Int J Adv Life Sci Res. Volume 9(4) 56-68
https://doi.org/10.31632/ijalsr.2026.v09i04.004

International Journal of Advancement in Life Sciences Research

Online ISSN: 2581-4877

Journal homepage http://ijalsr.org



Review Article

Advances in SGLT2 Inhibitor Therapy: Comparative Evidence for Empagliflozin and Dapagliflozin in Cardio-Renal-Metabolic Disorders

Saravanan Subramanian[1], Magendran Rajendiran[2*], Maheshwari Paramasivam[1*], Indhupriyadharshini Murugesan[3], Shanmugasundaram Palani[2], Sivakumar Velusamy[3]

[1] *Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Velan Nagar, Krishnapuram, Pallavaram, Tambaram, Tamil Nadu 600117, India*

[2] *Department of Chemistry & Analysis, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Velan Nagar, Krishnapuram, Pallavaram, Tambaram, Tamil Nadu 600117, India*

[3] *Department of Pharmacy Practice, PSG College of Pharmacy, Peelamadu, Coimbatore 641004, Tamilnadu, India*

***Corresponding Author's Email:** magendran1988@gmail.com ; meswari.sps@vistas.ac.in*

Abstract

Cardiovascular disease, Type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) interact to cause the progressive multisystem condition known as cardio-renal-metabolic (CRM) syndrome. With pleiotropic advantages that go beyond glycaemic control, sodium-glucose cotransporter-2 (SGLT2) inhibitors have completely changed the way CRM is managed. To compile and contrast clinical data on dapagliflozin and empagliflozin throughout the CRM continuum's glycaemic, cardiovascular, renal, and metabolic outcomes. Pharmacokinetic studies, real-world observational cohorts, randomized cardiovascular and renal outcome trials, and regulatory guidelines were all narratively reviewed. A summary was provided of head-to-head meta-analytic data evaluating HbA1c, cardiovascular risk scores, and estimated glomerular filtration rate (eGFR). Regardless of diabetes status, both drugs showed class-consistent benefits, such as decreases in heart failure hospitalization, cardiovascular events, and CKD progression. HbA1c reduction, cardiovascular risk scores, and renal outcomes by eGFR did not differ significantly, according to pooled head-to-head analyses. Comparable long-term risks for severe adverse cardiovascular events, acute renal injury, and the progression of chronic kidney disease were observed in large real-world registries, although differences in study populations and designs limit direct comparisons. Dapagliflozin slightly improved blood pressure and cholesterol, while empagliflozin showed better weight reduction and glycaemic control, although these findings should be interpreted cautiously because of variation in study design and population characteristics. Overall, the available evidence suggests broadly comparable cardio-renal-metabolic benefits between empagliflozin and dapagliflozin but does not establish formal therapeutic equivalence or non-inferiority. Therapeutic selection should therefore be based on individual patient characteristics, clinical priorities, and the strength of evidence for the specific indication.

Keywords: *Cardio-Renal-Metabolic Syndrome; Dapagliflozin; Empagliflozin; Phenotype-Based Precision Medicine; SGLT2 Inhibitors*

Received on :18th June 2026; Revised version received on :13th September 2026; Accepted:23rd September 2026

Introduction

The global healthcare landscape is currently addressing the rising prevalence of cardio-renal-metabolic (CRM) syndrome (Figure 1), a complex multisystem disorder characterized by the pathological interplay of adipose tissue dysfunction, type 2 diabetes mellitus (T2DM), and chronic kidney disease (CKD) (Abdul-Ghani & DeFronzo, 2008; Anker *et al*., 2021; Baker *et al*., 2015). Within this continuum, cardiac and renal functions are involved in bidirectional “crosstalk,” whereby the failure of one organ system accelerates the failure of the other (Palmer & Clegg, 2022). The American Heart Association (AHA) has recently emphasized that cardiovascular mortality in patients with metabolic disorders is rarely a result of an isolated event but rather a systemic consequence of interactions along the cardio-renal-metabolic axis (Brownlee, 2005).

Historically, the management of T2DM was focused on glycaemic stabilization. However, the emergence of sodium-glucose cotransporter-2 (SGLT2) inhibitors has fundamentally shifted the treatment paradigm (Cai *et al*., 2018). While these agents were initially developed to induce glucosuria by inhibiting proximal tubular glucose reuptake, large-scale cardiovascular outcome trials (CVOTs) revealed clinical benefits that far exceeded their glucose-lowering potency (Mullens *et al*., 2020; DeFronzo *et al*., 2012). These pleiotropic effects, ranging from natriuresis and the reduction of intraglomerular pressure to the optimization of myocardial energetics, have positioned SGLT2 inhibitors as foundational therapies in Stage 2 and Stage 3 CRM syndromes (European Medicines Agency, 2026; Forbes & Cooper, 2013).

Empagliflozin and dapagliflozin are the two most widely utilized molecules within this class (Ghezzi *et al*., 2018). Although they share a common mechanism of action, subtle differences in molecular selectivity (SGLT2 vs. SGLT1) and pharmacokinetic profiles have led to significant clinical debate regarding their comparative efficacy (Scheen, 2014; Kasichayanula *et al*., 2014). In real-world clinical practice, particularly in high-risk Asian populations, clinicians are often faced with the challenge of choosing between these two agents for long-term multi-organ preservation. While landmark trials like EMPEROR and DAPA-HF have validated the two drugs separately, head-to-head comparisons remain limited in the primary literature.

There is a critical need to synthesize evidence regarding how these two agents modulate not just blood glucose but also the broader markers of atherosclerotic risk and renal integrity (Heerspink *et al*., 2020). As the study move toward phenotype-driven medicine, understanding whether empagliflozin and dapagliflozin offer distinct clinical advantages or represent a truly comparable class effect is essential for optimizing the clinical trajectory of patients with CRM syndrome (Herrington *et al*., 2026; Anker *et al*., 2021).

Therefore, this narrative review aims to critically synthesize and compare the available evidence on empagliflozin and dapagliflozin across the cardio-renal-metabolic (CRM) continuum, with particular emphasis on their pharmacological characteristics, glycaemic, cardiovascular, renal, and metabolic effects, and potential phenotype-based considerations for clinical use. The review also aims to identify areas of uncertainty and evidence gaps in direct comparative data and to highlight priorities for future research.

The cardiovascular-kidney-metabolic (CRM) syndrome is recognized as a multisystem disorder where the pathological intersection of obesity, diabetes, and renal impairment accelerates cardiovascular decline (Jankauskas *et al*., 2026). Recently, the American Heart Association (AHA) formalized the CRM staging framework (Stages 0–4) to categorize patients based on the progression from "at-risk" adiposity (Stage 1) to clinical cardiovascular disease (Stage 4) (Brownlee, 2005). At the core of this continuum is a vicious bidirectional cycle. Heart failure leads to reduced cardiac output and subsequent renal hypoperfusion. In response to this perceived volume depletion, the kidneys upregulate the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (Kasichayanula *et al*., 2014). While intended as a compensatory mechanism, this chronic neurohormonal activation leads to systemic vasoconstriction and pathological fluid retention, which further increases the cardiac workload

(preload and afterload), exacerbating myocardial strain (Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group, 2022).

