Review Article *Volume 6, Issue 1*

JCMCRI

Journal of Clinical & Medical Case Reports, Images

Received: May 25, 2026 Published: June 08, 2026

DOI: 10.55920/3064-8025/1210

Empagliflozin versus Dapagliflozin: a guidance to primary care physicians

Almoutaz Alkhier Ahmed*

A/Professor - Family Medicine- MBRU, SSR family medicine -Nad Alhamar Health Center. DAHC

FRCGP [int], MSc Diabetes, MSc endocrinology, Senior fellow of IDF, MPH, FESC, FASLM, Dip IBLM, ELMC, Pg Cer medical education.

Abstract

Introduction: Sodium–glucose cotransporter-2 (SGLT2) inhibitors are an important class of anti-hyperglycaemic medications that have significantly improved the management of type 2 diabetes mellitus (T2DM) and its related cardiovascular and renal complications. Initially introduced for glycaemic control, agents such as dapagliflozin, empagliflozin, canagliflozin and ertugliflozin have shown additional benefits in heart failure and chronic kidney disease (CKD). These drugs act by inhibiting SGLT2 proteins in the proximal renal tubules, reducing glucose reabsorption and increasing urinary glucose excretion through an insulin-dependent mechanism. In addition to lowering blood glucose, SGLT2 inhibitors promote natriuresis, osmotic diuresis, weight reduction and blood pressure control, thus improving overall cardiometabolic health.

Objective: This review aims to evaluate the efficacy and safety of Dapagliflozin vs Empagliflozin in patients with T2DM, heart failure, CKD and hypertensive non diabetic with proteinuria. Special emphasis is placed on their effects on glycaemic control, cardiovascular outcomes, renal protection, hospitalization for heart failure and mortality, as well as associated adverse effects.

Methods: A narrative review approach was used using evidence from randomized controlled trials, meta-analyses, observational studies and current clinical guidelines. Landmark studies, including EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS, DAPA-HF, DAPA-CKD and EMPA-KIDNEY, were critically examined to assess clinical efficacy and safety characteristics of major SGLT2 inhibitors. Data related to cardiovascular outcomes, renal function, glycaemic improvement and adverse events were synthesized and analysed.

Results: Clinical evidence consistently demonstrated that SGLT2 inhibitors significantly improve glycaemic control while reducing body weight and blood pressure. Major trials reported significant reductions in hospitalization for heart failure, progression of CKD and cardiovascular mortality in both diabetic and non-diabetic populations. Dapagliflozin and empagliflozin showed particularly strong cardio-renal protective effects, including slower decline in estimated glomerular filtration rate (eGFR) and reduced albuminuria progression. Common adverse effects included genital infections, urinary tract infections, volume depletion and rare diabetic ketoacidosis. Trotz these risks, the overall safety and efficacy profile remained favourable.

Conclusion: SGLT2 inhibitors have emerged as the core therapy in modern cardiometabolic management. Their benefits extend beyond glucose-lowering to include significant cardiovascular and renal protection. Current evidence supports their broad use in patients with T2DM, heart failure and CKD, although further long-term studies are needed to clarify real-world safety and optimize individual treatment strategies.

Keywords: SGLT2 inhibitors, T2DM, heart failure, CKD, cardio-renal protection.

Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a relatively recent class of anti-hyperglycaemic agents that have markedly improved the management of type 2 diabetes mellitus (T2DM), cardiovascular disease, heart failure and chronic kidney disease (CKD) [1]. Although originally designed to improve glycaemic control, these agents have demonstrated substantial cardiovascular and renal protective effects that go beyond their glucose lowering properties [1]. Commonly used SGLT2 inhibitors include Ertugliflozin, Empagliflozin, Canagliflozin and Dapagliflozin.

SGLT2 inhibitors exert their therapeutic effects by inhibiting sodium-glucose cotransporter-2 (SGLT2) proteins in the proximal renal tubules [2]. Under normal physiological conditions, these transporters reabsorb approximately 90% of the filtered glucose back into the systemic circulation [2]. Pharmacological inhibition of SGLT2 increases urinary glucose excretion, thereby lowering blood glucose levels independent of insulin secretion or insulin sensitivity [2]. In addition, these agents promote natriuresis, osmotic diuresis, modest weight loss and reduced blood pressure, collectively resulting in their favourable cardiometabolic profile [2].

Evidence from large-scale randomized controlled trials has shown that SGLT2 inhibitors significantly reduce hospitalization for heart failure, delay the progression of CKD and lower cardiovascular mortality in selected patient populations [3]. Landmark clinical trials, including EMPA-REG OUTCOME [3], DECLARE-TIMI 58 [4], DAPA-HF [5] and EMPA-KIDNEY [6], have established these medications as core therapies in both diabetic and non-diabetic individuals with cardiovascular and renal disease.

Despite their clinical benefits, SGLT2 inhibitors are associated with several possible adverse effects, including genital mycotic infections, volume depletion, diabetic ketoacidosis and rare occurrences of Fournier's gangrene [7]. Therefore, careful patient selection, monitoring and risk assessment are essential during therapy. Overall, SGLT2 inhibitors represent a major therapeutic progress in contemporary medicine by addressing the interconnected burden of diabetes, cardiovascular disease and renal dysfunction through multiple defensive mechanisms.

SGLT receptors

Sodium-glucose co-transporters (SGLTs) are membrane-bound trans-

***Corresponding Author:** *Almoutaz Alkhier Ahmed, A/Professor -MBRU, SSR family medicine -Nad Alhamar Health Center. DAHC

Citation: Almoutaz Alkhier Ahmed*, Empagliflozin versus Dapagliflozin: a guidance to primary care physicians. Jour of Clin & Med Case Rep, Imag 2026; 6(1): 1210.

port proteins that facilitate the active transport of glucose across cellular membranes in conjunction with sodium ions [1]. These transporters belong to the solute carrier family, specifically the SLC5 gene family, and are integral to maintaining glucose homeostasis (). Among the various isoforms identified, SGLT1 and SGLT2 are considered the most clinically relevant [1]. SGLT2 is predominantly expressed in the proximal convoluted tubule of the kidney, particularly within the S1 segment, where it is responsible for reabsorbing approximately 90% of filtered glucose from the glomerular filtrate into the systemic circulation [8]. This mechanism prevents excessive urinary glucose excretion under physiological conditions [8]. In comparison, SGLT1 is primarily localized in the small intestine and the distal segments of the renal proximal tubule [8]. It mediates the remaining 10% of renal glucose reabsorption and plays a critical role in intestinal glucose and galactose absorption [8].

