Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: June 30, 2022

Citation Shaban M, Sosa F, et al., 2022. The Metabolic Model of Heart Failure; the Role of Sodium-Glucose Co-transporter 2(SGLT2) Inhibition, Medical Research Archives, [online] 10(6). https://doi.org/10.18103/mra.v10i6.2828

DOI
https://doi.org/10.18103/mra.v10i6.2828

ISSN: 2375-1924

RESEARCH ARTICLE

The Metabolic Model of Heart Failure; the Role of Sodium-Glucose Co-transporter 2(SGLT2) Inhibition

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ABSTRACT

The sodium-glucose co-transporter-2-inhibitors (SGLT2I) recently gained a unique role in managing the heart failure reduced ejection fraction. These inhibitors reduce cardiovascular (CV) risk factors, including plasma glucose, blood pressure, albuminuria, body weight, and renal events in the long term. The clinical trials proved their role in reducing hospitalization for HF, CV and all-cause mortality, atherosclerosis-related events, and CKD progression. Initiating this medication on decompensated heart failure or post-discharge reduces the risk of re-hospitalization. These co-transporter inhibitors reduced heart failure and kidney events regardless of baseline biomarker concentration or diabetes mellitus status. This article aims to the metabolic paradigm and cellular metabolism by exposing the available clinical trials of this novel therapy for heart failure, uncovering the possible mechanisms of action on the CV system, and describing the positive effect on prognostic markers as pro-BNP, as well as changing the plasma renin-aldosterone activity, cardiac troponin T (hs-cTnT), and insulin-like growth factor-binding protein 7 (IGFBP7).

Abbreviations:

Heart failure(HF), angiotensin-converting enzyme (ACE), angiotensin receptor blocker (ARB), sodium-glucose cotransporter (SGLT), HF and preserved Ejection Fraction (HFpEF), HF and reduced Ejection Fraction (HFrEF), pro-B-type natriuretic peptide (proBNP), cardiovascular (CV), type 2 diabetes (T2DM), chronic kidney disease (CKD), New York Heart Association functional class (NYHA-fc), ejection fraction (EF), coronary artery disease (CAD), brain natriuretic peptide (BNP), glomerular filtration rate (GFR), left ventricular (LV), primary (1ry), Secondary (2ry), nitric oxide (NO), Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CS).

Introduction

Heart failure (HF) is a pathological condition characterized by the inability of the myocardium to pump sufficient blood supplies to meet the metabolic demand. The number of hospitalized patients with cardiovascular diseases is estimated to be more than 1 million each year, of which 80% to 90% of patients ultimately progress to decompensated HF. [6] Comprehending the complex human physiology would allow us to understand heart failure pathophysiology and its paradigms, including cardiorenal, hemodynamic, neurohormonal, mechanical, genetic, and metabolic paradigms. [7] With the advances in medicine, newer medications in the metabolic paradigm of heart failure have been approved (Table 1).

Table 1 shows newer medications for the metabolic paradigm of heart failure.

	Mechanism	Trials/evidence
Febuxostat	Potent non-purine selective xanthine oxidase inhibitor, widely used for symptomatic hyperuricemia [1] The underlying molecular mechanisms of xanthine oxidase inhibitors to improve CV outcomes in cardiac patients are still unknown. [2] It is also unclear whether UA-lowering treatment (ULT) can benefit heart failure patients with asymptomatic hyperuricemia. [2]	Cicero et al. [3] conducted a study comparing treatment effects with allopurinol versus febuxostat in elderly patients with mild-to-moderate chronic HF. They recruited 255 patients with HF secondary to chronic arterial hypertension or CAD who were not previously hospitalized for HF. After five years, the cumulative CV survival was 0.96 with febuxostat versus 0.89 with the allopurinol group. It was concluded that febuxostat might favorably affect CV mortality compared to allopurinol in elderly patients with mild-to-moderate HF. [3] Suzuki et al. [1] has included 263 patients with UA >7.0 mg/dL and chronic HF randomly assigned to allopurinol or febuxostat for three years. The rate of patients free from hospitalization due to worsening HF tended to be higher in the febuxostat than in the allopurinol group (89.0% vs. 83.0%). [1]
Trimetazidine	Shifts energy production from fatty acid oxidation to glucose oxidation. Reduces oxidative damage, inflammation, and apoptosis and improves endothelial function. [4]	Zhang et al[5] performed a meta-analysis of Sixteen RCTs with 884 CHF patients. They suggested that trimetazidine in CHF patients may decrease hospitalization for cardiac causes, improve clinical symptoms and cardiac function, and simultaneously lessen left ventricular remodeling. [5]
Neladenoson bialanate (partial adenosine A1 receptor agonist)	Improve cardiomyocyte energetics, calcium homeostasis, cardiac structure, and function [6] Interacts with the mitochondrial permeability transition pore leading to decreased levels of cytosolic cytochrome c and improvement of cell viability and mitochondrial function. [7]	Clinical trials were designed to study the impact of neladenoson in patients with chronic heart failure with reduced (PANTHEON trial) and preserved (PANACHE trial) ejection fractions. [8] In the PANTHEON trial, Voors et al. [8] assessed the dose-response effect of neladenoson bialanate in our hundred sixty-two patients in 92 centers in 11 countries. The trial did not meet the primary endpoints of the 20-week change in LVEF and NT-proBNP from baseline. [8]
Elamipretide (MTP-131); Cardiolipin stabilizer	stabilizes cardiolipin and protects it from ROS-mediated oxidation and subsequent dysfunction. [7]	The safety, tolerability, and therapeutic effect on human cardiac structure and function were assessed by Daubert et al. [9] in 36 patients with HFrEF. Elamipretide was well-tolerated and safe. High-dose elamipretide resulted in favorable changes in LV volumes. [9] Three-phase II trials are currently underway.[7]
Coenzyme Q10 (CoQ10)	Facilitates the mitochondrial production of ATP by participating in redox reactions within the electron transport chain. [10]	Mortensen et al. [11] evaluated CoQ10 as an adjunctive treatment for chronic HF in the Q-SYMBIO trial. They recruited 420 patients with moderate to severe HF and randomly assigned them to either CoQ10 100 mg 3 times daily versus placebo for 2-year. The trial achieved the long-term endpoint at two years in terms of reducing cardiovascular mortality (9% vs. 16%), all-cause mortality (10% vs. 18%), the incidence of hospital stays for HF, and improvement of NYHA class.[11]
Asprosin	Fasting glucogenic adipokine that induces rapid glucose release from the liver. The exact mechanism of action is under investigation. Theories suggest that the asprosin can modulate cardiac mitochondrial functions and has important prognostic implications in dilated cardiomyopathy (DCM) patients. [12]	Wen et al. [12] conducted a prospective study including 50 DCM patients followed for five years. DCM patients had higher asprosin levels than healthy individuals (191.2 versus 79.7 ng/mL). Among DCM patients with lower Asprosin levels (< 210 ng/mL), there was an increased risk of adverse clinical outcomes with an HR of 7.94 when compared to patients with higher asprosin levels (≥ 210 ng/mL). [12]
Myocardial BH4	Induces of NO/sGC (soluble guanylate cyclase)/ (protein kinase G)-dependent increase in glucose uptake via GLUT-1, Preserves mitochondrial creatine kinase activity, oxygen consumption rate, LV energetics, and myocardial function. [13]	Using mice models and human myocardial samples, Carnicer et al. [13] found that myocardial BH4 prevents and reverses LV diastolic and systolic dysfunction associated with DM. [13]

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Among the novel pharmacological approaches for heart failure, therapeutic interventions are developed to act more on the intracellular components, especially the second messenger level. [8]Cyclic GMP has emerged as a critical intracellular second messenger that mediates protective CV, renal, neurohormonal, and metabolic actions in maintaining whole-body homeostasis. [9] NO is an endothelial relaxing factor that mediates favorable CV actions with the effector molecule 3′,5′-cyclic guanosine monophosphate (GMP). [9] The NO pathway is a crucial regulator in the CV system that interacts with the myocardial performance and vascular tone. vasotone dysregulation could complicate the NO-cyclic guanosine monophosphate (cGMP) signaling axis disruption with resultant impaired cGMP formation by endothelial dysfunction, vascular and ventricular stiffening, fibrosis, and hypertrophy with a net result of a decline in heart as well as kidney function. [10] The NO-cGMP pathway has become a common treatment target in HF, which eventually affects the natriuretic peptides. The natriuretic peptide family includes atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide. All natriuretic peptides are cyclic GMP activators functioning through pGC. [9] One-quarter of patients with ADHF were shown to lack the activation of ANP and subsequently lower cyclic GMP levels. The differential regulation of ANP and BNP reflects compromised compensatory cardiac and endocrine responses in ADHF. [11]. Sacubitril–valsartan increases natriuretic peptides by inhibiting neprilysin; eventually, it emerged as a critical strategy in treating HF.[9]

