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SGLT2 Inhibitors in Cardiovascular Disease: Mechanisms, Clinical Evidence and Evolving Therapeutic Applications

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ABS TRAC T

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, originally developed as glucose-lowering agents for type 2 diabetes mellitus, have undergone one of the most consequential therapeutic repositionings in modern cardiovascular medicine, transforming from antidiabetic adjuncts into first-line treatments for heart failure and chronic kidney disease irrespective of glycaemic status. The cardiovascular benefits of SGLT2 inhibitors — encompassing reductions in hospitalisation for heart failure, attenuation of adverse ventricular remodelling, slowing of cardiorenal axis deterioration, and a modest but consistent reduction in cardiovascular mortality — operate through a constellation of interacting mechanisms that extend far beyond glucosuric diuresis: haemodynamic unloading, restoration of tubuloglomerular feedback, myocardial metabolic reprogramming towards ketone body oxidation, cardiac sodium-hydrogen exchanger (NHE1) inhibition, NLRP3 inflammasome suppression, and attenuation of both sympathetic overactivation and the renin-angiotensin-aldosterone system. Landmark randomised trials — including EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, DAPA-CKD, CREDENCE, and SCORED — have collectively established the cardiovascular and renoprotective efficacy of SGLT2 inhibitors across the spectrum of patients with established cardiovascular disease, heart failure with reduced and preserved ejection fraction, and chronic kidney disease, with and without type 2 diabetes. Safety considerations including genital mycotic infections, diabetic ketoacidosis risk, and the canagliflozin-associated lower limb amputation signal require contextualised clinical appraisal. Current international guidelines from the ESC, ACC/AHA, ADA, KDIGO, and others now recommend SGLT2 inhibitors as a cornerstone of management in heart failure, CKD, and cardiometabolic risk reduction. This review comprehensively synthesises the mechanistic basis, landmark trial evidence, guideline positioning, special population considerations, and emerging indications of SGLT2 inhibitors in cardiovascular medicine.

Keywords: *SGLT2 Inhibitors, Empagliflozin, Dapagliflozin, Canagliflozin, Heart Failure, Cardiovascular Outcomes, EMPA-REG OUTCOME, DAPA-HF, EMPEROR, Renal Protection, NLRP3, NHE1, Cardiorenal Syndrome, HFpEF, HFrEF, Type 2 Diabetes.*

1. INTRODUCTION

The sodium-glucose cotransporter-2 (SGLT2) inhibitor class — encompassing empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, and sotagliflozin, among others — has fundamentally altered the therapeutic landscape for cardiovascular disease, heart failure, and chronic kidney disease over the past decade through a series of large, rigorously conducted randomised cardiovascular outcome trials (CVOTs) that were not anticipated by their regulatory sponsors to reveal benefits of the magnitude ultimately observed [1]. Originally developed and approved as antidiabetic agents for type 2 diabetes mellitus (T2DM), acting through the inhibition of renal glucose reabsorption in the proximal convoluted tubule to produce euglycaemic glucosuria and lower HbA1c by 0.5–1.0%, SGLT2 inhibitors were first required to complete mandatory large-scale CVOTs by regulatory agencies following the safety concerns raised by rosiglitazone in 2007.

The results of EMPA-REG OUTCOME, published in 2015, constituted a scientific landmark: empagliflozin reduced the composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (three-point MACE) by 14% relative to placebo in high-risk T2DM patients, with a striking 38% reduction in cardiovascular death and a 35% reduction in hospitalisation for heart failure [2]. The speed and magnitude of the cardiovascular mortality reduction — evident within the first few months of treatment, too rapid to be fully explained by conventional risk factor modification — immediately challenged the scientific community to propose alternative mechanistic explanations and prompted a cascade of dedicated heart failure and renal outcome trials across the drug class that have since delivered equally compelling evidence.

In the span of fewer than ten years since EMPA-REG OUTCOME, SGLT2 inhibitors have accumulated an evidence base that now supports their use across a spectrum of patients extending far beyond those with T2DM: individuals with heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), chronic kidney disease (CKD) of diabetic and non-diabetic aetiology, and atherosclerotic cardiovascular disease. The drugs have been incorporated into the highest recommendation tiers of guidelines issued by the European Society of Cardiology (ESC), the American College of Cardiology/American Heart Association (ACC/AHA), the American Diabetes Association (ADA), the Kidney Disease Improving Global Outcomes (KDIGO) initiative, and others [3, 4].

The objective of this narrative review is to provide a comprehensive, clinically focused synthesis of the mechanisms by which SGLT2 inhibitors exert cardiovascular and renal benefits, the landmark trial evidence across cardiovascular disease subgroups, guideline-based positioning, safety and tolerability considerations, special population evidence, and evolving investigational indications that may further expand the therapeutic footprint of this drug class in cardiovascular medicine over the coming decade.

2. PHARMACOLOGY AND MECHANISM OF THE SGLT2 RECEPTOR

2.1 The SGLT Family and Renal Glucose Handling

Glucose reabsorption in the kidney is mediated by two sodium-glucose cotransporter isoforms: SGLT2, located in the S1 and S2 segments of the proximal convoluted tubule, responsible for approximately 90% of the filtered glucose load reabsorption; and SGLT1, situated in the S3 segment of the proximal straight tubule, responsible for the remaining 10% [5]. Under normal physiological conditions, virtually all 160–180 g of glucose filtered daily by the glomeruli is reclaimed by this system, maintaining zero urinary glucose excretion. SGLT2 is a high-capacity, low-affinity cotransporter that couples the translocation of one glucose molecule with one sodium ion down the electrochemical gradient maintained by the basolateral Na^+/K^+-ATPase. In individuals with T2DM, the maximal glucose transport capacity (Tm for glucose) is paradoxically upregulated — an adaptive but ultimately maladaptive response that perpetuates hyperglycaemia by reabsorbing glucose that should be excreted.