The functional activity of SGLT receptors is dependent on the sodium gradient generated by the Na^+/K^+-ATPase pump [8]. Through secondary active transport, glucose is transported against its concentration gradient, coupled with sodium influx into the cell. Subsequently, intracellular glucose is released into the circulation via facilitative glucose transporters (GLUTs). SGLT receptors have emerged as significant therapeutic targets in the management of type 2 diabetes mellitus, chronic kidney disease, and heart failure [8]. Pharmacological inhibition of SGLT2 decreases renal glucose reabsorption, thereby promoting glucosuria and reducing blood glucose concentrations independently of insulin activity [8]. Agents such as Dapagliflozin and Empagliflozin have demonstrated substantial cardiovascular and reno-protective benefits that extend beyond glycaemic control [8]. Furthermore, emerging evidence indicates that SGLT inhibition may improve endothelial function, attenuate inflammatory pathways, reduce intraglomerular pressure, and optimize myocardial energy metabolism. Consequently, SGLT receptors are increasingly recognized as pivotal therapeutic targets in contemporary cardiometabolic medicine [8].

Structure of SGLT2 receptor: The sodium-glucose cotransporter 2 (SGLT2) receptor is a membrane-associated transport protein predominantly expressed in the S1 segment of the proximal convoluted tubule of the kidney. It belongs to the solute carrier family 5 member 2 (SLC5A2) and consists of approximately 672 amino acids organized into 14 transmembrane -helical domains. The amino (N-) and carboxyl (C-) termini are extracellularly located, helping to the physical integrity and functional stability of the transporter [9].SG LT2 acts as a sodium-dependent glucose transporter by coupling the reabsorption of one glucose molecule with one sodium ion across the apical membrane of renal tubular epithelial cells. This transport process is driven by the sodium electrochemical gradient established by the Na+/K+-ATPase pump, thereby enabling active glucose reabsorption from the glomerular filtrate into the systemic circulation. Structurally, distinct binding sites within the transmembrane domains facilitate the recognition and transport of sodium and glucose, inducing conformational alterations required for substrate translocation [8].

Functionally, SGLT2 is a low-affinity, high-capacity transporter that absorbs approximately 90% of filtered glucose under normal physiological conditions (8). Drug agents such as dapagliflozin and empagliflozin selectively inhibit SGLT2 by binding to its glucose-binding domain, thus reducing renal glucose reabsorption and enhancing urinary glucose excretion (glycosuria) [8]. The structural selectivity and functional role of SGLT2 form the basis for the therapeutic application of SGLT2 inhibitors in the management of chronic kidney disease, heart failure and diabetes mellitus [8].

Factors affecting SGLT2 receptor: The activity and expression of the sodium-glucose cotransporter 2 (SGLT2) receptor are regulated by a variety of physiological, pathological, genetic and pharmacological factors [10]. SGLT2 receptors are predominantly expressed in the proximal convoluted tubules of the kidneys where they mediate the reabsorption of approximately 90% of filtered glucose [8]. The blood glucose concentration is a major determinant of SGLT2 activity [11]. In hyperglycaemic conditions, particularly in type 2 diabetes mellitus (T2DM), the expression of SGLT2 is frequently upregulated, causing enhanced renal glucose reabsorption and worsening hyperglycaemia [11].

Renal function plays also a key role in affecting SGLT2 activity (12). In patients with chronic kidney disease (CKD), impaired renal function reduces glomerular filtration and alters SGLT2-mediated glucose transport [12]. Hormonal mediators, including insulin, glucagon and angiotensin II, contribute additionally to the regulation of receptor expression and renal glucose handling [12]. Moreover, inflammatory cytokines and oxidative stress associated with diabetes and cardiovascular disorders may adversely affect the function and expression of SGLT2 receptors [10]. Genomic variations within the SLC5A2 gene, which encodes the SGLT2 receptor, may influence the transporter efficiency and personal susceptibility to glucosuria [9]. Pharmacological compounds, particularly SGLT2 inhibitors such as dapagliflozin and empagliflozin, inhibit direct receptor activity, consequently reducing renal glucose reabsorption, promoting glucosuria and improving glycaemic control [9].

Approved indications for dapagliflozin and empagliflozin: Da agliflozin and Empagliflozin are sodium–glucose cotransporter-2 (SGLT2) inhibitors [13]. Both have several approved uses in diabetes mellitus, cardiovascular disease, heart failure, and chronic kidney disease (CKD). Their clinical applications have expanded following evidence from outcome trials [1]. Dapagliflozin was first approved by the FDA in January 2014 for the treatment of glycaemic control in adults with type 2 diabetes mellitus (T2DM) [14]. It acts by inhibiting glucose reabsorption in the proximal renal tubules. This enhances urinary glucose excretion. In May 2020, dapagliflozin was approved for reducing cardiovascular death and hospitalization in patients with heart failure with reduced ejection fraction (HFrEF), regardless of diabetes status [15]. This approval was based on the DAPA-HF trial (). In April 2021, dapagliflozin was approved for CKD [16], based on the DAPA-CKD trial [17], which showed significant reductions in disease progression and cardiovascular mortality. In 2023, FDA approval expanded to include all ranges of ejection fraction in heart failure [18]. Empagliflozin was approved by the FDA in August 2014 for the treatment of glycaemic control in adults with T2DM [19]. After the EMPA-REG OUTCOME trial [3], it gained approval in December 2016 for reducing cardiovascular mortality in adults with T2DM and established cardiovascular disease [19]. In August 2021, approval was extended to the management of HFrEF based on EMPEROR-Reduced trial results [20]. The EMPEROR-Preserved trial [21] supported its 2022 approval for heart failure with preserved ejection fraction (HFpEF) [22]. In September 2023, empagliflozin received approval for CKD after studies showed substantial reno-protective and cardiovascular benefits [23]. Overall, dapagliflozin and empagliflozin have advanced beyond glucose-lowering agents. They are now seen as cardio-respiratory protective therapies. These drugs reduce hospitalization rates, slow disease progression, and lower mortality in patients with diabetes mellitus, heart failure, and CKD.

Efficacy, safety and cost of Dapagliflozin and Empagliflozin

Empagliflozin and Dapagliflozin are sodium–glucose cotransporter-2 (SGLT2) inhibitors extensively used in the management of type 2

diabetes mellitus (T2DM), heart failure and chronic kidney disease (CKD) [1]. Both agents act by inhibiting proximal renal tubular glucose reabsorption, consequently increasing urinary glucose excretion, osmotic diuresis, natriuresis and modest weight reduction [3]. Over the past decade, these medications have significantly advanced cardiometabolic therapeutics owing to their demonstrated cardiovascular and renal protective effects that extend beyond glycaemic control. Although both drugs belong to the same pharmacological class and exhibit broadly comparable clinical efficacy, notable differences exist in their pharmacodynamic properties, cardiovascular outcome evidence, renal protective effects, adverse-effect profiles, and recommendations within clinical guidelines.