Vericiguat is a soluble guanylate cyclase stimulator developed to treat chronic HF. Vericiguat stimulates the cGMP production independent of NO and enhances NO's effects by stabilizing the NO-sGC binding.[12] The victory of Vericiguat was achieved by PW et al. in the VICTORIA trial[13]. This trial included 5050 patients with chronic HF (NYHA-fc II, III, or IV) and an EF < 45% receiving vericiguat 10 mg once daily) vs. placebo, in addition to guideline-based medical therapy. The 1ry outcome of a composite of death from CV causes or first hospitalization for HF occurred in 35.5% in the vericiguat group and 38.5% in the placebo group (HR: 0.90) within a median duration of 10.8 months. [13]

The sodium-glucose Cotransporter 2 Inhibitors (SGLT2i), initially designed for the management of type 2 diabetes mellitus (T2DM), have recently been demonstrated to improve outcomes in HF. The SGLT2Is, together with other metabolic paradigm therapeutic tools, are acquiring more attention in the therapy of HF rather than the neurohormonal paradigm. Various publications report improvement of cardiac contractility, metabolic, fibrosis, and remodeling using these new agents. 14 The initial trials for SGLT2i came in 2015 after the EMPA-REG and DECLARE–TIMI 58 trials, driven by the benefit of the reductions in hospitalization for HF and CV mortality, however, not by lower rates of myocardial infarction or stroke. Moreover, empagliflozin appeared to slow deterioration in renal function, and the heart-failure benefits persisted in the presence of renal dysfunction. 15

The initial results from large randomized clinical trials supported the use of empagliflozin (EMPA-REG, Empagliflozin, CV Outcomes, and Mortality in T2DM) and Dapagliflozin (DECLARE–TIMI 58, Dapagliflozin and CV Outcomes in T2DM) for the reduction in hospitalization for HF, in CV and all-cause mortality, in atherosclerosis-related events and the progression of CKD in large cohorts of diabetic patients. These data were later strengthened with results of the EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic HF With Reduced EF).8 Moreover, The EMPEROR-Reduced trial also showed that the effects of empagliflozin to reduce the risk of HF and renal events are not diminished in intensively treated patients receiving sacubitril/valsartan. Combined treatment with both SGLT2 and neprilysin inhibitors can be

expected to yield substantial additional benefits.16 Until 2021, results from 10 large SGLT2I placebo-controlled clinical outcome trials randomizing around 71 000 individuals have confirmed that SGLT2Is can provide clinical benefits for each of these outcomes in different populations. The CV and renal benefits of SGLT2Is appear to be larger than their comparatively modest effect on glycemic control or glycosuria alone.5

The SGLT2i also showed a positive impact on several CV risk factors, including plasma glucose, blood pressure, albuminuria, and body weight. Canagliflozin improved CV and renal outcomes consistently across patients with a broad range of BMI levels.1 DAPA-HF (Dapagliflozin in Patients with HFrEF) showed that among patients with heart failure reduced ejection fraction (HFrEF), the risk of worsening HF or death from CV causes was lower in those who received dapagliflozin, regardless of the DM status. 17 The patients of DAPA-HF were similar to those in other contemporary HFrEF registries and trials. These patients received recommended HFrEF therapy, and those with DM were also treated with conventional glucose-lowering treatment. 18 The frequency of volume depletion, hypoglycemia, and renal dysfunction adverse events did not differ between Dapagliflozin and placebo groups. 17 Furthermore, although adverse events and medication discontinuation increased with age, there were no significant imbalance, intolerability, or safety events with dapagliflozin compared to placebo, even in elderly individuals. 19 In addition, baseline creatinine did not alter the benefits of dapagliflozin on morbidity and mortality in HF. Dapagliflozin also slowed the rate of decline in eGFR, including in patients without diabetes.20 In another sub-analysis of DAPA-HF by Shen et al. 21, dapagliflozin was similarly effective and safe in patients with HFrEF taking or not taking an MRA, supporting the use of both drugs together. 21

Hypoglycemia and volume depletion were uncommon with SGLT2i, meaning that it could be added to background therapy of HF without significant concerns about blood pressure or heart rate tolerability for dose titration. 15 SGLT2I magnitude of benefit was similar to sacubitril–valsartan, an angiotensin-receptor neprilysin inhibitor, in the PARADIGM-HF (Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortality and morbidity in HF) trial 22 PARADIGM-HF trial included 8442 patients with extensive background therapy with beta-blockers (93% patients) and mineralocorticoid receptor antagonists (60%), however, persisting symptoms and signs, reduced health-related quality of life, and elevated proBNP22

This article will review the randomized clinical trials that initially support the use of SGLT2I for heart failure for major adverse cardiovascular event (MACE) benefits. We will discuss the trials trying to formulate the mechanism of action of SGLT2I on the cardiovascular system. The trials on the use of SGLT-2 in the settings of acute heart failure will be summarized. To write this article, MESH words "SGLT2i" and "heart failure" were used to collect all randomized control trials published until March 2022 in PubMed.

1- SGLT2i Trials For Major Adverse Cardiovascular Events (MACE)

The DECLARE-TIMI 58 was the most extensive study to address the MACE with SGLT2Is in patients with T2DM and established CV disease and in multiple risk factors for ASCVD without CV disease. 23 Results in 2021 showed that dapagliflozin reduced the risk of HF hospitalization and adverse renal outcomes in patients with T2DM and multiple risk factors regardless of the baseline characteristics. 24 Table 2 shows SGLT2Is trials assessing for the major adverse cardiovascular events (MACE).

Table 2 shows SGLT 2 I trials for major adverse cardiovascular events (MACE)

Author/study name:	Selected population	Patients (n)	Agent	Endpoint/ tested parameters	Significant results
DAPA-HF (Dapagliflozin in Patients with HFrEF) [14]	NYHA-fc II, III, or IV HF and an EF of 40% or less	4744	Dapagliflozin 10 mg for a median of 18.2 months.	Worsening HF (hospitalization or an urgent visit) or CV death.	1ry outcome in 16.3% versus 21.2% in placebo group (HR, 0.74). CV Death in 9.6% versus 11.5% in the placebo group (HR, 0.82) Findings in patients with DM were similar to those in patients without DM.
DAPA-HF trial (The Dapagliflozin And Prevention of Adverse-outcomes in HF) [15]	HF in NYHA-fc ≥ II, LV EF ≤ 40%, elevated N-terminal pro-BNP	4742	Dapagliflozin 10 mg once daily	CV death or worsening HF according to eGFR category at baseline (<60 and ≥60 mL·min-1·1.73 m-2).	No difference in the primary and secondary outcomes by eGFR category or examining eGFR as a continuous measurement. HR for the primary endpoint in CKD patientswas 0.71 versus 0.77 in those with an eGFR ≥60 mL·min-1·1.73 m2. Dapagliflozin did not reduce the composite renal outcome, but the rate of decline in eGFR between days 14 and 720 was less.

