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Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: Mechanisms of Cardiovascular Benefits

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Abstract: The cardiovascular effects of sodium glucose co-transport 2 (SGLT2) inhibitors have been demonstrated to be quite helpful in recent clinical trials. Both diabetics and non-diabetics, as well as those with and without chronic heart failure, have a lower risk of cardiovascular death and hospitalization due to heart failure. It is not quite apparent what mechanism(s) are responsible for these positive outcomes. The cardioprotective effects of SGLT2 inhibition have been hypothesized to be due to a number of processes, including but not limited to the following: reduction of inflammation, improvement of cardiac energy metabolism, reduction of blood pressure, erythropoiesis, prevention of adverse cardiac remodeling, prevention of ischemia/reperfusion injury, inhibition of the Na+/H+-exchanger, inhibition of SGLT1, reduction in hyperuricemia, increase in autophagy and lysosomal degradation, decrease in epicardial fat mass, increase in erythropoietin levels, increase in circulating pro-vascular progenitor cells, decrease in oxidative stress, and improve vascular function. In an attempt to consolidate and rank the mechanisms in relation to clinical event reduction, we examine the benefits and drawbacks of these suggested processes.

Keywords: *Sodium Glucose Co-Transporter 2, Cardiovascular Benefits*

Introduction.

Sodium glucose co-transport 2 (SGLT2) inhibitors have had impressively positive effects on cardiovascular outcomes in recent clinical trials. This includes a decrease in the occurrence of cardiovascular deaths and hospitalizations due to heart failure in both diabetics and non-diabetics, as well as in individuals with and without prevalent heart failure. It is yet unclear what mechanism, if any, is responsible for these positive outcomes. The cardioprotective effects of SGLT2 inhibition have been hypothesized to be due to a number of processes, including but not limited to the following: reduction of inflammation, improvement of cardiac energy metabolism, reduction of blood pressure, erythropoiesis, prevention of adverse cardiac remodeling, prevention of ischemia/reperfusion injury, inhibition of the Na+/H+-exchanger, inhibition of SGLT1, reduction in hyperuricemia, increase in autophagy and lysosomal degradation, decrease in epicardial fat mass, increase in erythropoietin levels, increase in circulating pro-vascular progenitor cells, decrease in oxidative stress, and

improve vascular function. This review aims to summarize and prioritize the postulated mechanisms in relation to clinical event reduction by analyzing their strengths and shortcomings.

Heart failure is one of the leading causes of death globally, affecting more than 50 million people (1). The prognosis and quality of life for those diagnosed with heart failure remain dismal, even if there have been advancements in the treatment of this condition. When it comes to the elderly, it is still the leading cause of hospitalization (1). Heart failure is the leading cause of death and morbidity in patients with type 2 diabetes mellitus (T2DM) and is more likely to occur in these patients (2, 3, 4). Therefore, new treatments and methods to prevent and cure heart failure must be developed immediately.

To alleviate hyperglycemia caused by type 2 diabetes, several drugs have been developed that block the sodium glucose co-transporter 2 (SGLT2) enzyme, which is responsible for reabsorbing glucose in the kidney's proximal tubule (5). The safety and effectiveness of SGLT2 inhibitors have been studied in numerous large-scale clinical trials in patients with diabetes (including those with vascular disease, multiple risk factors for cardiovascular disease, or renal insufficiency) and in patients with heart failure (including those with reduced ejection fraction) and type 2 diabetes (6, 7, 8, 9, 10, 11, 12, 13). Significant reductions in major cardiovascular and renal outcomes were observed in type 2 diabetes mellitus patients at high risk of cardiovascular disease in the EMPA-REG OUTCOME trial, which removed excess glucose from patients' blood. Patients treated with empagliflozin had a significantly lower risk of cardiovascular death and heart failure-related hospitalizations. These findings were confirmed in a larger group of patients undergoing primary and secondary prevention in subsequent large trials involving other SGLT2 inhibitors, such as canagliflozin (CANVAS [Canagliflozin Cardiovascular Assessment Study] [9] and CREDENCE [Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy] trials [10]) and dapagliflozin (DECLARE-TIMI 58 [Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes] trial [11]; for discussions of these trials, see Zelniker et al. [12] and Verma et al. [13].

Despite the strong evidence that SGLT2 inhibitors can prevent incident heart failure from the trials discussed above, two crucial problems were left unresolved. Is there any evidence that these treatments help those who do not have type 2 diabetes, and can they also be used to treat the common form of heart failure? Notably, in this context, the recently concluded DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial showed a significant decrease in worsening heart failure or cardiovascular death in addition to excellent standard-of-care therapy for heart failure (6). The trial included 4,744 patients with heart failure and reduced ejection fraction. And it was true across the board for A1cs measured categorically or continuously; furthermore, this effect was comparable in people with and without type 2 diabetes.

Possible Processes Why Is SGLT2 Inhibition Beneficial for Heart Health?

Several hypotheses have been advanced to account for the positive effects of SGLT2 inhibitors (14, 15, 16, 17, 18). Inhibiting SGLT2 has positive impacts on the following, among others: 1) reducing blood pressure; 2) increasing diuresis/natriuresis; 3) improving cardiac energy metabolism; 4) preventing inflammation; 5) weight loss; 6) improving glucose control; 7) inhibiting the sympathetic nervous system; 8) preventing adverse cardiac remodeling; 9) preventing ischemia/reperfusion injury; 10) inhibiting the cardiac Na+/H+ exchanger; 11) inhibiting SGLT1; 12) reducing hyperuricemia; 13) increasing autophagy and lysosomal degradation; 14) decreasing epicardial fat mass; 15) increasing erythropoietin (EPO) levels; 16) increasing circulating provascular progenitor cells; 17) decreasing oxidative stress; and 18) improving vascular function (Figure 1). What follows is a synopsis of these hypothesized mechanisms, followed by an analysis of the clinical data to determine which one (or ones) are most crucial