Empagliflozin shows greater selectivity for the SGLT2 receptor than dapagliflozin, which may theoretically confer more pronounced glucose lowering and natriuretic effects [24]. Dapagliflozin, in contrast, exhibits relatively broader tissue activity and has shown considerable benefit in patients with heart failure, including those without diabetes mellitus [24,25]. Both medications are administered once daily and possess similar pharmacokinetic characteristics with elimination half-lives of approximately 10–12 hours [8]. In the context of glycaemic management, both agents reduce glycated haemoglobin (HbA1c), fasting plasma glucose levels and body weight effectively [8]. Clinical trials generally reported HbA1c reductions ranging from 0.5% to 1.0%, depending on baseline glycaemic status and concomitant therapeutic regimens [26]. Certain comparative observational studies [27] suggest that empagliflozin may provide a slightly greater reduction in HbA1c than dapagliflozin, however, the difference is modest and often of limited clinical significance. Additionally, both medications contribute to modest reductions in systolic blood pressure through mechanisms related to osmotic diuresis and natriuresis [28].

The cardiovascular effects of sodium–glucose cotransporter-2 (SGLT2) inhibitors represent a major advancement in contemporary diabetes therapeutics. The EMPA-REG OUTCOME trial [3] identified empagliflozin as the first glucose-lowering agent to demonstrate a significant reduction in cardiovascular mortality among patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease [3]. Empagliflozin significantly reduced cardiovascular death, hospitalization for heart failure, and all-cause mortality. In comparison, the DECLARE–TIMI 58 trial [4] evaluating dapagliflozin demonstrated significant reductions in hospitalization for heart failure and adverse renal outcomes, although reductions in major adverse cardiovascular events were comparatively less pronounced [4]. These differences may partially reflect variations in baseline cardiovascular risk among the study populations rather than intrinsic pharmacological superiority between the agents [4].

Subsequent heart failure trials further expanded the therapeutic indications of both medications beyond glycaemic control. In the DAPA-HF trial [5], dapagliflozin significantly reduced worsening heart failure and cardiovascular mortality in patients with heart failure with reduced ejection fraction (HFrEF), irrespective of diabetic status. Similarly, empagliflozin demonstrated substantial clinical benefit in the EMPEROR-Reduced [20] and EMPEROR-Preserved [21] trials. Collectively, these findings established SGLT2 inhibitors as foundational therapies in the management of heart failure. Current evidence indicates that both agents provide substantial and broadly comparable benefits across the spectrum of heart failure.

Renal protection represents another important therapeutic advantage associated with both medications. SGLT2 inhibitors reduce intraglomerular pressure, decrease albuminuria, and attenuate the decline in estimated glomerular filtration rate (eGFR) [29]. Dapagliflozin demonstrated significant reno-protective effects in the DAPA-CKD trial [17], including among patients without diabetes. Subsequently, empagliflozin showed similar renal benefits in the EMPA-KIDNEY trial [6]. Large observational cohort studies comparing empagliflozin and dapagliflozin have generally reported no statistically significant differences in major renal outcomes [30], although some analyses suggested a slightly lower risk of renal replacement therapy with empagliflozin [31].

Head-to-head comparative studies further indicate that both agents possess highly similar clinical efficacy. A large Scandinavian cohort study [31] involving approximately 200,000 patients demonstrated no significant differences between empagliflozin and dapagliflozin with respect to major cardiovascular events, heart failure outcomes, renal events, or diabetic ketoacidosis. These findings support the concept that many of the therapeutic benefits associated with SGLT2 inhibitors are attributable to a class effect rather than drug-specific superiority. Both medications exhibit relatively favourable safety profiles. However, both have clinically significant adverse effects. The most reported complications occur with both agents, including genital mycotic infections, urinary tract infections, polyuria, volume depletion, and hypotension [32]. Rare but serious adverse events, such as diabetic ketoacidosis, particularly euglycemic diabetic ketoacidosis, as well as acute kidney injury during dehydration or severe systemic illness, may occur with either medication [33]. Comparative studies have not identified substantial differences in safety between empagliflozin and dapagliflozin [34]. Nevertheless, caution is warranted for both agents in elderly patients, those receiving loop diuretics, and patients with advanced renal impairment.

Major guidelines recommend both drugs for people with type 2 diabetes and cardiovascular disease, heart failure, or chronic kidney disease. International groups such as the American Diabetes Association and the European Society of Cardiology support SGLT2 inhibitors as first-line treatments for these patients [35-37]. Early guidelines often favoured empagliflozin because of stronger initial evidence for lowering cardiovascular mortality. Newer advice treats empagliflozin and dapagliflozin as equally useful. Drug selection between dapagliflozin and empagliflozin may be influenced by cost, formulary availability, and regional prescribing practices. In several healthcare systems, dapagliflozin is more accessible due to broader insurance coverage and availability of generics [38]. Conversely, some clinicians favour empagliflozin, primarily because its early landmark trials provided strong evidence for cardiovascular mortality reduction [39]. This preference is not based on major comparative efficacy differences but rather on evidence and accessibility.

Both dapagliflozin and empagliflozin demonstrate broadly comparable cost-effectiveness profiles. Their economic value comes from favourable cardiovascular and renal outcomes for both agents, rather than glycaemic control alone. Dapagliflozin has shown favourable cost-effectiveness in multiple analyses, especially following the DAPA-HF [5] and DAPA-CKD [17] Trials, which demonstrated significant reductions in heart failure hospitalizations and slowing of CKD progression. These benefits contribute to substantial healthcare savings, like those observed with empagliflozin, by reducing recurrent admissions and delaying renal replacement therapy. Long-term models consistently indicate that dapagliflozin is cost-effective in both diabetic and non-diabetic populations with heart failure or CKD, paralleling findings for empagliflozin.

Empagliflozin also shows strong economic value. The EMPA-REG OUTCOME Trial [3] found that it lowers cardiovascular deaths and

heart failure hospitalizations in people with type 2 diabetes. Later studies, including EMPEROR-Reduced [20] and EMPEROR-Preserved [21], found benefits for people with heart failure, with both reduced and preserved ejection fraction. These findings support the intervention's cost-effectiveness, driven by improved survival and fewer hospital stays. Both drugs are highly cost-effective versus standard therapy. Small cost differences depend on local prices, reimbursement, and formulary agreements. In practice, doctors base their choice mainly on trial evidence and healthcare economics, not drug price or overall value.

In summary, Empagliflozin and dapagliflozin are effective SGLT2 inhibitors with comparable glycaemic, cardiovascular and renal benefits. Empagliflozin shows stronger evidence for reducing cardiovascular mortality, while dapagliflozin shows robust success in chronic kidney disease and heart failure. Overall, their benefits are considered largely a class effect, and treatment choice should be individualized based on patient characteristics, renal function, tolerability, cost, and availability.

SGLT2inhipitor and eGFR: The therapeutic role of sodium-glucose cotransporter-2 (SGLT2) inhibitors, particularly dapagliflozin and empagliflozin, has evolved considerably from sole glucose-lowering agents to essential therapies in the management of chronic kidney disease (CKD) and heart failure [3]. A major factor affecting their clinical use is the estimated glomerular filtration rate (eGFR), which determines both initiation and continuation on criteria [40].

