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SGLT2 inhibitors and new frontiers in heart failure treatment regardless of ejection fraction and setting

Anna Merlo[1,2], Emilia D'Elia [1,2]*, Luca Di Odoardo[1], Edoardo Sciatti[1], and Michele Senni[1,2]

[1]Cardiovascular Department, Papa Giovanni XXIII Hospital, Piazza OMS 1, 24127 Bergamo, Italy; and [2]University of Milano-Bicocca, Piazza dell'Ateneo Nuovo 1, 20126 Milano, Italy

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Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been shown to reduce cardiovascular (CV) mortality and heart failure (HF) hospitalizations, independently from left ventricular ejection fraction (EF). Their efficacy has been assessed both in patients with reduced and preserved EF, with notable benefits in renal outcomes as well. The initiation of SGLT2i in the early phase of hospitalization for acute HF has proven to be safe and beneficial. The EMPULSE and DICTATE-AHF trials support early empagliflozin and dapagliflozin use, respectively, reducing worsening HF events, improving quality of life, and enhancing diuretic efficiency. Notably, these benefits emerge shortly after the initiation of therapy, underscoring the importance of early integration into guideline-directed medical therapy (GDMT). Despite concerns regarding deterioration of renal function, SGLT2i appear to be safe even in patients with low estimated glomerular filtration rates (eGFR). Data suggest that SGLT2i benefits persist without increased safety risks, reassuring clinicians of their efficacy in patients experiencing renal decline. Concerns about volume depletion induced by SGLT2i have also been addressed, with documented enhanced diuresis without adverse renal impacts. Moreover, SGLT2i have been associated with a lower risk of hyperkalaemia events, thus allowing for better optimization of GDMT, including the use of mineralocorticoid receptor antagonists. Overall, these findings highlight the broad CV, renal, and metabolic benefits of SGLT2i, advocating for their early and widespread use in HF management, regardless of EF or eGFR.

Introduction

It is well established that sodium-glucose cotransporter 2 inhibitors (SGLT2i), namely empagliflozin and dapagliflozin, decrease the risk of cardiovascular (CV) mortality or heart failure (HF) hospitalizations, not only in patients with HF and a left ventricular ejection fraction (EF) of 40% or lower[1,2] but also in individuals with HF and preserved EF.[3,4] Notably, Butler *et al.*[5] reported that the beneficial effect of empagliflozin on HF outcomes was both clinically significant and consistent across patients with EF ranging from <25 to <65%, with a diminished effect observed in those with EF ≥ 65%. The consistency of this response across the entire EF spectrum distinguishes SGLT2i from other therapeutic agents for HF. Besides, a meta-analysis using data from DAPA-HF and EMPEROR-Reduced revealed that the effects of SGLT2i go beyond CV outcomes as these drugs significantly reduced the risk of a composite renal endpoint of sustained decline in estimated glomerular filtration rate (eGFR), end-stage renal disease, or renal death.[6] The renal benefits of SGLT2i are also evident in the population with mildly reduced and preserved EF, although to a more modest extent. Indeed, a prespecified analysis of the DELIVER trial revealed that dapagliflozin did not significantly reduce the incidence of the composite kidney outcome; however, it did slow the rate

*Corresponding author. Tel: +390352673589, Fax: +393396694210, Email: edelia@asst-pg23.it

of decline in eGFR compared to placebo.[7] Similarly, data from the EMPEROR-Preserved trial demonstrated that empagliflozin significantly reduced the rate of eGFR decline and slowed the progression to macroalbuminuria, without, though, reducing the risk of major renal outcomes.[8] Given the broad benefits of SGLT2i therapy that extend beyond CV outcomes, it is essential to overcome any therapeutic hesitation and implement guideline-directed medical therapy (GDMT) as early as possible in the patient's clinical course.

Grey zones to overcome in SGLT2i management

One of the crucial aspects of SGLT2i in daily management is the early onset of benefit after initiation of therapy, which is relevant not only for the mortality and morbidity outcomes but also for enhancing patients' quality of life (QoL). In the aforementioned randomized controlled trials, a statistically significant benefit was evident within 12–28 days post-randomization. Collectively, these findings underscore the early and sustained improvements in clinical outcomes, health status, and QoL associated with SGLT2i, emphasizing the necessity for early initiation of therapy.[9]

However, in clinical practice, there are situations where uncertainties remain, and clinicians may not always feel confident in initiating SGLT2i therapy in the acute phase of hospitalization, where concerns persist regarding the safety and immediate benefits of SGLT2i initiation.