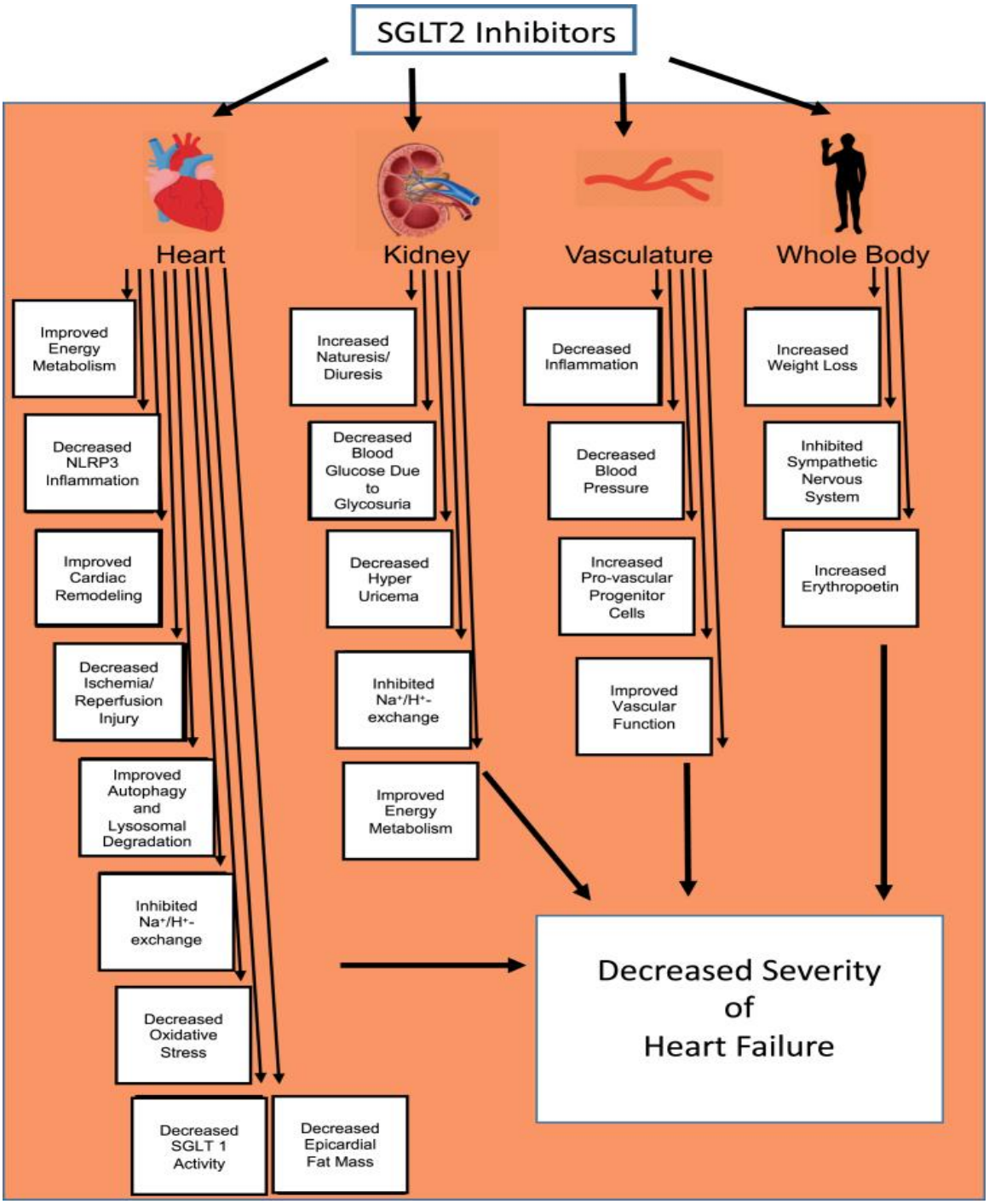

Figure 1 : Possible Mechanisms by Which SGLT2 Inhibitors Decrease the Severity of Heart Failure

Improved cardiac energetics with SGLT2 inhibition. NLRP3 = nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3; SGLT2 = sodium glucose co-transporter 2.

Blood pressure lowering

One common and manageable risk factor for heart failure is hypertension. One possible explanation for the positive benefits of SGLT2 inhibitors in the context of heart failure is that they reduce blood pressure (19). This, in turn, improves cardiac energetics by lowering blood pressure. Inhibiting salt reabsorption in the kidney's proximal tubules is believed to be the underlying mechanism(s) responsible for the antihypertensive effects of

SGLT2 inhibitors, which are likely to be mediated by the osmotic and diuresis actions of these drugs. The amount of sodium excreted in the urine might rise by 30–60% when SGLT2 is inhibited (20). Inhibiting SGLT2 in conjunction with ß-blockers or calcium antagonists had a stronger antihypertensive impact than thiazide diuretics alone (21,22). Improved ventricular arterial coupling and cardiac efficiency may follow from SGLT2 inhibitor-induced hypotension, which in turn reduces cardiac afterload. The dying heart is likely to gain from this. Nevertheless, the positive effects on the kidneys and cardiovascular system are likely due to more than just the slight reduction in blood pressure caused by SGLT2 inhibition. There was also no evidence that reducing blood pressure had a bigger impact on stroke rates than other cardiovascular outcomes in the EMPA-REG OUTCOME trial (8). Lastly, the DAPA-HF trial had small blood pressure decreases that were probably unrelated to the big drop in failure occurrences (6).

Glucosuria and increased natriuresis are side effects of SGLT2 inhibitors, which may improve heart failure outcomes due to the increased osmotic diuresis. Indeed, the EMPA-REG OUTCOME trial's mediation analysis indicated that hemoconcentration, which is thought to be a result of volume contraction, was responsible for approximately half of the cardiovascular benefit that was observed (8). Since other diuretic techniques have not been linked to an improved event reduction in heart failure trials, it is challenging to explain the benefits of SGLT2 inhibitors solely based on diuresis. There is considerable speculation that SGLT2 inhibitors are different from traditional diuretics. For instance, when tested side-by-side with hydrochlorothiazide and dapagliflozin, researchers found that the former reduced plasma volume and increased erythrocyte mass, but the latter did not (23). There was a greater decrease in interstitial vs intravascular volume with dapagliflozin than with bumetanide, a loop diuretic (24). Theoretically, conventional diuretics cause a reflex neurohumoral stimulation in response to a decrease in intravascular volume; however, SGLT2 inhibition may have a distinct impact on controlling interstitial fluid (as opposed to intravascular volume).

Enhanced metabolic rate of cardiac energy

The failing heart undergoes profound alterations in its energy metabolism. Glycolysis takes over as the primary energy source for the heart in advanced heart failure, and mitochondrial oxidative metabolism steadily declines (25). A failing heart has less energy output and is fuel-starved because mitochondrial glucose oxidation drops (26, 27, 28). Cardiac efficiency (cardiac work/O2 consumed) decreases as a result of increased proton generation due to the uncoupling of glycolysis and glucose oxidation in a failing heart (25, 26, 27, 28). Patients with heart failure and preserved ejection fraction with left ventricular (LV) hypertrophy also experience a drop in LV mechanical efficiency (30), which leads to a decrease in cardiac efficiency. This is not limited to patients with heart failure and reduced ejection fraction, though.

Some research suggests that SGLT2 inhibitors may help heart failure patients by increasing cardiac efficiency and enhancing cardiac energetics. By releasing fatty acids from adipose tissue, SGLT2 inhibitors raise blood ketone levels, which the liver uses for ketogenesis (31, 32, 33). Even in the absence of diabetes, circulating ketone levels can increase following therapy with SGLT2 inhibitors (33). Some have speculated that these ketones, as a "thrifty" fuel for the heart, might enhance cardiac energetics and efficiency (34,35). Ketones provide an extra fuel source for a failing heart, but our research shows that they aren't a more efficient fuel source overall (36,37). The failure of the heart's mitochondria to carry out oxidative metabolism causes it to be "energy starved" (25,29). The failing heart improves its energy supply by increasing cardiac ketone oxidation rates, which is thought to be an adaptive metabolic process (37, 38, 39, 40). This is achieved through an increase in plasma ketone levels in the blood, which is caused by SGLT2 inhibition (41). Empagliflozin improves cardiac function in diabetic cardiomyopathic rats by increasing myocardial ketone oxidation, which provides an extra fuel supply for the heart (Figure 2) (41). Santos-Gallego et al. (42) provided evidence that empagliflozin can improve cardiac energetics and reduce unfavorable remodeling and heart failure in a pig model of the disease. Additionally, SGLT2 inhibitors have been demonstrated to enhance mitochondrial respiratory performance in diabetic rats (43), which could potentially lead to better energy production in the heart. Positive adjustments in the heart's energy supply may influence some of these mitochondrial respiration changes. A better contractile performance has also been linked to the administration of ketones into heart

failure patients (44). Curiously, there is no correlation between the enhancement of contractile function brought about by ketone use and an improvement in cardiac efficiency. Since oxidizing ketones does not provide more energy than oxidizing glucose, this makes sense. Consequently, it is unclear whether the favorable benefits of SGLT2 inhibition in heart failure are due to providing the failing heart with more fuel or to providing a more efficient source of fuel. Furthermore, there is no correlation between the decline in glucose and fatty acid oxidation and the rise in cardiac ketone oxidation in a failing heart, leading to an increase in adenosine triphosphate generation overall (37,41). Thus, although SGLT2 inhibitors might not improve cardiac efficiency in a failing heart, they could provide an additional fuel source, which could be especially helpful for a failing heart that is already struggling with energy.