Contemporary evidence and updated guidelines recommendations from the kidney disease: Improving Global Outcomes (KDIGO) [37], the American Diabetes Association (ADA) [35], and the European Society of Cardiology (ESC) [36] between 2024 and 2026 support the use of both agents at substantially lower eGFR levels than previously recommended, mainly because of their established cardiovascular and renal protective effects independent of glycaemic control. Dapagliflozin is generally recommended for initiation in patients with an eGFR 25 mL/min/1.73 m2 for CKD and heart failure indications [40]. Although its glucose-lowering efficacy declines with worsening renal function [40], landmark trials such as the DAPA-CKD study [17] showed significant reductions in CKD progression and cardiovascular events in patients with eGFR values as low as 25 mL/min/1.73 m2. Furthermore, treatment may be continued under this threshold if the medication remains well tolerated and dialysis has not been initiated [40].

Empagliflozin, by comparison, has demonstrated efficacy in a slightly broader range of renal function in cardiorenal populations [41]. Current recommendations support initiation in patients with an eGFR as low as 20 mL/min/1.73 m^2, particularly in those with CKD or heart failure, as evidenced by the EMPA-KIDNEY and EMPEROR [40] trials. Like dapagliflozin, the maintenance of therapy below the initiation threshold is considered appropriate, provided that renal replacement therapy is not required, and ongoing clinical benefit is observed [40]. Both agents are associated with an initial, reversible decline in eGFR, typically 3–5 mL/min/1.73 m^2, reflecting hemodynamic alterations rather than structural renal injury [42]. This transient reduction generally stabilizes over time and, in the absence of additional adverse clinical findings, should not necessitate discontinuation of therapy. To summarize, dapagliflozin is commonly initiated at an eGFR as low as 25 mL/min/1.73 m^2, whereas empagliflozin may be initiated at an eGFR as low as 20 mL/min/1.73 m^2. Both agents continue to show substantial cardiovascular and renal benefits, even in patients with advanced renal impairment.

Empagliflozin and Dapagliflozin in Recent Clinical Guidelines: Empagliflozin and dapagliflozin are sodium-glucose cotransporter-2 (SGLT2) inhibitors that have advanced beyond their original role as glucose-lowering agents to become key therapies for cardiovascular and renal protection. Contemporary clinical guidelines, including those of the American Diabetes Association [35], kidney disease: Improving Global Outcomes [37] and the European Society of Cardiology [36], consistently endorse both agents as core treatments for patients with type 2 diabetes mellitus (T2DM) who are at elevated cardiovascular or renal risk.

According to the current ADA standards of care [35], empagliflozin and dapagliflozin are preferred SGLT2 inhibitors for individuals with T2DM and established atherosclerotic cardiovascular disease, heart failure or chronic kidney disease, irrespective of baseline glycated haemoglobin (HbA1c) levels in many clinical scenarios. Their early incorporation into therapeutic algorithms, often alongside metformin, is supported under robust evidence demonstrating reductions in heart failure hospitalization and progression of renal disease.

In heart failure management, ESC guidelines [36] strongly recommend empagliflozin and dapagliflozin across the full spectrum of left ventricular ejection fraction, including heart failure with reduced and preserved ejection fraction. These recommendations are largely derived from landmark clinical trials such as DAPA-HF [5], EMPEROR reduced [20] and DELIVER trial [43], all of which showed significant reductions in cardiovascular mortality and hospitalizations related to heart failure. In patients with chronic kidney disease, joint consensus recommendations of KDIGO [37] and ADA [35] support initiating either empagliflozin or dapagliflozin in individuals with an estimated glomerular filtration rate (eGFR) 20 mL/min/1.73 m^2. Clinical evidence indicates that these therapies significantly delay the progression of kidney dysfunction and reduce the risk of kidney failure. Notably, their reno-protective benefits remain, despite relatively modest glycaemic effects, underscoring their broader organ-protective mechanisms [44]. Overall, contemporary guidelines increasingly consider empagliflozin and dapagliflozin interchangeable within the SGLT2 inhibitor class. Therapeutic selection is therefore often affected by factors such as local availability, cost-effectiveness, renal function and individual patient comorbidities. Their established role as first-line cardio-renal protective therapies shows a major paradigm shift from a glucose-centred approach in diabetes management towards comprehensive cardiovascular and renal risk reduction.

Side effects of empagliflozin vs dapagliflozin

Dapagliflozin and empagliflozin, both sodium–glucose cotransporter-2 (SGLT2) inhibitors, exhibit broadly comparable adverse effect profiles. The most frequently reported adverse events include genital mycotic infections, urinary tract infections, and polyuria secondary to osmotic diuresis [32]. Volume depletion associated with these agents may result in hypotension, dizziness, and acute kidney injury, particularly among older adults and patients receiving concomitant diuretic therapy [45]. Rare but clinically significant complications include euglycemic diabetic ketoacidosis [46] and Fournier's gangrene [47]. In addition, both medications are associated with modest reductions in body weight and blood pressure, effects that are generally considered therapeutically advantageous [48]. Current evidence has not demonstrated consistent or clinically significant differences in overall safety between the two agents, although individual patient tolerability may differ. Accordingly, regular monitoring of hydration status and renal function is recommended during treatment.

Sodium–glucose cotransporter-2 (SGLT2) inhibitors are central to managing type 2 diabetes mellitus, heart failure, and chronic kidney disease. Large-scale trials and post-marketing surveillance link SGLT2

inhibitors to increased risk of diabetic ketoacidosis (DKA), including euglycemic DKA. EMPA-REG OUTCOME [3], CANVAS trial [49] and DECLARE-TIMI 58 [4] reported uncommon but clinically significant cases of ketoacidosis versus placebo. The mechanisms involve reduced insulin, increased glucagon and increased hepatic ketogenesis due to glycosuria. Euglycemic ketoacidosis, where normal glucose levels with ketosis should be screened (46). Key risk factors for DKA with SGLT2 inhibitors are prolonged fasting, infection, surgical stress, dehydration, excessive alcohol intake, and inappropriate insulin reduction [50]. Act quickly: recognize symptoms, educate patients, and stop SGLT2 inhibitors during acute illness to lower the risk of severe metabolic complications and morbidity [50].

Major Clinical Trials of Dapagliflozin and Empagliflozin

Major Clinical Trials of Dapagliflozin: DECLARE–TIMI 58 trial [4]
These large-scale cardiovascular outcomes trial evaluated the safety and efficacy of dapagliflozin in patients with type 2 diabetes mellitus (T2DM), enrolling more than 17,000 participants. The study demonstrated a significant reduction in hospitalization for heart failure and renal composite outcomes. However, there was no significant reduction in major adverse cardiovascular events (MACE) in the overall population. DAPA-HF trial [5]
This trial assessed dapagliflozin in patients with heart failure with reduced ejection fraction (HFrEF), including both diabetic and non-diabetic individuals. It demonstrated a significant reduction in worsening heart failure events and cardiovascular mortality, thereby establishing dapagliflozin as an effective therapy in HFrEF.

