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A review of potential mechanisms and uses of SGLT2 inhibitors in ischemia-reperfusion phenomena

Quentin V et al. SGLT2 inhibitors in ischemia-reperfusion injuries

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Abstract

The antidiabetic drug-class sodium-glucose cotransporter-2 inhibitors (SGLT2i) showed efficacy in decreasing mortality in patients with chronic heart failure, in whom ischemia counts among the first cause. Remarkably, this benefit was observed independently from diabetic status. This feature, yielded from several randomized controlled trials, suggests additional effects from SGLT2i beyond isolated glycemia control. Indeed, previous in-vitro and animal models analyzed altogether suggests the role of the inhibition of the Na⁺/H⁺ exchanger, which holds a pivotal role in ischemia/reperfusion injuries. In this review, we aim to summarize evidence which associate SGLT2i and ischemia/reperfusion injuries, by first listing known mechanisms which portend the latter, and second, hypothesize how the former may interact with these mechanisms.

Key Words: SGLT2 inhibitors; Ischemia-reperfusion injuries; Sodium-proton exchanger

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Core Tip: The antidiabetic drug-class sodium-glucose cotransporter-2 inhibitors (SGLT2i) showed efficacy in decreasing mortality in patients with chronic heart failure, in whom ischemia counts among the first cause. Remarkably, this benefit was observed independently from diabetic status. This feature, yielded from several randomized controlled trials, suggests additional effects from SGLT2i beyond isolated glycemia control. Indeed, previous in-vitro and animal models analyzed altogether suggests the role of the inhibition of the Na⁺/H⁺ exchanger, which holds a pivotal role in ischemia/reperfusion injuries. In this review, we aim to summarize evidence which associate SGLT2i and ischemia/reperfusion injuries, by first listing known mechanisms which portend the latter, and second, hypothesize how the former may interact with these mechanisms.
INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors inhibitors, from antidiabetic to cardioprotective agents

Although sodium-glucose cotransporter-2 inhibitors (SGLT2i) represent a decade-old drug class, the range of their indications has expanded since the first Food and Drug Administration label in 2013 in patients with type 2 diabetes\(^1,2\). Indeed, SGLT2i which include empagliflozin, dapagliflozin and canagliflozin are now indicated in patients with heart failure, independently from their status towards diabetes\(^3\).

To understand how SGLT2i went from an antidiabetic to a cardioprotective treatment, one must recall how in patients with type 2 diabetes treated by SGLT2i, there were numerous observations of a decrease in heart failure events, all-cause mortality, cardiovascular mortality\(^4\). Furthermore, subgroup analyses confirmed that this risk decrease was consistent across a wide range of cardiovascular risk\(^5,6\).

Hence, specific randomized controlled trials were launched to assess the hypothesis of a benefit to be treated by SGLT2i for patients with heart failure, regardless of the presence or absence of diabetes. Preliminary reports were then confirmed, and SGLT2i improved clinical outcomes in patients presenting with heart failure, be they with preserved and reduced ejection fraction\(^2,7-9\).

Nevertheless, while the main pharmacological effect of SGLT2i is to decrease renal glucose reabsorption, thereby increasing urinary glucose excretion, the benefits observed even in non-diabetic patients question off-target mechanisms. As an illustration, in the EMPA-REG OUTCOME trial which compared empagliflozin to placebo in patients with type 2 diabetes at high risk for cardiovascular events, the proportion of acute myocardial or cerebral ischemic event was similar in both groups, however, patients in the treatment group were more likely to surviving a cardiovascular event. This element may be supportive of a cellular protective association in ischemic injury\(^10\). In the dapagliflozin and prevention of adverse-outcomes in heart failure trial (DAPA-HF), administration of dapagliflozin reduced risk of serious ventricular arrhythmia, cardiac arrest or sudden death\(^11\).
In the following review, we aimed to suggest several mechanisms which may explain how SGLT2i act as immunomodulators, and how they may act beyond the sole increase in urinary loss of glucose. We first described the ischemia-reperfusion injury phenomenon and then expanded on the interactions between SGLT2i and ischemia-reperfusion mechanisms. Our main assumption lied on a protective role against ischemia-reperfusion lesions, which involve an increase in functional ketones, associated with a metabolic change, an impact on sodium/hydrogen exchanger, endothelial dysfunction, inflammation biomarkers, and platelet function.