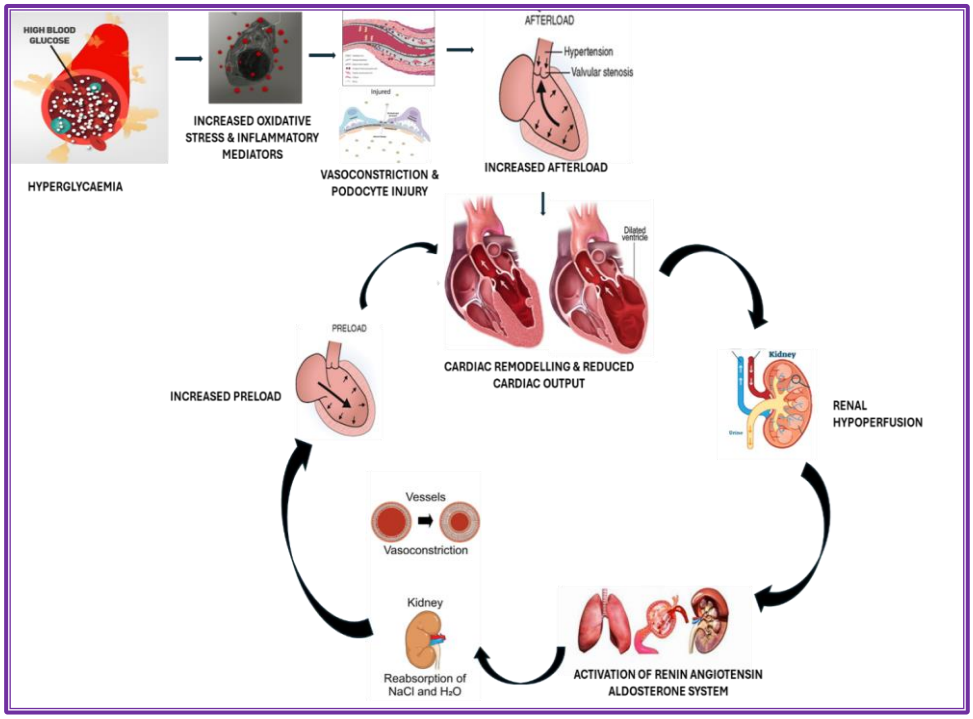


Figure 1: *The Cardio-Renal-Metabolic (CRM) Syndrome*

The Cardio-Renal-Metabolic (CRM) Continuum: Pathophysiological Foundations. Bidirectional Organ Cross-Talk

Concurrently, metabolic drivers such as hyperglycaemia and visceral adiposity exacerbate this damage. Elevated glucose levels induce oxidative stress and chronic inflammation, leading to microvascular thickening and podocyte damage within the nephrons (González *et al*., 2023). This metabolic insult synergizes with hemodynamic stress, resulting in a self-perpetuating loop of organ damage. SGLT2 inhibitors have emerged as a foundational therapy in this context precisely because they interrupt these pathways at multiple points (González *et al*., 2023).

Pleiotropic Effects

Natriuresis, Anti-Inflammatory Pathways, And Myocardial Energetics

While initially indicated for glycaemic control, SGLT2 inhibitors exert profound pleiotropic effects that stabilize the cardio-renal axis. By inhibiting proximal tubular glucose and sodium reuptake, these agents promote osmotic diuresis and natriuresis. This reduces systemic plasma volume and effectively lowers cardiac preload and pulmonary congestion (Patel & Strong, 2019). Crucially, this hemodynamic "unloading" mitigates mechanical wall stress on the endothelium, thereby suppressing the release of pro-inflammatory cytokines and preventing subsequent endothelial dysfunction (Cai *et al*., 2025). Beyond fluid dynamics, SGLT2 inhibitors significantly optimize myocardial energetics through the "thrifty fuel" hypothesis. In the setting of heart failure, the myocardium becomes metabolically insufficient, struggling to utilize glucose or fatty acids. SGLT2 inhibition induces a mild state of ketosis, increasing the availability of β-hydroxybutyrate (McDonagh & Metra, 2023). This ketone body serves as a more oxygen-efficient substrate for mitochondrial ATP production, improving cardiac contractility under conditions of ischemic stress. Furthermore, these agents trigger erythropoietic signalling by mimicking a state of nutrient deprivation within the kidney. This stimulates the interstitial fibroblasts to produce endogenous erythropoietin (EPO), resulting in a modest elevation of haematocrit and haemoglobin levels (Packer *et al*., 2023). This rise in oxygen-carrying capacity, coupled with the induction of autophagy (the maintenance of cellular proteostasis) and the suppression of the NLRP3 inflammasome,

collectively slows the progression of tissue fibrosis and organ remodelling in both the heart and the kidney (McMurray *et al*., 2019).

Therapeutic Synergy: The Scientific Basis for Multi-Organ Preservation

Effective management of CRM syndrome necessitates a transition from generalized risk reduction to individualized, phenotype-driven interventions. While HMG-CoA reductase inhibitors (statins) remain the gold standard for reducing atherosclerotic cardiovascular disease (ASCVD) risk by targeting LDL-C, they may not sufficiently address the specific hemodynamic of heart failure or the metabolic drivers of renal decline (Ndumele *et al*., 2023).The rationale for SGLT2 inhibition lies in its ability to provide non-atherosclerotic organ protection (Neal *et al*., 2017).For patients presenting with a high "Cardio-Renal" risk profile characterized by fluid overload, albuminuria, or reduced ejection fraction SGLT2 inhibitors offer additional benefits compared with statin monotherapy by directly modulating intraglomerular pressure and myocardial strain. Conversely, for patients with high "Atherosclerotic" risk (previous MI or stroke), Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may be prioritized due to their potent anti-atherogenic effects (Heidenreich *et al*., 2022). Therefore, the therapeutic synergy of SGLT2 inhibitors in multi-organ preservation is not merely about glucose lowering; it is about choosing the right agent for the specific organ system at greatest risk (Packer *et al*., 2020). This "tailored" approach ensures that interventions are aligned with the patient's unique CRM stage and clinical trajectory (Packer *et al*., 2022).

