REVIEW

Эмпаглифлозин как новая стратегия управления исходами у пациентов с сахарным диабетом 2 типа и высоким кардиоваскулярным риском

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У пациентов с сахарным диабетом 2 типа (СД2) наблюдается повышенный риск развития сердечно-сосудистых осложнений. Хотя гипергликемия способствует развитию и прогрессированию атеросклероза и сердечной недостаточности, существующие до настоящего времени подходы по нормализации уровня глюкозы не оказывали заметного влияния на снижение кардиоваскулярного риска. Ингибиторы натрий-глюкозного котранспортера 2 (SGLT2) типа представляют собой новый класс антигипергликемических препаратов, которые улучшают гликемический контроль благодаря инсулинонезависимому механизму действия, связанному с увеличением экскреции глюкозы с мочой. В обзоре представлен анализ результатов исследования EMPA-REG Outcome, посвященного долгосрочной оценке сердечно-сосудистой безопасности эмпаглифлозина – ингибитора SGLT2. Обсуждаются впечатляющие результаты этого исследования, которые позволяют судить о кардио- и нефропротективных свойствах эмпаглифлозина. В статье приводятся и анализируются существующие в настоящее время гипотезы механизма действия этого сахароснижающего препарата, предопределившего столь выраженное и комплексное влияние на исходы у пациентов с СД2 и высоким кардиоваскулярным риском. Рассматривается место ингибиторов SGLT2 в современных алгоритмах оказания помощи больным СД2, а также роль эмпаглифлозина в комплексном многофакторном управлении СД2.
Ключевые слова: *сахарный диабет 2 типа; хроническая сердечная недостаточность; сердечно-сосудистая смертность; гипергликемия; инсулинорезистентность; факторы риска; эмпаглифлозин*

Empagliflozin as a new management strategy on outcomes in patients with type 2 diabetes mellitus

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Patients with type 2 diabetes mellitus have an increased risk of cardiovascular (CV) complications. Although hyperglycaemia contributes to the pathogenesis of atherosclerosis and heart failure in these patients, glucose-lowering strategies did not have a significant effect on reducing CV risk, particularly in patients with a long duration of type 2 diabetes mellitus and prevalent CV disease (CVD). Sodium-glucose linked transporter-2 (SGLT2) inhibitors are a new class of anti-hyperglycaemic medications that increase glycaemic control via insulin-dependent mechanism of action associated with increased urinary glucose excretion.

In this review, we present an analysis of the Empa-Reg Outcomes investigation, focussed on assessing the CV safety of empagliflozin, an inhibitor of SGLT2. We discuss the impressive results of trials that provide evidence on the cardiac and renal properties of empagliflozin. We present and analyse the current hypothesis on the mechanism of action of glucose-lowering medication, which has such a severe and complex impact on outcomes in patients with type 2 diabetes at high CV risk.
Keywords*: type 2 diabetes mellitus; chronic heart failure; cardiovascular mortality; hyperglycemia; insulin resistance; risk factors; empagliflozin*

For a long time, doctors considered diabetes mellitus (DM) to be an urination disorder, characterized by excessive urination. In the beginning of the 20th century, the special role of pancreatic beta cells in the pathogenesis of type 2 DM (DM2) was revealed; as a result, these cells have become the main target of drug development. However, more recent studies questioned the role of the kidneys in disorders of carbohydrate metabolism. Glucose reabsorption in the kidneys is an evolutionarily established mechanism, aimed at maintaining energy balance and preserving glucose as the main source of energy. Approximately 180 g of glucose is filtered daily by renal glomeruli into the primary urine, and typically 99% of this glucose is complexed with

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sodium ions for reabsorption from the primary urine. Type 1 and 2 sodium/glucose cotransporters are involved in this process and ensure that glucose returns to the bloodstream. When the level of glucose reaches 10–11 mmol/L (the so-called 'renal threshold'), the kidneys fail to reabsorb all of the initially filtered glucose. At the same time, long-term hyperglycaemia, typically observed in cases of decompensated DM, increases the expression and activity of the glucose and sodium transport proteins in the renal tubules, raising the renal threshold and allowing higher amounts of substances to return to the bloodstream. This closes the vicious circle of pathological processes at the level of the kidneys, sustains and further aggravates hyperglycaemia, increases insulin resistance (IR) and beta cell dysfunction, worsens the course of DM2 and hampers adequate metabolic control [1].

Studying new pathogenic mechanisms that underlie chronic hyperglycaemia has led to the development of extremely promising antidiabetic drugs that block renal glucose reabsorption: SGLT2 inhibitors. Not only this mechanism of inhibition of SGLT2 can improve glycaemic control, but also it provides cardio-renal protection in DM2 patients at increased cardiovascular risk. Currently, only one of the drugs from this class—empagliflozin—has this described effect.

The aim of the current review is to analyse existing clinical and experimental data regarding the impact of empagliflozin on the cardiovascular system, the kidneys and the risk factors for cardiovascular complications (CVCs).

Risk of CVCs and chronic kidney disease in patients with DM2

Patients with DM2 have an increased risk of cardiovascular diseases (CVDs), the most serious of which are- myocardial infarction (MI), stroke and chronic heart failure (CHF) [2]. The latest data regarding the impact of risk factors on CVD prognosis suggest that DM2 is still associated with an increased risk of death from CVCs, and the combination of DM2 and prior MI is associated with a fourfold increase in cardiovascular risk compared to patients without DM2 or MI [3].

Today, there is no convincing evidence that glycaemic control itself has a significant impact on cardiovascular risk. During the last decade, different studies have assessed the effect of glucose-lowering therapy on CVD outcomes. The largest of them—ADVANCE, ACCORD, VADT (conducted in patients with a long history of DM2 and either CVD or risk factors for CVD)—demonstrated no difference between a more intensive glucose-lowering therapy and standard treatment schemes in terms of macrovascular complications. Intensive glucose-lowering strategies did not show greater efficacy; moreover, they were found to increase cardiovascular risk (like in the ACCORD study) [4].

Perhaps this phenomenon can be attributed to the fact that DM2 is associated with multiple metabolic disorders, including obesity, dyslipidaemia and arterial hypertension, and each of them is an independent risk factor for CVCs [5]. These metabolic disorders, also called metabolic syndrome, are based on IR of varying severity, which significantly increases cardiovascular risk in patients with DM2 [6]. Thus, overweight people with IR only (without DM2) also have increased cardiovascular risk, similar to patients with DM2 [7]. This fact suggests that IR, but not hyperglycaemia, is a key factor for CVD development in diabetic patients. Moreover, lowering blood pressure (BP) and improving the lipid profile have a significantly greater impact on reducing cardiovascular risk than normalizing carbohydrate metabolism [8]. It is thus not surprising that antidiabetic agents, such as insulin [9], sulfonylureas [10] and dipeptidyl peptidase-4 inhibitors, which are only characterized by their glucose-lowering activity, confer no significant benefits in terms of cardiovascular outcomes compared to placebo. This finding is obviously due to the absence of nonglycaemic effects, which can influence IR and other metabolic disorders. At the same time, pioglitazone is associated with a decreased (by 16%, $P = 0.025$) risk of composite endpoints (cardiovascular death, non-fatal MI and stroke) compared to placebo in the prospective clinical trial PRO-ACTIVE [11]. The most convincing explanation for this result is the ability of pioglitazone to improve insulin sensitivity [12] and affect various components of metabolic syndrome (decreases in BP and atherogenic cholesterol levels), which was confirmed by the reduction in cardiovascular risk observed for DM2 patients in the study, regardless of the hypoglycaemic action of the drug [11].

After CVD, diabetic nephropathy (DN) is the second leading cause of mortality among DM2 patients. Published data suggest that chronic kidney disease (CKD), which develops as a result of DN, is an important independent risk factor for CVD. Population-based studies have demonstrated that the combination of CKD and DM2 significantly increases the probability of CVCs. The results of the ACCOMPLISH, ALTITUDE, SHARP, ADVANCE, ROADMAP, CARRESS-HF and other studies have allowed CKD to be considered equivalent to coronary heart disease, taking into account the risk of complications [13].

A glomerular filtration rate (GFR) less than 60 mL/min/1.73 m2 was recognised as an independent risk factor for stroke in a meta-analysis of 21 studies. Additionally, albuminuria is a risk factor for death from CVD. According to these data, patients with a GFR less than 60 mL/min/1.73 m2 and simultaneous macroalbuminuria have the highest cardiovascular risk. Furthermore, a strong correlation was identified between CKD and atherosclerosis of the peripheral arteries, which commonly manifests in diabetic patients. Therefore, numerous studies have demonstrated that DN promotes CVD development, since it aggravates cardiovascular risk factors, such as arterial hypertension, dyslipidaemia, anaemia, endothelial dysfunction, vascular inflammation, etc.

