



Submitted: 22.02.2023
Accepted: 13.03.2023
Early publication date: 30.06.2023

Endokrynologia Polska
DOI: 10.5603/EPa2023.0039
ISSN 0423–104X, e-ISSN 2299–8306

The influence of SGLT2 inhibitors on oxidative stress in heart failure and chronic kidney disease in patients with type 2 diabetes

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Abstract

There is increasing interest in sodium-glucose cotransporter 2 inhibitors (SGLT2i) as not only a new oral glucose-lowering drug class but also one with cardio- and nephroprotective potential. Understanding the underlying mechanisms is therefore of great interest, and postulated benefits have included increased natriuresis, lower blood pressure, increased haematocrit, enhanced cardiac fatty acid utilization, reduced low-grade inflammation, and decreased oxidative stress. In particular, redox homeostasis seems to be crucial in the pathogenesis of heart and kidney disease in diabetes, and there is accumulating evidence that SGLT2i have beneficial effects in this perspective.

In this review, we aimed to summarize the potential mechanisms of the influence of SGLT2i on oxidative stress parameters in animal and human studies, with a special focus on heart failure and chronic kidney disease in diabetes mellitus.

Key words: sodium-glucose cotransporter 2 inhibitors; oxidative stress; diabetes mellitus; chronic kidney disease; heart failure

Introduction

Oxidative stress (OS), defined as a disturbance of pro- and antioxidant homeostasis, leads to cellular damage [1, 2]. The oxidative imbalance stems from both excessive generation of highly reactive oxygen (ROS) and reactive nitrogen species (RNS) and/or reduced antioxidative potential of the organism [1, 2]. Overproduction of highly reactive species is an important factor in the pathogenesis of cardiovascular (CV) complications in the course of diabetes mellitus (DM).

DM affects 537 million adults worldwide, and patients with diabetes mellitus type 2 (T2DM) account for about 90% of them [3]. Cardiovascular diseases (CVDs) are the leading cause of death in T2DM patients, with heart failure (HF) emerging as a new epidemic both among patients with and without diabetes [4,

5]. Moreover, chronic kidney disease (CKD), a microvascular complication of DM, adds another puzzle to the increased incidence of CVD and cardiovascular deaths as a part of cardio-renal continuum [6].

Since the early 2000s, new classes of glucose-lowering drugs emerged, namely sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1 RAs), which changed the perspective on the treatment algorithms in T2DM patients. Nowadays the glucocentric approach prevailing for decades has been changed towards a more cardio- and nephroprotective approach, in which the choice of glucose-lowering drug in a particular patient is driven mainly by the presence of cardiovascular and renal diseases. This shift has been made following the publication of the landmark cardiovascular outcome trials, such as the Canagliflozin Cardiovascular Assess-



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ment Study (CANVAS) program, the Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME), and the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial [7–9]. These studies prove that new classes of glucose-lowering drugs are not only safe in terms of the cardiovascular system but also clearly decrease the risk of cardiovascular and renal events.

Specifically, it has been suspected and then confirmed that the cardiac and renal benefits of SGLT2i may be independent of glycaemic control. Following further studies like the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR- Preserved), the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced), the Study of Heart and Kidney Protection With Empagliflozin (EMPA-Kidney), the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER), and the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD), SGLT2i are now considered the first-line treatment in patients with HF and CKD, both with and without DM [10–15]. These trials were overviewed more thoroughly in a recent editorial [16]. Hence, there has been much interest on the possible pathophysiology and mechanistic insights into the universally positive influence of these drugs on cardiovascular and renal systems. Possible pathways include increased osmotic diuresis and natriuresis [17], mild hypotensive effect [18], increased haematocrit – possibly secondary to hypoxia inducible factor signalling [19], reduced low-grade inflammation by reduced proinflammatory cytokine production [20], enhanced myocardial metabolism – including increased fatty acid or glucose oxidation or ketogenesis [21, 22], and decreased OS [23, 24].

In particular, their interference with oxidative stress has emerged as one of the biochemical pathways involved in this protective process [25, 26].

The aim of this narrative review is to analyse the influence of SGLT2i on OS as one of the possible mechanisms of its protective action in HF and CKD.

Search strategy

A search of the Medline, Embase, and Scopus databases as well as the search engine Google Scholar was conducted to find published research about mechanisms of SGLT2i related to OS. Additionally, we searched for relevant studies in the references of other included articles. The search was limited to English language articles published up to 31 December 2022.

The inclusion criteria were as follows:

1. Original research studies that tested the effects of SGLT2i on OS:
 - in animal models of either HF or CKD, or diabetes when tested samples included myocardial, vascular, or kidney tissue;
 - in humans with HF, CKD, or diabetes type 2 (either patients treated or tissues treated ex vivo).
2. Original research studies on the influence of diabetes type 2, HF, or CKD on OS in human subjects

The exclusion criteria were as follows:

- studies that researched mechanisms of action of SGLT2i but did not assess its impact on the extent of ROS generation, any markers of OS, or markers of antioxidant capacity;
- studies on animal models of a disease did not include any of the following groups: healthy controls, a model of the disease untreated, and a model of the disease treated with SGLT2i.

The search included terms such as: “SGLT2 inhibitors”, “oxidative stress”, “diabetes”, “heart failure”, and “chronic kidney disease”.

Oxidative stress and heart failure in diabetes mellitus type 2

T2DM is a significant risk factor for the development of HF [27]. Similarly, HF predisposes to new-onset T2DM [28]. The fact that consequences of one disease underly the pathogenesis of another one is thought to explain this peculiar relationship.

For example, hyperglycaemia appearing in T2DM can lead to myocardial and endothelial damage, which may result in HF development. On the other hand, metabolic changes seen in HF, such as increased lipolysis and increased insulin resistance, increase the risk of new-onset T2DM [29, 30]. Both phenomena are also associated with increased OS. This interaction is sometimes referred to as a vicious circle because both T2DM and HF exacerbate each other [31].

Increased OS has long been associated with T2DM and HF. Sources of ROS in diabetic heart and endothelial cells include leakage of superoxide anions generated in mitochondrial electron transport chain (ETC), and excess activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), xanthine oxidase, uncoupled nitric oxide synthase, and arachidonic acid metabolism [32]. In both T2DM and HF sources of ROS are upregulated, and the hyperglycaemic state elevates ROS by several mechanisms. Various studies related to OS in HF of patients with T2DM are summarized in Table 1.

Glucose autooxidation delivers additional substrates for ETC in mitochondria, thus increasing output of su-

Table 1. Oxidative stress and heart failure in type 2 diabetes mellitus

Study	Participants	Sample	Outcomes	Conclusion
Anderson et al. (2009) [78]	11 T2DM patients and 13 nondiabetic patients undergoing CABG	Atrial tissue obtained during CABG	<p>↑ mitochondrial H₂O₂ generation, HNE, 3-NT</p> <p>↓ GSH/GSSG ratio</p> <p>↓ fatty acid and glutamate oxidative capacity</p> <p>↑ intramyocellular triglyceride content</p>	<p>Increased OS and impaired antioxidant defence in patients with T2DM</p> <p>Deranged mitochondrial metabolism among T2DM patients is associated with lipid accumulation in cardiomyocytes</p>
Montaigne et al. (2014) [79]	45 T2DM patients and 94 nondiabetic patients undergoing CABG	Atrial tissue obtained during CABG	<p>↑ ROS, MnSOD, catalase activities</p> <p>↑ mitochondrial dysfunction</p> <p>↓ impaired intrinsic contraction</p> <p>Increased OS and disturbances of the mitochondrial function correlated with HbA_{1c}, but not with BMI or HOMA-IR</p>	<p>Increased OS, upregulated antioxidant enzymes, dysfunctional mitochondria and myocardial contraction are associated with worse glycaemic control, but not with insulin resistance or obesity</p>
Connelly et al. (2014) [80]	7 T2DM patients and 7 nondiabetic patients undergoing CABG	Atrial myocardium obtained during CABG	<p>↓ thioredoxin expression and activity</p> <p>↑ expression of TxnIP</p>	<p>Diminished thioredoxin antioxidant system is associated with increased expression of TxnIP.</p> <p>Experimental studies on animal models showed that increased TxnIP expression appears in diabetes, and it both increases OS and reduces antioxidant capacity of thioredoxin.</p>
Wang et al. (2011) [81]	18 T2DM patients and 18 nondiabetic patients undergoing CABG	Atrial tissue and coronary sinus blood collected during CABG	<p>↑ 15-F_{2t}-isoprostane in coronary sinus plasma</p> <p>↑ PTEN expression in atrial myocardium</p> <p>↓ Bcl-2 expression, eNOS and Akt phosphorylation</p> <p>Highly significant correlation between 15-F_{2t}-isoprostane concentration, PTEN expression, and fasting plasma glucose</p>	<p>PTEN and Akt signalling is inversely correlated in diabetic hearts, with downstream effects of increased OS and downregulation of cardioprotective signalling pathways</p>
Polidori et al. (2004) [82]	30 patients with class II or III NYHA heart failure and 30 controls	Blood	<p>↑ levels of 8,12-isoprostane F2a-VI, levels correlate with HF severity</p> <p>↓ vitamins A, C, and E</p> <p>↓ uric acid, carotenoids</p> <p>↓ SOD and GPx activities</p>	<p>Patients with HF had increased OS and depleted antioxidative systems</p>
Gupte et al. (2007) [83]	8 heart failure patients with HF secondary to infarction undergoing surgical ventricular restoration and 5 donor hearts not suitable for transplantation as control	Non-infarcted left ventricular tissue obtained during surgery or from donor hearts	<p>↑ superoxide and hydrogen peroxide</p> <p>↑ expression of NOX2, NOX4 and G6PD</p> <p>↑ activity of NOX, G6PD</p> <p>Inhibition of NOX, PKC, Src kinase or G6PD decreased superoxide generation</p>	<p>NOX is a major source of OS in failing hearts</p> <p>OS attenuation is achieved by inhibition of NOX, G6PD, which produces substrate for NOX, or signalling pathways that activate G6PD</p>

3-NT — 3-nitrotyrosine; Bcl-2 — B-cell lymphoma 2; BMI — body mass index; CABG — coronary artery bypass grafting; CVD — cardiovascular disease; eNOS — endothelial nitric oxide synthase; G6PD — glucose-6-phosphate dehydrogenase; GPx — glutathione peroxidase; GSH — glutathione; GSSG — glutathione disulphide; HbA_{1c} — glycated hemoglobin; HF — heart failure; HNE — 4-hydroxynonenal; H₂O₂ — hydrogen peroxide; HOMA-IR — homeostatic model assessment for insulin resistance; MnSOD — manganese-dependent superoxide dismutase; NOX — NADPH oxidase; NOX2 — NADPH oxidase 2; NOX4 — NADPH oxidase 4; NYHA — New York Heart Association; OS — oxidative stress; PKC — protein kinase C; PTEN — phosphatase and tensin homolog; ROS — reactive oxygen species; SOD — superoxide dismutase; Src kinase — tyrosine protein kinase; T2DM — type 2 diabetes mellitus; TxnIP — thioredoxin-interacting protein

peroxide anions [32]. Another mechanism is activation of polyol pathway [33]. High glucose concentration can activate Ca²⁺/calmodulin-dependent protein kinase

II [34], protein kinase C [35] and stimulate production of angiotensin II [36] and advanced glycation end-products (AGE) in cardiomyocytes or endothelial

cells, all of which activate NOX and thus induce ROS production [34–37].