Martinez et al. [16] **Subanalysis From DAPA-HF**	NYHA-fc II or greater with LV EF ≤40% and modest elevation of NT-proBNP Excluded patients with SBP <95 mm Hg or estimated GFR<30 mL·min-1·1.73 m-2.	4744		Worsening HF (HF hospitalization or urgent visit) or CV death,	Rate of the 1ry outcome in each age group was 13.6, 15.7, 15.1, and 18.0, with corresponding dapagliflozin/placebo HRs of 0.87, 0.71, 0.76, and 0.68. Consistent benefits for each component of the 1ry outcome, all-cause mortality, and symptoms.
Shen et al. [17] subanalysis of **DAPA-HF**	a subanalysis of HFrEF patients enrolled in the DAPA-HF trial	3,370	Dapagliflozin 10 mg	CV death or episode of worsening HF, according to MRA use	The benefit of Dapagliflozin compared with placebo was similar in patients taking or not taking an MRA: HR: 0.74 versus 0.74, respectively, for the 1ry endpoint; similar findings were observed for 2ry endpoints.
EMPagliflozin outcomE tRial in Patients With chrOnic HF With Reduced EF [EMPEROR-Reduced]. [18]	HF and a reduced EF, with or without DM.	3,730	Empagliflozin for 16 months	Composite risk of CV death or hospitalization for HF, total hospitalizations for HF, change in health status, and functional class.	Reduction in the composite risk of CV death or hospitalization for HF Decreased total hospitalizations for HF Improved health status and functional class. Magnitude of these benefits (even after one month of treatment) was not more marked in patients with recent volume overload. Slower annual rate of reduction in GFR with a lower risk of renal severe outcomes.
Levin et al. [19] Post Hoc Analysis of EMPA-REG trial	T2DM established atherosclerotic CV disease, and eGFR≥30 ml/min per 1.73 m2	6952	Empagliflozin 10 mg, 25 mg,	CV, kidney outcomes, and safety	Consistent risk reductions across KDIGO categories for CV outcomes and kidney outcomes. Similar adverse event rates
Effect of Dapagliflozin worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes [20]	HFrEF with and without DM + elevated plasma N-terminal pro-BNP	4744 (at 410 sites in 20 countries)	Dapagliflozin 10 mg.	Worsening HF or CV death	1ry outcome in 13.2% in the dapagliflozin group and 17.7% in the placebo group. Among patients without DM, 12.1% were in the dapagliflozin group and 16.9% in the placebo group.
DECLARE-TIMI 58 [21]	T2DM and an established ASCVD or multiple risk factors for ASCVD	17,160	Dapagliflozin 10 mg	Composite of CV mortality, myocardial infarction, or ischemic stroke and the composite of CV death or hospitalization for HF	Still ongoing; however, a subanalysis was published by Cahn et al. [22] Reduced risk of CV death or hospitalization for HF (CVD/HHF) and the renal-specific outcome among patients with MRF(did not differ from that for patients with ASCVD. A reduction in HHF entirely drove the effect on CVD/HHF). The benefits of Dapagliflozin on HHF and the renal-specific outcome among the subset with MRF were directionally consistent across clinically relevant subgroups. Lower, HbA1c, weight, systolic blood pressure, and urinary albumin-to-creatinine ratio at 48 months [22]
SOLOIST-WHF ClinicalTrials [23]	T2DM, recently hospitalized for worsening HF	1222	Sotagliflozin for 9 months.	Mortality from CV causes and hospitalizations and urgent HF visits.	The trial ended early because of a loss of funding. The CV death was 10.6 in the sotagliflozin vs. 12.5 in the placebo.
CREDENCE [24]	T2DM and albuminuric, CKD, GFR of 30 to <90 ml per minute per 1.73 m2	4401	Canagliflozin 100 mg for 2.62 years	ESRD (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2), doubling of the serum creatinine level, or death from renal or CV causes.	The trial was stopped early after the interim analysis. 30% lower1ry outcome. 34%lower relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes. 32% lower relative risk of ESRD. Lowered risk of CV death, myocardial infarction, or stroke and hospitalization for HF.
DAPA-CKD (Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and CV Mortality in Patients With CKD) [25]	CKD, with and without HF	4,304	Dapagliflozin 10 mg daily	≥50% decline in estimated GFR, ESRD, or kidney/CV death. 2ry endpoints: kidney composite (1ry endpoint minus CV death), the composite of CV death/HF hospitalization, and all-cause death.	Reduced the risk of the 1ry outcome equally in patients with HF and without HF. The proportional risk reductions were similar in patients with and without HF for the composite CV death/HHF and all-cause death. However, absolute risk reductions were more significant in HF patients.
Effects of Dapagliflozin in Stage 4 Chronic Kidney Disease [26]	eGFR of 25-75 ml/min per 1.73 m2 and urinary albumin-to-creatinine ratio of 200-5000 mg/g	293	Dapagliflozin 10 mg/d	Composite of time to ≥50% sustained decline in eGFR, ESKD, or kidney or CV death. 2ry endpoints: kidney composite (same as the 1ry endpoint but without CV death), a composite of CV death or HHF, and all-cause death.	Patients with stage 4 CKD experienced a 27% reduction in the 1ry composite endpoint and 29%, 17%, and 32% reductions in the kidney, CV and mortality endpoints, respectively. The eGFR slope declined by 2.15 and 3.38 ml/min per 1.73 m2 per year in the dapagliflozin and placebo groups.
CANVAS Program [27] Subgroup analysis of CANVAS Program (Canagliflozin CV Assessment Study)	T2DM and high CV risk.	10.142	Canagliflozin for 188 weeks	Adjudicated CV death or hospitalized HF.	CV death or hospitalized HF was reduced (16.3 versus 20.8 for placebo), as was fatal or hospitalized HF (HR, 0.70) and hospitalized HF alone (HR, 0.67). The benefit of CV death or hospitalized HF may be more significant in patients with a prior history of HF (HR, 0.61) than those without HF at baseline (HR, 0.87).

Neuen et al.[28] Post hoc analysis of the CANagliflozin CV Assessment Study (CANVAS) Program	T2DM at high CV risk and with eGFR≥30mL/min/1.73m2	10,142	Canagliflozin	CV death, nonfatal myocardial infarction, or nonfatal stroke, with a set of other CV and kidney prespecified outcomes.	The relative effect of canagliflozin on the 1ry outcome was consistent across KDIGO risk categories, with similar results for other CV and kidney outcomes. Absolute reductions in the 1ry outcome were more significant within higher KDIGO risk categories with a similar pattern of effect for the composite of CV death or hospitalization for HF and chronic eGFR slope.
EMPEROR-Preserved trial [29]	HFpEF	5 988	Empagliflozin 10 mg	major HF outcomes	21% risk reduction of the composite of CV death or hospitalization for HF, which was mainly related to a 29% lower risk of hospitalization for HF rather than the effect on CV death empagliflozin. The effects of SGLT2 inhibitors were consistent in all patients.
The eValuation of ERTugliflozin efflcacy and Safety CV outcomes trial (VERTIS-CV) [30]	≥40 years old with T2DM (HbA1c 7.0-10.5%) and established atherosclerotic CV disease (ASCVD) of the coronary, cerebral, and/or peripheral arterial systems,	8238	Ertugliflozin 5 mg or 15 mg	non-inferiority of ertugliflozin on major adverse CV events as the composite outcome of CV death or hospitalization for HF (HF); CV death; and the composite outcome of renal death, dialysis/transplant, or doubling of serum creatinine from baseline.	Ongoing trial

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Abbreviations: End-stage renal disease (ESRD), Glomerular filtration rate(GFR), multiple risk factors (MRF), hospitalization for heart failure (HHF)

The evaluation of the safety and efficacy of SGLT2Is, when initiated soon after an episode of decompensated HF, was the aim of the SOLOIST-WHF trial. They found that sotagliflozin therapy significantly lowered the total number of deaths from CV causes and hospitalizations and urgent visits for HF than placebo in patients with DM and recent worsening HF. 25

The CREDENCE trial 26 concluded after including 4401 patients with T2DM and albuminuric, CKD, GFR of 30 to <90 ml per minute per 1.73 m2 that the risk of kidney failure and CV events was lower if treated with canagliflozin for a median duration of 2.62 years. These results were promising in progressive CKD, where few effective long-term treatments are available. [26]

The Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) [27] trial protocol was published in 2020, aiming to enroll more than 4300 patients with CKD Stages 2-4 and elevated urinary albumin excretion. DAPA-CKD determines whether the dapagliflozin, added to guideline-recommended therapies, safely reduces the rate of renal and cardiovascular events in patients across CKD stages with or without diabetes. [27] Early results after

analyzing 293 by Chertow et al. showed that the effects of dapagliflozin were consistent among patients with stage 4 CKD and albuminuria without evidence of increased risks. [28] Furthermore, independently of the history of HF, Dapagliflozin reduced the risk of kidney failure, CV death, and HF hospitalization. It also prolonged survival in CKD patients with or without T2DM. Adverse event rates did not differ among patients with or without HF. [29]

The CANVAS Program [30] included more than 10.140 patients. It gave us better information about the effects of canagliflozin on clinical outcomes across different KDIGO (Kidney Disease: Improving Global Outcomes) risk categories. They found that the relative impacts of canagliflozin are similar across KDIGO risk categories. However, the absolute risk reductions are likely more significant for individuals at higher KDIGO risk. They put the light on the likelihood of the KDIGO classification system to identify candidates with expected more excellent benefits for end-organ protection by canagliflozin. [31]

The EMPA-REG Outcome trial (Empagliflozin CV Outcome Event Trial in T2DM Patients) showed that Empagliflozin significantly reduced the risk of CV death by 38%, hospitalization for HF by 35%, and incident or worsening nephropathy by 39%. [32]. In addition, Levin et al. performed a sub-analysis of the EMPA-REG Outcome trial to prove that empagliflozin versus placebo on CV and renal outcomes were consistent through the KDIGO risk categories, showing that the effect of treatment benefit of empagliflozin was unaffected by baseline CKD status. 32

The heart failure preserved ejection fraction (HFpEF) is a complex disease that accounts for more than half of all HF hospital admissions with a high prevalence and lack of effective evidence-based management. SGLT2I recently gained a unique role in managing HFrEF. The EMPEROR-Preserved trial was the initial randomized controlled trial that proves that SGLT2Is (empagliflozin) can significantly reduce HF hospitalization by 29% lower than the placebo arm; however, no effect on CV mortality. 2

The eValuation of ERTugliflozin efflcacy and Safety CV outcomes trial (VERTIS-CV) 33 is another large RCT including 8238 T2DM patients with HbA1c 7.0-10.5% and established atherosclerotic CV disease (ASCVD) of the coronary, cerebral, and/or peripheral arterial systems; They were randomized to a newer SGLT2I, Ertugliflozin 5 mg or 15 mg. The study looks for a primary endpoint of non-inferiority of ertugliflozin on MACE and a composite outcome of renal death, dialysis/transplant, or doubling of serum creatinine from baseline. The results from the VERTIS-CV trial will outline the CV and renal safety and efficacy of ertugliflozin in ASCVD patients. [33]

2- SGLT2I trials uncovering its mechanisms of action

Diabetes mellitus increases the risk for CV events. The use of SGLT2i inhibitors leads to a reduction in CV outcomes in patients with T2DM (T2DM), including mortality and HF hospitalization, but the exact mechanisms are not clearly understood yet. [34] [35] The moderate glucose-lowering effect of SGLT2 inhibitors is unlikely to explain SGLT2I-mediated beneficial outcomes. [4]

