Kidneys in heart failure: Impact of flozins

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ABSTRACT

Chronic kidney disease (CKD) and heart failure (HF) represent two modern diseases of civilization and are closely related. According to the concept of cardio-renal and reno-cardiac syndromes, most patients with CKD are affected by cardiovascular disease (CVD), and CVD (including HF) is one of the factors not only promoting progression of established CKD but also triggering its onset and development. Treatment of CVD and HF in CKD patients remains challenging since CKD patients are characterized by extremely diverse and strongly expressed risk profiles, and the data from well-designed clinical trials addressing this population are scarce. Nevertheless, it seems that most of the drugs used in the treatment of CVD and HF (including beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blocking agents, mineralocorticosteroid receptor antagonists, and sacubitril/valsartan) are of similar efficacy in patients with glomerular filtration rate (GFR) ranging between 45 and 60 ml/min/1.73 m^2 (although higher prevalence of side effects may limit their use). The data on cardiovascular (CV) drug efficacy in patients with lower GFR values (i.e., below 30–45 ml/min/1.73 m^2) remain limited. In this review, we focused on the efficacy of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in the treatment of CVD and HF in CKD patients with or without diabetes. SGLT2i are clearly cardioprotective in a wide spectrum of estimated GFR although the data for HF patients with respect to urine albumin-creatinine ratio (UACR) are scarce, and for those with significantly reduced estimated GFR are still not available or not convincing, even after completion of large-scale high-quality major cardiovascular outcome trials (CVOT) in type 2 diabetes mellitus (T2DM) or trials with flozins in CKD and HF.

Key words: cardiovascular disease, cardiovascular events, chronic kidney disease, heart failure, sodium-glucose co-transporter type 2 inhibitors

CHRONIC KIDNEY DISEASE AND HEART FAILURE: MODERN CIVILIZATION DISEASES

Chronic kidney disease has only recently been recognized as a prevalent worldwide disease. According to different national and international registries, between 7 and 15% of the whole world population suffers from the disease [1–3]. CKD is not a particular diagnosis but rather describes common pathways and consequences of several specific pathologies which significantly differ in terms of etiology, dynamics of progression, and prognosis. The leading one is diabetic kidney disease (DKD) accounting for 20%–30% of all patients who suffer from diabetes (i.e. up to 3%–4% of whole populations in Western societies) [4, 5]. Glomerular, cystic, tubulointerstitial, and other well-defined renal pathologies together with DKD allow explanation of the background of up to 60% of CKD cases; even in best-functioning health systems, more than 40% of CKD patients have their underlying cause of CKD undefined. CKD developing as a consequence of diverse cardiac and vascular pathologies may be an important part of this undefined number and best fits the definition of cardio-renal syndrome type 2 (according to the classification developed by Claudio Ronco, with further modifications) [6]. It is fair to assume that renal injury secondary to cardiovascular disease (CVD) (beyond primary hypertension which seems to be heavily overestimated as a cause of renal failure) may account for or at least significantly contribute to the de-

velopment of CKD in many patients in whom no certain underlying renal pathology has been established [7, 8].

The kidney is not only the target organ suffering from CVD but also the culprit accelerating and worsening the course of CVD (Ronco's cardio-renal syndrome type 4) [6]. Heart failure (HF) is highly prevalent among patients with CKD (and vice versa — CKD is one of the leading comorbidities in patients with HF). The incidence of HF in patients with CKD is extremely high: 15%–20% of patients with CKD and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 would develop this disease — the risk of HF is on average 3 times higher in patients with eGFR below this threshold as compared to people with normal renal function. It increases further by a factor enormously high – 12 to 36 – in subjects treated with dialysis [9]. CKD is also a universal risk factor for adverse outcomes in many other CV diseases, in addition to HF [10, 11].

Looking at the other side of the coin, as mentioned above, 7%–15% of the general population may suffer from CKD (defined as GFR <60 ml/min/1.73 m^2) – the prevalence rises to as high as 35%–55% in patients with HF, both with preserved (HFpEF) and reduced (HFrEF) ejection fraction [12–15]. These epidemiological data have been reproduced by the key HF trials with SGLT2i (Table 1) [16–19]. The four pivotal HF trials with SGLT2i reflect real life practice when looking at their renal aspects and should convince the medical community that CKD is the leading comorbidity in the HF population.