Both T2DM and HF are characterized by metabolic alterations. Failing hearts rely increasingly on glucose metabolism; however, in experimental studies, diabetic hearts shift from glucose metabolism toward free fatty acid (FFA) oxidation [38]. An increase of circulating FFA in patients with either HF or T2DM is observed [39, 40]. Elevated uptake of FFA by cardiomyocytes activates peroxisome proliferator-activated receptor α (PPAR- α), which in turn increases fatty acid oxidation [41]. Despite increased FFA oxidation, superfluous FFA is combined to form triglycerides and other lipid intermediates. This may lead to intramyocardial lipid accumulation, which was observed in patients with either T2DM or HF [42, 43] and was experimentally shown to impair cardiac function [44, 45]. In addition, FFA oxidation has been shown to decline in advanced HF, though high FFA serum levels persist [46], which could exacerbate intracellular lipid accumulation. Both overload of cardiac mitochondria with FFA and increased FFA oxidation in PPAR- α overexpressing mice has been shown to increase ROS generation [47, 48]. Trimetazidine, which has been shown to be beneficial in HF in some studies [49], acts by decreasing FFA oxidation in patients with HF [50]. However, it attenuates OS as well, which could be responsible for its cardioprotective properties [51].

Despite compensatory metabolic changes, HF results in an “energy crisis”, with a decreased phosphocreatine to adenosine triphosphate ratio [52], which is also a predictor of mortality in patients with dilated cardiomyopathy [53]. In this energetic state, a “low-energy sensor” such as Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) becomes activated in HF [54]. On the other hand, diabetes is perceived by cardiomyocytes as a state of energy abundance because AMPK phosphorylation was shown to be decreased in a model of diabetic cardiomyopathy [55]. Sirtuin 1 (SIRT1) is another enzyme responsible for energy metabolism, dependent on the nicotinamide adenine dinucleotide+/nicotinamide adenine dinucleotide hydrogen (NAD+/NADH) ratio. However, SIRT1 is downregulated in both diabetes and HF alone [56], [57]. Furthermore, AMPK and SIRT1 signalling are also related to OS. SIRT1 overexpression by transgenic mice is protective against oxidative stress, and it reduces cardiomyocyte apoptosis [58]. Moreover, decreased SIRT1 expression is associated with OS in HF [57].

Robust evidence exists on the importance of OS in the pathogenesis of T2DM and HF. OS in DM facilitates the development of HF and comorbidities predisposing to HF due to damage to the endothelium, contributing to both macrovascular and microvascular complications

as well as to cardiac remodelling [33]. Even when DM is not complicated by hypertension or coronary artery disease, diabetic cardiomyopathy may still be present, a condition with a pathophysiology strictly associated with OS [34]. Cardiac hypertrophy, interstitial fibrosis, cardiomyocyte apoptosis, and disturbed calcium handling are thought to result from increased OS, mediated by various signalling pathways [35–37].

Oxidative stress and chronic kidney disease in diabetes mellitus type 2

OS plays an important role in the pathogenesis of CKD in DM, especially because the kidneys are particularly vulnerable to OS due to their high energy consumption and content of mitochondria (especially in proximal tubules) [1, 38]. The main kidney sources of ROS include mitochondrial respiratory chain and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) activities [39]. Under normal conditions, only 1% of molecular oxygen (O_2) is converted to superoxide anion O_2^- in the final stage of the mitochondrial respiratory chain [40]. However, the state of chronic hyperglycaemia (in the course of DM) leads to electron deficiency in the mitochondrial respiratory process, which becomes the main O_2^- generator [40]. Hyperglycaemia, both acute and chronic, also affects endothelial nitric oxide synthase (eNOS), causing an excess synthesis of nitric oxide (NO), one of the RNS agents and a factor contributing to OS [41].

Studies related to OS in CKD in T2DM are summarized in Table 2. Another contributor to excess OS in patients with CKD is an overproduction of indoxyl sulphate (uraemic toxin that also accelerates CKD progression) inducing NOX and mitochondrial respiratory chain and entailing renal endothelial damage in the mechanism of OS [42]. Moreover, one of the relevant factors in the hyperoxidation is zinc deficiency (ZnD), observed among CKD patients [43]. Of note, zinc ions (Zn^{2+}) possess antioxidative properties, and a Zn^{2+} shortage induces NOX enzymes, a major renal source of ROS [43].

In the pathophysiology of OS, apart from intensification of prooxidative mechanisms, there is also an antioxidant inefficiency [44]. The picture of CKD also includes reduction of enzymatic antioxidant agents, proportionally to the advancement of the disease [45, 46]. Studies analysing one of the main intracellular (superoxide dismutase [SOD], peroxidase) and extracellular (reduced glutathione [GSH]) antioxidative enzymes indicate significant impairment of antioxidant capabilities among CKD patients [47, 48].

OS as a crucial factor in the pathogenesis of CKD has been investigated for decades [49–51]. In rats

Table 2. Oxidative stress and chronic kidney disease in type 2 diabetes mellitus

Study	Participants	Samples	Outcomes	Conclusions
Aksun et al. (2003) [57]	68 T2DM patients with or without albuminuria aged 57 ± 9.7 years and 32 healthy controls	Blood and urine	↑ both serum and urine NO and MDA levels in diabetic patients with and without albuminuria	NO and MDA upregulation may lead to renal hyperfiltration and hyperperfusion, and causes progression of CKD
Bondor et al. (2015) [56]	44 patients T2DM lasting for at least 6 months with GFR > 30 mL/min and 20 healthy controls	Blood	↑ levels of serum MDA in diabetic patients ↑ correlation between MDA and adiponectin in patients with DKD	Adiponectin is a significant predictor of DKD

CKD — chronic kidney disease; DKD — diabetic kidney disease; GFR — glomerular filtration rate; MDA — malondialdehyde; NO — nitric oxide; T2DM — type 2 diabetes mellitus

with streptozotocin-induced diabetes, increased production of ROS, the source of which is to be found in NAD(P)H and NO synthase, is suspected to be a common pathway connecting different pathogenic mechanisms of microvascular complications of diabetes, including CKD [52, 53]. In diabetic db/db mice, agents with antioxidative properties such as rosiglitazone and pigment epithelium-derived factor were found to relieve diabetic renal injuries [54, 55]. Nonetheless, only limited research on animal models has been performed in relation to levels of OS markers in the kidney in the course of diabetes.

Studies performed among CKD patients with T2DM treated with SGLT2i analysed various OS markers and antioxidative enzymes to identify factors correlated with diabetic kidney disease (DKD). Analogous to the animal models, hyperglycaemia leads to enhanced levels of oxidative stress markers such as serum and urine nitric oxide (NO), malondialdehyde (MDA), and SOD, observed among patients with DM [56, 57]. OS markers were higher not only among patients with DKD but also in normoalbuminuric DM patients presenting with hyperfiltration [57]. In addition, Roumeliotis et al. identified specific genetic factors (e.g. secreted phosphoprotein 1 [SPP1], thyroid peroxidase [TPO], shugoshin 2 [SGO2] and others) that were related to OS and had an impact on the risk of DKD occurrence [58].

In summary, hyperglycaemia leads to suppression of antioxidative potential and an increase in OS. Consequently, progressive oxidative damage of renal tissue and microvasculature constitutes a significant component of the subsequent complications of T2DM, such as CKD, atherosclerosis, and CVD.

SGLT2i — mechanisms of action

Physiologically, in healthy organisms, glucose becomes completely reabsorbed in the proximal tubules

of the kidneys. The renal threshold for glucose is approximately 160–180 g/day, which means that this amount of glucose could be filtered without resulting in glycosuria [59]. Exceeding this threshold, as caused by profoundly impaired carbohydrate metabolism, leads to marked glycosuria – a distinctive feature of poorly controlled DM [60]. Resorption of 80–90% of glucose is provided by SGLT2, a glucose transporter located in the first segment (S1) of proximal renal tubules. The process consists of transporting one molecule of glucose coupled with 2 sodium ions through epithelial tubular cells via a sodium-potassium pump (Na⁺/K⁺-ATPase). Next, glucose exits the cell passively by facilitated diffusion through glucose transporter 2 (GLUT2) [61]. Afterwards, 10–20% of residual glucose is reabsorbed by other glucose transporters (SGLT1 and GLUT1) located in the following segments (S2/S3) of proximal tubules [60].

The newly developed SGLT2i drugs may act selectively on SGLT2 and interact with the renal (tubular) handling of glucose. Inhibiting SGLT2 leads to increased excretion of glucose in urine. Consequently, SGLT2i decrease blood glucose levels and improve glycated haemoglobin A1c by about 0.5–1% [86]. Moreover, glycosuria causes body weight loss (2–3 kg in the first 6 months of treatment) because glucose urine excretion equates to about 200 kcal/day [84]. Through simultaneous inhibition of glucose and sodium reabsorption, SGLT2i improve tubule-glomerular feedback in kidneys, decrease renal hyperfiltration, and reduce sodium and glucose levels in proximal tubules [87]. In addition, SGLT2i exert protective action on beta-cell function [88].

