Earlier is Better. New Options for Acute Heart Failure: When, Who, How Much?

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Abstract
Heart failure (HF) is a major public health problem characterised by a high rate of hospitalisation and death. The risk is maximal for patients admitted with acute heart failure (AHF). New therapies with solid proof of mortality reduction in both groups of patients with reduced and preserved ejection fraction (EF) are now available (valsartan/sacubitril and SGLT₂ inhibitors). The purpose of this article is to review the main data available and to clarify the role of these new therapies in AHF. The precise moment of initiating these therapies is still a matter of debate. This paper presents the recommended criteria for clinical stability that the clinician could use in deciding to initiate therapy. There is a growing amount of evidence that initiating these therapies sooner provides more benefits to patients.

Keywords
Heart failure, Valsartan/Sacubitril, SGLT₂ inhibitors

Rezumat
Insuficiența cardiacă (IC) este o problemă majoră de sănătate publică caracterizată printr-o rată ridicată de spitalizare și deces. Riscul este maxim pentru pacienții internați cu insuficiență cardiacă acută (ICA). La momentul actual sunt disponibile noi terapii cu dovezi solide de reducere a mortalității în ambele grupuri de pacienți cu fracție de ejacție (FE) redusă și prezervată (valsartan/sacubitril și inhibitori SGLT₂).

Scopul acestui articol este de a revizui principalele date disponibile în literatură și de a clarifica rolul acestor noi terapii în ICA. Momentul precis al inițierii acestor terapii este încă un subiect de debat, iar această lucrare prezintă criteriile recomandate de stabilitate clinică pe care clinicianul le-ar putea folosi pentru a decide momentul inițierii terapiei. Există un număr tot mai mare de dovezi că inițierea cât mai devreme a acestor terapii oferă mai multe beneficii pacienților.

Cuvinte cheie
Insuficiență cardiacă, Valsartan/Sacubitril, inhibitori SGLT₂

Introduction

Despite therapeutic achievements in the field, heart failure (HF) is a major public health problem characterised by a high rate of hospitalisation and death. [1] The risk is maximal for patients admitted with acute heart failure (AHF), reaching in-hospital mortality rates up to 10% and a composite of rehospitalisation and death rates around 30% at the one-year mark, depending on the series analysed. [2, 3, 4]

New therapeutical options were made possible after the results of randomised trials with valsartan/sacubitril (Val/Sac) and SGLT₂ inhibitors were published. This has established solid proof of mortality reduction in both groups of patients with reduced and preserved ejection fraction (EF). [5]

These new therapeutical classes provide patients with better outcomes through continuous intervention, which seems to be more effective if the drugs are initiated as soon as possible after admission. Recent data from trials and registries support the administration of Val/Sac and SGLT₂ inhibitors even in the congestive phase of AHF. The precise moment of initiating these therapies, the sequence of administration, and interactions with other drugs are still up for debate. We must take into account the profile of the patient determined mainly by the substrate of HF and concomitant organ dysfunction, which should yield a personalised decision.

The purpose of this article is to review the main data available and to clarify the roles of these new therapies in AHF.

SGLT₂ Inhibitor Trials

Inhibitors of the receptors SGLT₂ demonstrated very good efficacy and tolerability for a broad spectrum of patients independent of age and the presence of diabetes and renal dysfunction. [6, 7]

Before early and sustained volemic depletion, they also showed a series of pleiotropic effects [8] such as reduction of oxidative stress, [9] reduction of the sympathetic activity, increased erythropoietin production [10], and anti-inflammatory and possibly antiarrhythmic effects [11]. SGLT₂ inhibitors have also had a positive effect on markers of renal injury. [12] The quantification

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of the pleiotropic effect by various biomarkers was also tried, but found little success. [13]

Before conducting trials designed to measure the effect in AHF, investigators noticed a reduction of HF hospitalisations as a secondary positive outcome in studies on patients with diabetes mellitus. [14]

SOLOIST-WHF was the first trial designed to assess the effect of SGLT2 inhibitors in patients with recent AHF decompensation episodes (the screening period was 14 days after discharge) and associated diabetes mellitus. The study drug, sotagliflozin, has both SGLT2 and SGLT1 inhibitory effects. The SGLT1 receptor is located within the intestinal wall and plays an important role in reducing postprandial hyperglycaemia by decreasing glucose absorption. The study included both patients with reduced and preserved EF. The average value of NT-proBNP was 1800 pg/mL and 80% of the study population had an EF < 50%. The concomitant therapy was with insulin (35%), angiotensin receptor – neprilysin inhibitors (ARNI 15%), mineralocorticoid receptor antagonists (MRA 66%) and beta-blockers (92%). The start dose of the sotagliflozin dose was 200 mg, up titrated to 400 mg, and the average duration of therapy was 7 to 8 months. The investigators adjudicated 245 adverse events on the active arm, compared to 355 for the placebo. The event rate per 100 patient-years was lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; HR 0.67; 95% confidence interval, 0.52–0.85; P < 0.001).