**ISCHEMIA-REPERFUSION INJURY, AN OVERVIEW**

While mortality of acute myocardial infarction, has been decreasing over time\[^{12}\], subsequent morbidity manifested by heart failure has grown. Mitigating infarct size is a therapeutic goal which may be attained by decreasing the delay between first signs of ischemia and revascularization\[^{13}\], and by managing secondary lesions.

Myocardial ischemia is often caused by the occlusion of epicardial artery resulting in the ischemia of the coronary vascular territory which it depends upon. If prolonged, it may lead to myocardial infarction, an irreversible condition\[^{14,15}\]. Therefore, quickly restoring blood flow in the occluded artery is the only way to limit the extent of infarction and subsequent complications including mortality. The reperfusion phenomenon however has been associated with secondary lesions\[^{16}\], responsible for additional cardiomyocyte injuries\[^{17,18}\]. These additional lesions may be partly responsible of final infarction size and therefore associated with adverse outcomes as there is a link between infarction size and long-term mortality or heart failure\[^{19}\].

In cardiac surgery, these lesions are detected in 25% to 45% of patients\[^{20}\]. They may be assessed by CK-MB and/or troponin levels, associated with postoperative adverse events\[^{21}\]: arrhythmias, myocardial stunning, low cardiac output syndrome and perioperative infarction\[^{22}\]. Although, situations leading to these myocardial injuries are either unpredictable (i.e., acute myocardial infarction) or unavoidable (i.e., cardiac
surgery), cardioprotective strategies aiming at reducing ischemia/reperfusion injury are critical\cite{23}.

**Myocardial ischemia**

Defined by a mismatch between supply and need in oxygen and nutrients, its consequences depend on its severity, duration and the existence of collateral circulation\cite{24}. In normal blood flow situation, oxygen is used by mitochondrial respiratory chain to produce ATP by using fatty acids (65\%), glucose (15\%), lactate (15\%) and amino-acids and ketones (5\%). Ninety percent of produced ATP are used by cardiomyocytes for contraction and the rest for homeostasis\cite{25}. Following arterial occlusion and oxygen supply arrest, oxidative phosphorylation by mitochondrial respiratory chain stops and metabolism becomes anaerobic with the use of anaerobic glycogenolysis, leading to formation of H\(^+\) and lactates\cite{26}. Hence, during ischemia, ATP is mainly produced from glucose instead of fatty acids, due to a higher energy-consumption rate of fatty acids catabolism\cite{27}. This metabolic shift leads to the accumulation of AcylCoA and AcylCarnitine, both considered toxic for cardiomyocytes (enzymatic inhibition, alters cell membrane...). The small amount of produced ATP is used to maintain cellular homeostasis by using ATP-dependent ion pumps, until all ATP are depleted. Owing to ATP deficiency some cellular functions are not further ensured such as myocardial contraction, protein synthesis\cite{28}.

Then, an intracellular sodium accumulation creates a cellular oedema due to the activation of Na\(^+\)/H\(^+\) exchanger (NHE) and inhibition of NA/K ATPase, which in turn, leads to a cytosolic calcium overload by activation of Na\(^+\)/Ca\(^{2+}\) exchanger\cite{29,30}, inhibition of SERCA\cite{30}, and increased calcium entry \textit{via} other channels\cite{30}.

The subsequent activation of protease, lipase, nuclease\cite{27}, and mitochondrial ultrastructural damage, are associated with myocardial stunning. In normal conditions, mitochondria’s membrane is impermeable to ions and proteins\cite{22}, with a channel on the inner membrane called the mitochondrial permeability transition pore (mPTP)\cite{23}. During ischemia, this permeability transitions, opening mPTP\cite{22}, leading to
mitochondrial oedema and death and release of its contents: cytochrome c, apoptosis-inducing factor AIF, reactive oxygen species (ROS)[31,32].

ROS are highly reactive elements responsible for cellular injury because of reactions with lipids, proteins, and nucleic acids. The accumulation of xanthine and hypoxantine during ischemia[33], allows for their use by xanthine oxidase, activated during reperfusion and leading to the formation of ROS[34]. One of the many sources of hypoxanthine during ischemia, is ATP degradation by adenine nucleotide translocase which synthesize ADP, then degraded into hypoxanthine. This phenomenon increases energetic deficiency.