It is worth mentioning that controlling glycaemia, lipid profile parameters and BP using drugs affecting the renin-

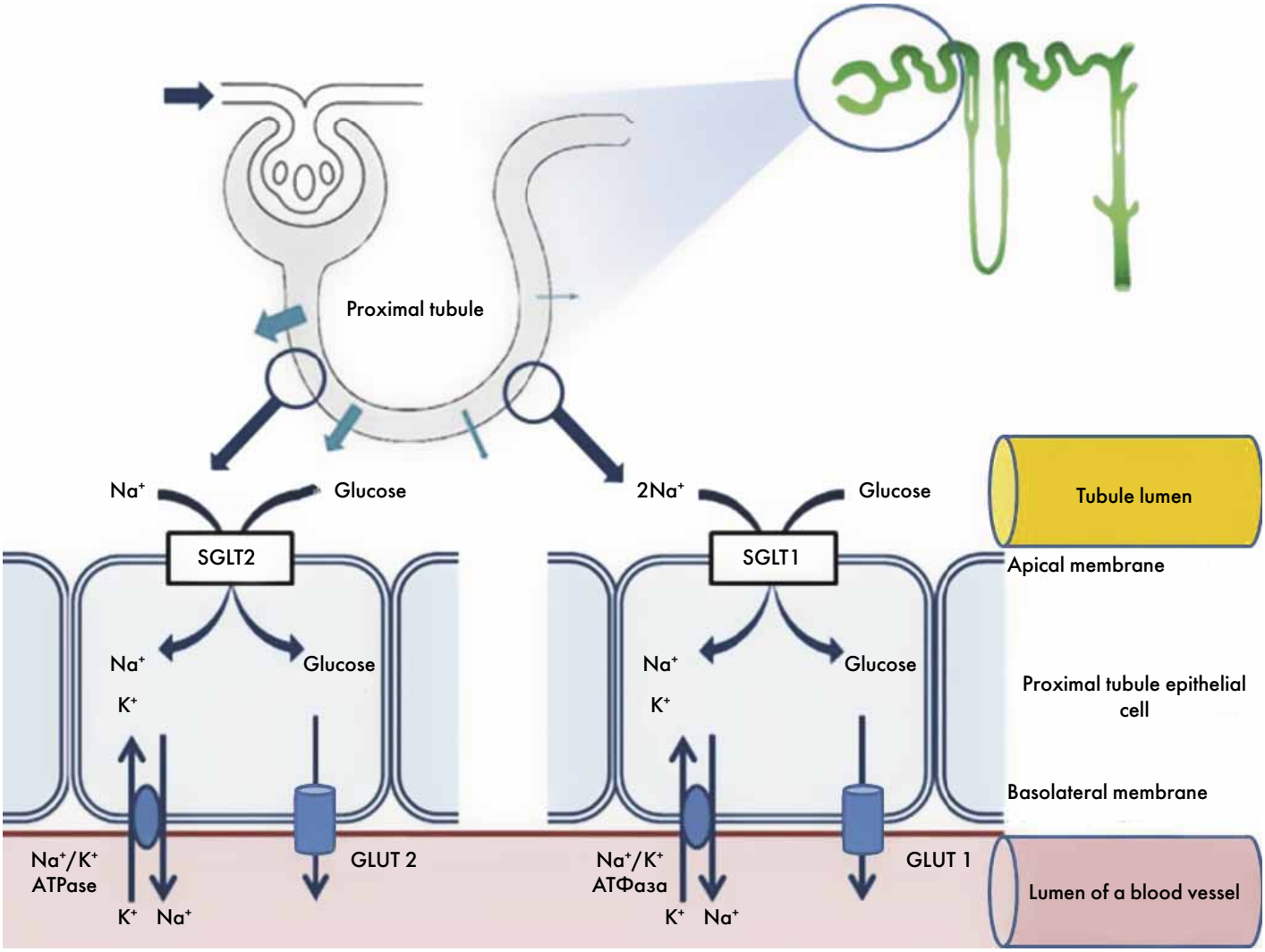


Fig. 1. Glucose and sodium transport in the proximal tubule.

angiotensin-aldosterone system (RAAS) can slow the progression, but is unable to prevent, chronic renal failure (CRF) [14].

Thus, there is an urgent (although not yet realized) need for additional therapeutic measures to improve the prognosis of DM2 patients with an extremely high risk of CVCs.

Patients in this category were included in the recently completed EMPA-REG Outcome study, which investigated the effect of the SGLT2 inhibitor empagliflozin on CVD outcomes, compared to placebo.

The mechanism of glucose reabsorption and inhibition of sodium/glucose cotransporter 2 by empagliflozin

As glucose is the main substrate for energy metabolism, there is a mechanism implemented by the kidneys that preserves glucose, which involves glucose reabsorption from the primary urine and its return to the bloodstream. A secondary active transport mechanism works in the S1 segment of the proximal convoluted tubule; this process is mediated by SGLT2 (Fig. 1).

SGLT2 has a low affinity but high capacity for sodium and glucose; it can simultaneously transport sodium ions (Na+) and glucose in the same direction at a 1:1 ratio. While passing through the apical membranes of proximal tubule epithelial cells, Na+ creates an electrochemical gradient that allows glucose to passively enter the cell. SGLT2 ensures the reabsorption of approximately 90% of the initially filtered glucose by the proximal tubule. The S3 segment of the proximal straight tubule contains another cotransporter, SGLT1, which is also located on the apical membrane, has low capacity but high affinity for sodium and glucose and transports glucose and Na+ at a 1:2 ratio. SGLT1 ensures the reabsorption of the remaining glucose, so secondary urine contains only one-thousandth of the initially filtered glucose. Glucose transport from the tubule lumen into peritubular capillaries is passive. It is carried out by the GLUT2 transporter located on the basolateral membrane and is driven by a chemical glucose gradient (so-called 'facilitated diffusion'). Glucose reabsorption occurs mainly at the beginning of the proximal tubule. If the amount of filtered glucose increases, along with the saturation of cotransporters at the beginning of the proximal tubule, then distal segments of the proximal

tubule become involved in the reabsorption process; thus, glucose is almost completely reabsorbed [15].

A universal sodium pump (the sodium/potassium adenosine triphosphatase, Na+/K+ ATPase), located on the basolateral membrane, plays an important role in pumping Na+ out of cells. This active transport of Na+ helps to maintain its low intracellular concentration, which is crucial for passive glucose transport from the renal tubule into cells. Moreover, this mechanism has great importance for Na+ transfer from the tubules into the bloodstream (i.e. its reabsorption).

Empagliflozin is a reversible, highly potent, highly selective, competitive inhibitor of SGLT2. Special pharmacological properties of empagliflozin ensure good clinical outcomes in patients with DM2. Even a small concentration of the substance (1.3 nmol) is sufficient to inhibit 50% of SGLT2 activity. Empagliflozin increases natriuresis, leads to excretion of up to 80 g of glucose per day, reduces fasting glucose levels by up to 2.01 mmol/L and decreases HbA1 levels by up to 0.85%.

Empagliflozin has a prolonged elimination half-life (10–19 h); its pharmacokinetics are unaffected by food. Its once-daily administration (at a dose of 10 or 25 mg, with or without a meal) is a substantial benefit, ensuring patient compliance. Empagliflozin does not inhibit, inactivate or induce CYP450 isoenzymes, allowing its simultaneous use with other drugs. There are no active metabolites. The drug is excreted by the kidneys and the liver equally [16].

EMPA-Reg outcome study

The impressive results of an international, multicentre study (EMPA-REG Outcome) were presented in September 2015. This study was devoted to the assessment of the impact of empagliflozin (oral administration, at a dose of 10 or 25 mg) on CVD incidence and mortality in patients with DM2 and high cardiovascular risk, receiving standard therapy.

A total of 590 clinical sites from 42 countries (including Europe, North and Latin America, Asia and Africa) participated in the study. Inclusion criteria were as follows: patients over 18 years of age with DM2, a BMI less than or equal to 45 kg/m2, a HbA1c of 7%–10%, an eGFR greater than or equal to 30 mL/min/1.73 m2 (MDRD) and at least one confirmed CVD (coronary heart disease, multiple lesions of the coronary arteries and lesion of one coronary artery, history of coronary artery bypass grafting, MI, stroke or peripheral arterial disease; heart failure was considered separately).

