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Unexpected therapeutic scenarios: initiating SGLT2 inhibitors in de novo heart failure without echocardiography

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In the field of heart failure, sodium–glucose cotransporter 2 inhibitors (SGLT2-i) have demonstrated robust efficacy and have received a Class I, Level A recommendation for reducing the risk of heart failure hospitalizations and cardiovascular mortality across the entire spectrum of left ventricular ejection fraction. The therapeutic effect occurs early, with the first statistical significance observed as soon as 12–28 days after treatment initiation. Evidence suggests that early introduction during hospitalization may reduce the short-term risk of cardiovascular death or worsening heart failure. SGLT2 inhibitors display a favourable safety and tolerability profile, without an increased incidence of adverse events compared with placebo. Furthermore, they are indicated for the treatment of type 2 diabetes mellitus and chronic kidney disease, irrespective of the presence of heart failure. Therefore, we propose that in patients presenting with signs and/or symptoms of heart failure and elevated natriuretic peptide levels, SGLT2 inhibitors may be initiated even before echocardiographic confirmation of the diagnosis. Given the favourable risk–benefit profile, this approach may help avoid therapeutic delay, which could otherwise be associated with an increased risk of early adverse events, and may ultimately improve prognosis.

Introduction

Recent data indicate that heart failure has a growing prevalence (1–3%), high mortality rates (2–3% at 30 days, 15–30% at 1 year, and up to 50–75% at 5 years) and an annual per-patient cost of up to €25 000.[1] The 2021 universal definition of heart failure defines it as a clinical syndrome characterized by signs and symptoms resulting from a structural and/or functional cardiac abnormality, supported by at least one of the following: (i) elevated natriuretic peptide levels or (ii) objective evidence of cardiogenic pulmonary or systemic congestion at rest or during exercise, assessed by instrumental testing.[2]

In recent years, substantial evidence has accumulated regarding the SGLT2 inhibitors dapagliflozin and empagliflozin, leading to a Class I recommendation, Level of Evidence (LoE) A in heart failure with reduced ejection fraction (HFrEF), where they are considered one of the fundamental 'pillars' of therapy, as well as in heart failure with mildly reduced (HFmrEF) and preserved (HFpEF) ejection fraction. As early as 2021, Milton Packer and John McMurray advocated for their early initiation.[3] Subsequently, the update of the

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Table 1 Arguments for and against early initiation of SGLT2 inhibitors before echocardiography in suspected heart failure

In Favour	Against
The treatment effect is independent of ejection fraction values.	Echocardiography is required to identify structural and/or functional cardiac abnormalities underpinning the universal definition of heart failure.
SGLT2 inhibitors have a Class I recommendation, Level of Evidence A, for reducing the risk of heart failure hospitalization or cardiovascular death.	Echocardiography may not confirm the suspected diagnosis of heart failure.
Clinical benefit occurs early, with first statistical significance observed between 12 and 28 days across pivotal trials.	Echocardiography may reveal specific cardiomyopathies not represented in pivotal randomized clinical trials.
Early initiation during hospitalization for heart failure may reduce the early risk of cardiovascular death or worsening heart failure.	—
Diagnostic delays may lead to therapeutic delay, exposing patients to an increased risk of adverse events.	—
SGLT2 inhibitors have a favourable safety and tolerability profile, allowing early initiation without increased risk of adverse events.	—
SGLT2 inhibitors are indicated and reimbursable for the treatment of type 2 diabetes mellitus and chronic kidney disease, irrespective of a history of heart failure.	—

European Society of Cardiology heart failure guidelines emphasized the importance of rapid initiation and titration of disease-modifying therapies for HFrEF, including SGLT2 inhibitors. An analysis of the Swedish Heart Failure Registry further demonstrated that real-world eligibility for SGLT2 inhibitor therapy is high, encompassing approximately 80% of patients with HFrEF and 75% of those with HFmrEF and HFpEF.[4]

More recently, the question has arisen as to whether SGLT2 inhibitors could be initiated early in patients with a clinical diagnosis of heart failure, without waiting for echocardiographic evaluation, which may be subject to significant delays. In the following sections, we aim to provide a conceptual framework to address this issue (*Table 1*).