Pharmacokinetics And Pharmacodynamics: A Comparative Analysis

Both dapagliflozin and empagliflozin exhibit favorable pharmacokinetic profiles that support their use in complex cardio-renal-metabolic (CRM) regimens (Packer *et al*., 2020). Both agents are characterized by rapid oral absorption, reaching peak plasma concentrations within 2 hours for dapagliflozin and within 3 hours for empagliflozin (Scheen, 2014; Kasichayanula *et al.,* 2014). Notably, the absolute bioavailability of these agents is high, and their absorption is not clinically altered by high-fat meals, allowing for flexible administration with or without food (Kasichayanula *et al.,* 2014; Macha *et al*., 2013). A defining feature of their metabolic pathway is the reliance on glucuronidation via uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes, specifically UGT1A9 for dapagliflozin and UGT2B7, UGT1A3, UGT1A8, and UGT1A9 for empagliflozin. By bypassing the cytochrome P450 (CYP) system, both drugs minimize the risk of significant drug-drug interactions with common concomitant CRM therapies, such as statins, beta-blockers, or ACE inhibitors (Table 1) (Scheen, 2014; Kasichayanula *et al*., 2014).

Table 1: *Comparative Pharmacokinetic and Pharmacodynamic Characteristics*

Parameter	Empagliflozin	Dapagliflozin	References
Time to peak concentration (Tmax)	1.33–3 hours	Within 2 h	Scheen , 2014; Kasichayanula *et al*., 2014
Bioavailability	78%	78 %	Scheen, 2014; Ndefo *et al*., 2015
Major metabolism	UGT2B7, UGT1A3, UGT1A8, UGT1A9	UGT1A9	Scheen, 2014; Kasichayanula *et al*., 2014
CYP involvement	Minimal	Minimal	Scheen, 2014; Kasichayanula *et al*., 2014
Half-life	13.1 hour	12.9 h for 10 mg	Scheen, 2014; Kasichayanula *et al*., 2014
AUC increase in severe renal impairment	~66%	~122%	Scheen, 2014; DeFronzo *et al*., 2013
Key mechanism	SGLT2 inhibition with high selectivity	SGLT2 inhibition	Scheen, 2014; Kasichayanula *et al*., 2014

Renal Impairment and the Pharmacodynamic Paradox

A critical nuance in the clinical utility of SGLT2 inhibitors is the alteration of their pharmacokinetic and pharmacodynamic profiles in the setting of renal insufficiency. As renal function declines, systemic exposure, measured by the area under the plasma concentration-time curve (AUC), increases for both empagliflozin and dapagliflozin (Macha *et al*., 2014; DeFronzo et al., 2013). In the empagliflozin study, AUC increased by approximately 18%, 20%, 66%, and 48% in subjects with mild, moderate, severe

renal impairment, and renal failure/end-stage renal disease (ESRD), respectively, compared with healthy subjects; this increase was attributed to decreased renal clearance (Macha *et al*., 2014). Similarly, dapagliflozin plasma concentrations increased progressively with declining kidney function, and AUC was likewise higher in patients with renal impairment (DeFronzo et al., 2013). Despite the increased systemic exposure, the pharmacodynamic effects of both agents were attenuated with worsening renal impairment. For dapagliflozin, steady-state renal glucose clearance was reduced by 42%, 83%, and 84% in patients with mild, moderate, and severe renal impairment, respectively, compared with patients with normal renal function (DeFronzo et al., 2013). Empagliflozin urinary glucose excretion also decreased with increasing renal impairment and correlated with decreased eGFR and renal clearance (Macha *et al*., 2014). These findings illustrate a pharmacodynamic paradox in which increased systemic drug exposure with declining renal function does not translate into greater glucose-lowering activity, because the filtered glucose load available for SGLT2 inhibition is reduced (Macha *et al*., 2014; DeFronzo et al., 2013)

Global Regulatory Benchmarks: FDA and EMA Indications

The regulatory landscape for SGLT2 inhibitors has evolved from glycaemic control toward broader cardiovascular and renal risk reduction. Current FDA and EMA labelling supports the use of empagliflozin and dapagliflozin beyond type 2 diabetes mellitus in selected heart-failure and chronic-kidney-disease populations, although the specific indications and labelling details are not completely identical between regulatory agencies (U.S. Food and Drug Administration, 2025; European Medicines Agency, 2026). Heart Failure (HF): Both agents are approved for adults with heart failure, with current EMA labelling covering symptomatic chronic heart failure, while current FDA labelling supports cardiovascular risk reduction in adults with heart failure (U.S. Food and Drug Administration, 2025; European Medicines Agency, 2026). These label expansions followed landmark outcome trials including EMPEROR and DAPA-HF/DELIVER (Anker *et al*., 2021; McMurray *et al*., 2019; Vaduganathan *et al*., 2020). Chronic Kidney Disease (CKD): Both empagliflozin and dapagliflozin are approved for adults with chronic kidney disease at risk of progression, with the FDA indications extending beyond patients with type 2 diabetes. The renal-function thresholds and limitations for initiation differ between individual product labels and should therefore not be presented as a single universal eGFR threshold (U.S. Food and Drug Administration, 2025; European Medicines Agency, 2026). Diabetes Status: Importantly, the FDA and EMA have expanded indications for heart failure and CKD beyond the requirement for a type 2 diabetes diagnosis, reflecting evidence of cardiovascular and renal benefits that extend beyond glycaemic control (U.S. Food and Drug Administration, 2025; European Medicines Agency, 2026).

Comparative Analysis of Glycaemic Indices and Body Composition

In the clinical management of CRM syndrome, the metabolic efficacy of SGLT2 inhibitors is measured by their ability to provide sustained HbA1c reduction and favorable shifts in body composition. Head-to-head comparisons and real-world data from cohorts reveal differences between Empagliflozin and Dapagliflozin (Table 2) (Crabtree, 2024).

Table 2: *Glycaemic and Metabolic Outcomes*

Outcome	Empagliflozin	Dapagliflozin	Reference
HbA1c reduction	−10.6 mmol/mol (~0.97%)	−9.1 mmol/mol (~0.83%)	Crabtree, 2024
Weight reduction	−2.8 kg	−3.5 kg	Crabtree, 2024
BMI reduction	−1.0 kg/m²	−1.2 kg/m²	Crabtree, 2024
SBP reduction	−1.0 mmHg	−0.6 mmHg	Crabtree, 2024
Lipid profile	↓ TC and LDL-C; no significant change in HDL-C or TG	↓ TC and LDL-C; no significant change in HDL-C or TG; greater reduction in TC than empagliflozin (p = 0.044)	Özgöl *et al*., 2025

Glycaemic Control: Potency And Thresholds

Both agents demonstrate significant, dose-dependent reductions in HbA1c. In Indian clinical settings, Dapagliflozin has shown HbA1c reductions of approximately 1.05% at 12 months, moving patients from a mean baseline of 7.85% toward 6.8% (Jadhav *et al*., 2025). However, comparative trials suggest a superior glycaemic potency for Empagliflozin. Longitudinal data indicates that empagliflozin can achieve an HbA1c reduction of up to 0.55% over six months, significantly outperforming dapagliflozin's 0.36% reduction in the same period (Velusamy & Kumar, 2025). This higher efficacy is likely attributed to empagliflozin's greater molecular selectivity and its ability to achieve a more pronounced reduction in fasting blood sugar (FBS) (Brown *et al*., 2019).

