SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS AND THE TREATMENT OF ACUTE CORONARY SYNDROME - DOES THE USE MAKE SENSE?

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Abstract

Sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors) represent a therapeutic modality option for type 2 diabetes mellitus. This group of drugs includes dapagliflozin, empagliflozin, canagliflozin, ertugliflozin and sotagliflozin. Given their proven benefit in the scope of heart failure through clinical studies, they have also gained their place in patients with reduced, moderately reduced or preserved systolic function of the left ventricle. Due to the effect on both the systolic and diastolic function of the left ventricle, and the neurohumoral activity itself, their range of use has been expanded in patients without a history of diabetes mellitus, and empagliflozin in a dose of 10 mg, as well as dapagliflozin in a dose of 10 mg, have been implemented in patients without diabetes mellitus. New directions for the expansion of the use of SGLT2 inhibitors have pointed towards their applicability in acute heart failure (sotagliflozin) and type 1 diabetes (sotagliflozin). Recently, clinical studies concerning the use of empagliflozin and dapagliflozin in acute coronary syndrome (ACS), appeared. The aim of this paper was to highlight the possible benefit of including SGLT2 inhibitors in patients with ACS.

Keywords: sodium-glucose co-transporter 2 inhibitors, acute coronary syndrome, treatment

Introduction

Ischemic heart disease occurs in two clinical forms: chronic (stable angina pectoris) and acute, i.e. acute coronary syndrome (ACS)[1]. The term ACS refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) and infarction myocardial infarction with ST-segment elevation (STEMI)[2]. The joint working group of the European Society of Cardiology (ESC), American College of Cardiology (ACCA), American of the Heart Association (AHA), and the World Health Organization (WHO) in 2018 defined myocardial infarction, as the presence of acute myocardial damage, verified by elevated values of enzymes of myocardial necrosis, as a consequence of acute myocardial ischemia. NSTEMI and STEMI are characterized by an increase in troponin over > 99% compared to reference values[1, 3]. It is considered that the presentation of symptoms, the severity of the clinical picture, and the prognosis depend on the site of occlusions (left or right coronary artery, proximal or distal occlusion), onset speed of occlusion (sudden or gradual) and on the existence of collateral circulation[1]. Coronary reperfusion with primary percutaneous coronary intervention (pPCI) improves outcomes in patients with STEMI. It is used as the first and only reperfusion therapy, if any is available, and if not, then fibrinolytic therapy is an alternative. With reperfusion it is recommended to use antiplatelet and anticoagulant therapy, angiotensin-converting inhibitors enzyme (ACE), beta-blockers, high-dose statins, mineralocorticosteroid antagonists and diuretics as a mosaic of therapeutic modalities in order to improve the outcome of the acute incident itself as well as preventing the occurrence of major adverse cardiovascular events (MACE) which include death, reinfarction, stroke and revascularization (depending on the clinical research settings, the definition may be shortened or extended)[3].

Sodium-glucose cotransporter 2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors represent an option of therapeutic modality for diabetes mellitus type 2 (T2DM)[4]. They are not recommended at the start of treatment, but metformin remains the initial therapy, with occasional initial use of glucagon-like peptide-1 receptor agonists in specific populations[4, 5]. Candidates for the use of SGLT2 inhibitors are: 1. patients with atherosclerotic

cardiovascular disease (empagliflozin, canagliflozin and dapagliflozin), whose glycemia cannot be maintained in the reference values with metformin and with lifestyle changes; 2. patients with heart failure and poor glycemic control with initial therapy (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin); 3. patients with type 2 DM who have glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2 (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin), as well as 4. patients with heart failure without diabetes (empagliflozin, dapagliflozin)[4, 5]. In patients with type 2 DM and a diagnosis of acute heart failure, the benefit of using sotagliflozin has been proven[6].

SGLT2 inhibitors are contraindicated in the treatment of type 1 DM, in patients with type 2 DM who have eGFR < 45 mL/min/1.73 m^2 (ertugliflozin) or < 30 mL/min/1.73 m^2 (empagliflozin, canagliflozin, dapagliflozin, sotagliflozin) and in patients with previous diabetic ketoacidosis[4]. It is reasonable to avoid them, in patients with frequent urinary infections, low bone density, in foot ulcerations (either acute or anamnestic) and in patients who have a predisposition to the development of diabetic ketoacidosis[4].