Apart from their impact on renal sodium handling, SGLT2i may also decrease the cutaneous (interstitial) Na⁺ content (correlated with left ventricular (LV) hypertrophy) and thus may improve LV remodelling and ejection fraction (EF) [60, 62]. The other mecha-

nisms of action improving cardiovascular condition include reduction of cardiac preload and afterload, improvement of myocardial metabolism with reduction of cardiomyocyte apoptosis, reduction of epicardial adipose tissue, and attenuation of sympathetic nerve activity [60, 62].

Antioxidative potential of SGLT2i in heart failure

Several mechanisms have been proposed to explain the protective effects of SGLT2i in HF. These mechanisms include the following: increased osmotic diuresis and natriuresis [17], mild hypotensive effect [18], increased haematocrit [19], reduced low-grade inflammation and proinflammatory cytokine production [20], as well as increased fatty acid oxidation as a source of energy [21] and decreased OS [23, 24].

Treatment with empagliflozin in animal models of diabetes attenuates ROS generation in myocardium [90–92] and endothelium [90, 92, 93]. Moreover, reduced levels of myocardial and vascular OS biomarkers of lipid peroxidation and nitrosative stress are evident and consistent among most published studies using either empagliflozin or dapagliflozin [90, 94, 95]. However, one study found no influence of empagliflozin treatment on OS biomarkers [96]. Reduction of OS has been associated with improved functional and structural parameters such as increased left ventricular systolic and diastolic function, vascular dilatation, and decreased cardiac fibrosis and hypertrophy [55, 91, 92, 94–96]. Decreased OS results from reduced NOX expression and activity [55, 90, 93–95], and increased activation of eNOS [91, 93] and AMPK [55, 91].

Nonetheless, there is some inconsistency regarding the impact of SGLT2i on antioxidative systems. Li et al. [94] reported increased myocardial SOD and glutathione peroxidase (GPx) activities with the use of empagliflozin, while another study using dapagliflozin showed decreased SOD activity and no change of GPx or catalase activities [95]. Similarly, conflicting results exist regarding the role of heme oxygenase-1 (HO-1) and AGE/receptors of AGEs (RAGE) signalling, though some studies found an association between RAGE downregulation and SGLT2i treatment [90, 93]. These discrepancies among animal studies may be due to the large heterogeneity of methodologies, such as the use of various models of diabetes and analysis of different tissues (e.g. HO-1 expression was increased in myocardium [94] but decreased in aorta [90, 93]). Notably, no studies have assessed the influence of SGLT2i on OS in animal models of HF.

Studies on human subjects analysing the association between SGLT2i and OS in diabetes and HF are lack-

ing. In the only randomized clinical trial, dapagliflozin reduced the urine 8-hydroxy-2'-deoxyguanosine (8-OHdG)/creatinine ratio in patients with T2DM [22]. Other studies were ex vivo analyses of tissues obtained from patients without prior treatment with SGLT2i. For example, Kondo et al. [97] showed that canagliflozin reduces OS by AMPK and eNOS activation in patients with T2DM, but this was not repeated when empagliflozin was used. On the other hand, a study utilizing myocardium of patients with heart failure with preserved ejection fraction (HFpEF) showed a reduction of OS with the use of empagliflozin, which was associated with decreased cardiomyocyte stiffness [23]. Details of animal and human studies related to the potential influence of SGLT2i on OS in diabetes and HF are presented in Tables 3 and 4.

Although SGLT2 protein is not expressed in the heart, it can still stimulate the activity of low-energy sensors [63], which has an impact on sustaining the cardiac muscle in the optimal state [64]. The protective role of SGLT2i in the HF may be driven by activation of SIRT1/AMPK and inhibition of protein kinase B/mammalian target of rapamycin (Akt/mTOR) signalling, which can lead to improved autophagy and reduced OS, lowering the inflammation state, resulting in improvement in heart contractility [63, 65]. Moreover, cardiac benefits may be driven by enhancement of hypoxia-inducible factor (HIF-1 α /HIF-2 α) signalling by SGLT2i, which in turn can increase autophagy by AMPK/SIRT1 signalling pathways [66].

Antioxidative potential of SGLT2i in chronic kidney disease

OS partakes in the pathogenesis of CKD; however, the exact mechanisms of the link between OS and CKD development are unknown. SGLT2i can directly reduce oxidative stress induced by high glucose levels in the proximal tubules, as was presented in experimental studies [67–69].

Several animal studies examined renal OS factors, [NOX, nuclear factor kappa B (NF- κ B), ribonucleic acid (RNA)/deoxyribonucleic acid (DNA) damage], messenger RNA (mRNA) expression of OS cytokines, glycation end-product levels, and markers of renal inflammation, as an effect of increased OS in renal tissues [70–72]. Most of the studies confirmed the impact of SGLT2i treatment on decreased markers of OS or reduced levels of inflammation markers [70, 73, 74]. Two studies analysed the effects of SGLT2i in combination with ursolic acid or irbesartan in the treatment of DKD [75, 76]. In both studies, the groups treated with a combination of the drugs achieved improved renal parameters due to improving the antioxidative effect [75, 76].

Table 3. Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in myocardial and vascular tissues of animal models of diabetes

Study	SGLT2i	Animal model	Material	Outcomes after treatment with SGLT2i (compared to diabetic untreated)	Conclusion
Li et al. (2019) [84]	Empagliflozin	Diabetic KK-Ay mice and control C57BL/6J mice	Myocardium	<ul style="list-style-type: none"> ↓ lipid hydroxyperoxide, MDA ↑ SOD, GPx activity ↓ NOX4 expression ↑ Nrf, HO-1 expression ↓ LVH, myocardial fibrosis ↑ systolic and diastolic function 	Empagliflozin attenuates cardiac OS by downregulating NOX and by activating Nrf2/ARE signalling and alleviates myocardial remodelling, thereby improving cardiac function
Steven et al. (2017) [85]	Empagliflozin	Zucker diabetic fatty rats (ZDF-Lepr ^{fa/fa}) and lean control (ZDF-Lepr ^{+/+})	Myocardium	<ul style="list-style-type: none"> ↓ superoxide, 3NT, HNE ↑ ALDH-2 activity 	Empagliflozin attenuates cardiac and aortic OS, increases activity of cardioprotective ALDH-2 and inhibits AGE/RAGE signalling, a major pathway inducing OS
			Aorta	<ul style="list-style-type: none"> ↓ superoxide, 3NT, HNE ↓ NOX2, HO-1 expression ↓ methylglyoxal, RAGE expression 	Effects of SGLT2 inhibition were not dose-dependent for most of the studied parameters
Habibi et al. (2017) [86]	Empagliflozin	Diabetic db/db mice and control wild-type C57BLKS/J mice	Left ventricular myocardium	<ul style="list-style-type: none"> ↓ LVH, myocardial fibrosis ↑ diastolic function No change in diabetes-induced increase of 3-NT levels, AGE and RAGE expression 	Empagliflozin improves cardiac structure and function but does not alleviate OS
Zhou et al. (2018) [65]	Empagliflozin	Streptozotocin-induced diabetic C57BL/6J and control C57BL/6J wild-type mice	Myocardium	<ul style="list-style-type: none"> ↓ mitochondrial and intracellular ROS generation, mitochondrial fission ↑ eNOS phosphorylation ↑ AMP/ATP ratio, AMPK phosphorylation ↑ myocardial blood flow ↑ systolic and diastolic function ↓ myocardial and vascular fibrosis 	Empagliflozin attenuates cardiac OS by suppressing diabetes-induced mitochondrial fission probably via AMPK activation Empagliflozin ameliorates microvascular dysfunction and improves myocardial perfusion, systolic and diastolic function
Oelze et al. (2014) [87]	Empagliflozin	Streptozotocin-induced diabetic Wistar rats and control healthy Wistar rats	Aorta	<ul style="list-style-type: none"> ↓ aortic and endothelial superoxide generation ↓ NOX2 activity ↓ NOX1, NOX2, HO-1, eNOS expression ↓ AGE, RAGE expression ↓ aortic fibrosis ↑ endothelial function Significant changes compared to untreated rats usually achieved only with high dose of empagliflozin 	Empagliflozin attenuates vascular OS by inhibiting NOX and HO-1 expression and AGE/RAGE axis Empagliflozin ameliorates structural and functional vascular disturbances Empagliflozin effects are dose-dependent
Lin et al. (2014) [88]	Empagliflozin	Diabetic db/db mice and lean, control db/m mice	Myocardium	<ul style="list-style-type: none"> ↓ superoxide ↓ myocardial fibrosis, coronary arterial fibrosis and thickening 	Empagliflozin attenuates cardiac and vascular OS
			Thoracic aorta	<ul style="list-style-type: none"> ↓ superoxide ↑ vascular dilating function 	Empagliflozin ameliorates cardiac fibrosis, coronary arterial remodelling, and vascular dysfunction

Table 3. Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in myocardial and vascular tissues of animal models of diabetes

Study	SGLT2i	Animal model	Material	Outcomes after treatment with SGLT2i (compared to diabetic untreated)	Conclusion
Xing et al. (2021) [89]	Dapagliflozin	Streptozotocin-induced diabetic Sprague-Dawley rats and control healthy Sprague-Dawley rats	Left ventricular myocardium	↓NOX subunits expression, gp91phox, p22phox, membrane p67phox ↓MDA, Cu/Zn-SOD expression, total SOD activity No change of GPx, Mn-SOD, and catalase expression ↑ Systolic function	Dapagliflozin improves LV systolic function, possibly by alleviating OS via NOX inhibition Dapagliflozin normalizes diabetes-induced upregulation of antioxidative enzymes
Tian et al. (2021) [90]	Dapagliflozin	Sprague-Dawley rats fed with high-fat diet followed by streptozotocin injection, and control healthy Sprague-Dawley rats	Myocardium	↓NOX4 ↑AMPKa phosphorylation ↓myocardial fibrosis and endothelial-to-mesenchymal transition ↑ systolic and diastolic function ↓ superoxide in endothelial cell line (HUVECs) AMPKa siRNA suppressed antioxidant effects of dapagliflozin	Dapagliflozin ameliorated structural and functional cardiac disturbances by AMPK activation, which is engaged in antioxidative response

3-NT — 3-Nitrotyrosine; AGE — advanced glycation end product; ALDH-2 — mitochondrial aldehyde dehydrogenase; AMPK — AMP-activated protein kinase; eNOS — endothelial nitric oxide synthase; GPx — glutathione peroxidase; HNE — 4-Hydroxynonenal; HO-1 — heme oxygenase-1; HUVECs — human umbilical vein endothelial cells; LVH — left ventricular hypertrophy; NOX — NADPH oxidase; OS — oxidative stress; PKC — protein kinase C; RAGE — receptor for AGE; ROS — reactive oxygen species; SOD — superoxide dismutase