DELIVER trial [43]
The DELIVER trial evaluated dapagliflozin in patients with heart failure with preserved or mildly reduced ejection fraction (HFpEF/HFmrEF). The findings showed a significant reduction in the composite endpoint of cardiovascular death or worsening heart failure.

DAPA-CKD trial [17]
This study examined the effects of dapagliflozin in patients with chronic kidney disease, with and without diabetes. It demonstrated substantial reductions in the progression of renal disease, end-stage kidney disease, and all-cause mortality, establishing a pivotal role for SGLT2 inhibition in nephroprotection.

DERIVE trial [51]
The DERIVE trial focused on patients with type 2 diabetes and moderate renal impairment, evaluating glycaemic efficacy and renal safety. It confirmed modest glucose-lowering effects alongside preservation of renal function.

DEFINE-HF trial [52]
This study investigated the impact of dapagliflozin on symptoms, functional status, and biomarkers in HFrEF. It demonstrated improvements in patient-reported outcomes and reductions in NT-proBNP levels in selected subgroups.

DAPA-MI trial [53]
The DAPA-MI trial explored the use of dapagliflozin following acute myocardial infarction, focusing on cardiometabolic outcomes and prevention of heart failure progression in the post-infarction setting.

Major Clinical Trials of Empagliflozin

EMPA-REG OUTCOME [3]
This landmark cardiovascular outcome trial evaluated empagliflozin in patients with T2DM and established cardiovascular disease, enrolling over 7,000 participants. It demonstrated significant reductions in cardiovascular mortality, all-cause mortality, and hospitalization for heart failure, representing the first evidence of cardiovascular mortality benefit with an SGLT2 inhibitor.

EMPEROR-Reduced [20]
This trial assessed empagliflozin in patients with HFrEF, with and without diabetes. It demonstrated significant reductions in cardiovascular death and heart failure hospitalization, along with a slower decline in renal function.

EMPEROR-Preserved [21]
This study investigated empagliflozin in patients with HFpEF. It showed a significant reduction in the composite outcome of cardiovascular death or heart failure hospitalization, representing a major advance in HFpEF therapy.

EMPA-KIDNEY [6]
This trial evaluated empagliflozin in patients with chronic kidney disease, including a substantial proportion without diabetes. It demonstrated reduced progression of kidney disease and lower risk of cardiovascular death, confirming broad reno-protective effects.

EMPERIAL-Reduced trial [54]
This study focused on functional capacity and exercise performance in patients with HFrEF, assessing improvements in exercise tolerance and quality-of-life measures.

EMPERIAL-Preserved trial [55]
A parallel study to EMPERIAL-Reduced, this trial evaluated functional outcomes in HFpEF, with emphasis on exercise capacity and patient-reported functional status.

The EMPEROR-Reduced Trial [20]
It showed that empagliflozin markedly reduced the risk of cardiovascular death and heart failure hospitalization in patients with heart failure with reduced ejection fraction (HFrEF), regardless of diabetes status. It also slowed the decline in renal function and improved heart failure outcomes, establishing SGLT2 inhibitors as a key element of guideline-directed medical therapy for heart failure by reducing cardiovascular events, slowing renal deterioration, and improving overall prognosis.

The EMPEROR-Preserved Trial [21]
It evaluated empagliflozin in patients with heart failure with preserved ejection fraction (HFpEF). The trial found a 21% reduction in cardiovascular death or heart failure hospitalization, mainly due to fewer hospitalizations. Benefits were consistent for patients with or without diabetes, confirming SGLT2 inhibitors as an effective treatment for HFpEF with significant cardiorenal protection.

EMPA-HEART CardioLink-6 trial [56]
This mechanistic trial assessed cardiac remodelling effects, demonstrating a reduction in left ventricular mass and regression of left ventricular hypertrophy.

EMPULSE trial [57]
This trial investigated initiation of empagliflozin during hospitalization for acute heart failure. It demonstrated clinical benefit and safety in the acute care setting, supporting early in-hospital initiation.

Critical Appraisal of Trials on Empagliflozin versus Dapagliflozin

Sodium–glucose cotransporter-2 (SGLT2) inhibitors have significantly reshaped the therapeutic landscape of type 2 diabetes mellitus (T2DM), heart failure (HF), and chronic kidney disease (CKD) [1]. Within this pharmacological class, empagliflozin and dapagliflozin

represent the most extensively studied agents. A robust body of evidence from major randomized controlled trials (RCTs), including EMPA-REG OUTCOME [3], EMPEROR-Reduced [20], EMPEROR-Preserved [21], DECLARE–TIMI 58 [4], DAPA-HF (5), and DAPA-CKD [17], has consistently demonstrated substantial cardiovascular and renal benefits that extend beyond glycaemic control. Nevertheless, a critical evaluation of these trials is necessary to appraise their comparative efficacy, methodological rigor, limitations, and generalizability to routine clinical practice.

The EMPA-REG OUTCOME trial [3] was a pivotal cardiovascular outcomes study assessing empagliflozin in patients with T2DM and established cardiovascular disease. This multicentre, randomized, double-blind, placebo-controlled trial enrolled 7,020 participants and demonstrated significant reductions in major adverse cardiovascular events (MACE), cardiovascular mortality, all-cause mortality, and hospitalization for heart failure. Notably, cardiovascular death was reduced by 38%, representing one of the most pronounced mortality benefits reported in diabetes-related cardiovascular outcome trials.
From a methodological perspective, the trial [3] exhibited several strengths, including a rigorous randomized controlled design, adequate statistical power, and the use of clinically meaningful primary and secondary endpoints. The high baseline cardiovascular risk of the study population, all of whom had established atherosclerotic cardiovascular disease, enhanced event rates and improved the ability to detect treatment effects. In addition, the median follow-up period of approximately 3.1 years was sufficient for the assessment of cardiovascular outcomes, and independent endpoint adjudication reduced the risk of outcome assessment bias.

However, several limitations should be acknowledged. The study [3] population was predominantly composed of individuals with established cardiovascular disease, thereby limiting the external validity of the findings to lower-risk populations with T2DM. Furthermore, the early divergence of cardiovascular mortality curves raised questions regarding the underlying biological mechanisms, as such rapid benefits are not typically consistent with slower atherosclerotic modification. Consequently, it has been proposed that haemodynamic effects, including natriuresis, osmotic diuresis, and reductions in preload and afterload, may have contributed more substantially to the observed early cardiovascular benefits than direct anti-atherosclerotic effects.
A further critique concerns the relatively modest reduction observed in glycated haemoglobin (HbA1c), in contrast to the substantial reductions in mortality outcomes. This dissociation implies that clinical benefits are predominantly mediated by mechanisms independent of glycaemic control; however, it additionally complicates the causal interpretation of the observed cardiovascular benefits. Moreover, subgroup analyses were often underpowered, thereby increasing the risk of type I error in the interpretation of secondary endpoints.

