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Review

Exploring the Cardiorenal Benefits of SGLT2i: A Comprehensive Review

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Abstract: The history of sodium-glucose cotransporter 2 inhibitors (SGLT2i) is so long and started in 1835 when Petersen extracted a compound called phlorizin from apple tree bark. About fifty years later, von Mering discovered its glucosuric properties. In the 1980s, it was discovered that the glucosuria resulted from inhibition by phlorizin of glucose reabsorption by the renal tubules, which lowered blood glucose levels in diabetic rats. Nowadays, beyond their glucose-lowering effects, growing evidence suggests significant cardiorenal benefits associated with SGLT2i therapy. Indeed, several clinical trials, including landmark studies such as EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58, have demonstrated robust reductions in cardiovascular events, particularly heart failure hospitalizations and cardiovascular mortality, among patients treated with SGLT2i. However, subsequent trials showed that SGLT2i benefits extend beyond the diabetic population, encompassing individuals with and without diabetes. Additionally, SGLT2i exhibit nephroprotective effects, manifesting as a slowing of the progression of chronic kidney disease and a reduction in the risk of end-stage kidney disease. The mechanisms underlying the cardiorenal benefits of SGLT2i are multifactorial and include improvements in glycemic control, reduction in arterial stiffness, modulation of inflammation and oxidative stress, reduction of intraglomerular pression and promotion of natriuresis and diuresis through inhibition of SGLT2 in the luminal brush border of the first segments of the proximal kidney tubule. This narrative review aims to explore the cardiorenal outcomes of SGLT2i, encompassing their mechanisms of action, clinical evidence, safety profile, and implications for clinical practice.

Keywords: SGLT2 inhibitors; diabetes mellitus; chronic kidney disease; cardiovascular disease; heart failure

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1. Introduction

Impaired renal function is a prevalent concern, affecting more than 30% of individuals with heart failure (HF) and significantly influencing prognosis [1]. Diabetes plays a dominant role in impaired renal function, contributing to approximately 44% of new kidney failure cases [2]. This condition is typified by glomerular sclerosis or fibrosis, along with stable reductions in estimated glomerular filtration rate (eGFR) or urinary protein excretion [2]. Moreover, HF exacerbations often accelerate renal damage, highlighting the urgent need to intervene and mitigate the decline in renal function to improve patient outcomes [1]. HF represents a substantial public health challenge, marked by heightened morbidity, mortality, and economic burden [3]. Currently, this condition afflicts 1–2% of the general population and over 10% of those aged 70 years or older, with projections indicating a staggering 46% rise in diagnoses by 2030 [4,5]. Originally considered only as hypoglycemic agents due to their ability to block the sodium-glucose cotransporter 2 (SGLT2) in the proximal renal tubule and induce glycosuria, sodium-glucose cotransporter inhibitors (SGLT2i) have now emerged as cornerstone therapies in HF management [3,6].

Like all new antidiabetic drugs, SGLT2i underwent cardiovascular (CV) safety studies as mandated in 2008 by the Food and Drug Administration (FDA) and in 2012 by the European Medicines Agency (EMA). Canagliflozin was the first FDA-approved SGLT2i accepted in March 2013, followed by dapagliflozin and empagliflozin in 2014. Ertugliflozin is the latest accepted in 2018. The studies conducted with SGLT2i unexpectedly demonstrated significant CV protective effects, with a focus on HF related events [7–10]. The trials, conducted in diabetic patients, revealed a remarkable protective role of SGLT2i against HF events, even in individuals at risk without evident symptoms or structural cardiac changes. This discovery marked a pivotal shift in perspective, positioning SGLT2i as potential game-changers in HF management. Subsequently, further studies have unveiled a groundbreaking discovery: SGLT2i not only significantly curtails renal adverse events and HF exacerbations, irrespective of established cardiovascular damage, but also offers remarkable benefits for those with advanced renal failure and HF, regardless of glycemic status [11–15]. The magnitude of these benefits transcends diverse clinical conditions, leading to a substantial reduction in major adverse cardiovascular events across studies. Empagliflozin and dapagliflozin have emerged as star players, demonstrating a reduction in mortality and hospitalization rates for HF among subjects with severe to preserved ejection fraction (EF), while also enhancing renal function [11–15]. Therefore, a meta-analysis encompassing over 90,000 patients, solidifies the SGLT2i renal benefits [16]. Indeed, in both chronic kidney disease (CKD) and HF populations, SGLT2i demonstrated a remarkable reduction in the risk of renal damage progression by 37% and acute kidney injury by 23% when compared to placebo. Notably, these benefits remained consistent across varying baseline eGFR, never dipping below 20 mL/min/1.73 m^2 in any trial, and irrespective of the presence or absence of diabetes mellitus [16]. The cardio and renal protective effects of these medications mark a pivotal advancement in HF and renal management, transcending their initial application in diabetic care [17]. The magnitude of these unexpected benefits highlights the transformative potential of SGLT2i in reshaping the cardio-renal landscape, promising improved outcomes and enhanced quality of life for a broader spectrum of patients.

This narrative review aims to explore the cardiorenal outcomes of SGLT2i, encompassing their mechanisms of action, clinical evidence, safety profile, and implications for clinical practice.

2. Effects of SGLT2i

The mechanism by which the kidney recovers glucose from the glomerular filtrate relies on the coordinated function of sodium (Na+) and glucose transport in the renal tubules. This process primarily involves the sodium-glucose cotransporters SGLT2 and SGLT1, along with their associated glucose transporters located on the basolateral membrane, GLUT2 and GLUT1, respectively. SGLT2 is responsible for the bulk of glucose reabsorption, operating with high transport capacity but a lower affinity for glucose. In detail, SGLT2 facilitates the passive movement of glucose and Na+ from the renal tubular cells into the interstitial space, maintaining a 1:1 ratio of Na+ to glucose [18]. As opposite, SGLT1, though responsible for a smaller fraction of glucose recovery, has a higher affinity for glucose and maintains a 2:1 ratio of Na+ to glucose. However, under normal physiological conditions, SGLT1 contributes minimally to glucose reabsorption, with its role becoming significant only when glucose levels in the filtrate exceed the renal threshold of approximately 180 mg/dL [18]. Therefore, SGLT1 also plays a key role in glucose absorption in the distal small intestine, where it regulates glucose uptake and stimulates the secretion of glucagon-like peptide-1 (GLP-1) from L cells. This regulatory function is closely tied to SGLT1 activity and is subject to GLP-1 inhibition [19].