In this regard, the EMPA-RESPONSE-AHF trial evaluated the effects of empagliflozin in patients with acute HF. The study not only demonstrated that empagliflozin was safe and well tolerated but also it led to a reduction in a combined endpoint of worsening HF, rehospitalization for HF, or mortality within 60 days.[10] Furthermore, results from the EMPULSE trial indicate that in patients hospitalized for acute HF (both acute *de novo* and decompensated chronic HF), early initiation of empagliflozin (median of 3 days after hospitalization) appears to be well tolerated and effective in reducing the hierarchical composite endpoint of death from any cause, number of HF events, and time to first HF event, when analysed using the win ratio approach. Moreover, its beneficial clinical effect on QoL questionnaires was observed regardless of EF.[11] In addition, also dapagliflozin has been studied in the acute setting in the DICTATE-AHF trial,[12] demonstrating that it can be safely initiated in the first day of hospitalization for AHF, even prior to patient stabilization, thereby facilitating rapid GDMT optimization. Furthermore, although it did not achieve the primary outcome of weight-based diuretic efficiency, dapagliflozin was associated to an enhanced diuresis, a reduced intravenous loop diuretic up-titration, and a shortened duration of intravenous diuretics. In light of the aforesaid points, the authors convincingly postulate that, given the well-known benefit of SGLT2i in reducing HF hospitalizations and CV mortality through mechanisms beyond diuresis, early initiation of this pleiotropic drug should be prioritized over other diuretic combinations.

A second main concern for the clinician in initiating SGLT2i is the deterioration of renal function. Indeed, HF and chronic kidney disease (CKD) often coexist, and many patients with HF may experience fluctuations in kidney function or its progressive deterioration over time. This issue raises concerns regarding safety and efficacy of GDMT at lower level of eGFR. Nearly every major SGLT2i trial has revealed that eGFR trajectory exhibits a slight initial dip within the first 4 weeks of treatment, followed by stabilization over time. This initial decline is explained by the mechanism of action of these drugs, which ultimately results in vasoconstriction of the glomerular afferent arteriole. After this phase, a slower rate of eGFR decline is observed in the SGLT2i group compared to the placebo one with a crossover point around 12–18 months post-randomization, highlighting the long-term renal benefits of SGLT2i.[13]

Chatur *et al.*[14] analysed the safety and efficacy of continuing SGLT2i in HF when the eGFR falls below the thresholds for initiation. The authors found that deterioration of kidney function to an eGFR threshold below that allowed for trial inclusion (eGFR <25 mL/min/1.73 m^2) was infrequent, but it was associated with heightened risk of the development of subsequent CV outcomes. However, the beneficial effects of dapagliflozin compared to placebo on CV outcomes appeared to be preserved, with no excess in safety outcomes between treatment groups. Taken together, these data reassure on this controversial point and encourage the wide use of SGLT2i even in HF patients experiencing a deterioration of kidney function to eGFR <25 mL/min/1.73 m^2.

A third main concern for the clinician is the unexpected diuretic effect of SGLT2i and potentially the related risk of volume depletion. As already mentioned before, the use of dapagliflozin 10 mg did not determine a statistically significant reduction in weight-based diuretic efficiency, but was associated with evidence for enhanced diuresis among patients with AHF.[12] The EMPAG-HF study shows that in patients with acute decompensated HF, initiation of empagliflozin 25 mg within 12 h after hospital admission seemed to be safe and effective in increasing urine output by 25% on top of standard diuretic therapy, with no effect on eGFR slope. This study also showed that empagliflozin led to an increase in diuretic efficiency as well as greater reduction in NT-proBNP, and a trend towards lower body weight. Of note, the 25 mg dosage of empagliflozin was chosen to maximize potential diuretic effects and to explore its potentially negative effects in acute decompensated HF in combination with high-dose loop diuretic and other HF drugs.[15] Thus, SGLT2i not only appears to be safe in the acute setting but, when combined with standard diuretic therapy, represents a promising strategy for enhancing early decongestion in acute HF.