A total of 7,020 enrolled patients (mean age, 63 years) were randomized into three groups to receive placebo (n = 2,333), 10 mg empagliflozin (n = 2,345) or 25 mg empagliflozin (n = 2,342) once daily. The comparative efficacy of two empagliflozin doses and placebo, in addition to standard therapy, was evaluated. Standard therapy included hypoglycaemic agents (metformin, sulfonylureas, thiazolidinediones and insulin) and adequate treatment of CVDs (using antihypertensive, antiplatelet or anticoagulant lipid-lowering drugs).

The trial was continued until 691 primary outcome events occurred (including cardiovascular death, non-fatal MI or non-fatal stroke). Median treatment duration was 2.6 years; median follow-up time was 3.1 years.

The secondary composite endpoint included all the components of the primary composite endpoint with the addition of hospitalisation for unstable angina. The following additional endpoints were also evaluated: frequency of hospitalisations for heart failure (HF), unstable angina, frequency of non-fatal MI, non-fatal stroke, transient ischaemic attack and coronary revascularisation.

The frequency of confirmed hypoglycaemic adverse events, urinary tract infections, genital infections, hypovolemic events, acute renal failure, bone fracture, diabetic ketoacidosis and thromboembolic events were also assessed [17].

The main effects of empagliflozin on cardiovascular outcomes

Multiple effects of empagliflozin were, for the first time, demonstrated by the results of the EMPA-REG Outcome study. These effects included a 38% reduction in the relative risk (RR) of cardiovascular mortality compared to placebo, a 32% reduction in the RR of overall mortality, a 14% reduction in the RR of a primary outcome event (cardiovascular death, non-fatal MI, non-fatal cerebral stroke) and a 35% reduction in the frequency of hospitalisation for CHF compared to placebo [17] (Table 1).

There were no significant differences in the frequency of secondary outcome events between the empagliflozin group and the placebo group. The assessment of additional endpoints also did not show any differences between the groups.

Particular attention should be paid to several key aspects of the study results:

1. There was a paradoxical lack of correlation between the components of the primary composite endpoint. Indeed, the use of empagliflozin ensured a statistically significant 2.2% reduction of absolute risk (AR) of cardiovascular death ($P < 0.001$). Nevertheless, the reduction of AR of non-fatal MI was only 0.6% and was not significant ($P = 0.23$). AR of a stroke slightly increased (0.5%), but after the completion of empagliflozin therapy, the difference was not significant.
2. In contrast to previously used interventions to lower LDL cholesterol and BP, which resulted in a long-term decline in the rate of cardiovascular death, the current study showed an early divergence in cardiovascular outcome curves in the empagliflozin and placebo groups; the differences became statistically significant beginning in the second or third month of treatment.
3. The study revealed an additional advantage of the drug in terms of its impact on cardiovascular outcomes in patients at high cardiovascular risk, who were already receiving

Table 1

The main cardiovascular outcomes in the EMPA-REG Outcome study

Cardiovascular Events	Placebo (n = 2,333) No. of Events (%)	Empagliflozin (n = 4,687) No. of Events (%)	HR (95% CI)	P
Cardiovascular death, non-fatal MI, non-fatal stroke: primary composite endpoint	282 (12.1)	490 (10.5)	0.86 (0.74-0.99)	0.04
Cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalisation for unstable angina: secondary composite endpoint	333(14.3)	599(12.8)	0.89 (0.78-1.01)	0.08
All-cause death	194(8.3)	269 (5.7)	0.68 (0.57-0.82)	<0.001
Cardiovascular death	137 (5.9)	172 (3.7)	0.62 (0.49-0.77)	<0.001
Hospitalisation for HF	95 (4.1)	126 (2.7)	0.65 (0.5-0.85)	0.002
Hospitalisation for HF or cardiovascular death, except for fatal stroke	198 (8.5)	265 (5.7)	0.66 (0.55-0.79)	<0.001

special therapy for cardiometabolic disorders to decrease the risk of cardiovascular death [statins, aspirin, RAAS inhibitors (ACE inhibitors or sartans), beta-blockers, etc.].

4. The use of empagliflozin resulted in a decline in the number of deaths and hospitalisations for HF; such beneficial effects were observed during the entire study period and after the completion of treatment (up to 3.1 years).
5. Both empagliflozin doses (10 mg and 25 mg) had similar impacts on cardiovascular outcomes, demonstrating no dose-dependent effects.

The impact of SGLT2 inhibition on cardiovascular risk factors and metabolic parameters

A. Declines in the levels of HbA1c, insulin and IR

According to its mechanism of action, SGLT2 inhibition leads to chronic glycosuria and lowers glycaemia in patients with DM2. A decline in the levels of glycated haemoglobin (–0.5% in the 10 mg group and –0.6% in the 25 mg group) was observed after 12 weeks of treatment with empagliflozin in the EMPA-REG Outcome study [17]. Thus, a dose-dependent decrease in glycaemia was observed. (By the end of treatment with empagliflozin, the difference in HbA1c levels declined due to corrections of the background antihyperglycaemic therapy permitted by the study design.) At the same time, SGLT2 inhibitors have a glucose-dependent mechanism of action, implying a very low risk of hypoglycaemia. Various studies suggest that SGLT2 inhibitors can improve the utilisation of glucose by skeletal muscle, probably due to decreases in glucose toxicity and the volume of adipose tissue. Moreover, the reduction in glycaemia itself is accompanied by a decrease in insulin secretion. Both mechanisms stimulate a decline in IR and insulin levels in patients with DM2, which positively impact many organs, including the kidneys [18, 19]. Several studies have shown that hyperinsulinaemia, through the activation of phosphatidylinositol-3 kinase, lowers nitric oxide synthesis, which impairs the microcirculation and leads to the progression of microangiopathy [20]. Insulin, acting through extracellular pathways, stimulates pathological responses of blood vessels, angiogenesis, fibrogenesis and other processes that affect the progression of renal disease [21].

Experimental data suggest that SGLT2 inhibitors decrease the secretion of glucagon by pancreatic alpha cells. This finding was confirmed by increased plasma levels of glucagon in DM2 patients in response to therapy with SGLT2 inhibitors [18, 19], which can boost endogenous glucose production in such patients [22].

However, the positive glucose-lowering effects of SGLT2 inhibitors on carbohydrate metabolism are likely to eliminate the negative consequences of glucagon-dependent increases in glucose levels.

It is necessary to stress the metabolic advantages of this class of drugs in clinical practise, taking into account the insulin-independent hypoglycaemic effects of the SGLT inhibitors. Such drugs can be administered regardless of DM2 duration and beta cell function and can be combined with other antihyperglycaemic agents because their mechanism of action differs significantly from that of other available classes of drugs.

B. Weight loss

SGLT2 inhibition causes glycosuria, which leads to negative energy balance, because the excretion of 50–80 g of glucose per day is equivalent to reducing daily nutritional intake by 200–300 kcal. Furthermore, this inhibition also ensures a decline in the level of insulin (known to have an anabolic effect) and intensifies the oxidative metabolism of adipose tissue [23].

As a result, DM2 patients have a gradual (over several months) decrease in body weight by 2–3 kg, on average, with subsequent stabilisation of body weight after 3–6 months [24]. An average weight loss of 2 kg, accompanied by a decrease in waist circumference by 2 cm after empagliflozin cessation, was observed in the participants of the EMPA-REG Outcome study.

The impact of SGLT2 inhibitors on visceral fat is particularly interesting, because its presence is associated with an increased risk of DM2, CVCs and death [25]. Daily empagliflozin, at a dose of 25 mg, facilitated a decrease in body weight by 3.1 kg and waist circumference by 2.1 cm after 104 weeks of therapy. In this case, both subcutaneous and visceral fat were involved in the decrease

of body weight, which was proven using dual energy X-ray absorptiometry, CT and MRI [26].

Studies exploring the dynamics of adipokines in response to anti-SGLT2 therapy are very rare. One study described a minor decrease in the levels of adiponectin and leptin after 24 weeks of daily dapagliflozin therapy, at a dose of 10 mg [27].

C. Declines in BP levels

The reduction of BP is another effect of all SGLT2 inhibitors, in addition to glucose control and decreases in body weight. Numerous studies have revealed reductions in systolic BP (BPsyst) in the range of 3–5 mm Hg, diastolic BP (BPdiast) in the range of 2–3 mm Hg, pulse pressure and mean arterial pressure by SGLT2 inhibitors [28]. The decreases of 4 mm Hg in BPsyst and 2 mm Hg in BPdiast in response to empagliflozin therapy were documented in the EMPA-REG Outcome study. Interestingly, there was no increase in heart rate (HR), which resulted in a decreased doubled product (HR multiplied by BPsyst), suggesting that the absence of the compensatory reflex activation of the sympathetic nervous system, as well as the existence of SGLT2 inhibitors, impact some mediators of arterial stiffness.