SGLT1 is also expressed in other tissues, such as myocardial capillaries, where its presence has been confirmed by immunofixation studies [20]. Emerging evidence suggests that SGLT1 is involved in the biological processes activated during reperfusion following myocardial ischemia [21], though data on its role in cardiac muscle are still limited.

In patients with diabetes, there is an overexpression of SGLT2 in the kidneys, which is responsible for increased renal tubular reabsorption and consequent exacerbation of hyperglycemia [22]. In detail, SGLT2i inhibit the reabsorption of sodium in the luminal brush border of the first segments of the proximal kidney tubule, leading to an increase in urinary sodium excretion by 30% to 60% [23]. This natriuretic effect is accompanied by osmotic diuresis, resulting in a reduction of intraglomerular pression, extracellular fluid volume and blood pressure, differently from traditional diuretics [24]. For instance, a study comparing dapagliflozin with hydrochlorothiazide found that dapagliflozin reduced plasma volume and increased erythrocyte mass, unlike hydrochlorothiazide [25]. Additionally, when compared to the loop diuretic bumetanide, dapagliflozin resulted in a greater reduction in interstitial fluid volume rather than intravascular volume [26]. This suggests that SGLT2i may have a distinct effect on regulating interstitial fluid, which could minimize the reflex neurohumoral activation that typically occurs with the intravascular volume contraction seen with traditional diuretics [27]. Evidences suggest that SGLT2 inhibition can reduce sympathetic nerve activity, inhibit norepinephrine turnover in brown adipose tissue, and decrease tyrosine hydroxylase production [27,28]. Reduced sympathetic nervous system (SNS) activity through decreased renal stress, inhibits sympathetic afferent activation to the renal system resulting in lowered blood pressure without increased heart rate [29]. Hypertension, in fact, is a common modifiable risk factor for developing HF [3]. However, the modest blood pressure-lowering effects of SGLT2i are unlikely to fully explain their cardiovascular and renal benefits. By reducing blood pressure, SGLT2i may decrease cardiac afterload, thereby improving ventricular-arterial coupling and cardiac efficiency, which would benefit a failing heart by improving cardiac energetics [30]. As HF progresses, there is a continued decline in mitochondrial oxidative metabolism, causing the heart to increasingly rely on glycolysis for energy [31]. The uncoupling of glycolysis and glucose oxidation increases proton production, which reduces cardiac efficiency (the ratio of cardiac work to oxygen consumed) regardless of the HF phenotype [32,33]. By raising plasma ketone levels, SGLT2 inhibition boosts cardiac ketone oxidation rates, thus improving energy supply to the "starving" heart [34]. Therefore, SGLT2-mediated inhibition of the mammalian target of rapamycin (mTOR) pathway might further stimulate autophagy and lysosomal degradation, facilitating the removal of dysfunctional organelles and promoting cellular health. These changes result in a reduction of oxidative stress, leading to a decrease in inflammation [35]. In the kidney, cell function is improved through the promotion of autophagy, with reduced podocyte damage, less extracellular matrix accumulation, and reduced glomerulosclerosis and fibrosis [36]. Inflammatory cytokines not only cause endothelial dysfunction but also increase extracellular matrix turnover and fibrosis [37]. Indeed, dapagliflozin has demonstrated significant antifibrotic effects in post-infarct rat hearts by suppressing collagen synthesis [38], while empagliflozin showed a significant reduction of cell-mediated extracellular matrix collagen remodeling in humans [39]. However, the exact mechanism by which SGLT2i modulate inflammation remains unclear. Lowering glucose levels with SGLT2i might reduce macrophage inflammatory response, as macrophages primarily utilize glucose from glycolysis for energy [40]. Alternatively, SGLT2i may directly target inflammatory pathways independently of glucose lowering. Recent studies indicate that empagliflozin can inhibit the nucleotide-binding domain-like receptor protein (specifically, nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3 [NLRP3]) inflammasome in various tissues, including kidney, liver, vasculature, and heart [41,42]. The NLRP3 inflammasome plays, in fact, a crucial role in mediating inflammation and contributes to chronic inflammation in HF, thereby exacerbating the condition [43]. As opposite, the ketone β-hydroxybutyrate, which is increased by SGLT2i, is an effective inhibitor of NLRP3 inflammasome-mediated inflammation [44]. For this reason, some of the benefits of SGLT2i may be attributed to the inhibition of the NLRP3 inflammasome by elevated levels of β-hydroxybutyrate. Recent experimental findings indicate that SGLT2 inhibition provides cardio-protection against ischemia/reperfusion injury in both diabetic and non-diabetic rats [45]. This protective effect involves a reduction

in calmodulin kinase II activity by SGLT2i, which increases mitochondrial calcium levels and improves contractility [46]. Moreover, SGLT2i inhibit the cardiac Na^+/H^+ exchanger, potentially decreasing myocardial sodium levels and consequently, reduced the risk of arrhythmias and progression to HF [47]. However, it remains uncertain whether the exact mechanisms occur in humans. Lastly, glycosuria reduces plasma insulin levels and promote glucagon secretion, responsible for lipolysis and lipid oxidation, with the effect of a reduction in visceral and subcutaneous fat and consequent weight loss [48]. In the DAPA-HF trial, weight reduction was observed, with a more pronounced effect in patients with diabetes [14].

Figure 1 summarize the main SGLT2i features while Table 1 showed pharmacodynamic and pharmacokinetic characteristics of SGLT2i.

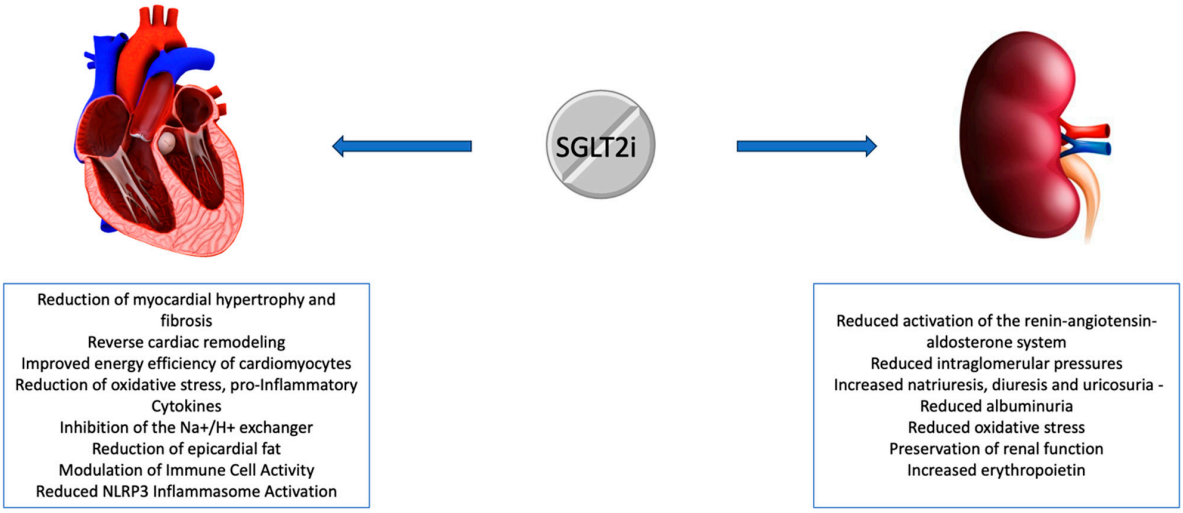

Figure 1. Cardio-Renal effects of SGLT2i.