Table 4. Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in diabetes type 2 or heart failure: human studies

Study	SGLT2i	Participants	Sample	Outcomes after treatment with SGLT2i	Conclusion
Kondo et al. (2021) [91]	Canagliflozin (<i>ex vivo</i>)	364 patients with or without T2DM undergoing cardiac surgery not treated with SGLT2i	Right atrial appendage biopsy obtained during cardiac surgery	↓ superoxide (NOX- and uncoupled NOS-derived) ↓ NOX activity, Rac1 activation ↑ AMPK α 2, eNOS phosphorylation No change in OS markers after empagliflozin use	Canagliflozin attenuated OS, reduced Nox activity via SGLT1/AMPK/Rac1 signalling and improved NOS coupling to a greater extent in diabetic patients Empagliflozin, the most selective SGLT2i, did not influence oxidative stress <i>ex vivo</i>
Shigiyama et al. (2017) [23]	Dapagliflozin	80 patients with T2DM treated with 750 mg/day metformin randomized to metformin or dapagliflozin (5 mg/day) added to metformin for 16 weeks	Urea	↓ urine 8-OHdG/creatinine ratio No change in FMD ↑ FMD in the subgroup of patients with HbA _{1c} at baseline over 7.0%	Dapagliflozin reduces OS in diabetic patients and improves endothelial function only in subgroup with inadequately controlled diabetes
Kolijn et al. (2021) [24]	Empagliflozin (<i>ex vivo</i>)	30 patients with HFpEF and 10 healthy donor hearts not treated with SGLT2i	Left ventricular biopsy	↓ cytosolic and mitochondrial H ₂ O ₂ ↓ lipid peroxidation, 3-NT ↑ GSH ↓ uncoupled eNOS ↑ NO/sGC/cGMP/PKG and PKA activity ↓ cardiomyocyte stiffness	Empagliflozin reversed OS dependent impairment of NO/sGC/cGMP/PKG signalling and reduced cardiomyocyte stiffness likely by its antioxidative properties

3-NT — 3-Nitrotyrosine; 8-OHdG — 8-hydroxy-2-deoxyguanosine; AMPK — adenosine monophosphate-activated protein kinase; AMPK α 2 — adenosine monophosphate-activated protein kinase alpha 2; cGMP — cyclic guanosine monophosphate; eNOS — endothelial nitric oxide synthase; FMD — flow mediated dilation; GSH — glutathione; HbA_{1c} — glycated hemoglobin; H₂O₂ — hydrogen peroxide; HFpEF — heart failure with preserved ejection fraction; NO — nitric oxide; NOS — nitric oxide synthase enzyme; NOX — NADPH oxidase; OS — oxidative stress; PKA — protein kinase A; PKG — protein kinase G; Rac1 — ras-related C3 botulinum toxin substrate 1; sGC — soluble guanylate cyclase T2DM — type 2 diabetes mellitus

Table 5. Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) — animal diabetic kidney disease studies

Study	SGLT2i	Animal model	Samples	Outcomes after treatment with SGLT2i (compared to untreated diabetic)	Conclusion
Vallon et al. (2014) [71]	Empagliflozin	Akita/+ (Ins2 ^{+/G96Y}) and littermate Ins2 ^{+/+} control mice	Kidney tissue	<ul style="list-style-type: none"> ↓ NF-κB ↓ CCL2, CD14 ↓ IL-6, TIMP2 No change in expression of NADPH oxidases, NOX2, NOX4, CCL5 cytokine	Empagliflozin attenuated the increase in renal inflammatory markers, but not the OS ones. Diabetes-induced renal changes may be caused by renal hyperfunction, albuminuria and inflammation rather than increased OS.
Terami et al. (2014) [92]	Dapagliflozin	db/db and db/m mice	Kidney tissue	<ul style="list-style-type: none"> ↓ gene expression of CD14, CD11c ↓ gene expression of TGF-β, MCP-1, OPN and ICAM ↓ NOX4 ↓ ROS ↓ NOX4 ↓ ROS ↓ gene expression of MCP-1 and ^{OPN} 	Dapagliflozin ameliorated diabetic nephropathy by reducing hyperglycaemia and macrophage infiltration in the kidney and suppressing OS and proinflammatory gene expression both in the renal tissue and mProx24 cells.
Ojima et al. (2015) [71]	Empagliflozin	Streptozotocin-induced diabetic and non-diabetic Sprague-Dawley rats	Kidney tissue Urine	<ul style="list-style-type: none"> ↓ expression of AGEs, RAGEs, 8-OHdG and F4/80 ↓ gene expression of MCP-1, ICAM-1, PAI-1, CTGF, TGF-β ↓ 8-OHdG ↓ L-FABP 	Empagliflozin treatment could decrease oxidative, inflammatory, and fibrotic reactions in DKD models via suppression of AGE-RAGE axis.
Shin et al. (2016) [93]	Dapagliflozin	Otsuka Long-Evans Tokushima Fatty rats and Long-Evans Tokushima Otsuka rats	Kidney tissue	<ul style="list-style-type: none"> ↓ H₂O₂ ↓ MDA ↓ interstitial fibrosis ↑ SOD, CAT 	Dapagliflozin treatment could be beneficial in DKD via suppression of OS and interstitial fibrosis.
Tang et al. (2017) [73]	Dapagliflozin	uninephrectomized db/db and db/m mice	Kidney cortex Urine	<ul style="list-style-type: none"> ↓ TGF-β1, PAI-1, FN, a1(IV) collagen ↓ expression of NF-κB, p65, MCP-1, NOX4, NOX2, p47phox ↓ TBARS ↓ MCP-1 	Dapagliflozin could slow the progression of diabetes-induced glomerulosclerosis improving the hyperglycaemia-induced inflammation and OS.
Abdel-Wahab et al. (2018) [75]	Dapagliflozin	nicotinamide-streptozotocin-induced diabetic and non-diabetic Wistar rats	Plasma Kidney tissue	<ul style="list-style-type: none"> ↓ TGF-β ↓ TOS ↑ sRAGE ↓ MDA ↑ GSH-Px, SOD 	Treatment with dapagliflozin, led to increased sRAGE level and reduced inflammatory and oxidative markers with amelioration of renal histopathological changes.

Table 5. Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) — animal diabetic kidney disease studies

Study	SGLT2i	Animal model	Samples	Outcomes after treatment with SGLT2i (compared to untreated diabetic)	Conclusion
Tanaka et al. (2018) [74]	Ipragliflozin	BTBR <i>ob/ob</i> and BTBR wild type mice	Kidney cortex	<ul style="list-style-type: none"> ↓ GSH ↓ GSSG signals ↓ MDA ↓ mesangial expansion 	Ipragliflozin is efficient in reducing the OS in the renal tissue.
Kamezaki et al. (2018) [94]	Ipragliflozin	<i>db/db</i> and <i>db/m</i> mice	Kidney cortex	<ul style="list-style-type: none"> ↓ 8-OHdG ↓ NOX4 ↓ S1c34a1, megalin, KIM-1, NGAL ↑ oxygen tension in the kidney cortex 	Ipragliflozin treatment reduced renal cortical hypoxia on early DKD in vivo. Dapagliflozin dose-dependently reduced OS in tubular epithelia and glomerular podocytes.
Cooper Woods et al. (2019) [95]	Canagliflozin	New Zealand obese mice with and without diet-induced T2DM	Urine Kidney tissue	<ul style="list-style-type: none"> ↓ urinary 8-isoprostane levels ↓ tubular fibrosis ↓ macrophage infiltration ↓ cell proliferation 	Canagliflozin prevented the upregulation of OS, renal tubular fibrosis, and renal inflammation in T2DM.
Ali et al. (2019) [96]	Canagliflozin	Wistar rats with and without adenine-induced CKD	Plasma	<ul style="list-style-type: none"> ↓ IL-6, IL-1β and TNF-α ↑ SOD, CAT, GR, and TAC 	Canagliflozin given with adenine ameliorated adenine-induced CKD in rats reducing inflammatory and OS parameters.
Hasan et al. (2020) [97]	Canagliflozin	Long Evans rats with and without ISO-induced oxidative stress	Plasma and kidney tissue	<ul style="list-style-type: none"> ↓ MDA, NO, MPO, APOP ↑ CAT, SOD 	Canagliflozin reduced ISO-induced OS in the kidney and improved endogenous antioxidant action.
Kim et al. (2021) [98]	Dapagliflozin	<i>Db/db</i> and <i>db/+</i> mice	Kidney tissue Human renal tubular epithelial cell line (HK-2)	<ul style="list-style-type: none"> ↓ gene expression of p21, p16, p53 ↓ β-gal and γH2AX ↓ ROS ↑ SOD ↑ β-HB ↑ Nrf2 	Dapagliflozin treatment inhibited senescence processes and reduced OS, both in vitro and in the kidney tissue. Its anti-senescent and anti-inflammatory properties could exist independently of glucose-lowering effects of SGLT2i.
Wu et al. (2021) [76]	Empagliflozin	Sprague Dawley rats with and without streptozotocin-induced DM	Kidney tissue	<ul style="list-style-type: none"> ↓ TNF-α, IL-1β, IL-6 ↓ MDA, NO ↑ SOD, GSH, CAT 	Empagliflozin is effective in treatment of DKD, and its protective effect is related to reduced inflammation, renal fibrosis, and OS in the kidney tissue.
Ahmed et al. (2021) [99]	Empagliflozin	Streptozotocin-induced diabetic and non-diabetic Albino Wistar rats	Kidney tissue	<ul style="list-style-type: none"> ↓ NGAL, KIM-1 ↓ NOX-2.4, TLR-2.4, MyD88 ↓ TNF-α, IL-1β 	Empagliflozin can protect against subclinical AKI after myocardial infarction, reducing kidney injury, inflammation, and OS.