Left ventricular ejection fraction and SGLT2 inhibitors

The most relevant argument regarding the role of left ventricular ejection fraction (EF) is that it allows heart failure to be categorized into distinct phenotypes (HFrEF, HFmrEF, HFpEF), which is fundamental for defining therapeutic strategies. Indeed, the available evidence on drugs efficacy derives from a series of clinical trials that were designed using EF thresholds as key inclusion criteria for patient selection. However, EF *per se* is not required to establish a diagnosis of heart failure.

With regard to HFrEF, in the DAPA-HF (Dapagliflozin And Prevention of Adverse Outcomes in Heart Failure) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) trials, dapagliflozin and empagliflozin demonstrated a statistically significant reduction in the composite primary endpoint of cardiovascular death or heart failure hospitalization, by 26% (HR 0.74; 95% CI, 0.65–0.85) and 25% (HR 0.75; 95% CI, 0.65–0.86), respectively. In addition, dapagliflozin was associated with an 18% reduction in cardiovascular death (HR 0.82; 95% CI, 0.69–0.98).[5] On the basis of these findings, the use of SGLT2 inhibitors in HFrEF has received a Class I recommendation, LoE A to reduce the risk of heart failure hospitalizations and cardiovascular death.

Subsequently, in the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trials, dapagliflozin and empagliflozin were evaluated in patients with HFmrEF and HFpEF. Both agents demonstrated a statistically significant reduction in the composite primary endpoint of cardiovascular death or heart failure hospitalization, by 18% (HR 0.82; 95% CI, 0.73–0.92) and 21% (HR 0.79; 95% CI, 0.69–0.90), respectively. In both trials, the observed benefit was mainly driven by a significant reduction in heart failure hospitalizations, while no significant reduction in cardiovascular death was observed.[5] Based on these results, the use of SGLT2 inhibitors in HFmrEF and HFpEF has received a Class I recommendation, LoE A for reducing the risk of heart failure hospitalizations and cardiovascular death.

Moreover, two pooled analyses—one for dapagliflozin and one for empagliflozin—were subsequently conducted using data from their respective pivotal trials, with the aim of assessing efficacy across the entire EF spectrum. These analyses demonstrated that the effects of both agents on clinical outcomes were clinically meaningful irrespective of EF values, with dapagliflozin also showing a significant reduction in cardiovascular death (HR 0.86; 95% CI, 0.76–0.97).[6,7]

Therefore, for the first time in the history of pharmacological treatment of heart failure, a drug class has demonstrated efficacy regardless of EF and has received a Class I, LoE A recommendation across all EF-based heart failure phenotypes (HFrEF, HFmrEF,

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HFpEF). Thus, SGLT2 inhibitors can be used irrespective of EF.

Early clinical benefit of SGLT2 inhibitors

In the pivotal clinical trials, the time to first statistical significance and the onset of clinical benefit of dapagliflozin and empagliflozin occurred early, within days to weeks after treatment initiation. In the DAPA-HF trial, separation of the Kaplan–Meier curves for the composite primary endpoint reached the first statistical significance 28 days after randomization (HR 0.51; 95% CI, 0.28–0.94), and similar findings were observed for the individual components of the composite endpoint. In the EMPEROR-Reduced trial, empagliflozin achieved first statistical significance as early as 12 days after randomization (HR 0.42; 95% CI, 0.19–0.92).[8] Comparable results were also reported in the DELIVER and EMPEROR-Preserved trials, in which the time to first statistical significance for the composite primary endpoint was 13 days (HR 0.45; 95% CI, 0.20–0.99) and 18 days (HR 0.41; 95% CI, 0.17–0.99), respectively. Furthermore, a recent meta-analysis of randomized clinical trials evaluating early initiation of SGLT2 inhibitors during hospitalization for acute heart failure demonstrated a significant reduction in the early risk of cardiovascular death or worsening heart failure (HR 0.71; 95% CI, 0.54–0.93), as well as in all-cause death (HR 0.57; 95% CI, 0.41–0.80).