Both reduced GFR and albuminuria significantly and synergistically increase the risk of adverse outcomes in HF [20, 21]. It has been repeatedly confirmed in such trials as SOLVD, CHARM, GISSI, RENAAL, MESA, and ARIC that albuminuria predicts HF incidence and/or progression. Even more importantly, in contrast to GFR, which is associated with increased CVD risk when decreased to less than 45–60 ml/min/1.73 m^2, the relationship between albuminuria and CVD is linear and starts to increase from values as low as 6–10 mg/g of creatinine. i.e. below the traditionally defined threshold of microalbuminuria (30 mg/g of creatinine) [22–25].

Several mechanisms explain the increased risk of CVD and HF in CKD patients. They include, among others: fluid overload and sodium retention, hypertension (which is likely to be resistant and require three or more antihypertensive drugs), increased activity of the renin-angiotensin-aldosterone system, increased sympathetic nervous system activity (with a special role of afferent sympathetic signaling from injured kidneys to the central nervous system as a contributing factor), systemic inflammation, endothelial dysfunction and many others [6, 26–32]. Although most of these mechanisms are not specific to CKD, they are more pronounced as compared with patients with preserved kidney function. Some factors considered more specific for CKD that may contribute to CVD and HF include arterial stiffness, mineral and bone disorders of CKD (including severely disturbed metabolism of vitamin D), renal anemia, and accumulation of uremic toxins (cardiotoxins) [33].

HOW TO TREAT HF IN CKD PATIENTS?

Patients with CKD were for decades abandoned as candidates for clinical trials investigating therapeutic interventions aimed at decreasing CVD events. "Big Pharma" sponsors and independent investigators were reluctant to include these patients for several reasons: they were considered non-representative of an "average" population (CKD has only recently been recognized as a highly prevalent risk factor of CVD), were likely to increase heterogeneity of the study samples, their inclusion might have been associated with results less positive than expected. It resulted in the general rule to exclude subjects with eGFR of less than 30 or even less than 45 ml/min/1.73 m^2 from pivotal clinical trials in CVD, HF, and hypertension (or — at best — they were present but underrepresented). This, in turn, resulted in the lack of direct evidence considering treatment efficacy in these groups. For decades, there was a general assumption that CKD patients are too sick to be helped, which led to "renalism" in therapy (advanced CKD patients were deprived of life-saving therapies just because of their CKD). Guidelines covering CVD treatment in the setting of CKD were not developed — patients were treated based on extrapolation of data from the general population. Interestingly, when analyzing the HF literature with a focus on CKD patients, it seems that this pessimistic view was not justified. For example, in the HOPE trial, ramipril tended to be more effective in cardiovascular event prevention (including death) in patients with baseline serum creatinine exceeding 1.4 mg/dl as compared to those with normal kidney function [34]. Pivotal trials showing the benefit of

Table 1. Heart failure trials with SGLT2i — not designed for CKD but largely addressing CKD populations

Study (acronym)	Investigated drug	Exclusion eGFR cut-off (ml/min/1.73 m^2)	Patients with eGFR <60 ml/min/1.73 m^2	Mean eGFR (ml/min/1.73 m^2)
EMPEROR-Reduced, 2020 [18]	Empagliflozin	<20	48% (empagliflozin); 48.6% (placebo)	61.8 ± 21.7 (empagliflozin) 62.2 ± 21.5 (placebo)
EMPEROR-Preserved, 2021 [19]	Empagliflozin	<20	50.2% (empagliflozin) 49.6% (placebo)	60.6 ± 19.8 (empagliflozin) 60.6 ± 19.9 (placebo)
DAPA-HF, 2019 [17]	Dapagliflozin	<30	40.6% (dapagliflozin) 40.7% (placebo)	66.0 ± 19.6 (dapagliflozin) 65.5 ± 19.3 (placebo)
DELIVER, 2022 [20]	Dapagliflozin	<25		61 ± 19 (identical for both groups – dapagliflozin and placebo)