2.2 Drug-Receptor Interaction and Glucosuria

SGLT2 inhibitors are orally bioavailable competitive inhibitors of the SGLT2 transporter, structurally based on the natural glucoside phlorizin, modified to achieve SGLT2 selectivity over SGLT1 (selectivity ratios: empagliflozin >2,500-fold; dapagliflozin ~1,200-fold; canagliflozin ~250-fold, making canagliflozin a partial dual SGLT1/SGLT2 inhibitor at clinical doses) [6]. Therapeutic inhibition of SGLT2 lowers the Tm for glucose by approximately 40–50%, causing the urinary glucose threshold to fall from approximately 10–11 mmol/L in health to around 4–5 mmol/L, producing euglycaemic glucosuria of 50–90 g glucose per day. This glucosuria results in an obligatory osmotic diuresis and natriuresis, with associated reductions in plasma volume, body weight, systolic blood pressure, and serum urate — effects that are collectively relevant to their cardiovascular mechanism but only partially explain the magnitude of benefit observed in outcome trials.

3. CARDIOVASCULAR AND RENOPROTECTIVE MECHANISMS

A summary of the principal mechanisms mediating SGLT2 inhibitor cardiovascular and renoprotective effects is presented in Table 1.

Table 1: Mechanisms of SGLT2 Inhibitor Cardiovascular and Renoprotective Effects

Mechanistic Category	Specific Mechanism	Cardiovascular / Renal Consequence
Haemodynamic	Osmotic diuresis via glucosuria; natriuresis reducing preload and afterload	Reduced cardiac filling pressures; lower systolic BP (2–4 mmHg); reduced congestion
Tubuloglomerular feedback restoration	Reduced proximal tubule Na^+/glucose reabsorption → increased NaCl delivery to macula densa → afferent arteriolar vasoconstriction	Reduced intraglomerular pressure; attenuation of glomerular hyperfiltration; slowed CKD progression
Metabolic / Energetic	Shift from glucose to fatty acid and ketone body oxidation; elevated circulating beta-hydroxybutyrate	Improved myocardial energetics (ketone bodies = 'super fuel'); reduced cardiac oxygen demand; improved mitochondrial efficiency

Anti-fibrotic / Anti-inflammatory	NLRP3 inflammasome inhibition; downregulation of NF-kB; reduced TGF-β1 signalling; attenuation of RAAS activation	Reduced myocardial and renal fibrosis; attenuated inflammatory cytokine production; slowed ventricular and renal remodelling
Cardiac structural	Reduction in epicardial adipose tissue; attenuation of LV hypertrophy and LV end-diastolic volume	Improved LV geometry; reduced LV mass index; improved diastolic function parameters
Ion transport / NHE inhibition	Off-target inhibition of cardiac sodium-hydrogen exchanger (NHE1) in cardiomyocytes	Reduced intracellular Na^+ and Ca^{2+} overload; attenuated myocardial hypertrophy, ischaemia-reperfusion injury, and arrhythmogenesis
Erythropoietic	Increased erythropoietin secretion via renal cortical hypoxia sensing; elevated haematocrit (2–3%)	Improved oxygen-carrying capacity; potential contribution to cardioprotection via haemoconcentration and viscosity effects
Sympathetic nervous system	Attenuation of sympathetic nervous system overactivation; possible reduction in cardiac adrenergic tone	Reduced heart rate; improved heart rate variability; potential antiarrhythmic effect
Uric acid lowering	Increased urinary uric acid excretion via competition with URAT1 transporter in proximal tubule	Reduced serum urate; potential reduction in hyperuricaemia-mediated endothelial inflammation and CKD progression
Abbreviations: NHE1 = sodium-hydrogen exchanger isoform 1; NLRP3 = NOD-like receptor protein 3; NF-kB = nuclear factor kappa B; TGF-β1 = transforming growth factor beta-1; RAAS = renin-angiotensin-aldosterone system; LV = left ventricular; CKD = chronic kidney disease		

3.1 Haemodynamic Effects

The osmotic diuresis and natriuresis induced by SGLT2 inhibition produce reductions in intravascular volume and cardiac preload that are quantitatively modest but haemodynamically relevant, reducing systolic blood pressure by approximately 2–4 mmHg and diastolic pressure by 1–2 mmHg in clinical trials [7]. The diuretic profile of SGLT2 inhibitors is mechanistically distinct from conventional loop or thiazide diuretics in several important respects. Unlike loop diuretics, SGLT2 inhibitors do not activate the renin-angiotensin-aldosterone system (RAAS) and do not cause neurohormonal activation in the long term; unlike thiazides, they do not impair glucose tolerance or worsen insulin resistance. The haemoconcentration effect — reflected by consistent increases in haematocrit of 2–3 percentage points across trials — increases blood viscosity and oxygen-carrying capacity and may contribute to myocardial oxygen delivery improvements.

3.2 Tubuloglomerular Feedback Restoration

One of the most mechanistically compelling explanations for the renoprotective effect of SGLT2 inhibitors is the restoration of tubuloglomerular feedback (TGF). In diabetic nephropathy, increased proximal tubular glucose and sodium reabsorption reduces solute delivery to the macula densa at the end of the loop of Henle, impairing the TGF mechanism and causing afferent arteriolar vasodilatation and consequent glomerular hyperfiltration — a haemodynamic state that sustains an elevated glomerular filtration rate in the early stages of CKD while simultaneously promoting glomerular hypertension and progressive structural damage [8]. SGLT2 inhibition restores macula densa NaCl sensing by redirecting sodium away from the proximal tubule, re-activating TGF-mediated afferent arteriolar constriction, reducing intraglomerular pressure, and attenuating the mechanical and haemodynamic drivers of glomerulosclerosis and proteinuria. This mechanism elegantly explains the initial reversible decline in eGFR observed at SGLT2 inhibitor initiation — a dip analogous to that seen with RAAS inhibitors — and the subsequent long-term preservation of renal function relative to placebo over months to years.