In contrast, dapagliflozin was primarily evaluated in the DECLARE-TIMI 58 trial [4], which enrolled 17,160 patients with type 2 diabetes mellitus (T2DM). Unlike EMPA-REG OUTCOME [3], only approximately 40% of participants had established atherosclerotic cardiovascular disease, while the rest exhibited multiple cardiovascular risk factors. DECLARE-TIMI 58 [4] demonstrated superiority for the composite outcome of cardiovascular death or hospitalization for heart failure; however, it did not achieve statistical significance for major adverse cardiovascular events (MACE). However, hospitalization for heart failure was significantly reduced, strengthening a class effect of SGLT2 inhibitors in heart failure prevention.

The wider inclusion criteria of DECLARE-TIMI 58 [4] enhanced external validity, as the study population more closely reflected routine clinical practice in T2DM. The inclusion of a substantial primary prevention cohort improved generalisability, but simultaneously reduced overall event rates, thus diminishing statistical power to detect differences in MACE. Consequently, the neutral MACE results may reflect differences in baseline cardiovascular risk rather than a lack of therapeutic efficacy.

A further methodological consideration relates to protocol modifications following the publication of the EMPA-REG OUTCOME [3], including the introduction of dual primary efficacy endpoints during trial conduct. Although these amendments were prespecified before unblinding, they raise concerns regarding multiplicity and potential inflation of type I error and thus constitute a point of methodological debate. Direct comparison between EMPA-REG OUTCOME [3] and DECLARE-TIMI 58 [4] is inherently limited by substantial differences in baseline patient characteristics and cardiovascular risk profiles. EMPA-REG OUTCOME [3] enrolled exclusively patients with established cardiovascular disease, whereas DECLARE–TIMI 58 [4] included a significant proportion of primary prevention participants. Any apparent differences in cardiovascular efficacy between empagliflozin and dapagliflozin are therefore more plausibly attributable to trial design and population variability than to true pharmacological superiority, as supported by multiple systematic reviews.

Subsequent dedicated heart failure trials have further clarified cardiovascular benefits of dapagliflozin. The DAPA-HF trial [5] evaluated dapagliflozin in patients with heart failure with reduced ejection fraction (HFrEF), including individuals without diabetes mellitus, and showed significant reductions in the worsening of heart failure and cardiovascular mortality. Notably, these benefits were consistent across the diabetic and non-diabetic subgroups, supporting mechanisms of action that go beyond glycaemic lowering. Similarly, the EMPEROR reduced trial [20] evaluated empagliflozin in patients with heart failure with reduced ejection fraction (HFrEF) and exhibited a significant reduction in the composite outcome of cardiovascular death or hospitalization for heart failure. Subsequently, the EMPEROR-Preserved trial extended these outcomes to patients with heart failure with preserved ejection fraction (HFpEF), a population for which therapeutic options have historically been limited and showed a significant clinical benefit.

A critical evaluation of the DAPA-HF [5] and EMPEROR [20,21] program indicates high methodological strictness across both trials. Each study was randomized, placebo-controlled and used clinically meaningful primary endpoints with solid statistical frameworks. However, differences in baseline disease severity limit the validity of indirect comparisons. Notably, EMPEROR-Reduced [20] enrolled patients with more advanced heart failure and lower left ventricular ejection fractions compared with DAPA-HF may partially justify observed differences in mortality outcomes. An additional consideration is if observed benefits represent a class effect of sodium–glucose co-transporter-2 inhibitors (SGLT2) or drug-specific advantages. Emerging meta-analyses and systematic reviews increasingly support a class-wide effect on the heart failure and renal protection. However, empagliflozin demonstrated a more significant reduction in cardiovascular mortality in EMPA-REG OUTCOME [3], whereas dapagliflozin has shown strong and consistent efficacy across more extensive heart failure and primary prevention cohorts. Whether these differences indicate true pharmacodynamic variation or trial design heterogeneity remains unclear.

Renal outcomes further complicate comparative interpretation. The DAPA-CKD trial [17] demonstrated significant reno-protective effects of dapagliflozin in patients with chronic kidney disease, with and

without diabetes. Similarly, empagliflozin demonstrated nephroprotective benefits in the EMPA-REG OUTCOME [3] and EMPEROR [20,21] trials. Overall, the treatment effect appears to be strongly influenced by the baseline renal function and the degree of albuminuria.

In terms of safety, both agents demonstrate generally favourable profiles. Genital mycotic infections occur more often with SGLT2 inhibitor therapy, consistent with their mechanism of glucosuria [45]. Although rare, diabetic ketoacidosis remains a clinically important adverse event. Importantly, neither empagliflozin nor dapagliflozin has been associated with the increased risk of lower limb amputation observed with canagliflozin in the CANVAS [49] program. A further limitation of the existing evidence base is the insufficient representation of elderly, frail and ethnically diverse populations across major trials. Participants were predominantly white males from high-income countries, thereby limiting external validity towards broader global populations. In addition, follow-up durations were relatively short given the chronic nature of the cardiovascular and renal disease progression.

Direct, head-on randomized controlled trials comparing empagliflozin and dapagliflozin are currently lacking. Therefore, clinical decision-making relies largely on indirect comparisons across heterogeneous study populations. Although observational analyses and target trial emulation studies have tried to address this gap, residual confounding continues to limit causal inference. As such, the definitive superiority of one agent over the other has not been established. In conclusion, both empagliflozin and dapagliflozin have demonstrated substantial cardiovascular and renal benefits across multiple high-quality randomized controlled trials. EMPA-REG OUTCOME [3] established empagliflozin as a landmark therapy in high-risk patients with type 2 diabetes, while DECLARE-TIMI 58 [4], DAPA-HF [5], and DAPA-CKD (17) expanded the evidence base supporting dapagliflozin across a wider spectrum of cardiovascular, heart failure, and renal disease populations. Observed differences between trials are more plausibly attributable to variations in study design, baseline risk and patient selection, rather than true pharmacological superiority. Despite research limitations and heterogeneity across studies, the cumulative evidence convincingly supports SGLT2 inhibitors as a core therapy in diabetes, heart failure and chronic kidney disease. Further head-to-head trials are justified to clarify whether there are clinically significant differences between these two agents.

Dapagliflozin vs empagliflozin in glycaemic control: Dapagliflozin and empagliflozin are sodium-glucose cotransporter-2 inhibitors (SGLT2) widely used in the management of type 2 diabetes mellitus (T2DM). Both agents improve glycaemic control by inhibiting renal glucose reabsorption, consequently increasing urinary glucose excretion and reducing plasma glucose concentrations. Although they share a common mechanism of action and a common pharmacological class, multiple clinical trials have investigated potential differences in their glycaemic efficacy.