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter 2 inhibitors

mineralocorticosteroid receptor antagonists, i.e. RALES (with spironolactone) and EMPHASIS-HF (with eplerenone), demonstrated no significant interaction between efficacy in reducing the cardiac endpoints and GFR; patients with eGFR <60 ml/min/1.73 m^2 or in the GFR range between 30 and 60 ml/min/1.73 m^2 were doing as well as those with preserved renal function (although in both trials the risk of hyperkalemia was significantly higher in patients with CKD stage 3 or higher) [35–37]. The Val-HEFT trial, was generally negative, demonstrating no benefit of adding valsartan or placebo to the standard of care in patients with HF. The study showed some CVD benefits only in patients with CKD, in whom the first morbid event occurred statistically less frequently in subjects receiving valsartan (even though most patients were also treated with background ACEi) [38]. The efficacy of a drug combining valsartan and neprilysin inhibitor sacubitril was equal in patients with eGFR above and below 60 ml/min/1.73 m^2 in terms of reducing the primary endpoint and CV death [39]. Finally, most pivotal trials with beta-blockers in HF (such as MERIT-HF with metoprolol or CAPRICORN and COPERNICUS with carvedilol) demonstrated equal efficacy of these drugs in preventing CV events in patients with and without CKD [40–42]. Interestingly, in the MERIT trial, there was an interaction with eGFR — the benefit in terms of reduced total mortality, all-cause mortality plus all-cause hospitalization, or all-cause mortality plus HF hospitalization rose with decreasing GFR and was most pronounced in patients with eGFR of less than 45 ml/min/1.73 m^2 as compared to those with eGFR in the range of 45–60 and >60 ml/min/1.73 m^2 [42]. Finally, one of the key trials that paved the way to contemporary CVD prevention (though not directly HF), namely the HOT trial, has demonstrated that acetylsalicylic acid in secondary CVD prevention provides the greatest benefit in reducing major CV events, myocardial infarction, stroke, and CV mortality in patients with eGFR less than 45 ml/min/1.73 m^2 [43].

Taking into account these retrospective data, one could conclude that therapeutic nihilism in relation to CKD (and more specifically HF/CVD treatment in CKD patients) is not justified. Unfortunately, such a conclusion cannot be fully supported. First, retrospective analyses are not equivalent to trials with pre-specified analyses of outcomes in patients with low GFR. Second, in most of the trials, patients with eGFR in the range between 30 and 60 ml/min/1.73 m^2 were underrepresented, and subjects with CKD 4 (eGFR of less than 30 ml/min/1.73 m^2) were virtually absent. Third, in most of these reports, an independent impact of GFR and albuminuria on outcomes, as well as their possible synergism, could not be analyzed.

TREATMENT OF CARDIOVASCULAR DISEASE USING SGLT2i — ARE THEY EFFECTIVE IN CKD?

SGLT2i seem to be the true game-changers in cardio-nephro-metabolic medicine. The nephroprotective effects of this class of drugs are not the main scope of this review — nevertheless, it must be emphasized that there is a class effect on nephroprotection (at least for three agents in the class — canagliflozin, dapagliflozin, and empagliflozin and somewhat less convincingly — for sotagliflozin). The three mentioned drugs showed their efficacy regardless of baseline eGFR (in the range between normal to as low as 20 ml/min/1.73 m^2), albuminuria (from low grade, i.e., below microalbuminuria to the nephrotic range), cardiovascular risk profile, and definitions of the renal endpoints. In addition, two of them (dapagliflozin and empagliflozin) have shown their efficacy both in diabetic and non-diabetic kidney disease. The universally observed nephroprotective effect was demonstrated in cardiovascular outcome trials (CVOT) performed in diabetic patients with high CV risk but otherwise well-preserved renal function (EMPAREG-Outcome, DECLARE-TIMI, CANVAS), in patients with diabetic and non-diabetic CKD (CREDENCE, DAPA-CKD, EMPA-KIDNEY), and in studies performed in HF patients (the most pronounced and statistically significant renal benefit was achieved in the EMPEROR-Reduced trial, whereas in other HF trials, trends towards better kidney protection were observed, with no signal towards renal function worsening in any trial) [17–20, 46–55]. For this review, it is important to take a closer look at the cardio-vascular endpoints in some of the mentioned studies in the context of the presence and severity of CKD (as measured by both eGFR and urine albumin-creatinine ratio [UACR]).