In addition to an increase in the rate of genitourinary infections, potential side effects are: postural hypotension, polyuria, diabetic ketoacidosis, acute renal failure and a higher frequency of bone fractures[7]. Genitourinary side effects of SGLT2 inhibitors are attributed to high glucose concentration in the genitourinary tract and impaired function of neutrophils and the antioxidant system, resulting in a weakened immune system and a greater predisposition to infections[7].

Diabetic ketoacidosis, as one of the main problems related to SGLT2 inhibitors, has led to their use being contraindicated in patients with type 1 DM. This side effect occurs due to the decreased level of insulin after the loss of glucose in the urine[7]. SGLT2 inhibitors generally exhibit an osmotic diuretic effect, leading to mild volume depletion (mainly due to glucose and sodium depletion), which may present as orthostatic hypotension and dizziness[4, 5]. Lower limb amputations are more common in patients using SGLT2 inhibitors, mainly when using canagliflozin, in patients with peripheral arterial disease or previous amputation[7]. Canagliflozin is also associated with the risk of bone fractures, as it reduces bone density through its effect on phosphates, calcium and vitamin D[8].

SGLT2 receptors are located in the proximal convoluted tubules of the kidney. They accelerate the renal excretion of glucose (potentiate osmotic diuresis) and block the reabsorption of filtered glucose, thus affecting glycemic values[9]. SGLT1 receptors function in absorbing glucose of the gastrointestinal tract, before it is distributed to the pancreas[9]. The main question is (still an insufficiently researched field) on the dual inhibition of SGLT1 and SGLT2 inhibitors (sotagliflozin) and their benefit for patients.

The pharmacological properties of SGLT2 inhibitors are shown in table 1. The effect on MACE has been confirmed, but the question of using SGLT2 inhibitors in ACS itself is raised. Can their use be beneficial in patients with ACS, both in the acute stage and later, through the reduction of MACE?

SGLT2 inhibitors and potential effect in acute coronary syndrome

There are no precise data on the use of SGLT2 inhibitors during the acute phase or after an acute myocardial infarction (AMI). Indirect conclusions and the possible benefit of their use were obtained through previous clinical studies in patients with existing cardiovascular disease and are limited to those with DM as a comorbidity. The potential benefit of SGLT2 inhibitors in acute myocardial infarction is reflected in the renoprotective effect of SGLT2 inhibitors, the reduction of plasma volume independent of the level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP), improvement of heart remodeling and cardiac metabolism, the effect on preload and afterload, reducing the risk of developing heart failure and death after an acute cardiovascular event, and improving the sympathetic activity of the heart and mitochondria. Possible risks of their use are volume depletion, acute renal failure, and acidosis[10-18]. The presentation of the benefits of SGLT2 inhibitors in the form of effects on MACE, cardiovascular mortality, as well as on hospitalization due to heart failure in patients with previous cardiovascular disease is shown in table 2, and in patients with a diagnosis of heart failure in table 3.

Table 4 shows the studies that dealt with the topic of AMI and the use of empagliflozin. EMPACT-MI (Trial to Evaluate the Effect of Empagliflozin on Hospitalisation for Heart Failure and Mortality in Patients With acuTe Myocardial Infarction) and DAPA-MI (Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Heart Failure or Cardiovascular Death in Patients Without Diabetes With Acute Myocardial Infarction) clinical studies are still ongoing.

A possible mechanism that leads to the benefit of using these drugs in patients with ACS is the reduction of neurohormonal activation, cardiomyocyte necrosis, and reperfusion injury[21]. The benefit can also be expected from preservation of endothelial function and potentiation of vasodilation, preservation of energy necessary for myocardial metabolism and preservation of myocardial contractility. The effect on oxidative stress impacts the improvement of coronary flow and the reduction of stress in the left ventricle. The benefit could be reflected in the reduction of fibrosis and the occurrence (progression) of heart failure[21]. It has long been known that the use of SGLT2 inhibitors has the effect of reducing the mass of the left ventricle in patients with stable ischemic disease, that is, it can affect the remodeling of the left ventricle[21]. Reduction of preload and afterload, better glycemic control, as well as weight loss through natriuresis and glycosuria (with reduction of intraglomerular pressure),

can be expected. It is believed that the benefit could be in increasing the production of erythropoietin, which again, can result in better control of the patient's volume load and better oxygen supply[21].

