

# The Potential Role and Rationale for Treatment of Heart Failure with SGLT2 Inhibitors

## Brief Title: SGLT2 inhibitors in Heart Failure

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## **ABSTRACT**

Heart failure (HF) and type 2 diabetes mellitus (T2DM) are both growing public health concerns contributing to major medical and economic burdens to society. T2DM increases the risk of HF, frequently occurs concomitantly with HF, and worsens the prognosis of HF. Several anti-hyperglycemic medications have been associated with a concern for worse HF outcomes. More recently, the results of the EMPAREG OUTCOME trial showed that the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin was associated with a pronounced and precocious 32% reduction in cardiovascular mortality in subjects with T2DM and established cardiovascular disease. These benefits were more related to a reduction in incident HF events rather than to ischemic vascular endpoints. Several mechanisms have been put forward to explain these benefits, which also raise the possibility of using these drugs as therapies not only in the prevention of HF, but also for the treatment of patients with established heart failure regardless of the presence or absence of diabetes. Several large trials are currently exploring this postulate.

**Keywords:** diabetes mellitus; heart failure; SGLT-2 inhibitor; empagliflozin

Heart failure (HF) is a global health problem with a prevalence of ~26 million worldwide. Patients with HF are at a 40%-50% risk of mortality within five years of diagnosis,<sup>1</sup> and suffer from recurrent hospitalizations and poor quality of life. Type 2 diabetes mellitus (T2DM) is growing with a prevalence of over 400 million globally.<sup>2</sup> The deleterious effects of T2DM can be separated into microvascular (neuropathy, nephropathy, retinopathy) and macrovascular (coronary disease, stroke, peripheral arterial disease) complications. While there is moderate to high quality evidence that glucose control reduces the risk of microvascular complications, its beneficial effect on macrovascular complications are less apparent and appear to take longer to manifest.<sup>3</sup> Cardiovascular diseases (CVD) account for approximately half of the deaths in T2DM.<sup>4</sup> CVD, HF, and T2DM are all associated with chronic kidney disease (CKD), which together further worsen prognosis.<sup>5, 6</sup>

There is now an increased recognition of the association between HF and T2DM,<sup>7</sup> with increasing prevalence of patients with both diseases concomitantly. The patients with a concomitant disease have a worse prognosis compared to those with either disease alone. HF is more than twice as likely to develop in patients with T2DM and may develop independent of coronary disease.<sup>8</sup> Conversely, HF is associated with insulin resistance and a higher risk for developing T2DM.<sup>9</sup> The prevalence of T2DM among patients with HF is as high as 40-45%<sup>10</sup> and the prevalence of HF in patients with T2DM is reported to be 10-23%.<sup>11</sup> Indeed, HF was the second most common initial CVD presentation in patients with T2DM, at 14.1%.<sup>12</sup>

The results of the recently published EMPA-REG OUTCOME trial, with the sodium-glucose cotransporter 2 (SGLT2) inhibitor, empagliflozin hold promise for CV risk reduction in diabetes. Particularly intriguing are the potential benefit with regards to HF. The current review aims to examine the potential role of this class of drugs in patients with HF with and without DM.

## **HEART FAILURE OUTCOMES IN DIABETES MELLITUS CLINICAL TRIALS**

In 2008, the US Food and Drug Administration (FDA) put forth guidelines for drug manufacturers to demonstrate that new anti-hyperglycemic medications should not increase the risk for CVD, with a focus on cardiovascular death, myocardial infarction, or

stroke.<sup>13</sup> Until recently, there was no evidence for HF risk reduction; conversely there were some concerns of worsening HF risk with therapies targeting glucose control.<sup>14</sup> For example, several trials showed an increased risk of HF with thiazolidinediones,<sup>15 16</sup> thus these agents are not recommended in patients with HF.<sup>17</sup> Interestingly, the dipeptidyl peptidase 4 inhibitor (DPP4i) saxagliptin and alogliptin but not sitagliptin may increase the risk of HF.<sup>18</sup> Sulfonylureas have been associated with increased risk of developing HF, but most data were derived from observational studies and definitive prospective trials are needed.<sup>19, 20</sup>

### *The EMPA-REG OUTCOME Trial*

The EMPA-REG OUTCOME trial was the first trial to show cardiovascular mortality reduction in high-risk patients with T2DM treated with empagliflozin, an SGLT2 inhibitor. This trial randomized 7020 patients with T2DM and CVD to 10mg or 25mg of empagliflozin daily or to placebo.<sup>21</sup> The primary endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was seen in 10.5% in the pooled empagliflozin group vs. 12.1% with placebo (hazard ratio [HR] 0.86; 95% confidence interval [CI], 0.74 to 0.99; P=0.04) in the 3.1 year follow up period. There were no significant differences in rates of myocardial infarction or stroke but there was a 38% lower risk of cardiovascular death and 32% risk reduction in all-cause death (both P<0.001) with empagliflozin.