3.3 Myocardial Metabolic Reprogramming and the Ketone Hypothesis

The failing heart is an energy-starved organ characterised by reduced fatty acid oxidation, impaired mitochondrial efficiency, and increasing dependence on glucose as a fuel source — a metabolic phenotype termed 'metabolic remodelling' that is associated with reduced ATP production efficiency and progressive contractile dysfunction [9]. SGLT2 inhibitors induce a mild physiological ketosis — characterised by modest elevations in circulating beta-hydroxybutyrate (typically 0.2–0.5 mmol/L, well below the diabetic ketoacidosis threshold) — by shifting hepatic substrate utilisation toward fatty acid oxidation and ketogenesis. Beta-hydroxybutyrate and acetoacetate are thermodynamically more efficient fuels than glucose or fatty acids per mole of oxygen consumed, potentially providing the failing myocardium with a metabolic advantage. Lopaschuk and Verma proposed that SGLT2 inhibitors function as a form of 'super fuel' delivery system for the heart, improving cardiac efficiency without increasing oxygen demand [9]. This hypothesis is supported by echocardiographic studies demonstrating improvements in myocardial work indices and cardiac energy reserve in SGLT2 inhibitor-treated patients with heart failure, though direct causal attribution to ketonaemia remains an active area of investigation.

3.4 Cardiac Sodium-Hydrogen Exchanger Inhibition

An off-target effect of SGLT2 inhibitors — particularly empagliflozin — on the cardiac sodium-hydrogen exchanger isoform 1 (NHE1) has emerged as a potentially important mechanism explaining the rapid cardiovascular benefits observed in trials, which occur too early to be attributed to structural remodelling or metabolic adaptation [10]. NHE1 is a transmembrane antiporter in cardiomyocytes that extrudes protons in exchange for sodium during ischaemia-reperfusion and neurohormonal activation, leading to intracellular sodium and calcium overload via the reversed sodium-calcium exchanger (NCX). Elevated intracellular calcium promotes hypertrophy, arrhythmogenesis, and mitochondrial dysfunction. In vitro and ex vivo studies have demonstrated that empagliflozin directly inhibits NHE1 at concentrations achievable with standard therapeutic dosing, reducing cardiomyocyte sodium and calcium content, improving mitochondrial function, and attenuating ischaemia-reperfusion injury. Whether this mechanism fully operates in the clinical setting remains to be definitively established, but NHE1 inhibition represents the most mechanistically coherent explanation for the rapid cardiovascular protection observed with SGLT2 inhibitors.

3.5 Anti-inflammatory and Anti-fibrotic Effects

Chronic low-grade inflammation and progressive fibrosis are shared pathological substrates of heart failure, CKD, and atherosclerosis, and their attenuation by SGLT2 inhibitors may contribute to the pleiotropic clinical benefits observed across these conditions. Experimental and human translational data demonstrate that SGLT2 inhibitors suppress NLRP3 inflammasome activation — the innate immune pathway responsible for IL-1β and IL-18 maturation — in both cardiac and renal tissue, potentially through ketone body-mediated inhibition of NLRP3 assembly [11]. Downregulation of nuclear factor kappa B (NF-kB), reduced production of pro-inflammatory cytokines including tumour necrosis factor-alpha and interleukin-6, attenuation of RAAS hyperactivation, and reduced TGF-β1 expression in proximal tubular cells collectively contribute to a pro-resolution inflammatory milieu that decelerates both myocardial and renal fibrotic remodelling. Echocardiographic studies in T2DM patients with LV hypertrophy demonstrate significant reductions in LV mass index, epicardial adipose tissue volume, and markers of myocardial fibrosis after 6–12 months of SGLT2 inhibitor therapy, consistent with these mechanistic predictions.

3.6 Sympathetic Nervous System and Neurohormonal Modulation

Heart failure is characterised by chronic sympathetic nervous system overactivation, which drives adverse cardiac remodelling, arrhythmogenesis, and progressive haemodynamic deterioration. Emerging evidence suggests that SGLT2 inhibitors attenuate sympathetic outflow through mechanisms that may include afferent renal nerve deactivation consequent to the reduction in renal ischaemic signalling, improved baroreceptor sensitivity, and correction of the metabolic milieu that drives central sympathoexcitation in insulin-resistant states [12]. Consistent with reduced sympathetic tone, SGLT2 inhibitor-treated patients demonstrate modest but consistent reductions in resting heart rate and improved heart rate variability in several clinical studies, findings that carry potential antiarrhythmic implications in a population at high risk of sudden cardiac death and new-onset atrial fibrillation.

4. CARDIOVASCULAR OUTCOME TRIALS — EVIDENCE SYNTHESIS

The major cardiovascular and renal outcome trials with SGLT2 inhibitors are summarised in Table 2.