Weight and BMI Dynamics

Weight reduction is a hallmark of the SGLT2i class, driven by both caloric loss through glucosuria and the "thrifty fuel" metabolic shift (Verma & McMurray, 2018). In the obese population (BMI > 30 kg/m²), dapagliflozin users experienced a maximum weight loss of approximately 2.56 kg at 6 months (Viswanathan & Singh, 2019). Nevertheless, multiple studies support the preferential use of empagliflozin for weight management; in head-to-head trials, empagliflozin demonstrated a significantly greater body weight reduction (4.5 kg) compared to dapagliflozin (1.0 kg) over 3-year follow-up. This makes empagliflozin better than dapagliflozin for CRM Stage 1 and 2 patients where dysfunctional adiposity is the primary driver of disease (Ku EJ *et al*., 2021; Ndumele *et al.,* 2023).

Hemodynamic and Lipid Profiles

Beyond glucose, these agents act as mild antihypertensives. Both drugs achieve a reduction in systolic blood pressure (SBP) of approximately 3–4 mmHg, though some studies suggest dapagliflozin may offer a more pronounced effect on SBP (up to 10.26 mmHg in certain cohorts) (Velusamy & Kumar, 2025; Weber *et al*., 2016). Regarding lipids, a divergence is observed: Empagliflozin appears to have more favorable effects on HDL cholesterol, whereas Dapagliflozin has shown significant reductions in LDL-c, triglycerides (TG), and VLDL levels.

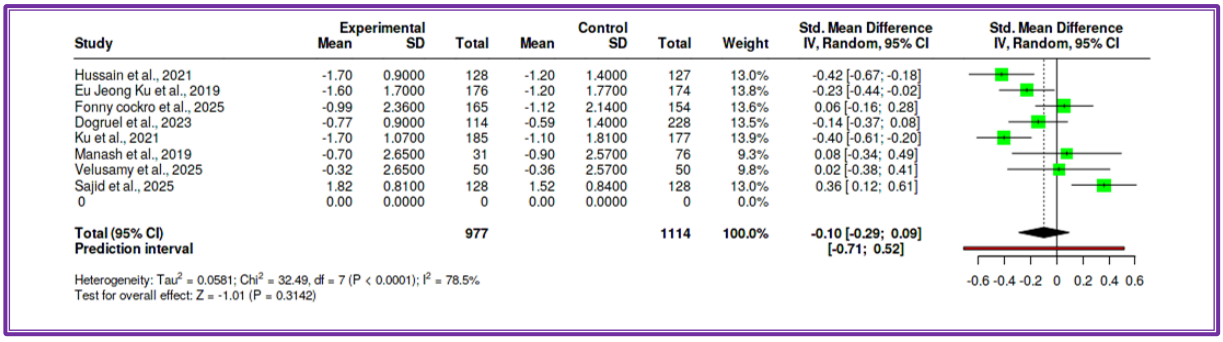


Figure 2: *Exploratory Pooled Analysis of Direct Head-To-Head Comparisons of Empagliflozin Versus Dapagliflozin on HbA1c Outcomes*

An exploratory pooled analysis was performed using studies that directly compared empagliflozin and dapagliflozin and reported HbA1c outcomes (Figure 2). Eight studies were included, comprising 977 participants in the empagliflozin group and 1,114 participants in the dapagliflozin group. The pooled standardized mean difference (SMD) was −0.10 (95% confidence interval [CI]: −0.29 to 0.09). As the 95% CI included zero, no statistically significant difference in HbA1c outcomes was observed between empagliflozin and dapagliflozin.

Cardiovascular Outcomes: Evidence Synthesis

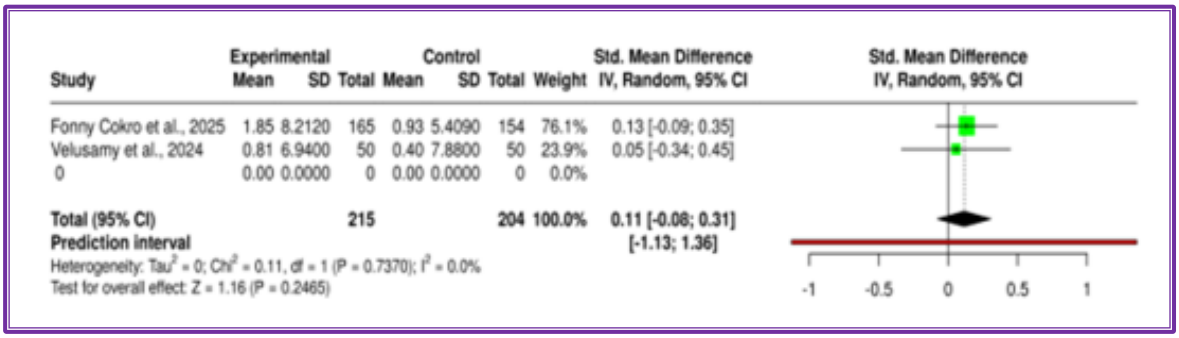


Figure 3: *Exploratory Pooled Analysis of Direct Head-To-Head Comparisons of Empagliflozin Versus Dapagliflozin on Cardiovascular Risk Score*

An exploratory pooled analysis was performed using studies that directly compared empagliflozin and dapagliflozin and reported cardiovascular risk-score outcomes (Figure 3). Two studies were included, comprising 215 participants in the empagliflozin group and 204 participants in the dapagliflozin group. The pooled standardized mean difference (SMD) was 0.11 (95% confidence interval [CI]: −0.08 to 0.31). As the 95% CI included zero, no statistically significant difference in cardiovascular risk scores was observed between empagliflozin and dapagliflozin.

Empagliflozin reduced cardiovascular death by 38%, hospitalization for heart failure by 35%, and the primary composite outcome by 14% for high-risk type 2 diabetes patients (Zinman *et al*., 2015). Dapagliflozin lowered hospitalization for heart failure or cardiovascular death by 17% and met noninferiority for major adverse cardiovascular events (MACE) in DECLARE-TIMI (Wiviott *et al*., 2019). Head-to-Head Comparisons - A Danish registry study of over 57,000 type 2 diabetes patients found no difference in 6-year MACE risk (10.0% for both; risk ratio 1.00, 95% CI 0.91-1.11), consistent across subgroups with or without heart failure or atherosclerotic disease (Bonnesen K *et al*. 2025). A Korean propensity-matched analysis of 1,074 patients also showed no significant MACE difference (3.7% vs. 4.8%; HR 1.31, 95% CI 0.73-2.35) (Kim *et al*., 2024).

