Kidneys in heart failure: Impact of flozins and beyond

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**ABSTRACT**

Chronic kidney disease (CKD) and heart failure (HF) represent two modern epidemics and are closely related. According to the concept of cardio-renal and reno-cardiac syndromes most of 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 to be challenging since CKD patients are characterized by extremely diverse and strongly expressed risk profile 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, 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 m² (although higher prevalence of side effect 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 m²) remains limited. In this review we focused on the efficacy of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in the treatment of CVD and HF in patients with CKD with or without diabetes. Sodium-glucose co-transporter type 2 inhibitors (SGLT2i) are clearly cardioprotective in wide spectrum of estimated GFR although the data for HF patients with respect to urine albumin-creatinine ratio (UACR) remain limited and for those with significantly reduced estimated GFR are still not available or not
convincing, even after completion of large-scale, high quality major cardio-vascular outcome trials (CVOT) in type 2 diabetes melitus (T2DMM) or trials with flozins in CKD and HF.

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

**CHRONIC KIDNEY DISEASE AND HEART FAILURE: MODERN EPIDEMIES**

Chronic kidney disease has only recently been recognized as a true epidemy of the world-wide dimension — 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 a common pathways and consequences of several specific pathologies which significantly differ in terms of etiology, dynamics of progression, 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 Westerns societies) [4, 5]. Glomerular, cystic, tubulo-interstitial and other well-defined renal pathologies together with DKD allow to explain 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 pathology may be an important part of this “missing” 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 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 development of CKD in many patients in whom no certain underlying renal pathology has been established [7, 8].

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 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./1.73m² 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 factor enormously high 12 to 36 in subjects treated with dialysis [9]. CKD is also an universal risk factor for adverse outcome in many other CV diseases, beyond HF [10, 11].
Looking at the other side of the coin: as mentioned above, 7%–15% of general population may suffer from CKD (defined as GFR <60 ml/min/1.73 m²) – 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 are reproduced by the key HF trials with SGLT2i (Table 1) [16–19]. Four presented pivotal HF trials with SGLT2i mirror real life when looking at their renal aspects and should convince the medical community that HF population suffers from CKD as the leading comorbidity.

Both reduced GFR and albuminuria significantly and synergistically increase the risk of adverse outcome in HF [20, 21]. It has been repeatedly confirmed in such trials as: SOLVD, CHARM, GISSI, RENAAL, MESA and ARIC that albuminuria predicts the progression of HF and/or its incidence; even more importantly — in opposite to GFR) associated with increased CVD risk when decreased to less than 45–60 ml/min/1.73 m²), the link between albuminuria and CVD is linear and starts to increase from the 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 patients with CKD. They include, among others: fluid overload and sodium retention, hypertension (which is likely to be resistant and needing three or more antihypertensive drugs), increased activity of the renin-angiotensin-aldosterone system, increased sympathetic nervous system activity (with 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 for CKD, they are more pronounced as compared with patients with preserved kidney function. Some factors considered more specific for CKD that may contribute 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 to decrease CVD events. “Big Pharma” sponsors and independent investigators were reluctant to include these patients for several reasons: they were considered non-representative for 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 a general rule of excluding subjects with eGFR of less than 30 or even...
less 45 ml/min/1.73 m² 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 the “renalism” in therapy (advanced CKD patients were deprived life-saving therapies just because of suffering from CKD). Guidelines covering several aspects of 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 retrospectively HF literature with the focus on CKD patients, it seems that pessimistic view was not justified. For example, in the HOPE Trial ramipril tended to be more effective in the 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 mineralocorticosteroid receptor antagonists, i.e. RALES with spironolactone and EMPHASIS-HF with eplerenone demonstrated no significant interaction between efficacy in reducing the cardiac end-points and GFR; patients with eGFR <60 ml/min./1.73 m² or in the GFR range between 30 and 60 ml/min./1.73 m² were doing as good 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]. Val-HEFT Trial, generally negative, i.e. proving no benefit of adding valsartan or placebo to standard of care in patients with HF, shown 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 of patients were also treated with background ACEi) [38]. The efficacy of a drug combining valsartan and neprilisine inhibitor sacubitril was equal in patients with eGFR above and below 60 ml/min./1.73 m² in terms of reducing primary end-point and CV death [39]. Finally, most of 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 MERIT trial there was an interaction with eGFR — the benefit in terms of reduced total mortality, all-cause mortality + all-cause hospitalization or all-cause mortality + HF hospitalization was increasing with decreasing GFR and was most pronounced in patients with eGFR of less than 45 ml/min/1.73 m² as compared to those with eGFR in the range of 45–60 and >60 ml/min./1.73 m² [42]. Finally, one of the key trials that paved the way to contemporary prevention of CVD (though not directly HF), namely HOT, has demonstrated that acetylsalicylic acid in secondary CVD prevention provides the highest benefit in reducing
major CV events, myocardial infarction, stroke and CV mortality in patients with eGFR less than 45 ml/min/1.73 m² [43].