Table 2: Summary of Major Cardiovascular and Renal Outcome Trials with SGLT2 Inhibitors

Trial	Drug	Population (n)	Primary Endpoint	Follow-up (median)	Primary Outcome HR (95% CI)	Key Secondary Findings
EMPA-REG OUTCOME (2015)	Empagliflozin	T2DM + CVD (n=7,020)	3P-MACE	3.1 years	HR 0.86 (0.74–0.99) p=0.04	CV death ↓38%; HHF ↓35%; all-cause mortality ↓32%
CANVAS Program (2017)	Canagliflozin	T2DM + CVD risk (n=10,142)	3P-MACE	2.4 years	HR 0.86 (0.75–0.97) p<0.001	HHF ↓33%; CKD progression ↓40%; amputations ↑ (HR 1.97)
DECLARE-TIMI 58 (2018)	Dapagliflozin	T2DM + CVD or risk (n=17,160)	3P-MACE + CV death/HHF	4.2 years	MACE HR 0.93 (0.84–	CV death/HHF ↓17%; renal

					1.03) p=0.17 (ns)	composite ↓24%
CREDENCE (2019)	Canagliflozin	T2DM + CKD (n=4,401)	Renal/CV composite	2.6 years	HR 0.70 (0.59–0.82) p=0.00001	HHF ↓39%; CV death/HHF ↓31%; ESRD ↓32%
DAPA-HF (2019)	Dapagliflozin	HFrEF ± T2DM (n=4,744)	CV death/WorsHF/symptoms	18.2 months	HR 0.74 (0.65–0.85) p<0.001	Benefit equal in T2DM and non-T2DM; all-cause mortality ↓17%
EMPEROR-Reduced (2020)	Empagliflozin	HFrEF ± T2DM (n=3,730)	CV death/HHF	16 months	HR 0.75 (0.65–0.86) p<0.001	HHF ↓31%; eGFR decline slowed; total HHF events ↓30%
EMPEROR-Preserved (2021)	Empagliflozin	HFpEF ± T2DM (n=5,988)	CV death/HHF	26.2 months	HR 0.79 (0.69–0.90) p<0.001	First SGLT2i trial positive in HFpEF; benefit regardless of EF
DAPA-CKD (2020)	Dapagliflozin	CKD ± T2DM (n=4,304)	Renal/CV composite	2.4 years	HR 0.61 (0.51–0.72) p<0.001	ESRD/death ↓39%; all-cause mortality ↓31%; early stopped
SCORED (2020)	Sotagliflozin (SGLT1+2)	T2DM + CKD (n=10,584)	CV death/HHF/urgent HF visits	16 months	HR 0.74 (0.63–0.88) p<0.001	Benefit driven by urgent HF visits; early stopped (COVID-19)
DELIVER (2022)	Dapagliflozin	HFmrEF/HFpEF (n=6,263)	CV death/WorsHF	2.3 years	HR 0.82 (0.73–0.92) p<0.001	Confirmed SGLT2i benefit across full EF spectrum; symptoms improved
3P-MACE = composite of CV death, non-fatal MI, non-fatal stroke; HHF = hospitalisation for heart failure; WorsHF = worsening HF event; HFrEF/HFpEF/HFmrEF = HF with reduced/preserved/mildly reduced EF; ns = not significant; CKD = chronic kidney disease; ESRD = end-stage renal disease						

4.1 T2DM Patients with Established Cardiovascular Disease

4.1.1 EMPA-REG OUTCOME

The EMPA-REG OUTCOME trial, published in the New England Journal of Medicine in 2015, enrolled 7,020 adults with T2DM and established cardiovascular disease randomised to empagliflozin (10 mg or 25 mg) or placebo in addition to standard care.[2] The primary three-point MACE endpoint was reduced by 14% (HR 0.86; 95% CI 0.74–0.99; p=0.04 for superiority) — a result driven predominantly by a 38% relative reduction in cardiovascular mortality (HR 0.62; 95% CI 0.49–0.77) rather than reductions in myocardial infarction or stroke. Hospitalisation for heart failure was reduced by 35% and all-cause mortality by 32%. The pattern of benefit — rapid divergence of the

cardiovascular mortality curves, absence of early benefit on atherothrombotic events, and prominent heart failure effects — pointed strongly toward haemodynamic and metabolic mechanisms rather than direct anti-atherothrombotic effects as the primary drivers of cardiovascular protection.

4.1.2 CANVAS Program

The CANVAS Program combined two trials — CANVAS and CANVAS-R — enrolling 10,142 adults with T2DM and established cardiovascular disease or elevated cardiovascular risk randomised to canagliflozin or placebo [13]. The primary MACE endpoint was reduced by 14% (HR 0.86; 95% CI 0.75–0.97; p<0.001 for non-inferiority, p=0.02 for superiority), consistent with the EMPA-REG OUTCOME result. Hospitalisations for heart failure were reduced by 33%, and progression of albuminuria and the renal composite endpoint by approximately 40%. However, the CANVAS Program identified a doubling of the risk of lower limb amputation with canagliflozin (HR 1.97; 95% CI 1.41–2.75) — predominantly affecting below-the-knee amputations in patients with prior amputation or peripheral arterial disease — a safety signal that has not been consistently replicated with other SGLT2 inhibitors and remains a class-specific drug label warning for canagliflozin.

4.1.3 DECLARE-TIMI 58

DECLARE-TIMI 58 enrolled 17,160 adults with T2DM, the majority (59%) with cardiovascular risk factors rather than established cardiovascular disease — the broadest primary prevention population of the three initial CVOTs [14]. Dapagliflozin did not significantly reduce the primary three-point MACE endpoint (HR 0.93; 95% CI 0.84–1.03; p=0.17), though the co-primary endpoint of cardiovascular death or hospitalisation for heart failure was significantly reduced by 17% (HR 0.83; 95% CI 0.73–0.95; p=0.005). The renal composite endpoint was reduced by 24%. The overall pattern of DECLARE-TIMI 58 confirmed that the heart failure and renal benefits of SGLT2 inhibitors are more consistent and robust than MACE benefits — a distinction with direct clinical implications for patient selection.