Table 5. Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) — animal diabetic kidney disease studies

Study	SGLT2i	Animal model	Samples	Outcomes after treatment with SGLT2i (compared to untreated diabetic)	Conclusion
Hudkins et al. (2022) [72]	Empagliflozin	BTBR <i>ob/ob</i> mice	Kidney tissue	<p>↓ 8-OHdG, 8-OHG</p> <p>↓ carbonyl oxidation in situ</p> <p>No change in accumulation of glycation-end products.</p> <p>↓ TNF-α, IL-1β, IL-6</p>	Empagliflozin treatment may DKD through the mechanisms leading to podocyte restoration and delay of DKD progress.
Po-Jui et al. (2022) [100]	Dapagliflozin	Streptozotocin-induced diabetic and non-diabetic C57BL6 mice	NRK52E cells	<p>↓ NFκB</p> <p>↓ CCL2, TNF-α, IL-1β, IL-6</p> <p>↑ AMPK, Nrf2, HO-1</p>	Dapagliflozin decreased inflammatory cytokines and ROS levels after LPS-induced endotoxemic shock.
			Kidney tissue	<p>↓ renal tubular injury score</p> <p>↑ E-cadherin</p>	

8-OHdG — 8-hydroxy-2'-deoxyguanosine; 8-OHG — 8-hydroxyguanine; AGE — advanced glycation end product; AKI — acute kidney injury; AMPK — adenosine monophosphate-activated protein kinase; APOP — advanced photochemical oxidation process; b-gal — b-galactosidase activity; b-HB — b-hydroxybutyrate; CAT — catalase; CCL2 — chemokine (C-C motif) ligand 2; CCL5 — chemokine (C-C motif) ligand 5; CD11c — integrin alpha X; CD14 — a cell surface marker of macrophages; CTGF — connective tissue growth factor; DKD — diabetic kidney disease; F4/80 — EGF-like module-containing mucin-like hormone receptor-like 1; FN — fibronectin; gH2AX — phosphorylated form of H2A histone family member X; GR — glutathione reductase; GSH — glutathione; HO-1 — heme oxygenase 1; H2O2 — hydrogen peroxide; ICAM-1 — intercellular adhesion molecule-1; IL — interleukin; KIM-1 — kidney injury molecule-1; L-FABP — L-fatty acid binding protein; LPS — lipopolysaccharides; MCP-1 — monocyte chemoattractant protein-1; MDA — malondialdehyde; MPO — myeloperoxidase; mProx24 — murine proximal tubular epithelial cells; MyD88 — myeloid differentiation primary response 88; NADPH — nicotinamide adenine dinucleotide phosphate; NF- κ B — nuclear factor kappa B; NGAL — neutrophil gelatinase-associated lipocalin; NO — nitric oxide; NOX — NADPH oxidase; Nrf2 — nuclear erythroid 2-related factor 2; NRK52E cells — immortalized rat tubular epithelial cell line; OPN — osteopontin; OS — oxidative stress; PAI-1 — plasminogen activator inhibitor-1; p47phox — neutrophil cytosol factor 1; RAGE — receptor of AGEs; ROS — reactive oxygen species; SA b-gal — senescence-associated b-galactosidase activity; Slc34a1 — solute carrier family 34 member 1; SOD — superoxide dismutase; sRAGE — soluble receptor for AGEs; TAC — total antioxidant capacity; TBARS — thiobarbituric acid-reactive substances; TGF- β — transforming growth factor beta; TIMP2 — tissue inhibitor of matrix metalloproteinases; TLR-2,4 — toll-like receptor 2,4; TNF- α — tumour necrosis factor alpha; TOS — total oxidant status. Mice types: db/db — diabetic mice; db/m — non-diabetic mice; Akita/+ (Ins2+/c96y) — diabetic mice; littermate Ins2+/+ — non-diabetic mice; BTBR *ob/ob* — diabetic mice; BTBR wild type — non-diabetic mice

Table 6. Antioxidative potential of sodium-glucose cotransporter 2 inhibitors (SGLT2i) — chronic kidney disease human studies

Study	SGLT2i	Participants	Samples	Outcomes after treatment with SGLT2i (compared to untreated diabetic)	Findings
Osonoi et al. (2018) [101]	Canagliflozin	20 patients with T2DM and microalbuminuria	Urine	<p>↓ 8-OHdG</p> <p>No changes in other kidney injury and inflammation markers.</p>	Canagliflozin treatment was associated with decrease of one urinary OS marker
Liu et al. (2021) [102]	Ertugliflozin	468 adults with T2DM and CKD stage 3	Plasma	<p>↓ KIM-1</p> <p>↑ eotaxin-1</p> <p>No changes in the other OS, inflammatory and tubular injury markers.</p>	Ertugliflozin treatment was associated with reduced kidney injury marker regardless of baseline renal function

8-OHdG — 8-hydroxy-2'-deoxyguanosine; KIM-1 — kidney injury molecule-1; OS — oxidative stress; T2DM — type 2 diabetes mellitus

There are only a few reports analysing the antioxidative potential of SGLT2i per se in patients with DKD. Two recent studies reported on the antioxidative and anti-inflammatory activity of these agents on renal tissue in patients with DM and impaired renal function [93, 94]. Both studies analysed diverse parameters, e.g. kidney injury molecule-1 (KIM-1), eotaxin, and 8-OHdG in different study groups; consequently, more human studies are needed (see Tab. 5 and Tab. 6).

Conclusions

Since being registered as a new class of oral glucose-lowering drugs (canagliflozin being the first one approved by the FDA in March 2013), almost 10 years later SGLT2i has apparently become not only an glucose-lowering but maybe a new class of cardio- and nephro-protective agent [77]. The underlying mechanisms of this phenomenon are still being studied, but one of the possible mechanisms of these protective properties is the reduction of OS and inflammation.

The reduction of OS as a part of interplay between heart and kidney may link the 2 newly acknowledged protective actions of this class of drugs, namely cardiac and renal protection. Under disease circumstances, the heart and the kidney create a deadly axis of pathophysiological linkage known as the cardio-renal continuum. Increasing evidence suggests that SGLT2i may help to restore the heart-kidney partnership.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

Medical University of Silesia through the statutory work (PCN-1-185/N/0/K).

References

- Ling X, Kuo KL. Oxidative stress in chronic kidney disease. *Renal Replace Ther.* 2018; 4(1), doi: [10.1186/s41100-018-0195-2](https://doi.org/10.1186/s41100-018-0195-2).
- Marrocco I, Altieri F, Peluso I. Measurement and Clinical Significance of Biomarkers of Oxidative Stress in Humans. *Oxid Med Cell Longev.* 2017; 2017: 6501046, doi: [10.1155/2017/6501046](https://doi.org/10.1155/2017/6501046), indexed in Pubmed: 28698768.
- IDF Diabetes Atlas. <https://diabetesatlas.org>.
- Einarson TR, Acs A, Ludwig C, et al. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol.* 2018; 17(1): 83, doi: [10.1186/s12933-018-0728-6](https://doi.org/10.1186/s12933-018-0728-6), indexed in Pubmed: 29884191.
- World Health Organization. Cardiovascular diseases (CVDs). <https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-cvds>.
- Lovre D, Shah S, Sihota A, et al. Managing Diabetes and Cardiovascular Risk in Chronic Kidney Disease Patients. *Endocrinol Metab Clin North Am.* 2018; 47(1): 237-257, doi: [10.1016/j.ecl.2017.10.006](https://doi.org/10.1016/j.ecl.2017.10.006), indexed in Pubmed: 29407054.
- Zinman B, Wanner C, Lachin JM, et al. EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015; 373(22): 2117-2128, doi: [10.1056/NEJMoa1504720](https://doi.org/10.1056/NEJMoa1504720), indexed in Pubmed: 26378978.
- Neal B, Perkovic V, Mahaffey KW, et al. CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med.* 2017; 377(7): 644-657, doi: [10.1056/NEJMoa1611925](https://doi.org/10.1056/NEJMoa1611925), indexed in Pubmed: 28605608.
- Akinci B. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2019; 380(19): 1880-1882, doi: [10.1056/nejmc1902837](https://doi.org/10.1056/nejmc1902837), indexed in Pubmed: 31067394.
- Anker S, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med.* 2021; 385(16): 1451-1461, doi: [10.1056/nejmoa2107038](https://doi.org/10.1056/nejmoa2107038), indexed in Pubmed: 34449189.
- Packer M, Anker SD, Butler J, et al. EMPEROR-Reduced Trial Committees and Investigators. Empagliflozin in Patients With Heart Failure, Reduced Ejection Fraction, and Volume Overload: EMPEROR-Reduced Trial. *J Am Coll Cardiol.* 2021; 77(11): 1381-1392, doi: [10.1016/j.jacc.2021.01.033](https://doi.org/10.1016/j.jacc.2021.01.033), indexed in Pubmed: 33736819.
- Herrington WG, Staplin N, Wanner C, et al. The EMPA-KIDNEY Collaborative Group. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2023; 388(2): 117-127, doi: [10.1056/NEJMoa2204233](https://doi.org/10.1056/NEJMoa2204233), indexed in Pubmed: 36331190.
- McMurray JJV, Solomon SD, Inzucchi SE, et al. DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med.* 2019; 381(21): 1995-2008, doi: [10.1056/NEJMoa1911303](https://doi.org/10.1056/NEJMoa1911303), indexed in Pubmed: 31535829.
- Solomon SD, McMurray JJV, Claggett B, et al. DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med.* 2022; 387(12): 1089-1098, doi: [10.1056/NEJMoa2206286](https://doi.org/10.1056/NEJMoa2206286), indexed in Pubmed: 36027570.
- Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020; 383(15): 1436-1446, doi: [10.1056/NEJMoa2024816](https://doi.org/10.1056/NEJMoa2024816), indexed in Pubmed: 32970396.
- Wróbel M, Rokicka D, Strojek K. Flosins - in the light of the latest recommendations. *Endokrynol Pol.* 2021; 72(6): 589-591, doi: [10.5603/EPa.2021.0098](https://doi.org/10.5603/EPa.2021.0098), indexed in Pubmed: 34970990.
- Griffin M, Rao VS, Ivey-Miranda J, et al. Empagliflozin in Heart Failure: Diuretic and Cardiorenal Effects. *Circulation.* 2020; 142(11): 1028-1039, doi: [10.1161/CIRCULATIONAHA.120.045691](https://doi.org/10.1161/CIRCULATIONAHA.120.045691), indexed in Pubmed: 32410463.
- Baker WL, Smyth LR, Riche DM, et al. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. *J Am Soc Hypertens.* 2014; 8(4): 262-75.e9, doi: [10.1016/j.jash.2014.01.007](https://doi.org/10.1016/j.jash.2014.01.007), indexed in Pubmed: 24602971.
- Fitchett D, Inzucchi SE, Zinman B, et al. Mediators of the improvement in heart failure outcomes with empagliflozin in the EMPA-REG OUTCOME trial. *ESC Heart Fail.* 2021; 8(6): 4517-4527, doi: [10.1002/ehf2.13615](https://doi.org/10.1002/ehf2.13615), indexed in Pubmed: 34605192.
- Kim SoRa, Lee SG, Kim SH, et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. *Nat Commun.* 2020; 11(1): 2127, doi: [10.1038/s41467-020-15983-6](https://doi.org/10.1038/s41467-020-15983-6), indexed in Pubmed: 32358544.
- Verma S, Rawat S, Ho KL, et al. Empagliflozin Increases Cardiac Energy Production in Diabetes: Novel Translational Insights Into the Heart Failure Benefits of SGLT2 Inhibitors. *JACC Basic Transl Sci.* 2018; 3(5): 575-587, doi: [10.1016/j.jacbs.2018.07.006](https://doi.org/10.1016/j.jacbs.2018.07.006), indexed in Pubmed: 30456329.
- Ferrannini E, Baldi S, Frascerra S, et al. Shift to Fatty Substrate Utilization in Response to Sodium-Glucose Cotransporter 2 Inhibition in Subjects Without Diabetes and Patients With Type 2 Diabetes. *Diabetes.* 2016; 65(5): 1190-1195, doi: [10.2337/db15-1356](https://doi.org/10.2337/db15-1356), indexed in Pubmed: 26861783.
- Shigiyama F, Kumashiro N, Miyagi M, et al. Effectiveness of dapagliflozin on vascular endothelial function and glycemic control in patients with early-stage type 2 diabetes mellitus: DEFENCE study. *Cardiovasc Diabetol.* 2017; 16(1): 84, doi: [10.1186/s12933-017-0564-0](https://doi.org/10.1186/s12933-017-0564-0), indexed in Pubmed: 28683796.
- Kolijn D, Pabel S, Tian Y, et al. Empagliflozin improves endothelial and cardiomyocyte function in human heart failure with preserved ejection fraction via reduced pro-inflammatory-oxidative pathways and protein kinase G oxidation. *Cardiovasc Res.* 2021; 117(2): 495-507, doi: [10.1093/cvr/cvaa123](https://doi.org/10.1093/cvr/cvaa123), indexed in Pubmed: 32396609.
- Nabrdalik-Leśniak D, Nabrdalik K, Sedlaczek K, et al. Influence of SGLT2 Inhibitor Treatment on Urine Antioxidant Status in Type 2 Diabetic Patients: A Pilot Study. *Oxid Med Cell Longev.* 2021; 2021: 5593589, doi: [10.1155/2021/5593589](https://doi.org/10.1155/2021/5593589), indexed in Pubmed: 34336104.
- Winiarska A, Knysak M, Nabrdalik K, et al. Inflammation and Oxidative Stress in Diabetic Kidney Disease: The Targets for SGLT2 Inhibitors and GLP-1 Receptor Agonists. *Int J Mol Sci.* 2021; 22(19), doi: [10.3390/ijms221910822](https://doi.org/10.3390/ijms221910822), indexed in Pubmed: 34639160.
- He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med.* 2001; 161(7): 996-1002, doi: [10.1001/archinte.161.7.996](https://doi.org/10.1001/archinte.161.7.996), indexed in Pubmed: 11295963.
- Guglin M, Lynch K, Krischer J. Heart failure as a risk factor for diabetes mellitus. *Cardiology.* 2014; 129(2): 84-92, doi: [10.1159/000363282](https://doi.org/10.1159/000363282), indexed in Pubmed: 25138610.