In terms of secondary endpoints, only the decrease in hospitalization and emergency visits for HF reached statistical significance (HR = 0.64, 95%CI, 0.49–0.83, p < 0.001). There were no differences regarding cardiovascular and total mortality (10.6% vs. 12.5% and 13.5% vs. 16.3%) for sotagliflozin vs. placebo. The most frequent adverse events for the study drug vs. placebo were hypotension (6% vs 4.6%), urinary tract infection (4.8% vs. 5.1%), acute kidney injury (4.1% vs. 4.4%) and severe hypoglycaemia (1.5% vs. 0.3%). The results were biased by the early termination of the trial due to funding discontinuation. [15] The EMPULSE trial randomised 530 patients with de novo or acutely decompensated chronic HF, to receive either empagliflozin 10 mg or placebo. The clinical benefit expected was a hierarchised composite of the following: death of any cause, HF events, time to the first event or a change with 5 points at 90 days of the Kansas QOL questionnaire. The result of the trial was positive, with a win rate of 1.36 (95% CI: 1.09–1.68, p = 0.0054). Regarding the secondary composite endpoint of cardiovascular death and a HF event, an insignificant statistical difference was recorded, favouring empagliflozin (12.8% vs. 18.5%, HR = 0.69; 95% CI: 0.45–1.08). Safety data showed treatment discontinuation in 8.5% with empagliflozin vs. 12.8% with placebo. Volume depletion was more pronounced in the empagliflozin group (12.7%) vs. the placebo group (10.2%). Kidney failure appeared more often in the placebo group (12.1% vs. 7.7%). Surprisingly, there were fewer urinary tract infections in empagliflozin group, and no episodes of ketoacidosis were noted. The rates of guideline therapies administered before randomization were also high: 80% beta-blockers, 57% MRA, 15% ARNI, and almost 80% received loop diuretics. The percentage of those with valvular disease was significant (65%), and over 50% of patients were in atrial fibrillation or were diabetics. The positive clinical effect was maintained throughout the entire spectrum of patients with small differences between the value of the EF, kidney function and initial value of NT-proBNP. One of the important limitations of the study was the relative late initiation after admission of the drug, which probably resulted in exclusion of the sickest or frailest subjects. [16, 17] Empagliflozin stimulates osmotic diuresis through a mechanism of increased fractional excretion of glucoses without a significantly larger natriuresis [18, 19, 20]. This resulted from a predefined substudy of the EMPA-RESPONSE AHF trial which included 40 patients in each study arm (80 patients in total). The investigators followed markers of sodium and glucose kidney dynamics in the first 96 hours and at 30 days. The mechanism of action was represented by the blockage of the sodium-glucose co-transporter (SGLT2), which results in glucose and water excretion in order to maintain urinary osmolarity. Sodium is reabsorbed, resulting in a neutral balance. The mean values of NT-proBNP and glomerular filtration rate (GFR) in the study group were 5236 pg/mL and 54 ± 17mL/min/1.73m2. 33% of the patients were diabetics and the mean value of glycaemia was 140mg/dl. No significant increase in sodium excretion was noted over 24 hours in those receiving the study drug. The urinary sodium decrease recorded was compensated by an increase in the glomerular filtration rate; thus, plasma sodium remained unchanged for both study arms. A similar pattern was noted for chloride. Fractional glucose excretion was maximal at 24 hours in the empagliflozin group (21.8% vs. 0.1%, p <0.001). After this time, the difference was attenuated (6.0% vs. 0.1%, p < 0.001). A small but significant reduction in GFR was observed in the first 24 hours (~10 ± 12 vs. ~2 ± 12mL/min/1.73m2, p = 0,009), and modification improved at the 30-day evaluation. This seems to be connected to the juxtaglomerular feedback mechanism, which is meant to correct glomerular hyperfiltration. Urinary volume on the active arm increased after 24 hours by 6084 ± 2480 mL vs. 4222 ± 1911 mL; thus, the fluid balance was modified by more than three litres. Renin levels recorded a slight increase in the empagliflozin group, but with a return to the initial value, while aldosterone value was not changed. These results explain partially why SGLT2 inhibitors reduce by double the interstitial volume compared to the plasmatic volume when compared with bumetanide (only 22% reduction of the interstitial volume), hence resulting in a better control of congestion without decreasing vascular filling. In this pilot study in patients with acute (decompensated) HF, empagliflozin was safe and well tolerated, but did not improve dyspnoea, NT-proBNP, diuretic response, and length of hospital stay. These results, however, suggest that this novel HF treatment can safely be initiated in a high-risk population of acute HF patients and should pave the way for larger studies. [21] In order to assess the effect of dapagliflozin on the kidney function, a group of investigators randomised patients with AHF early after hospitalisation. They were followed through the hospitalisation period and after up to 30 days. 102 patients were enrolled and received dapagliflozin or placebo at an average of 17 hours after admission. 37% of them had preserved EF while 26% had EF<
35%. 33% were diabetics and the mean value of NT-proBNP was 4706 pg/mL, higher than in other randomised trials, but relatively equal to that from registries. The mean GFR in the two study groups was similar (dapagliflozin 55.65 ± 18.17 mL/min, placebo 52.7 ± 17.34 mL/min, p = 0.62). At 48 hours, a significant difference in GFR was noted between the two groups, but at discharge, the difference disappeared. Decrease in the kidney function by 0.3 mg/dL was more frequent in the dapagliflozin group (34.4% vs. 15.2%; p = 0.07). The average daily dose of the diuretic was smaller for those receiving dapagliflozin vs. placebo (78.46 ± 38.95 mg/day vs. 102.82 ± 31.26 mg/day). Transient GFR reduction is considered a sign of successful decongestion and it is not associated with loss of functional nephrons. [22]