4.2 Heart Failure — Across the Ejection Fraction Spectrum

4.2.1 DAPA-HF

DAPA-HF was the first dedicated heart failure trial of an SGLT2 inhibitor, enrolling 4,744 patients with HFrEF (LVEF ≤40%) and NYHA Class II–IV symptoms, with or without T2DM [15]. Dapagliflozin 10 mg daily significantly reduced the composite of worsening heart failure or cardiovascular death by 26% (HR 0.74; 95% CI 0.65–0.85; p<0.001). Critically, the benefit was of identical magnitude in patients with and without T2DM (interaction p=0.55), definitively establishing that the heart failure benefits of SGLT2 inhibitors are independent of glycaemic effects. All-cause mortality was reduced by 17%, and health-related quality of life, measured by the Kansas City Cardiomyopathy Questionnaire, was significantly improved.

4.2.2 EMPEROR-Reduced and EMPEROR-Preserved

EMPEROR-Reduced enrolled 3,730 patients with HFrEF (LVEF ≤40%) and demonstrated that empagliflozin 10 mg daily reduced the primary composite of cardiovascular death or hospitalisation for heart failure by 25% (HR 0.75; 95% CI 0.65–0.86; p<0.001), with a 31% reduction in first and recurrent hospitalisations [16]. The rate of eGFR decline was significantly attenuated with empagliflozin, providing the first direct evidence of renal protection in a dedicated heart failure trial population. A pooled analysis of DAPA-HF and EMPEROR-Reduced confirmed a consistent 26% relative risk reduction in the combined primary endpoint across both trials (HR 0.74; 95% CI 0.68–0.82).

EMPEROR-Preserved addressed the critically important and previously therapeutically unmet population of patients with HFpEF or HFmrEF (LVEF >40%), enrolling 5,988 patients [17]. Empagliflozin produced a significant 21% reduction in the primary composite of cardiovascular death or hospitalisation for heart failure (HR 0.79; 95% CI 0.69–0.90; p<0.001) — the first pharmacological treatment to demonstrate a significant reduction in outcomes in HFpEF in a large randomised trial. The benefit was consistent across subgroups defined by the presence or absence of T2DM and across the full range of ejection fractions above 40%.

4.2.3 DELIVER

The DELIVER trial randomised 6,263 patients with HFmrEF or HFpEF (LVEF >40%) to dapagliflozin 10 mg or placebo, confirming and extending the EMPEROR-Preserved findings [18]. Dapagliflozin reduced the primary composite of worsening heart failure or cardiovascular death by 18% (HR 0.82; 95% CI 0.73–0.92; p<0.001), with consistent benefits across the full ejection fraction range. A combined meta-analysis of DELIVER and EMPEROR-Preserved, encompassing over 12,000 patients, demonstrated a 20% relative risk reduction in the primary endpoint (HR 0.80; 95% CI 0.73–0.87) with no significant heterogeneity by ejection fraction, definitively establishing the SGLT2 inhibitor class effect in heart failure across the entire ejection fraction spectrum.

4.3 Chronic Kidney Disease — The Renal Outcome Trials

4.3.1 CREDENCE

CREDENCE was the first dedicated renal outcome trial of an SGLT2 inhibitor, enrolling 4,401 patients with T2DM and CKD (eGFR 30–90 mL/min/1.73 m² and urinary albumin-to-creatinine ratio

300–5000 mg/g) randomised to canagliflozin 100 mg or placebo, on background RAAS inhibitor therapy [19]. The trial was stopped early at a median follow-up of 2.6 years due to overwhelming efficacy: the primary renal composite (doubling of serum creatinine, ESRD, or death from renal or cardiovascular causes) was reduced by 30% (HR 0.70; 95% CI 0.59–0.82; p=0.00001). Hospitalisation for heart failure was reduced by 39%, and the cardiovascular death or hospitalisation for heart failure composite by 31%. ESRD was reduced by 32%. CREDENCE firmly established canagliflozin as the first agent beyond RAAS inhibition to demonstrate significant renoprotection in a dedicated CKD trial.

4.3.2 DAPA-CKD

DAPA-CKD enrolled 4,304 patients with CKD (eGFR 25–75 mL/min/1.73 m² and UACR 200–5000 mg/g), with and without T2DM, randomised to dapagliflozin 10 mg or placebo on background RAAS inhibition [20]. The trial was also stopped early: the primary composite of ≥50% eGFR decline, ESRD, or cardiovascular or renal death was reduced by 39% (HR 0.61; 95% CI 0.51–0.72; p<0.001). All-cause mortality was reduced by 31%. Crucially, the renoprotective and survival benefits were statistically equivalent in patients with and without T2DM (interaction p=0.77), establishing dapagliflozin as the first agent approved for CKD reduction independently of glycaemic status. This represented a paradigm shift: SGLT2 inhibitors had transcended their antidiabetic origins to become disease-modifying renoprotective agents.

4.4 Meta-Analyses and Class Effect Synthesis

Several individual patient data meta-analyses and systematic reviews have synthesised the SGLT2 inhibitor trial evidence across populations. The Cardiorenal Council meta-analysis of three CVOTs demonstrated that SGLT2 inhibitors reduced hospitalisation for heart failure by 31% (HR 0.69; 95% CI 0.61–0.79) and the renal composite by 45% (HR 0.55; 95% CI 0.48–0.64) across the combined population [21]. A 2022 meta-analysis encompassing all major trials confirmed consistent benefits on hospitalisation for heart failure and CKD progression across diverse patient populations, reinforcing the concept of a robust class effect that is substantially independent of T2DM status, ejection fraction, baseline eGFR, and background therapy [22].