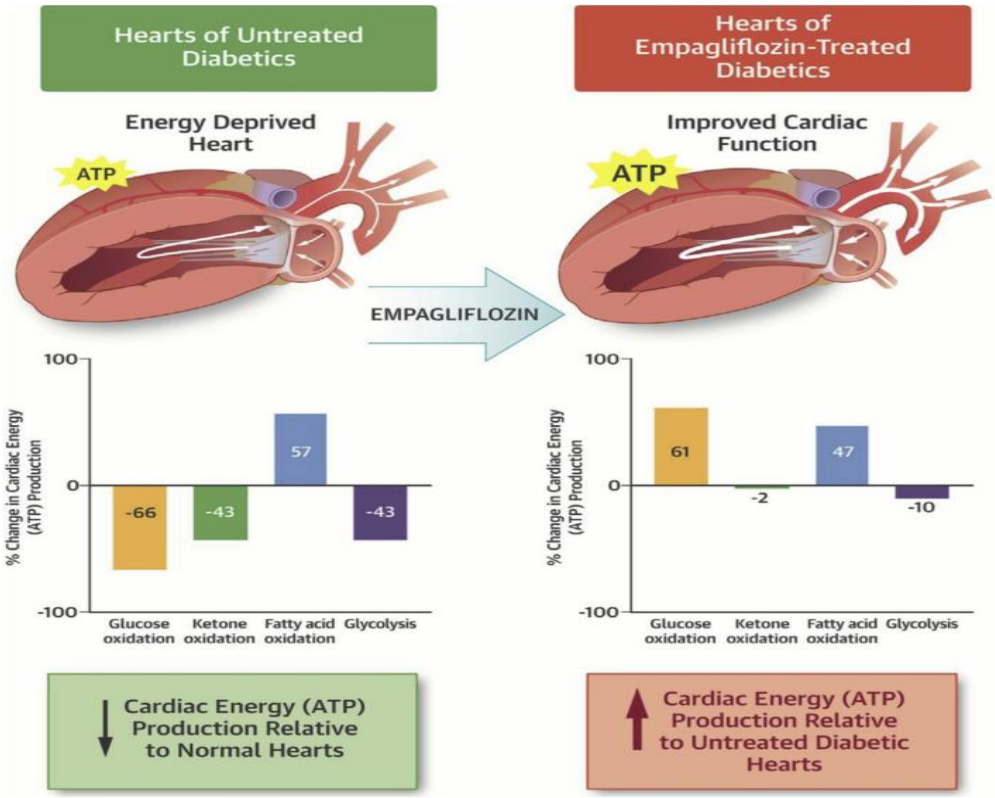

Figure 2: SGLT2 Inhibition Increases Cardiac Energy Production

SGLT2 inhibitors can increase cardiac energy metabolism. Reproduced with permission from Verma et al. (41). ATP = adenosine triphosphate; SGLT2 = sodium glucose co-transporter 2.

Reduction in inflammation

Patients with heart failure have higher levels of proinflammatory biomarkers, which correlate with the severity of the disease (45,46), suggesting that inflammation is a significant factor in the severity of heart failure. Both individuals with reduced and retained ejection fraction show this connection between inflammatory indicators and heart failure (47). Inflammatory cytokines have multiple effects, including malfunction of endothelial cells, increased fibrosis, and increased turnover of the extracellular matrix.There is evidence that the SGLT2 inhibitors dapagliflozin (50), empagliflozin (48), and canagliflozin (49) can reduce or improve the inflammatory profile in diabetic patients. Molecular processes associated with inflammation, including fibrosis and extracellular matrix turnover, may be attenuated as a result of SGLT2 inhibitors' diminished anti-inflammatory effects (51).This is corroborated by the fact that dapagliflozin inhibits collagen formation, leading to strong antifibrotic effects in the hearts of rats after myocardial infarct (51). Additionally, empagliflozin considerably reduces the remodeling of the extracellular matrix collagen that is mediated by cells (52).

It is unclear how SGLT2 inhibitors affect inflammation. Since macrophages preferentially use glucose from glycolysis as an energy source, lowering glucose levels with SGLT2 inhibitors may diminish the inflammatory response of macrophages 52. Instead of focusing on reducing glucose levels, SGLT2 inhibitors may go after the inflammatory pathways directly. One crucial element in the process of inflammation is the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3 [NLRP3] inflammasome. The severity of heart failure is worsened by chronic inflammation, which is in turn brought about by the NLRP3 inflammasome (54). There is new evidence that empagliflozin can block the NLRP3 inflammasome, and this can happen even without glucose lowering, in several organs including the kidneys, liver, macrophages, vasculature, and heart (55, 56, 58, 59, 60). The exact nature of the relationship between SGLT2 inhibitors and NLRP3 remains unclear. The ß-hydroxybutyrate ketone effectively inhibits the inflammatory process that is mediated by the NLRP3 inflammasome (61). Some of the good benefits of SLT2 inhibition may be due to ketone suppression of the NLRP3 inflammasome, since SGLT2 inhibitors raise levels of ß-hydroxybutyrate in the blood.

Dropping pounds

Calorie loss occurs as a result of glucose excretion by the kidneys after SGLT2 inhibitor medication. The mobilization of fatty acids from adipose tissue storage leads to a subsequent drop in body weight. The use of SGLT2 inhibitors has been associated with a steady decrease in patient body weight in clinical trials (62). Weight loss programs have been considerably less successful in reducing the severity of heart failure compared with SGLT2 inhibition, so it is unlikely that this is a major mechanism of the observed benefit to heart failure, although it may contribute to the beneficial effects of SGLT2 inhibition. Other mechanisms must also be at work. As an example, the DAPA-HF experiment found a little numerical weight loss, but the magnitude of this loss seemed to be higher in the diabetic group (63). In addition, counter-regulatory mechanisms (such as increased energy intake) are triggered to try to maintain weight, therefore the effects of SGLT2 inhibition on weight loss are moderate and decline with time (64).

Glycemic management made easier

While SGLT2 inhibitors do a good job of decreasing blood sugar, it's highly improbable that this is the primary mechanism by which they alleviate heart failure. The presence of hyperglycemia is associated with a lower risk of cardiovascular disease (65). Furthermore, it is challenging to reconcile the fast efficacy observed (within days of treatment commencement) with an impact that lowers glucose levels. In addition, post hoc analyses from trials indicated that baseline A1c or changes in A1c were not associated with any treatment modification with SGLT2 inhibitors (65), and the differences in glycemic control were small in the cardiovascular outcome trials (an attempt to fulfill the trials' glycemic equipoise principle). Final evidence for this idea came from the DAPA-HF study, which found that dapagliflozin was just as effective in those with diabetes as it was in people without the disease. Efficacy was comparable in those with pre-diabetes or poor glucose tolerance compared to those who were truly euglycemic, even in the absence of diabetes. The effectiveness of dapagliflozin in reducing heart failure and mortality in DAPA-HF was unrelated to baseline A1c when investigated continuously using fractional polynomial analysis. Moreover, SGLT2 inhibition has been shown to be beneficial in heart failure models in experimental settings, and this effect has been shown even in the absence of diabetes or hyperglycemia (60,66,67).

Restriction of the SNS

One possible indirect association between SGLT2 inhibitors and reduced sympathetic nervous system (SNS) activity is the fact that these drugs lower blood pressure without raising heart rate. Evidence is mounting that SGLT2 inhibition may decrease sympathetic nerve activity, brown adipose tissue norepinephrine turnover, and tyrosine hydroxylase synthesis (68, 69, 70, 71, 72). Animal models of diabetes and obesity (in the absence of diabetes) seem to share these sympathoinhibitory effects (68, 69, 70, 71, 72). Another possible explanation for the observed decrease in SNS activity after SGLT2 inhibition is a decrease in renal stress, which in turn inhibits renal afferent sympathetic activation (73).

Averting Unfavorable Heart Remodeling

One major factor that increases the severity of heart failure is adverse cardiac remodeling. Cardiomyocyte cell loss, inflammation, fibrosis, and hypertrophy are all part of this process. The favorable effects of SGLT2 inhibition on cardiac remodeling have been documented in multiple experimental and human studies (23,67,74, 75, 76, 77). Empagliflozin or placebo was given to patients with type 2 diabetes and a past history of coronary artery disease for a duration of 6 months in a randomized trial (76). The main result, which was the change in left ventricular mass index as measured by cardiac magnetic resonance imaging, was considerably lower in the empagliflozin group compared to the placebo group. These results do not explain how SGLT2 inhibitors work, but they do show that even brief exposure can cause cardiac reverse remodeling. Possible involvement of SGLT2 suppression of the mammalian target of rapamycin pathway, a key mechanism in cardiac hypertrophy (76). The anti-inflammatory effects of SGLT2 inhibition may play a role in the association between a reduction in fibrosis and the prevention of unfavorable remodeling with SGLT2 inhibition (52,78). For more information on this, refer to the section on reduction in inflammation. Therefore, SGLT2 inhibition has the potential to reduce left ventricular wall stress and improve cardiac function by reversing the cardiac remodeling observed in heart failure.

Reducing the risk of ischemia and reperfusion damage

Heart failure and cell death in cardiomyocytes can be accelerated by ischaemia/reperfusion damage. There is new evidence from experiments that shows inhibiting SGLT2 protects the heart against ischemia/reperfusion injury in rats, regardless of whether they have diabetes or not (79). Reducing calmodulin kinase II activity, which in turn improves sarcoplasmic reticulum Ca2+ flow and increases contractility, is related with the positive effect of SGLT2 inhibition on ischemia/reperfusion injury. It is not yet known, however, if this impact manifests in people.