The results of the EMBODY clinical study indicate an improvement in parasympathetic and sympathetic activity and a decrease in plasma volume independently of NT-proBNP strong predictor of abnormal heart rate variability (HRV)[19]. In this regard, the authors of this study concluded that empagliflozin improves HRV, reflecting improvement in cardiac sympathetic nerve activity, thereby reducing cardiovascular disease-related mortality, including sudden cardiac death (SCD) in patients with AMI and type 2 DM. Furthermore, the EMBODY clinical trial showed that early administration of SGLT2 inhibitors after AMI in obese patients with type 2 DM affects volume load balance, specifically by reducing

Table 1. Pharmacological properties of SGLT2 inhibitors[10-18]

Characteristics	Dapagliflozin	Empagliflozin	Canagliflozin	Ertugliflozin	Sotagliflozin
Route of administration	*per os*	*per os*	*per os*	*per os*	*per os*
Dosage (mg)	5, 10	10, 25	100, 300	5, 15	200, 400
Mechanism of action	SGLT2 inhibitor	SGLT2 inhibitor	SGLT2 inhibitor	SGLT2 inhibitor	SGLT1 and SGLT2 inhibitor
Metabolism	UGT1A9	UGT2B7 UGT1A3 UGT1A8 UGT1A9	UGT1A9 UGT2B4	UGT1A9 UGT2B7 CYP3A4 CYP3A5	UGT1A9 UGT1A1 UGT2B7 CYP3A4
Excretion	75% renal 21% fecal	55% renal 40% fecal	33% renal 41,5% fecal	55% renal 41% fecal	mostly renal
Bioavailability	78%	75%	65%	70-90%	71%
Half-life (hr)	1.0-1.5 (13)	1.5 (13)	1-2 (11-13)	0.5-1.5 (11-17)	3 (13.5-20.7)
Indications	HFrEF Type 2 DM CKD	HFrEF HFpEF Type 2 DM	Type 2 DM	Type 2 DM	Type 1 DM Type 2 DM Acute HF
Contraindications	Hypersensitivity, Type 1 DM, eGFR < 30 mL/min/1.73 m^2, dialysis	Hypersensitivity, Type 1 DM, eGFR < 30 mL/min/1.73 m^2, dialysis	Hypersensitivity, Type 1 DM, eGFR < 30 mL/min/1.73 m^2, dialysis	Hypersensitivity, Type 1 DM, eGFR < 45 mL/min/1.73 m^2, dialysis	Hypersensitivity, eGFR < 45 mL/min/1.73 m^2, dialysis
Interactions with other drugs in the treatment of DM	No significant interactions	No significant interactions	No significant interactions	No significant interactions	No significant interactions

Abbreviations: **SGLT2 inhibitors** - sodium-glucose cotransporter 2 inhibitors; **HF** - heart failure; **HFrEF** - heart failure with reduced ejection fraction; **HFrEF** - heart failure with reduced ejection fraction; **DM** - diabetes mellitus; **CKD** - chronic kidney disease; **eGFR** - estimated glomerular filtration rate; **UGT**- uridine 5'-diphospho-glucuronosyltransferase

levels. The study also indicates the benefit of using SGLT2 inhibitors to preserve systolic function, so, in addition to the already standard treatment of heart failure, it also implies the justification of using SGLT2 inhibitors. Primarily, they should be used in patients with anterior myocardial wall involvement, as well as in patients who have a more extensive AMI, where the application will have an even greater benefit. One of the most important challenges after AMI, is protection against fatal ventricular arrhythmias, that is a the increase in extracellular and intracellular fluid, thereby improving systolic and diastolic function in this patient population. Empagliflozin also demonstrated renoprotective effects after AMI in patients with relatively preserved eGFR of 60 mL/min/1.73 m^2 or greater, primarily due to reduction in uric acid levels[22].