The HF is characterized by fluid accumulation in the vascular compartment and interstitial space. Arterial underfilling could be present in advanced HF patients, secondary to low cardiac output, which would be, in turn, aggravated by the excessive diuretic treatment. A relative reduction of interstitial fluid volume rather than blood volume would be expected to better control congestion without reducing arterial filling and perfusion. [36] SGLT-2 inhibitors are known to promote glycosuria through urinary glucose reabsorption inhibition with a subsequent improvement of blood glucose. Dapagliflozin also results in glucose-induced osmotic diuresis, weight loss, and lowering blood pressure. [23] These diuretic effects contribute to their ability to reduce serious HF events, and this action is critical in patients with fluid retention. In the subanalysis of the EMPEROR-Reduced Trial, Packer and his colleagues [37] found no evidence supporting a dominant role of diuresis in mediating the clinical benefits of SGLT2Is on the HFrEF pathogenesis. [37]

A differential volume regulation hypothesis was suggested by Hallow et al. [36]. They hypothesize that osmotic diuresis induced by SGLT2Inhibition causes increased electrolyte-free water clearance and relatively higher fluid clearance from the interstitial fluid (IF) space than circulation, resulting in congestion relief with minimal impact on blood volume, arterial filling, and organ perfusion. To approve their hypothesis, Hallow et al. [36] created a mathematical model of the electrolyte-free water clearance combined with healthy individual response data after

either dapagliflozin or bumetanide. They found that dapagliflozin produces a 2-fold greater reduction in IF volume than blood volume, while the decrease in IF volume with bumetanide is only 78% of the reduction in blood volume. [36]

These agents reduce oxidative stress, inflammation, and fibrosis in the small blood vessels, with the resultant prevention of shear stress-related renal damage; they also reduce cardiac cytosolic Na+ and Ca2+ concentrations through inhibition of Na+/H+ exchanger, promote weight loss by inducing a fasting-like state with increased production of ketones, a good substrate for the failing heart. [8]

The SGLT2i may exert some beneficial effects via sympathetic inhibition. Some animal experiments suggest a bidirectional interaction between sympathetic nervous system activation and SGLT2 expression, leading to improved glucose metabolism, weight loss, increased diuresis, and lower blood pressure. [4] By enhancing glucosuria, natriuresis, and osmotic diuresis, SGLT2i improves glucose control, promotes weight loss, and lowers arterial blood pressure; however, no reflex heart rate increase despite blood pressure and plasma volume lowering. This stationary heart rate could be explained by attenuated sympathetic activity. SGLT2Is are suggested to inhibit sympathetic activation and reduce renal and cardiac levels of tyrosine hydroxylase and norepinephrine. The hypotensive effect is maintained regardless of renal function worsening. [38]

High serum uric acid levels are associated with worse myocardial function and with a doubled risk of death from any cause among patients with HF. [39] Zhao et al. conducted a meta-analysis using 62 studies with 34,941 patients to describe the effects of SGLT2Is on serum uric acid (UA) in patients with type 2 diabetes mellitus (T2DM). They concluded that SGLT2Is significantly decreased UA levels during short and long-term treatment. In addition, dapagliflozin decreased UA in a dose-dependent manner (from 5 to 50 mg) with more significant reductions in early diabetes, suggesting that SGLT2Is might be beneficial for diabetic patients with hyperuricemia. ⁴⁰(Zhao et al. 2018) The UA-lowering effect was abolished in patients with CKD (eGFR <60 mL/min per 1.73 m2). [40] Despite the extensive literature about UA in CV pathologies, the DAPA-HF trial did not address the possible role of a change in uric acid levels as a mediator in improving CV outcomes in the enrolled patients. [39]

The compelling results of DAPA-HF still require clarification and further studies to understand the underlying mechanisms. In addition, almost all the DAPA-HF patients had moderate HF, which means that we need more studies on SGLTI-2 efficacy and safety in patients with more severe HF or acute heart failure (AHF). [15] Furthermore, the limited (only in 10%) background use of sacubitril–valsartan raised concerns about the concomitant use of both. Some authors raised other concerns about the attenuated magnitude of SGLT2 with concomitant higher doses of anti-failure medications. [15]

In the next part of our review, we will discuss the SGLT2I trials looking for laboratory, imaging, and hemodynamic parameters that tried to hypothesize the Multiple mechanisms for the SGLT2I benefit.

2-A- Association between pro-BNP changes induced by SGLT2I and HFpEF

The elevated amino-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations are associated with HF diagnosis and predict CV risk. Januzzi et al. performed a subanalysis of the CANVAS trial where they assessed 4,330 patients randomized to Canagliflozin versus placebo. [41] They measured NT-proBNP at baseline, one year, and six years. They found that only a substantial percentage of patients in the CANVAS trial had elevated NT-proBNP values. Canagliflozin reduced NT-proBNP concentrations versus placebo; however, reduction in NT-proBNP explained only a small proportion of the benefit of canagliflozin on HF events. [41] Table 3 shows SGLT2I trials for pro-BNP changes in HFrEF and HFpEF.

Table 3 shows SGLT 2 I trials for pro-BNP changes, HFpEF.

Author/study name:	Selected population	Patients (n)	Agent	Tested parameters	Significant results
Januzzi et al. [31] **Subanalysis of CANVAS trial**	Participants in the CANVAS trial; T2DM	4,330	Canagliflozin for 6 years	NT-proBNP at baseline, 1 year, and 6 years	By 1 year, reduced NT-proBNP by 11% Lower NT-proBNP at 6 years. In adjusted models, baseline NT-proBNP ≥125 pg/ml was prognostic for incident HHF (HR: 5.40), HHF/CV death, and all-cause death.

					Mediation analyses suggested that 10.4% of the effects of canagliflozin on HHF were reflected in NT-proBNP lowering.
The SGLT2 inhibitor dapagliflozin in HF with preserved EF [32]	HFpEF	324	Dapagliflozin for 12 weeks	KCCQ-CS, 6MWT, KCCQ-OS, and changes in weight, natriuretic peptides, glycated hemoglobin, and systolic blood pressure.	Improvements in both KCCQ total symptom score (KCCQ-TS) (5.8 points) and physical limitations scores (5.3 points). Improved 6MWT. No significant differences in other endpoints. Similar adverse events.
CANDLE [33]	T2D and stable CHF	233	canagliflozin 100 mg vs. glimepiride for 24 weeks	Non-inferiority of canagliflozin vs. glimepiride for percentage change in NT-proBNP.	Non-significant lower NT-proBNP trend. However, it did not meet the non-inferiority margin.
Kusunose et al.[34] **Subgroup analysis of CANDLE trial**	T2DM (T2DM) and chronic HF	233	canagliflozin for 24 weeks	changes in NT-pro BNP levels, stratified according to baseline ventricular diastolic function	No marked heterogeneity in treatment effect between subgroups. Patients with SEP-e' < 4.7 cm/s showed an association with lower NT-proBNP levels in the canagliflozin group.
MUSCAT-HF [35]	T2DM and HFpEF (EF >45%)	190	Luseogliflozin 2.5 mg versus voglibose 0.2 mg three times per day for 12 weeks	Proportional change in BNP. 2ry endpoints; change in the ratio of E/e`, body weight, and glycaemic control.	Ongoing trial

31. Januzzi JL, Xu J, Li JW, et al. Effects of Canagliflozin on Amino-Terminal Pro-B-Type Natriuretic Peptide: Implications for Cardiovascular Risk Reduction. J Am Coll Cardiol. 2020;76(18):2076-2085. doi:10.1016/J.JACC.2020.09.004
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33. Tanaka A, Hisauchi I, Taguchi I, et al. Effects of canagliflozin in patients with type 2 diabetes and chronic heart failure: a randomized trial (CANDLE). ESC Hear Fail. 2020;7(4):1585-1594. doi:10.1002/EHF2.12707
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35. Ejiri K, Miyoshi T, Nakamura K, et al. The effect of luseogliflozin and alpha-glucosidase inhibitor on heart failure with preserved ejection fraction in diabetic patients: rationale and design of the MUSCAT-HF randomised controlled trial. BMJ Open. 2019;9(3). doi:10.1136/BMJOPEN-2018-026590

Abbreviations: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CS), 6-minute walk test (6MWT), KCCQ Overall Summary Score (KCCQ-OS), septal annular velocity (SEP-e'). early mitral inflow velocity to mitral annular early diastolic velocity(E/e`)

Patients with HFpEF have a high burden of symptoms and functional limitations, and poor quality of life. To assess the possible relation between SGLT2I Dapagliflozin and HF-related health status, and parameters such as natriuretic peptides, glycated hemoglobin, and systolic blood pressure, 6-minute walk test, KCCQ-OS, and changes in weight, Nassif and his colleagues [42] included 324 patients with HFpEF. They found that 12 weeks of dapagliflozin treatment significantly improved patient-reported symptoms, physical limitations, and exercise function. No significant differences in changes in weight, natriuretic peptides, glycated hemoglobin, and systolic blood pressure. Adverse events were similar between both groups. [42]