5. GUIDELINE POSITIONING

5.1 Heart Failure Guidelines

The ESC 2021 Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure conferred Class I, Level of Evidence A recommendations for both dapagliflozin and empagliflozin in patients with HFrEF (LVEF ≤40%) with persistent symptoms despite optimal medical therapy with ACE inhibitor/ARB/ARNI, beta-blocker, and MRA, with the goal of reducing the risk of hospitalisation for heart failure and cardiovascular death [3]. Following the positive results of EMPEROR-Preserved and DELIVER, the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure was updated to incorporate SGLT2 inhibitors as a Class IIa, Level B-R recommendation in patients with HFpEF (LVEF ≥50%) to reduce hospitalisation and cardiovascular mortality, acknowledging the class as the first pharmacological therapy with a positive randomised trial outcome in this historically therapeutically intractable phenotype of heart failure.

5.2 T2DM and Cardiometabolic Guidelines

The ADA Standards of Medical Care in Diabetes, updated annually, currently recommend SGLT2 inhibitors with proven cardiovascular benefit (empagliflozin, canagliflozin, dapagliflozin) as preferred second-line agents after metformin for patients with T2DM and established atherosclerotic cardiovascular disease, heart failure, or CKD, with a Level of Evidence A designation [4]. The ESC 2023 Guidelines on the Management of Cardiovascular Disease in Patients with Diabetes similarly position SGLT2 inhibitors as first-line therapy in T2DM patients with heart failure or CKD, irrespective of HbA1c levels and independent of the need for glycaemic improvement — a recommendation that reflects the recognition of SGLT2 inhibitors primarily as cardiovascular and renoprotective drugs that coincidentally lower blood glucose, rather than antidiabetic drugs that incidentally protect the heart and kidney.

5.3 CKD Guidelines

KDIGO 2022 Clinical Practice Guideline for Diabetes Management in CKD recommends SGLT2 inhibitors for all patients with T2DM and CKD with eGFR ≥20 mL/min/1.73 m² who are not already receiving them, unless contraindicated or not tolerated, with a Grade 1A (strong) recommendation [23]. Following the DAPA-CKD results, guidelines now also support SGLT2 inhibitor use in non-diabetic CKD with significant proteinuria, reflecting the extension of renoprotective evidence beyond the T2DM-CKD overlap into CKD of any aetiology.

6. SAFETY PROFILE AND ADVERSE EFFECTS

6.1 Genital Mycotic Infections

The most consistently reported adverse effect of SGLT2 inhibitors is an increased incidence of genital mycotic infections — predominantly vulvovaginal candidiasis in women and balanitis or balanoposthitis in men — attributable to glucosuria creating a locally nutrient-rich environment conducive to Candida colonisation [24]. The absolute risk increase is approximately 3–5% for vulvovaginal candidiasis and 1–2% for male genital infections across trials. These events are generally mild to moderate in severity, respond well to standard antifungal treatment, and rarely require drug discontinuation. Urinary tract infections, while historically associated with SGLT2

inhibitors based on mechanistic concerns, have not been consistently increased in randomised trial meta-analyses.

6.2 Diabetic Ketoacidosis

SGLT2 inhibitor-associated diabetic ketoacidosis (DKA) is a rare but serious adverse event that characteristically occurs at blood glucose levels lower than classical DKA — so-called euglycaemic DKA — attributed to the combined effects of increased glucagon-to-insulin ratio, enhanced lipolysis, impaired renal ketone excretion from glucosuria-induced volume contraction, and relative insulin deficiency [25]. The absolute incidence of DKA with SGLT2 inhibitors in randomised trials is approximately 0.1–0.6%, with higher rates in T1DM (where off-label use occurs) and in the peri-operative or prolonged fasting context. Current guidelines mandate temporary discontinuation of SGLT2 inhibitors at least two to four days before elective surgery — the so-called 'sick day rules' — and avoidance in the setting of prolonged fasting, very low carbohydrate diets, or intercurrent illnesses causing reduced oral intake.

6.3 Lower Limb Amputations

The CANVAS Program identified a two-fold increase in the risk of lower limb amputation with canagliflozin, predominantly below-the-knee and in patients with prior amputation history or peripheral arterial disease, generating a Boxed Warning for canagliflozin. Subsequent analysis of CREDENCE, DECLARE-TIMI 58, EMPA-REG OUTCOME, and multiple real-world studies have not consistently confirmed a class-wide amputation risk, suggesting that the canagliflozin signal may reflect drug-specific haemodynamic effects on peripheral perfusion or may be a statistical artefact [13]. Current clinical guidance recommends caution with all SGLT2 inhibitors in patients with active or prior peripheral vascular disease, neuropathic foot wounds, or recent lower limb amputation, with particular vigilance for canagliflozin.

6.4 Volume Depletion and Hypotension

The diuretic and natriuretic effects of SGLT2 inhibitors can cause symptomatic volume depletion, particularly in elderly patients, those on concurrent diuretic therapy, or individuals with poor oral intake. Across cardiovascular outcome trials, symptomatic hypotension occurred in approximately 1–3% of SGLT2 inhibitor-treated patients. The initial reversible eGFR decline at treatment initiation — observed in up to 30% of patients and typically amounting to 2–5 mL/min/1.73 m² — should be distinguished from true nephrotoxicity; this dip reflects tubuloglomerular feedback-mediated intraglomerular pressure reduction and does not predict long-term renal deterioration [26].

6.5 Hypoglycaemia

SGLT2 inhibitors have an inherently low risk of causing hypoglycaemia as a monotherapy or in combination with non-secretagogue antidiabetic agents, because the glucosuric mechanism is insulin-independent and self-limiting — as plasma glucose falls, less glucose is filtered and therefore less is available for inhibition of reabsorption. Hypoglycaemia risk is relevant only when SGLT2 inhibitors are co-administered with insulin or sulphonylureas, necessitating dose reduction of the secretagogue in such combinations.