Table 1. Main pharmacodynamic and pharmacokinetic characteristics of SGLT2i.

Drug	Daily Dose (mg)	Selectivity (SGLT2:SGLT1)	Bioavailability (%)	Half-Life (h)	Excretion
Empaglifozin	10 or 25	1:2500–2700	90–97 (mice) 89 (dogs) 31 (rats)	13.2 (10 mg) 13.3 (25 mg)	Glucuronidation Excretion fecal (41%) and renal (54%).
Dapaglifozin	10	1:1200	78	12.9	Glucuronidation Excretion fecal (21%) and renal (75%).
Canaglifozin	100 or 300	1:250–414	65	10.6 (100 mg) 13.1 (300 mg)	Glucuronidation Excretion fecal (42%) and renal (33%).
Ertuglifozin	5 or 15	1:2200	70–90	12.2	Glucuronidation (86%) Excretion fecal (50%) and renal (41%).
Sotaglifozin	800	1:20	71	35	Glucuronidation (94%) Excretion fecal (37%) and renal (57%).
Ipraglifozin	50	1:360	90	15–16	Glucuronidation (92%) Excretion fecal (27%) and renal (73%).
Luseoglifozin	2.5 or 5	1:1650	35.3 (male rats) 58.2 (female rats) 92.7 (male dogs)	9.24	Glucuronidation Excretion fecal (31%) and renal (69%).
Tofoglifozin	10	1:2900	97.5	6.8	Glucuronidation (90%) Excretion fecal (22%) and renal (78%).
Bexagliflozin	20	1:2435	93%	12	Glucuronidation Excretion fecal (51%) and renal (40.5%).

3. SGLT2i on Heart: Across the Trials

In 2008, concerns about the cardiovascular safety of rosiglitazone, a widely used antidiabetic drug [49], prompted the FDA to issue guidelines requiring new or recently approved antidiabetic therapies to demonstrate that they do not significantly increase cardiovascular (CV) risk [50]. To meet this requirement, extensive clinical outcome trials were conducted for various agents, including SGLT2i. The first large clinical outcome trial of an SGLT2i, conducted in patients with type 2 diabetes and cardiovascular disease, compared empagliflozin with placebo in 7020 patients [9]. The primary endpoint was a composite of major adverse cardiac events (MACE), including death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The empagliflozin group not only proved to be safe but also demonstrated cardioprotective properties, with a hazard ratio (HR) of 0.86 (95% confidence interval (CI) 0.74–0.99). Significant reductions were observed in prespecified secondary endpoints, including a 38% reduction in CV death, a 35% reduction in hospitalization for heart failure (HHF), and a 32% reduction in all-cause death. Benefits were evident across a wide range of HF risks and became apparent as early as 2 to 3 weeks after starting therapy [9]. Therefore, these surprising results for the endocrine and cardiology communities were soon validated by subsequent HHF prevention trials. A similar trial with dapagliflozin enrolled 17,160 patients and did not reduce cardiovascular adverse events, one of the co-primary endpoints [8]. However, this trial showed a 17% reduction in CV death (HR 0.83; 95% CI, 0.73–0.95). Additionally, significant reductions in cardiovascular death and death from any cause were observed among high-risk patients, including those with HF with reduced ejection fraction (HFrEF) and those with previous myocardial infarction (MI). Notably, 59% (n = 10,186) of the enrolled patients were in primary prevention, representing a diabetic population at lower risk than in previous studies, as they did not have established atherosclerotic disease [8]. Similarly, ertugliflozin demonstrated no significant effect on cardiovascular death but showed a 30% reduction in first HHF [51]. Inhibiting SGLT1 and SGLT2 in the diabetic heart has the potential to reduce myocardial sodium and glucose uptake, thereby lowering hyperglycemia-induced generation of reactive oxygen species (ROS) [30]. Canagliflozin, albeit with lower affinity, can also inhibit sodium-glucose co-transporter type 1 (SGLT1). However, the concentration required for significant SGLT1 inhibition is much higher than the plasma levels typically achieved during clinical use of SGLT2i [52]. The CANVAS Program [7], which included the CANVAS and CANVAS-Renal (CANVAS-R), assessed canagliflozin in 10,142 patients, with two-thirds having a history of cardiovascular disease [7]. The primary endpoint of major adverse cardiac events (MACE) was significantly reduced by 14% in the canagliflozin group (HR 0.86, 95% CI 0.75–0.97). Moreover, this benefit was consistent across various subgroups defined by baseline glycated hemoglobin levels, presence or absence of albuminuria, and the duration of diabetes. Among the prespecified secondary endpoints, a 33% reduction in HHF stands out [7]. The subsequent CREDENCE trial [10] evaluated canagliflozin in 4401 patients with type 2 diabetes (DM2), atherosclerotic CV disease and kidney disease. Although primarily focused on renal outcomes, the study demonstrated a significant 20% reduction in MACE, a 39% reduction in HHF, and a 31% reduction in the combined endpoint of HHF and CV death [10]. Sotagliflozin, inhibiting both SGLT1 and SGLT2 receptors, was evaluated in a trial that enrolled 1222 patients recently hospitalized for decompensated HF, with treatment starting either in the hospital or within two days after discharge [53]. The primary endpoint, a composite of cardiovascular death, HHF, or urgent HF visits, was reduced by 33% in the sotagliflozin group (HR 0.67; 95% CI 0.52–0.85), although the trial ended early. Similarly, in the SCORED trial, the primary endpoint was significantly reduced by 26% [54]. The trend of HHF reduction was observed across all clinical cardiovascular outcome trials with SGLT2, led to sub-analyses of the EMPA-REG OUTCOME [9] and DECLARE-TIMI 58 [8] trials. The first substudy [55] analyzed the effects of empagliflozin in patients with HF at baseline (n = 706, 10.1%) and reported a 36% reduction in HHF or CV death with empagliflozin compared to placebo (5.7% vs. 8.5%), with a corresponding "number needed to treat" (NNT) of 35 over three years. Instead, the subanalysis of the

