REVIEW ARTICLE

Can sodium-glucose cotransporter 2 inhibitors be beneficial in patients with acute myocardial infarction?

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Kardiol Pol. 2021; 79 (5): 503–509; DOI: 10.33963/KP.15969

Received: April 12, 2021

Revision accepted: April 13, 2021

Published online: April 20, 2021

ABSTRACT

The sodium-glucose cotransporter 2 inhibitors (SGLT2i), empagliflozin, dapagliflozin, and canagliflozin, have shown impressive beneficial effects in patients with type 2 diabetes mellitus in mandatory cardiovascular outcome trials. Retrospective data analysis revealed signals that pointed towards positive effects independent of the antidiabetic effects. This could be confirmed for empagliflozin and dapagliflozin in chronic heart failure with reduced ejection fraction alone, where rates of hospitalization for heart failure and cumulative major adverse cardiovascular events were reduced to a similar extent in patients with and without diabetes mellitus as in corresponding outcome trials. Cardiac remodeling following myocardial infarction leads to heart failure with reduced ejection fraction in many patients and aggravates morbidity and mortality. Clinical data of SGLT2i treatment after acute myocardial infarction is sparse. This review focuses on available experimental data on the effects of SGLT2i used before, during, and after myocardial infarction as well as already published and currently ongoing clinical trials.

Key words: sodium-glucose cotransporter 2 inhibitors, myocardial infarction, metabolism, clinical trials

Kardiol Pol 2021; 79, 5: 503–509

INTRODUCTION

Diabetes mellitus is a risk factor and aggravates other potential risk factors of the cardiovascular system, such as arterial hypertension [1] or smoking [2], and is associated with increased levels of blood lipids, and obesity [3]. These conditions pave the way towards coronary artery disease (CAD), which indeed represents a common disease in diabetic patients [4]. CAD often triggers heart failure (HF) via myocardial infarction (MI) and ischemia/reperfusion damages that induce acute and/or chronic maladaptive remodeling processes. CAD and HF represent the two most important causes of cardiovascular morbidity and mortality. Therefore, the central therapeutic aim in CAD is the prevention of MI in patients at atherosclerotic risk, and reducing the burden of HF in patients after MI. Attention has been caught recently by 3 clinical trials that proved impressive beneficial effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on HF hospitalization in diabetic patients with either established atherosclerotic cardiovascular diseases or multiple risk factors — namely the EMPA-REG OUTCOMES trial for empagliflozin [5], the CANVAS program for canagliflozin [6], and the DECLARE TIMI-58 trial for dapagliflozin [7]. More than 50% of the patients included in these 3 trials had CAD, and relevant subgroups had experienced previous MI, as shown in Table 1. A meta-analysis of these 3 outcome trials revealed an 11% reduction of major adverse cardiovascular events defined as MI, stroke, and cardiovascular death mainly driven by a strong effect in patients with established atherosclerotic cardiovascular disease. In detail, this analysis showed an overall reduction of MI by 11% in all patients and by 15% in those with previous atherosclerotic cardi-

Table 1. The number of patients with myocardial infarction (MI) and/or coronary artery disease (CAD) within each trial

	Previous MI	CAD
EMPA-REG-OUTCOME [5]	3273 (46.6)	5308 (75.6)
DECLARE-TIMI [7]	3584 (20.9)	5658 (32.9)
CANVAS [6}	Not reported	5721 (56.4)

Data are presented as number (percentage)

ovascular disease [8]. This data is confirmed by a broader and earlier meta-analysis of 71 trials including more than 47 000 diabetic patients treated with all available SGLT2i that demonstrated a reduction of MI by 23% after SGLT2i treatment [9]. A recent comparative cohort study on newly initiated therapy with SGLT2i or dipeptidyl-peptidase 4 inhibitors in diabetic patients also revealed significantly reduced rates of MI in those initiating SGLT2i, in this analysis with the strongest effects observed in patients without previously known cardiovascular disease [10]. Similar results were derived from a huge retrospective analysis comparing newly initiated SGLT2i matched with any other newly initiated oral antidiabetic drug in over 470 000 diabetic patients [11]. Comparable effect sizes can also be observed with some glucagon-like peptide 1 receptor agonists [12–14] and — to a smaller degree and retrospectively analyzed — with metformin [15]. Therefore, SGLT2i, metformin, and glucagon-like peptide 1 receptor agonists should be considered in all patients with increased risk of MI.