The blocking of the cardiac sodium/potassium exchanger

According to Wakabayashi et al. [80], an increase in the Na+/H+ exchanger in a failing heart might cause an overflow of Na+ and Ca2+ in the heart. Multiple animal models of heart failure have shown that blocking the Na+/H+ exchanger protects the heart (for a review, see Wakabayashi et al. [80]). One possible explanation for the favorable benefits of SGLT2 inhibitors in heart failure is that they block the Na+/H+ exchanger (81, 82, 83, 84, 85). Inhibitors of SGLT2 can reduce myocardial Na+ levels by blocking the cardiac Na+/H+ exchanger (81). The question of whether SGLT2 inhibitor doses that are clinically relevant directly affect the cardiac Na+/H+ exchanger remains unanswered. Furthermore, there is little evidence that developing inhibitors of Na+/H+ exchangers would be helpful in the clinical context of heart failure (85).To what extent the favorable effects of SGLT2 inhibition in the context of heart failure are due to direct inhibition of the cardiac Na+/H+ exchanger remains unclear.

Downregulating SGLT1

Even though SGLT2 is not expressed in the heart, SGLT1 is. Inhibiting SGLT1 in the heart may reduce glucose and Na+ absorption by the myocardium and the production of reactive oxygen species (ROS) caused by hyperglycemia (86). Although canagliflozin and other SGLT2 inhibitors slow SGLT1, the plasma concentrations required to block SGLT1 are far higher than those observed in clinical settings. Furthermore, rat studies have shown that simultaneous SGLT2 and SGLT1 inhibitors worsen cardiac dysfunction following myocardial infarction (87). Therefore, it is highly improbable that any secondary effect on SGLT1 inhibition could account for the favorable benefits of SGLT2 inhibitors.

Lowered uric acid levels

Reducing plasma uric acid, an unfavorable effect of SGLT2 inhibitors on heart failure prognosis (88). Uric acid levels have been found to decrease slightly when treated with SGLT2 inhibitors (89).One possible explanation is that inhibiting SGLT2 increases uric acid production, leading to increased glycosuria in the proximal tubules (90). However, it is still unclear if a decrease in hyperuricemia caused by SGLT2 inhibition is merely a marker or if it has a causal effect.

Degradation of lysosomes and autophagy

Hypoglycemia and heart failure can impede cardiac autophagy and lysosomal degradation (77,91). As a result of persistent glycosuria, SGLT2 inhibition may enhance mitochondrial shape and function by boosting catabolic rates, which in turn stimulate autophagy and lysosomal degradation (77). The accelerated destruction of defective organelles may be caused by an SGLT2-mediated suppression of the mammalian target of rapamycin, which may also stimulate autophagy and lysosomal degradation. Thus, it is not completely out of the question that SGLT2 inhibition's beneficial effects on heart failure may be due in part to their ability to stimulate autophagy.

Minimizing the amount of fat surrounding the heart

An elevated risk of cardiovascular events is linked to high computed tomography attenuation of epicardial adipose tissue (92). A variety of bioactive chemicals can be produced by epicardial adipose tissue, and these compounds can have detrimental effects on cardiac function and even lead to coronary artery disease. Further, SGLT2 inhibitors lessen inflammation and peri-vascular adipose tissue accumulation, which in turn reduces leptin release and the paracrine activities it promotes on the heart, which in turn promotes fibrosis (84). Inhibition of SGLT2 decreases the bulk of epicardial adipose tissue and levels of bioactive molecules such tumor necrosis factor-α and plasminogen activator inhibitor-1 in diabetic individuals with coronary artery disease (93). A lessening of the unfavorable remodeling of the failing heart may result from this.

Raising EPO concentrations

It has been proposed that SGLT2 inhibitors may stimulate erythropoiesis via higher EPO production by the kidney (95), since they elevate the hematocrit (94) even in individuals without diabetes (as demonstrated in DAPA-HF). Raising EPO levels in this way may improve oxygen transport to cardiac tissue while also having beneficial effects on inflammation, angiogenesis, cell proliferation, and mitochondrial function (95). In a recent randomized clinical trial called EMPA-Heart CardioLink-6, Mazer et al. (95) found that after one month of empagliflozin treatment, EPO levels increased significantly in patients with type 2 diabetes and coronary artery disease. This was accompanied by an increase in hematocrit, a decrease in ferritin, and an increase in red blood cell hemoglobin concentration It is unclear whether EPO levels rise in those who do not have type 2 diabetes.

Raising Numbers of Provascular Progenitor Cells in the Blood

Human preliminary data suggests that SGLT2 inhibitors may help type 2 diabetics restore their provascular progenitor cells. The number of proinflammatory M1 cells was found to decrease and the number of M2 polarized, anti-inflammatory cells to increase in one study that used empagliflozin (Hess et al., 96). Through the utilization of the Aldeflour assay (STEMCELL Technologies, Cambridge, Massachusetts), the researchers discovered that SGLT2 inhibition led to a decrease in systemic granulocyte burden in type 2 diabetics, an increase in circulating ALDHhiSSCmid monocytes, and a change from M1 to M2 polarization. These findings are in line with the maturation of collateral vessels during arteriogenesis. The researchers came to the conclusion that blocking SGLT2 might be an effective way to help circulating provascular cells recover in type 2 diabetes. How often this happens in the general population is uncertain.

Reducing the effects of free radicals

Zhou and Tian [97] reviewed the literature on the topic and found that excessive production of reactive oxygen species (ROS) by cardiac mitochondria is a key factor in contractile dysfunction observed in both animal models of heart failure and human patients with heart failure. Mitochondrial dysfunction can occur as a result of elevated oxidative stress during the progression of heart failure. Adenosine triphosphate synthesis and enhanced electron transport chain activity may be the mechanisms responsible for this rise in reactive oxygen species (ROS) generation. Reducing myocardial ROS generation and cardiac fibrosis can be achieved in diabetic mice by enhancing glycemic control by SGLT2 inhibition (97). Additionally, SGLT2 inhibition can reduce ROS production in human coronary artery endothelial cells (98). Exactly how SGLT2 inhibition reduces ROS production is unclear; however, it may be a byproduct of other beneficial effects on inflammation (refer to the section on inflammation reduction), mitochondrial oxidative metabolism in the heart (refer to the section on improved cardiac energy metabolism), or the reduction of the risk of cardiac glucotoxicity (which can increase

ROS production). And without type 2 diabetes, there is a lack of information about the effects of SGLT2 inhibition on ROS production.

Promoting better vascular health

An imbalance between the vascular smooth muscle and the endothelial cells plays a role in the pathogenesis of heart failure (99,100). Its presence raises the risk of death and morbidity in heart failure patients. Inhibiting SGLT2 has been demonstrated to enhance vascular function through a number of mechanisms, including a reduction in vascular resistance, a loosening of the arterial walls, a dampening of endothelial cell activation, and a reduction in endothelial cell dysfunction and molecular changes linked to early atherogenesis (101, 102, 103, 104). Impairment of mitochondrial function and suppression of inflammatory pathways are two potential underlying mechanisms by which SGLT2 inhibition exerts its therapeutic effects (101). It has also been suggested that SGLT2 inhibitors can induce vasodilation via activating voltage-gated potassium channels and protein kinase G (105). The beneficial hemodynamic effects observed with SGLT2 inhibition may be due to both the direct impacts on the vascular system and the natriuresis effects of SGLT2 inhibition.