Reperfusion injury

After myocardial ischemia, restoring blood flow is an emergency, and clinical guidelines all advocate for the shortest delay possible[13,25]. However, reperfusion is also associated with secondary injuries[35], due to the sudden oxygen supply which allows for the formation of superoxide anions. The mechanisms which are hypothesized include: (1) the activation of oxidative phosphorylation; (2) the activation of xanthine oxidase; and (3) local neutrophil accumulation and NADPH oxidase activation, also leading to ROS accumulation[25]. In normal conditions, superoxide anions are antagonized by antioxidant elements (catalase, superoxide dismutase, glutathione peroxidase, vitamins, etc.). However, in case of massive ROS production and altered defense mechanisms by ischemia, the balance is tipped off towards ROS accumulation.

Another mechanism of reperfusion injury is the pH paradox[25,36]. Reperfusion restores pH by quickly extracting accumulated H⁺, by activating of NHE; yet, pH restoration has been associated with deleterious outcomes[37]. Indeed, an abrupt accumulation of Na⁺ may lead to cellular oedema and calcium overload (due to a Na⁺/Ca²⁺ exchanger), and since cytoplasmic acidosis inhibits the mPTP opening, rapid normalization of intracellular pH leads to mitochondrial permeability transition with mPTP reopening[27]. Hence, phenomena similar to that of ischemia may occur even though reperfusion was achieved[29].
**Cardioprotective strategies**

Cardioprotective strategies aim to reduce cardiomyocytes injuries, secondary to ischemia-reperfusion phenomena, and include 4 methods: preconditioning, postconditioning, remote conditioning and pharmacological treatment.

Preconditioning consists in applying cycles of brief coronary occlusion immediately before sustained occlusion. Clinical benefit has been observed in dog models, where repetitive short coronary occlusions preceding sustained occlusion resulted with an infarction smaller more delayed than that of a sustained occlusion without preconditioning\[38\]. While the benefit was initially observed shortly after ischemia, more lasting effects have been recently highlighted suggesting the role of protein synthesis (inducible nitric oxide (NO) synthase, cyclooxygenase, aldose reductase, superoxide dismutase)\[38\]. Elements which are thought to mediate preconditioning benefit include but are not limited to adenosine, bradykinin or mechanical stretch activating various intracellular signaling pathways including RISK-pathway (increasing AKT and ERK1/2) and SAFE-pathway (increasing JAK and STAT) whose end targets are inhibition of mPTP opening, inhibition of Na/H exchanger or upregulation of antioxidant systems (superoxide dismutase, aldose reductase, etc.)\[38,39\].

Although promising, preconditioning is not reliable in clinical practice since it could not be used before acute coronary syndrome because of the brief effects of such procedure or the unpredictability of ACS. Hence, preconditioning could only be used in patient before CABG, by cross-clamping the aorta and then releasing for several minutes. Studies showed that it decreased post-operative ventricular arrhythmias, inotrope use and limited ICU stay\[40\].

On the other end, ischemic postconditioning consists in the same procedure, performed after the ischemic event, during reperfusion procedures. Similarly, it was associated with smaller infarct size\[41,42\], a more progressive pH restoration, decreasing ROS production and calcium-induced mPTP opening, resulting in anti-apoptotic, anti-autophagic et anti-arrhythmic benefit\[25\].
While pre- and postconditioning aim at stimulating local anti-inflammatory pathways, remote conditioning consists in applying cycles of brief occlusion in other territories than that which is affected by ischemia (i.e., neighboring coronary artery, limb). Theoretical advantages of this method lie in the fact that it may be applied at any time, is non-invasive and easily feasible. On top of the abovementioned mechanisms, additional systemic signal pathways may be involved with neuronal (peripheral sensory nerves, spinal cord, brainstems and vagal nerves) and humoral inducing renal production of adenosine\cite{43}. While this approach also aims at diminishing infarct size, mortality, and hospitalization for heart failure, phase III clinical trials failed to yield significant benefit, excepts in the most severe patients (cardiogenic shock or cardiac arrest)\cite{18}.

Yet, while multiple drugs have been tested, none showed clinical significance in human patients. Na/H exchangers inhibitors showed improvement in cardiovascular outcomes but increased stroke incidence\cite{25,44,45}. Cyclosporine A, a nonspecific inhibitor of mPTP\cite{46}, promising initial results infarct, which were not translated in clinical studies\cite{18}. Adenosine, acting as a vasodilator, was associated with pre- and postconditioning-like effects\cite{47}, through inhibition of mPTP opening\cite{48}. Similarly, results were not conclusive in clinical trials\cite{49}. Finally, NO was associated with potentially benefit in ischemia-reperfusion injuries by acting on oxygen consumption\cite{50}, platelet aggregation\cite{51}, leucocyte adhesion\cite{52}, and free radical scavenging\cite{53}.