Based on the available convincing data and given the fact that some other antidiabetic concepts did not consistently show a reduction in major adverse cardiovascular events in diabetic patients [16–18], SGLT2i were soon after examined in HF patients irrespective of their diabetes status. So far, two landmark trials with SGLT2i in HF have been published [19, 20] and SGLT2i are likely to be integrated into the treatment algorithm for HF with reduced ejection fraction (HFrEF) in diabetic and non-diabetic patients soon. Although more than half of the patients in those 2 trials had ischemic heart disease as their principal cause of HF, no data on MI incidence during the study periods is reported, yet. More data in this context might soon also be derived from the DAPA-CKD trial [21] leaving the question of whether SGLT2i may exert beneficial effects in patients after MI, too.

PATHOPHYSIOLOGY OF MYOCARDIAL INFARCTION AND EARLY TREATMENT INITIATION

Myocardial damage in MI derives mainly from two different causes. Firstly, acute ischemia causes energy depletion within the area at risk and irreversible necrotic cell damage within the infarcted area. Secondly, acute MI triggers a neurohumoral response mainly driven by an uncontrolled upregulation of the renin–angiotensin–aldosterone system and activation of the sympathetic nervous system. Both processes induce myocardial remodeling that will finally affect non-ischemic areas of the heart, too. Therefore, therapies improving the acute damage need to be present during the index event, whereas therapies interacting with the remodeling process might also be efficient if applied afterward. As remodeling starts immediately after the ischemic event, early initiation of a potentially beneficial drug seems to be desirable. Robust evidence exists for all drug classes used in HF with reduced ejection fraction (HFrEF) that show beneficial effects in post MI treatment, and early initiation of these drugs obviously improves these beneficial effects. A huge meta-analysis including ~100 000 patients indicated that 85% of the survival benefit with angiotensin-converting-enzyme inhibitors after MI was accomplished within the first 7 days after MI [22]. Early initiation of β-blocker therapy is recommended in the guidelines [23] — even before the intervention of the affected coronary vessel — as an anti-anginal and energy-saving drug [24, 25], but very early therapy needs to be limited to patients without increased risk of cardiogenic shock that can be triggered or aggravated by the negative inotropic and negative chronotropic effects of β-blockers as shown in the COMMIT trial [26]. Mineral receptor antagonist treatment with eplerenone within 24 hours after MI in the setting of ST-segment myocardial infarction (STEMI) improved the primary endpoint of the REMINDER trial [27]. The same is true for the STEMI-subgroup of the ALBATROSS trial that investigated the early use of spironolactone after MI [28], while in the non-STEMI subgroup no beneficial treatment effect could be observed indicating that larger MI will benefit most from (early) initiation of mineral receptor antagonist treatment. Outcome data on early angiotensin receptor-neprilysin inhibitor treatment is not yet available. However, the PARADISE-MI trial comparing sacubitril-valsartan vs ramipril starting within 7 days after the index event just completed final visits and data will be available soon. So far, hardly any clinical data is available on SGLT2i in STEMI patients. Figure 1 summarizes respective clinical trials for empagliflozin [29] and dapagliflozin where first outcome data will be published soon. For other SGLT2i, such as canagliflozin, sotagliflozin, ipragliflozin, and tofogliflozin, currently, no trials after acute MI are ongoing. Yet, more and more experimental data sheds light on the potential beneficial effects of SGLT2i after MI.

SGLT2 INHIBITOR TREATMENT BEFORE MYOCARDIAL INFARCTION

Various animal models describe attenuated MIs after SGLT2i pretreatment. In a study focusing on SGLT2i mediated protective effects in the setting of ischemia/reperfusion, Andreadou et al. [30] used a mice model being fed for 6 weeks with empagliflozin before a temporal surgical ligation of the left anterior descending coronary artery (LAD) was performed for 30 minutes followed by reperfusion period of 2 hours. Empagliflozin pretreatment reduced infarct size by approximately 50% and left ventricular fractional shortening was improved from 41% to 44% compared to vehicle-treated control animals post ischemia. Detailed biochemical analysis revealed significant activation of signal transducer and activator of transcription 3 (STAT3) transcription factor expression and phosphorylation in the empagliflozin-treated animals while reduced levels of myocardial interleukin-6 and inducible nitric oxide (NO) synthase expression were measured. Potential other candidates of mediating protective effects such as Akt, eNos, p44/42 MAPK, or AMPKa phosphorylation were not affected by empagliflozin pretreatment. Similar data