Empagliflozin also reduces BPsyst (by 2.7 mm Hg, on average) in young patients with uncomplicated DM1 [29]. It was noted that the drug decreases pulse wave velocities of both carotid and radial arteries without affecting reflex sympathomimetic activity. It is noteworthy that empagliflozin causes a hypotensive effect, even in healthy people without diabetes [30].

Studies evaluating daily BP profiles have revealed that empagliflozin lowers BPsyst during the entire day, but at night, its hypotensive effects are slightly lower [31]. Several reasons may explain this result: declines in glycosuria and natriuresis at night with a lack of food; sodium redistribution in sectors and systemic circulation at night, which reduces the effectiveness of a volume-dependent, BP-lowering mechanism; and a fall in renal blood flow and/or GFR due to a horizontal body position during sleep.

D. Impacts on lipid profiles

In terms of lipid profiles, SGLT2 inhibitors slightly increase both LDL and HDL cholesterol levels with a simultaneous small reduction in triglyceride levels. Empagliflozin, at a dose of 10 mg for 24 weeks, raises both HDL cholesterol (+0.08 mmol/L) and LDL cholesterol (+0.07 mmol/L) levels and lowers triglyceride levels (-0.11 mmol/L) [17]. The mechanism underlying these changes is not yet clarified but can be attributed to direct impacts on lipoprotein particle metabolism as well as on the reduction of plasma volume and increased blood thickening due to the diuretic effects of SGLT2 inhibitors [32].

E. Declines in uric acid levels

SGLT2 inhibitors enhance uric acid excretion and reduce its concentration in the plasma by 10%–15%; these effects account for approximately 24 mkmol/L in the EMPA-REG Outcome study.

For a long time, hyperuricaemia was considered to be a component of metabolic syndrome; furthermore, it was associated with an increased incidence of CVDs [33], although the causal relationship between these associations remains controversial. Nonetheless, the results of studies, both in experimental models and humans, suggest that increased levels of uric acid in the plasma can cause arterial hypertension, endothelial cell dysfunction in blood vessels, congestive HF and impaired kidney function [34].

Although such rapid improvements in cardiovascular outcomes can hardly be explained by decreases in uric acid levels by empagliflozin, these effects may play a role in the further divergence of cardiovascular mortality curves seen in the empagliflozin and placebo groups over time; it may also slow the progression of DN.

It is for these reasons that researchers are now particularly interested in exploring the mechanisms underlying uric acid elimination and uricaemia lowering that are mediated by SGLT2 inhibitors. Recent studies have shown that these effects are very likely induced by GLUT9 (isoform 2), located in the proximal tubule, which is responsible for glucose transfer from the primary urine and the simultaneous return of uric acid into the tubule lumen [35] (Fig. 2). The increase in glycosuria by SGLT2 inhibition presumably leads to more intensive glucose reabsorption by GLUT9, which is accompanied by elevated uric acid excretion.

F. Impacts on the myocardium

Experimental data in obese mice with DM2 showed that empagliflozin leads to positive changes in myocardial fibrosis, myocardial inflammation, macrophage infiltration and narrowing of the coronary arteries. These findings suggest that the action of this drug is not limited to mediating effects on the heart indirectly but is likely to have direct impacts as well [36].

According to some authors, the action of SGLT2 inhibitors on the heart involves both direct and indirect effects on improvements in myocardial energetics and antiarrhythmic effects. SGLT1 expression was identified in cardiomyocytes. SGLT2 inhibition in the kidneys leads to glucose excretion into the urine, simultaneously enhancing compensatory glucose reabsorption by SGLT1. Since this reaction is humourally mediated, we can presume that SGLT1 activity increases in the heart. This activation, in turn, stimulates a shift from beta-oxidation of free fatty acids to enhanced glucose metabolism, ensuring a positive impact on myocardial function and reducing the arrhythmogenic effects of free fatty acid metabolites [37].

The impact of SGLT2 inhibition on renal outcomes

Studying renal outcomes in patients with DM2 was a separate component of the EMPA-REG Outcome study. Since kidneys are the main target organ of empagliflozin, this parameter was crucial for the assessment of drug effects.

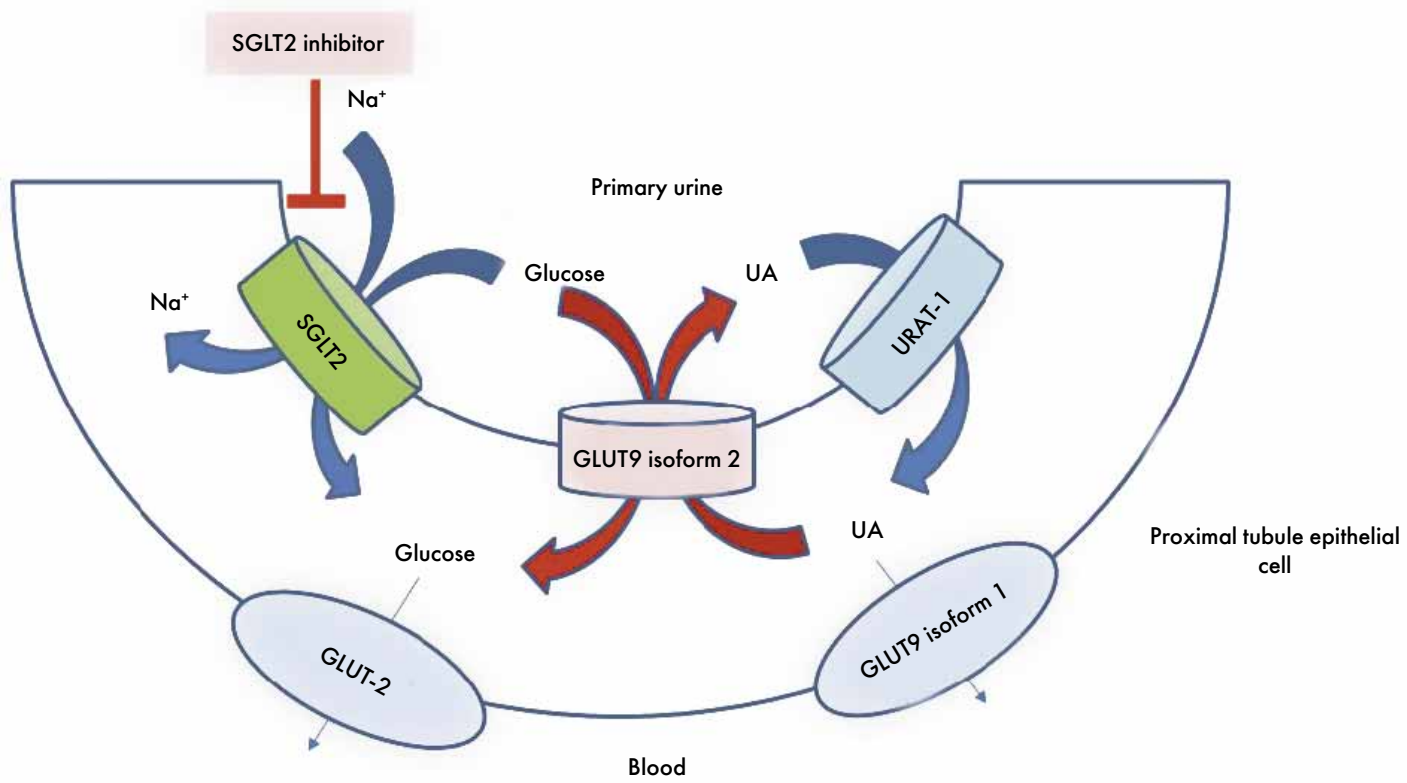


Fig. 2. Hypothesized mechanism of elevated uric acid excretion by SGLT2 inhibition (adopted from [35]).

Predetermined surrogate markers of renal events were evaluated within this component of the study; they included incident or worsening nephropathy (determined by the incidence or progression of macroalbuminuria), doubling of serum creatinine levels accompanied by a GFR less than or equal to 45 mL/min/1.73 m2, initiation of renal replacement therapy or death from renal disease [38]. The following parameters were additionally evaluated within the study: separate components of incident or worsening nephropathy, incident albuminuria in patients with a normal albumin level in the urine at baseline and composite endpoints of incident or worsening nephropathy and cardiovascular death. The study population included patients with a GFR greater than or equal to 30 mL/min/1.73 m2, since a lower GFR is associated with both the significantly decreased inhibition of SGLT2 and the neutralisation of the glucose-lowering effects of empagliflozin.