The story begins with three major CVOT trials performed in patients with diabetes mellitus type 2 (T2DM) and high or very high cardiovascular risk profiles. In these trials, the impact of SGLT2i on cardiovascular outcomes in the context of eGFR and UACR was defined as a pre-specified analysis. CVOT results with regard to renal function and/or injury are summarized in Table 2 [46, 48, 49, 56–60]. As in the case of later trials, performed in HF and CKD patients, there was no interaction between the effect of SGLT2i on CV outcome and baseline eGFR and/or UACR. Data from studies performed in the HF patients are also presented in Table 2 and the same conclusion could be drawn — SGLT2i were equally effective in different eGFR ranges (the most detailed data are available for the EMPEROR-Reduced trial) [17–20]. Overall, in the CVOT trials, there was a general trend towards a greater CV benefit with increasing UACR and increasing eGFR. The same holds true for HF trials, in which, unfortunately, the impact of UACR on CV endpoints was not adequately addressed (again, except for the EMPEROR-Reduced trial). Studies in CKD patients recruiting patients with diabetes only (CREDENCE) and with or without diabetes (DAPA-CKD and EMPA-KIDNEY) defined several secondary cardiovascular endpoints, analyzed death of any cause and incorporated CV death into the primary composite endpoint identifying progression of CKD (primary composite outcome in these trials was defined as the first occurrence of the following: a permanent decline in eGFR of ≥50%, ≥40%, end-stage kidney disease (ESKD) [commencement of dialysis, renal transplantation,

Table 2. Efficacy of SGLT2i on primary or key secondary cardiovascular endpoints in cardiovascular outcome trials in type 2 diabetes mellitus, heart failure trials, and chronic kidney disease (CKD) trials depending on CKD (GFR and/or UACR)

Study (acronym)	Investigated drug	Key eligibility criteria	CVD outcome definition[a]	CV outcome depending on eGFR (ml/min/1.73 m^2) at baseline (HR, 95% CI)	CV outcome depending on UACR (mg/g) at baseline (HR, 95% CI)
Cardiovascular outcome trials in diabetes					
EMPAREG-Outcome, 2015 [46, 47, 56]	Empagliflozin	T2DM, established CV risk, eGFR ≥30 ml/ /min/1.73 m^2	Primary endpoint: 3-point MACE and its components (MI, stroke, and CV death)	Primary endpoint ≥90: 1.1 (0.77–1.57) 60–90: 0.67 (0.71–0.94) <60: 0.88 (0.69–1.13) CV death ≥90: 0.7 (0.39–1.25) 60–90: 0.49 (0.35–0.68) <60: 0.78 (0.54–1.12)	Primary endpoint <30: 0.89 (0.72–1.1) 30–300: 0.89 (0.69–1.16) >300: 0.69 (0.49– 0.96) CV death <30: 0.77 (0.55–1.10) 30–300: 0.49 (0.33–0.74) >300: 0.55 (95 CI, 0.35–0.86)
CANVAS, 2017 [49, 57]	Canagliflozin	T2DM, established CV risk, eGFR ≥30 ml/ /min/1.73 m^2	Primary endpoint: composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	≥90: 0.84 (0.62–1.12) 60–90: 0.95 (0.80–1.13) <60: 0.70 (0.55–0.90)	Primary CV outcome <30: 0.83 (0.71–0.96) 30–300: 0.76 (0.76–1.25) >300: 0.75 (0.53–1.06)
DECLARE-TIMI, 2019 [48, 58]	Dapagliflozin	T2DM, established CV risk, eGFR ≥60 ml/ /min/1.73 m^2	Primary endpoint: Composite of cardiovascular death, myocardial infarction, or ischemic stroke	≥90: 0.94 (0.80–1.10) 60–90: 0.95 (0.82–1.09) <60: 0.92 (0.69–1.23)	
Heart failure trials					
EMPEROR-Reduced, 2019 [18, 54]	Empagliflozin	Chronic HF (NYHA class II, III, or IV) with LVEF of 40% or less	Primary outcome: adjudicated hospitalized HF or CV death	≥60: 0.67 (0.55–0.83) <60: 0.83 (0.69–1.00) ≥90: 0.51 (0.33–0.80) 60–90: (0.73 (0.58–0.92) 45–60: 0.76 (0.57–1.02) 30–45: 0.92 (0.69–1.23) <30: 0.68 (0.68–1.09)	<30: 0.84 (0.68–1.03) 30–300: 0.69 (0.56–0.86) >300: 0.71 (0.50–1.00)
EMPEROR-Preserved, 2021 [23]	Empagliflozin	NYHA class II–IV chronic heart failure and LVEF >40% and NT-proBNP >300 pg/ml (>900 pg/ml in patients with AF)[b]	Primary outcome: adjudicated cardiovascular death or hospitalization for heart failure	≥60: 0.81 (0.65–1.00) <60: 0.78 (0.66–0.92)	
DAPA-HF, 2019 [17, 62]	Dapagliflozin	HF with ejection fraction of 40% or less, and NYHA class II, III, or IV symptoms (eGFR >30 ml/ /min/1.73 m^2); no UACR criterion[b]	Primary outcome: composite of worsening heart failure or death from cardiovascular causes	>60: 0.72 (0.59–0.86) ≤ 60: 0.76 (0.63–0.92)	
DELIVER, 2022 [20]	Dapagliflozin	Stabilized HF with LVEF >40% and evidence of structural heart disease and an elevated natriuretic peptide level[b]	Primary outcome: worsening heart failure, defined as either unplanned hospitalization for heart failure, an urgent visit for heart failure, or cardiovascular death	>60: 0.81 (0.69–0.94) ≤ 60: 0.84 (0.70–1.00)	
CKD Trials					
CREDENCE, 2019 [50, 69, 60]	Canagliflozin	T2DM, CKD with eGFR 30 to <90 ml/min/1.73 m^2 and albuminuria 300 to 5000 mg/g	Secondary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke	≥60: 0.90 (0.66– 1.23) 45–60: 0.83 (0.59–1.17) <45: 0.70 (0.52–0.93)	≤1000: 0.82 (0.63– 1.03) >1000: 0.78 (0.61– 0.99)
DAPA-CKD, 2020 [51]	Dapagliflozin	T2DM (67.5%), CKD without diabetes (32.5%); eGFR 25–75 ml/ /min/1.73 m^2 and UACR 200–5000 mg/g	Secondary outcome: hospitalization for heart failure or death from cardiovascular causes	Results not provided in the core publication and following publications with regard to baseline eGFR (please refer to the text)	Results not provided in the core publication and following publications with regard to baseline UACR (please refer to the text)
EMPA-KIDNEY, 2022 [52]	Empagliflozin	T2DM (46%), CKD without diabetes (54%); eGFR 20–45 ml/min/1.73 m^2 regardless albuminuria or eGFR 45–90 and UACR at least 200 mg/g	Secondary outcome: composite of hospitalization for heart failure or death from cardiovascular causes		