Taking into account all these retrospective data one could come to the conclusion that therapeutic nihilism in relation to CKD (and more specifically HF/CVD treatment in patients with CKD) is not justified. Unfortunately, such a conclusion cannot be fully supported. First, retrospective analyses are not equal to trials with pre-specified analyses of outcome 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 m² were underrepresented and subjects with CKD 4 (eGFR of less than 30 ml/min/1.73 m²) — virtually absent. Third, in most of these analyses an independent impact of GFR and albuminuria on outcome 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 (at least for three agents in a class — canagliflozin, dapagliflozin and empagliflozin and somewhat less convincingly — for sotagliflozin) on nephroprotection. Three mentioned drugs documented their efficacy regardless of the baseline eGFR (in the range between normal to as low as 20 ml/min/1.73 m²), albuminuria (from low grade, i.e. below microalbuminuria to nephrotic range), cardiovascular risk profile and definitions of the end-points. In addition, two of them (namely dapagliflozin and empagliflozin) have proven their efficacy both in diabetic and non-diabetic kidney disease. Universally observed nephroprotective effect was demonstrated in CVOT performed in diabetic patients with high CV risk but otherwise well-preserved renal function (EMPAREG-Outcome, DECLARE-TIMI, CANVAS), 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 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]. From the scope of this review it is important to take the closer look at the cardio-vascular end-points in some of the mentioned studies in the context of presence and severity of CKD (as measured by both eGFR and UACR).

