


A break in pharmacotherapy with empagliflozin in a patient with heart failure with reduced ejection fraction and hospitalization caused by exacerbation of heart failure

Przerwa w terapii empagliflozyną u pacjenta z niewydolnością serca z obniżoną frakcją wyrzutową i hospitalizacją z powodu zaostrzenia niewydolności serca

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Abstract

A 56 year-old man with severe left ventricular dysfunction was admitted due to exacerbation of chronic heart failure with reduced left ventricular ejection fraction. During hospitalisation, standard heart failure treatment was used, but with a modification of pharmacotherapy to address concurrent conditions including diabetes. Here we discuss this case and the current state of knowledge regarding the beneficial effects of empagliflozin.

Key words: heart failure with reduced ejection fraction, empagliflozin

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Introduction

Guidelines from the European Society of Cardiology (ESC) [1] state that heart failure (HF) is a set of typical secondary symptoms including shortness of breath, swelling of the lower limbs, and reduced tolerance to strain. These symptoms can be accompanied by neck vasodilation, lung crackles, and peripheral oedema caused by disturbances in cardiac structure and/or function, causing reduced cardiac output and/or increased intracardiac pressure at rest and during strain. Symptom intensity is based on the New York Heart Association's classification, an important measure for assessing patients with heart failure, even though it correlates only weakly with most of the parameters relevant to left ventricular function [1]. It is recognised that any exacerbation of symptoms in the NYHA classification is linked to higher risks of hospitalisation and death [2, 3].

Moreover, concurrent conditions can exacerbate symptoms of HF, thus increasing the risk of hospitalisation and death due to worsening HF. According to ESC guidelines, the additional presence of diabetes is linked to reduced physical function and a worse prognosis. Studies by Framingham [4] showed that the risk of HF in a diabetic patient is almost 2.4 times higher in men, and 5 times higher in women, compared to non-diabetic individuals. It was also shown that a 1% increase in glycated haemoglobin causes an 8% increase in the risk of heart failure, irrespective of age, presence of coronary heart disease, blood pressure, or obesity [5].

In addition, the relationship between heart failure and diabetes is a double-edged sword, because diabetic patients are at greater risk of developing heart failure due to processes taking place in the cardiovascular system. Hyperinsulinaemia, hyperglycaemia, acidosis and insulin

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resistance are factors causing heart remodelling by modifying cellular pathways in cardiomyocytes. Two dominant processes in the diabetic heart have been identified. The first is left ventricular (LV) dysfunction caused mostly by the intoxication of cardiomyocytes by the substrates of incorrect metabolic processes taking place in the cell, including storage of free fatty acids, leading to lipidoses of heart cells, altered intra- and extracellular metabolite balance, and cardiomyocyte electrophysiological properties. In this respect, one should also consider modifications to metabolic pathways, mitochondrial dysfunction and oxidative stress, and damage to the vascular endothelium, which can all lead to heart muscle necrosis. The second process is that of chronic inflammation, which is associated with increased collagen synthesis and fibrosis [6].

Diabetic patients commonly have systolic and diastolic dysfunction and arrhythmia. Diabetic polyneuropathy and the involvement of the sympathetic nervous system, along with fibrotic changes in the heart and reduced ejection function, predispose these patients to the development of arrhythmias, including life-threatening ventricular arrhythmias.

Case description

A 56 year-old male was admitted with class III heart failure according to the NYHA, i.e. shortness of breath, oedema of the lower limbs up to the knees, and blood pressure of 135/85 mm Hg. The patient was warm and damp as per Forrester's classification.