The REVOLUTION-HF study (suspected *de novo* heart failure in the outpatient setting)

The REVOLUTION-HF study recently focused on the management of patients with a clinical suspicion of heart failure in the outpatient setting, evaluating diagnostic delay, therapeutic consequences, and adverse outcomes.[9] Specifically, this was a population-based study conducted in Sweden that retrospectively evaluated 5942 patients (mean age 78.7 years; 54% women) who presented in an outpatient setting between 2015 and 2020 with suspected *de novo* heart failure. Clinical suspicion was defined by the presence of at least one sign (peripheral oedema) or symptom (dyspnoea), together with an NT-proBNP measurement >300 ng/L obtained within ±30 days from symptom registration. These patients were matched to controls without a history of heart failure, signs or symptoms suggestive of heart failure, or elevated NT-proBNP levels. Matching was performed according to age, sex, level of care (primary care vs. specialist evaluation), and year of presentation.

At 1-year follow-up, patients with suspected heart failure exhibited a substantial increase in all-cause death (11.7 vs. 6.5 events per 100 person-years), heart failure hospitalizations (12.5 vs. 2.2 events per 100 person-years), and the composite outcome of heart failure hospitalizations or all-cause death (22.3 vs. 8.4 events per 100 person-years). Each of these outcomes was significantly associated with NT-proBNP levels, with a marked risk increase for NT-proBNP values >2000 ng/L. Approximately, one third of all heart failure hospitalizations in the subgroup with NT-proBNP >2000 ng/L occurred within the first 4–6 weeks of follow-up, and adverse events were higher in the days immediately following clinical suspicion of heart failure, irrespective of NT-proBNP levels. The study demonstrated that the median time to echocardiography was 40 days, with variability depending on NT-proBNP values. Despite clinical signs suggestive of *de novo* heart failure, only 29% of patients received a formal diagnosis within 1 year of follow-up (64% among those with NT-proBNP >2000 ng/L) and of these, 37% were diagnosed during hospitalization.

Overall, 57% of patients with NT-proBNP >2000 ng/L and 41% of those with NT-proBNP ≤2000 ng/L experienced an all-cause hospitalization. Moreover, despite clinical suspicion, there was only a minimal increase in the use of renin–angiotensin system inhibitors, mineralocorticoid receptor antagonists, and/or beta-blockers while awaiting echocardiography, in contrast to loop diuretics, whose use increased rapidly by approximately five-fold (from ≈10% to ≈50%).

The results of this study showed that a large proportion of patients remained undiagnosed or underwent echocardiographic phenotyping after a prolonged delay despite elevated NT-proBNP levels. This significantly contributed to limited and delayed initiation of disease-modifying heart failure therapies and translated into an increased risk of heart failure hospitalizations and all-cause death, that was proportional to NT-proBNP levels. Therefore, in order to reduce the risk of early adverse outcomes while patients await echocardiography, the authors suggested to maintain a lower threshold for early initiation of treatment with SGLT2 inhibitors, at least in patients at highest risk.

In light of the early risk reduction demonstrated by SGLT2 inhibitors irrespective of EF, it is reasonable to question whether postponing SGLT2 inhibitor initiation until after echocardiographic evaluation remains justified. In this regard, and by way of example, in Italy the national waiting list platform estimated that during the first half of 2025, 75% of requests for urgent echocardiography (within 3 days) were fulfilled only within 17 days.[10]

Safety and tolerability of SGLT2 inhibitors

Overall, dapagliflozin and empagliflozin have demonstrated an adequate safety and tolerability profile in pivotal clinical trials, in which fewer adverse events and serious adverse events were observed compared with placebo. Use of SGLT2 inhibitors was associated with an initial reduction in estimated glomerular filtration rate (eGFR); however, this early decline was linked to a slower long-term deterioration of renal function and improved clinical outcomes, with no evidence of an increased risk of acute kidney injury. When combined with mineralocorticoid receptor antagonists, SGLT2 inhibitors have been shown to reduce the risk of hyperkalaemia. Although SGLT2 inhibitors may theoretically predispose to volume depletion, clinical trials have shown only a modest effect on blood pressure. Compared with placebo, they were not associated with an increased incidence of

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hypoglycaemic events—regardless of the presence or absence of diabetes mellitus—nor with diabetic ketoacidosis. A finding of potential clinical relevance is the higher incidence of uncomplicated genital and urinary tract infections; however, the clinical impact of treatment discontinuation due to these events remains unclear. In this regard, a recent cohort study in patients with diabetes observed that discontinuation of SGLT2 inhibitors was associated with a higher risk of cardiovascular and renal events, while the risk of recurrent urinary tract infections was unchanged.[11] Finally, a meta-analysis of five randomized controlled trials confirmed the overall safety profile of SGLT2 inhibitors in heart failure across 21 947 patients.[5]

Therefore, the favourable safety and tolerability profile of SGLT2 inhibitors supports their early initiation while awaiting echocardiographic confirmation of the diagnosis, without exposing patients to an increased risk of adverse events.