The story begins from three major CVOT performed in patients with T2DM and high or very high cardiovascular risk profile. In these trials the impact of SGLT2i on cardiovascular
outcome in the context of eGFR and UACR was defined as pre-specified analysis. Results of CVOT 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 an 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 notion could be made — SGLT2i were equally effective in different eGFR ranges (the most detailed data are available for the EMPEROR-Reduced Trial) [17–20]. Overall, in CVOT trials there was a general trend towards the 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 end-points 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 primary composite end-point identifying progression of CKD (primary composite outcome in these trials was defined as the first occurrence of the following: the permanent decline of eGFR of ≥50% or ≥40%, end stage kidney disease (ESKD) [commencement of dialysis, renal transplantation or permanent reduction of eGFR <15 ml/min/1.73 m²] or death from the renal or cardiovascular causes [50, 51, 52, 59, 60]. Despite efforts made we failed to identify publications presenting secondary CV outcomes with regard to baseline eGFR nor UACR values for 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. Hospitalization for heart failure or death from cardiovascular causes, the key secondary CV end-point was reduced by 29%, and all-cause mortality by 31% in DAPA-CKD Study [50]. Spectacular effect of slowing down the 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 outcome, renal outcome, composite cardiovascular outcome and all-cause death, though all listed benefits in patients without diabetes tended to be greater in non-diabetic patients [51, 61]. However, the separate analysis performed in patients with CKD stage 4 demonstrated no benefit of dapagliflozin in any of the analyzed outcomes [62]. Key secondary endpoints of 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 m² in the EMPA-KIDNEY trial was the lowest
value ever among all large SGLT2i trials performed to date; 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 m² [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 has also been achieved in empagliflozin–treated patients in 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 case of hospitalization for heart failure or death from cardiovascular causes and death from cardiovascular causes. As we mentioned above, CV outcome with regard to baseline eGFR/UACR could not be extracted from 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 a 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 subgroups with eGFR <30, ≥30 to <45 and ≥45 ml/min/1.73 m² 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 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 nor all-cause death in advanced CKD. However as already mentioned, DAPA-CKD has demonstrated a significant risk reduction of the composite of death from cardiovascular reasons or hospitalization for heart failure, 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]. As for today, 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 CARDIO-RENAL AXIS**
The adjective “pleiotropic” became one of the most fashioned words to describe successful drugs. This word is probably most suitable one to describe the mode of action of SGLT2i. In patients with T2DM both cardiac and renal protection are related to the better control of diabetes (although these drugs virtually loose this function in patients with eGFR below 30 or even below 45 ml/min/1.73 m²) [64–66]. SGLT2i are not considered antihypertensive agents, but 2 — 3 mm Hg of blood pressure reduction achieved with their use are 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 the serum uric acid — SGLT2i are potent uricosuric agents, although the extend of the contribution of this effect to protection of the heart and kidney is difficult to be assessed [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 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 hypoxia-inducible factor system beyond erythropoietin gene (which leads to protection of cardiomyocytes) [76, 77]. SGLT2i improve metabolism of cardiomyocytes promoting ketone utilization; they improve mitochondrial function, promote autophagy (including mitophagy and pexophagy, i.e. “recycling” of damaged mitochondria and peroxysomes), decrease oxidative stress. These drugs decrease availability of calcium ions in cardiomyocyte cytosol during diastole — this mechanism may markedly improve myocardial relaxation and may explain unique effectiveness of SGLT2i in the treatment of heart failure with preserved ejection fraction [78, 79]. SGLT2i have also been demonstrated to decrease sympathetic tone — it may be one of the 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 some of the mechanisms that may explain cardioprotection exerted by SGLT2i — proposed mechanisms of SGLT2i influence on reno-cardiac axis are summarized on Figure 1.

Summary

In summary, SGLT2i became undoubtfully 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 the special sections covering treatment of HF and CKD in patients with this metabolic disorder. SGLT2i are recommended in the treatment of heart failure with reduced ejection fraction (EF) with the level of evidence IA (the strength of evidence shared with sacubitril/valsartan, beta-blockers and mineralocorticosteroid receptor antagonists). It is worth to mention that three agents are recommended in this indication: dapagliflozin, empagliflozin and sotagliflozin (sotagliflozin is replaced by canagliflozin as a drug that prevents CVD and CKD in T2DM; see below) [85]. With this regard ESC guidelines for diabetics repeat guidelines on diagnosis and treatment of acute and chronic HF released by 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 make a step forward: both documents state (based on the firm data originating from SGLT2i trials in patients with HFpEF) that SGLT2i should also be used in patients with heart failure 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 EBM; 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 renal sections. 2023 ESC update on management and treatment of HF states that SGLT2i should also be used for prevention of HF in patients with CKD and T2DM (more specifically — to reduce risk of hospitalization for HF and CV death; level of evidence IA) [87]. Renal section of the ESC guidelines on the management of CVD in diabetes state that CKD patients with T2DM should receive statins and RAA 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 (of note, although SGLT2i are acknowledged as anti-hyperglycemic drugs, they should be used regardless of metabolic control of a 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 little side effects, 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, interacting with renin-angiotensin-aldosterone axis [88–90]. A critical appraisal of 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 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 m²) 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 m² — due to markedly reduced nephron number exerting nephroprotective effect is rather theoretical 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 m² 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 into many national and international guidelines are still the subject of clinical research — new trials are planned or ongoing in order to make indications to SGLT2i even broader. The key directions of such a research include: use of SGLT2i in heart transplant and kidney transplant recipients, in acute heart failure, in coronary artery disease and acute myocardial infarction or in the 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 proven cardiovascular and renal benefits in T2DM patients, namely finerenone, one-in-the class non-steroidal mineralocorticosteroid receptor antagonist [97]. Efficacy of dapagliflozin in combination with zibotentan, novel endothelin receptor antagonist is also evaluated in nephroprotection in prospective clinical trial [98]. Although probably this indication would not be the priority for cardiologists, we as nephrologists are extremely interested in efficacy of SGLT2i in preventing the development of kidney stones the effect hypothesized based on observational data [99]. Several observational or registry-based ‘real life’ trials are also run worldwide in order 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, although hold their promise in nephro- and cardioprotection, remain in their ‘diabetic niche’ due to lack of data beyond diabetes and advanced CKD [100].