DECLARE-TIMI 58 trial [8], which included 11.6% of patients of whom 3.9% had HFrEF and 7.7% had HF with preserved ejection fraction (HFpEF), observed a benefit of dapagliflozin on HHF and CV mortality especially in patients with HFrEF [56]. For instance, the DAPA-HF [14] evaluated the efficacy of dapagliflozin versus placebo on a primary endpoint of worsening HF (hospitalization or urgent visit requiring intravenous therapy) and CV death in 4744 HFrEF patients over a median observation period of 18.2 months. The enrolled patients had a mean EF of approximately 31% and were predominantly classified between NYHA class II and III. Notably, this study also included nondiabetic patients, who comprised 58% of the total population. The primary composite endpoint (CV death and HHF) was reduced by 26%, occurring in 386 (16.3%) patients in the dapagliflozin group and 502 (21.2%) patients in the placebo group (HR 0.74, 95% CI 0.65–0.85) with an NNT of 21. Additionally, there was an 18% reduction in CV mortality in patients treated with dapagliflozin, along with improvements in quality of life and HF symptoms. The benefits of dapagliflozin were consistent across all prespecified subgroups, including patients with and without diabetes, highlighting the drug's cardiovascular benefits independent of its glycemic effects [14]. This groundbreaking evidence supported the use of dapagliflozin beyond its original antidiabetic indications. Building on these findings, the EMPEROR-Reduced trial [11] analyzed the effects of empagliflozin versus placebo in 3730 patients with HFrEF (mean EF 27%). After a median follow-up of 16 months, empagliflozin was superior to placebo in reducing adverse events (19.4% vs. 24.7%; HR 0.75; 95% CI 0.65–0.86), primarily driven by a reduction in HHF, though mortality was not significantly reduced. However, compared with DAPA-HF, this trial included patients with more severe systolic dysfunction and advanced NYHA class.

In industrialized nations, about half of HF patients have HFpEF [57]. Although several drugs have been trialed in HFpEF patients with limited success in improving cardiac function, two trials have shown promising results: one with a mineralocorticoid antagonist [58] and the other with sacubitril–valsartan, an angiotensin receptor–neprilysin inhibitor [59]. Building on the success observed in HFrEF, dapagliflozin and empagliflozin were also investigated in HFpEF patients. The largest placebo-controlled study for HFpEF enrolled 5988 patients with EF of 40% or higher [12]. In the empagliflozin group, there was a significant reduction (21%) in the primary endpoint of CV death or HHF (HR 0.79; 95% CI 0.69–0.90) and a 27% reduction in the secondary HHF endpoint. Furthermore, a pooled analysis of the EMPEROR-Reduced and EMPEROR-Preserved trials demonstrated benefits across ejection fractions ranging from less than 25% to 65% [60]. Similarly, the DELIVER trial [61] included 6263 HFpEF patients. The primary outcome, a composite of worsening HHF (defined as either unplanned HHF or an urgent visit for HF) or CV events, was reduced by 18% in the dapagliflozin group. These benefits were consistent among patients with left ventricular (LV) EF of 60% or more and those with less than 60% [61]. Additionally, the SOLOIST-WHF trial [53] showed improvement in the primary outcome for a group of 250 patients with diabetes and HFpEF treated with sotagliflozin. These findings collectively highlight the potential of SGLT2i in improving outcomes for HFpEF patients, marking significant advancements in the treatment landscape for this challenging condition.

Acute heart failure (AHF) represents a critical phase in managing patients with HF, often linked with high morbidity and mortality rates [3]. Building on the observed benefits of SGLT2i in HF, the EMPULSE study [62] aimed to evaluate the initiation of empagliflozin during the primary diagnosis of acute de novo or decompensated chronic HF. The primary composite and hierarchical endpoint, assessed at 90 days, included death from all causes, first and total HHF, and a change of at least 5 points on the Kansas City Cardiomyopathy Questionnaire (KCCQ) from baseline. Safety parameters considered were volume depletion, hypotension, and renal failure. In this trial, empagliflozin demonstrated superiority independent of HF type (de novo vs. recurrent) and ejection fraction (<40% vs. >40%) [62]. Adverse cardiac remodeling significantly contributes to HF severity, involving processes like cardiac hypertrophy, fibrosis, inflammation, and cardiomyocyte cell

death [63]. Both experimental and clinical studies have shown beneficial effects of SGLT2i on cardiac remodeling [64–69]. Indeed, a recent meta-analysis of 9 randomized clinical trials involving 1385 patients reported that SGLT2i treatment significantly reversed cardiac volumes, improved LV systolic function, and reduced LV mass [70].

Coronary artery disease (CAD) is the most prevalent and potentially treatable cause of HF, necessitating suspicion in every patient newly diagnosed with HF [3]. Moreover, when myocardial infarction (MI) presents with ventricular dysfunction, patients face an increased risk of adverse outcomes during follow-up [71]. The EMMY trial [72] documented a significant reduction in natriuretic peptide levels and an improvement in systolic-diastolic function among MI patients treated with empagliflozin; however, due to its small sample size (476 patients enrolled), other endpoints could not be fully evaluated. Subsequently, the DAPA-MI trial [73] illustrated cardiometabolic benefits associated with early dapagliflozin use in MI patients complicated by LV dysfunction, though the limited number of events during follow-up precluded evaluation of the drug's effect on the composite outcome of HHF or CV death. Following these trials, the EMPACT-MI [74] investigated empagliflozin in 6522 patients with acute MI and high HF risk. Participants were randomized 1:1 to receive either empagliflozin 10 mg or placebo within 14 days of the index event, alongside standard medical therapy. High HF risk was defined by left ventricular dysfunction (EF < 45%) and/or clinical signs of congestion, with additional criteria including age > 64 years, severe new ventricular dysfunction (EF < 35%), prior MI history, atrial fibrillation, type 2 diabetes mellitus, renal impairment (glomerular filtration rate < 60 mL/min/1.73 m^2), elevated natriuretic peptide or uric acid levels, elevated pulmonary systolic blood pressure, trivasal coronary artery disease, peripheral vasculopathy, or failure to revascularize during the index event. Median follow-up duration was 17.9 months. The study's primary endpoint (HHF or all-cause death) occurred in 8.2% of the empagliflozin group versus 9.1% of the placebo group (HR 0.90; 95% CI 0.76–1.06). Notably, the empagliflozin group experienced significantly fewer HHF events (118 vs. 153; HR 0.77; 95% CI 0.60–0.98), while rates of all-cause death were similar to placebo group (5.2% vs. 5.5%; HR 0.96; 95% CI 0.78–1.19) [74].