29. Lommi J, Kupari M, Yki-Järvinen H. Free fatty acid kinetics and oxidation in congestive heart failure. *Am J Cardiol.* 1998; 81(1): 45–50, doi: [10.1016/s0002-9149\(97\)00804-7](https://doi.org/10.1016/s0002-9149(97)00804-7), indexed in Pubmed: 9462605.
30. Suskin N, McKelvie RS, Burns RJ, et al. Glucose and insulin abnormalities relate to functional capacity in patients with congestive heart failure. *Eur Heart J.* 2000; 21(16): 1368–1375, doi: [10.1053/euhj.1999.2043](https://doi.org/10.1053/euhj.1999.2043), indexed in Pubmed: 10952826.
31. Maack C, Lehrke M, Backs J, et al. Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. *Eur Heart J.* 2018; 39(48): 4243–4254, doi: [10.1093/eurheartj/ehy596](https://doi.org/10.1093/eurheartj/ehy596), indexed in Pubmed: 30295797.
32. Kayama Y, Raaz U, Jagger A, et al. Diabetic Cardiovascular Disease Induced by Oxidative Stress. *Int J Mol Sci.* 2015; 16(10): 25234–25263, doi: [10.3390/ijms161025234](https://doi.org/10.3390/ijms161025234), indexed in Pubmed: 26512646.
33. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes.* 2005; 54(6): 1615–1625, doi: [10.2337/diabetes.54.6.1615](https://doi.org/10.2337/diabetes.54.6.1615), indexed in Pubmed: 15919781.
34. Wold LE, Ceylan-Isik AF, Ren J. Oxidative stress and stress signaling: menace of diabetic cardiomyopathy. *Acta Pharmacol Sin.* 2005; 26(8): 908–917, doi: [10.1111/j.1745-7254.2005.00146.x](https://doi.org/10.1111/j.1745-7254.2005.00146.x), indexed in Pubmed: 16038622.
35. Alvarez MC, Caldiz C, Fantinelli JC, et al. Is cardiac hypertrophy in spontaneously hypertensive rats the cause or the consequence of oxidative stress? *Hypertens Res.* 2008; 31(7): 1465–1476, doi: [10.1291/hypres.31.1465](https://doi.org/10.1291/hypres.31.1465), indexed in Pubmed: 18957818.
36. Aragno M, Mastrocola R, Alloati G, et al. Oxidative stress triggers cardiac fibrosis in the heart of diabetic rats. *Endocrinology.* 2008; 149(1): 380–388, doi: [10.1210/en.2007-0877](https://doi.org/10.1210/en.2007-0877), indexed in Pubmed: 17901230.
37. Fu YC, Chi CS, Yin SC, et al. Norepinephrine induces apoptosis in neonatal rat cardiomyocytes through a reactive oxygen species-TNF alpha-caspase signaling pathway. *Cardiovasc Res.* 2004; 62(3): 558–567, doi: [10.1016/j.cardiores.2004.01.039](https://doi.org/10.1016/j.cardiores.2004.01.039), indexed in Pubmed: 15158148.
38. Che R, Yuan Y, Huang S, et al. Mitochondrial dysfunction in the pathophysiology of renal diseases. *Am J Physiol Renal Physiol.* 2014; 306(4): F367–F378, doi: [10.1152/ajprenal.00571.2013](https://doi.org/10.1152/ajprenal.00571.2013), indexed in Pubmed: 24305473.
39. Sedeek M, Callera G, Montezano A, et al. Critical role of Nox4-based NADPH oxidase in glucose-induced oxidative stress in the kidney: implications in type 2 diabetic nephropathy. *Am J Physiol Renal Physiol.* 2010; 299(6): F1348–F1358, doi: [10.1152/ajprenal.00028.2010](https://doi.org/10.1152/ajprenal.00028.2010), indexed in Pubmed: 20630933.
40. Kashiwara N, Haruna Y, Kondeti VK, et al. Oxidative stress in diabetic nephropathy. *Curr Med Chem.* 2010; 17(34): 4256–4269, doi: [10.2174/092986710793348581](https://doi.org/10.2174/092986710793348581), indexed in Pubmed: 20939814.
41. Srinivasan S, Hatley ME, Bolick DJ, et al. Hyperglycaemia-induced superoxide production decreases eNOS expression via AP-1 activation in aortic endothelial cells. *Diabetologia.* 2004; 47(10): 1727–1734, doi: [10.1007/s00125-004-1525-1](https://doi.org/10.1007/s00125-004-1525-1), indexed in Pubmed: 15490108.
42. Yu M, Kim YJ, Kang DH. Indoxyl Sulfate-Induced Endothelial Dysfunction in Patients with Chronic Kidney Disease via an Induction of Oxidative Stress. *Clin J Am Soc Nephrol.* 2011; 6(1): 30–39, doi: [10.2215/CJN.05340610](https://doi.org/10.2215/CJN.05340610), indexed in Pubmed: 20876676.
43. Dou L, Jourde-Chiche N, Faure V, et al. The uremic solute indoxyl sulfate induces oxidative stress in endothelial cells. *J Thromb Haemost.* 2007; 5(6): 1302–1308, doi: [10.1111/j.1538-7836.2007.02540.x](https://doi.org/10.1111/j.1538-7836.2007.02540.x), indexed in Pubmed: 17403109.
44. Tbahriti HF, Kaddous A, Bouchenak M, et al. Effect of different stages of chronic kidney disease and renal replacement therapies on oxidant-antioxidant balance in uremic patients. *Biochem Res Int.* 2013; 2013: 358985, doi: [10.1155/2013/358985](https://doi.org/10.1155/2013/358985), indexed in Pubmed: 24416590.
45. Zachara BA. Selenium and selenium-dependent antioxidants in chronic kidney disease. *Adv Clin Chem.* 2015; 68: 131–151, doi: [10.1016/bs.acc.2014.11.006](https://doi.org/10.1016/bs.acc.2014.11.006), indexed in Pubmed: 25858871.
46. Ceballos-Picot I, Witko-Sarsat V, Merad-Boudia M, et al. Glutathione antioxidant system as a marker of oxidative stress in chronic renal failure. *Free Radic Biol Med.* 1996; 21(6): 845–853, doi: [10.1016/0891-5849\(96\)00233-x](https://doi.org/10.1016/0891-5849(96)00233-x), indexed in Pubmed: 8902530.
47. Hasdan G, Benchetrit S, Rashid G, et al. Endothelial dysfunction and hypertension in 5/6 nephrectomized rats are mediated by vascular superoxide. *Kidney Int.* 2002; 61(2): 586–590, doi: [10.1046/j.1523-1755.2002.00166.x](https://doi.org/10.1046/j.1523-1755.2002.00166.x), indexed in Pubmed: 11849400.
48. Ceballos-Picot I, Witko-Sarsat V, Merad-Boudia M, et al. Glutathione antioxidant system as a marker of oxidative stress in chronic renal failure. *Free Radic Biol Med.* 1996; 21(6): 845–853, doi: [10.1016/0891-5849\(96\)00233-x](https://doi.org/10.1016/0891-5849(96)00233-x), indexed in Pubmed: 8902530.
49. Ha H, Lee HB. Reactive oxygen species as glucose signaling molecules in mesangial cells cultured under high glucose. *Kidney Int Suppl.* 2000; 77: S19–S25, doi: [10.1046/j.1523-1755.2000.07704.x](https://doi.org/10.1046/j.1523-1755.2000.07704.x), indexed in Pubmed: 10997686.