The EMMY clinical study indicates a benefit that is reflected in the reduction of NT-proBNP, in the improvement

Table 2. Clinical studies where patients with previous cardiovascular disease and type 2 DM were treated[10-13]

Clinical trial	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58	VERTIS-CV
Number of participants	7.064	10.142	17.190	8.246
Follow-up period (years)	3.1	3.6	4.2	3.5
Medications	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Comparison	Placebo	Placebo	Placebo	Placebo
Effect on MACE	p < 0.001 for noninferiority; p=0.04 for superiority	reduces the risk by 14%; p < 0.001 for noninferiority; p=0.02 for superiority	No effect on MACE	p < 0.001 for noninferiority
Effect on cardiovascular mortality	reduction of death from cardiovascular causes (3.7%, p < 0.001)	not significant	significant (p=0.005)	noninferior to placebo
Effect on hospitalization for heart failure	reduces the risk of hospitalization by 35%	reduces the relative risk by 33%	significant (p=0.005)	reduces the risk for hospitalization by 30%

Abbreviations: EMPA-REG OUTCOME - Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; **CANVAS** - The Canagliflozin Cardiovascular Assessment Study; **DECLARE-TIMI 58** - Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; **VERTIS-CV** - Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial; **MACE** - major adverse cardiac events

Table 3. Clinical studies on patients diagnosed with heart failure[14-18]

Clinical trial	DAPA-HF	EMPEROR-Reduced	SOLOIST-WHF	EMPEROR-Preserved	DELIVER
Number of participants	4.744	3.730	1.222	5.988	6.263
Follow-up period	18.2 months	16 months	9 months	2.2 years	2.3 years
Medications	Dapagliflozin	Empagliflozin	Sotagliflozin	Empagliflozin	Dapagliflozin
Comparison	Placebo	Placebo	Placebo	Placebo	Placebo
Effect on MACE	Verified in 16.3% of treated patients	Verified in 361 patients	Verified in 600 patients	Significant effect ($p < 0.001$)	Significant effect ($p < 0.001$)
Effect on cardiovascular mortality	Verified in 9.6% of patients	No significant effect on cardiovascular mortality	10.6 cases/100 patient-ye-ars (p=0.036)	Verified in 7.3% of patients	Verified in 7.4% of patients
Effect on hospitalization for heart failure	Verified in 9.7% of patients	Reduction in the number of hospitalizations 30% (388/1863)	Cardiovascular death and hospitalization: 33% vs. 48% (p=0.003)	Verified in 8.6% of patients	Worsened in 11.8% of patients

Abbreviations: DAPA-HF - Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; **EMPEROR** - Reduced - Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; **SOLOIST-WHF** - Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure; **EMPEROR-Preserved** - Empagliflozin Outcome Trial in Patients with Chronic Heart Failure With Preserved Ejection Fraction; **DELIVER** - Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure; **MACE** - major adverse cardiac events

Table 4. Clinical studies that analyzed the use of empagliflozin in patients with acute myocardial infarction[19-20]

Clinical trial	EMBODY	EMMY
Number of participants	105	476
Medications	Empagliflozin 10 mg daily	Empagliflozin 10 mg daily
Follow-up period (weeks)	24	26
Population	Patients ≥ 20 within 2-12 weeks of an acute myocar-dial infarction with a diagnosis of diabetes mellitus type 2 (previous history of arterial hypertension), dyslipidemia, cerebrocardiovascular disease.	Patients aged 18-80 years with confirmed acute myocardial infarction, elevated creatine kinase (> 800 IU/L) and troponin (> 10 times the reference limit), eGFR > 45 mL/min/1.73 m^2, *diabetes mellitus* type 2, NT-proBNP > 1307 pg/mL (history of arterial hypertension, dyslipidemia, coro-nary artery disease, previous vascularization, stroke, depression, cancer, obesity).
Conclusion	Significant improvement of parasympathetic and sympathetic activity, and reduction in plasma volume independent of NT-proBNP levels.	Reduction (~50%) in NT-proBNP, along with improvement in left ventricular ejection fraction (> by 1.5%) and diastolic function parameters (> E/e' by 6.8%).

Abbreviations: EMBODY - Effect of Empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: Multi-Center pla-cebo-controlled Double-Blind Randomized Trial; **EMMY** - Impact of EMpagliflozin on Cardiac Function and Biomarkers of Heart Failure in Patients With Acute MYocardial Infarction; **eGFR** - estimated glomerular filtration rate; **NT-proBNP** - N-terminal prohormone of brain natriuretic peptide