What are the most probable mechanisms that explain the observed benefits, moving from a list to a synthesis? Multiple randomized controlled trials have shown that SGLT2 inhibitors significantly improve cardiovascular outcomes for both diabetic and non-diabetic individuals with heart failure. Consequently, SGLT2 inhibitors represent a potent new tool in the fight against heart failure. Nevertheless, the precise mechanism by which SGLT2 inhibitors cause their remarkable therapeutic advantages in heart failure patients is still unknown (Central Illustration). These benefits cannot be adequately explained by its conventional actions of decreasing blood glucose. It appears that the positive effects of SGLT2 inhibitors are not happening because they slow the atherosclerotic process, since they are already apparent in clinical trials. The published papers offer a plethora of potential mechanisms that link SGLT2 inhibition to cardiovascular protection. The question is, how can we organize and rank these processes to shed light on the reported clinical benefits? Based on the clinical data, the underlying mechanism(s) should be able to do the following: 1) effectively treat and prevent heart failure; 2) work in conjunction with excellent background therapy, such as neprilysin inhibition; 3) have a quick effect; 4) be effective regardless of glycemic status; and 5) be associated with renal protection. Some of the cardiovascular benefits are secondary, in our opinion, to the major mechanism of action of SGLT2 inhibitors, which is their renal effects. The proximal renal tubule is the site of the initial hemodynamic effect, as a consequence of SGLT2 suppression, states this idea. This leads to afferent arteriolar constriction and increased sodium and water loss via tubule-glomerular feedback. Protecting the kidneys is the goal of lowering intraglomerular pressure. By lowering inflammation, ROS production, and afferent SNS activation, among other mechanisms, improving renal function and/or decreasing renal stress can indirectly enhance cardiac performance. We suggest that these options should be investigated in future research. Since the DAPA-HF study found an early decrease in estimated glomerular filtration rate in both diabetics and non-diabetics, we further contend that the renal hemodynamic effects are seen independently of glycemia. It is possible that the same rise in hematocrit in DAPA-HF patients with and without diabetes is due to an increase in EPO generation as a byproduct of better renal function. Reducing inflammation in the heart and enhancing cardiac energy metabolism are two other intriguing ways that SGLT2 inhibition helps heart failure patients. Since ketones can inhibit the inflammatory pathway, additional research is required to determine the effects of SGLT2 inhibition on these pathways in the context of heart failure and whether or not there is a relationship between them. To better understand how SGLT2 inhibitors achieve their remarkable effects on the cardiovascular system, more research is needed.

References

1.Braunwald E. The war against heart failure: the Lancet lecture. Lancet. 2015;385:812–824. doi: 10.1016/S0140-6736(14)61889-4. [DOI] [PubMed] [Google Scholar]
2.Khan S.S., Butler J., Gheorghiade M. Management of comorbid diabetes mellitus and worsening heart failure. JAMA. 2014;311:2379–2380. doi: 10.1001/jama.2014.4115. [DOI] [PubMed] [Google Scholar]
3.Swoboda P.P., McDiarmid A.K., Erhayiem B. Diabetes mellitus, microalbuminuria, and subclinical cardiac disease: identification and monitoring of individuals at risk of heart failure. J Am Heart Assoc. 2017;6 doi: 10.1161/JAHA.117.005539. [DOI] [PMC free article] [PubMed] [Google Scholar]
4.American Diabetes Association Cardiovascular disease and risk management: standards of medical care in diabetes—2019. Diabetes Care. 2019;42:S103–S123. doi: 10.2337/dc19-S010. [DOI] [PubMed] [Google Scholar]
5.Gallo L.A., Wright E.M., Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. Diab Vasc Dis Res. 2015;12:78–89. doi: 10.1177/1479164114561992. [DOI] [PMC free article] [PubMed] [Google Scholar]
6.McMurray J.J.V., Solomon S.D., Inzucchi S.E., for the DAPA-HF Trial Committees and Investigators Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381 doi: 10.1056/NEJMoa1911303. 1995–200. [DOI] [PubMed] [Google Scholar]
7.Bhatt D.L., Verma S., Braunwald E. The DAP-HF trial: a momentous victory in the war against heart failure. Cell Metab. 2019;30:847–849. doi: 10.1016/j.cmet.2019.10.008. [DOI] [PubMed] [Google Scholar]
8.Zinman B., Wanner C., Lachin J.M., for the EMPA-REG OUTCOME Investigators Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720. [DOI] [PubMed] [Google Scholar]
9.Neal B., Perkovic V., Mahaffey K.W., for the CANVAS Program Collaborative Group Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–657. doi: 10.1056/NEJMoa1611925. [DOI] [PubMed] [Google Scholar]
10.Perkovic V., Jardine M.J., Neal B., for CREDENCE Trial Investigators Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295–2306. doi: 10.1056/NEJMoa1811744. [DOI] [PubMed] [Google Scholar]
11.Wiviott S.D., Raz I., Bonaca M.P., for the DECLARE-TIMI 58 Investigators Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380 doi: 10.1056/NEJMc1902837. 380:347–357. [DOI] [PubMed] [Google Scholar]
12.Zelniker T.A., Wiviott S.D., Raz I. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393:31–39. doi: 10.1016/S0140-6736(18)32590-X. [DOI] [PubMed] [Google Scholar]
13.Verma S., Juni P., Mazer C.D. Pump, pipes, and filter: do SGLT2 inhibitors cover it all? Lancet. 2019;393:3–5. doi: 10.1016/S0140-6736(18)32824-1. [DOI] [PubMed] [Google Scholar]
14.Verma S., McMurray J.J.V. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018;61:2108–2117. doi: 10.1007/s00125-018-4670-7. [DOI] [PubMed] [Google Scholar]
15.Staels B. Cardiovascular protection by sodium glucose cotransporter 2 inhibitors: potential mechanisms. Am J Cardiol. 2017;120:S28–S36. doi: 10.1016/j.amjcard.2017.05.013. [DOI] [PubMed] [Google Scholar]
16.Butler J., Handelsman Y., Bakris G., Verma S. Use of sodium-glucose co-transport inhibitors in patients with and without type 2 diabetes: implication for incident and prevalent heart failure. Eur J Heart Fail. 2020 Jan 11 doi: 10.1002/ejhf.1708. [E-pub ahead of print] [DOI] [PubMed] [Google Scholar]
17.Filippatos T.D., Liontos A., Papakitsou I., Elisaf M.S. SGLT2 inhibitors and cardioprotection: a matter of debate and multiple hypotheses. Postgrad Med. 2019;131:82–88. doi: 10.1080/00325481.2019.1581971. [DOI] [PubMed] [Google Scholar]
18.Lam C.S.P., Chandramouli C., Ahooja V., Verma S. SGLT-2 inhibitors in heart failure: current management, unmet needs, and therapeutic prospects. J Am Heart Assoc. 2019;8 doi: 10.1161/JAHA.119.013389. [DOI] [PMC free article] [PubMed] [Google Scholar]
19.Mazidi M., Rezaie P., Gao H.K., Kengne A.P. Effect of sodium-glucose cotransport-2 inhibitors on blood pressure in people with type 2 diabetes mellitus: a systematic review and meta-analysis of 43 randomized control trials with 22 528 patients. J Am Heart Assoc. 2017;6 doi: 10.1161/JAHA.116.004007. [DOI] [PMC free article] [PubMed] [Google Scholar]
20.Ferrannini E., Baldi S., Frascerra S. Renal handling of ketones in response to sodium-glucose cotransporter 2 inhibition in patients with type 2 diabetes. Diabetes Care. 2017;40:771–776. doi: 10.2337/dc16-2724. [DOI] [PubMed] [Google Scholar]
21.Weber M.A., Mansfield T.A., Cain V.A. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Diabetes Endocrinol. 2016;4:211–220. doi: 10.1016/S2213-8587(15)00417-9. [DOI] [PubMed] [Google Scholar]
22.Kario K., Bohm M., Mahfoud F. Twenty-four-hour ambulatory blood pressure reduction patterns after renal denervation in the SPYRAL HTN-OFF MED Trial. Circulation. 2018;138:1602–1604. doi: 10.1161/CIRCULATIONAHA.118.035588. [DOI] [PubMed] [Google Scholar]
23.Lambers Heerspink H.J., de Zeeuw D., Wie L., Leslie B., List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metab. 2013;15:853–862. doi: 10.1111/dom.12127. [DOI] [PMC free article] [PubMed] [Google Scholar]

