily in patients with sarcopenia or low BMI, abrupt insulin dose reduction after starting therapy, dehydration or hypovolemia, low food intake, or recent episodes of ketoacidosis.[5,8,20]

SGLT2i have a relatively mild effect on systolic blood pressure (SBP), lowering it by approximately 3–5 mmHg. In any case, the favorable effects and safety of SGLT2i do not depend on baseline BP, as demonstrated in EMPEROR-Reduced and DAPA-HF.[14,15]

Initiation and maintenance of SGLT2 inhibitors

Whenever possible, given their unquestionable beneficial effect on morbidity and mortality, SGLT2i should be initiated or maintained in patients with HF during emergency care. Before initiating the drug upon ED discharge or at hospital admission for AHF, the patient must be clinically and hemodynamically stable and able to tolerate oral intake. Due to their favorable safety profile, initiating and continuing SGLT2i is likely easier to achieve than with other HF prognostic-modifying drugs, which are frequently discontinued or require titration. In contrast, SGLT2i are prescribed as a single fixed dose (eg, empagliflozin 10 mg every 24 h) without the need for titration.[5]

A special mention must be made regarding patients with HFpEF, as SGLT2i are the only treatment that provides proven morbidity and mortality benefit. Therefore, emergency physicians must consider and encourage their use over any other medical therapy in this population, both for initiation and continuation.

Another important point is recognizing that the clinical benefit of SGLT2i begins rapidly. For instance, empagliflozin reduced the combined risk of death, HF hospitalization, or urgent visit as early as 12 days after therapy initiation.[11]

Figure 2 illustrates an algorithm for initiating SGLT2i in AHF patients in the ED, including general recommendations for patients with T2DM, older adults, and groups at higher risk for adverse events.

Contraindications and precautions for SGLT2i

Sotagliflozin and dapagliflozin may be initiated only in patients with an eGFR > 25 mL/min, whereas empagliflozin may be started at an eGFR of ≥ 20 mL/min. Current data

on the use of SGLT2i in end-stage renal disease or in patients on hemodialysis are limited.

As previously noted, SGLT2i are associated with an increased risk of ketoacidosis. Although most patients with T2DM are eligible for SGLT2 therapy, caution is warranted when risk factors are present (shown in Figure 2). Nevertheless, in the context of the clinical trials referenced, the absolute risk of ketoacidosis remained < 2%.[11-15]

Conclusions

Overall, the evidence from multiple clinical trials conducted in different settings—both acute and chronic— and in various HF phenotypes (HFrEF, HFmrEF, HFpEF) demonstrates a beneficial effect of SGLT2i on all-cause mortality, CV mortality, the need for hospitalization or urgent visits, and HF worsening, with good tolerance in most clinical scenarios. Therefore, emergency physicians cannot afford to miss opportunities[21,22] when evaluating HF patients in the ED and must avoid contributing to the therapeutic inertia observed in HF management over recent decades.[23,24] For these reasons, not prescribing SGLT2i to HF patients should be the exception.

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