7. SPECIAL POPULATIONS AND EMERGING INDICATIONS

7.1 Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF)

HFmrEF, defined as LVEF 41–49%, has historically occupied an uncertain therapeutic zone between HFrEF and HFpEF, with limited dedicated trial evidence. The DELIVER and EMPEROR-Preserved trials both enrolled HFmrEF patients as a pre-specified subgroup and demonstrated consistent benefit with SGLT2 inhibitors across the ejection fraction range from 41% to approximately 60% [18]. Combined analyses confirm that the benefit is of broadly similar magnitude to that observed in HFrEF, supporting the use of SGLT2 inhibitors across the full HF ejection fraction spectrum — a recommendation reflected in updated 2022 heart failure guideline updates.

7.2 Atrial Fibrillation

Atrial fibrillation is the most prevalent sustained cardiac arrhythmia and shares pathophysiological substrates — atrial fibrosis, structural remodelling, sympathetic activation, and inflammation — with the conditions in which SGLT2 inhibitors demonstrate benefit. Post-hoc analyses and observational data suggest a reduction in new-onset atrial fibrillation with SGLT2 inhibitors, potentially mediated by reductions in atrial filling pressure, atrial volume, and NHE1-driven atrial cardiomyocyte calcium overload [27]. The ongoing EMPA-AF trial and several other prospective investigations are evaluating SGLT2 inhibitor effects on atrial fibrillation recurrence and progression as primary endpoints, and positive results in this indication would further extend the cardiovascular therapeutic scope of the class.

7.3 Acute Myocardial Infarction

The rapid cardiovascular benefit demonstrated in EMPA-REG OUTCOME — with cardiovascular mortality curves separating within the first 30–90 days of treatment — has prompted investigation of SGLT2 inhibitors in the acute and early post-myocardial infarction context. The EMPACT-MI trial evaluated empagliflozin initiated within 14 days of acute MI in patients with reduced ejection fraction or signs of congestion, reporting a 23% reduction in total hospitalisations for heart failure (HR 0.77; 95% CI 0.60–0.98), though the primary composite endpoint was not significantly reduced [28]. These results support the safety and potential utility of early SGLT2 inhibitor

initiation post-MI, with active ongoing investigation in this area.

7.4 Cardiorenal Syndrome

The cardiorenal syndrome — in which acute or chronic cardiac dysfunction adversely affects renal function or vice versa — represents a clinical context of particular therapeutic relevance for SGLT2 inhibitors, given their simultaneous cardioprotective and renoprotective mechanisms acting along the cardiorenal axis. DAPA-CKD, CREDENCE, and the heart failure trials collectively demonstrate that SGLT2 inhibitors not only slow eGFR decline in patients with CKD but also protect cardiac structure and function in patients with CKD-related cardiomyopathy, offering a uniquely integrated pharmacological approach to what has historically been an elusive therapeutic target [29].

7.5 Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) and its progressive form non-alcoholic steatohepatitis (NASH) are closely associated with T2DM, obesity, and insulin resistance, and with elevated cardiovascular risk. SGLT2 inhibitors have demonstrated reductions in hepatic fat content, liver stiffness, and transaminase elevation in clinical studies of NAFLD, likely through weight reduction, visceral fat mobilisation, and attenuation of hepatic inflammation and lipogenesis [30]. Although no large randomised trial has evaluated SGLT2 inhibitors as primary therapy for NAFLD/NASH, current evidence supports their use as part of a cardiometabolic risk reduction strategy in this overlapping patient population.

7.6 Heart Failure with Acute Decompensation

The safety and benefit of SGLT2 inhibitors initiated or continued during acute decompensated heart failure hospitalisation has been evaluated in the EMPULSE trial, which randomised 530 patients hospitalised for acute heart failure to empagliflozin or placebo initiated during the hospitalisation [31]. Empagliflozin resulted in a significant clinical benefit, defined as a win ratio composite of mortality, number of heart failure events, time to first heart failure event, or change in KCCQ-TSS score (win ratio 1.36; 95% CI 1.09–1.68; p=0.0054), establishing that SGLT2 inhibitors can be safely and beneficially initiated in the acute heart failure setting without waiting for clinical stabilisation.

8. PRACTICAL PRESCRIBING AND PATIENT SELECTION

8.1 Initiation and Dosing

The approved and trial-validated doses are dapagliflozin 10 mg once daily, empagliflozin 10 mg once daily (or 25 mg for additional glycaemic lowering in T2DM), and canagliflozin 100 mg once daily (or 300 mg for additional glycaemic and renal benefits in T2DM). Ertugliflozin is approved at 5 or 15 mg once daily. For cardiovascular and renal endpoints, the lower doses have generally been evaluated and demonstrated benefit. SGLT2 inhibitors are administered orally, once daily, with or without food, and require no dose adjustment for hepatic impairment. Renal function should be checked before initiation; use is generally not recommended below eGFR 20 mL/min/1.73 m² for the cardiovascular and heart failure indication, though emerging data from DAPA-CKD suggest potential benefit at lower eGFR thresholds.

8.2 Practical Considerations and Sick Day Rules

Practical prescribing of SGLT2 inhibitors requires patient education on several key safety principles: temporary discontinuation during acute intercurrent illness, prolonged fasting, or peri-operative periods ('sick day rules'); prompt recognition of DKA symptoms including nausea, vomiting, and abdominal pain even in the absence of marked hyperglycaemia; meticulous foot care and regular podiatric assessment in patients with peripheral arterial disease or prior neuropathy; and adequate hydration to minimise volume depletion risk [32]. SGLT2 inhibitors should be withheld at least two days before elective surgery and restarted only when the patient is eating and drinking normally and renal function has stabilised post-operatively.