Patient history:

- severe systolic dysfunction of the LV;
- implantation of a cardiac resynchronisation therapy defibrillator (CRT-D);
- moderate aortic stenosis;
- chronic coronary heart disease – cardiac infarction with ST-segment elevation in the wall of the lower and right ventricles treated with two unsuccessful attempts at revascularisation of the right coronary artery, complicated by transient third degree atrioventricular block; following the infarction, ST-segment was no longer elevated, and was treated with angioplasty of the circumflex branch of the coronary artery with implantation of two drug-eluting stent (DES) stents;
- arterial hypertension (blood pressure max. 170/90 mm Hg);
- type 2 diabetes currently treated with metformin therapy;
- mixed hyperlipidemia currently treated with statins;
- obesity [body mass index (BMI) 40.56 kg/m², height: 172 cm, body weight: 120 kg], metabolic syndrome;
- paroxysmal atrial fibrillation.

Laboratory studies found significant deviations from the norm in the following parameters: reduced kidney

parameters, increased levels of glucose, triglycerides and N-terminal pro-B-type natriuretic peptide (NT-proBNP), though, due to the patient's obesity, these parameters are consistent with the other symptoms presented by the patient (Table 1 – stay 1).

On admission to the hospital, an electrocardiogram (ECG) found a regular sinus rhythm of 90/min with type atrial synchronous biventricular pacing (AS-BiVP) stimulation, and correct stimulation and sensing was found.

During hospitalisation, another ECG confirmed severe systolic dysfunction of the left ventricle [left ventricular ejection fraction (LVEF) 24%, left ventricular end-diastolic diameter (LVEDd) 65 mm, end-diastolic volume/exhalation volume [EDV/EV] 250/190 mL) with segmental dysfunction of contractility of the lower and back walls and moderate aortic stenosis and impaired contractile function of the enlarged right ventricle [tricuspid annular plane systolic excursion (TAPSE) 16 mm, S' 9 cm/s, right ventricular diameter proximal (RVD prox) 35 mm].

During hospitalisation, the patient received intensive intravenous diuretics and standard therapy for HF was maintained [angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRA)]. The patient's general condition and heart failure symptoms improved. A 6-minute walk test (6-MWT) was conducted, in which the patient achieved 290 m.

A control coronary angiography showed a good response to the stent implanted in the circumflex branch and the amputated right coronary artery, creating collateral circulation. The patient qualified for further conservative treatment.

The patient's MAGIC (Meta-Analysis Global Group in Chronic Heart Failure) prognostic score was found to be serious – 26 points, with 1-year mortality of 17.5% and 3-year mortality of 39.7%. Prior to being discharged, the patient's diabetes treatment was modified with the addition of empagliflozin to metformin.

The patient was discharged to outpatient care on the following medications: dabigatran 2 × 110 mg, atorvastatin 20 mg, bisoprolol 7.5 mg, amiodarone 200 mg, ramipril 5 mg, lercanidipine 10 mg, eplerenone 50 mg, pantoprazole 20 mg, empagliflozin 10 mg, torasemide 10 mg, and metformin 3 × 850 mg.

Two months after hospitalisation, during a follow-up visit at a cardiology clinic, a stable clinical state was observed with a satisfactory (NYHA class II) strain tolerance, and with NT-proBNP of 153 pg/dL. The CRT found a significant reduction in obstruction, corresponding with improved clinical outcomes.

After four months, the patient was once again hospitalised due to an exacerbation of HF, with NT-proBNP of 1,586 pg/mL, and during this stay he was included in a sacubitril/valsartan treatment programme at a dosage