The estimation of changes in renal function over time in patients with DM2 was among the most important objectives of the EMPA-REG Outcome study. Study results showed a steady decline in mean GFR, calculated using the CKD-EPI formula (Fig. 3).

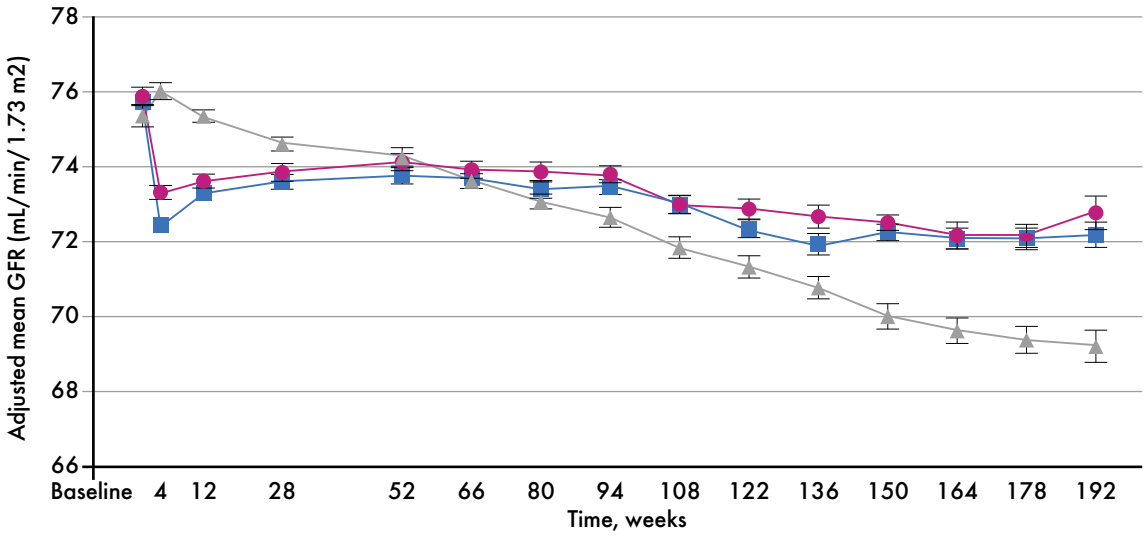
During the first four weeks of the study, there was a short-term decrease in the GFR in both the 10 mg and 25 mg empagliflozin groups, with mean weekly decreases of 0.62 ± 0.04 mL/min/1.73 m2 and 0.82 ± 0.04 mL/min/1.73 m2, respectively [38]. A small increase in the GFR of 0.01 ± 0.04 mL/min/1.73 m2 was observed in the placebo group ($P < 0.001$ for both groups, compared with placebo). However, until the last week of follow up, the GFR remained stable in both empagliflozin groups and declined steadily in the placebo group, with adjusted estimates of annual decreases of 0.19 ± 0.11 mL/min/1.73 m2 in both empagliflozin groups compared with a decrease of 1.67 ± 0.13 mL/min/1.73 m2 in the placebo group ($P < 0.001$ for both groups, compared with placebo). The period after empagliflozin cessation is particularly interesting, because the GFR, in the absence of drug, increased in both empagliflozin groups, with adjusted estimates for weekly increases of 0.48 ± 0.04 mL/min/1.73 m2 in the 10 mg group and 0.55 ± 0.4 mL/min/1.73 m2 in the 25 mg group compared with a small decrease (0.04 ± 0.04 mL/min/1.73 m2) in the placebo group ($P < 0.001$ for both groups, compared with placebo).

By the end of study, the adjusted mean difference in the GFR change from baseline was 4.5 mL/min/1.73 m2 in the placebo group and only 2.7 mL/min/1.73 m2 in the empagliflozin groups ($P < 0.001$ compared to placebo).

The renal outcomes, like the cardiovascular outcomes, were largely unexpected (Table 2).

Patients in the empagliflozin groups were found to have a significantly lower risk of progression to macroalbuminuria or clinically relevant renal outcomes, such as doubling of the serum creatinine level and initiation of renal replacement therapy, than those in the placebo group. Thus, the study results allow us to confidently attribute empagliflozin actions to nephroprotective effects.

These results were confirmed by a number of experimental studies demonstrating that SGLT2 inhibition significantly reduces kidney lesions. Studies using experimental animal models of DM (types 1 and



Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

Fig. 3. Changes in mean GFR during treatment with empagliflozin compared with placebo in the EMPA-REG Outcome study.

2) showed that SGLT2 inhibition promoted a decrease in albuminuria by approximately 30% [39]. Notably, the use of empagliflozin in mice with DM2 decreased albuminuria, regardless of BP or extent of hyperglycaemia [40]. Empagliflozin lowered intraglomerular pressure by approximately 6–8 mm Hg in patients with DM1 and hyperfiltration [41].

Therapy with phlorizin (a non-selective inhibitor of SGLT1/2) in experimental DM also caused reductions of both hyperfiltration and macroalbuminuria [42].

Other SGTL2 inhibitors—dapagliflozin and canagliflozin—also caused short-term (during the first 3–6 weeks of treatment), insignificant GFR depression, followed by a period of stable renal function for 52–104 weeks, which was accompanied by a similar decrease in both micro- and macroalbuminuria [43, 44]. In one study, dapagliflozin demonstrated no significant effects on HbA1c after 24 weeks of therapy in patients with stage 3 CKD but decreased albuminuria, BP and body weight [43].

Therefore, existing experimental and clinical data suggest that SGLT2 inhibition can reduce hyperfiltration, glomerular hypertension and albuminuria.

Hypothesis of the empagliflozin nephroprotective effect

Studies over the last decade have demonstrated that renal function impairment and albuminuria progression are likely to be different, but interconnected, manifestations of DN rather than two consecutive stages of the same process. Renal function impairment and increased albumin excretion can arise, progress and disappear under the influence of different factors, but they don't always occur in parallel [45].

Increased GFR and intraglomerular pressure, induced by chronic hyperglycaemia, play an important role in the pathogenesis of DN. A GFR greater than 135 mL/min/1.73 m2 is usually defined as glomerular hyperfiltration and is associated with early stage DN. Subsequent declines in the GFR, along with a gradual decrease in the total number of functioning nephrons, further exacerbate hyperfiltration at the single-nephron level. It was experimentally established that for a single nephron, hyperfiltration is a risk factor for DN progression and can be used as a marker of intraglomerular hypertension, which, in turn, causes mechanical lesions in glomerulus-surrounding structures, induces collagen overproduction and its accumulation in the mesangium, initiates sclerotic processes and alters the architecture and permeability of the glomerular basal membrane.

The fact that SGLT2 inhibition improves renal function and reduces albuminuria can be explained by several mechanisms.

The first mechanism appears to be associated with an intrarenal haemodynamic effect, connected with a decrease in nephron hyperfiltration, which indirectly indicates the lowering of intraglomerular hypertension [46].

In the absence of disorders in carbohydrate metabolism, SGLT2 reabsorbs approximately 5% of renal Na+. However, under conditions of hyperglycaemia, the expression levels of SGLT2 and SGLT1 are increased by 36% and 20%, respectively, ensuring a more effective reabsorption of glucose [47, 48]. As soon as these cotransporters simultaneous coordinate glucose and Na+ transport, this increase in SGLT1/2 activity is realized by the significant increase in Na+ reabsorption, accounting for approximately 14% of the total Na+ in the organism [47, 48]. This finding implies a decrease in the delivery of

Table 2

Main renal outcomes in the EMPA-REG Outcome study (adopted from [38]).