[a]For clarity of presentation, we have chosen the most representative secondary CV outcomes, in our opinion (where applicable); [b]eGFR data for HF trials provided in Table 1
Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular event; NYHA New York Heart Association; T2DM, diabetes mellitus type 2; UACR, urine albumin-creatinine ratio; other — see Table 1

or permanent reduction in eGFR <15 ml/min/1.73 m^2], or death from the renal or cardiovascular causes) [50–52, 59, 60]. Despite efforts, we failed to identify publications presenting secondary CV outcomes with regard to baseline eGFR or UACR values for the DAPA-CKD and EMPA-KIDNEY trials (even after reviewing supplementary appendixes to respective core publications). Such data were available for the CREDENCE trial and are presented in Table 2. The rates of hospitalization for HF or death from cardiovascular causes, the key secondary CV endpoints, were reduced by 29% and all-cause mortality by 31% in the DAPA-CKD study [50]. Describing the spectacular effect of slowing down CKD progression in both diabetic and non-diabetic patients (and in the latter group — especially in patients with IgA nephropathy) is beyond the scope of this review. Dapagliflozin was equally effective in diabetic and non-diabetic patients included in the study, regarding the primary composite, renal, composite cardiovascular outcomes as well as all-cause death, though all benefits listed for patients without diabetes tended to be greater for non-diabetic patients [51, 61]. However, a separate analysis performed in patients with CKD stage 4 demonstrated no benefit of dapagliflozin for any of the analyzed outcomes [62].