Table 1. Results of basic laboratory studies during consecutive hospitalisations

Parameter	Result			Normal
	Stay 1	Stay 2	Stay 3	
WBC [$\times 10^3/\mu\text{L}$]	7.30	10.57	6.84	4.00–11.00
RBC [$\times 10^6/\mu\text{L}$]	5.32	4.38	4.84	4.20–6.10
Hb [g/dL]	15.9	14.2	15.1	14.0–18.0
TC [mmol/L]	3.83	Not determined	5.07	3.00–5.00
LDL [mmol/L]	1.25	Not determined	2.59	< 1.80
HDL [mmol/L]	0.95	Not determined	1.24	> 1.00
TG [mmol/L]	3.58	Not determined	2.73	< 1.70
Glucose [mg/dL]	8.55	8.28	7.97	4.1–5.5
Creatine [$\mu\text{mol/L}$]	148	150	131.7	59–104.0
eGFR [mL/min/1.73 m ²]	46.5	54.44	67	> 60
Na [mmol/L]	136	141	140.1	136–146
K [mmol/L]	4.38	4.30	4.26	3.5–5.1
AspAT [U/L]	34	Not determined	36.7	0–35
AlAT [U/L]	35	30	28.8	0–45
CRP [mg/L]	2.9	8.48	2.8	0–6.0
TSH [$\mu\text{IU/L}$]	0.672	Not determined	0.588	0.27–4.20
NT-proBNP [pg/mL]	488	Not determined	324.7	< 125
TnT [ng/mL]	Not determined	Not determined	39	< 14

WBC – white blood count; RBC – red blood count; Hb – haemoglobin; TC – total cholesterol; LDL – low-density lipoproteins; HDL – high-density lipoproteins; TG – triglycerides; eGFR – estimated glomerular filtration rate; Na – calcium; K – potassium; AspAT – aspartate aminotransferase; AlAT – alanine aminotransferase; CRP – C-reactive protein; TSH – thyroid-stimulating hormone; NT-proBNP – N-terminal pro-B-type natriuretic peptide; TnT – troponin T

of 97/103 mg. For more than a year he was clinically stable and did not require further hospitalisation due to HF exacerbations.

The next hospitalisation was due to an airway infection, during which his HF worsened. The patient was hospitalised in the regional department for internal medicine due to orthopnea, coughing up yellow-grey fluid over the course of the airway infection, and increasing lower limb oedema. While being admitted, a urine test detected glycosuria, with venous blood glucose levels of 149 mg/dL (Table 1 – stay 2), which was considered to be the result of empagliflozin treatment. Following antibiotic treatment and intravenous diuretics, the patient was discharged with clinical improvements. Empagliflozin treatment was discontinued.

After a visit to a cardiology clinic three months after the previous hospitalisation, due to a notable increase in body weight (around 10 kg), exacerbation of lower limb oedema up to the knees, and worsening of HF up to NYHA Class III/IV, the patient was referred to the hospital with acute heart failure. Results of laboratory studies are shown in Table 1 – stay 3. Full treatment for cardiac failure was given, including intravenous diuretics and levosimendan infusion, resulting in significant clinical improvement, reduced body weight and decreased oedema and breathlessness. Following

discharge, due to a resting heart rate (HR) above 75/min, additional treatment with the beta-blocker ivabradine was prescribed. Glycated haemoglobin was 9.10%, suggestive of unsatisfactory levels of glycaemia in the last three months in the range of 11.8 mmol/L (212 mg/dL).

For this patient, previous non-pharmacological treatments were unfortunately unsuccessful. It should be emphasised that morbid obesity (BMI 40.56 kg/m²) is linked to hyperinsulinemia, leading to the activation of the renin-angiotensin-aldosterone (RAA) system and renewed HF exacerbations. On the other hand, treating this type of patient with insulin, which causes sodium retention with simultaneous decrease of glycosuria, can increase fluid retention and would therefore not be an optimal solution. After the patient became clinically stable during the peri-discharge period, empagliflozin treatment was resumed. In a 6-MWT, the patient achieved a distance of 330 m. The patient was given full information regarding HF and diabetes.