8.3 Drug Interactions

SGLT2 inhibitors have relatively few clinically significant drug interactions. Concurrent use with diuretics — particularly loop diuretics in heart failure patients — may increase the risk of volume depletion and electrolyte imbalances, necessitating careful haemodynamic monitoring at initiation and consideration of diuretic dose adjustment. Co-administration with insulin or sulphonylureas increases hypoglycaemia risk and typically warrants dose reduction of the secretagogue agent. There are no significant CYP450-mediated interactions of clinical importance for empagliflozin or dapagliflozin; canagliflozin is a weak inhibitor of P-glycoprotein and may slightly increase plasma levels of co-administered P-gp substrates.

9. FUTURE DIRECTIONS AND EVOLVING EVIDENCE

9.1 Combination with Other Cardiorenal Agents

The combination of SGLT2 inhibitors with GLP-1 receptor agonists, which act through complementary and largely non-overlapping cardiometabolic mechanisms, is emerging as a particularly promising therapeutic strategy for the overlapping T2DM, heart failure, CKD, and obesity phenotype. Both drug classes independently reduce cardiovascular events and CKD progression, and preliminary data suggest additive effects on cardiac and renal endpoints, body weight, blood pressure, and inflammation [33]. The combination of SGLT2 inhibitors with finerenone — a non-steroidal mineralocorticoid receptor antagonist demonstrating

renal and cardiovascular protection in the FIDELIO-DKD and FIGARO-DKD trials — is being prospectively evaluated in the CONFIDENCE trial, with the expectation that complementary anti-fibrotic and haemodynamic mechanisms may produce additive benefits in T2DM-CKD patients.

9.2 T1DM and Ketosis-Prone Populations

Dapagliflozin and sotagliflozin have received regulatory approval in some jurisdictions for T1DM as adjunctive therapy to insulin. The DEPICT and inTandem trials demonstrated HbA1c reductions, weight loss, and blood pressure benefits, but with significantly elevated DKA risk (approximately 3–4 times placebo rates), necessitating careful patient selection, education, and monitoring. Whether the cardiovascular and renal benefits demonstrated in T2DM translate fully to T1DM populations — who have longer diabetes duration, different comorbidity profiles, and fundamentally different insulin physiology — remains to be established in dedicated cardiovascular outcome trials [34].

9.3 Cardiac Arrhythmia, Sudden Cardiac Death, and Device Outcomes

The potential antiarrhythmic properties of SGLT2 inhibitors — mediated through NHE1 inhibition, sympathetic attenuation, potassium retention, and atrial structural remodelling mitigation — are being prospectively evaluated in dedicated trials. If confirmed, antiarrhythmic benefits could substantially reduce the risk of sudden cardiac death and ICD therapies in the heart failure population, where ventricular arrhythmias and sudden death remain major contributors to overall mortality despite current therapies [35].

9.4 Cardiovascular Benefits in CKD Without T2DM

The demonstration in DAPA-CKD that dapagliflozin reduces cardiovascular and renal outcomes in CKD patients without T2DM — including those with IgA nephropathy, focal segmental glomerulosclerosis, and hypertensive nephrosclerosis — has opened a major new indication that is independent of glycaemic biology. The EMPA-KIDNEY trial, published in 2023, confirmed this across a broader eGFR range (20–45 mL/min/1.73 m²) and confirmed that empagliflozin reduces the risk of kidney disease progression or cardiovascular death in patients with CKD (HR 0.72; 95% CI 0.64–0.82; $p<0.001$), further consolidating the renoprotective role of SGLT2 inhibitors independent of diabetes status [36].

10. CONCLUSION

SGLT2 inhibitors have undergone a remarkable scientific and clinical transformation since their introduction as antidiabetic agents, evolving into one of the most consequential drug classes in cardiovascular medicine over the past decade. Their cardiovascular benefits — encompassing reductions in hospitalisation for heart failure across the ejection fraction spectrum, slowing of CKD progression regardless of diabetes status, reduction in cardiovascular mortality in high-risk T2DM, and the attenuation of adverse cardiorenal remodelling — are grounded in a rich mechanistic framework of haemodynamic unloading, tubuloglomerular feedback restoration, myocardial metabolic reprogramming, NHE1 inhibition, inflammasome suppression, and sympathetic modulation. Landmark randomised trials including EMPA-REG OUTCOME, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, DAPA-CKD, CREDENCE, and EMPA-KIDNEY have collectively transformed clinical practice and guideline recommendations across cardiology, diabetology, and nephrology.

SGLT2 inhibitors now occupy first-line or preferred-agent status in multiple international guidelines for patients with heart failure irrespective of ejection fraction, CKD with significant proteinuria, and T2DM with established cardiovascular disease or high cardiometabolic risk. Their tolerability profile — dominated by manageable genital mycotic infections and the important but rare risk of euglycaemic DKA — is favourable relative to the magnitude of cardiovascular benefit across the patient populations examined. Ongoing investigations into atrial fibrillation, acute myocardial infarction, non-alcoholic fatty liver disease, and combination cardiorenal regimens promise to further expand the therapeutic horizon of this drug class. For the practising cardiologist, endocrinologist, and nephrologist, SGLT2 inhibitors represent not merely an additional therapeutic option but a fundamental reorientation of the pharmacological approach to cardiometabolic disease — one in which organ protection across the cardiovascular-renal-metabolic axis is achievable through a single, well-tolerated, once-daily oral agent.

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