Surrogate Markers of Renal Events	Placebo No. of Events/ No. of Patients	Empagliflozin No. of Events/No. of Patients	HR (95% CI)	P
Incident or worsening nephropathy or cardiovascular death	497/2102 (23.6%)	675/4179 (16.2%)	0.61 (0.55-0.69)	<0.001
Incident or worsening nephropathy	388/2061 (18.8%)	525/4124 (12.7%)	0.61 (0.53-0.7)	<0.001
Progression of macroalbuminuria	330/2033 (16.2%)	459/4091 (11.2%)	0.62 (0.54-0.72)	<0.001
Doubling of serum creatinine level accompanied by a GFR ≤ 45 mL/min/1.73 m2	60/2333 (2.6%)	70/4645 (1.5%)	0.56 (0.39-0.79)	<0.001
Initiation of renal replacement therapy	14/2333 (0.6%)	13/4687 (0.3%)	0.45 (0.21-0.97)	0.04
Doubling of serum creatinine level accompanied by a GFR ≤ 45 mL/min/1.73 m2, initiation of renal replacement therapy or death from renal disease	71/2323 (3.1%)	81/4645 (1.7%)	0.54 (0.4-0.75)	<0.001
Incident albuminuria in patients with a normal albuminuria at baseline	703/1374 (51.2%)	1430/2779 (51.5%)	0.95 (0.87-1.04)	0.25

Na+ from the distal tubule to the macula densa, which is a kind of sensor of fluid composition and flow rate [49] (Fig. 4). According to the tubular hypothesis of hyperfiltration, the decline in NaCl concentration in the macula densa is erroneously estimated by the juxtaglomerular apparatus as a reduction in circulating blood volume (BV). This condition requires increased renal blood flow, which is achieved through a tubuloglomerular feedback mechanism via afferent arteriole vasodilatation [49]. This vasodilatation increases intraglomerular pressure and the GFR, which lead to the development of intraglomerular hypertension and hyperfiltration by adaptive mechanisms.

SGLT2 inhibition increases natriuresis, thus causing increased Na+ delivery to the macula densa. Elevated Na+ levels activate adenosine-dependent pathways, recovering and triggering a tubuloglomerular feedback mechanism and leading to the constriction of the afferent arteriole in the glomerulus. As a result, intraglomerular hypertension and GFR both decrease [50]. This particularly rapid decline in hyperfiltration after the initiation of empagliflozin therapy is likely the reason for the initial drop in the GFR in the EMPA-REG Outcome study; the decrease in albuminuria is likely caused by the decrease of intraglomerular hypertension.

The second mechanism by which empagliflozin influences renal outcomes can probably be attributed to its systemic vascular effects. SGLT2 inhibition decreases BP and arterial wall stiffness, and these factors are associated with nephroprotection [51]. Additionally, these factors contributed significantly to empagliflozin's effects on haemodynamics in the EMPA-REG Outcome study. However, these effects cannot be explained solely by the proper control of arterial hypertension in these patients. One study of DM1 patients demonstrated a decline in hyperfiltration by approximately 20% and a reduction in BP by 3 mm Hg (which accounted for only a 3% reduction), because of the effects on haemodynamics by SGLT2 inhibition [52]. Therefore, the systemic vascular effects of empagliflozin are beneficial for the kidneys, ensuring declines in intraglomerular pressure and albuminuria; however, this mechanism is not of great importance.

The third mechanism of renal protection may be associated with the direct impact of empagliflozin on inflammatory processes, because inflammation, fibrosis and oxidative stress are closely connected to intraglomerular hypertension [53]. The results of in vitro and in vivo experiments suggest that SGLT2 inhibition suppresses these processes [39]. Although such studies of empagliflozin did not explore inflammatory markers, some data suggest that dapagliflozin lowers C-reactive protein levels [54]. Perhaps this topic will be a subject of further investigations.

Finally, the fourth mechanism is likely connected to the decrease in BV due to natriuresis. It is well known that limiting salt intake or administering thiazide diuretics induces a drop in BV with a subsequent decrease in albuminuria [55]. As SGLT2 inhibition causes osmotic diuresis, the potential magnitude of the decrease in albuminuria in response to empagliflozin therapy can be clinically significant [39]. Moreover, SGLT2 inhibition can lead to a decrease in atrial natriuretic peptide (ANP) levels by enhancing natriuresis. ANP levels are usually increased in animals with experimental diabetes [56]. Effects of ANP include increases in intraglomerular pressure and the GFR, which are why the lowering of ANP levels can contribute to improved single-nephron function [57].

It is important to mention that the combination of empagliflozin and RAAS blockers (80.7% of patients) in the EMPA-REG Outcome study demonstrated additional benefits in terms of renal outcomes compared to the placebo group, where only RAAS blockers were used. In our opinion, the combination of SGLT2 inhibitors and RAAS blockers had paramount value in this study, because some effects of SGLT2 inhibition (constriction of the afferent arteriole in the nephron, BV reduction and BP decrease) inevitably activate both local intrarenal and general RAASs. These effects were confirmed by increased blood renin levels in response to dapagliflozin therapy in DM2 patients [58] and by increased aldosterone levels in response to empagliflozin in patients with DM1 (regardless of glycaemia level) [29]. In addition, it is necessary to stress that, in addition to inhibiting SGLT2 to mediate their intrarenal haemodynamic effects on hyperfiltration and

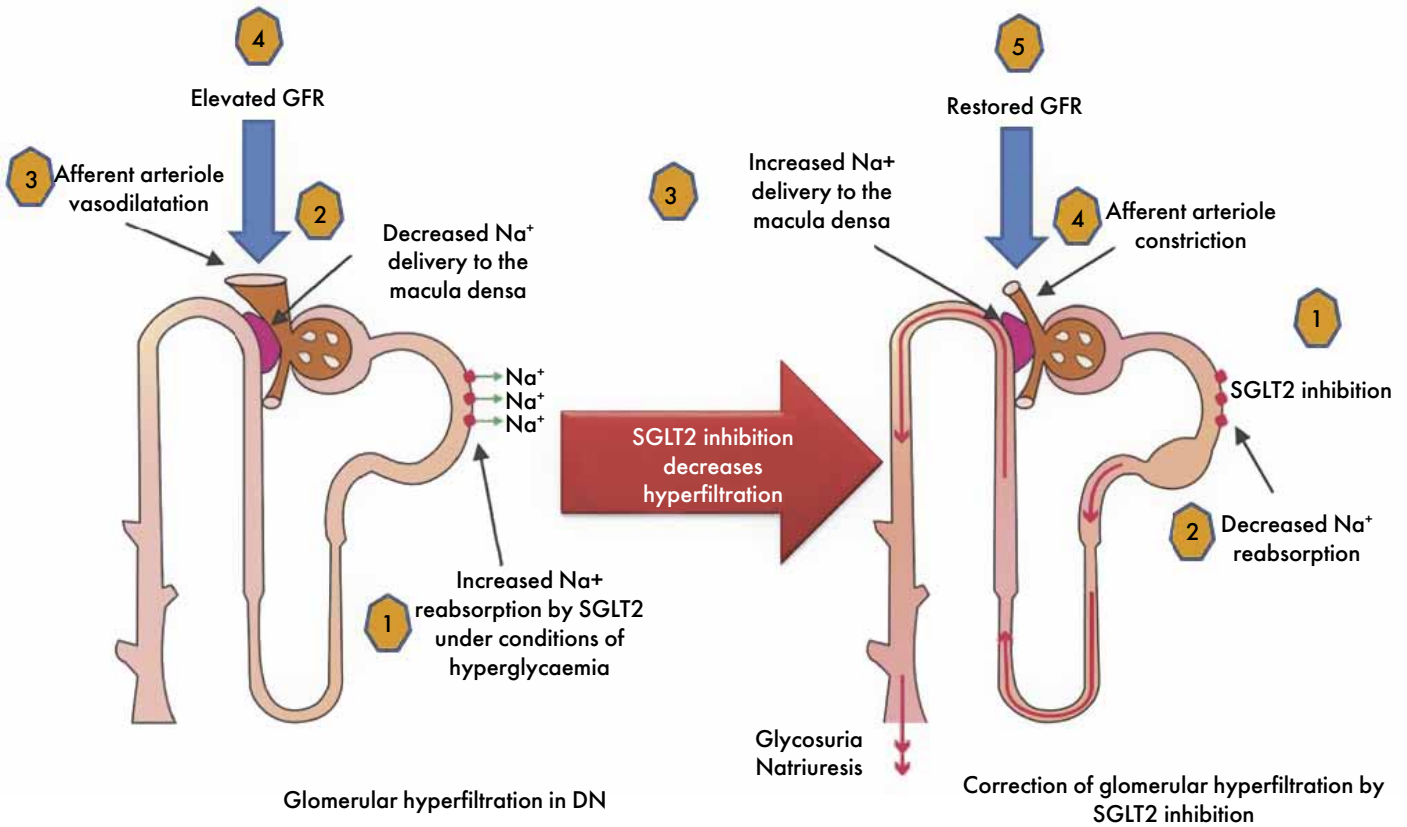


Fig. 4. Haemodynamic changes in the nephron of a patient with DN after SGLT2 inhibition (adopted from [20]).

intraglomerular hypertension, RAAS blockers affect the dilation of the efferent arteriole.