Table 3: *Cardiovascular Outcomes from Major Trials and Registries*

Study	Drug	Key Findings	References
EMPA-REG OUTCOME	Empagliflozin	38% ↓ CV death; 35% ↓ HF hospitalization	Zinman *et al*., 2015
DECLARE-TIMI 58	Dapagliflozin	17% reduction inn cardiovascular death or hospitalisation for heart failure; hospitalisation for heart failure was reduced by 27%	Wiviott *et al*., 2019
Danish heart failure registry	Both	Empagliflozin initiation was associated with a lower risk of heart failure rehospitalisation or all-cause death than dapagliflozin initiation (HR-0.85,95% CI 0.76-0.93	Bonnesen *et al*., 2025
Korean propensity balanced cohort study	Both	No significant MACE difference	Kim *et al*., 2024

An exploratory pooled analysis was performed using studies that directly compared empagliflozin and dapagliflozin and reported eGFR outcomes (Figure 4). Two studies were included, comprising 304 participants in the empagliflozin group and 271 participants in the dapagliflozin group. The pooled standardized mean difference (SMD) was 0.02 (95% confidence interval [CI]: −0.14 to 0.19). As the 95% CI included zero, no statistically significant difference in eGFR outcomes was observed between empagliflozin and dapagliflozin.

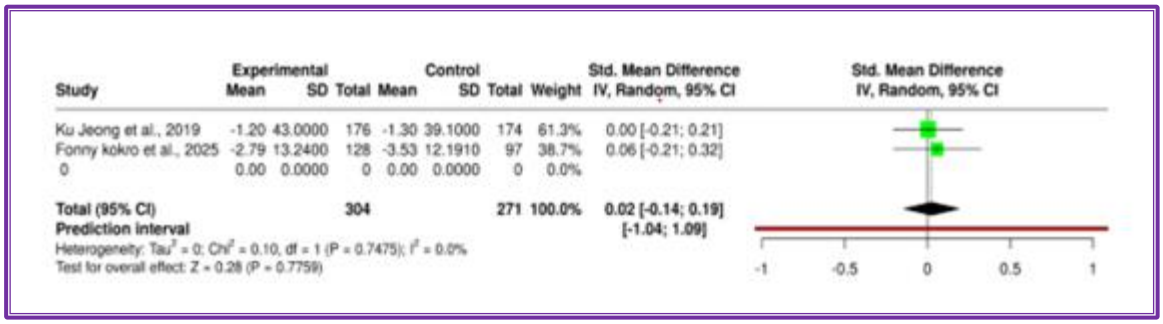


Figure 4:*Exploratory Pooled Analysis of Direct Head-To-Head Comparisons of Empagliflozin Versus Dapagliflozin on Egfr*

Table 4: *Renal Outcomes Comparison*

Outcome	Empagliflozin	Dapagliflozin	Reference
Acute kidney injury, 6-year risk	18.2%	18.5%	Bonnesen *et al*., 2024
CKD stages G3–G5, 6-year risk	11.8%	12.1%	Bonnesen *et al*., 2024
CKD stages A2/A3, 6-year risk	14.8%	14.3%	Bonnesen *et al*., 2024
CKD progression, 6-year risk	5.3%	5.7%	Bonnesen *et al*., 2024

A 2025 nationwide Danish cohort study of 50,283 adults with type 2 diabetes found comparable 6-year kidney outcomes between empagliflozin and dapagliflozin. The 6-year risks of acute kidney injury were 18.2% and 18.5%, respectively, while the risks of incident CKD stages G3–G5 were 11.8% and 12.1%, respectively. Among patients with reduced kidney function, the risk of CKD progression, defined as a ≥40% decline in eGFR from baseline, was 5.3% with empagliflozin versus 5.7% with dapagliflozin (Bonnesen *et al*., 2025). Independent randomized trials have also demonstrated renal benefits for both agents. In DAPA-CKD, dapagliflozin reduced the risk of sustained ≥50% eGFR decline, end-stage kidney disease, or death from renal or cardiovascular causes compared with placebo (HR 0.61, 95% CI 0.51–0.72) (Heerspink *et al*., 2020). In EMPA-KIDNEY, empagliflozin reduced the risk of kidney disease progression or cardiovascular death compared with placebo (HR 0.72, 95% CI 0.64–0.82) (Herrington *et al*., 2026). These findings support renal benefits of both agents, although the separate placebo-controlled trials do not establish comparative superiority between empagliflozin and dapagliflozin. Direct head-to-head comparative evidence remains predominantly observational and suggests broadly comparable kidney outcomes rather than superiority of either agent (Table 4) (Bonnesen *et al*., 2025).

Discussion

SGLT2 inhibitors like empagliflozin and dapagliflozin have transformed the management of cardio-renal-metabolic (CRM) syndrome by targeting the bidirectional organ crosstalk at its core. Both agents interrupt the vicious cycle of neurohormonal activation, hemodynamic stress, and metabolic inflammation through natriuresis, optimized myocardial energetics, and anti-fibrotic signalling. Landmark trials such as EMPA-REG OUTCOME, EMPEROR, DAPA-HF, DAPA-CKD, EMPA-KIDNEY, and DECLARE-TIMI 58 independently confirm their pleiotropic benefits, including reductions in heart failure hospitalization, cardiovascular death, and CKD progression, independent of glycaemic control or diabetes status. Head-to-head comparative evidence from real-world cohorts and exploratory quantitative analyses suggests broadly comparable cardio-renal-metabolic outcomes between the two agents, although the available evidence does not establish therapeutic equivalence or non-inferiority. Our exploratory quantitative analysis of 8 studies (N=2,091) evaluating HbA1c showed no statistically significant difference between the two agents (SMD −0.10, 95% CI −0.29 to 0.09), consistent with the direction of findings from a larger comparative analysis of 12 studies (N=7,164; SMD 0.09, 95% CI −0.08 to 0.26; P=0.30). Exploratory analysis of cardiovascular risk scores from 2 studies (N=419) showed no statistically significant difference between empagliflozin and dapagliflozin (SMD 0.11, 95% CI −0.08 to 0.31), consistent with findings from a Danish registry of 57,000 patients and a Korean

comparative analysis. Renal outcomes showed no statistically significant difference in the exploratory eGFR analysis (N=575; SMD 0.02, 95% CI −0.14 to 0.19), while a 2025 cohort of 50,283 patients reported broadly similar 6-year risks for AKI (18.2% vs. 18.5%), CKD incidence (11.8% vs. 12.1%), and CKD progression (5.3% vs. 5.7%) (Bonnesen *et al*., 2025). Subtle pharmacodynamic distinctions emerge in specific phenotypes. Empagliflozin's higher SGLT2 selectivity drives superior long-term HbA1c reduction (1.7% vs. 1.1% over 3 years) and weight loss (4.5 kg vs. 1.0-2.56 kg), favoring CRM Stage 1-2 patients with adiposity-driven disease (Table 5) (Ku EJ *et al*., 2021).