24.Hallow K.M., Helmlinger G., Greasley P.J., McMurray J.J.V., Boulton D.W. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes Obes Metab. 2018;20:479–487. doi: 10.1111/dom.13126. [DOI] [PubMed] [Google Scholar]
25.Lopaschuk G.D., Ussher J.R., Folmes C.D., Jaswal J.S., Stanley W.C. Myocardial fatty acid metabolism in health and disease. Physiol Rev. 2010;90:207–258. doi: 10.1152/physrev.00015.2009. [DOI] [PubMed] [Google Scholar]
26.Zhang L., Jaswal J., Ussher J.R. Cardiac insulin-resistance and decreased mitochondrial energy production precede the development of systolic heart failure after pressure-overload hypertrophy. Circ Heart Fail. 2013;6:1039–1048. doi: 10.1161/CIRCHEARTFAILURE.112.000228. [DOI] [PubMed] [Google Scholar]
27.Wang W., Zhang L., Battiprolu P.K. Malonyl CoA decarboxylase inhibition improves cardiac function post-myocardial infarction. J Am Coll Cardiol Basic Trans Science. 2019;4:385–400. doi: 10.1016/j.jacbts.2019.02.003. [DOI] [PMC free article] [PubMed] [Google Scholar]
28.Mori J., Basu R., McLean B.A. Agonist-induced hypertrophy and diastolic dysfunction are associated with selective reduction in glucose oxidation: a metabolic contribution to heart failure with normal ejection fraction. Circ Heart Fail. 2012;5:493–503. doi: 10.1161/CIRCHEARTFAILURE.112.966705. [DOI] [PubMed] [Google Scholar]
29.Neubauer S. The failing heart—an engine out of fuel. N Engl J Med. 2007;356:1140. doi: 10.1056/NEJMra063052. [DOI] [PubMed] [Google Scholar]
30.AbouEzziddine O.F., Kemp B.J., Borlaug B.A. Energetics in heart failure with preserved ejection fraction. Circ Heart Fail. 2019;12 doi: 10.1161/CIRCHEARTFAILURE.119.006240. [DOI] [PMC free article] [PubMed] [Google Scholar]
31.Ferrannini E., Muscelli E., Frascerra S. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest. 2014;124:499–508. doi: 10.1172/JCI72227. [DOI] [PMC free article] [PubMed] [Google Scholar]
32.Al Jobori H., Daniele G., Adams J. Determinants of the increase in ketone concentration during SGLT2 inhibition in NGT, IFG and T2DM patients. Diabetes Obes Metab. 2017;19:809–813. doi: 10.1111/dom.12881. [DOI] [PubMed] [Google Scholar]
33.Ferrannini E., Baldi S., Frascerra S. Shift to fatty substrates utilization in response to sodium-glucose co-transporter-2 inhibition in nondiabetic subjects and type 2 diabetic patients. Diabetes. 2016;65:1190–1195. doi: 10.2337/db15-1356. [DOI] [PubMed] [Google Scholar]
34.Mudaliar S., Alloju S., Henry R.R. Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG OUTCOME study? A unifying hypothesis. Diabetes Care. 2016;39:1115–1122. doi: 10.2337/dc16-0542. [DOI] [PubMed] [Google Scholar]
35.Ferrannini F., Mark M., Mayoux E. CV Protection in the EMPA-REG OUTCOME trial: a “thrifty substrate” hypothesis. Diabetes Care. 2016;39:1108–1114. doi: 10.2337/dc16-0330. [DOI] [PubMed] [Google Scholar]
36.Lopaschuk G.D., Verma S. Empagliflozin’s fuel hypothesis: not so soon. Cell Metab. 2016;24:200–202. doi: 10.1016/j.cmet.2016.07.018. [DOI] [PubMed] [Google Scholar]
37.Ho K.L., Zhang L., Wagg C. Increased ketone body oxidation provides additional energy for the failing heart without improving cardiac efficiency. Cardiovas Res. 2019;115:1606–1616. doi: 10.1093/cvr/cvz045. [DOI] [PMC free article] [PubMed] [Google Scholar]
38.Bedi K.C., Snyder N.W., Brandimarto J. Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. Circulation. 2016;133:706–716. doi: 10.1161/CIRCULATIONAHA.115.017545. [DOI] [PMC free article] [PubMed] [Google Scholar]
39.Aubert G., Martin O.J., Horton J.L. The failing heart relies on ketone bodies as a fuel. Circulation. 2016;133:698–705. doi: 10.1161/CIRCULATIONAHA.115.017355. [DOI] [PMC free article] [PubMed] [Google Scholar]
40.Horton J.L., Davidson M.T., Kurishima C. The failing heart utilizes 3-hydroxybutyrate as a metabolic stress defense. JCI Insight. 2019;4 doi: 10.1172/jci.insight.124079. [DOI] [PMC free article] [PubMed] [Google Scholar]
41.Verma S., Rawat S., Ho K.L. Empagliflozin increases cardiac energy production in diabetes: novel translational insights into the heart failure benefits of SGLT2 inhibitors. J Am Coll Cardiol Basic Trans Science. 2018;3:575–587. doi: 10.1016/j.jacbts.2018.07.006. [DOI] [PMC free article] [PubMed] [Google Scholar]
42.Santos-Gallego C.G., Requena-Ibanez J.A., San Antonio R. Empagliflozin ameliorates adverse left ventricular remodeling in nondiabetic heart failure by enhancing myocardial energetics. J Am Coll Cardiol. 2019;73:1931–1944. doi: 10.1016/j.jacc.2019.01.056. [DOI] [PubMed] [Google Scholar]
43.Shao Q., Meng L., Lee S. Empagliflozin, a sodium glucose co-transporter-2 inhibitor, alleviates atrial remodeling and improves mitochondrial function in high-fat diet/streptozotocin-induced diabetic rats. Cardiovasc Diabetol. 2019;18:165. doi: 10.1186/s12933-019-0964-4. [DOI] [PMC free article] [PubMed] [Google Scholar]
44.Nielsen R., Moller N., Gormsen L.C. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. Circulation. 2019;139:2129–2141. doi: 10.1161/CIRCULATIONAHA.118.036459. [DOI] [PMC free article] [PubMed] [Google Scholar]
45.Dick S.A., Epelman S. Chronic heart failure and inflammation: what do we really know? Circ Res. 2016;119:159–176. doi: 10.1161/CIRCRESAHA.116.308030. [DOI] [PubMed] [Google Scholar]
46.Mehta J.L., Pothineni N.V. Inflammation in heart failure: the holy grail? Hypertension. 2016;68:27–29. doi: 10.1161/HYPERTENSIONAHA.116.07307. [DOI] [PubMed] [Google Scholar]