In the CANDLE trial that included 233 patients with T2D and stable CHF, Tanaka et al.[43] compared NT-proBNP changes after 24 weeks of using canagliflozin or glimepiride in patients with T2D and stable CHF. This study did not meet the predefined 1ry endpoint of non-inferiority of canagliflozin vs. glimepiride for percentage change in NT-proBNP. More doubts were raised about whether HFpEF patients, regardless of DM status, could potentially benefit from treatment with SGLT2Is or not. [43] In the analysis of CANDLE trial subgroups stratified by LV diastolic function, Kusunose et al. [44] found that canagliflozin resulted in lower NT-pro BNP levels than those with glimepiride in patients with a lower LV diastolic function. SEP-e' showed no marked heterogeneity in treatment effect; however, septal annular velocity < 4.7 cm/s was associated with lower NT-proBNP levels in the canagliflozin group. Kusunose et al. suggested selective beneficial effects of canagliflozin based on the severity of LV diastolic dysfunction. [44]

The MUSCAT-HF trial [45] is an ongoing RCT to assess the newer SGLT2I, Luseogliflozin 2.5 mg, versus voglibose (alpha-glucosidase inhibitor after12 weeks of therapy. They included 190 HFpEF to evaluate the primary endpoint of proportional change in BNP. The 2ry endpoints are the changes in the early mitral inflow velocity, mitral annular early diastolic velocity, body weight, and glycaemic control. [45] In General, Recent guidelines recommend SGLT2Is in patients with T2DM and HF, irrespective of their glycemic control status and background use of other glucose-lowering agents. The impact of canagliflozin treatment on NT-proBNP

concentration is independent of the background use of DM therapy. [46]

2- B Renal mechanisms and circulatory markers;

Renal-induced fluid volume changes are still considered the most important mechanism of the beneficial clinical effects of SGLT2Is. [47] Table 4 shows SGLT2I trials for renal mechanisms and circulatory markers.

Table 4 shows SGLT 2 I trials for renal mechanisms and circulatory markers.

Author/study name:	Selected population	Patients (n)	Agent	Endpoint/ tested parameters	Significant results
Empire HF Renal (Effects of empagliflozin on estimated extracellular volume, estimated plasma volume, and measured GFRin patients with HF) [36] **a substudy of the Empire HF trial.**	Outpatient clinics patients with NYHA-fc I-III symptoms, with LV EF of 40% or lower	391	Empagliflozin 10 mg for 12 weeks	Changes in estimated extracellular volume, estimated plasma volume, and GFR.	Reduced estimated extracellular volume, plasma volume, GFR.
Thiele et al [37] **Analysis of the EMPA hemodynamic study**	T2D	44	Empagliflozin 10 mg for 3 months	Haemoglobin, hematocrit levels, erythropoiesis, and iron metabolism	Increase in urinary glucose excretion, urinary volume after 1 day and throughout 3-month. Increased hematocrit, hemoglobin, red blood cell count, and transferrin concentrations only after 3 months. Urinary glucose increase correlated with erythropoietin induction.
Solini et al. [38]	hypertensive patients with T2DM	40	dapagliflozin 10 mg for 4-week vs. hydrochlorothiazide (HCT) 12.5 mg	Plasma renin activity; catecholamine, aldosterone. 24-hour urinary electrolyte. FMD of the brachial artery; carotid-femoral PWV; augmentation index; and resistive index and DRIN Circulating miRNAs related to HF (miR30e-5p, miR199a-3p), endothelial dysfunction (miR27b and miR200b), and renal function (miR130b-3p, miR21-5p)	lower fasting glucose, Increased 24-hour diuresis, glycosuria, and osmolar clearance No effect on sodium excretion and glomerular filtration rate. Increase Magnesium levels.
SGLT2 Inhibition in Combination With Diuretics in HF(RECEDE-CHF) trial [39]	T2DM and HFrEF taking a loop diuretic	23	Empagliflozin 25 mg for 6 weeks with a 2-week washout period	Change in 24-hour urinary volume from baseline to week 6	Increase in 24-hour urinary volume at both day 3 and week 6 No significant change in 24-hour urinary sodium at 6 weeks. Reduction in body weight and serum urate.
Zanchi et al. [40]	Healthy volunteers	45	10 mg empagliflozin for 1 month.	Renal oxygenation as assessed by blood oxygenation level-dependent MRI before and 180 minutes after administration of 10 mg empagliflozin. Proximal sodium reabsorption, fractional excretion of lithium.	No effect on Cortical and medullary renal oxygenation Increased 24-hour glucosuria at 1 month. Acute decrease in proximal sodium reabsorption, compensated at 1 month by increased plasma renin activity and aldosterone. Decreased 24-hour systolic and diastolic ambulatory blood pressures after 1 month. Decreased serum uric acid (-28.4%), increased hemoglobin (+1.7%), and same erythropoietin levels.
Vaduganathan et al. 2022 [41] **a** substudy of CANVAS (CANagliflozin CV Assessment Study)	T2DM	4,330	canagliflozin	Prognostic value of baseline hs-cTnT, sST2, and IGFBP7 on CV and kidney outcomes.	Slower increases of hs-cTnT and sST2 through 6 years, independently associated with CV and kidney outcomes, reduced HF and kidney events regardless of baseline biomarker concentration. Patients with hs-cTnT ≥14 ng/L and those with sST2 >35 ng/mL had a more significant relative benefit for MACE.
Empire HF Biomarker substudy [42]	Stable ambulatory HFrEF patients with EF of ≤ 40%	187	empagliflozin 10 mg for 12 weeks	Changes from baseline to 12 weeks in plasma levels of GDF-15, high-sensitive C-reactive protein (hsCRP), and hsTNT.	Increased plasma GDF-15, inversely associated with a decrease in LV end-systolic, and end-diastolic volume. No change in plasma hsCRP or plasma hsTNT. Patients with DM and treated with metformin demonstrated no increase in plasma GDF-15 with empagliflozin.

36. Jensen J, Omar M, Kistorp C, et al. Effects of empagliflozin on estimated extracellular volume, estimated plasma volume, and measured glomerular filtration rate in patients with heart failure (Empire HF Renal): a prespecified substudy of a double-blind, randomised, placebo-controlled trial. lancet Diabetes Endocrinol. 2021;9(2):106-116. doi:10.1016/S2213-8587(20)30382-X
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40. Zanchi A, Burnier M, Muller ME, et al. Acute and Chronic Effects of SGLT2 Inhibitor Empagliflozin on Renal Oxygenation and Blood Pressure Control in Nondiabetic Normotensive Subjects: A Randomized, Placebo-Controlled Trial. J Am Heart Assoc. 2020;9(13). doi:10.1161/JAHA.119.016173
41. Vaduganathan M, Sattar N, Xu J, et al. Stress Cardiac Biomarkers, Cardiovascular and Renal Outcomes, and Response to Canagliflozin. J Am Coll Cardiol. 2022;79(5):432-444. doi:10.1016/J.JACC.2021.11.027
42. Omar M, Jensen J, Kistorp C, et al. The effect of empagliflozin on growth differentiation factor 15 in patients with heart failure: a randomized controlled trial (Empire HF Biomarker). Cardiovasc Diabetol. 2022;21(1):34. doi:10.1186/S12933-022-01463-2

Abbreviations: Flow-mediated dilation (FMD), pulse-wave velocity (PWV), dynamic renal resistive index (DRIN), high-sensitivity cardiac troponin T (hs-cTnT), soluble suppression of tumorigenesis-2 (sST2), and insulin-like growth factor-binding protein 7 (IGFBP7), major adverse CV events (MACE), growth differentiation factor-15 (GDF-15)

To better understand the impacts of SGLTi on fluid compartments, Jensen et al. [47] performed a subanalysis of the Empire HF trial using data from 391 patients with HFrEF. They found that empagliflozin reduced estimated extracellular volume, estimated plasma volume, and measured GFR after 12 weeks of empagliflozin. [47] That might be related to the unknown mechanism by which SGLT2Inhibition stimulates erythropoiesis with subsequent increased hemoglobin levels [48]. hemoglobin and hematocrit increase was an independent predictor of the CV benefit of SGLT2I in the EMPA-REG OUTCOME trial [49]. In addition, In the Analysis of the EMPA hemodynamic study, Thiele et al.[48] noticed the same hemoglobin and hematocrit increase with a delayed time kinetic in 44 T2DM patients after three months of use of Empagliflozin. They attributed this increase to augmented iron utilization and increased renal erythropoietin secretion facilitated by diminished cellular stress and reduced tubular glucose reabsorption in response to SGLT2 inhibition. [48]

Solini et al. [35] measured the changes in plasma renin activity; aldosterone, catecholamine, and 24-hour urinary electrolyte levels; flow-mediated dilation (FMD) of the brachial artery; carotid-femoral pulse-wave velocity (PWV); augmentation and resistive renal resistive indices in response to 4-week of Dapagliflozin 10 mg vs. hydrochlorothiazide 12.5 mg to investigate the renoprotective benefits of SGLT2i. They found the nephroprotection effect of dapagliflozin through preserving renal vasodilating capacity "putative epigenetic regulation[35]