Table 5: *Phenotype-Based Clinical Selection*

Patient Profile	Potential Consideration	Rationale	References
Obesity / metabolically dominant CRM phenotype	Either agent; individualize according to metabolic response and patient characteristics	Both empagliflozin and dapagliflozin are associated with reductions in body weight and glycaemic parameters. Comparative real-world evidence demonstrates metabolic improvement with both agents but does not establish consistent superiority of either drug for weight management.	Crabtree, 2024; exploratory comparative evidence
Hypertension / atherosclerotic cardiovascular risk phenotype	Either agent; individualize according to blood-pressure and lipid response	Both agents may provide modest haemodynamic and metabolic benefits. Some comparative evidence suggests potentially greater lipid-modulating effects with dapagliflozin, but this finding is insufficient to establish overall cardiovascular superiority.	Crabtree, 2024; Özgöl *et al*., 2025
Heart failure	Either agent, based on indication-specific evidence	Both agents have established benefits in appropriate heart-failure populations, with broadly consistent reductions in heart-failure hospitalization and cardiovascular outcomes across trials.	McMurray *et al*., 2019; Packer *et al*., 2020
CKD progression risk	Either agent, based on indication-specific evidence	Both agents demonstrate renal protective effects in dedicated outcome trials. Available direct comparative evidence suggests broadly similar long-term kidney outcomes, although it remains predominantly observational and does not establish therapeutic equivalence.	Heerspink *et al*., 2020; Herrington *et al*., 2026; 2025 Danish nationwide comparative study

Dapagliflozin may edge in SBP reduction and LDL/triglyceride lowering, potentially benefiting atherosclerotic-high-risk profiles. Both retain cardio-renal efficacy down to eGFR 20 mL/min/1.73 m² despite attenuated glucosuria, owing to preserved tubule glomerular feedback and erythropoiesis (Packer, 2023). Taken together, these findings do not provide sufficient evidence to establish the superiority of either agent across the CRM spectrum and support a patient-centred approach to treatment selection rather than assuming agent-specific superiority. Limitations include reliance on observational head-to-head data, underrepresentation of Asian cohorts, and short-term meta-analyses that may miss durability. Future randomized trials should prioritize diverse phenotypes, combination therapies, and cost-effectiveness in real-world CRM trajectories.

Future Perspectives

The evidence base for SGLT2 inhibitors in cardio-renal-metabolic (CRM) syndrome is evolving rapidly, reflecting not simply a refinement of existing practice but a fundamental rethinking of the approach to multi-organ disease. empagliflozin and dapagliflozin have earned their place as foundational therapies, yet the priority now shifts from class-level validation toward precise, individualized, mechanism-based prescribing. Combination therapy trials represent one of the most promising directions ahead, pairing SGLT2 inhibitors with GLP-1 receptor agonists such as semaglutide or tirzepatide, as these agents target atherogenic risk and visceral adiposity through different pathways. Investigators must also examine the interplay between these drugs and finerenone in diabetic kidney disease, given the limited prospective evidence currently guiding their combined use. Further evaluation of SGLT2 inhibitor use in non-diabetic CKD, heart failure with preserved ejection fraction subtypes, type 1 diabetes, and elderly cohorts remains an important clinical research priority. Researchers must advance precision medicine

approaches, including pharmacogenomic profiling of UGT enzyme polymorphisms, proteomics-based biomarker discovery, and machine learning applied to real-world clinical data to identify patients who may respond differently to one agent or the other, thereby moving beyond population-level comparisons toward more individualized prescribing. Scientists must further clarify mechanistic uncertainties surrounding differential SGLT1 selectivity, myocardial fuel utilization, and gut microbiome modulation. Alongside these priorities, the field must generate long-term safety data, health economic evidence from low- and middle-income countries, and trial data among different ethnicities.

Research Gaps

Despite all the progress that landmark cardiovascular and renal outcome trials have delivered, clinicians and researchers continue to face important evidence gaps, particularly in selecting between empagliflozin and dapagliflozin for an individual patient. A head-to-head randomized controlled trial directly comparing these two agents remains an important unmet research need. Every comparative conclusion drawn to date, including the exploratory quantitative findings across glycaemic (SMD −0.10), cardiovascular risk (SMD 0.11), and renal (eGFR; SMD 0.02) domains, is based on a combination of observational cohorts, registry analyses, and comparative quantitative evidence that cannot substitute for a well-designed randomized trial. Researchers must recognize that statistical non-significance in these analyses reflects limited precision as much as true equivalence, and that distinction carries direct clinical consequences. Asian and South Asian populations carry a disproportionate CRM burden and present with a phenotypically distinct profile, lean-body-mass diabetes, earlier nephropathy onset, and visceral adiposity at lower BMI thresholds, rendering direct extrapolation from Western cohorts unreliable. Differential UGT enzyme expression patterns further complicate pharmacokinetic assumptions across ethnicities. Investigators must generate comparative data for several high-risk subgroups currently lacking evidence, like non-diabetic CKD patients with eGFR between 20 and 45 mL/min/1.73m², distinct HFpEF endotypes, acute decompensated heart failure, and elderly patients over 75 years. Mechanistic uncertainties surrounding SGLT1 selectivity, anti-fibrotic signalling, and erythropoietic kinetics demand dedicated translational study. Finally, researchers and health economists must produce head-to-head cost-effectiveness analyses from low- and middle-income countries where the CRM burden is greatest and generic availability reshapes prescribing decisions.

Conclusion

Empagliflozin and dapagliflozin show broadly comparable cardio-renal-metabolic benefits across the CRM continuum, although the available comparative evidence does not establish formal therapeutic equivalence or non-inferiority. While empagliflozin may offer advantages in weight management and HbA1c reduction, and dapagliflozin in lipid/hemodynamic modulation, these differences have not consistently demonstrated statistical superiority and should be interpreted cautiously in view of differences in study populations and designs. Clinicians should consider individual patient characteristics, clinical priorities, and indication-specific evidence when selecting between the two agents, rather than assuming superiority of either drug across all CRM phenotypes. As phenotype-driven medicine evolves, these agents remain important components of multi-organ risk reduction, while further head-to-head trials in high-risk and diverse populations are needed to refine personalized treatment strategies.

Data Availability

No datasets were generated or analysed during the current study

Clinical Trial Registration

Not applicable, as this study was not registered as a clinical trial.

Conflict of Interest

The authors have declared that no competing interests exist.

Author Contribution

The authors confirm their contribution to the paper as follows: study conception and design: SS, MR; data collection: SS, MR, MP, IM, SP, and SV; Interpretation: SS, MP, SP, IM, MR, and SV; methodology: SS, MP and MR: investigation: SS, MP, SP, IM, MR, and SV; Conceptualization: SP and MR; draft manuscript: SS, MP, MR. Author. SS, MP, MR. Author. All authors reviewed the results and approved the final version of the manuscript.

Acknowledgement

Authors are thankful to the School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies, Chennai, India and PSG College of Pharmacy, Coimbatore, India.