47.Briasoulis A., Androulakis E., Christophides T., Tousoulis D. The role of inflammation and cell death in the pathogenesis, progression and treatment of heart failure. Heart Fail Rev. 2016;21:169–176. doi: 10.1007/s10741-016-9533-z. [DOI] [PubMed] [Google Scholar]
48.Iannantuoni F., de Marañon A.M., Diaz-Morales N. The SGLT2 inhibitor empagliflozin ameliorates the inflammatory profile in type 2 diabetic patients and promotes an antioxidant response in leukocytes. J Clin Med. 2019;8:1814. doi: 10.3390/jcm8111814. [DOI] [PMC free article] [PubMed] [Google Scholar]
49.Heerspink H.J.L., Perco P., Mulder S. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. Diabetologia. 2019;62:1154–1166. doi: 10.1007/s00125-019-4859-4. [DOI] [PMC free article] [PubMed] [Google Scholar]
50.Leng W., Wu M., Pan H. The SGLT2 inhibitor dapagliflozin attenuates the activity of ROS-NLRP3 inflammasome axis in steatohepatitis with diabetes mellitus. Ann Transl Med. 2019;7:429. doi: 10.21037/atm.2019.09.03. [DOI] [PMC free article] [PubMed] [Google Scholar]
51.Lee T.-M., Chang N.-C., Lion S.-Z. Dapagliflozin, a selective SGLT2 inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. Free Radic Biol Med. 2017;104:298–310. doi: 10.1016/j.freeradbiomed.2017.01.035. [DOI] [PubMed] [Google Scholar]
52.Kang S., Verma S., Hassanabad A.F. Direct effects of empagliflozin on extracellular matrix remodelling in human cardiac myofibroblasts: novel translational clues to explain EMPA-REG OUTCOME results. Can J Cardiol. 2019 Aug 29 doi: 10.1016/j.cjca.2019.08.033. [E-pub ahead of print] [DOI] [PubMed] [Google Scholar]
53.Rotkvić P.G., Berković M.C., Bulj N., Rotkvić L. Minireview: are SGLT2 inhibitors heart savers in diabetes? Heart Fail Rev. 2019 Aug 13 doi: 10.1007/s10741-019-09849-3. [E-pub ahead of print] [DOI] [PubMed] [Google Scholar]
54.Butts B., Gary R.A., Dunbar S.B., Butler J. The importance of NLRP3 inflammasome in heart failure. J Card Fail. 2015;21:586–593. doi: 10.1016/j.cardfail.2015.04.014. [DOI] [PMC free article] [PubMed] [Google Scholar]
55.Benetti E., Mastrocola R., Vitarelli G. Empagliflozin protects against diet-induced NLRP-3 inflammasome activation and lipid accumulation. J Pharmacol Exp Ther. 2016;359:45–53. doi: 10.1124/jpet.116.235069. [DOI] [PubMed] [Google Scholar]
56.Tahara A., Kurosaki E., Yokono M. Effects of SGLT2 selective inhibitor ipragliflozin on hyperglycemia, hyperlipidemia, hepatic steatosis, oxidative stress, inflammation, and obesity in type 2 diabetic mice. Eur J Pharmacol. 2013;715:246–255. doi: 10.1016/j.ejphar.2013.05.014. [DOI] [PubMed] [Google Scholar]
57.Lee Y.-H., Kim S.R., Han D.H. Senescent T cells predict the development of hyperglycemia in humans. Diabetes. 2019;68:156–162. doi: 10.2337/db17-1218. [DOI] [PubMed] [Google Scholar]
58.Leng W., Ouyang X., Lei X. The SGLT-2 inhibitor dapagliflozin has a therapeutic effect on atherosclerosis in diabetic ApoE−/− mice. Mediators Inflamm. 2016;2016:6305735. doi: 10.1155/2016/6305735. [DOI] [PMC free article] [PubMed] [Google Scholar]
59.Ye Y., Jia X., Bajaj M., Birnbaum Y. Dapagliflozin attenuates Na+/H+exchanger-1 in cardiofibroblasts via AMPK activation. Cardiovasc Drugs Therap. 2018;32:553–558. doi: 10.1007/s10557-018-6837-3. [DOI] [PubMed] [Google Scholar]
60.Byrne N.J., Matsumura N., Maayah Z.H. Empagliflozin blunts worsening cardiac dysfunction associated with reduced NLRP3 (nucleotide-binding domain-like receptor protein 3) inflammasome activation in heart failure. Circ Heart Fail. 2020;13 doi: 10.1161/CIRCHEARTFAILURE.119.006277. [DOI] [PubMed] [Google Scholar]
61.Youm Y.H., Nguyen K.Y., Trant R.W. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. Nat Med. 2015;21:263–269. doi: 10.1038/nm.3804. [DOI] [PMC free article] [PubMed] [Google Scholar]
62.Cai X., Yang W., Gao X. The association between the dosage of SGLT2 inhibitor and weight reduction in type 2 diabetes patients: a meta-analysis. Obesity (Silver Spring) 2018;26:70–80. doi: 10.1002/oby.22066. [DOI] [PubMed] [Google Scholar]
63.Pereira M.J., Eriksson J.W. Emerging role of SGLT-2 inhibitors for the treatment of obesity. Drugs. 2019;79:219–230. doi: 10.1007/s40265-019-1057-0. [DOI] [PMC free article] [PubMed] [Google Scholar]
64.Lee P.C., Ganguly S., Goh S.Y. Weight loss associated with sodium-glucose cotransporter-2 inhibition: a review of evidence and underlying mechanisms. Obes Rev. 2018;19:1630–1641. doi: 10.1111/obr.12755. [DOI] [PubMed] [Google Scholar]
65.Sattar N. Revisiting the links between glycaemia, diabetes and cardiovascular disease. Diabetologia. 2013;56:686–695. doi: 10.1007/s00125-012-2817-5. [DOI] [PubMed] [Google Scholar]
66.Cannon C.P., Perkovic V., Agarwal R. Evaluating the effects of canagliflozin on cardiovascular and renal events in patients with type 2 diabetes and chronic kidney disease according to baseline HbA1c, including those with HbA1c <7%: results from the CREDENCE trial. Circulation. 2019;141:407–410. doi: 10.1161/CIRCULATIONAHA.119.044359. [DOI] [PubMed] [Google Scholar]
67.Connelly K.A., Zhang Y., Vistram A. Empagliflozin improves diastolic function in a nondiabetic rodent model of heart failure with preserved ejection fraction. J Am Coll Cardiol Basic Trans Science. 2019;4:27–37. doi: 10.1016/j.jacbts.2018.11.010. [DOI] [PMC free article] [PubMed] [Google Scholar]
68.Chiba Y., Yamada T., Tsukita S. Dapagliflozin, a sodium-glucose co-transporter 2 inhibitor, acutely reduces energy expenditure in BAT via neural signals in mice. PLoS ONE. 2016;11 doi: 10.1371/journal.pone.0150756. [DOI] [PMC free article] [PubMed] [Google Scholar]

69.Yoshikawa T., Kishi T., Shinohara K. Arterial pressure lability is improved by sodium-glucose cotransporter 2 inhibitor in streptozotocin-induced diabetic rats. Hypertens Res. 2017;40:646–651. doi: 10.1038/hr.2017.14. [DOI] [PubMed] [Google Scholar]
70.Matthews V.B., Elliot R.H., Rudnicka C., Hricova J., Herat L., Schlaich M.P. Role of the sympathetic nervous system in regulation of the sodium glucose cotransporter 2. J Hypertens. 2017;35:2059–2068. doi: 10.1097/HJH.0000000000001434. [DOI] [PubMed] [Google Scholar]
71.Kimmerly D.S., Shoemaker J.K. Hypovolemia and neurovascular control during orthostatic stress. Am J Physiol. 2002;282:H645–H655. doi: 10.1152/ajpheart.00535.2001. [DOI] [PubMed] [Google Scholar]
72.Jordan J., Tank J., Heusser K. The effect of empagliflozin on muscle sympathetic nerve activity in patients with type II diabetes mellitus. J Am Soc Hypertens. 2017;11:604–612. doi: 10.1016/j.jash.2017.07.005. [DOI] [PubMed] [Google Scholar]
73.Sano M. A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity. J Cardiol. 2018;71:471–476. doi: 10.1016/j.jjcc.2017.12.004. [DOI] [PubMed] [Google Scholar]
74.Byrne N.J., Parajuli N., Levasseur J.L. Empagliflozin prevents worsening of cardiac function in an experimental model of pressure overload-induced heart failure. J Am Coll Cardiol Basic Trans Science. 2017;2:347–354. doi: 10.1016/j.jacbts.2017.07.003. [DOI] [PMC free article] [PubMed] [Google Scholar]
75.Shi L., Zhu D., Wang S. Dapagliflozin attenuates cardiac remodeling in mice model of cardiac pressure overload. Am J Hypertens. 2019;32:452–459. doi: 10.1093/ajh/hpz016. [DOI] [PubMed] [Google Scholar]
76.Verma S., Garg A., Yan A.T. Effect of empagliflozin on left ventricular mass and diastolic function in individuals with diabetes: an important clue to the EMPA-REG OUTCOME trial? Diabetes Care. 2016;39:e212–e213. doi: 10.2337/dc16-1312. [DOI] [PubMed] [Google Scholar]
77.Esterline R.L., Vaag A., Oscarsson J., Vora J. SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism? Eur J Endocrinol. 2018;178:R113–R125. doi: 10.1530/EJE-17-0832. [DOI] [PubMed] [Google Scholar]
78.Lee H.C., Shiou Y.L., Jhuo S.J. The sodium-glucose co-transporter 2 inhibitor empagliflozin attenuates cardiac fibrosis and improves ventricular hemodynamics in hypertensive heart failure rats. Cardiovasc Diabetol. 2019;18:45. doi: 10.1186/s12933-019-0849-6. [DOI] [PMC free article] [PubMed] [Google Scholar]
79.Lim V.G., Bell R.M., Arjun S., Kolatsi-Joannou M., Long D.A., Yellon D.M. SGLT2 inhibitor, canagliflozin, attenuates myocardial infarction in the diabetic and nondiabetic heart. J Am Coll Cardiol Basic Trans Science. 2019;4:15–26. doi: 10.1016/j.jacbts.2018.10.002. [DOI] [PMC free article] [PubMed] [Google Scholar]
80.Wakabayashi S., Hisamitsu T., Nakamura T.Y. Regulation of the cardiac Na^+/H^+ exchanger in health and disease. J Mol Cell Cardiol. 2013;61:68–76. doi: 10.1016/j.yjmcc.2013.02.007. [DOI] [PubMed] [Google Scholar]
81.Baartscheer A., Schumacher C.A., Wust C.A. Empagliflozin decreases myocardial cytoplasmic Na+ through inhibition of the cardiac Na+/H+ exchanger in rats and rabbits. Diabetologia. 2017;60:568–573. doi: 10.1007/s00125-016-4134-x. [DOI] [PMC free article] [PubMed] [Google Scholar]
82.Uthman L., Baartscheer A., Schumacher C.A. Direct cardiac actions of sodium glucose cotransporter 2 inhibitors target pathogenic mechanisms underlying heart failure in diabetic patients. Front Physiol. 2018;9:1575. doi: 10.3389/fphys.2018.01575. [DOI] [PMC free article] [PubMed] [Google Scholar]
83.Packer M. Do sodium-glucose co-transporter-2 inhibitors prevent heart failure with a preserved ejection fraction by counterbalancing the effects of leptin? A novel hypothesis. Diabetes Obes Metab. 2018;20:1361–1366. doi: 10.1111/dom.13229. [DOI] [PubMed] [Google Scholar]
84.Iborra-Egea O., Santiago-Vacas E., Yurista S.R. Unraveling the molecular mechanism of action of empagliflozin in heart failure with reduced ejection fraction with or without diabetes. J Am Coll Cardiol Basic Trans Science. 2019;4:831–840. doi: 10.1016/j.jacbts.2019.07.010. [DOI] [PMC free article] [PubMed] [Google Scholar]
85.Mentzer R.M., Bartels C., Bolli R., for the EXPEDITION Study Investigators Sodium-hydrogen exchange inhibition by cariporide to reduce the risk of ischemic cardiac events in patients undergoing coronary artery bypass grafting: results of the EXPEDITION study. Ann Thorac Surg. 2008;85:1261–1270. doi: 10.1016/j.athoracsur.2007.10.054. [DOI] [PubMed] [Google Scholar]
86.Bell R.M., Yellon D.M. SGLT2 inhibitors: hypotheses on the mechanism of cardiovascular protection. Lancet Diabetes Endocrinol. 2017;6:435–437. doi: 10.1016/S2213-8587(17)30314-5. [DOI] [PubMed] [Google Scholar]
87.Connelly K.A., Zhang Y., Desjardins J.F., Thai K., Gilbert R.E. Dual inhibition of sodium-glucose linked cotransporters 1 and 2 exacerbates cardiac dysfunction following experimental myocardial infarction. Cardiovasc Diabetol. 2018;17:99. doi: 10.1186/s12933-018-0741-9. [DOI] [PMC free article] [PubMed] [Google Scholar]
88.Hare J.M., Johnson R.J. Uric acid predicts clinical outcomes in heart failure: insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. Circulation. 2003;107:1951–1953. doi: 10.1161/01.CIR.0000066420.36123.35. [DOI] [PubMed] [Google Scholar]
89.Schernthaner G., Gross J.L., Rosenstock J. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. Diabetes Care. 2013;36:2508–2515. doi: 10.2337/dc12-2491. [DOI] [PMC free article] [PubMed] [Google Scholar]
90.Chino Y., Samukawa Y., Sakai S. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. Biopharm Drug Dispos. 2014;35:391–404. doi: 10.1002/bdd.1909. [DOI] [PMC free article] [PubMed] [Google Scholar]