The SGLT2i will likely be prescribed with a loop diuretic in patients with HF, but this combined effect is not well-defined. Renal and CV effects of SGLT2i in combination with loop diuretics in patients with T2DM and chronic HF were evaluated by Mordi et al. in the RECEDE-CHF trial (SGLT2Inhibition in Combination With Diuretics in HF)[50]. Empagliflozin caused a significant rise in 24-hour urine volume without increasing urinary sodium when used in combination with a loop diuretic. The trial also reported a reduction in body weight and serum urate after six weeks of use of empagliflozin. [50]

Zanchi et al. [51] recruited 45 healthy volunteers to investigate empagliflozin-induced renal oxygenation modification to study the metabolic, renal, and hemodynamic effects of empagliflozin in nondiabetic individuals; an immediate and significant impact on tubular function, with sustained glucosuria and transient natriuresis in nondiabetic normotensive subjects, was reported after Empagliflozin administration. These effects favor blood pressure reduction. The investigators did not find acute or sustained changes in renal cortical or medullary tissue oxygenation. They suggested extending similar testing to prove the findings in nondiabetic or diabetic patients with congestive HF or kidney disease. [51]

Circulating cardiac stress biomarkers, such as high-sensitivity cardiac troponin T (hs-cTnT), insulin-like growth factor-binding protein 7 (IGFBP7), and soluble suppression of tumorigenesis-2 (sST2) levels reflect different mechanistic pathways that are commonly associated with the microvascular complication of T2DM. They may also identify at-risk T2DM patients who may benefit from SGLT2i [52]. Vaduganathan et al. [52] performed a subanalysis of the CANVAS trial to assess the prognostic significance of these biomarkers on CV and kidney outcomes in the 4,330 T2DM randomized to canagliflozin versus placebo. Interestingly, they found that Canagliflozin delays longitudinal rise in hs-cTnT and sST2 compared with placebo out to 6 years. Canagliflozin reduced HF and kidney events regardless of baseline biomarker concentration. Elevated CV biomarkers, either alone or in combination, may identify individuals who may derive more significant MACE benefits from SGLT2Inhibition. [52]

The Empire HF Biomarker substudy done by Omar et al. [53] enrolling 187 patients with stable HFrEF, Empagliflozin increased plasma levels of Plasma growth differentiation factor-15 (GDF-15) in patients with HFrEF. GDF-15 is an inflammatory biomarker that increases in response to tissue injury and is associated with increased mortality risk in patients with HFrEF. However, the GDF-15 increase in the Empire HF Biomarker substudy was inversely associated with decreased LV end-systolic and end-diastolic volume. GDF-15 increase was not associated with a concomitant rise in hsTNT nor hsCRP. Furthermore, Patients with DM and treated with metformin demonstrated no increase in plasma GDF-

15 with empagliflozin. SGLT2I might interfere with GDF-15 pharmacokinetics directly through the renal tubular transport mechanisms with subsequent blood level increase irrespective of tissue damage. [53]

2-C- Myocardial imaging evidence of SGLT2I effect on the heart

Large clinical trials established the benefits of SGLT2Is in patients with DM with HF. The improvement in clinical outcomes was explained beyond the hyperglycemia reduction. [54] . Empagliflozin significantly reduced HF hospitalization (HHF) in T2DM patients and established CV disease. In the EMPA-REG OUTCOME trial (Empagliflozin CV Outcome Event Trial), The early separation of the HHF event curves within the first three months of the trial suggests that immediate hemodynamic effects may play a role. [55] Rau et al., [49] investigated the early results of SGLT2Is on hemodynamic parameters and cardiac function. They measured the hemodynamic and echocardiographic parameters after one day, three days, and three months of empagliflozin use. They found that Empagliflozin treatment leads to rapid and sustained significant improvement of diastolic function; however, there was no significant effect on hemodynamic parameters after 1 or 3 days or three months. [49] Santos-Gallego et al., [54] evaluated LV imaging parameter change in response to 6-month treatment with Empagliflozin in 86 nondiabetic HFrEF patients in the ATRU-4/EMPA-TROPISM trial (Are the "Cardiac Benefits" of Empagliflozin Independent of Its Hypoglycemic Activity?); surprisingly, they found that Empagliflozin improved LV volumes, LV mass, LV systolic function, functional capacity, and quality of life independently of their glycemic status [54]. Table 5 shows trials that included myocardial imaging modalities to assess the benefits of SGLT2I.

Table 5 shows SGLT 2 I trials for myocardial imaging.

Author/study name:	Selected population	Patients (n)	Agent	Endpoint/ tested parameters	Significant results
Rau et al.[43]	T2D	42	empagliflozin 10 mg for 3 months	Hemodynamic and echocardiographic parameters after 1 day, 3 days, and 3 months.	Increased urinary glucose excretion, urinary volume after 1 day. Improved LV filling pressure assessed by E/e' (became significant at day 1, remained throughout the study) No effect on the systemic vascular resistance index, cardiac index, stroke volume index, or pulse rate. No difference in LV EF and strain analysis.
Are the "Cardiac Benefits" of Empagliflozin Independent of Its Hypoglycemic Activity? [ATRU-4] [EMPA-TROPISM] [44]	Nondiabetic HFrEF patients	84	Empagliflozin 10 mg for 6 months.	Change in LV end-diastolic volume, LV end-systolic volume, LV mass, and LV sphericity assessed by cardiac magnetic resonance. Changes in LV mass, LV EF, peak oxygen consumption in the cardiopulmonary exercise test, 6-min walk test, and quality of life.	Reduction of LV end-diastolic volume, LV end-systolic volume, LV mass, and LV sphericity Improvements in LV EF, peak O2 consumption, oxygen uptake efficiency slope, 6-min walk test, and quality of life.
DAPACARD [45 46]	T2DM that are on stable metformin therapy	52	Dapagliflozin for 42 days	Change in GLSLV measured with MRI. Corresponding change in myocardial efficiency measured as external LV work divided by total LV work, using [11C]-acetate clearance using positron emission tomography (PET).	Improved the global longitudinal strain and myocardial efficiency within the first 14 days. Slightly worse global longitudinal strain and myocardial efficiency. [46]
Oldgren et al. 2021 [47]	T2DM on metformin treatment	49	Dapagliflozin 10 mg 6-week	Cardiac function and structure with myocardial resonance imaging. Cardiac oxygen consumption, perfusion, and efficiency with [11 C]-acetate positron emission tomography (PET); and cardiac and hepatic fatty acid uptake with [18 F]-6-thia-heptadecanoic acid PET	Decreased body weight, HbA1c. No effect on myocardial efficiency, but reduced external LV work and LV oxygen consumption. Decreased peak global radial strain, unchanged peak global longitudinal and circumferential strains. Increased hepatic fatty acid uptake, unchanged cardiac uptake.
The SIMPLE Trial [48]/	T2DM at high CV disease risk	90	empagliflozin 25 mg for 13 weeks	Change in MFR quantified by Rubidium-82 PET/CT. Changes in rate-pressure product adjusted MFR during rest and stress, and reversible cardiac ischemia.	No change in MFR or other parameters.
The EMPA-VISION trial [49]	HF with reduced EF or preserved EF, with or without T2DM,	86	Empagliflozin 10 mg for 12 weeks.	31 Phosphorus-MRS to assess resting *phosphocreatine-to-adenosine triphosphate ratio.*	Still ongoing.
Mason et al. [50] **Substudy of the EMPA-HEART**	T2DM and CAD	97	empagliflozin 10 mg for six months	Change in LV ECV by CMR. Change in LVMi, iICV, iECV. Fibrosis biomarkers; sST2, MMP-2.	Reduced ECV, iECV. A trend toward reduction in iICV. No impact on MMP-2 or sST2.
Requena-Ibáñez et al. [51] sunbanalysis of of the EMPA-TROPISM trial .	nondiabetic patients with HF with reduced EF (HFrEF).		empagliflozin	EAT, interstitial myocardial fibrosis, and aortic stiffness changes	Reduced EAT volume; subcutaneous adipose tissue area Reduced extracellular volume, matrix volume (-7.24 mL) , cardiomyocyte volume (-11.08 mL), pulsed wave velocity (-0.58 cm/s) and inflammatory biomarkers.

REFORM trial [52] phase IV RCT.	T2DM + HF.		Dapagliflozin 10 mg for 1 year	Change in LV end-systolic and LV end-diastolic volumes. 2ry outcome: LV EF, LV mass index, exercise tolerance, fluid status, quality of life.	Still ongoing.
Impact of EMpagliflozin on cardiac function and biomarkers of HF in patients with acute MYocardial infarction-The EMMY trial [53]	AMI + characteristics suggestive of severe myocardial necrosis (phase 3b trial)		Empagliflozin (10 mg once daily)	Changes in NT-proBNP within 6 months after AMI. 2ry endpoints include changes in echocardiographic parameters, ketone body concentrations, HbA1c levels, and body weight.	Still ongoing.