The efficacy of dapagliflozin has been extensively evaluated in the DECLARE-TIMI 58 trial [4], which enrolled over 17,000 patients with T2DM and either established cardiovascular disease or multiple cardiovascular risk factors. While the primary endpoint focused on cardiovascular safety and outcomes, dapagliflozin was associated with modest but persistent improvements in glycaemic parameters, including reductions in HbA1c and fasting plasma glucose compared to placebo. Further evidence from the DAPA-HF [5] and DAPA-CKD [17] trials has reinforced its wider metabolic benefits, demonstrating improvements in glycaemic control along with reductions in body weight and blood pressure, particularly among patients with heart failure and chronic kidney disease.

Similarly, empagliflozin showed strong glycaemic success in the EMPA-REG OUTCOME trial, which included more than 7,000 patients with T2DM and established cardiovascular disease. In addition to significant reductions in cardiovascular mortality and heart failure hospitalization, empagliflozin produced clinically significant decreases in HbA1c, fasting plasma glucose and body weight relative to placebo. Subgroup analyses indicated consistent glycaemic efficacy across a range of baseline HbA1c levels and degrees of renal function, although attenuated glucose lowering effects were observed in more advanced chronic kidney disease.

Comparative evidence shows a potential, although modest, advantage of empagliflozin over dapagliflozin in glycaemic lowering. A network meta-analysis of SGLT2 inhibitors reported HbA1c reductions of approximately 0.69% with empagliflozin 25 mg and 0.51% with dapagliflozin 10 mg compared to placebo (). The magnitude of this difference is however small and of uncertain clinical significance. Direct comparative studies have similarly demonstrated slightly greater HbA1c reductions with empagliflozin during short-term follow-up, however, these data are limited by relatively small sample sizes and short study durations. Despite such observations, the overall evidence base indicates that the glycaemic efficacy of dapagliflozin and empagliflozin is broadly comparable in clinical practice. Observed differences in HbA1c reduction are generally minor and may be influenced by baseline glycaemic control, renal function, disease duration, and concomitant antidiabetic therapy [27]. Both agents typically achieve HbA1c reductions in the range of approximately 0.5–1.0%, which remains clinically meaningful, particularly when considered alongside their favourable effects on weight and blood pressure.

Importantly, contemporary diabetes management prioritizes cardiovascular and renal outcomes along with glycaemic control. Major outcome trials, including EMPA-REG OUTCOME [3], DECLARE-TIMI 58 [4], DAPA-HF [5] and DAPA-CKD [17], have demonstrated that both empagliflozin and dapagliflozin confer substantial cardio-renal protection that appears largely independent of glucose lowering. Empagliflozin has been associated with pronounced reductions in cardiovascular mortality, while dapagliflozin has shown particularly strong benefits in heart failure and chronic kidney disease populations, including individuals without diabetes. Collectively these data support the concept of a class effect of SGLT2 inhibitors on cardio-renal outcomes. In conclusion, dapagliflozin and empagliflozin are highly effective SGLT2 inhibitors that provide significant improvements in glycaemic control in patients with T2DM. Although empagliflozin may demonstrate a slightly greater HbA1c reduction in certain analyses, the difference between agents is generally modest and of limited clinical relevance. Therefore, therapeutic selection should be guided by more comprehensive clinical considerations, including cardiovascular and renal complications, safety profile, cost, and patient-focused factors. Overall, both agents represent essential parts of current diabetes management strategies.

Dapagliflozin vs empagliflozin in major cardiovascular adverse events

Dapagliflozin and empagliflozin are sodium–glucose cotransporter-2 (SGLT2) inhibitors recognized for cardiovascular protective properties in type 2 diabetes mellitus (T2DM). Both agents improve glycaemic control. Their effects on major adverse cardiovascular events (MACE), such as cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke, have been evaluated in large cardiovascular outcome trials (CVOTs) [3,4]. Both agents show cardiovascular benefit,

but empagliflozin has stronger evidence supporting MACE reduction compared to dapagliflozin.

Empagliflozin's most pivotal evidence comes from the EMPA-REG OUTCOME trial [3], a randomized controlled study of over 7,000 patients with T2DM and established cardiovascular disease. Empagliflozin reduced the primary composite MACE endpoint by 14% compared to placebo (HR] 0.86; 95% confidence interval [CI] 0.74–0.99). Cardiovascular mortality dropped by 38%, and heart failure hospitalizations by 35%. The early divergence in the curve suggests benefits beyond glycaemic control. These may include osmotic diuresis, lower blood pressure and body weight, improved cardiac preload and afterload, and better endothelial function.

DECLARE–TIMI 58 [4] evaluated dapagliflozin in over 17,000 patients with T2DM. Participants included those with established atherosclerotic cardiovascular disease (ASCVD) and those with multiple risk factors but without prior events. Dapagliflozin was non-inferior for MACE but did not outperform placebo for the primary composite endpoint (HR 0.93; 95% CI 0.84–1.03). However, it did reduce heart failure hospitalizations and improved renal outcomes, indicating cardiorenal benefits.

Differences between EMPA-REG OUTCOME [3] and DECLARE–TIMI 58 [4] are likely due to differences in study populations. EMPA-REG OUTCOME [3] enrolled only patients with established cardiovascular disease. This increased event rates and statistical power for reductions in cardiovascular outcomes. DECLARE–TIMI 58 [4] included about 60% of patients without prior ASCVD, creating a lower-risk group with fewer MACE events.

DAPA-HF [5] showed that dapagliflozin reduced worsening heart failure and cardiovascular death in patients with heart failure with reduced ejection fraction, including those without diabetes. EMPEROR reduced [20] confirmed that empagliflozin lowers heart failure hospitalization and cardiovascular mortality in a similar population. Meta-analyses support the class effect of SGLT2 inhibitors, especially in reducing heart failure hospitalizations and protecting kidney function. Zelniker et al. [58] found an approximate 31% reduction in heart failure hospitalizations across CVOTs. MACE reduction is more pronounced in patients with established ASCVD; effects are less consistent in lower-risk groups.

Both agents can cause adverse effects such as genital mycotic infections, volume depletion, and rarely, euglycemic diabetic ketoacidosis. Still, their overall safety profile is favourable. Major cardiovascular outcomes trials (CVOTs) show empagliflozin provides stronger evidence for reducing MACE, especially cardiovascular mortality. Dapagliflozin shows notable benefits in heart failure and kidney outcomes. Direct comparisons are limited by differences in trial design and patient characteristics. Both agents are essential in cardiovascular risk reduction for T2DM. Selection should be guided by patient risk profiles and comorbidities.

Dapagliflozin vs Empagliflozin on heart failure and hospitalization

Dapagliflozin and empagliflozin, both sodium-glucose cotransporter-2 inhibitors (SGLT2), have markedly transformed the therapeutic field of heart failure (HF), particularly by reducing hospitalization rates and advancing cardiovascular outcomes. Originally developed for glycaemic control in type 2 diabetes mellitus, subsequent large-scale randomized controlled trials have demonstrated that these agents confer significant cardioprotective benefits that are largely independent of baseline diabetes status.