The benefit in terms of reduced CV mortality and HHF, also translates to improved HF biomarkers. For instance, SGLT2i have been shown to significantly reduce N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels across various clinical settings, including both diabetic and non-diabetic HF patients [8,9,11,14]. Indeed, dapagliflozin improved NT-proBNP values regardless of baseline levels or EF [75], while empagliflozin also reduced NT-proBNP in patients with HFrEF, both as monotherapy [76] and in combination with insulin [77]. Similarly, canagliflozin significantly lowered NT-proBNP and High-Sensitivity Cardiac Troponin (hs-cTn) levels in patients with DM2 and stable or acute HF [78]. In patients with DM2 and CAD, dapagliflozin significantly decrease hs-cTn levels compared to vildagliptin [79].As opposite, Griffin et al. did not find a significant effect of empagliflozin on troponin levels in diabetic patients with stable HF [80]. In terms of inflammatory biomarkers, both empagliflozin and canagliflozin demonstrated reductions in high-sensitivity C-reactive protein (hsCRP) in DM2 patients [81,82], although Sposito et al. found no significant change in hsCRP following dapagliflozin treatment [83]. Given their pleiotropic effects and proven efficacy, SGLT2i have become a cornerstone therapy for HF, irrespective of EF or DM2. Table 2 summarize the principal CV outcomes and efficacy of SGLT2i across different trials.

Table 2. Key cardiovascular outcomes and highlights the efficacy of SGLT2 inhibitors across different trials and patient populations.

Study	Drug	Dose	Population	Primary CV Outcome	HR(95% CI)
Canvas [7]	Canaglifozin	300/100	DM2 and high CV risk	14% reduction in 3-point MACE (CV death, non-fatal MI, non-fatal stroke)	0.86 (0.75–0.97)
Credence [10]	Canaglifozin	300/100	DM2 and high CV risk	30% reduction in composite outcome (doubling serum creatinine, ESRD, or renal/CV death)	0.70 (0.59–0.82)
DAPA-HF [14]	Dapaglifozin	10	HFrEF	26% reduction the primary outcome (CV death, HHF)	0.74 (0.65–0.85)
DAPA-MI [73]	Dapaglifozin	10	MI and HFpEF	5%-no reduction in composite outcome (CV death or HHF)	0.95 (0.64–1.40)
DAPA-LVH [66]	Dapaglifozin	10	DM2 and LV hypertrophy	Reduction of LV hypertrophy	NA
Declare-TIMI [8]	Dapaglifozin	10	DM2 and high CV risk	17% reduction in 3-point MACE (CV death, non-fatal MI, non-fatal stroke)	0.83 (0.73–0.95)
Deliver [61]	Dapaglifozin	10	HFpEF	18% reduction the primary outcome (CV death, HHF)	0.82 (0.73–0.92)
Emmy [72]	Empaglifozin	10	MI	Reduction in NT-pro-BNP and LV echocardiographic parameters	NA
Empact-MI [74]	Empaglifozin	10	MI	10% reduction of composite outcome (death from any cause or HHF)	0.90 (0.76–1.06)
Empareg-outcome [9]	Empaglifozin	25/10	DM2 and high CV risk	14% reduction in 3-point MACE (CV death, non-fatal MI, non-fatal stroke)	0.86 (0.74–0.99)
Empa-Heart Cardio-link 6 [84]	Empaglifozin	10	DM and CAD	Reduction in LV mass index	NA
Empa-response AHF [85]	Empaglifozin	10	AHF	reduction of composite outcome (progression of kidney disease and CV death)	NA
Empa-kidney [86]	Empaglifozin	10	CKD	28% reduction of composite (progression of kidney disease and CV death)	0.72 (0.64–0.82)
Empa tropism [67]	Empaglifozin	10	HFrEF	Improvement of LV parameters	NA
Emperor-Reduced [11]	Empaglifozin	10	HFrEF	25% Reduction in composite outcome (CV death or HHF); 30% reduction HHF	0.75 (0.65–0.86) for primary composite outcome 0.70 (0.58–0.85) for HHF
Emperor-Preserved [12]	Empaglifozin	10	HFpEF	21% Reduction in composite outcome (CV death or HHF); 30% reduction HHF	0.79 (0.69–0.90) for primary composite outcome 0.70 (0.59–0.83) for HHF

Table 2. *Cont.*

Study	Drug	Dose	Population	Primary CV Outcome	HR(95% CI)
Empulse [62]	Empaglifozin	10	AHF	36% reduction in composite outcome (death from any cause, number of HF events)	1.75 (1.37–2.23)
Reform [87]	Dapaglifozin	10	HF	No change in LV CMR parameters	NA
Scored [54]	Sotaglifozin	200/400	DM2, CKD and high CV risk	16% reduction in composite (CV death or HHF)	0.84 (0.72–0.99)
Soloist-WHF [53]	Sotaglifozin	200/400	DM2 and HF	33% reduction in composite (CV death or HHF)	0.67 (0.52–0.85)
Sugar-DM [64]	Empaglifozin	10	DM2 and HFrEF	Reduction of LV volumes	NA
Vertis-CV [51]	Ertuglifozin	15/5	DM2 and high CV risk	13%-No significant difference in 3-point MACE (CV death, non-fatal MI, non-fatal stroke)	0.87 (0.70–1.1)

Legend. MI: myocardial infarction; MACE: major adverse cardiovascular events; HHF: hospitalization for Heart Failure, HF: heart failure; CV: cardiovascular;DM2: Type 2 diabetes; LV: left ventricular; CMR: cardiac magnetic resonance; CAD: coronary artery disease; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; AHF: acute heart failure; CKD: chronic kidney disease; ESRD: End-Stage Renal Disease; HR: Hazard Ratio; CI: Confidence Interval; NA: not available.