A retrospective study from the EMPA REG OUTCOMES trial database divided the patients into three groups depending on the GFR decrease during therapy with empagliflozin: >10%, 0-10%, and no change. For those patients exposed to empagliflozin 10 - 25 mg, there were 41% non-dippers, 31% with intermediary response, and 28% dippers. In the placebo group, the values were lower: 47%, 39% and 13%, respectively. The dipper subjects had the following characteristics: older, longstanding diabetes, present albuminuria, lower levels of haemoglobin, inadequate blood pressure control, and a higher rate of insulin therapy. The highest decrease in GFR was up to 30% in patients with an important cardiovascular burden. The GFR dippers recorded a higher rate of cardiovascular risk rates, but without statistical significance. That trend was cancelled after treatment exposure. [23]

A group of researchers from Spain conducted an observational study in patients with diabetes mellitus admitted for AHF who received either basal insulin and bolus or basal insulin and empagliflozin. The matching case method was applied. After a propensity analysis, each group included 91 subjects. There were no differences regarding the average value of blood glucose (152.1 ± 17.8 vs. 155.2 ± 19.7 mg/dL, p = 0.289). At discharge, the NT-proBNP value was lower for the empagliflozin group compared with the insulin-alone arm (1652 ± 501 vs. 2101 ± 522 pg/mL, p = 0.032), and the total urine output was higher (16,100 ± 1510 mL vs. 13,900 ± 1220 mL, p = 0.037). There were no differences in hospitalization duration and death rate between the two study groups. [24]

Anxiety regarding dapagliflozin-induced hypotension diminished after the analysis of data from the DECLARE -TIMI 58 trial, which showed a small reduction of systolic blood pressure of 2.4 mm Hg (95% CI, 1.9-2.9; p < 0.0001), and the EMPULSE trial (adjusted mean change in systolic blood pressure from baseline to 90 days was 0.1mmHg (95% CI: −2.5 to 2.7) in the empagliflozin group and 1.0 mmHg (95% CI: −1.6 to 3.6) in the placebo group). [25, 16]