These discrepancies between theoretical promises and disappointing clinical results require further research in the field, investigating novel pathways.

**THE SGLT2 PATHWAY**

*Metabolic shift to a sparing substrate*

In normal oxygenation conditions, myocardial mitochondrial oxidative metabolism exploits fatty acids (60%), glucose (30%), lactate and to a lesser degree ketones and amino acids, with a capacity to rapidly change substrates depending on workload or conditions. Under hypoxic conditions, myocardial substrate oxidation switches from
free fatty acids to glucose and carbohydrate oxidation, because transformation of glucose to lactate is independent of oxygen supply\[^{54}\]. During prolonged anaerobia, ketone becomes predominant as a resource. For instance, in animal models increasing the uptakes of 3-hydroxybutyrate (3HB) is associated with an improvement in cardiac function, pathologic cardiac remodeling, and oxygen consumption, whereas the capacity to oxidate substrate such as fatty acid is reduced\[^{55}\]. Of note, 3HB is generated in the liver and may be used as a substrate for generating acetyl-CoA leading to increased production of NADH to drive energy transfer and ATP production.

Remarkably, in patient treated by SGLT2i, an uprising of ketone circulation was observed\[^{56,57}\].

One of the hypotheses is that SGLT2i improves myocardial fuel metabolism, contractility, and cardiac efficiency by shifting catabolism away from lipids and glucose to that of ketone bodies\[^{58}\]. Improved oxygen consumption and work efficiency at a mitochondrial level have been hypothesized\[^{59}\]. Similarly as fasting, with the expected glucose depletion under SGLT2i, insulin-glucagon ratio is modulated, delivery of free fatty acids is increased to the liver which then stimulates ketogenesis\[^{60}\]. Metabolomic profiles of patients with type 2 diabetes further support this hypothesis\[^{54}\]. In addition to an expected reduction in glucose, SGLT2i increased 3HB levels suggesting an accrued utilization of ketone bodies. Moreover, increased intermediate metabolites of the urea cycle may indicate its use as well as amino-acids\[^{56}\]. Remarkably, the same metabolic changes were observed in non-diabetic patients: Ferrannini et al\[^{55}\] showed that SGLT2i reduced end-tissular glucose catabolism, accelerated lipolysis and fat oxidation. While these changes were more prominent after long-term exposition, an effect was observed as early as the first administration\[^{54}\]. When compared to serum profiles of patients under corticoids treatment (widely tested in ischemia-injury model), SGLT2 might represent a different therapeutic candidate because of alternative energy income pathways involved\[^{61}\].

Because use of ketone bodies depends on the targeted organ, heart as well as kidneys may be those which benefit the most from an increase in 3HB\[^{58}\]. Furthermore, similarly
to an ischemia-hypoxia setting, during incremental atrial pacing, fractional extraction of 3HB persist, with improved energy efficiency; and a lower use of free fatty acids in low oxygenation conditions prevents the formation of ROS\textsuperscript{[60]}. Of note, even if data from animal studies are promising and suggest benefit regarding infarct size and recovery, opposite signals appear when focusing on ketone bodies\textsuperscript{[58,62]}. A recent work reported a suppression in ketone body utilization by myocardial during ischemia, based on levels of β-hydroxybutyrate in patient presenting chest pain in a retrospective population\textsuperscript{[63]}. Animal models with low-carbohydrate diet inducing mild nutritional ketosis showed a worse recovery and survival, more arrhythmias after induced ischemia\textsuperscript{[64,65]}. However, these contradictory results, well summarized in Kolwicz and al. review\textsuperscript{[66]}, only raise the need for additional studies at the metabolic level.