91.Nussenzweig S.C., Verma S., Finkel T. The role of autophagy in vascular biology. Circ Res. 2015;116:480–488. doi: 10.1161/CIRCRESAHA.116.303805. [DOI] [PMC free article] [PubMed] [Google Scholar]
92.Raggi P., Gadiyaram V., Zhang C., Chen Z., Lopaschuk G., Stillman A.E. Statins reduce epicardial adipose tissue attenuation independent of lipid lowering: a potential pleiotropic effect. J Am Heart Assoc. 2019;8 doi: 10.1161/JAHA.119.013104. [DOI] [PMC free article] [PubMed] [Google Scholar]
93.Sato T., Aizawa Y., Yuasa S. The effect of dapagliflozin treatment on epicardial adipose tissue volume. Cardiovasc Diabetol. 2018;17:6. doi: 10.1186/s12933-017-0658-8. [DOI] [PMC free article] [PubMed] [Google Scholar]
94.Sano M., Takei M., Shiraishi Y., Suzuki Y. Increased hematocrit during sodium-glucose cotransporter 2 inhibitor therapy indicates recovery of tubulointerstitial function in diabetic kidneys. J Clin Med Res. 2016;8:844–847. doi: 10.14740/jocmr2760w. [DOI] [PMC free article] [PubMed] [Google Scholar]
95.Mazer C.D., Connelly P.W., Gilbert R.E. Effect of empagliflozin on erythropoietin levels, iron stores and red blood cell morphology in patients with type 2 diabetes and coronary artery disease. Circulation. 2019 Nov 11 doi: 10.1161/CIRCULATIONAHA.119.044235. [E-pub ahead of print] [DOI] [PubMed] [Google Scholar]
96.Hess D.A., Terenzi D.C., Trac J.Z. SGLT2 Inhibition with empagliflozin increases circulating provascular progenitor cells in people with type 2 diabetes mellitus. Cell Metab. 2019;30:609–613. doi: 10.1016/j.cmet.2019.08.015. [DOI] [PubMed] [Google Scholar]
97.Zhou B., Tian R. Mitochondrial dysfunction in pathophysiology of heart failure. J Clin Invest. 2018;128:3716–3726. doi: 10.1172/JCI120849. [DOI] [PMC free article] [PubMed] [Google Scholar]
98.Li C., Zhang J., Xue M. SGLT2 inhibition with empagliflozin attenuates myocardial oxidative stress and fibrosis in diabetic mice heart. Cardiovasc Diabetol. 2019;18:15. doi: 10.1186/s12933-019-0816-2. [DOI] [PMC free article] [PubMed] [Google Scholar]
99.Uthman L., Homayr A., Juni R.P. Empagliflozin and dapagliflozin reduce ROS generation and restore NO bioavailability in tumor necrosis factor α-stimulated human coronary arterial endothelial cells. Cell Physiol Biochem. 2019;53:865–886. doi: 10.33594/000000178. [DOI] [PubMed] [Google Scholar]
100.Endemann D.H., Schiffrin E.L. Endothelial dysfunction. J Am Soc Nephrol. 2004;15:1983–1992. doi: 10.1097/01.ASN.0000132474.50966.DA. [DOI] [PubMed] [Google Scholar]
101.Patel A.R., Kuvin J.T., Pandian N.G. Heart failure etiology affects peripheral vascular endothelial function after cardiac transplantation. J Am Coll Cardiol. 2001;37:195–200. doi: 10.1016/s0735-1097(00)01057-3. [DOI] [PubMed] [Google Scholar]
102.Gaspari T., Spizzo I., Liu H. Dapagliflozin attenuates human vascular endothelial cell activation and induces vasorelaxation: a potential mechanism for inhibition of atherogenesis. Diabetes Vasc Dis Res. 2017;15:64–73. doi: 10.1177/1479164117733626. [DOI] [PubMed] [Google Scholar]
103.Mancini S.J., Boyd D., Katwan O.J. Canagliflozin inhibits interleukin-1β-stimulated cytokine and chemokine secretion in vascular endothelial cells by AMP-activated protein kinase-dependent and -independent mechanisms. Sci Rep. 2018;8:5276. doi: 10.1038/s41598-018-23420-4. [DOI] [PMC free article] [PubMed] [Google Scholar]
104.Juni R.P., Kuster D.W.D., Goebel M. Cardiac microvascular endothelial enhancement of cardiomyocyte function is impaired by inflammation and restored by empagliflozin. J Am Coll Cardiol Basic Trans Science. 2019;4:575–591. doi: 10.1016/j.jacbts.2019.04.003. [DOI] [PMC free article] [PubMed] [Google Scholar]
105.Li H., Shin S.E., Seo M.S. The anti-diabetic drug dapagliflozin induces vasodilation via activation of PKG and Kv channels. Life Sci. 2018;197:46–55. doi: 10.1016/j.lfs.2018.01.032. [DOI] [PubMed] [Google Scholar]