50. Baynes JW. Role of oxidative stress in development of complications in diabetes. *Diabetes.* 1991; 40(4): 405–412, doi: [10.2337/diab.40.4.405](https://doi.org/10.2337/diab.40.4.405), indexed in Pubmed: 2010041.
51. Salahudeen AK, Kanji V, Reckelhoff JF, et al. Pathogenesis of diabetic nephropathy: a radical approach. *Nephrol Dial Transplant.* 1997; 12(4): 664–668, doi: [10.1093/ndt/12.4.664](https://doi.org/10.1093/ndt/12.4.664), indexed in Pubmed: 9140991.
52. Satoh M, Fujimoto S, Haruna Y, et al. NAD(P)H oxidase and uncoupled nitric oxide synthase are major sources of glomerular superoxide in rats with experimental diabetic nephropathy. *Am J Physiol Renal Physiol.* 2005; 288(6): F1144–F1152, doi: [10.1152/ajprenal.00221.2004](https://doi.org/10.1152/ajprenal.00221.2004), indexed in Pubmed: 15687247.
53. Gorin Y, Block K, Hernandez J, et al. Nox4 NAD(P)H oxidase mediates hypertrophy and fibronectin expression in the diabetic kidney. *J Biol Chem.* 2005; 280(47): 39616–39626, doi: [10.1074/jbc.M502412200](https://doi.org/10.1074/jbc.M502412200), indexed in Pubmed: 16135519.
54. Zhang L, Liu J, Zhou F, et al. PGC-1 α ameliorates kidney fibrosis in mice with diabetic kidney disease through an antioxidative mechanism. *Mol Med Rep.* 2018; 17(3): 4490–4498, doi: [10.3892/mmr.2018.8433](https://doi.org/10.3892/mmr.2018.8433), indexed in Pubmed: 29344670.
55. Li Li, Zhang L, Chen D, et al. PEDF relieves kidney injury in type 2 diabetic nephropathy mice by reducing macrophage infiltration. *Endokrynol Pol.* 2021; 72(6): 643–651, doi: [10.5603/EPa2021.0085](https://doi.org/10.5603/EPa2021.0085), indexed in Pubmed: 34647607.
56. Bondor CI, Potra AR, Moldovan D, et al. Relationship of adiponectin to markers of oxidative stress in type 2 diabetic patients: influence of incipient diabetes-associated kidney disease. *Int Urol Nephrol.* 2015; 47(7): 1173–1180, doi: [10.1007/s11255-015-1004-2](https://doi.org/10.1007/s11255-015-1004-2), indexed in Pubmed: 25971352.
57. Apakkan Aksun S, Ozmen B, Ozmen D, et al. Serum and urinary nitric oxide in Type 2 diabetes with or without microalbuminuria: relation to glomerular hyperfiltration. *J Diabetes Complications.* 2003; 17(6): 343–348, doi: [10.1016/s1056-8727\(02\)00196-4](https://doi.org/10.1016/s1056-8727(02)00196-4), indexed in Pubmed: 14583179.
58. Roumeliotis A, Roumeliotis S, Tsetsos F, et al. Oxidative Stress Genes in Diabetes Mellitus Type 2: Association with Diabetic Kidney Disease. *Oxid Med Cell Longev.* 2021; 2021: 2531062, doi: [10.1155/2021/2531062](https://doi.org/10.1155/2021/2531062), indexed in Pubmed: 34545296.
59. DeFronzo RA, Hompesch M, Kasichayanula S, et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. *Diabetes Care.* 2013; 36(10): 3169–3176, doi: [10.2337/dcl3-0387](https://doi.org/10.2337/dcl3-0387), indexed in Pubmed: 23735727.
60. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020; 75(4): 422–434, doi: [10.1016/j.jacc.2019.11.031](https://doi.org/10.1016/j.jacc.2019.11.031), indexed in Pubmed: 32000955.
61. Vallon V, Rose M, Gerasimova M, et al. Knockout of Na-glucose transporter SGLT2 attenuates hyperglycemia and glomerular hyperfiltration but not kidney growth or injury in diabetes mellitus. *Am J Physiol Renal Physiol.* 2013; 304(2): F156–F167, doi: [10.1152/ajprenal.00409.2012](https://doi.org/10.1152/ajprenal.00409.2012), indexed in Pubmed: 23152292.
62. Ni L, Yuan C, Chen G, et al. SGLT2i: beyond the glucose-lowering effect. *Cardiovasc Diabetol.* 2020; 19(1): 98, doi: [10.1186/s12933-020-01071-y](https://doi.org/10.1186/s12933-020-01071-y), indexed in Pubmed: 32590982.
63. Aragón-Herrera A, Feijóo-Bandín S, Otero Santiago M, et al. Empagliflozin reduces the levels of CD36 and cardiotoxic lipids while improving autophagy in the hearts of Zucker diabetic fatty rats. *Biochem Pharmacol.* 2019; 170: 113677, doi: [10.1016/j.bcp.2019.113677](https://doi.org/10.1016/j.bcp.2019.113677), indexed in Pubmed: 31647926.
64. Salt I, Hardie D. AMP-Activated Protein Kinase. *Circul Res.* 2017; 120(11): 1825–1841, doi: [10.1161/circresaha.117.309633](https://doi.org/10.1161/circresaha.117.309633).
65. Zhou H, Wang S, Zhu P, et al. Empagliflozin rescues diabetic myocardial microvascular injury via AMPK-mediated inhibition of mitochondrial fission. *Redox Biol.* 2018; 15: 335–346, doi: [10.1016/j.redox.2017.12.019](https://doi.org/10.1016/j.redox.2017.12.019), indexed in Pubmed: 29306791.
66. Chen R, Dioum EM, Hogg RT, et al. Hypoxia increases sirtuin 1 expression in a hypoxia-inducible factor-dependent manner. *J Biol Chem.* 2011; 286(16): 13869–13878, doi: [10.1074/jbc.M110.175414](https://doi.org/10.1074/jbc.M110.175414), indexed in Pubmed: 21345792.
67. Lee WC, Chau YY, Ng HY, et al. Empagliflozin Protects HK-2 Cells from High Glucose-Mediated Injuries via a Mitochondrial Mechanism. *Cells.* 2019; 8(9), doi: [10.3390/cells8091085](https://doi.org/10.3390/cells8091085), indexed in Pubmed: 31540085.
68. Liu X, Xu C, Xu L, et al. Empagliflozin improves diabetic renal tubular injury by alleviating mitochondrial fission via AMPK/SPI1/PGAM5 pathway. *Metabolism.* 2020; 111: 154334, doi: [10.1016/j.metabol.2020.154334](https://doi.org/10.1016/j.metabol.2020.154334), indexed in Pubmed: 32777444.
69. Lee YH, Kim SH, Kang JM, et al. Empagliflozin attenuates diabetic tubulopathy by improving mitochondrial fragmentation and autophagy. *Am J Physiol Renal Physiol.* 2019; 317(4): F767–F780, doi: [10.1152/ajprenal.00565.2018](https://doi.org/10.1152/ajprenal.00565.2018), indexed in Pubmed: 31390268.
70. Vallon V, Gerasimova M, Rose MA, et al. SGLT2 inhibitor empagliflozin reduces renal growth and albuminuria in proportion to hyperglycemia and prevents glomerular hyperfiltration in diabetic Akita mice. *Am J Physiol Renal Physiol.* 2014; 306(2): F194–F204, doi: [10.1152/ajprenal.00520.2013](https://doi.org/10.1152/ajprenal.00520.2013), indexed in Pubmed: 24226524.
71. Ojima A, Matsui T, Nishino Y, et al. Empagliflozin, an Inhibitor of Sodium-Glucose Cotransporter 2 Exerts Anti-Inflammatory and Anti-