4. SGLT2i on Kidney: Across the Trials

Before 2015, hypoglycemic drugs were found to modestly reduce the progression of diabetic nephropathy with intensive treatment, but showed no benefit for macrovascular complications or cardiovascular death [88]. However, recent years have seen the emergence of a new class of drugs, SGLT2i, which have demonstrated significant efficacy in slowing the progression of diabetic kidney disease and improving cardiovascular outcomes in large clinical trials [7–15,51,89]. The FDA and EMA have approved four SGLT2i for diabetic nephropathy: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. To date, results from four large international randomized controlled trials (RCTs) involving SGLT2i in patients with type 2 diabetes mellitus (DM2) have been published, collectively enrolling 38,723 patients across 6 continents [7–11,14,15,51]. Although these studies were not specifically designed to evaluate the effect of SGLT2i inhibition on the progression of diabetic kidney disease, few trials reported prespecified or post hoc effects on a composite renal outcome (i.e., dialysis, transplantation, or a sustained estimated GFR of <15 mL per minute per 1.73 m^2).The first study, specifically designed to determine the effects of SGLT2 inhibition in patients with established kidney disease and higher risk of renal disease progression, was conducted with canagliflozin [10]. This trial included diabetic patients with an eGFR between 30 and less than 90 mL/min/1.73 m^2 and macroalbuminuria (between >300 and $\leq$5000 mg/g). The subpopulation with an eGFR between 20 and $\leq$45 mL/min/1.73 m^2 was included, and subjects could present with microalbuminuria or macroalbuminuria to provide a broad spectrum of outcomes for efficacy against diabetic nephropathy. The study was stopped early due to the unequivocal beneficial effect of 30% reduction in the primary composite renal outcome (HR 0.70; 95% CI 0.59–0.82). Moreover, there was also evidence of benefit for end-stage renal disease alone (HR 0.68; 95% CI 0.54–0.86) [10]. In the VERTIS CV trial [51], 8246 patients with type 2 diabetes, atherosclerotic disease, and an estimated glomerular filtration rate (eGFR) of $\geq$30 mL/min/1.73 m^2 were randomized to receive either ertugliflozin (5 mg or 15 mg) or placebo. The secondary endpoint was a composite renal of doubling of serum creatinine, renal dialysis or transplantation, or renal death. Among the trial participants, 22% had a baseline eGFR between 30 and 60 mL/min/1.73 m^2, and 40% were albuminuric (31% with microalbuminuria and 9.4% with macroalbuminuria). Approximately 50% of the trial population was at moderate to very high risk of chronic kidney disease progression. Results showed the risk of the secondary renal composite outcome was reduced by 19% in the ertugliflozin group (HR 0.81, 95% CI 0.63–1.04). However, a significant risk reduction was observed when the com-

posite renal outcome was defined as a 40% decline in eGFR, renal dialysis/transplantation, and renal death (HR 0.66 95% CI 0.50–0.88), primarily due to a slower decline in eGFR in the ertugliflozin-treated group. Subgroup analysis demonstrated similar benefits across different categories of renal disease. Additionally, the risk of albuminuria progression was significantly reduced by 21% with ertugliflozin, which also promoted greater regression to microalbuminuria or normo-albuminuria (HR 1.23 95% CI 1.10–1.36), especially in advanced chronic kidney disease [51]. The study conducted with dapagliflozin [15], enrolled 4304 patients with macroalbuminuria and an eGFR between 25 and 75 mL/min/1.73 m^2. A predefined subgroup included 33.5% of non-diabetic patients with chronic renal failure. The study was also discontinued at the time of the interim analysis due to the clear superiority of dapagliflozin for reducing the incidence of the composite renal outcome by 44% compared to placebo (HR 0.56; 95% CI 0.45–0.68), regardless of the degree of eGFR reduction or the extent of pre-existing albuminuria. Dapagliflozin's efficacy was similar in both diabetic and non-diabetic subjects, and its safety profile was confirmed in both groups [15].

The reduction of the intraglomerular pressure by restoring afferent arteriole tone is the main nephroprotective role of SGLT2i, which leads to better outcomes in decompensated patients and influences adverse cardiovascular outcomes [17]. In the study with empagliflozin involving HFrEF patients and more advanced chronic kidney disease (CKD) (stages II to IV), the composite renal outcome significantly improved in empagliflozin group (HR 0.70; 95% CI 0.32–0.77) [11]. Indeed, empagliflozin administration was associated with an immediate reduction in eGFR, which then tended to return toward baseline values and remained stable over time. As opposite, the placebo group initially had a higher eGFR, which subsequently declined slowly and progressively, intersecting with the eGFR values of the treated patient group over the long term, documenting a later but more significant loss of renal function [11]. Conversely, empagliflozin did not have a significantly favorable effect on major renal outcomes in HFpEF patients regardless their glycemic status (HR 0.95; 95% CI 0.73–1.24) [12].

The SGLT1 is primarily found in the intestines, where facilitates the absorption of glucose from the diet. By inhibiting both SGLT1 and SGLT2, sotagliflozin reduces glucose absorption from the intestines and increases glucose excretion through the urine [17]. In the SCORED trial [54], enrolling 10,584 DM2 patients with an eGFR between 25 and 60 mL/min/1.73 m^2, sotagliflozin was investigated. Unfortunately, the study was halted after 16 months due to loss of funding and showed a no statistically significant reduction of the secondary composite renal endpoint (HR 0.71 95% CI 0.46–1.08). An ongoing trial (NCT06217302) will evaluate Sotaglifozin 200 mg/day for the prevention of kidney function decline in patients with type 1 diabetes mellitus and CKD (20 and 60 mL/min/1.73 m^2) with a urinary albumin/creatinine ratio (UACR) $\geq$ 200 mg/g.

Although studies conducted with empagliflozin, dapagliflozin, canagliflozin consistently showed that the reduction in renal outcomes was associated with a reduction in hospitalizations for heart failure, the meta-analysis by Zelniker et al. [90] highlighted a peculiar distribution of efficacy. The analysis revealed that the effect of SGLT2i on the composite renal outcome (defined as worsening renal function, need for renal replacement therapy, or death from renal causes) was statistically greater in subjects with better-preserved renal function compared to those with more impaired function. Study populations were stratified based on their GFR values (<60, 60–<90, $\geq$90 mL/min/1.73 m^2) and the significance value for the downward trend of events across the subgroups was 0.0258. Studies in patients with stage 4 chronic kidney disease (CKD) (GFR < 30 mL/min/1.73 m^2) remain limited. However, the EMPA-Kidney study [86], which evaluated the effect of empagliflozin in adult CKD patients, including those with eGFR > 20 mL/min/1.73 m^2, recently reported clear efficacy of empagliflozin compared to placebo. In this trial, the primary composite cardio-renal outcome was reduced by 28% in the empagliflozin group (HR 0.72, 95% CI 0.64–0.82). Results were consistent among patients with or without diabetes and across subgroups defined by eGFR ranges [86].