Empagliflozin overall reduced the risk for HF hospitalization by 35% and HF death or hospitalization by 39% (both P<0.001), with benefits seen in both patients with and without documented HF at baseline.<sup>22</sup> The reduced adjudicated endpoint of HF hospitalization was supported by similar reductions of investigator reported HF, and the introduction of loop diuretics (as a surrogate for HF). The prevalence of manifest HF at baseline was 10% in the trial. HF ascertainment was based on self-reports without characterization of functional class, ejection fraction, or biomarker data. Detailed HF phenotyping, including echocardiography, was not performed in the EMPA-REG OUTCOME trial and it is unclear whether the HF-related benefits seen were limited to development of HFrEF or HFpEF. When compared with other hypertension,<sup>23-27</sup> HFpEF<sup>28-32</sup> and HFrEF<sup>33-35</sup> trials, the mortality and HF hospitalization rates in the EMPA-REG OUTCOME trial are comparable to other high

risk population trials, and the event rates among those who had baseline HF were comparable to those observed in HFpEF trials. (**Figure 1A and B**) This may suggest unsuspected high prevalence of HF in this population at baseline. This also raises the possibility that among those with HF-associated endpoints in this study, there perhaps may be more patients with HFpEF compared to those with HFrEF. This is consistent with what prior epidemiological studies suggesting an increase in HFpEF in patients with T2DM. This work is also consistent with rising evidence of a link between obesity, renal disease and HFpEF.<sup>36</sup>

### **DISSOCIATION BETWEEN GLUCOSE CONTROL AND HEART FAILURE OUTCOMES**

Interestingly, there was no significant relationship between glycemic control and HF outcomes in the EMPA-REG OUTCOME trial. Both the 10mg and 25mg doses had similar effects on outcomes. HbA1c level at randomization was not a determinant of benefit and patients across the spectrum of initial HbA1c values benefited from the treatment with empagliflozin. Similarly, HF patients who had a larger ( $\geq 0.3\%$ ) vs. a more modest ( $\leq 0.3\%$ ) reduction in HbA1c benefited equally from empagliflozin.<sup>37</sup> These observations suggest that the benefit with this agent is not related entirely to glucose control per se and other mechanisms mediate its cardiovascular-protective effects. It is noteworthy that another class of drug, glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide and semaglutide, were effective in lowering HbA1C and significantly improved other cardiovascular outcomes but not HF events.<sup>38-40</sup> However, when used in patients with stable chronic HF with or without DM, liraglutide was associated with higher cardiac adverse events.<sup>41</sup>

### **MECHANISM OF ACTION OF SGLT2-INHIBITORS FOR GLUCOSE CONTROL**

SGLT2 is located almost exclusively in the kidney, while SGLT1 transporters are also located in the intestines, heart, and skeletal muscles.<sup>42</sup> Glucose reabsorption in the kidneys occurs in a sodium-dependent manner via SGLT proteins, with most reabsorption occurring at the proximal convoluted tubule through SGLT2 and a smaller portion in the distal segment of the proximal tubule by SGLT1.<sup>43</sup> Once the maximum glucose transport capacity has been

reached, excess glucose is excreted into the urine. SGLT2 inhibitors lead to increased urinary glucose excretion by blocking SGLT2-mediated glucose reabsorption. (**Figure 2**)

### **POTENTIAL MECHANISM BENEFITING HEART FAILURE**

While the exact mechanism by which empagliflozin may impact HF outcomes is not understood, several effects of SGLT2 inhibitors can potentially be of benefit. Any potential mechanism of SGLT2 inhibitors benefiting HF should take into account the simultaneous reduction of CV mortality and the very rapid reduction of HF and cardiovascular mortality as well. (**Figure 3**, partially adapted from <sup>44</sup>)