SGLT2 inhibitors and the cardio-renal-metabolic syndrome

SGLT2 inhibitors were initially developed as oral glucose-lowering agents and currently play a central role in the management of type 2 diabetes mellitus, due to the significant reduction in adverse events demonstrated in cardiovascular outcome trials. The 2025 *Standards of Care in Diabetes* guidelines issued by the American Diabetes Association recommend SGLT2 inhibitors as first-line therapy, together with GLP-1 receptor agonists, to reduce cardiovascular and renal risk in high-risk patients with diabetes—defined by the presence of atherosclerotic cardiovascular disease, multiple cardiovascular risk factors, or chronic kidney disease—irrespective of a history of heart failure.

More recently, empagliflozin and dapagliflozin have also demonstrated a pivotal role in chronic kidney disease in the EMPA-KIDNEY (Study of Heart and Kidney Protection with Empagliflozin) and DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trials, both of which were stopped early for evidence of benefit. EMPA-KIDNEY enrolled patients with an eGFR of 20–45 mL/min/1.73 m^2, or with an eGFR of 45–90 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio (UACR) ≥ 200 mg/g, demonstrating at a median follow-up of 2.0 years a 28% reduction in the composite primary endpoint of kidney disease progression (defined as end-stage kidney disease, sustained eGFR decline ≥40% or to <10 mL/min/1.73 m^2, or renal death) or cardiovascular death (HR 0.72; 95% CI, 0.64–0.82; $P < 0.001$). Similarly, DAPA-CKD enrolled patients with an eGFR of 25–75 mL/min/1.73 m^2 and a UACR ≥200 mg/g and demonstrated, at a median follow-up of 2.4 years, a 39% reduction in the composite primary outcome of sustained eGFR decline ≥50%, end-stage kidney disease, or renal or cardiovascular death (HR 0.61; 95% CI, 0.51–0.72; $P < 0.001$), as well as a 29% reduction in the secondary composite outcome of heart failure hospitalization or cardiovascular death (HR 0.71; 95% CI, 0.55–0.92; $P = 0.009$).

Diabetes mellitus and chronic kidney disease define the so-called cardio-renal-metabolic syndrome and represent highly prevalent and prognostically relevant comorbidities in patients with heart failure. For example, in two recent phase 3 trials—VICTOR (Vericiguat in Adults with Chronic Heart Failure and Reduced Ejection Fraction) and FINEARTS (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure with Ejection Fraction >40%)—the prevalence of diabetes mellitus was 42% and 40%, while chronic kidney disease was present in 36% and 48% of patients, respectively. Therefore, in the presence of these comorbidities, it is not necessary to await echocardiographic evaluation in order to initiate dapagliflozin or empagliflozin early in patients with suspected heart failure.

Conclusions

In heart failure, the SGLT2 inhibitors dapagliflozin and empagliflozin have demonstrated an early clinical benefit that is independent of ejection fraction values, with consistent effects not only on mortality but also on morbidity and quality of life, together with a favourable safety and tolerability profile. As we have previously suggested, the growing body of evidence should prompt consideration of early SGLT2 inhibitor use during the diagnostic work-up for heart failure.[12] The REVOLUTION-HF study demonstrated that delays in diagnosis and echocardiographic evaluation lead to failure or delays in treatment initiation, with a significant impact on the risk of all-cause death and heart failure hospitalizations. These findings support the initiation of SGLT2 inhibitors in the presence of clinical suspicion of heart failure.

In conclusion, we endorse the recommendation put forward in a recent consensus paper of the Heart Failure Association of the European Society of Cardiology, according to which treatment with SGLT2 inhibitors—and, when indicated, mineralocorticoid receptor antagonists—should be initiated promptly after heart failure diagnosis to reduce the risk of hospitalization and death, regardless of the availability of echocardiography (that remains essential for subsequent optimization of pharmacological and no pharmacological treatments based on ejection fraction values).[13]

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