A recent meta-analysis, which analyzed 23 studies encompassing more than 20,000 patients [91], confirmed that the overall mean difference in the rate of eGFR decline was 0.02 mL/min/1.73 m^2 per year, while the mean difference in the change in uACR was −141.34 mg/g. Moreover, SGLT2i are responsible for the reduction of 36% (HR 0.64, 95% CI 0.57–0.72) of the secondary renal composite endpoint (>40% decline in eGFR, doubling of serum creatinine, chronic dialysis, kidney transplantation, or renal death). Lastly, subgroup analyses indicated that long-term renal function was better preserved in participants with baseline macroalbuminuria and in those with stage 4 CKD when treated with SGLT2is compared to placebo [91].

Key renal outcomes and efficacy of SGLT2i across different trials and patient populations are shown in Table 3.

Table 3. Key renal outcomes and highlights the efficacy of SGLT2 inhibitors across different trials and patient populations.

Study	Drug	Dose	eGFR (mL/min/ 1.73 m^2)	UACR (mg/g)	Primary Renal Outcome	HR (95% CI)
Bexagliflozin study [92]	Bexaglifozin	20	30–59	>300	63% reduction in eGFR decline and UAR	0.37 (0.20–0.54) for eGFR 30–60
Canvas [7]	Canaglifozin	300/100	30–59	>300	40% reduction in eGFR, renal-replacement therapy, or renal death	0.73 (0.67–0.79) for albuminuria 0.60 (0.47–0.77) for reduction in eGFR, renal-replacement therapy, or renal death
Credence [10]	Canaglifozin	300/100	30–59	>300	30% reduction in composite outcome (doubling of serum creatinine, ESRD, or death)	0.70 (0.59–0.82)
DAPA-CKD [15]	Dapaglifozin	10	25–45	>1000	44% reduction in composite outcome (worsening renal function, transplant, death)	0.56 (0.45–0.68)
DAPA-HF [14]	Dapaglifozin	10	30–59	NA	29% reduction in eGFR decline, ESKD, or renal death	0.71 (0.44–1.16)
Declare-TIMI [8]	Dapaglifozin	10	<60	>300	40% reduction in eGFR decline, ESKD, or renal death	0.53 (0.43–0.66)
Deliver [61]	Dapaglifozin	10	30–59	NA	No significant reduction in renal composite outcome	1.08 (0.79–1-49)
Derive [93]	Dapaglifozin	10	30–59	30 >1000	No significant change in UAR or eGFR	NA
Diamond [94]	Dapaglifozin	10	>25	30–3500	No significant change in 24-h proteinuria and eGFR	NA
Empareg-outcome [95]	Empaglifozin	25/10	30–60	30–300	39% reduction of incident or worsening nephropathy 46% reduction of post hoc renal composite outcome (a doubling of the serum creat-inine level, the initiation of renal-replacement therapy, or death from renal disease)	0.61 (0.53–0.70) 0.54 (0.40–0.75)

Table 3. *Cont.*

Study	Drug	Dose	eGFR (mL/min/ 1.73 m^2)	UACR (mg/g)	Primary Renal Outcome	HR (95% CI)
Empa-kidney [86]	Empaglifozin	10	20–89	30–1000	28% reduction in progression of kidney disease or cardiovascular outcomes	0.72 (0.64–0.82)
Emperor-Reduced [11]	Empaglifozin	10	20–59	>300	30% reduction in composite renal outcome (chronic dialysis, RRT, sustained ≥40% eGFR reduction)	0.70 (0.32–0.77)
Emperor-Preserved [12]	Empaglifozin	10	30–60	>300	5%-No significant effect on major renal outcomes	0.95 (0.73–1.24)
Scored [54]	Sotaglifozin	200/400	25–59	>300	29% reduction in composite renal outcome (≥50% GFR decline, ESKD, renal death)	0.71 (0.46–1.08)
Vertis-CV [51]	Ertuglifozin	15/5	30–59	>300	19% reduction in composite renal outcome (doubling of serum creatinine, renal dialysis or transplantation, or renal death, sustained ≥40% GFR reduction, Progression or regression of albuminuria and change)	0.81 (0.63–1.04)
Wada et al. [96]	Canaglifozin	100	30–89	NA	40% reduction in eGFR, renal or cardiovascular death	0.60 (0.23–1.55)

Legend. eGFR: Estimated Glomerular Filtration Rate; UACR: Urine Albumin-to-Creatinine Ratio; ESRD: End-Stage Renal Disease; RRT: Renal Replacement Therapy; HR: Hazard Ratio; CI: Confidence Interval; NA: not available.

5. Additional Molecular Targets of SGLT2i and Limitations

SGLT2i, in addition to their primary mechanism of action by inhibiting sodium-glucose cotransporters (SGLT2), also exhibit beneficial effects on other metabolic pathways. These include lowering blood pressure, promoting natriuresis, and reducing uric acid levels [97]. Therefore, this class of drugs is responsible for lipolysis and lipid oxidation through reducing plasma insulin and glucose levels and promoting glucagon secretion, which result in decreasing visceral and subcutaneous fat and consequently weight loss (2–3 kg). Moreover, an increasing HDL cholesterol and decreasing triglycerides, which can contribute to reducing atherosclerotic risk, was observed in patients treated with SGLT2i [98]. Reduction in endothelial damage, inflammation, weight and body fat loss, together with improved lipid profile could lead to the use of SGLT2i in acute myocardial injury in the future as well, although for now results are mixed [72,73]. The production of ketone bodies used by cardiomyocytes, would improve their energy efficiency compensating for the reduced oxidation capacity at the mitochondrial level present in patients with HF [30]. The loss of body fluid and sodium inhibit renin-angiotensin-aldosterone system (RAAS) activation resulting in an average reduction of 3.62 mmHg of systolic and a 1.70 mmHg of diastolic pressure [99]. Possibly due to its diuretic effects and hemoconcentration, SGLT-2i increase hematocrit. Several studies highlighted SGLT2i promote erythropoiesis and hematocrit through the suppression of hepcidin, the modulation of iron regulatory proteins the increased in erythropoietin (EPO) synthesis, which promotes adenosine triphosphate (ATP) production [100,101]. In postinfarction rats, the dapaglifozin administration increase M2 macrophages levels and decreasing M1 macrophages, via the acute phase response factor (STAT3) signaling pathway, resulting in reduction of cardiac fibrosis [102]. Furthermore, the anti-fibrotic effects of SGLT2i may be mediated by inhibiting RAAS, which leads to changes in the shape, size and function of heart and kidney [30]. Although generally well-tolerated, SGLT2i are associated with specific side effects. Notably, the incidence of mycotic genital infections is higher among patients receiving any type of SGLT2i. This is

due to the pharmacologically-induced urinary glucose excretion, which can promote the growth of genital microorganisms, increasing the risk of genital and urinary tract infections. Additionally, among patients with CKD, the incidence of euglycemic diabetic ketoacidosis is a concern, likely due to significant glycosuria. Early recognition and prompt treatment of this condition are crucial to reduce morbidity and mortality [91]. Extensive studies on dapagliflozin and empagliflozin have attested to their safety and low risk of adverse events. However, further research is needed for other drugs in the SGLT2i class to clearly define side effects, such as the risk of fractures and lower limb amputations, particularly associated with canagliflozin [103]. Additionally, the effectiveness of SGLT2i in type 1 diabetes or gestational diabetes has not yet been established [104]. Although the potential cardiorenal benefits of SGLT2i therapy have not yet been confirmed in patients with transplanted kidneys, there is reassuring evidence of a physiological decrease in eGFR consistent with an appropriate hemodynamic response and a reduction in hyperfiltration, which may result in long-term benefits [105]. However, current data are limited, and ongoing large RCTs (NCT05788276, NCT04743453, NCT04965935) are expected to provide further guidance on the safe use of SGLT2i in this population.