Finally, a significant challenge in optimizing GDMT for HF is represented by hyperkalaemia, which frequently leads to interruption and/or discontinuation of GDMT. In this regard, the EMPEROR-Pooled analysis by Ferreira *et al.*[16] showed that, in >9500 HF patients across a wide range of EF, empagliflozin effectively reduced the incidence of new-onset hyperkalaemia or new initiation of potassium binders compared to placebo without significant increase in hypokalaemia events. Recently, Greene *et al.*[17] convincingly postulated that the combined use of SGLT2i and angiotensin receptor-neprilysin inhibitors (ARNIs) reduces the risk of hyperkalaemia and subsequent mineralocorticoid receptor antagonist discontinuation, therefore

promoting their efficiency in facilitating the up-titration of GDMT. In this scenario, the authors suggest that hyperkalaemia should no longer be excessively feared, but viewed as something that can be prevented and managed without sacrificing GDMT (*Figure 1*).

Future perspective and practical approach

SGLT2i are of proven benefit in HF across a wide spectrum of EF.[5] The consistency of their effect on outcomes should help in implementing their use, at the beginning of HF

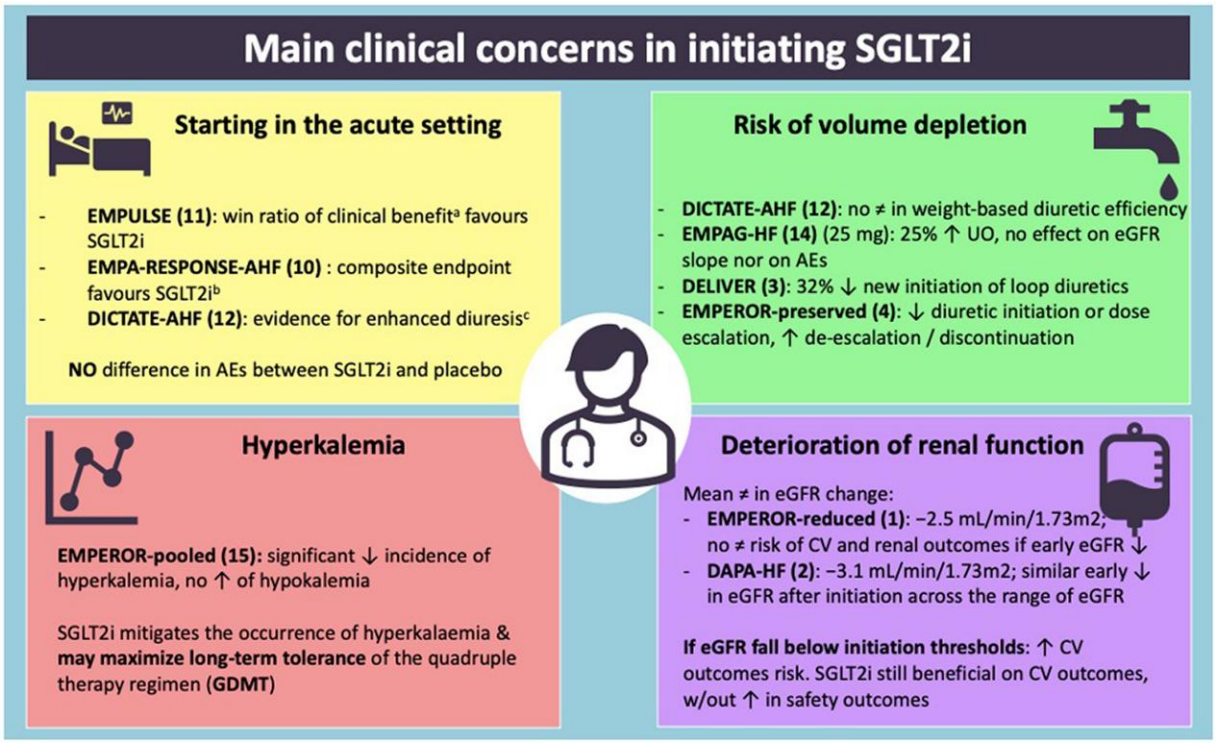

Figure 1 Common clinical concerns in starting SGLT2i in heart failure patients. AEs, adverse events; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; UO, urine output.