**Inhibition of the NHE**
SGLT2i were also associated with the inhibition of the NHE in myocardial cells\textsuperscript{[67]}. We previously described the role of NHE in the homeostasis of ischemic cells, which induce oxidative stress with elevated cytosolic Na\textsuperscript{+} and increased mitochondrial formation of ROS through a final intracellular calcium overload. The counterbalance of such mechanism requires the regeneration of antioxidative enzymes by mitochondria, relying on NADPH, indirectly produced by the Krebs cycle, in turn activated by intramitochondrial calcium\textsuperscript{[68]}. NHE inhibitors were associated with cardioprotective features in animal models of acute myocardial infarction\textsuperscript{[69]}. Moreover, a chronic inhibition of NHE was associated with improvement against cardiomyocyte injury, remodeling, and systolic dysfunction\textsuperscript{[70]}. Remarkably, SGLT2i indirectly interacts with NHE. In mice, empagliflozin reversed the effects of ouabain (an agent increasing intracellular sodium)\textsuperscript{[71]}. Moreover, this effect was independent from SGLT2 and indirectly caused a decreased activation of the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger. The same results were observed with other SGLT2i (dapagliflozin, canagliflozin)\textsuperscript{[67]}.
This inhibition with empagliflozin was associated with lower rates of tumor necrosis factor alpha (TNF-α), attesting of a cell preservation and lowered inflammation through NHE inhibition.

Additional mechanisms which were hypothesized include: improved AMPK activation in myocytes[72], and cardio-fibroblasts[73]. In contrast, another study showed that concrete benefit on AMPK-pathway with SGLT2 in human cells and mouse cells in vitro seems unlikely because activation appeared with concentrations corresponding to the peak plasma concentrations of therapeutic doses[74].

In human cells, NHE inhibition showed similar results in atrial and ventricular myocytes, as compared to that of mice ventricular myocytes. Heart failure and atrial fibrillation were associated with increased NHE expression[75]. Finally, in human coronary endothelial cells, empagliflozin was associated with a similar reduction of oxidative stress supporting the previous hypothesis[76].

Positive effects of inhibition of NHE are not limited to better myocardial function, ionic homeostasis, or reduction of myocyte ischemic inflammation. Empagliflozin and canagliflozin in short-term treatment enhanced coronary vasodilation through NHE inhibition[67], whereas dapagliflozin needed a more prolonged treatment to reach comparable effect[77]. However, in cases of acute inflammation, a non-specific vasodilatation may occur, making it difficult to interpret supposed effect of inhibition of SGLT2[78].

Prevention of arrhythmia and sudden death in ischemia-reperfusion injury

Sudden deaths and ventricular arrhythmias may occur after acute ischemia and reperfusion events, and SGLT2i were associated with fewer such events. Yet, because SGLT2i do not inherently feature anti-arrhythmic properties, several mechanisms have been hypothesized[79]. An improved ionic homeostasis through NHE inhibition has been suggested in the DAPA-HF trial, where 5.9% of the subjects assigned to the dapagliflozin group experimented serious rhythm event (sudden death, cardiac arrest, ventricular arrhythmias), with 7.4% in the placebo group[11]. In animal models, pre-
treatment with empagliflozin reduced the incidence of reperfusion-induced ventricular arrhythmia after an ischemia/reperfusion event, with the participation of the ERK1/2 pathway, involved in the RISK reperfusion-signaling pathway\cite{6}.

Role of the autonomous nervous system has also been investigated. In 2020, effects of empagliflozin vs placebo on cardiac sympathetic activity in acute myocardial infarction patients with T2DM (EMBODY Trial) compared empagliflozin with placebo for various electrocardiographic parameters. Heart rate variability, heart rate turbulence and electrocardiographic variations were recorded after acute myocardial infarction. Authors aimed to assess the variables associated with lethal ventricular arrhythmias. With a 6-mo-follow-up, a difference was observed between the two groups regarding sympathetic and parasympathetic stimulation\cite{81}. Of note, to date, no study described these elements in the first few hours after an ischemic event index.

Finally, in a recent meta-analysis which analyzed the effects of SGLT2i on atrial arrhythmia, sudden death and ventricular arrhythmia which included 34 trials in patients with diabetes, use of SGLT2i were protective towards atrial arrhythmia and sudden cardiac death, albeit several limitations existed\cite{82}.

Even if ionic homeostasis is the main hypothesis for the observed data, a plausible mechanism concurring to these results may lie on inhibition of platelet function, and antithrombin generation observed with SGLT2i. Unbalanced platelet activation and coagulation disturbance have been described during ischemic stress and associated with arrhythmia. SGLT2i have recently been associated with antiplatelet and antithrombotic features. Empagliflozin and dapagliflozin partially reduced the effects of stearic acid, an inflammatory agent inducing oxidative stress and impaired endothelial repair processes. As a result, platelets were less activated, in addition to that of ADP inhibition\cite{83}. In male mice with T2DM model, administration of dapagliflozin showed a decreased activation and recruitment with an improved thrombin-platelet-mediated inflammation profile \textit{in vivo} and less activated platelet with thrombin stimulation or CRP. Prolonged treatment did not affect hemostasis suggesting safety of utilization\cite{84}. Gliflozin via NHE inhibition participate to maintain endothelial function\cite{85} and
endothelial production of NO. In a recent study, pharmacological analysis in vitro suggested that the gliflozin’s antiplatelet activity synergize with NO and prostacyclin\textsuperscript{86}. Substantial evidence sustaining an intricated mechanism.