During the COVID-19 pandemic, a multinational group of researchers has put to trial the hypothesis of an eventual protective effect of dapagliflozin vs. placebo in patients with a severe form and cardio-metabolic risk factor such as hypertension, type 2 diabetes, atherosclerotic cardiovascular disease, HF, and chronic kidney disease. The study hypothesis was developed given the capabilities of SGLT₂ inhibitors to reduce oxidative stress, inflammation, glycolysis and lipogenesis. This class of drugs also improves endothelial dysfunction and oxygen transportation capacity. The study included 1250 subjects divided in two equal groups, but it did not show any significant statistical differences on the occurrence of the composite endpoint of organic dysfunction or death, although there were some numerical differences favouring dapagliflozin. The safety profile was good, suggesting that SGLT₂ inhibitors can be continued with no concerns in patients admitted with a severe form of COVID-19. [26]

The ongoing DICTATE AHF trial follows the efficacy of dapagliflozin 10 mg administration vs. placebo in the first 24 hours in patients with AHF and diabetes mellitus. The primary endpoint of this trial is the ratio between the cumulative change in patients’ weight and the cumulative diuretic dose. The secondary endpoints were the worsening of HF, the relative change in NT-proBNP level, and natriuresis analysis. The safety objectives pursued were incidences of hypo- and hyperglycaemia, ketoacidosis, hypovolemic hypotension, and in-hospital mortality. [27]

The results of the ongoing trials DAPA MI and EMPACT MI are awaited as they will provide information about efficacy and safety of SGLT₂ inhibitors in another acute condition, acute myocardial infarction (MI). Data gathered until now has shown a 30% reduction of the risk of MI in diabetic patients who received SGLT₂ inhibitors. [28]

Euglycemic ketoacidosis was not reported in a meta-analysis of the trials with SGLT₂ inhibitors. There are case reports for this complication in diabetic patients with decreased or preserved EF and HF. Prompt recognition of this potentially fatal complication is mandatory. The therapy consists in fluid imbalance correction, I.V. insulin, glucose if serum glucose is less than 180 mg/dL, and sodium bicarbonate in case of severe acidosis. [29]

### Valsartan/sacubitril in AHF

The TRANSITION clinical trial randomised 1008 AHF patients with reduced EF who were given Val/Sac, either immediately before discharge or in the first two weeks after. The primary endpoint was the percentage of patients who reached the target dose of 97/103mg x 2/day after 10 weeks of therapy. The differences were small: 62.1% vs. 68.5% (RR = 0.91; 95% CI 0.83 - 0.99). This trial demonstrated that early administration of Val/Sac is feasible and that an important number of patients will reach the therapeutic target. [30]

In the PIONEER HF trial, 875 patients with AHF were included (mean EF = 24% and NT - proBNP = 4821pg/dL) and randomised to receive Val/Sac or enalapril. Medication was started during hospitalisation for 8 weeks. The primary objective, NT-proBNP decrease, was more pronounced in those patients receiving Val/Sac (percent of change −46.7% vs. −25.3%; 0.71; 95% CI, 0.63 - 0.81; p <0.001), and this difference became evident after the first week of therapy. The investigators recorded a lower readmission rate at 8 weeks for those receiving ARNi. [31]

A cohort study included 3736 AHF patients aimed to compare the effect of Val/Sac vs. ACEi or ARB on the composite end point of rehospitalisation and death. Val/Sac was administered in 384
patients and ACEI/ARB in 3352. The endpoint occurred in 22.9% of patients receiving Val/Sac compared with 32.6% in the ACEI/ARB group (HR = 0.71, 95% CI, 0.27-0.94). Val/Sac therapy decreased the risk of rehospitalisation (HR = 0.83, 95% CI 0.74 - 0.92) and all-cause mortality (HR = 0.51, 95%, CI 0.27 - 0.94). The average follow-up period in this trial was 11.8 months. The mean EF in both groups was 30% and one-third had significant mitral regurgitation or kidney failure with a GFR < 30 ml/min/1, 73 m2. Around 15% of the subjects were given I.V. inotropes, 3% were intubated, 13% had MI and 15.6% were submitted to a coronary revascularisation procedure. The value for NT-proBNP decreased significantly in the Val/Sac group from 3571 to 1707 pg/mL, compared with the ACEI/ARB group (2282 to 1631 pg/mL, p for interaction GEE model = 0.001). [32]

Using a cohort of AHF patients with low cardiac output and on vasoactive medication, a unicentric retrospective analysis demonstrated the possibility of transition to Val/Sac and then weaning from I.V. medication with the preservation of the cardiac output improvements and systemic vascular resistance decrease obtained in the initial phase. [33]