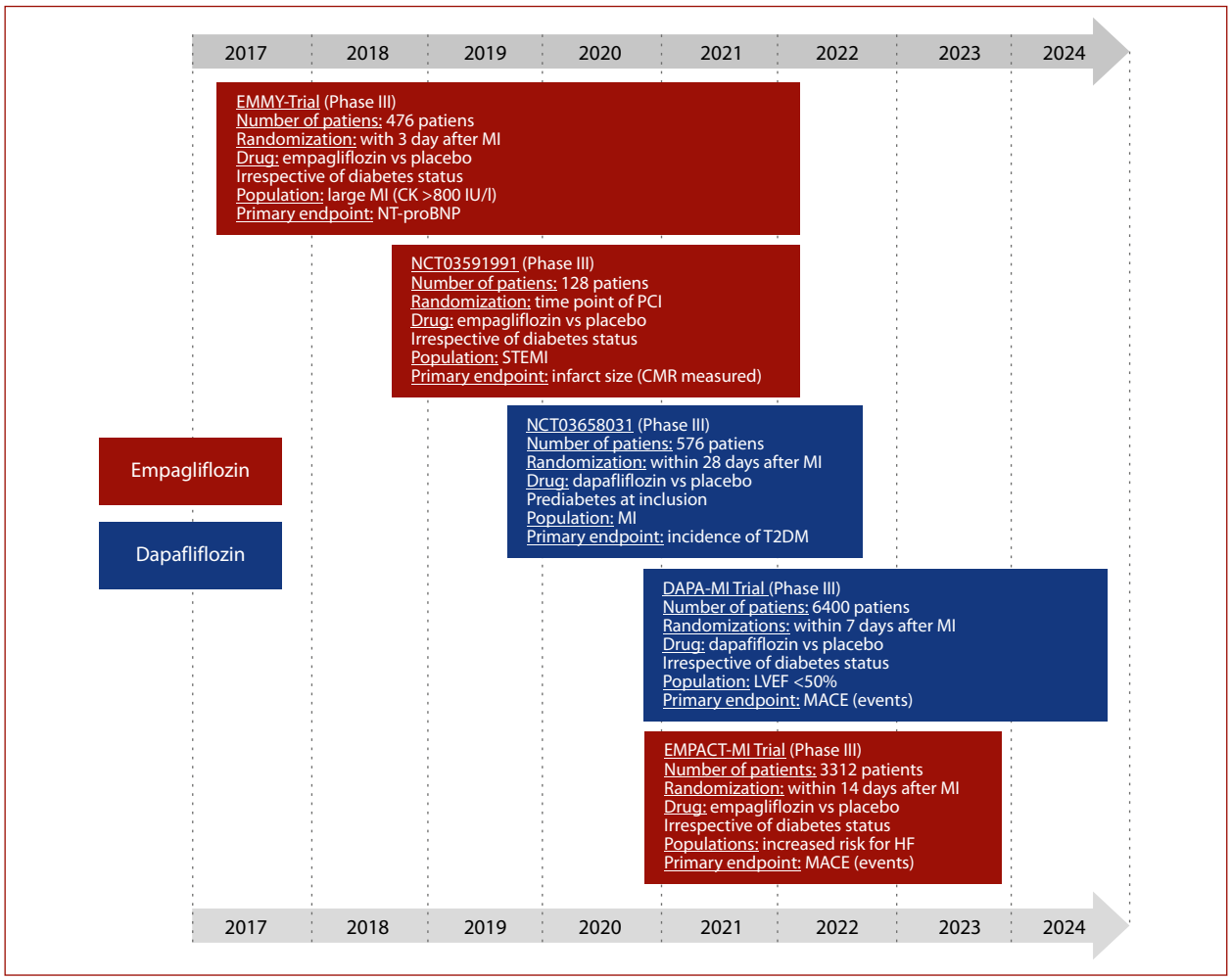

Figure 1. Timeline of already completed and still running trials with sodium-glucose cotransporter 2 inhibitors after myocardial infarction. Blue: dapagliflozin. Red: empagliflozin. Trial name, inclusion criterion, end points, and the number of planned included patients are given. End date is assumed based on the information given at www.clinicaltrials.org. All trials tested drugs versus placebo.