References

Abdul-Ghani, M. A., & DeFronzo, R. A. (2008). Inhibition of renal glucose reabsorption: A novel strategy for achieving glucose control in type 2 diabetes mellitus. *Endocrine Practice, 14*(6), 782–790. https://doi.org/10.4158/EP.14.6.782

Anker, S. D., Butler, J., Filippatos, G., Ferreira, J. P., Bocchi, E., Böhm, M., ... & Packer, M. (2021). Empagliflozin in heart failure with a preserved ejection fraction. *New England Journal of Medicine*, *385*(16), 1451-1461. https://doi.org/10.1056/NEJMoa2107038

Baker, W. L., Smyth, L. R., & McKeage, K. (2015). Empagliflozin: A review in diabetes mellitus. *Drugs, 75*(15), 1761–1773. https://doi.org/10.1007/s40265-015-0452-0

Bonnesen, K., Heide-Jørgensen, U., Christensen, D. H., Christiansen, C. F., Lash, T. L., Hennessy, S., ... & Schmidt, M. (2025). Effectiveness of empagliflozin vs dapagliflozin for kidney outcomes in type 2 diabetes. *JAMA Internal Medicine*, *185*(3), 314-323. https://doi.org/10.1001/jamainternmed.2024.7381

Bonnesen, K., Heide-Jørgensen, U., Christensen, D. H., Lash, T. L., Hennessy, S., Matthews, A., ... & Schmidt, M. (2024). Comparative cardiovascular effectiveness of empagliflozin versus dapagliflozin in adults with treated type 2 diabetes: A target trial emulation. *Circulation*, *150*(18), 1401-1411. https://doi.org/10.1161/CIRCULATIONAHA.124.068613

Brown, E., Rajeev, S. P., Cuthbertson, D. J., & Wilding, J. P. (2019). A review of the mechanism of action, metabolic profile and haemodynamic effects of sodium-glucose co-transporter-2 inhibitors. *Diabetes, Obesity and Metabolism*, *21*, 9-18. https://doi.org/10.1111/dom.13650

Brownlee, M. (2005). The pathobiology of diabetic complications: a unifying mechanism. *diabetes*, *54*(6), 1615. https://doi.org/10.2337/diabetes.54.6.1615

Cai, X., Cao, H., Wang, M., Yu, P., Liang, X., Liang, H., ... & Cai, M. (2025). SGLT2 inhibitor empagliflozin ameliorates tubulointerstitial fibrosis in DKD by downregulating renal tubular PKM2. *Cellular and Molecular Life Sciences*, *82*, 159. https://doi.org/10.1007/s00018-025-05688-8

Cai, X., Yang, W., Gao, X., Chen, Y., Zhou, L., Zhang, S., ... & Ji, L. (2018). The association between the dosage of SGLT2 inhibitor and weight reduction in type 2 diabetes patients: A meta-analysis. *Obesity*, *26*(1), 70-80. https://doi.org/10.1002/oby.22066

Crabtree, T. (2024). Real-world cross-comparison of metabolic outcomes with different sodium-glucose co-transporter 2 inhibitors agents in adults with type 2 diabetes: Results from the Association of British Clinical Diabetologists audit programme. *The British Journal of Diabetes*, *24*(1), 51-55. https://doi.org/10.15277/bjd.2024.449

DeFronzo, R. A., Davidson, J. A., & Prato, S. D. (2012). The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. *Diabetes, Obesity and Metabolism*, *14*(1), 5-14. https://doi.org/10.1111/j.1463-1326.2011.01511.x

DeFronzo, R. A., Hompesch, M., Kasichayanula, S., Liu, X., Hong, Y., Pfister, M., Morrow, L. A., Leslie, B. R., Boulton, D. W., Ching, A., LaCreta, F. P., & Griffen, S. C. (2013). Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. Diabetes Care, 36(10), 3169–3176. https://doi.org/10.2337/dc13-0387

European Medicines Agency. (2026). Forxiga: European Public Assessment Report (EPAR) – Product information. https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga

Forbes, J. M., & Cooper, M. E. (2013). Mechanisms of diabetic complications. *Physiological Reviews*, *93*(1), 137-188. https://doi.org/10.1152/physrev.00045.2011

Ghezzi, C., Loo, D.D.F. & Wright, E.M. (2018). Physiology of renal glucose handling via SGLT1, SGLT2 and GLUT2. *Diabetologia61,* 2087–2097. https://doi.org/10.1007/s00125-018-4656-5

González, P., Lozano, P., Ros, G., & Solano, F. (2023). Hyperglycemia and oxidative stress: an integral, updated and critical overview of their metabolic interconnections. *International Journal of Molecular Sciences*, *24*(11), 9352. https://doi.org/10.3390/ijms24119352

Heerspink, H. J., Stefánsson, B. V., Correa-Rotter, R., Chertow, G. M., Greene, T., Hou, F. F., ... & Wheeler, D. C. (2020). Dapagliflozin in patients with chronic kidney disease. *New England Journal of Medicine*, *383*(15), 1436-1446. https://doi.org/10.1056/NEJMoa2024816

Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., ... & Yancy, C. W. (2022). 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*, *145*(18), e895-e1032. https://doi.org/10.1161/CIR.0000000000001063

Herrington, W. G., Judge, P. K., Grams, M. E., & Wanner, C. (2026). Chronic kidney disease. *The Lancet*, *407*(10523), 90-104. https://doi.org/10.1016/s0140-6736(25)01942-7

Jadhav, U. M., Chawla, M., Rai, S., Manjula, S., & Kumar, M. K. (2025). Effectiveness of Dapagliflozin in Treating Type 2 Diabetes Mellitus in a Real-World Indian Setting. *Journal of Diabetology*, *16*(2), 176-181. https://doi.org/10.4103/jod.jod_109_24

Jankauskas, S. S., Komici, K., Varzideh, F., Aversa, L. S., Kansakar, U., D'Onghia, M. L., ... & Santulli, G. (2026). Cardiovascular–kidney–metabolic syndrome: A comprehensive review of pathophysiology, epidemiology, diagnosis, and management. *Cardiovascular Diabetology*, *25,* 182. https://doi.org/10.1186/s12933-026-03177-1

Kasichayanula, S., Liu, X., LaCreta, F., Griffen, S. C., & Boulton, D. W. (2014). Clinical pharmacokinetics and pharmacodynamics of dapagliflozin, a selective inhibitor of sodium-glucose co-transporter type 2. *Clinical Pharmacokinetics*, *53*, 17-27. https://doi.org/10.1007/s40262-013-0104-3

Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group (2022). KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney International*, *102*(5S), S1–S127. https://doi.org/10.1016/j.kint.2022.06.008

Kim, J. H., Yoon, Y. C., Kim, Y. H., Park, J. I., Choi, K. U., Nam, J. H., ... & Kim, U. (2024). Cardiovascular outcomes between dapagliflozin versus empagliflozin in patients with diabetes mellitus. *Clinical Cardiology*, *47*(3), e24248. https://doi.org/10.1002/clc.24248

Ku, E. J., Lee, D. H., Jeon, H. J., & Oh, T. K. (2021). Long-term effectiveness and safety of quadruple combination therapy with empagliflozin versus dapagliflozin in patients with type 2 diabetes: 3-year prospective observational study. Diabetes Research and Clinical Practice, 182, 109123. https://doi.org/10.1016/j.diabres.2021.109123