The patient was discharged home with non-pharmacological treatment suggestions and with the following recommendations of pharmacotherapy: dabigatran 2 \times \times 110 mg, sacubitril/valsartan 2 \times 97/103 mg, ivabradine 2 \times 5 mg, atorvastatin 80 mg, bisoprolol 10 mg, amiodarone 200 mg, lercanidipine 10 mg, eplerenone 25 mg,

Table 2. Selected clinical studies on the effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors on cardiovascular risk

Parameter	Name of study					
	EMPA-REG OUTCOME [10, 12]	CVD-REAL 2 [11, 12]	CVD-REAL [12]	EASEL [12]	CANVAS/ /CANVAS-R [12]	DECLARE-TIMI 58 [13]
Type of SGLT2 inhibitor used	Empagliflozin	Dapagliflozin (75%), empagliflozin (9%), ipragliflozin (8%), canagliflozin (4%), tofogliflozin (3%), luseogliflozin (1%)	Canagliflozin (53%), dapagliflozin (42%), empagliflozin (5%)	Canagliflozin (58%), empagliflozin (26%), dapagliflozin (16%)	Canagliflozin	Dapagliflozin
Number of participants	N > 7,000	N > 400,000	N > 300,000	N > 25,000	N > 10,000	N > 17,000
Heart attack	0.87 (0.70–1.09)	0.81 (0.74–0.88)	No data	0.81 (0.64–1.03)	0.89 (0.73–1.09)	0.89 (0.77–1.01)
Stroke	1.18 (0.89–1.56)	0.68 (0.55–0.84)	No data	0.85 (0.66–1.10)	0.87 (0.69–1.09)	1.01 (0.84–1.21)
Mortality	0.68 (0.57–0.82)	0.51 (0.37–0.70)	0.49 (0.41–0.57)	0.57 (0.49–0.66)	0.87 (0.74–1.01)	0.93 (0.82–1.04)
Hospitalisation due to heart failure	0.65 (0.50–0.85)	0.64 (0.50–0.82)	0.61 (0.51–0.73)	0.57 (0.45–0.73)	0.67 (0.52–0.87)	0.73 (0.61–0.88)

pantoprazole 20 mg, empagliflozin 10 mg, furosemide 40 mg, torasemide 20 mg, and metformin 3 × 1,000 mg. On the above treatment, subsequent control check-ups presented a stable clinical picture, with arterial blood pressure of 125/70 mm Hg, fasting glycaemia up to 150 mg/dL, and a reduction in body mass of 5 kg. In an ECG there was a slight improvement in left ventricular systolic function (LVEF 28%) and a reduction in LVEDd to 61 mm. In ergospirometry with a load of 100 W, the patient achieved a VO₂ of 12.74 mL/kg/min, respiratory exchange ratio (RER) 1.16, VO₂ anaerobic threshold (AT) 10.42 mL/kg/min. The current therapy was maintained.

Discussion

We present the case of a patient with heart failure and reduced ejection fraction of the left ventricle (HFrEF) treated according to current recommendations with the newest therapy for HFrEF, including AT₁ receptor antagonists for angiotensin II and neprilysin inhibitor (ARNI, angiotensin receptor-neprilysin inhibitor) and empagliflozin. Following guidelines, empagliflozin has class IIa recommendations with a data reliability level of B, and is recommended for the prevention or delay of HF and increased lifespan.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are among the newest drug classes for the treatment of diabetes. Their mode of action is thought to be linked to the renal tubule excretion of glucose into the urine (glycosuria) by reducing reverse glucose transport. Owing to the regulation of their strength in response to blood glucose concentration, the risk of hypoglycaemia with these drugs is relatively low, which allows for their combination with

practically all groups of antidiabetic drugs. The expected reduction in levels of glycated haemoglobin over the course of using the aforementioned group of drugs is 0.4–0.9 [7]. Due to the mechanism of reverse transport, glycosuria is accompanied in these patients by natriuresis. Because of this, the above medications are characterised by diuretic effects, which lead to reduced circulating blood volume, decreased body mass (reduced over-hydration), reduced arterial blood pressure, and increased haematocrit [8]. Moreover, the above group of drugs causes improvements in abdominal obesity, uric acid levels, and microalbuminuria [9].

A growing number of publications have shown a positive effect of empagliflozin on major adverse cardiac events (MACE – defined as death from cardiovascular causes, non-lethal strokes or cardiac infarctions) and decreased hospitalisations due to HF exacerbations – a result not seen with other commonly used diabetes drug groups.