Thus, the above data allow for the consideration the simultaneous administration of SGLT2 inhibitors and RAAS blockers as the most effective and reasonable treatment of DM2 patients.

Hypothesis of the empagliflozin cardioprotective effect

The main difficulties in the analysis of the results from the EMPA-REG Outcome study are associated with the search for and interpretation of the mechanisms underlying such outstanding effects of empagliflozin on cardiovascular outcomes. These issues can be explained by the fact that the trial was designed only as a cardiovascular safety study, without an assessment of the metabolic effects of empagliflozin in the list of objectives. The absence of appropriate laboratory and instrumentally evaluated parameters has led to the emergence of numerous hypotheses to explain the observed benefits of empagliflozin compared with placebo. Many of these ideas require further studies to identify new directions in diabetology. We are going to describe the most interesting and compelling hypotheses of empagliflozin's cardioprotective effects.

Diuretic theory

Empagliflozin has an osmotic/diuretic effect that increases natriuresis, which is a contributing factor to the decrease in the number of hospitalisations for CHF and cardiovascular mortality. It is well known that diabetic patients have excessive Na+ levels, because of its enhanced renal reabsorption due to hyperglycaemia, hyperinsulinaemia, RAAS activation, etc. [57]. Retention of both Na+ and water plays an important role in increasing both pre- and postload, leading to peripheral oedema, blood stasis in the lungs and, finally, to hospitalisation. Patients with diabetes, subclinical heart dysfunction and impaired kidney function may be particularly sensitive to fluid retention [15]. In such cases, excess Na+ is distributed not only throughout the extracellular space but also within cells. Experimentally increasing the levels of Na+ in cardiomyocytes escalates the risk of arrhythmia and can lead to myocardial dysfunction, most likely by disrupting mitochondrial function [59]. Thus, in addition to lowering both pre- and postload, empagliflozin directly affects the myocardium by increasing natriuresis.

The diuretic effects of empagliflozin are similar to those of loop diuretics: they induce BV reduction (indirectly confirmed by a 4.8% increase in haematocrit levels). Nonetheless, although loop diuretics and thiazides have nearly the same effects, they have not been shown to decrease cardiovascular mortality in previous studies. Their impact on the frequency of hospitalisations for HF is also much lower. Therefore, empagliflozin has additional advantages over traditional diuretics (Table 3).

The main advantages are the absence of sympathetic nervous system activation and lack of changes in blood K+ levels, since the occurrence of hypokalaemia reduces the positive effects of diuretic therapy on the incidence of

cardiovascular events [61].

This analysis allows the consideration of empagliflozin as a diuretic with unique properties. Large-scale studies are very likely to make SGLT2 inhibitors more popular than traditional diuretics in cardiology practise.

Haemodynamic theory

This hypothesis is based on the fact that empagliflozin, by lowering BP and vascular stiffness postload, improves the function of the left ventricle and reduces oxygen consumption by the myocardium. The average decrease in BPsyst/BPdiast for patients in the EMPA-REG Outcome study was 4/2 mm Hg, which continued for 3.1 years after termination of the study. Multiple cardiology studies have demonstrated that BP reduction has a greater impact on reducing the incidence of stroke than other cardiovascular events. Moreover, BP reduction decreases cardiovascular risk only after 6–12 months. However, results from the EMPA-REG Outcome study showed an increase (although not statistically significant) in the incidence of non-fatal stroke, a decline in the frequency of non-fatal MI and a reduction in cardiovascular mortality three months after the study ended. It is therefore unlikely that the decrease in the frequency of cardiovascular events in patients receiving empagliflozin can be attributed exclusively to peripheral BP lowering. At the same time, there is evidence that a decrease in central BP (BP of the aorta, which may differ from peripheral BP) is associated with a reduction in the frequency of cardiovascular events [61]. If empagliflozin induced a significant reduction in central BP, it would have had a greater impact on cardiovascular events and HF, rather than on stroke risk. This hypothesis is confirmed by the ability of empagliflozin to reduce the rigidity of the aorta in diabetic patients [57]. This effect correlates with decreases in markers of arterial stiffness in patients treated with SGLT2 inhibitors.

The haemodynamic theory considers the impact of empagliflozin on decreasing pre- and postload via reductions in BV, as described above. It is important that decreases in BV activate RAAS by stimulating type 1 and 2 angiotensin receptors along with increasing angiotensin II production. Compensatory production of angiotensin (1–7) presumably occurs in response to RAAS stimulation (and also from the chronic, pharmacological suppression of ACE in 81% of patients) with assistance from angiotensin-converting enzyme-2 (ACE-2). Angiotensin (1–7) is an endogenous, competitive inhibitor of native angiotensin II. It has vasodilatory, antiproliferative, antiarrhythmic, anti-inflammatory and inotropic effects and can also reduce microalbuminuria [62].

Further investigations of the impact of SGLT2 inhibitors on central BP, the function of the left ventricle and ANP dynamics will provide opportunities to explore this hypothesis more deeply.

Energy (ketone) theory

The increase in glucagon production mediated by SGLT2 inhibition is particularly interesting in light of the EMPA-REG Outcome study results. Research conducted in the 1970s showed that glucagon has inotropic effects, improving myocardial contractility and cardiac output in patients treated with glucagon for MI [57]. Glucagon stimulates cAMP synthesis in the myocardium, eliciting positive inotropic and chronotropic effects without stimulating adrenergic receptors. Additionally, glucagon was found to have antiarrhythmic effects. Elevated glucagon levels were observed in some inflammatory diseases, including severe sepsis; this effect was interpreted as a component of stress protection mechanisms [63].

Glucagon has been used in clinical practise with combined, intensive therapy for acute HF, but since catecholamines appear to be much more effective, the use of glucagon has stopped. Therefore, the slight but persistent increase in glucagon levels in response to SGLT2 inhibitors can be considered another possible mechanism of cardioprotection.

The effects of glucagon include slight hyperketonaemia (0.3–0.6 mEq/L in blood plasma), which is typical for SGLT2 inhibitors. The use of SGLT2 inhibitors probably causes a shift from glucose to fat oxidation. The end product of fatty acid oxidation is acetyl-CoA, which either enters the tricarboxylic acid cycle or is converted into ketones. SGLT2 inhibitors initiate ketogenesis by stimulating glucagon secretion. Beta-hydroxybutyric acid, produced during ketogenesis, is absorbed by the myocardium, where it undergoes a series of biochemical transformations and is converted into fatty acids. This process results in the intensification of cellular respiration at the mitochondrial level and increases myocardial oxygen consumption, which improves cardiac function [64].

Metabolic tuning theory

Patients receiving empagliflozin have reduced glycated haemoglobin levels and body weight, improved lipid profiles, lower BP, reduced uricaemia and albuminuria and slowing of the decrease in the GFR compared to patients receiving placebo. These individual benefits are unlikely to be the causative effects of the main EMPA-REG Outcome study results in the short term. However, according to this theory, the length of this study was likely too short for these positive metabolic effects to be discerned. Over time, these effects could have slowed atherogenesis, lesions in target organs and the development of complications [19]. For the first time, the list of medications used to treat DM2 contains drugs with complex effects on metabolic disorders. The diverse effects of empagliflozin, including its positive impact on cardiovascular outcomes, allow its use as a new strategy for the treatment of patients with comorbidities, termed ‘metabolic tuning’.

The theory of additional costs

In 1962, the anthropologist James Neel proposed a concept known as the ‘thrifty gene hypothesis’ [65]. This concept implies that ancient humans adapted to life during periods of temporary abundance (when hunting was successful), followed by periods of deficiency, when

Table 3

Comparison of SGLT2 inhibitors and traditional diuretics (adopted from [60])

Comparison Criteria	SGLT2 Inhibitors	Thiazides/Thiazide-Like Diuretics	Loop Diuretics	Aldosterone Antagonists
Drugs	Empagliflozin, Dapagliflozin, Canagliflozin	Hydrochlorothiazide, Indapamide	Furosemide, Torasemide	Spironolactone, Eplerenone
Site of Action in the Nephron	Proximal tubules	Distal tubules	The loop of Henle	Distal tubules, outflow tract
Diuretic Effect	Mild	Mild	Strong	Mild
Основные показания	DM2	HD, CHF	CHF, HD	CHF, refractory arterial hypertension
Blood K+ Levels	No changes	Hypokalaemia	Hypokalaemia	Hyperkalaemia
Blood Uric Acid Levels	Decreases	Increases	Increases	No changes
Insulin Resistance	Decreases	Increases	Increases	No changes
Lipid Profile	Almost neutral	Deteriorates	Almost neutral	Almost neutral
Haematocrit	Increases	No changes	Increases	No changes
Influence on the Sympathetic Nervous System	Нейтральное	Активация	Активация	Активация

the amount of available food was significantly less. This strategy successfully works in a world of feast and famine, but when high-calorie foods are easy accessible and require minor physical effort to obtain, this strategy leads to the development of obesity, DM and hypertension. The existence of SGLT1/2 is a component of the 'thrifty gene' mechanism, returning and preserving glucose as the main source of energy [15]. The theory of additional costs implies a new strategy for metabolic correction, which is based on switching from saving to spending. The emergence of SGLT2 inhibitors makes new, more effective and reasonable therapeutic approaches available and promises significant improvements in treatment results. These benefits were confirmed by the results of the EMPA-REG Outcome study, where cardiovascular mortality was reduced in response to glucose-lowering agents for the first time.