Abbreviations: CK, creatinine kinase; CMR, cardiac magnetic resonance; HF, heart failure; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; T2DM, type 2 diabetes mellitus

was observed by Lopez et al. [31] in rats after permanent surgical ligation of the LAD. Pretreatment of 25 days with empagliflozin reduced the infarct size by 30%–40% in non-diabetic and streptozotocin-induced diabetic rats. This effect was accompanied by significantly better contractility analyzed by left ventricular fractional shortening and left ventricular ejection fraction (LVEF). Within this model, significantly reduced concentrations of inducible NO synthase and superoxide levels were measured, too. The authors expanded their analysis towards the cardiac GTP enzyme cyclohydrolase 1 (cGCH1) which is rate-limiting and the first enzyme in the biosynthesis of the essential cofactor of all 3 NO isoforms of tetrahydrobiopterin (BH4). They observed significantly increased concentrations of myocardial cGCH1 and BH4 in the empagliflozin pretreated groups. Intriguingly, blocking this pathway using cGCH1 knockout models also abolished effects of empagliflozin treatment on BH4 concentrations, cell area, and the NO system including superoxide concentrations. In summary, this points towards a reduction of oxidative stress in the empagliflozin-treated hearts via this cGCH1-BH4 pathway.

Metabolic changes have been suggested as the underlying mechanism for the effects of SGLT2i by Oshima et al. [32]. Empagliflozin pretreatment 14 days before permanent occlusion of a marginal branch of the LAD resulted in increased myocardial and blood β-ydroxybutyrate (β-OHB) levels of diabetic rats as well as metabolomic patterns of increased glucose and ketone utilization. Metabolomic effects of external β-OHB in SGLT2i naive rats mimicked the empagliflozin effects indicating this as a potential mechanism of action. Empagliflozin pretreatment significantly improved 48-hour survival (40% vs 84%) despite unaltered infarct size. Interestingly, MI-induced acute kidney injury was also attenuated within the same model by empagliflozin pretreatment [33]. The functional protective data was also confirmed in a set of experiments by Lim et al. [34]

using canagliflozin in rats. After 4-week oral pre-treatment with canagliflozin the hearts were harvested and examined in a Langendorff setup. After 40 minutes of stabilization, a 35-minute regional ischemia was applied and followed by 2-hours of reperfusion. Canagliflozin pre-treatment significantly reduced ischemia/reperfusion injury by approximately 50% in both diabetic as well as in non-diabetic rats compared to vehicle-treated animals. The area at risk was not different in all groups.

SGLT2 INHIBITOR TREATMENT DURING MYOCARDIAL INFARCTION

In contrast to these matching beneficial results within various studies for chronic pretreatment, the acute treatment showed heterogeneous effects. The setting of initiating an SGLT2i shortly before or during ischemia excludes chronic changes in metabolism or myocardial energetics as underlying mechanisms of potential protective effects.

Lu et al. [35] treated murine cardiomyocytes with either empagliflozin, the adenosine monophosphate-activated protein kinase (AMPK) inhibitor compound C, both substances, and vehicle buffer solution briefly before these cardiomyocytes were exposed to hypoxic conditions for 20 minutes followed by a re-oxygenation period of another 20 minutes [35]. Empagliflozin triggered phosphorylation of AMPK, its upstream activator liver kinase B1, as well as its downstream target the peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α) within minutes. Interestingly, persistent activation of the AMPK-dependent pathway with empagliflozin was accompanied by improved cardiac contractility. Moreover, these beneficial molecular and functional effects were almost completely abolished in cells pretreated with the AMPK inhibitor compound C. These experiments were extended to an in-vivo model in which mice were treated with empagliflozin alone or in combination with compound C for 3 days before surgical temporal LAD ligation for 45 minutes followed by 24 hours of reperfusion. Rapidly performed post-procedural echocardiography indicated a preserved LVEF in the empagliflozin-treated mice while mice also pretreated with compound C had a reduced LVEF comparable to the LVEF in the vehicle-treated group. Interestingly, histological analysis revealed reduced infarction areas in the empagliflozin-treated mice. Lahnwong et al. [36] reported beneficial effects after pretreatment with dapagliflozin only 15 minutes before ischemia/reperfusion in a rat model expressed by improved LVEF, reduction of arrhythmias, reduced infarct size, and reduced rate of apoptosis. These effects were mainly attributed to mitochondrial protection, attenuation of reactive oxygen species production, and upregulation of antiapoptotic proteins. Translating a short pretreatment period into a large animal, Baker el al. [37] treated swine with a weight of approximately 50 kg with canagliflozin 24 hours before 60-minutes of total LAD occlusion. Canagliflozin pretreatment resulted in a 60% reduction in infarct size, higher stroke volume, and better myocardial efficiency (cardiac work divided by oxygen consumption) compared to non-treated animals.