The EMPA-REG OUTCOME study [10] found a 35% decrease in the risk of hospitalisation due to exacerbated heart failure in the group treated with empagliflozin. Due to the fact that the EMPA-REG OUTCOME study was not dedicated to an HF population, a further study was designed in this patient group to establish the place of empagliflozin in the treatment of HF patients.

The CVD-REAL 2 study [11], comprising over 300,000 patients with type 2 diabetes from six countries, confirmed that the use of drugs from the above group reduces the risk of hospitalisation due to exacerbation of heart failure as well as mortality. According to the authors of the study, a class effect may be possible, as using other SGLT2 inhibitors and not only empagliflozin (making up less than 10%

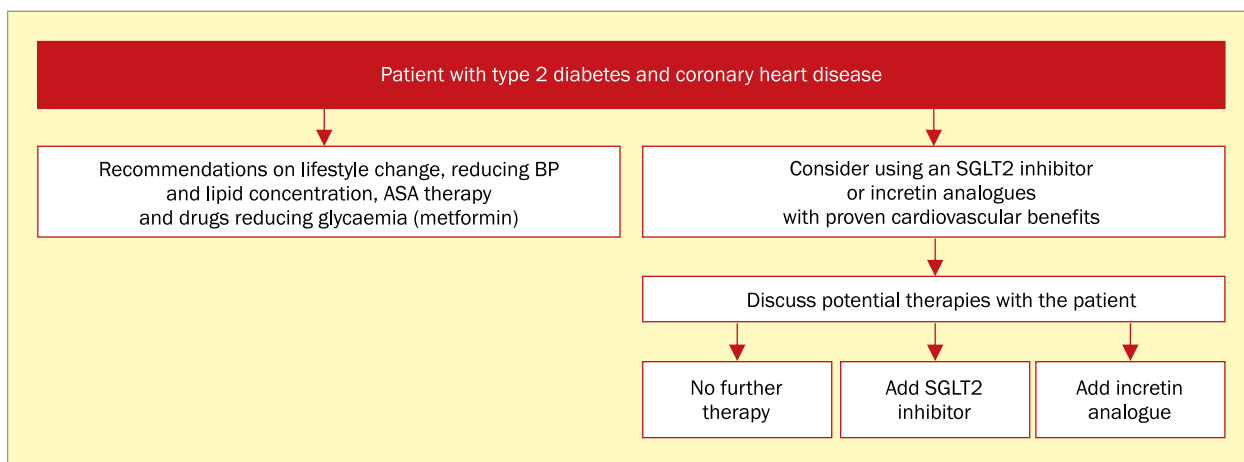


Figure 1. Treatment algorithm for a patient with type 2 diabetes and coronary heart disease (based on [12]); BP – blood pressure; ASA – acetylsalicylic acid; SGLT2 – sodium glucose co-transporter 2

of the drugs from this group in the above study), confirmed the reduction in the number of hospitalisations due to heart failure and a reduction in other adverse cardiac events such as stroke and cardiac infarction observed in the EMPA-REG OUTCOME study. Table 2 shows the most important studies on SGLT2 inhibitors conducted so far [10, 12, 13].

The mechanisms behind such a surprising reduction in major adverse cardiac events by SGLT2 inhibitors are not fully understood. However, it appears obvious that they are not caused only by the effects on SGLT2 or due to controlling levels of glycaemia, owing to (amongst other factors) a low expression of SGLT2 genes on the surface of cardiomyocytes, early action of the above drugs on important endpoints, and the absence of a correlation between levels of glycaemia and glycated haemoglobin during control visits, and a reduction in hospitalisations due to heart failure. Among the significant factors, the effect of these substances on haemostasis in diabetic myocardocytes is often cited. An appropriate Ca^{2+} concentration and rapid changes in its intracellular concentration play a key role in transmitting cellular signals, and is therefore responsible for the appropriate regulation of cardiac rhythm and myocardocyte contraction. The dynamics of calcium levels are affected by sodium levels, which are regulated by sodium-potassium pumps or Na^+/H^+ pumps (NHE). Sodium and calcium haemostasis in diabetic patients is dysregulated. Hypoxia, or the increase in intracellular anaerobic processes, triggers lactic acid production and a consequent decrease of intracellular pH and Na^+/H^+ pump activation, resulting in excessive intracellular sodium [14].