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

<table>
<thead>
<tr>
<th>Study (acronym)</th>
<th>Investigated drug</th>
<th>Exclusion eGFR cut-off (ml/min/1.73 m²)</th>
<th>Patients with eGFR &lt;60 ml/min/1.73 m²</th>
<th>Mean eGFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPEROR-Reduced, 2020 [18]</td>
<td>Empagliflozin</td>
<td>&lt; 20</td>
<td>48% (empagliflozin); 48.6% (placebo)</td>
<td>61.8 ± 21.7 (empagliflozin) 62.2 ± 21.5 (placebo)</td>
</tr>
<tr>
<td>EMPEROR-Preserved, 2021 [19]</td>
<td>Empagliflozin</td>
<td>&lt; 20</td>
<td>50.2% (empagliflozin) 49.6% (placebo)</td>
<td>60.6 ± 19.8 (empagliflozin) 60.6 ± 19.9 (placebo)</td>
</tr>
<tr>
<td>DAPA-HF, 2019 [17]</td>
<td>Dapagliflozin</td>
<td>&lt; 30</td>
<td>40.6% (dapagliflozin) 40.7% (placebo)</td>
<td>66.0 ± 19.6 (dapagliflozin) 65.5 ± 19.3 (placebo)</td>
</tr>
<tr>
<td>DELIVER, 2022 [20]</td>
<td>Dapagliflozin</td>
<td>&lt;25</td>
<td></td>
<td>61 ± 19 (identical for both)</td>
</tr>
</tbody>
</table>
Table 2. Efficacy of SGLT2i on primary or key secondary cardio-vascular end-points in cardio-vascular outcome trials in type 2 diabetes mellitus, heart failure trials and chronic kidney disease (CKD) trials depending on CKD (GFR and/or UACR)