Another study used an implantable pulmonary artery device to monitor pulmonary pressure variation after the transition from ACEI or ARB to Val/Sac. The study obtained a statistically significant decrease of the mean pulmonary artery pressure of -6.5 mmHg (p = 0.001). [34]

Val/Sac was also studied in the setting of MI. The PARADISE MI trial randomised 5661 patients with MI complicated by a reduced left ventricular EF, pulmonary congestion, or both to receive either Val/Sac (97 mg of sacubitril and 103 mg of valsartan twice daily) or ramipril (5 mg twice daily) in addition to recommended therapy. This trial did not show any significant difference between the two groups of patients in term of incidence of death from cardiovascular causes or incident HF. [35]

### Comparative Analysis of the Appropriate Criteria for the Onset of New Medications in AHF

For both SGLT₂ inhibitors and Val/Sac, the common denominator in deciding to start these drugs is clinical stability. This means that the sickest patients with a need for I.V. vasoactive drugs and mechanical ventilation are not immediate candidates after admission. On the other hand, patients with AHF who are in a more stable condition can be treated almost immediately with either SGLT₂ inhibitors or Val/Sac, depending on their clinical profile.

Stability criteria for Val/Sac in AHF are [41]:

a. Systolic blood pressure ≥ 100 mm Hg in at least three measurements within the last 6 - 12 hours
b. Euvolemic status
c. Unchanged I.V. diuretic dose for 6 - 12 hours, preferably oral administration
d. Cessation of I.V. vasodilator, inotrope, or vasopressor medication within 6 - 12 hours.

Hyponatremia is a relative contraindication, while hypovolemia is an absolute contraindication for Val/Sac initiation.

Tomassoni et al. [42] proposed a list of criteria inspired by the clinical trials for the SGLT₂ inhibitors initiation:

a. No diuretic dose increase in the last 6 hours
b. No I.V. inotrope or vasodilator therapy in the last 24 hours
c. SBP > 100 mmHg
d. eGFR ≥ 20 ml/min/1.73 m2. (empagliflozin), eGFR ≥ 25 ml/min/1.73 m2(dapagliflozin).

It is recommended to monitor renal function for 1-2 weeks, especially when the start values of GFR are lower. A decrease of 10% in GFR at treatment initiation is frequent and should not lead to dose adjustment.

The perspective of treating the patient “with everything available” is extremely tempting for the clinician, aiming to minimise the readmission and mortality rate. In theory, using quadruple therapy...
with ARNi, MRA, beta-blockers, and SGLT₂ inhibitors can lead to a 73% decrease in the annual mortality in patients with HF and reduced EF. [43, 40] The major difference between SGLT₂ inhibitors and the other three classes is the ease of administration, as it does not need up-titration or numerous successive laboratory determinations. On the other hand, HF population is heterogeneous. For the patient with de novo AHF, naïve to guideline medications, the implementation seems much simpler and the expected response is of a higher magnitude. At the opposite pole are the patients already on triple or quadruple therapy. One population that can be excluded from the beginning is the patients with signs of hypoperfusion and/or severe respiratory insufficiency in need of prolonged ventilatory support. Patients with acute coronary syndrome causing AHF also need a mixed approach which is both pharmacological and interventional; in this case, the efficacy of the first is dependent on the success of the latter.

Modulation of the renin-angiotensin-aldosterone and sympathetic nervous systems with angiotensin-converting enzyme inhibitors or an angiotensin receptor-neprilysin inhibitor, beta-blockers, and mineralocorticoid receptor antagonists has been shown to improve survival, reduce the risk of HF hospitalizations, and reduce symptoms in patients with HF and reduced EF [44]. SGLT₂ inhibitors added to therapy with ACE-I/ARNI/betablocker/MRA further reduced the risk of cardiovascular death and worsening HF in patients with reduced EF [45].

No substantial prospective randomised trial has been performed exclusively in patients with HF mildly reduced EF, and to date, no treatment has been shown to convincingly reduce mortality and morbidity in patients with HF and preserved EF. That being said, hospitalizations for HF were reduced by candesartan [46] and spironolactone [47] and there was a trend towards reduction with Val/Sac [48].

For AHF, diuretic and vasodilator drugs are the main classes of medication used, but the introduction of ARNi and SGLT₂ inhibitors in this high-risk population is a safe option after achieving clinical stability.

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List of abbreviations

REFERENCES