Better understanding the pathways involved in mediating these benefits may lead to the discovery of novel therapeutic targets and the development of next-generation SGLT2i with enhanced efficacy and specificity. Continued research in these areas may uncover additional cardiovascular and renal benefits of SGLT2 inhibitors and expand their clinical utility.

6. Future Directions in Cardiovascular and Renal Systems and Benefits of Other Anti-Diabetes Drugs

SGLT2i can be used as monotherapy in HF patients and renal impairment or in those who are intolerant to other medications [106]. However, combining SGLT2i with other drug classes, such as angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNI), or glucagon-like peptide-1 receptor agonists (GLP-1Ra), provides a synergistic effect, further improving both cardiovascular and renal outcomes. Current guidelines increasingly recommend combination therapy, especially for patients with multiple comorbidities, such as diabetes, renal impairment, and HF [3,6,17]. GLP-1 receptor agonists (GLP-1Ra) were first approved in 2005 for DM2 treatment [107]. GLP-1Ra mitigate glomerular hyperfiltration by increasing diuresis and natriuresis through the phosphorylation and direct inhibition of sodium-hydrogen exchanger 3 (NHE3). The increased sodium load reaching the macula densa restores normal tubulo-glomerular feedback, suppresses RAAS hyperactivation, and lowers serum angiotensin II levels [108]. Moreover, cardiovascular outcome trials with GLP-1Ra have not only confirmed their cardiovascular safety but have also demonstrated significant benefits in reducing adverse events in patients with pre-existing atherosclerotic cardiovascular disease [109–112]. A meta-analysis of all cardiovascular outcome trials for the GLP-1Ra class confirmed significant class-wide effects on hard endpoints [113]. This meta-analysis demonstrated that GLP-1Ra, regardless of structural homology to the native molecule, reduce cardiovascular risk in diabetes patients by lowering the incidence of individual MACE components (−10% myocardial infarction, −17% stroke), cardiovascular death (−13%), all-cause mortality (−12%), HHF (−11%), and worsening renal function (−21%), with a significant reduction in albuminuria [113]. In comparison with SGLT2i class, Joubert et al. demonstrated that dapagliflozin improves diastolic function and reduces left ventricular hypertrophy in a lipodystrophic *Bscl2*$^{-}$/$^{-}$ mouse model [114]. Additionally, their findings revealed that dapagliflozin was found to be more effective than pioglitazone in reducing glucose exposure and improving diabetic cardiomyopathy [114]. Therefore, a collaborative meta-analysis of 12 double-blind, placebo-controlled randomized trials evaluated the efficacy of SGLT2i in patients with DM2 [115]. The two primary cardiovascular endpoints were MACE and a composite of HHF or cardiovascular death. The renal endpoints included progression of CKD, defined by a $\geq$40% reduction in eGFR, renal failure

(eGFR < 15 mL/min/1.73 m^2, chronic dialysis, kidney transplantation, or death from renal failure), and the rate of decline in eGFR over time. Among the 73,238 participants with DM2 across the 12 trials, 3065 (4.2%) were using GLP-1Ra at baseline. SGLT2i reduced the risk of MACE in both those receiving GLP-1Ra and those not (p-heterogeneity = 0.31) [115]. Moreover, the effects on HHF or cardiovascular death (p-heterogeneity = 0.90), progression of CKD (p-heterogeneity = 0.81), and eGFR decline over time (p-heterogeneity = 0.92) were consistent, regardless of GLP-1Ra use. Additionally, the performance of SGLT2i in relation to adverse events was also independent of GLP-1Ra use (p-heterogeneity = 0.41) [115]. Therefore, SGLT2i class has been shown to be superior to GLP-1Ra due to the dual benefits of improving cardiovascular and renal outcomes, reducing HHF and slowing the progression of CKD, regardless of the presence of diabetes or HF subtype.

7. Conclusions

SGLT2i have emerged as groundbreaking therapies for managing DM2, offering significant cardiovascular and renal benefits. The impressive results from clinical trials have led to current recommendations advocating for the incorporation of SGLT2i in the treatment regimen for heart failure (HF) patients. The 2021 guidelines from the European Society of Cardiology (ESC) recommend SGLT2i as one of the four cornerstone therapies for patients with HFrEF, recognizing their potential to alter the syndrome's natural history with a Class I recommendation and Level of Evidence A. The recent 2023 update of the ESC 2021 guidelines on acute and chronic HF further underscores the importance of SGLT2i. For patients with ejection fractions greater than 40%, encompassing those with mildly reduced or preserved ejection fraction, SGLT2i receive a Class IA recommendation, the highest possible, comparable to diuretics. Additionally, the ESC 2023 guidelines for diabetes recommend SGLT2i (canagliflozin, empagliflozin, or dapagliflozin) for patients with type 2 diabetes and chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) $\geq$ 20 mL/min/1.73 m^2, aiming to reduce cardiovascular risk and kidney failure with a Class IA recommendation. Studies have consistently demonstrated SGLT2i's ability to markedly reduce renal damage, as evidenced by the combined outcomes of decreased filtrate levels and increased macroalbuminuria, which influence the need for renal replacement therapy. This benefit is largely attributed to the reduction in intra-glomerular filtration pressure, achieved by restoring sodium concentration in the filtrate reaching the juxtaglomerular apparatus. Based on the sodium detected in the filtrate, the kidney modulates renin release and angiotensin II production, thereby reducing intraglomerular pressure and hyperfiltration. This process mitigates glomerular damage and neurohormonal imbalances, leading to the alleviation of hydrosaline retention and congestion. Exploring future directions through innovative research and collaborative efforts will be crucial for maximizing the potential of SGLT2i in improving outcomes for patients with cardiovascular and renal diseases.

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