<table>
<thead>
<tr>
<th>Study (acronym)</th>
<th>Investigated drug</th>
<th>Key eligibility criteria</th>
<th>CVD outcome depending on eGFR (ml/min/1.73 m²) at baseline (HR, 95% CI)</th>
<th>CV outcome depending on UACR (mg/g) at baseline (HR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPAREG-Outcome, 2015 [46, 47, 56]</td>
<td>Empagliflozin</td>
<td>T2DM, established CV risk, eGFR ≥30 ml/min/1.73 m²</td>
<td>Primary end-point: 3-point MACE and its individual components (MI, stroke, and CV death)</td>
<td>Primary end-point ≥90: 1.1 (0.77–1.57) 60–90: 0.67 (0.71–0.94) &lt;60: 0.88 (0.69–1.13) CV death ≥90: 0.7 (0.39–1.25) 60–90: 0.49 (0.35–0.68)</td>
</tr>
<tr>
<td>Study</td>
<td>Drug</td>
<td>Population Details</td>
<td>Primary Endpoint</td>
<td>&lt; 60:</td>
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</tr>
<tr>
<td>CANVAS, 2017 [49, 57]</td>
<td>Canagliflozin</td>
<td>T2DM, established CV risk, eGFR ≥30 ml/min/1.73 m²</td>
<td>Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>0.78</td>
</tr>
<tr>
<td>DECLARE-TIMI, 2019 [48, 58]</td>
<td>Dapagliflozin</td>
<td>T2DM, established CV risk, eGFR ≥60 ml/min./1.73 m²</td>
<td>Composite of cardiovascular death, myocardial infarction, or ischemic stroke</td>
<td>0.84</td>
</tr>
<tr>
<td>EMPEROR-Reduced, 2019 [18, 54]</td>
<td>Empagliflozin</td>
<td>Chronic HF (functional class II, III, or IV) with a left ventricular ejection</td>
<td>Adjudicated hospitalized HF or CV death</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Heart failure trials
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>NYHA class</th>
<th>Ejection fraction criterion</th>
<th>Primary outcome</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPEROR-Preserved, 2021 [23]</td>
<td>Empagliflozin</td>
<td>II–IV chronic heart failure and a LVEF &gt;40% and NT-proBNP &gt;300 pg/ml (&gt;900 pg/ml in patients with AF)</td>
<td>adjudicated cardiovascular death or hospitalization for heart failure</td>
<td>60–90: 0.73 (0.58–0.92) 45–60: 0.76 (0.57–1.02) 30–45: 0.92 (0.69–1.23) &lt;30: 0.68 (0.68–1.09) &gt;300: 0.71 (0.50–1.00)</td>
<td></td>
</tr>
<tr>
<td>DAPA-HF, 2019 [17, 62]</td>
<td>Dapagliflozin</td>
<td>HF with ejection fraction of 40% or less, and NYHA class II, III, or IV symptoms (eGFR &gt;30 ml/min/1.73 m²); no UACR criterion</td>
<td>composite of worsening heart failure or death from cardiovascular causes</td>
<td>≥60: 0.81 (0.65–1.00) ≤ 60: 0.78 (0.66–0.92)</td>
<td></td>
</tr>
<tr>
<td>DELIVER, 2022 [20]</td>
<td>Dapagliflozin</td>
<td>Stabilized HF with LVEF &gt;40% and</td>
<td>worsening</td>
<td>&gt;60: 0.81 (0.69–0.94)</td>
<td></td>
</tr>
<tr>
<td>CKD Trials</td>
<td>Evidence of structural heart disease and had an elevated natriuretic peptide level(^b)</td>
<td>Heart failure, defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure, or cardiovascular death</td>
<td>≤ 60: 0.84 (0.70–1.00)</td>
<td></td>
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</tr>
<tr>
<td>CREDENCE, 2019 [50, 69, 60]</td>
<td>Canagliflozin T2DM, CKD with eGFR 30 to &lt;90 ml/min/1.73 m(^2) and albuminuria 300 to 5000 mg/g</td>
<td>Secondary end-point: composite of CV death, non-fatal MI or non-fatal stroke</td>
<td>≥60: 0.90 (0.66–1.23) 45–60: 0.83 (0.59–1.17) &lt;45: 0.70 (0.52–0.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1000: 0.82 (0.63–1.03)  &gt;1000: 0.78 (0.61–0.99)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DAPA-CKD, 2020 [51]</td>
<td>Dapagliflozin T2DM (67.5%), CKD without diabetes (32.5%); eGFR 25–75 ml/min/1.73 m(^2) and UACR 200–5000 mg/g</td>
<td>Secondary outcome: hospitalization for heart failure or death from cardiovascular causes</td>
<td>Results not provided in a core publication and following</td>
<td>Results not provided in a core publication and following</td>
<td></td>
</tr>
<tr>
<td>EMPA-KIDNEY, 2022 [52]</td>
<td>Empagliflozin</td>
<td>T2DM (46%), CKD without diabetes (54%); eGFR 20–45 ml/min/1.73 m² regardless albuminuria or eGFR 45–90 and UACR at least 200 mg/g</td>
<td>Secondary outcome: composite of hospitalization for heart failure or death from cardiovascular causes</td>
<td>publications with regard to baseline eGFR (please refer to the text)</td>
<td>publication(s) with regard to baseline UACR (please refer to the text)</td>
</tr>
</tbody>
</table>

*aFor the clarity of presentation we have chosen the most representative secondary CV outcome in our opinion (where applicable)*

*b*eGFR data for HF trials provided in Table 1

Abbreviations: UACR, urine albumin-creatinine ratio; other — see Table 1
Figure 1. A. Mechanisms contributing to the development of CVD that are influenced by renal dysfunction and may be ameliorated by SGLT2i actions in the kidneys. B. Intermediate effects of renal failure contributing to development of CVD that may be influenced by SGLT2i. C. Direct CV benefits of SGLT2i depending on their renal actions

Abbreviations: see Table 1