On the other hand, Lim et al. [34] treated isolated non-diabetic rat hearts in a Langendorff setup with canagliflozin only throughout the perfusion protocol. This approach failed to reduce infarct size despite areas at risk comparable to those in the protocol using 4-week pre-treatment. This observation is confirmed by unaltered MI size with only 2 days of empagliflozin pretreatment before MI in a rat model published by Yurista et al. [38]. However, this data might be biased as all animals with infarct areas smaller than 15% were excluded from the analysis. Nevertheless, mitochondrial protection could be demonstrated to a similar extent compared to the group that received an empagliflozin pretreatment for 2 weeks. Jespersen et al. [39] also described no effect on infarct size after a 10 minute pretreatment with empagliflozin in non-diabetic rats but acute improvements in mitochondrial function.

SGLT2 INHIBITION POST MYOCARDIAL INFARCTION

Treatment initiated after ischemia and reperfusion obviously cannot provide beneficial effects within the very early stages of MI. But the contribution of metabolic properties, cardiac remodeling, and potential arrhythmias following MI can be investigated in such experiments.

The first evidence was provided in 2017. Lee et al. [40] treated male Wistar rats with dapagliflozin 24 hours after MI induced by ligation of the LAD. Infarct size could not be changed with this delayed treatment, but dapagliflozin improved contractile kinetics and reduced structural changes (cardiac fibrosis) compared to the vehicle-treated group at the end of the study period of 4 weeks. Moreover, a reduced lung weight to body weight ratio was found indicating better remodeling in the treated group. The underlying mechanism seemed to be an early STAT3 dependent attenuation of activation of oxidative stress measured as increases of superoxide and nitrotyrosine already after 3 days of treatment. Co-administered of the STAT3 inhibitor S3I-201 dramatically reduced or nullified these effects.

This post-MI data was extended to a large animal model by Santos-Gallego et al. [42] using female Yorkshire pigs treated with 2-hour balloon occlusion of the LAD. Pigs were randomized to either empagliflozin or placebo and treatment was started the day after MI. A non-MI pig group that was not treated with empagliflozin served as a control. The observation period lasted for 2 months. As anticipated, empagliflozin initiation after reperfusion did not reduce infarct size, but myocardial metabolism and function differed considerably between the three groups. Placebo-treated MI animals were characterized by a reduced myocardial uptake of free fatty acids, an increased uptake of glucose, and a net lactate production — typical patterns of anaerobic metabolism. Empagliflozin-treated MI animals showed a less pronounced reduction of myocardial free fatty acids uptake while there was no difference in the uptake