Macha, S., Jungnik, A., Hohl, K., Hobson, D., Salsali, A., &Woerle, H. J. (2013). Effect of food on the pharmacokinetics of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, and assessment of dose proportionality in healthy volunteers. *International Journal of Clinical Pharmacology and Therapeutics*, *51*(11), 873-879. https://doi.org/10.5414/cp201948

Macha, S., Mattheus, M., Halabi, A., Pinnetti, S., Woerle, H. J., & Broedl, U. C. (2014). Pharmacokinetics, pharmacodynamics and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in subjects with renal impairment. Diabetes, Obesity and Metabolism, 16(3), 215–222. https://doi.org/10.1111/dom.12182

Mcdonagh, T. H., & Metra, M. (2023). 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Russian Journal of Cardiology*, *28*(1), 5168. https://doi.org/10.15829/1560-4071-2023-5168

McMurray, J. J., Solomon, S. D., Inzucchi, S. E., Køber, L., Kosiborod, M. N., Martinez, F. A., ... & Langkilde, A. M. (2019). Dapagliflozin in patients with heart failure and reduced ejection fraction. *New England Journal of Medicine*, *381*(21), 1995-2008. https://doi.org/10.1056/NEJMoa1911303

Mullens, W., Damman, K., Testani, J. M., Martens, P., Mueller, C., Lassus, J., ... & Coats, A. (2020). Evaluation of kidney function throughout the heart failure trajectory–a position statement from the Heart Failure Association of the European Society of Cardiology. *European Journal of Heart Failure*, *22*(4), 584-603. https://doi.org/10.1002/ejhf.1697

Ndefo, U. A., Anidiobi, N. O., Basheer, E., & Eaton, A. T. (2015). Empagliflozin (Jardiance): A novel SGLT2 inhibitor for the treatment of type-2 diabetes. *Pharmacy and Therapeutics*, *40*(6), 364-368.

Ndumele, C. E., Rangaswami, J., Chow, S. L., Neeland, I. J., Tuttle, K. R., Khan, S. S., ... & American Heart Association. (2023). Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*, *148*(20), 1606-1635. https://doi.org/10.1161/CIR.0000000000001184

Neal, B., Perkovic, V., Mahaffey, K. W., De Zeeuw, D., Fulcher, G., Erondu, N., ... & Matthews, D. R. (2017). Canagliflozin and cardiovascular and renal events in type 2 diabetes. *New England Journal of Medicine*, *377*(7), 644-657. https://doi.org/10.1056/NEJMoa1611925

Özgöl, I., Yigit Gencer, E., Yildiz, C., Karabulut, D., Turhan Çağlar, F. N., Bicakhan, B., Yucel, C., Ketenciler, S., Ay, A., & Yigit, Z. (2025). Effects of empagliflozin and dapagliflozin on lipid profiles and atherogenic risk indices in patients with heart failure and a history of CABG: First evidence in the literature. Journal of Clinical Medicine, 14(20), 7395. https://doi.org/10.3390/jcm14207395

Packer, M. (2023). Mechanisms of enhanced renal and hepatic erythropoietin synthesis by sodium–glucose cotransporter 2 inhibitors. *European Heart Journal*, *44*(48), 5027-5035. https://doi.org/10.1093/eurheartj/ehad235

Packer, M., Anker, S. D., Butler, J., Filippatos, G., Pocock, S. J., Carson, P., ... &Zannad, F. (2020). Cardiovascular and renal outcomes with empagliflozin in heart failure. *New England Journal of Medicine*, *383*(15), 1413-1424. https://doi.org/10.1056/NEJMoa2022190

Packer, M., Butler, J., & Anker, S. D. (2022). Mechanisms of cardiorenal protection by sodium-glucose cotransporter 2 inhibitors. *JAMA Cardiology, 7*(6), 603–613. https://doi.org/10.1001/jamacardio.2022.0968

Palmer, B. F., & Clegg, D. J. (2022). Kidney-protective effects of SGLT2 inhibitors. *Clinical journal of the American Society of Nephrology: CJASN*, *18*(2), 279-289. https://doi.org/10.2215/CJN.09380822

Patel, D. K., & Strong, J. (2019). The pleiotropic effects of sodium–glucose cotransporter-2 inhibitors: beyond the glycemic benefit. *Diabetes Therapy*, *10*(5), 1771-1792. https://doi.org/10.1007/s13300-019-00686-z

Scheen, A. J. (2014). Pharmacokinetic and pharmacodynamic profile of empagliflozin, a sodium glucose co-transporter 2 inhibitor. *Clinical Pharmacokinetics*, *53*(3), 213-225. https://doi.org/10.1007/s40262-013-0126-x

U.S. Food and Drug Administration. (2025). Jardiance (empagliflozin) tablets: Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/204629s063lbl.pdf

Vaduganathan, M., Claggett, B. L., Jhund, P. S., Cunningham, J. W., Ferreira, J. P., Zannad, F., ... & Solomon, S. D. (2020). Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: A comparative analysis of three randomised controlled trials. *The Lancet*, *396*(10244), 121-128. https://doi.org/10.1016/s0140-6736(20)30748-0

Velusamy, S., & Kumar, S. R. (2025). Safety and efficacy of dapagliflozin versus empagliflozin as add-on therapy in type 2 diabetes mellitus management. *Indian Journal of Physiology and Pharmacology*, *69*(2), 136-141. https://doi.org/10.25259/IJPP_257_2024

Verma, S., & McMurray, J. J. (2018). SGLT2 inhibitors and mechanisms of cardiovascular benefit: A state-of-the-art review. *Diabetologia*, *61*(10), 2108-2117. https://doi.org/10.1007/s00125-018-4670-7

Viswanathan, V., & Singh, K. P. (2019). Use of dapagliflozin in the management of type 2 diabetes mellitus: A real-world evidence study in Indian patients (FOREFRONT). *Diabetes Technology & Therapeutics*, *21*(8), 415-422. https://doi.org/10.1089/dia.2019.0052

Weber, M. A., Mansfield, T. A., Cain, V. A., Iqbal, N., Parikh, S., & Ptaszynska, A. (2016). Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: A randomised, double-blind, placebo-controlled, phase 3 study. *The Lancet Diabetes & Endocrinology*, *4*(3), 211-220. https://doi.org/10.1016/s2213-8587(15)00417-9

Wiviott, S. D., Raz, I., Bonaca, M. P., Mosenzon, O., Kato, E. T., Cahn, A., ... & Sabatine, M. S. (2019). Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *New England Journal of Medicine*, *380*(4), 347-357. https://doi.org/10.1056/NEJMoa1812389

Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., ... &Inzucchi, S. E. (2015). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *New England Journal Of Medicine*, *373*(22), 2117-2128. https://doi.org/10.1056/NEJMoa1504720