Thus, summarising the above-mentioned facts, we conclude that inhibition of SGLT2 by empagliflozin has complex and multifunctional effects on the organism, effectively influencing both cardiovascular and renal outcomes (Fig. 5).

The main EMPA-REG Outcome study results were determined by rapid improvements in haemodynamicsinduced by empagliflozin; however, over time, the contribution of the metabolic effects of the drug on outcomes increased.

Status of empagliflozin and SGLT2 inhibitors in the treatment of diabetes mellitus

The emergence of SGLT2-inhibiting drugs is an extremely important breakthrough for the treatment of DM2, which ensures significant reductions in pre- and postprandial glycaemia and HbA1c, regardless of diabetes duration and insulin secretion, and reductions of body weight and BP. Apparently there are no significant differences between various SGLT2 inhibitors in terms of these effects; all of them have favourable safety profiles and few potential side effects. Their mechanisms of action allow their combined use with any perioral or injectable antidiabetic agent, except for the combination of GLP-1 agonists and empagliflozin. Before administering these drugs, GFR should be measured because the glucose-lowering efficacy of SGLT inhibitors depends on renal function; it drops in cases of moderate CRF and is missing in cases of severe CRF. Thus, this is an important limitation for the use of SGLT2 inhibitors. For example, empagliflozin and canagliflozin require a GFR greater than 45 mL/min, whereas dapagliflozin requires a GFR greater than 60 mL/min.

The SGLT2 inhibitor empagliflozin has convincingly proved its nephro- and cardioprotective effects and its ability to decrease overall and cardiovascular mortality after three months of therapy. These effects allow the precise identification of the group of patients who would benefit from empagliflozin therapy. Such patients would be similar in their characteristics to the EMPA-REG Outcome study participants, that is, DM2 patients diagnosed with CVD. If a patient with DM2 at high cardiovascular risk does not currently receive empagliflozin, the EMPA-REG Outcome study results justify the receipt of this combined antihyperglycaemic therapy. It is quite possible that the canagliflozin cardiovascular assessment study and the trial devoted to dapagliflozin effects on cardiovascular events will show similar results on outcomes for patients with high cardiovascular risk; such a finding would expand the use of other SGLT2 inhibitors. As for patients with poor glycaemic control without CVD, there is no evidence confirming the advantage of a particular SGLT2 inhibitor over another.

The results of the EMPA-REG Outcome study have already been recognised by leading international associations of endocrinologists and cardiologists; the current recommendation is to implement this drug in routine clinical practise. These recommendations were recently published in the European Society of Cardiology clinical guidelines for the diagnosis and treatment of

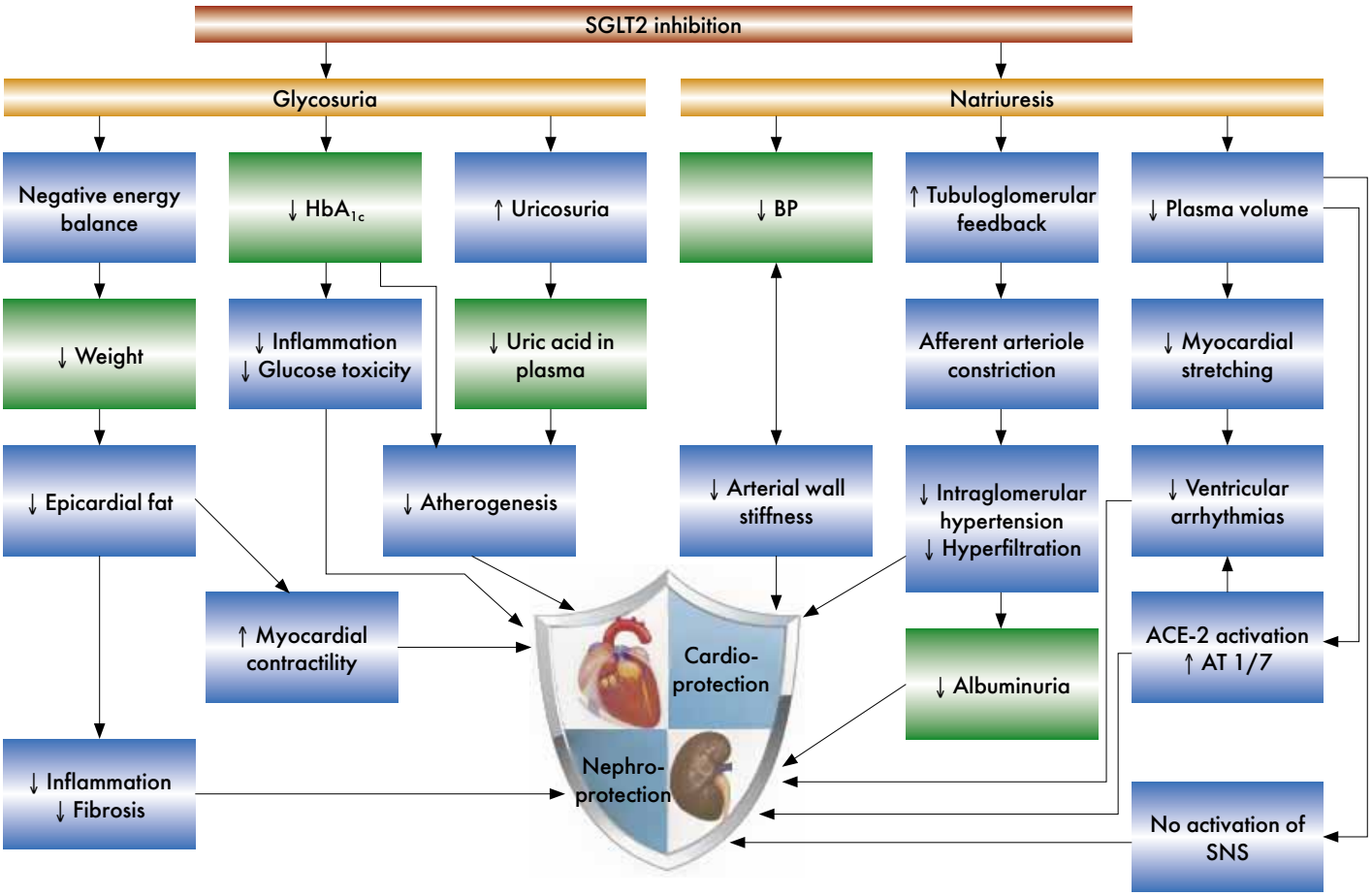


Fig. 5. Hypothesized mechanisms of cardioprotection and nephroprotection by the SGLT2 inhibitor empagliflozin (adopted from [30]).

acute and chronic heart failure, where empagliflozin is stated as the drug of choice for patients with DM2 and CHF [66].

Conclusion

The results of the EMPA-REG Outcome study reveal that preventing the most severe macrovascular complications is quite realistic in patients with a long history of DM2 and multiple comorbidities. SGLT2 inhibitors are antihyperglycaemic agents, simultaneously demonstrating hypotensive, weight-lowering, urate-lowering and diuretic effects. Empagliflozin improves cardio-renal outcomes and reduces the number of hospitalisations for CHF. According to the study results, the SGLT2 inhibitor empagliflozin plays a crucial role in the management of DM2 in patients with confirmed CVD. Its use at the onset of DM2 or in the absence of CVD is also very important, as empagliflozin has a significant impact on multiple cardiovascular risk factors and improves a number of metabolic parameters. The use of such a multifunctional drug will increase patient compliance and decrease the use of multiple drugs for each diagnosed disease.

Additional information

Conflict of interest

The authors declare no conflicts of interest connected with the publication of current article.

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Authors contribution

V.V. Salukhov - exploratory and analytical work, draughting and revising the manuscript; T. Yu Demidova - exploratory and analytical work, draughting the manuscript.

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