**Lowering Blood Pressure:** Treatment with an SGLT2 inhibitor is associated with reduction in systolic and diastolic blood pressure. Unlike vasodilators, this change in blood pressure is not associated with an increase in heart rate<sup>45</sup>, suggesting that the sympathetic nervous system is not activated.<sup>46</sup> Reduction in blood pressure is likely multifactorial related to natriuresis, reduced plasma volume, non-fluid weight loss, as well as direct vascular effects.<sup>47</sup>

**Sodium and Fluid Loss:** SGLT2 inhibitors induce osmotic diuresis and natriuresis through the decreased reabsorption of glucose and sodium, <sup>48</sup> resulting in less extracellular volume, possible reduction of vascular wall stress, improving cardiac function and potentially reducing congestion. Reduction in plasma volume may also lead to reduced myocardial stretch and natriuretic peptide levels,<sup>44, 49</sup> as well as improving symptom and functional capacity. Loop and thiazide diuretics work primarily by natriuresis, whereas vaptans mediate their effects via aquaresis. In contrast, SGLT2 inhibitors induce natriuresis as well as osmotic diuresis via glucosuria. The increase in sodium excretion is temporary,<sup>50</sup> thus the mechanism might be an initial reduction of whole body sodium content. This then translates into a benefit via hemodynamic effects as well as an effect on sodium content within cardiomyocytes, i.e. an increase in sodium in these cells favors arrhythmias in HF models.<sup>51</sup> In addition, compared with conventional osmotic diuretics, empagliflozin does not affect

plasma osmolality. While both SGLT2 inhibitors and thiazide-like diuretics work on the proximal tubule of the nephron, thiazides are associated with hypokalemia, increased serum uric acid, and impaired glucose tolerance while SGLT2 inhibitors are not associated with increased serum uric acid or impaired glucose tolerance and no changes in serum potassium levels occur.<sup>52</sup>

Under physiologic concentrations of glucose, SGLT2-mediated glucose uptake stimulates the sodium-hydrogen exchanger (NHE)<sub>3</sub>, involved in the reabsorption of sodium bicarbonate, while supra-physiologic glucose levels inhibit NHE<sub>3</sub>, inducing natriuresis.<sup>53, 54</sup> In a HF rat model, the up-regulation of NHE<sub>3</sub> likely contribute to attenuation of the natriuresis and volume expansion.<sup>55</sup> SGLT2 inhibitors result in decreased activity in NHE<sub>3</sub>, possibly contributing to natriuresis, and reduction in blood pressure.<sup>56</sup>

**Effects on the Renin Angiotensin System:** Under physiologic conditions, the majority of sodium is reabsorbed in the proximal tubule. This enables the macula densa, located at the transition between the ascending limb of the loop of Henle and the distal convoluted tubule to sense changes in sodium concentration and adjust glomerular filtration rate via tubuloglomerular feedback. The decrease in sodium delivery to the distal tubule leads to a compensatory increase in renin by the juxtaglomerular cells and activation of the downstream angiotensin system.<sup>48</sup> In the setting of HF, decreased renal blood flow leads to sodium reabsorption via the proximal tubule, likely enhanced by SGLT2 augmented by activation of the sympathetic nervous system and angiotensin II.<sup>57, 58</sup> While inhibition of SGLT2 may attenuate the downstream effects of neurohormonal activation in HF,<sup>59</sup> other studies suggest that in response to volume contraction, the levels of aldosterone and angiotensin II, may actually increase in response to SGLT2 inhibition.<sup>42</sup>

**Weight Loss:** Compared to some other anti-diabetic agents, SGLT2 inhibitors are associated with reduction in body weight.<sup>60</sup> This occurs rapidly initially and then gradually until a plateau is reached and it is sustained over time. The initial decline is thought to occur as a result of osmotic diuresis; however the subsequent gradual and predominant weight



reduction is likely caused caloric urinary glucose loss resulting in reduction in visceral fat mass.<sup>61</sup> There is ample evidence that obesity per se is a strong risk factor for incident HF but whether weight loss and the method of weight loss influence outcomes in patients with manifest HF,<sup>62</sup> or those with diabetes,<sup>63</sup> remains controversial.