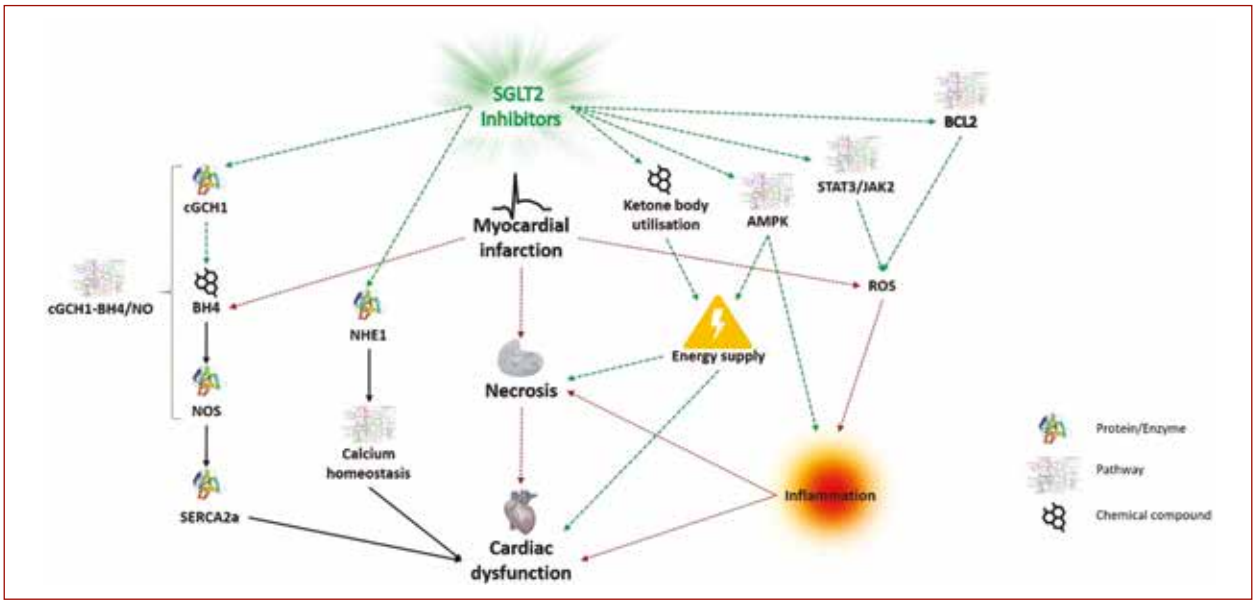

Figure 2. Interactions of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and myocardial infarction (MI) on the homeostasis of cardiomyocytes in different species and on different biological levels (full animals, organs, tissue, and single cells). MI leads directly to tissue necrosis and indirectly via reactive oxygen species (ROS) and inflammation. Additionally, MI negatively influences the downstream pathway of tetrahydrobiopterin (BH4) leading to a dysfunction of calcium homeostasis via sarco/endoplasmic reticulum Ca2+-ATPase (SERCA2a) (dotted red lines). SGLT2i interacted with and via various proteins, pathways, and compounds that counteract the negative effects induced by MI (dashed green lines). The wide interactions with cardiomyocytes via miscellaneous second messengers are not shown.

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; BCL2, B-cell lymphoma 2 gene; cGH1, cGH1 gene; JAK2, Janus kinase 2; NHE1, sodium-hydrogen antiporter 1; NOS, nitric oxide synthase; STAT3, signal transducer and activator of transcription 3 transcription factor

of glucose and lactate compared to non-MI animals. In conclusion, empagliflozin treatment preserves the aerobic metabolism after MI. Moreover, empagliflozin increased the myocardial uptake of ketone bodies resulting in an increased calculated myocardial work efficiency. Mechanistically, empagliflozin treatment leads to less reduced pAMPK/AMPK and PGC1α/glyceraldehyde 3-phosphate dehydrogenase (GAPDH) ratios as well as less reduced myocardial adenosine triphosphate (ATP) content compared to controls. This likely improves the energetic state of the cells. These data support the abovementioned findings of Lu et al. [35] on the murine single-cell level.

Finally, these beneficial metabolic changes translated into improved myocardial function analyzed by cardiac magnetic resonance imaging and three-dimensional echocardiography. Here, empagliflozin significantly attenuated left ventricle enlargement and significantly improved LVEF and longitudinal strain.

MYOCARDIAL PROTECTION BY PERSISTENT EFFECTS INDUCED BY SGLT2 INHIBITORS

The experimental evidence available clearly describes the beneficial effects of SGLT2i initiation after MI. Unfortunately, all these studies only used a small number of animals (4–6 animals per group), different treatment protocols, and different SGLT2 inhibitors. Therefore, only speculations and no final conclusions can be drawn from these observations. Examining hearts in Langendorff set-ups presume a crystalloid washout before the ischemia/reperfusion procedure can be induced. Data derived from these experiments are therefore likely unaffected by the metabolic effects or substrates originating from other organs such as liver-derived ketones. Next, the discrepancy of acute and chronic effects in ischemia/reperfusion damage speaks rather against a fast-acting membrane-based mechanism like the inhibition of the sodium-hydrogen antiporter 1 with consecutive alterations in the cellular calcium homeostasis reported earlier by Baartscheer et al. [42]. Of note, initiation of SGLT2i after ischemia/reperfusion damage cannot reduce infarct size per se too, therefore mechanisms to be addressed must positively influence cardiac remodeling.