- fibrotic Effects on Experimental Diabetic Nephropathy Partly by Suppressing AGEs-Receptor Axis. *Horm Metab Res.* 2015; 47(9): 686–692, doi: [10.1055/s-0034-1395609](https://doi.org/10.1055/s-0034-1395609), indexed in Pubmed: 25611208.
72. Hudkins KL, Li X, Holland AL, et al. Regression of diabetic nephropathy by treatment with empagliflozin in BTBR ob/ob mice. *Nephrol Dial Transplant.* 2022; 37(5): 847–859, doi: [10.1093/ndt/gfab330](https://doi.org/10.1093/ndt/gfab330), indexed in Pubmed: 34865099.
 73. Tang Li, Wu Y, Tian Mi, et al. Dapagliflozin slows the progression of the renal and liver fibrosis associated with type 2 diabetes. *Am J Physiol Endocrinol Metab.* 2017; 313(5): E563–E576, doi: [10.1152/ajpendo.00086.2017](https://doi.org/10.1152/ajpendo.00086.2017), indexed in Pubmed: 28811292.
 74. Tanaka S, Sugiura Y, Saito H, et al. Sodium-glucose cotransporter 2 inhibition normalizes glucose metabolism and suppresses oxidative stress in the kidneys of diabetic mice. *Kidney Int.* 2018; 94(5): 912–925, doi: [10.1016/j.kint.2018.04.025](https://doi.org/10.1016/j.kint.2018.04.025), indexed in Pubmed: 30021702.
 75. Abdel-Wahab AF, Bamagous GA, Al-Harizy RM, et al. Renal protective effect of SGLT2 inhibitor dapagliflozin alone and in combination with irbesartan in a rat model of diabetic nephropathy. *Biomed Pharmacother.* 2018; 103: 59–66, doi: [10.1016/j.biopha.2018.03.176](https://doi.org/10.1016/j.biopha.2018.03.176), indexed in Pubmed: 29635129.
 76. Wu X, Li He, Wan Z, et al. The combination of ursolic acid and empagliflozin relieves diabetic nephropathy by reducing inflammation, oxidative stress and renal fibrosis. *Biomed Pharmacother.* 2021; 144: 112267, doi: [10.1016/j.biopha.2021.112267](https://doi.org/10.1016/j.biopha.2021.112267), indexed in Pubmed: 34624679.
 77. Food and Drug Administration. Drug Approval Package. Invokana (canagliflozin) Tablets. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204042Orig1s000TOC.cfm.
 78. Anderson EJ, Kypson AP, Rodriguez E, et al. Substrate-specific derangements in mitochondrial metabolism and redox balance in the atrium of the type 2 diabetic human heart. *J Am Coll Cardiol.* 2009; 54(20): 1891–1898, doi: [10.1016/j.jacc.2009.07.031](https://doi.org/10.1016/j.jacc.2009.07.031), indexed in Pubmed: 19892241.
 79. Montaigne D, Marechal X, Coisne A, et al. Myocardial contractile dysfunction is associated with impaired mitochondrial function and dynamics in type 2 diabetic but not in obese patients. *Circulation.* 2014; 130(7): 554–564, doi: [10.1161/CIRCULATIONAHA.113.008476](https://doi.org/10.1161/CIRCULATIONAHA.113.008476), indexed in Pubmed: 24928681.
 80. Connelly K, Advani A, Advani S, et al. Impaired cardiac anti-oxidant activity in diabetes: human and correlative experimental studies. *Acta Diabetol.* 2014; 51(5): 771–782, doi: [10.1007/s00592-014-0608-9](https://doi.org/10.1007/s00592-014-0608-9).
 81. Wang B, Raedschelders K, Shrivah J, et al. Differences in myocardial PTEN expression and Akt signalling in type 2 diabetic and nondiabetic patients undergoing coronary bypass surgery. *Clin Endocrinol (Oxf).* 2011; 74(6): 705–713, doi: [10.1111/j.1365-2265.2011.03979.x](https://doi.org/10.1111/j.1365-2265.2011.03979.x), indexed in Pubmed: 21521253.
 82. Polidori MC, Praticó D, Savino K, et al. Increased F2 isoprostane plasma levels in patients with congestive heart failure are correlated with antioxidant status and disease severity. *J Card Fail.* 2004; 10(4): 334–338, doi: [10.1016/j.cardfail.2003.11.004](https://doi.org/10.1016/j.cardfail.2003.11.004), indexed in Pubmed: 15309701.
 83. Gupte RS, Vijay V, Marks B, et al. Upregulation of glucose-6-phosphate dehydrogenase and NAD(P)H oxidase activity increases oxidative stress in failing human heart. *J Card Fail.* 2007; 13(6): 497–506, doi: [10.1016/j.cardfail.2007.04.003](https://doi.org/10.1016/j.cardfail.2007.04.003), indexed in Pubmed: 17675065.
 84. Li C, Zhang J, Xue M, et al. SGLT2 inhibition with empagliflozin attenuates myocardial oxidative stress and fibrosis in diabetic mice heart. *Cardiovasc Diabetol.* 2019; 18(1): 15, doi: [10.1186/s12933-019-0816-2](https://doi.org/10.1186/s12933-019-0816-2), indexed in Pubmed: 30710997.
 85. Steven S, Oelze M, Hanf A, et al. The SGLT2 inhibitor empagliflozin improves the primary diabetic complications in ZDF rats. *Redox Biol.* 2017; 13: 370–385, doi: [10.1016/j.redox.2017.06.009](https://doi.org/10.1016/j.redox.2017.06.009), indexed in Pubmed: 28667906.
 86. Habibi J, Aroor AR, Sowers JR, et al. Sodium glucose transporter 2 (SGLT2) inhibition with empagliflozin improves cardiac diastolic function in a female rodent model of diabetes. *Cardiovasc Diabetol.* 2017; 16(1): 9, doi: [10.1186/s12933-016-0489-z](https://doi.org/10.1186/s12933-016-0489-z), indexed in Pubmed: 28086951.
 87. Oelze M, Kröller-Schön S, Welschof P, et al. The sodium-glucose co-transporter 2 inhibitor empagliflozin improves diabetes-induced vascular dysfunction in the streptozotocin diabetes rat model by interfering with oxidative stress and glucotoxicity. *PLoS One.* 2014; 9(11): e112394, doi: [10.1371/journal.pone.0112394](https://doi.org/10.1371/journal.pone.0112394), indexed in Pubmed: 25402275.
 88. Lin B, Koibuchi N, Hasegawa Yu, et al. Glycemic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive dysfunction in obese and type 2 diabetic mice. *Cardiovasc Diabetol.* 2014; 13: 148, doi: [10.1186/s12933-014-0148-1](https://doi.org/10.1186/s12933-014-0148-1), indexed in Pubmed: 25344694.
 89. Xing YJ, Liu BH, Wan SJ, et al. A SGLT2 Inhibitor Dapagliflozin Alleviates Diabetic Cardiomyopathy by Suppressing High Glucose-Induced Oxidative Stress and . *Front Pharmacol.* 2021; 12: 708177, doi: [10.3389/fphar.2021.708177](https://doi.org/10.3389/fphar.2021.708177), indexed in Pubmed: 34322029.
 90. Tian J, Zhang M, Suo M, et al. Dapagliflozin alleviates cardiac fibrosis through suppressing EndMT and fibroblast activation via AMPKa/TGF- β /Smad signalling in type 2 diabetic rats. *J Cell Mol Med.* 2021; 25(16): 7642–7659, doi: [10.1111/jcmm.16601](https://doi.org/10.1111/jcmm.16601), indexed in Pubmed: 34169635.
 91. Kondo H, Akoumianakis I, Badi I, et al. Effects of canagliflozin on human myocardial redox signalling: clinical implications. *Eur Heart J.* 2021; 42(48): 4947–4960, doi: [10.1093/eurheartj/ehab420](https://doi.org/10.1093/eurheartj/ehab420), indexed in Pubmed: 34293101.
 92. Terami N, Ogawa D, Tachibana H, et al. Long-term treatment with the sodium glucose cotransporter 2 inhibitor, dapagliflozin, ameliorates glucose homeostasis and diabetic nephropathy in db/db mice. *PLoS One.* 2014; 9(6): e100777, doi: [10.1371/journal.pone.0100777](https://doi.org/10.1371/journal.pone.0100777), indexed in Pubmed: 24960177.
 93. Shin SJ, Chung S, Kim SJ, et al. Effect of Sodium-Glucose Co-Transporter 2 Inhibitor, Dapagliflozin, on Renal Renin-Angiotensin System in an Animal Model of Type 2 Diabetes. *PLoS One.* 2016; 11(11): e0165703, doi: [10.1371/journal.pone.0165703](https://doi.org/10.1371/journal.pone.0165703), indexed in Pubmed: 27802313.
 94. Kamezaki M, Kusaba T, Komaki K, et al. Comprehensive renoprotective effects of ipragliflozin on early diabetic nephropathy in mice. *Sci Rep.* 2018; 8(1): 4029, doi: [10.1038/s41598-018-22229-5](https://doi.org/10.1038/s41598-018-22229-5), indexed in Pubmed: 29507299.
 95. Cooper Woods T, Satou R, Miyata K, et al. Canagliflozin Prevents Intrarenal Angiotensinogen Augmentation and Mitigates Kidney Injury and Hypertension in Mouse Model of Type 2 Diabetes Mellitus. *Am J Nephrol.* 2019; 49(4): 331–342, doi: [10.1159/000499597](https://doi.org/10.1159/000499597), indexed in Pubmed: 30921791.
 96. Ali BH, Al Salam S, Al Suleimani Y, et al. Effects of the SGLT-2 Inhibitor Canagliflozin on Adenine-Induced Chronic Kidney Disease in Rats. *Cell Physiol Biochem.* 2019; 52(1): 27–39, doi: [10.33594/000000003](https://doi.org/10.33594/000000003), indexed in Pubmed: 30790503.
 97. Hasan R, Lasker S, Hasan A, et al. Canagliflozin ameliorates renal oxidative stress and inflammation by stimulating AMPK-Akt-eNOS pathway in the isoprenaline-induced oxidative stress model. *Sci Rep.* 2020; 10(1): 14659, doi: [10.1038/s41598-020-71599-2](https://doi.org/10.1038/s41598-020-71599-2), indexed in Pubmed: 32887916.
 98. Kim MN, Moon JH, Cho YM. Sodium-glucose cotransporter-2 inhibition reduces cellular senescence in the diabetic kidney by promoting ketone body-induced NRF2 activation. *Diabetes Obes Metab.* 2021; 23(11): 2561–2571, doi: [10.1111/dom.14503](https://doi.org/10.1111/dom.14503), indexed in Pubmed: 34318973.
 99. Ahmed AS, Mona MM, Abdel-Kareem MA, et al. SGLT2 inhibitor empagliflozin monotherapy alleviates renal oxidative stress in albino Wistar diabetic rats after myocardial infarction induction. *Biomed Pharmacother.* 2021; 139: 111624, doi: [10.1016/j.biopha.2021.111624](https://doi.org/10.1016/j.biopha.2021.111624), indexed in Pubmed: 33915503.
 100. Chi PJ, Lee CJ, Hsieh YJ, et al. Dapagliflozin Ameliorates Lipopolysaccharide Related Acute Kidney Injury in Mice with Streptozotocin-induced Diabetes Mellitus. *Int J Med Sci.* 2022; 19(4): 729–739, doi: [10.7150/ijms.69031](https://doi.org/10.7150/ijms.69031), indexed in Pubmed: 35582427.
 101. Osonoi T, Gouda M, Kubo M, et al. Effect of Canagliflozin on Urinary Albumin Excretion in Japanese Patients with Type 2 Diabetes Mellitus and Microalbuminuria: A Pilot Study. *Diabetes Technol Ther.* 2018; 20(10): 681–688, doi: [10.1089/dia.2018.0169](https://doi.org/10.1089/dia.2018.0169), indexed in Pubmed: 30096243.
 102. Liu H, Sridhar VS, Lovblom LE, et al. Markers of Kidney Injury, Inflammation, and Fibrosis Associated With Ertugliflozin in Patients With CKD and Diabetes. *Kidney Int Rep.* 2021; 6(8): 2095–2104, doi: [10.1016/j.ekir.2021.05.022](https://doi.org/10.1016/j.ekir.2021.05.022), indexed in Pubmed: 34386658.