**Maintenance of Kidney Function:** Decline in renal function is accompanied by disruption in volume homeostasis and predisposition to progression of HF.<sup>64</sup> More recently, renal dysfunction has been proposed as a potential causal risk factor for HFpEF.<sup>36</sup> Albuminuria is an important marker of vascular resistance and progression of kidney disease.<sup>65</sup> SGLT2 inhibitors reduce urinary albumin excretion and potential preservation of glomerular filtration rate over time. Recently Wanner et al reported relevant data from EMPA-REG OUTCOME trial.<sup>66</sup> New onset or worsening of nephropathy, a pre-specified exploratory composite renal endpoint, was reduced by 39%. Compared with placebo, empagliflozin significantly reduced the initiation of renal replacement therapy by 55%, doubling of serum creatinine by 44%, and new onset of macroalbuminuria by 38%. Empagliflozin also significantly slowed the decline in estimated glomerular filtration rate over time compared with placebo. It is important to note that these renal effects occurred on the background of renin-angiotensin-aldosterone system blockers for renal protection.<sup>47, 66</sup> The preservation of renal function by empagliflozin may contribute to its beneficial effects on HF. It should also be noted that while the GLP-1 receptor agonists also lessened albuminuria, their effects on other renal outcomes appear less clear.<sup>38, 39</sup> In T2DM where there is increased glucose and sodium reabsorption via SGLT2, decreased sodium delivery at the distal tubule results in afferent arteriole vasodilation leading to an increase in glomerular filtration rate, which is also known as “hyperfiltration”. Chronic hyperfiltration contributes to nephron loss. The target of SGLT1 inhibitors (either for selective SGLT1 inhibitors or for combined SGLT1+SGLT2 inhibitors) is the intestinal SGLT1. These SGLT1 inhibitor-compounds do not reach a concentration in the renal tubules that would allow for a renal inhibition of SGLT1. Therefore, for renal hemodynamics, the SGLT1 inhibition part is negligible regarding renal hemodynamics, for all currently available compounds. Regarding urinary glucose excretion

(UGE), this is relatively comparable between selective and non-selective SGLT inhibitors and both are associated with reduced UGE in patients with chronic kidney disease.

**Reduced Uric Acid and Oxidative Stress:** Elevations in uric acid is associated with oxidative stress and increased reactive oxygen species, increase in numerous cytokines, activation of the renin angiotensin system, and hypertension.<sup>67, 68</sup> SGLT2 inhibitors result in reduction in uric acid levels.<sup>69</sup> In animal studies, empagliflozin reduced oxidative stress.<sup>70</sup> Given the association of uric acid on both the renal and CV systems, this may be a mechanism for the impact of SGLT2 inhibitors on HF.

**Increased Hematocrit:** SGLT 2 inhibitors also result in increased hemoglobin and hematocrit levels.<sup>71</sup> Univariate analysis of potential mediators for empagliflozin's CV mortality benefit demonstrated that hematocrit showed a 52% change in the hazard ratio for CV mortality.<sup>72</sup> This may be related to hemoconcentration of plasma volume, as discussed above. SGLT2 inhibitors ameliorate tubulointerstitial hypoxia through reduction in proximal tubule workload, though evidence for this theory is currently limited to animal models.<sup>73</sup> This allows for stimulation of erythropoiesis, which may partially explain the observed increase in hematocrit. However, the increase in erythropoietin is transient while the change in hematocrit is sustained over time.<sup>74</sup> Hemoglobin provides better tissue oxygenation and is regulated through hypoxia-inducible factor 1-alpha expression and subsequent erythropoietin secretion, factors influenced by SGLT2 inhibitors.<sup>75</sup>

**Decreased Inflammation:** SGLT2 inhibitors have been shown to reduce biomarkers of inflammation in animal models.<sup>76</sup> In a rat model, the anti-inflammatory effects may be mediated through inhibition of NADPH oxidase activity and decreased formation of advanced glycation end products.<sup>70</sup> This may benefit both the sequelae of T2DM and HF such as vascular dysfunction and fibrosis.<sup>70</sup>

**Decreased Arterial Stiffness:** Increased arterial stiffness is a predictor of HF events and death and is associated with hypertension, obesity, and worse HF.<sup>42</sup> Empagliflozin has been shown to reduce arterial stiffness in patients with type I DM.<sup>46</sup> This may be related to weight loss, improved arterial compliance and smooth muscle relaxation through a negative sodium balance,<sup>46</sup> which may be of particular benefit in HFpEF. In patients with T2DM and hypertension, empagliflozin was associated with reductions in markers of arterial stiffness and vascular resistance.<sup>77</sup> The reduction in arterial stiffness via SGLT2 inhibition, coupled with improved myocardial energetics and calcium handling could act together to improve HF.<sup>78</sup> Improvement in myocardial energetics would likely mean that systolic wall stress is shifted earlier rather than later, which is what is seen in HF. Thus, myocardial-arterial coupling improves. At the same time, the cardiomyocytes are less vulnerable to stress because of improved calcium handling.