Key secondary endpoints of the EMPA-Kidney trial included a composite of hospitalization or death from cardiovascular causes, hospitalization for any reason, or death from any cause. The mean baseline eGFR of 37.5 ± 14.8 ml/min/1.73 m^2 in the EMPA-KIDNEY trial was the lowest value ever among all large SGLT2i trials performed to date; the median UACR equaled 412 mg/g (interquartile range: 94–1190 mg/g). It is worth emphasizing that 34.2% of patients randomized to empagliflozin and 34.8% of those receiving placebo had eGFR< 30 ml/min/1.73 m^2 [52]. The primary composite outcome (i.e. "renal" plus CV death) in EMPA-KIDNEY was reduced by 28% in the empagliflozin group vs. placebo (hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.64–0.82; P <0.001). Significant risk reduction was also achieved in empagliflozin-treated patients for the following outcomes: hospitalization for any cause, progression of kidney disease, and ESKD or death from cardiovascular causes. In contrast to DAPA-CKD, all-cause mortality was not reduced in the EMPA-KIDNEY trial; such a reduction was also not observed in cases of hospitalization for HF or death from cardiovascular causes and death from cardiovascular causes. As mentioned above, CV outcomes with regard to baseline eGFR/UCAR could not be extracted from the available publications. As in the case of the DAPA-CKD trial, the effect of empagliflozin was independent of the presence/absence of diabetes, although numerically, the impact of the drug on primary composite outcome was more significant in diabetic patients (HR, 0.64; 95% CI, 0.54–0.77) as compared to those without T2DM (HR, 0.82; 95% CI, 0.68–0.99). The risk reduction was independent of baseline eGFR, and patients in the subgroups with eGFR <30, ≥30 to <45, and ≥45 ml/min/1.73 m^2 experienced similar benefits. This was, however, not true for baseline UACR ranges: the benefit of empagliflozin was noted only in subjects with UACR >300 mg/g (traditionally defined as "macroalbuminuria" or "overt proteinuria") but not in the two remaining UACR ranges (<30, ≥30 to ≤300 mg/g). Separate analyses of secondary CV outcomes have not yet been published [52].

It is worth mentioning that a meta-analysis of DAPA-CKD and EMPA-KIDNEY has demonstrated no benefit of SGLT2i on cardiovascular death or hospitalization for heart failure, cardiovascular death, non-cardiovascular death, or all-cause death in advanced CKD. However, as already mentioned, DAPA-CKD has demonstrated a significant risk reduction in the composite of death from cardiovascular reasons or hospitalization for HF non-cardiovascular death, and all-cause death. These results were essentially the same in patients with and without diabetes, with a trend towards more benefit in non-diabetic patients [55]. At the moment, the DAPA-CKD trial remains the only CKD trial demonstrating lower all-cause mortality in CKD patients using SGLT2i [63].

SGLT2i — HOW DO THEY INFLUENCE THE CARDIO-RENAL AXIS

The adjective "pleiotropic" became one of the most fashionable words to describe successful drugs. This word is probably the most suitable one to describe the SGLT2i mode of action. In patients with T2DM, both cardiac and renal protection are related to better control of diabetes (although these drugs virtually lose this function in patients with eGFR below 30 or even below 45 ml/min/1.73 m^2) [64–66]. SGLT2i are not considered antihypertensive agents, but 2–3 mm Hg of blood pressure reduction achieved with their use is not negligible for preventing renal and CV events; the same holds true for their natriuretic effect [67, 68]. Another classical risk factor modified by these drugs is serum uric acid — SGLT2i are potent uricosuric agents, although the extent of their protective effect on the heart and kidneys is difficult to assess [69–71]. SGLT2i were demonstrated to act as immunomodulatory drugs — they inhibit synthesis of several proinflammatory cytokines, inhibit activation of T cells, antigen-presenting cells, macrophages, and promote M1-to-M2 phenotype shift in the macrophage population (among many other anti-inflammatory effects) [72–75]. Flozins protect viability of specialized interstitial renal fibroblasts that synthesize erythropoietin and upregulate several genes controlled by the hypoxia-inducible factor system beyond the erythropoietin gene (which leads to protection of cardiomyocytes) [76, 77]. SGLT2i improve the metabolism of cardiomyocytes promoting ketone utilization; they improve mitochondrial function, promote autophagy (including mitophagy and pexophagy, i.e. "recycling" of damaged mitochondria and peroxysomes), and decrease oxidative stress. These drugs decrease availability of calcium ions in cardiomyocyte cytosol during diastole — this mechanism may markedly improve myocardial relaxation and may