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Abbreviations: Epicardial adipose tissue (EAT), global longitudinal strain of the left ventricle (GLSLV), cardiac magnetic resonance (CMR), indexed intracellular compartment volume (iICV), indexed extracellular compartment volume (iECV), soluble suppressor of tumorgenicity 2 (sST2), matrix metalloproteinase 2 (MMP)-2, Myocardial Flow Reserve (MFR), positron emission tomography(PET).Magnetic resonance spectroscopy (MRS)

Åkerblom et al., [34] published the protocol of the DAPACARD study (DAPAgliflozin on CARDiac substrate uptake, myocardial efficiency, and myocardial contractile work in T2DM patients) in 2019 to explore the possible effects of 6 weeks of dapagliflozin on cardiac work, metabolism, and biomarker levels. After analyzing the PET/CMR data of 52 T2DM patients on metformin therapy, [34], A second virtual population was generated by inducing a state of HFrEF in the DAPACARD virtual participants with type 2 diabetes mellitus for comparison. Cardiac response simulations were built up for placebo and SGLT2i over 42 days. [56] H. Yu et al.[56] published the results in 2022. They found that the SGLTI improved the global longitudinal strain and myocardial efficiency in DAPACARD-HFrEF virtual participants within the first 14 days. In contrast, the global longitudinal strain and myocardial efficiency in DAPACARD virtual participants were slightly worse; the authors attributed that effect to the diuretic and natriuretic effects of SGLT2I. [56]

To provide a more in-depth explanation of the effects of dapagliflozin on myocardial function and metabolism, Oldgren et al. [57] utilized [11 C]-acetate and [18 F]-6-thia-heptadecanoic acid PET to assess Cardiac oxygen consumption, perfusion, efficiency, and hepatic fatty acid uptake early in patients with T2DM without HF. They reported reduced heart work but limited effects on myocardial function, efficiency, and cardiac fatty acid uptake, while hepatic fatty acid uptake increased after six weeks of treatment with dapagliflozin. [57]

The SIMPLE trial (The Effects of Empagliflozin on Myocardial Flow Reserve in Patients With T2DM) [58] was another trial that utilized CMR to investigate the empagliflozin effects on microvascular perfusion in patients with T2DM at high CV disease risk. They found that 13 weeks of empagliflozin 25 mg did not improve Myocardial Flow Reserve (MFR); in other words, the reduction in CV events is not explained by a positive impact on the MFR [58]

Another new trial, the EMPA-VISION trial [59], is designed to assess the effects of empagliflozin treatment on cardiac energy metabolism. The study recruited 86 patients with HF with or without T2 DM to be randomized for empagliflozin 10 mg versus placebo for 12-week. Those patients would be checked for the change in resting phosphocreatine-to-adenosine triphosphate ratio, as measured by 31 Phosphorus- magnetic resonance spectroscopy (MRS)

aiming to look for the SGLT2I effect on cardiac energy metabolism and physiology. [59]

In the substudy of the EMPA-HEART trial, Mason et al. used CMR to assess the change of LV extracellular compartment volume (ECV), LV mass index (LVMi), indexed intracellular compartment volume (iICV), and indexed extracellular compartment volume (iECV) after six months of empagliflozin use. They proved that empagliflozin reduced ECV, iECV, and LVMi, supporting the remodeling reversal that is suggested to be related to SGLT2I use. However, the authors did find any effect of Empagliflozin on fibrosis biomarkers as soluble suppressor of tumorgenicity 2 (sST2), matrix metalloproteinase 2 (MMP)-2. [60]

The use of Empagliflozin in nondiabetic patients with HFrEF was evaluated in EMPA-TROPISM Study. A subanalysis of the EMPA-TROPISM trial was performed by Requena-Ibáñez et al., to assess the epicardial adipose tissue (EAT), interstitial myocardial fibrosis, and aortic stiffness changes after SGLT2I use. They found that Empagliflozin significantly improved adiposity, interstitial myocardial fibrosis, aortic stiffness, and inflammatory markers in nondiabetic patients with HFrEF. [61]

There is growing evidence suggesting beneficial effects of SGLT2I on myocardial remodeling, fluid balance, and cardiac function; however, not after acute myocardial infarction (AMI) yet. The EMMY trial (Impact of EMpagliflozin on cardiac function and biomarkers of HF in patients with acute MYocardial infarction) [62] is a large ongoing RCT recruiting patients with AMI with characteristics suggestive of severe myocardial necrosis regardless of their diabetic status. Results of the EMMY trial could be the rationale for the future CV outcome trial to test the effect of SGLT2i in patients with AMI. It would help uncover how SGLT2 inhibition could improve cardiac remodeling, pre-and afterload reduction, and cardiac metabolism regardless of its antidiabetic effects. [62]

2-D- Other hemodynamic parameters;

The EMPA-REG OUTCOME trial[55] showed that empagliflozin markedly reduced CV death and all-cause mortality and hospitalization for HF in patients with T2DM and established CV disease (CVD). [55] SGLT2Is are known to decrease plasma glucose levels and positively affect some metabolic and hemodynamic parameters related to CV pathways. [63] Table 6 shows trials that included hemodynamic parameters to assess the benefits of SGLT2I.

Table 6 shows SGLT 2 I trials for various hemodynamic parameters.

Author/study name:	Selected population	Patients (n)	Agent	Endpoint/ tested parameters	Significant results
EMBLEM trial [54 55]	T2DM with established CVD	110	Empagliflozin 10 mg	Change in the RH-peripheral arterial tonometry-derived RH index at 24 weeks from baseline. Change of vascular-related markers as arterial stiffness, sympathetic nervous activity, and cardiac and renal function parameters.	Reduced ePV by - 2.23% at week 4, - 8.07% at week 12, and - 5.60% at week 24. Reduced eEV by - 70.3 mL at week 4, - 135.9 mL at week 12, and - 144.4 mL at week 24. The change in log-transformed NT-proBNP was positively correlated with change in ePV (r = 0.351) but not with change in eEV.
Pietschner et al.[56]	CHF (LV EF 39.0 ± 8.2%)	75	Empagliflozin 10 mg for12 weeks	Ketone bodies (β-OHB). Changes in 24 h ABP monitoring, Vascular stiffness parameters	Increased β-OHB by 33.39%, Reduced 24 h systolic and diastolic ABP, weight loss Decrease of central systolic BP and central pulse pressure. The Increased β-OHB was related to an attenuated reduction of empagliflozin-induced 24 h systolic and diastolic ABP and less reduction of central systolic BP and central pulse pressure.
Papadopoulou et al. [57]	type-2 DM	85	Dapagliflozin 10 mg for 12 weeks.	24-h ABP monitoring with the Mobil-O-Graph NG monitor at baseline and study-end.	Decreased 24-h brachial SBP/DBP and central SBP/DBP. Decreased 24-h heart-rate adjusted augmentation index Change of estimated 24-h PWV favors Dapagliflozin.
EMBRACE-HF trial (Empagliflozin Evaluation by Measuring Impact on Hemodynamics in Patients With HF) [58]	HF with implanted pulmonary artery pressure sensor (CardioMEMS)	65	Empagliflozin 10 mg daily for 12 weeks.	Change in PADP	Reduced PADP at week 1, amplified reduction over time; average PADP was 1.5 mm Hg lower at weeks 8-12. At week 12, PADP was 1.7 mm Hg lower. Results consistent for PA systolic and PA mean pressures.
Omar et al. [59]	HFrEF	70	Empagliflozin 10 mg for 12 weeks	Ratio of PCWP to CI at peak exercise after 12 weeks assessed by right-heart catheterization at rest and during exercise	No significant treatment effect on peak PCWP/CI. Reduced PCWP over the full range of exercise loads, but not CI
Carbone et al.[60]	T2DM and HFrEF,	88	Canagliflozin 100 mg or sitagliptin 100 mg daily for 12 weeks	VO2, VE/VCO2 slope, lean peak VO2, VAT, cardiac function and quality of life (i.e., MLHFQ),	Study terminated early after the new guidelines No significant changes in peak VO_2 and VE/VCO_2 slope. Improved lean peak VO_2, VAT, and VO_2 matched for respiratory exchange ratio. Reduced MLHFQ score.

Nassif, Windsor, Tang, et al. [61] Subanalysis from the DEFINE-HF trial	HFrEF		Dapagliflozin for 12 weeks	LFVs measured by remote dieletric sensing	Improvement in LFVs

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Abbreviations: Reactive hyperemia (RH), ambulatory blood pressure (ABP), PA diastolic pressure (PADP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), Measured peak oxygen consumption (VO2), minute ventilation/carbon dioxide production (VE/VCO2), ventilatory anaerobic threshold (VAT), Minnesota Living with HF Questionnaire (MLHFQ), lung fluid volumes (LFVs)

It was noticed that blood ketone bodies increase with SGLT2i in patients with diabetes type 1 and 2. The ketone bodies are favored by the myocardium as a fuel substrate, especially in the context of CHF and increased myocardial oxygen demand. However, Experimental studies reported that ketone bodies, specifically beta-hydroxybutyrate (β-OHB), may increase blood pressure (BP) by impairing endothelium-dependant relaxation, leading to increased vascular stiffness. [64] Pietschner et al. performed a trial including 75 patients with HFrEF to calculate the endothelial function, ambulatory blood pressure (ABP) monitoring, and vascular stiffness parameters (β-OHB) to assess whether empagliflozin associated-increased ketone bodies impairs BP and vascular function. Their results showed Increased β-OHB by 33.39% and reduced 24 h systolic and diastolic ABP. The Increased β-OHB was related to an attenuated decrease of empagliflozin-induced 24 h systolic and diastolic ABP and less reduction of central systolic BP and central pulse pressure. Pietschner et al. [64] concluded that ketone bodies increase caused an attenuation of the positive effects of empagliflozin on BP and vascular parameters. [64]