**Metabolism:** SGLT2 inhibition increases glucagon levels.<sup>79</sup> In addition to its role in glucose homeostasis, glucagon also acts as a stress hormone.<sup>80</sup> Glucagon receptors expressed on cardiac myocytes facilitate its positive inotropic and chronotropic effects on the heart.<sup>81</sup> In the setting of T2DM, the hyperglycemic state results in increased glucose uptake by cardiac myocytes beyond its oxidative capacity (glucotoxicity), impairing cardiac function.<sup>61</sup> SGLT2 inhibitors as well as metformin decrease excess glucose uptake by the heart, albeit through different mechanisms.<sup>61</sup> Under normal circumstances, the heart is primarily fueled by fatty acids. In the setting of diabetes, the hyperglycemic state results in increased glucose uptake by cardiac myocytes, impairing cardiac function.<sup>61</sup> The elevated level of beta hydroxybutyrate seen with SGLT2 inhibitors<sup>82</sup> results in a shift in fuel supply from fatty acids and glucose, which are less energy efficient in the setting of T2DM, towards the more energy-efficient ketones. This in turn improves myocardial and renal metabolic efficiency while reducing oxygen consumption.<sup>83, 84</sup> This ketone hypothesis, however, is currently under study.<sup>85</sup>

## POTENTIAL BENEFIT ACROSS THE SPECTRUM OF HEART FAILURE

The exact mechanisms by which empagliflozin lowers the risk of cardiovascular death in patients with T2DM and might influence HF outcomes are not clearly understood. Most of the pharmacodynamic effects of SGLT2 inhibitors have the potential to reduce the development and progression of both HFrEF and HFpEF.<sup>86</sup> Thus, the potential for benefit with these agents should be properly tested across the left ventricular ejection fraction spectrum in patients with HF in carefully designed, randomized controlled trials with sufficient statistical power. Importantly, since the HF benefit of SGLT2 inhibitors does not seem to be related to glucose control and these agents are associated with low rates of hypoglycemia in states of normal glucose concentration, it is rational to postulate that SGLT2 inhibitors might be both safe and effective in HF patients without DM as well. In fact, in a zebrafish HF model, empagliflozin was able to attenuate HF in the absence of hyperglycemia.<sup>87</sup>

One unifying hypothesis is that the dominant mechanism of action of empagliflozin is a glucouretic effect without the usual adverse effects of conventional diuretics. In the EMPA-REG OUTCOME trial, the early, sizeable and persistent effect of empagliflozin in raising hematocrit and serum albumin, a drop in blood pressure, and a decrease in body weight may be interpreted as the effect on plasma volume and hemoconcentration, resulting from a benign “smart” or “diabetes-directed” diuretic effect. Indeed, this glucouretic effect is a striking variance with those observed with all other diuretics. The apparently adverse effects inherently associated with the pharmacology of the conventional loop diuretics and thiazides used in HF may counter and/or dampen their potential survival benefits. Still, other mechanism such as changes in cardiac metabolisms by SGLT2 inhibitor treatment may also contribute to beneficial effects in HF. In addition to clinical trials, further laboratory experimental data are warranted to further elucidate the underlying mechanisms of cardioprotection.

### **CLASS EFFECT OF SGLT2 INHIBITORS**

While empagliflozin has demonstrated a reduction in cardiovascular death and HF hospitalization risks, these analyses need to be replicated with other SGLT2 inhibitors before

it can be ascertained if this is a class effect or a drug-specific effect. In the near future, studies with canagliflozin and dapagliflozin will also report cardiovascular outcome results, shedding further light on this issue.<sup>88, 89</sup>

## **FUTURE DIRECTION**

The EMPA-REG OUTCOME trial was designed to study high-risk T2DM patients. This trial was not designed to assess the benefits of empagliflozin in patients with HF. Only a distinct minority of these patients (~10%) had a history of HF. Secondary analyses of the HF subgroup provides interesting hypotheses for potential benefits of this drug in HF; however the strength of evidence is not sufficient to recommend its use for the treatment of patients with HF and none of the HF guidelines currently recommend it for HF treatment. There have been examples in the past of cardiovascular drugs that have benefited patients with T2DM and CVD and were also shown to be of benefit in observational studies in HF. However, when dedicated adequately powered HF trials were done, no benefit was seen in improving HF outcomes.