As summarized in Figure 2, data derived from various experimental settings supports a persistent myocardial effect of SGLT2i with the best available evidence so far for the upregulation of the protective JAK/STAT3 [30, 40], the cGCH1-BH4/NO [31], the B-cell lymphoma 2 gene [36], and the AMPK [35, 41] pathway. Further pleiotropic mechanisms reducing oxidative stress [36] and inflammation as revealed by Koyani et al. [43] certainly play their part in this complex cascade of interactions too, although these pathways seem to be much more regulated and affected by SGLT2i treatment in the early phase after MI. Improved myocardial efficiency would obviously shift myocardial function towards a less energy-consuming mode of action which is likely delaying or preventing further cardiac deterioration. Increased myocardial ketone body consumption upon SGLT2i treatment [41, 44] supports this hypothesis. Finally,

structural decline as increased fibrosis typically observed in remodeling seems to be preventable by SGLT2i [40]. However, it remains unclear if a brief pretreatment can already mediate chronic metabolic or structural protective effects.

Regarding canagliflozin, another aspect must be kept in mind since this substance is less selective for SGLT2 compared to empagliflozin and dapagliflozin. Effects induced by canagliflozin might therefore also be attributed to SGLT1 mediated mechanisms. This might be of special importance in human myocardial tissue as SGLT2 is neither expressed in the atrial [45] nor in the ventricular myocardium [46].

FIRST CLINICAL DATA OF SGLT2 INHIBITORS AFTER MYOCARDIAL INFARCTION

Data from clinical trials specifically addressing acute MI patients is scarce. There is practically only a single study analyzing sympathetic and parasympathetic activity using heart rate variability and heart rate turbulence in 96 diabetic patients [47]. Patients were enrolled in the trial 2–12 weeks after MI. Average creatinine kinase was approximately 2200 IU/l and N-terminal pro–B-type natriuretic peptide was 1150 pg/ml indicating rather large MIs. The prescription rate of guidelines-recommended medication post-MI including β-blockers, renin–angiotensin–aldosterone system inhibitors, statins, and dual platelet inhibition was high. Follow-up of the patients was up to 24 weeks and the primary endpoint of heart rate variability was reported as the standard deviation of all 5-minute mean normal RR intervals. Low frequency to high frequency ratio was significantly changed only in the empagliflozin group but there was no significant difference compared to placebo. However, potentially even more interesting was the effect on average N-terminal pro-B-type natriuretic peptide levels. In the empagliflozin group, a reduction of 64% to baseline could be reached compared to a reduction of 53% in the placebo group. This data is in line with the known beneficial effects of SGLT2 i in HF.

CONCLUSIONS

Meta-analyses of clinical trials emphasize that SGLT2i treatment leads to a reduction of 10%–20% in the number of MI in diabetic patients. Experimental data highlights a reduction in infarct size and consecutively less remodeling and development of HF after MI in almost all experimental settings ranging from single cells to large animal models with and without diabetes. The reason for this finding is likely multifactorial, including delayed progression of diabetes, improved myocardial energetics, activation of cardioprotective downstream mechanisms counteracting remodeling processes, antifibrotic and antiapoptotic processes, potential anti-inflammatory mechanisms, and direct interaction with cardiomyocytes (Figure 2). Thereby, the heart may resist episodes of ischemia that would otherwise result in cell damage and MI. Importantly, experimental and first clinical data strongly point towards effects independent from the presence of diabetes. Therefore, it needs to be considered if treatment with SGLT2i irrespective of the diabetes status is reasonable to initiate in patients after MI. This claim is already heavily backed by experimental data and will soon be complemented by clinical data.

Article information

Acknowledgements: We thank Julia Schmidt, CBMed, Graz, Austria for the design of Figure 2.

Conflict of interest: The authors are investigators of the EMMY-trial, otherwise, no conflict of interest is declared.

How to cite: von Lewinski D, Benedikt M, Tripolt N, et al. Can sodium-glucose cotransporter 2 inhibitors be beneficial in patients with acute myocardial infarction? Kardiol Pol. 2021; 79(5): 503–509, doi: 10.33963/KP.15969.

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