Taken altogether, these elements encourage to explore concrete platelet and hemostasis parameters with SGLT2i in ischemic situation, to sustain a potential benefit in ischemic-reperfusion context.

**EXPERIMENTAL MODELS**

*Models of myocardial ischemia-reperfusion*

Beyond the theoretical data and focused exploratory clinical investigations, many animal models have been developed to assess the benefits of SGLT2 inhibitors in ischemia-reperfusion.

Acute administration of canagliflozin in male rat models of myocardial infarction showed decrease in infarct size, improved left ventricular systolic and diastolic function during and after ischemia, and decreased ROS\textsuperscript{87}. Similar results were obtained with dapagliflozin\textsuperscript{62}, and the delay before the first ventricular arrhythmia was lower when treated by SGLT2i. An improved communication between cardiac cells with preserved phosphorylation of gap junction protein connexin-43 was suggested\textsuperscript{88,89}. Empagliflozin also showed similar results: reduced infarction size, better ventricular parameters, reduced systemic inflammation and ROS production, in acute or chronic administration\textsuperscript{90,91}. The role of STAT3 phosphorylation was observed in several models\textsuperscript{90-92}. Even if the beneficial mechanism is not yet fully determined, acute lowering of the blood glucose might be one of the potential hypothesis\textsuperscript{93}. Interestingly, dipeptidyl peptidase 4 inhibitors were also compared to SGLT2i in murine models: SGLT2i showed greater efficacy than dipeptidyl peptidase 4 inhibitors to improve metabolic impairments and left ventricular function\textsuperscript{94}.

Recently, 16 independent animal models experiments which compared SGLT2i to control, and included 224 subjects overall, were summarized in a recent meta-analysis\textsuperscript{95}. Regardless of diabetes, SGLT2is were significantly associated with fewer
myocardial ischemia-reperfusion injuries and infarct size. Additionally, systemic treatment performed better than local administration, and longer-term treatment was associated with better results.

Other organ models
On top of myocardial protection, other organs have been tested.

In a model of lung injury due to ischemia-reperfusion, empagliflozin was tested on respiratory function, tissular and cellular analyses. Similarly, as in cardiac usage, SGLT2i was associated with lower levels of circulating cytokines in bronchoalveolar liquids, those were dependent on improved phosphorylation of pulmonary ERK1/2\textsuperscript{[96]},.

In models of ischemia-reperfusion-induced kidney injury, dapagliflozin was associated decreased biomarkers of renal failure (blood urea and creatinine) and fewer tubular injuries. Furthermore, under hypoxic condition, dapagliflozin reversed cellular death. Similarly, as in heart and lung, phosphorylation of AMPK and ERK1/2 was improved\textsuperscript{[97]}. Remarkably, similar observations were made in non-diabetic rats\textsuperscript{[98]}.

Finally, in neurons, SGLT2i may interact with SGLT2 and SGLT1, expressed in human center nervous system\textsuperscript{[99]}. Similar ischemia-reperfusion injuries may be performed in neurons, and empagliflozin in was associated with smaller infarct size and improved neuronal functions than in control rats. The main pathway studied was the HIF-1α/VEGF cascade, on which suppression of neuronal expression of Caspase-3 by empagliflozin had positive neuronal effects\textsuperscript{[100]}. Moreover, role of Caspase-3 repression in hyperglycemic rats suggested an association between empagliflozin use and a decrease in TNF-α\textsuperscript{[101]}.

CONCLUSION
Beyond the cardiovascular benefits observed in patients with chronic heart failure treated by SGLT2i, data from large clinical trials including EMPA-REG or DAPA-HF may suggest a benefit through ischemia-reperfusion events. The inhibition of the NHE
may play a pivotal role in such cardioprotective feature and further investigations towards the immunomodulatory properties of SCLT2i drug-class are warranted.
## PRIMARY SOURCES

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