A full characterization of the HF population, including information regarding left ventricular ejection fraction was not performed in the EMPAREG OUTCOME trial, as this was not a HF study. None of the therapies shown to improve survival in patients with HF with reduced ejection fraction, such as angiotensin-converting enzyme inhibitors or beta-blockers or mineralocorticoid antagonists have been conclusively shown to improve outcomes in patients with HFpEF conclusively. Thus outcomes related to HF therapies should be tested in specific populations. Also, while EMPA-REG OUTCOME trial was performed in patients with T2DM, the pharmacodynamics effects of empagliflozin lends itself to potentially also benefit patients with HF who do not have DM.

Based on these reasons, it is imperative to study this drug in adequately designed and powered dedicated HF clinical trials. This is of particular importance considering the increasing prevalence of patients with both HF and T2DM concomitantly. While this possibility remains, further studies to better understand the pharmacodynamic effects of SGLT inhibitors in patients with HF, including those without DM, are warranted. Importantly,

larger outcomes trials are needed with these agents. These should of course also determine the safety of these agents including assessing rates of genital infection and ketosis risks, in particular.<sup>21</sup> There are currently several phase III outcomes trials planned and just starting with empagliflozin and dapagliflozin. Empagliflozin will be studied in patients with HFpEF (EMPEROR-PRESERVED)<sup>90</sup> and HFrEF (EMPEROR-REDUCED)<sup>91</sup>, including HF patients without T2DM with the composite primary endpoint of time to first event of adjudicated CV death or adjudicated HF. Dapagliflozin will be studied in patients with HFrEF (Dapa-HF)<sup>92</sup> with the primary composite endpoint of CV death or hospitalization for HF or urgent HF visit as well as in patients with CKD (Dapa-CKD)<sup>93</sup> Sotagliflozin and luseogliflozin, non-selective SGLT 1 and 2 inhibitors, are also currently under development. (Table)

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## LEGENDS

### **Figure 1. Comparison of mortality and heart failure hospitalization rates in the EMPAREG OUTCOME versus other trials**

Comparison of overall mortality (A) and heart failure hospitalization (B) rates between hypertension, heart failure preserved ejection fraction (HFpEF) heart failure reduced ejection fraction (HFrEF) trials with EMPAREG OUTCOME trial. Participants with heart failure in the EMPAREG OUTCOME trials had comparable risk to that seen in patients with HFpEF.

ACCORD, Action to Control Cardiovascular Risk in Diabetes; LIFE, Losartan Intervention for Endpoint reduction in hypertension; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; ANBP-2, second Australian National, Losartan Intervention for Endpoint reduction in hypertension; CHARM-Preserved, CHARM-Added, CHARM-Alternative, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; I-PRESERVE, Irbesartan in Heart Failure with Preserved Systolic Function Trial; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; PEP-CHF, Perindopril in elderly people with chronic heart failure; DIG-PEF, Digitalis Investigation Group Congestive Heart Failure; PARADIGM-HF, Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure.

### **Figure 2. Mechanism of Action of SGLT-2 inhibitors**

The sodium glucose cotransporter (SGLT)-2 inhibitor empagliflozin works primarily at the proximal convoluted tubule of the nephron inhibiting the reabsorption of glucose and sodium.

### **Figure 3. Potential Pathways Linking Empagliflozin with Heart Failure Outcome Improvement**

CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; REG, removal of excess glucose; UNa, urinary sodium

**Table. Ongoing Trials with SGLT-2 Inhibitors**

Drug	Cohort	Primary Endpoint
Canagliflozin*	Chronic HF	Change from baseline aerobic exercise capacity at 12 weeks Change from baseline ventilator efficiency at 12 weeks
Dapagliflozin*	Chronic HF  CKD	Time to first occurrence of CV death or hospitalization for HF or urgent HF visit  Time to first occurrence of $\geq 50\%$ sustained decline in eGFR or reaching ESRD or CV death or renal death
Empagliflozin*	HFpEF HFrEF	Time to first adjudicated CV death or adjudicated hospitalization for HF
Luseogliflozin	HFpEF	Change in BNP at 12 weeks
Ertugliflozin	n/a	n/a
Sotagliflozin	n/a	n/a

\* Currently approved by Food and Drug Administration and European Medicines Agency  
BNP, b-type natriuretic peptide; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; HF, heart failure; HFpEF, heart failure preserved ejection fraction; HFrEF, heart failure reduced ejection fraction