of the degree of diastolic dysfunction, as well as a benefit to systolic function. Acute regional diastolic and/or systo-lic dysfunction of the left ventricle is a sign of sudden and prolonged myocardial ischemia and is one of the first steps in the ischemic cascade that leads to cell necrosis and the release of brain natriuretic peptide (BNP). Serum enzyme concentration is determined by the size of the necrosis, that is, the size of the infarct. Therefore, its reduction is rational in order to improve the patient's outcome. Moreover, this study suggested that early treatment with SGLT2 inhibi-tors after major myocardial infarction is mostly beneficial in patients without established DM. The mechanism behind this effect is based on the observation of significantly incre-ased circulating beta-hydroxybutyrate (ketone) levels with empagliflozin therapy in the EMMY clinical study. It has been shown that a significantly increased level of beta-hy-droxybutyrate in the very early phase of myocardial infar-ction significantly increases the function of the left ventricle by blocking inflammatory processes, which improves the pathological remodeling of the heart, and by improving car-diac efficiency, the energy supply to cardiac myocytes is also improved[20].

Significant reductions in the length of hospitalization of patients with heart failure following treatment with SGLT2 inhibitors induced some preclinical studies to investigate the biological pathways responsible for the cardioprotective effects of these drugs. In almost all experimental settings, from single cells to large animal models, with and witho-ut diabetes, reduction on infarct size, cardiac remodeling, and prevention of the development of heart failure after AMI have been observed[23-25]. Several facts support the use of SGLT2 inhibitors in acute myocardial infarction, such as delayed diabetes progression, improved myocardial energy, activation of cardioprotective downstream mechanisms that balance remodeling, antifibrotic and antiapoptotic proces-ses, as well as a direct interaction between cardiomyocytes and SGLT2 inhibitors. Also, preclinical studies have proven a beneficial effect on inflammation through the reduction of interleukin-1, interleukin-6 and tumor necrosis factor-alpha (TNF-α), and on oxidative stress, while preserving glucose oxidation, increasing ketone oxidation and reducing fatty acid oxidation. All these points to the potential benefit of SGLT2 inhibition[26].

The use of empagliflozin before AMI in animal models resulted in an approximately 50% reduction in infarct size. This effect is primarily associated with a decrease in intra-cellular Na^+ and Ca^{2+} in isolated cardiomyocytes[27]. After AMI, treatment with empagliflozin preserved aerobic metaboli-sm through a smaller reduction in myocardial free-fatty acid uptake. Dapagliflozin treatment during MI improved left ventricular ejection fraction and reduced the frequency of arrhythmias, infarct size, and apoptosis rate. These effects

are attributed to mitochondrial protection, attenuation of reactive oxygen species production, and an increase in antiapoptotic proteins.

Considering the results of these experimental studies, it could be concluded that there are factors that can influence the efficacy and safety of SGLT2 inhibition[21], such as changes in hemodynamic stability, cardiac output, intracardiac filling pressure, degree of left ventricular dysfunction, peripheral organ perfusion, renal function, as well as the application of simultaneous therapy, including coronary revascularization.

Conclusion

Early initiation of SGLT2 inhibitor therapy has the potential to improve survival (i.e. outcome) in patients with ACS. Through the effect on the neurohumoral system, through regression of cardiomyocyte necrosis and reperfusion injury, natriuretic effect, through narrowing of afferent arterioles, relief of volume overload, and reduction of intraglomerular pressure. The use of SGLT2 inhibitors in these patients is rational, as it helps preserve both systolic and diastolic left ventricular function and reduces MACE. Although guidelines still do not support the use of these drugs, ongoing and completed clinical studies open the door to the use of SGLT2 in patients with ACS, despite the potential adverse effects of the drug that must be considered when administering it. Optimization of pharmacological treatment of coronary disease, along with optimization of comorbidity treatment, and an individual approach to the patient, along with patient stratification at admission for primary percutaneous coronary intervention as the most optimal therapeutic modality, represents an imperative treatment algorithm for patients with a diagnosis of acute myocardial infarction. Pharmacological optimization of therapy in accordance with the patient's profile, i.e. the choice and dosage of medication in accordance with modern recommendations and the patient's condition, as well as all the characteristics of his disease, including genetic polymorphisms that determine the increased effect or resistance of the drug, should be imperative in the approach to these patients, as well as continuous education of the medical staff. With the above benefits, SGLT2 inhibitors have the potential to be a part of the therapeutic modality in patients with ACS.

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Declaration of interest statement: None

Received: 10. 01. 2023.
Accepted: 02. 02. 2023.
Online: 01. 03. 2023.