Another trial to assess the endothelial function by Papadopoulou et al. [65] was performed by enrolling 85 T2DM randomized to Daptoglifozin versus placebo. Pulse wave velocity (PWV) and ambulatory central blood pressure as markers of arterial stiffness were evaluated after 12 weeks of treatment. They concluded that dapagliflozin significantly reduces ambulatory brachial and central BP levels and PWV in patients with type-2 DM. It is still believed that arterial stiffness and endothelial function improvement would substantially contribute to the CV benefits of SGLT-2 inhibitors. [65]

The EMBLEM trial was designed by Tanaka et al. in 2017 [63] to investigate if empagliflozin improved endothelial function, with an expected positive impact on progressive atherosclerosis in patients with T2DM and established CVD. After assessing the endothelial function by reactive hyperemia (RH) and arterial stiffness for 110 patients, they published the results in 2021 with the observation of reduced estimated fluid volume parameters in patients with type 2 diabetes and CVD after empagliflozin treatment for 24 weeks. [66]

The EMBRACE-HF trial (Empagliflozin Evaluation by Measuring Impact on Hemodynamics in Patients with HF) was designed by Nassif, Qintar, et al. [67] to assess the effects of sodium-glucose cotransporter-2 inhibitor empagliflozin on central hemodynamics. They evaluated the change in PA diastolic pressure (PADP) in response to 12 weeks of empagliflozin in 65 HF patients with implanted pulmonary artery pressure sensors (CardioMEMS). They found that SGLT2i resulted in rapid PA pressure reductions after a single week; interestingly, this effect was amplified after 15 weeks with lower PADP values by 1.7 mm Hg independent of loop diuretic use. [67]

On the same principle, Omar et al. [68] built his study of 70 HFrEF patients to use right-heart catheterization for assessment of pulmonary capillary wedge pressure

(PCWP) and cardiac index (CI) during the peak exercise after 12 weeks of empagliflozin. They also found reduced PCWP values but no significant improvement in neither CI nor PCWP/CI at rest or exercise. [68]

To find how SGLT2Is improve HF symptoms and physical tolerance from a volumic perspective, Nassif and his colleagues [69] performed a Subanalysis of the DEFINE-HF trial to assess lung fluid volumes measured by remote dieletric sensing. The authors suggested an SGLT2I direct effect for more effective decongestion. [69] On the same principle, Carbone et al.[70] started a trial to measure peak oxygen consumption (VO2) and minute ventilation/carbon dioxide production (VE/VCO2) slope, lean peak VO2, cardiac function, and quality of life after 12 weeks Canagliflozin versus sitagliptin, however, the study was early terminated after the new guidelines recommending canagliflozin over sitagliptin in HF. They did not find any significant changes in peak VO2 and VE/VCO2 slope between both groups. They reported improved lean peak VO2 and VO2 matched for respiratory exchange ratio with better scores for quality of life with the SGLT2I. [70]As a result, SGLTI is one of the novel promising therapeutic tools for heart failure in the modern era.

3- Acute Heart Failure

There is uncertainty and limited data regarding the initiation of SGLT2 inhibitors among patients hospitalized with acute AHF. [3] SGLT2i reduce the risk of death and HF admissions in patients with chronic HF. However, the safety and clinical efficacy of this therapy in patients with acute decompensated HF are unknown [71]. Salah et al., [3] performed a meta-analysis including Three RCTs with 1831 patients to estimate the efficacy and safety of SGLT2Is initiated in patients hospitalized for AHF. They found that Initiating SGLT2i in patients hospitalized for AHF during hospitalization or early post-discharge (within three days) reduces the risk of re-hospitalization for HF and improves patient-reported outcomes with no excess risk of adverse outcomes effects; however, there was no statistically significant effect on all-cause mortality nor the incidence of acute kidney injury, hypotension, or hypoglycemia. [3] Table 7 shows trials for SGLT2I and acute HF.

Table 7 shows SGLT 2 I trials for Acute HF.

Author/study name:	Selected population	Patients (n)	Agent	Endpoint/ tested parameters	Significant results
EMPA-RESPONSE-AHF (effects of empagliflozin on clinical outcomes in patients with acute decompensated HF)[62]	AHF, with and without DM.	80	Empagliflozin 10 mg/day for 30 days	Change in VAS dyspnoea score, diuretic response, change in NT-proBNP, and length of stay.	No difference in VAS dyspnoea score, diuretic response, length of stay, or change in NT-proBNP. Reduced in-hospital worsening HF, rehospitalization for HF, or death at 60 days. Increased urinary output until day 4.
Sub-study of Effects of empagliflozin on renal sodium and glucose handling in patients with acute HF study (EMPA-RESPONSE-AHF) [63]	Within 24 h of AHF admission.	79	Empagliflozin 10 mg/day for 30 days	Markers of glucose and sodium handling were measured daily during the first 96 h and on day 30	Increased fractional glucose excretion with a peak after 24 h, without affecting plasma glucose. Increased plasma osmolality at 72 h. Early decline in estimated GFR, recovered within 30 days.
Voors et al. [64]	Acute de novo or DCHF regardless of LVEF.	530	Empagliflozin 10 mg for up to 90 days	Clinical benefit is defined as a hierarchical composite of death from any cause, number of HF events, and time to first HF event, or a 5 point or greater difference in change from baseline at 90 days, as assessed using a win ratio.	Met the 1ry endpoint. Clinical benefit was observed for both acute de novo and DCHF regardless of EF or the presence or absence of DM.
EMPULSE trial [65]	AHF, stratified to HF status (de-novo and DCHF), regardless of EF and DM status.	500	In-hospital start of empagliflozin (10 mg once daily) for 90 days	All-cause death, HF events, and change from baseline KCCQ-TSS ≥5 points. 2ry outcomes are safety, change in KCCQ-TSS from baseline to 90 days, and change in natriuretic peptides from baseline to 30 days.	Still undergoing

62. Damman K, Beusekamp JC, Boorsma EM, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). Eur J Heart Fail. 2020;22(4):713-722. doi:10.1002/EJHF.1713
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Abbreviations: decompensated chronic HF (DCHF), Kansas City Cardiomyopathy Questionnaire Total Symptom Score(KCCQ-TSS), visual analog scale (VAS)

EMPA-RESPONSE-AHF trial (effects of empagliflozin on clinical outcomes in patients with acute decompensated HF)[71] included 80 patients with AHF, with and without DM. They were randomized to Empagliflozin 10 mg/day for 30 days versus placebo. Although there was no difference in dyspnea score, diuretic response, length of stay, or change in NT-proBNP, the authors reported a reduction in a combined endpoint of in-hospital worsening HF, heart failure hospital readmission, or mortality within 60 days. In addition, urinary output up until day 4 was significantly greater with empagliflozin. [71] Using the data of EMPA-RESPONSE-AHF, Boorsma et al. evaluated the role of empagliflozin in renal sodium and glucose handling in patients with acute HF daily during the first 96 h and at day 30. They reported an increased fractional glucose excretion and plasma osmolality without affecting fractional sodium excretion or urine osmolality. In other words, empagliflozin stimulates osmotic diuresis through increased glycosuria rather than natriuresis in patients with acute HF. The estimated GFR has an early decline which recovered within 30 days. [72]

Recently, in 2022 Voors et al. published the data of 530 patients with acute de novo or decompensated chronic HF randomized to 3 months of Empagliflozin. The study Met the 1-year endpoint of Clinical benefit, defined as a hierarchical composite of death from any cause, the number of HF events and time to first HF event, or a 5 point or greater difference in KCCQ. The clinical benefits were observed regardless of EF or the presence or absence of DM. They concluded that the SGLT2i initiation was well tolerated with less severe adverse events in 32.3% compared to 43.6% in the placebo-treated patients. [73]

The EMPULSE trial [74] is a large RCT enrolling 500 hospitalized patients with de-novo AHF or decompensated chronic HF, regardless of EF and DM status. It is designed to assess the all-cause death, HF events after 90 days of empagliflozin therapy initiated during hospitalization. The two years outcomes are safety, change in KCCQ-TSS from baseline to 90 days, and change in natriuretic peptides from baseline to 30 days. [74]

Conclusion:

The mechanisms underlying the beneficial effects of SGLT2i in HF remain not fully understood. The reduction of the oxidative stress, inflammation, and fibrosis in the small blood vessels, preventing the shear stress-related renal damage play an important role on the mechanism of this drugs; these medications also reduces cardiac cytosolic Na+ and Ca2+ concentrations by inhibiting the Na+/H+ exchanger. These agents increases the electrolyte-free water clearance resulting in congestion relief with minimal impact on blood volume, arterial filling, and organ perfusion. This therapy have a positive impact in cardiovascular risk factors, including plasma glucose, blood pressure, albuminuria, and body weight. The SGLT2Is reduced HF and kidney events regardless of baseline biomarker concentration, or diabetes mellitus status; also reduce the heart failure hospitalization by more than 28%.

Grant support: none

Disclosures: none of the authors report any conflicts of interest

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