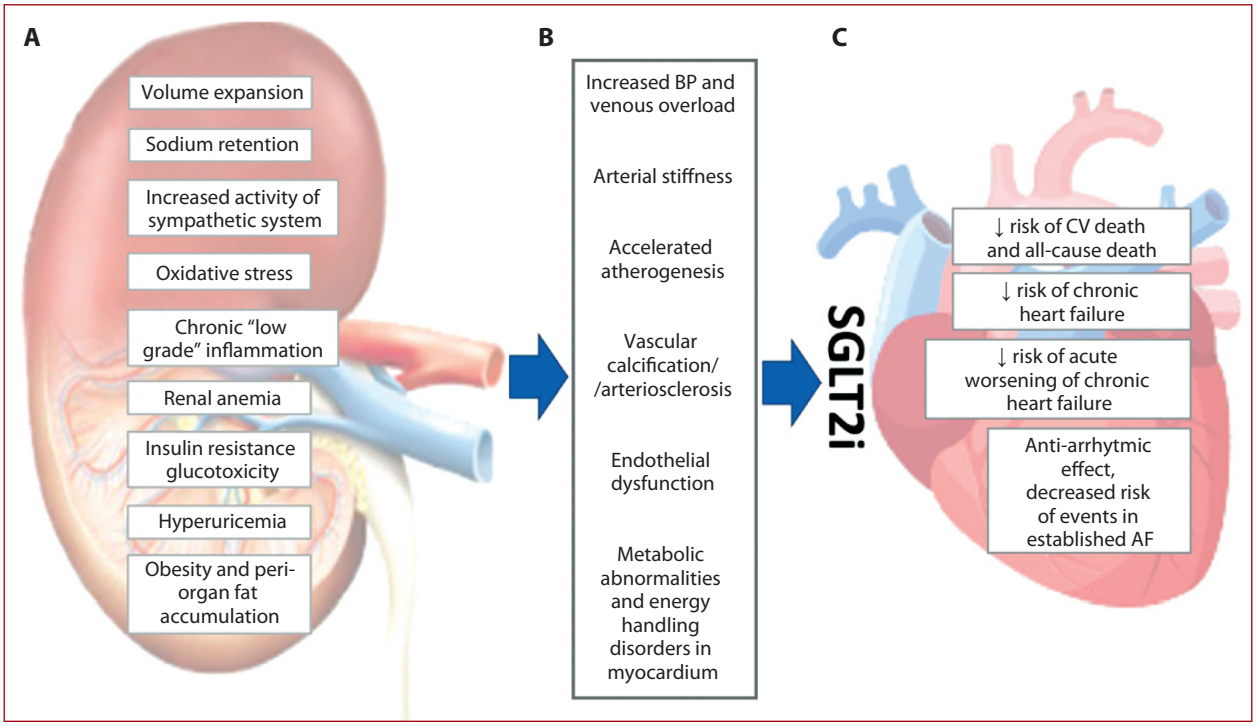

Figure 1. A. Mechanisms contributing to the development of CVD are influenced by renal dysfunction and may be ameliorated by SGLT2i actions in the kidneys. **B.** Intermediate effects of renal failure contributing to the development of CVD that may be influenced by SGLT2i. **C.** Direct CV benefits of SGLT2i depending on their renal actions

Abbreviations: see Table 1

explain the unique effectiveness of SGLT2i in the treatment of heart failure with preserved ejection fraction (HFpEF) [78, 79]. SGLT2i have also been demonstrated to decrease sympathetic tone — it may be one of several mechanisms of protection against atrial fibrillation with this drug group [80, 81]. Recently it has been demonstrated that dapagliflozin can lower plasminogen activator inhibitor 1 (PAI1), the potent inhibitor of fibrinolysis playing an important role in the development and progression of atherosclerosis and cardiovascular disease [82]. This short paragraph touches only on some of the mechanisms that may explain cardioprotection exerted by SGLT2i — proposed mechanisms of SGLT2i influence on the reno-cardiac axis are summarized in Figure 1.

CONCLUSIONS

To conclude, SGLT2i have undoubtedly become a cornerstone in the treatment of heart failure [83, 84]. The very recent European Society of Cardiology (ESC) guidelines on the management of CVD in diabetes contain special sections covering treatment of HF and CKD in patients with this metabolic disorder. SGLT2i are recommended in the treatment of HF with reduced EF with the level of evidence IA (the strength of evidence shared with sacubitril/valsartan, beta-blockers, and mineralocorticosteroid receptor antagonists). It is worth mentioning that three agents are recommended in this indication: dapagliflozin, empagliflozin, and sotagliflozin (sotaglilflozin is replaced by canagliflozin as the drug that prevents CVD and CKD in T2DM; see below) [85]. In this regard, the ESC guidelines for diabetics repeat guidelines on diagnosis and treatment of acute and chronic HF released by the ESC in 2021 [86]. The ESC document dedicated to patients with diabetes, along with the recent 2023 update of the ESC 2021 guidelines on diagnosis and treatment of HF, take a step forward: both documents state (based on hard data originating from SGLT2i trials in patients with HFpEF) that SGLT2i should also be used in patients with HF with mildly reduced EF and with preserved EF (with the same, highest level of evidence IA) [85, 87]. Expanding indications for SGLT2i to patients with HFmEF and HFpEF (regardless of diabetic status) is of paramount importance since SGLT2i and diuretics (in patients with symptomatic fluid retention) remain the only drug groups with such a high level of evidence in these two conditions. In fact, in HFpEF, no other drugs could be recommended based on evidence based medicine; in HFmEF, ACEi, sacubitril/valsartan, ARB, mineralocorticosteroid-receptor antagonists, and beta-blockers can be used based on the level of evidence IIB [85, 87].