Through a combination of reduced intracellular Na^+ levels and improved mitochondrial calcium transport, and consequently improved myocyte contraction strength, SGLT2 inhibitors lead to improved contractile function in the heart and reduce parasympathetic nervous system

activation. This is important in respect of coronary disease-afflicted hearts with left ventricle ejection fraction impairment, such as in the patient in our case.

According to another theory, the use of SGLT2 inhibitors reduces oxidative stress, which plays an important role in maintaining a chronic inflammatory response, apoptosis and fibrosis in diabetic patients' heart muscle, leading to unfavourable heart remodelling and fatty acid metabolism modification, with a preference for beta-hydroxybutyric acid as a substrate, which is the most energetically favourable compound [14].

It is also worth mentioning the safety profile of empagliflozin. When used as a monotherapy, it carries a low risk of hypoglycaemia. Due to the main hypoglycaemia-inducing effect being associated mainly with osmotic diuresis, use of this drug requires relatively normal kidney function. However, one of the most common complications of glycosuria is urogenital infection, with complications of urinary tract infections such as pyelonephritis or urosepsis occurring with similar frequency in patients taking either empagliflozin or a placebo. In this case, no urinary tract infections were observed over the course of treatment, while body mass reduction and improved glycaemic profile were observed, and the medication itself was well tolerated by the patient. It is also worth mentioning a different complication that is probably related to lipid oxidation pathway alterations, such as ketoacidosis with relatively normal glycaemic levels. However, randomised studies have shown that such complications are rare in patients not requiring insulin therapy [12].

Mechanisms leading to heart failure exacerbations mostly have three causes: increased preload, increased afterload, and decreased myocardocyte contractile ability. According to the current state of knowledge, SGLT2 inhibitors have multi-targeted effects. They decrease afterload

through osmotic diuresis and reduce circulating blood volume. They also influence sodium and calcium ion haemostasis in cells, thus impacting the force and 'quality' of myocardiocyte contractions.

In 2018, a consensus appeared in the US [12] that positioned SGLT2 inhibitors high in the algorithm for treating patients with type 2 diabetes and coronary heart disease. SGLT2 inhibitors were recommended to be considered in addition to lifestyle change education and metformin treatment (Figure 1).

Conclusions

Empagliflozin is a new therapeutic tool for patients with HFrEF with concurrent diabetes. The presented clinical

case of a patient suffering from multiple concurrent conditions implies an important role for empagliflozin in HFrEF therapy, which is demonstrated by the exacerbation of heart failure necessitating hospitalisation in a patient being treated with an optimal standard HFrEF therapy with ARNI when administration of empagliflozin was stopped. Our case demonstrates the importance of the early adoption of novel pharmacotherapies, and highlights the need for expert recommendations in everyday clinical practice.

Conflict(s) of interest

The authors are participating in a clinical trial using empagliflozin.

Streszczenie

Mężczyznę w wieku 56 lat z ciężką dysfunkcją lewej komory przyjęto na oddział z powodu zaostrzenia objawów przewlekłej niewydolności serca z obniżoną frakcją wyrzutową lewej komory. W trakcie hospitalizacji stosowano standardowe leczenie niewydolności serca, ale także modyfikowano terapię chorób współistniejących, w tym cukrzycy. Na podstawie opisu przypadku klinicznego w artykule przedstawiono aktualny stan wiedzy na temat korzystnego wpływu empagliflozyny na układ sercowo-naczyniowy.

Słowa kluczowe: niewydolność krążenia z obniżoną frakcją wyrzutową lewej komory, empagliflozyna

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