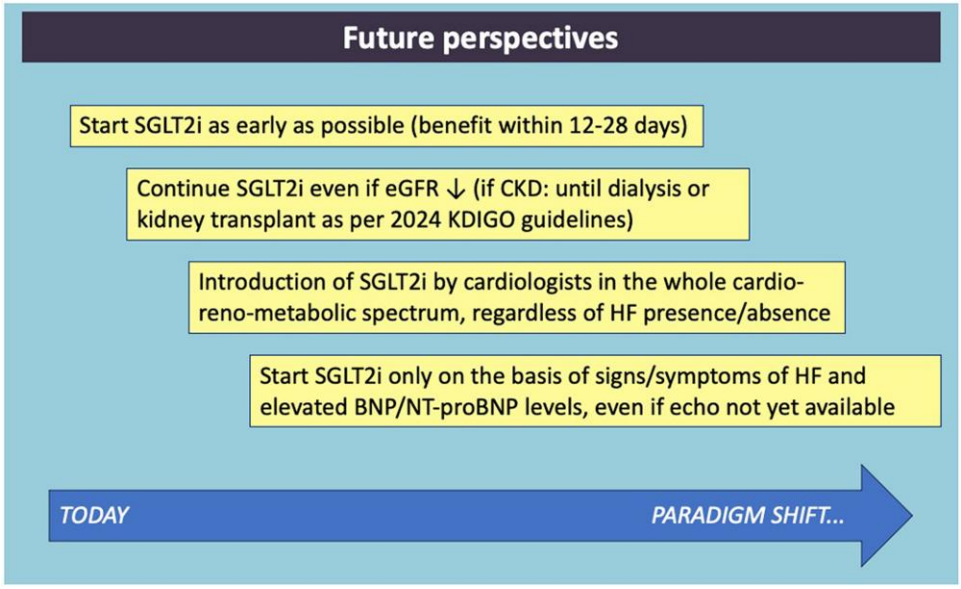

Figure 2 Future perspective in the initiation and early use of SGLT2i. CKD, chronic kidney disease; KDIGO, Kidney Disease Improving Global Outcomes.

diagnostic work-up. Virtually, when a patient is diagnosed as suffering from HF by means of symptoms/signs and natriuretic peptides, SGLT2i should be prescribed, even before performing echocardiography. This issue is of utmost importance if we consider the early CV benefit after introducing SGLT2i, as outlined above.[11,12] Moreover, in the REVOLUTION-HF (REal WOrLd EdUcaTION in HF) registry-based study aimed at determining the risk profile of ambulatory patients presenting with suspected *de novo* HF, only 29% of patients received a HF diagnosis in the year following the index date, and those awaiting echocardiography for diagnosis exhibited a high risk of mortality and hospitalization due to HF.[17] In this framework, SGLT2 inhibitors could be initiated immediately in patients with suspected HF and elevated NT-proBNP, if an echocardiogram cannot be performed promptly.

In addition to the earlier use of SGLT2i, in our opinion, the cardiologists of the near future may acquire greater confidence in extending SGLT2i administration to cover the whole cardio-reno-metabolic spectrum besides HF presence, in order to widely impact on patients' prognosis. In this regard, clinical and preclinical studies have shown promising results for the application of SGLT2i to patients with CKD stage IV or V, but further data are needed to confirm their usefulness as regards CV and renal outcomes.[18]

Finally, the role of SGLT2i in cardiomyopathies, both with reduced or preserved EF, or right ventricular HF or primary valvular heart disease is still to be determined, even if a pathophysiological background to their usefulness in these contexts should be hypothesized. Indeed, recently, a multicentre retrospective study sought to assess the effectiveness and tolerability of SGLT2i in patients with transthyretin cardiomyopathy (ATTR-CM). SGLT2i treatment in such patients was well tolerated and associated with favourable effects on HF symptoms, renal function, and diuretic agent requirement over time. SGLT2i treatment in ATTR-CM was associated with reduced risk of HF hospitalization and CV and all-cause mortality, regardless of the EF.[19] A dedicated randomized trial is necessary to confirm this issue (*Figure 2*).

Conclusions

SGLT2i have demonstrated early efficacy in improving CV outcomes across the entire spectrum of EF and providing benefits that extend to renal and metabolic outcomes. The consistency of their impact on outcomes should promote their implementation at the initial stages of HF diagnosis. Ideally, when HF is diagnosed based on symptoms, signs, and natriuretic peptide levels, SGLT2i should be prescribed even before performing echocardiography. Beyond their early use in HF, in our opinion, the cardiologists of the near future may acquire greater confidence in extending SGLT2i administration to cover the whole cardio-reno-metabolic spectrum besides HF presence, in order to widely impact on patients' prognosis.

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Data availability

No new data were generated or analysed in support of this research.

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