Both documents contain also kidney sections. The 2023 ESC update on management and treatment of HF states that SGLT2i should also be used for HF prevention in patients with CKD and T2DM (more specifically — to reduce the risk of hospitalization for HF and CV death; level of evidence IA) [87]. The renal section of the ESC guidelines on the management of CVD in diabetes states that CKD patients with T2DM should receive statins and renin–angiotensin–aldosterone blocking agents (first-line treatment)

to reduce CVD and renal risks, respectively, and SGLT2i, effective blood pressure control, and finerenone to further reduce CV risk (notably, although SGLT2i are acknowledged as anti-hyperglycemic drugs, they should be used regardless of metabolic control of disease). SGLT2i recommended to reduce CV and renal risks in CKD patients with T2DM include canagliflozin, dapagliflozin, and empagliflozin [85].

The outstanding safety of SGLT2i, with very few side effects and virtually no risk of hyperkalemia or acute kidney injury (acute-on-chronic renal injury), should be emphasized —using SGLT2i may add not only additional benefits but also enhance safety of other drugs by interacting with the renin-angiotensin-aldosterone axis [88–90]. A critical appraisal of the presented data leads, however, to some moderation of enthusiasm with regard to CKD patients with CV disease and/or HF. Indeed, SGLT2i are cardioprotective in a wide spectrum of eGFR, but the data for HF patients with respect to UACR are limited and for those with significantly reduced eGFR are still not available or not convincing. It seems that patients with moderately reduced eGFR (30–60 ml/min/1.73 m^2) and proteinuria/albuminuria of any value, regardless of their diabetes status are best suited to benefit from SGLT2i use both in terms of nephroprotection and cardioprotection. Renal benefits would apparently be limited in patients with eGFR of less than 30 ml/min/1.73 m^2 — due to markedly reduced nephron number exerting nephroprotective effect is rather theoretically below this eGFR value. According to the regulatory documents, empagliflozin can be prescribed when eGFR is ≥20, dapagliflozin — ≥25, and canagliflozin — ≥30 ml/min/1.73 m^2, and CV benefits can still be expected below respective GFR thresholds.

SGLT2i, though well-established in the treatment of diabetes, CVD, and CKD (and any combination of these diseases) and included in many national and international guidelines are still the subject of clinical research — new trials are planned or ongoing to make indications to SGLT2i even broader. The key directions of such research include use of SGLT2i in heart transplant and kidney transplant recipients, acute heart failure, coronary artery disease and acute myocardial infarction, or treatment of diseases contributing to increased risk of CVD and CKD, such as sleep apnea syndrome [91–96]. Randomized trials are also planned or ongoing that assess the efficacy of SGLT2i combined with another drug with confirmed cardiovascular and renal benefits in T2DM patients, namely finerenone, a one-in-the-class non-steroidal mineral corticosteroid receptor antagonist [97]. The efficacy of dapagliflozin in combination with zibotentan, a novel endothelin receptor antagonist, is also evaluated in nephroprotection in prospective clinical trials [98]. Nephrologists are extremely interested in the efficacy of SGLT2i in preventing the development of kidney stones and the effect hypothesized based on observational data although probably this indication would not be the priority for cardiologists [99]. Several observational or registry-based "real-life" trials are also run worldwide to confirm findings from randomized controlled trials in everyday practice and different clinical settings.

Another group of drugs developed for the treatment of diabetes, i.e. glucagon-like peptide 1 (GLP1) receptor agonists, despite their promise of nephro- and cardioprotection, are only used in the diabetic setting due to the lack of data beyond diabetes and advanced CKD [100].

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