The landmark DAPA-HF trial [5] evaluated dapagliflozin in 4,744 patients with heart failure with reduced ejection fraction (HFrEF). Treatment with dapagliflozin was associated with a 26% relative risk reduction in the composite endpoint of worsening HF or cardiovascular death compared to placebo (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.65–0.85). Notably, there was a significant reduction in HF hospitalizations, along with improvements in symptom burden and quality of life, with consistent benefits observed regardless of diabetes status. This evidence established dapagliflozin as an effective HF therapy beyond its glucose lowering properties.

In parallel, the EMPEROR-Reduced trial [20] evaluated empagliflozin in 3,730 patients with HFrEF. Empagliflozin demonstrated a 25% reduction in the composite outcome of cardiovascular death or HF hospitalization (HR 0.75, 95% CI 0.65–0.86), with the effect predominantly driven by a substantial reduction in HF admissions. Additional benefits included fewer recurrent hospitalizations and a slower decline in renal function, underscoring its cardiorenal protective profile. Comparative appraisal of these trials suggests broadly similar efficacy of dapagliflozin and empagliflozin in reducing HF hospitalization, supporting a class effect among SGLT2 inhibitors. The observed clinical benefits are likely mediated through multiple mechanisms, including osmotic diuresis, natriuresis, reductions in preload and afterload, improved myocardial energetics, and attenuation of inflammatory and fibrotic pathways.

Nevertheless, direct comparison is limited by differences in trial design and baseline patient characteristics. Participants in EMPEROR-Reduced [20] generally exhibited more advanced disease, characterized by lower left ventricular ejection fraction and higher natriuretic peptide concentrations compared with those enrolled in DAPA-HF. This higher-risk population may partly explain the more pronounced effect of empagliflozin on HF hospitalization, despite relatively modest reductions in cardiovascular mortality. Conversely, DAPA-HF [5] demonstrated more consistent mortality reduction alongside reductions in hospitalization.

Subsequent evidence from heart failure trials with preserved ejection fraction (HFpEF) further expanded the therapeutic scope of SGLT2 inhibitors. The EMPEROR-Preserved trial [21] showed that empagliflozin significantly reduced HF hospitalization in patients with HFpEF, representing a major therapeutic progress in this historically limited population. Similarly, the DELIVER trial [43] confirmed that dapagliflozin reduced the risk of worsening HF and cardiovascular death in HFpEF, strengthening its efficacy throughout the HF spectrum. Overall, the accumulated evidence indicates that both dapagliflozin and empagliflozin significantly reduce HF hospitalization and improve cardiovascular outcomes across a broad range of HF phenotypes. While subtle differences in mortality and hospitalization outcomes have been observed, these are not considered clinically decisive. Consequently, contemporary HF guidelines recommend SGLT2 inhibitors as a unified therapeutic class rather than favouring one agent over the other.

Dapagliflozin versus empagliflozin in the progression of chronic kidney disease (CKD)

Dapagliflozin and empagliflozin are pivotal agents in slowing CKD progression, especially in patients with type 2 diabetes, albuminuria, and cardiovascular disease. Both are SGLT2 inhibitors that protect the kidneys by reducing intraglomerular pressure, restoring tubuleglomerular feedback, lowering albuminuria, and modulating inflammatory and fibrotic pathways. However, differences in trial design and outcome definitions limit direct comparisons. Evidence for dapagliflozin primarily comes from the DAPA-CKD trial [17], a multicentre,

randomized, placebo-controlled study involving 4,304 patients with CKD (eGFR 25–75 mL/min/1.73 m² and albuminuria). Dapagliflozin showed a 39% relative risk reduction in the primary endpoint: sustained ≥50% decline in eGFR, ESKD, or renal/cardiovascular death versus placebo (HR 0.61; 95% CI 0.51–0.72). Treatment effects were consistent in diabetic and non-diabetic subgroups, suggesting renal protection is largely independent of glycaemic control.

Empagliflozin evidence is mainly from EMPA-KIDNEY [6], which enrolled 6,609 participants with a broad spectrum of CKD, including lower eGFR (down to 20 mL/min/1.73 m²) and less pronounced albuminuria. Empagliflozin reduced the risk of kidney disease progression or cardiovascular death by 28% compared with placebo (HR 0.72; 95% CI 0.64–0.82). The benefit was seen regardless of diabetes status, supporting SGLT2 inhibition in diverse CKD populations, including non-albuminuric disease.

Dapagliflozin shows higher risk reduction (39% vs 28%), but trial differences limit comparison. DAPA-CKD () recruited more proteinuric, high-risk participants and used a ≥50% decline in eGFR endpoint. EMPA-KIDNEY [6] used a ≥40% threshold and had a broader, often lower-risk cohort. These differences explain variation in effect size and prevent firm conclusions on superiority. Additional cardiovascular outcome trials provide supportive evidence. DECLARE–TIMI 58 [4] showed renal benefits of dapagliflozin as a secondary outcome in type 2 diabetes, while EMPA-REG OUTCOME [3] found slower progression of nephropathy and fewer adverse renal endpoints with empagliflozin in secondary analyses. Both dapagliflozin and empagliflozin slow CKD progression and reduce significant renal outcomes. Dapagliflozin is especially effective in proteinuric CKD. Empagliflozin proves benefit across wider CKD phenotypes. The data support a class effect for SGLT2 inhibitors, without clear evidence that one is clinically superior.

Dapagliflozin vs empagliflozin in hypertensive non- diabetic with proteinuria

In hypertensive non-diabetic proteinuric CKD, dapagliflozin and empagliflozin show clinically meaningful reno-protective effects, mainly through hemodynamic mechanisms. Comparative interpretation should rely on direct trial evidence rather than indirect subgroup analyses. The DAPA-CKD trial [17] gives strong evidence for dapagliflozin, including many non-diabetic patients with albuminuric CKD. It showed significant reductions in sustained eGFR decline, end-stage kidney disease, or renal/cardiovascular death. Benefits were consistent across non-diabetic subgroups and blood pressure categories, supporting use in hypertensive proteinuric CKD. The DIAMOND trial [59], focusing on non-diabetic proteinuric CKD, did not show a significant reduction in proteinuria in the short term, but did show reduced intraglomerular pressure and an initial reversible decline in eGFR. A longer treatment period may be needed to achieve antiproteinuric effects.

Empagliflozin is supported by the EMPA-KIDNEY trial [6], which included CKD patients with and without diabetes and varying levels of albuminuria. The trial [6] showed significant reductions in kidney disease progression and cardiovascular mortality consistent across diabetes status and blood pressure levels. Analyses showed reduced albuminuria and slower eGFR decline in non-diabetic patients, confirming strong class-wide reno-protective effects. Smaller studies in glomerular disease suggest that empagliflozin reduces proteinuria earlier than placebo, though no head-to-head comparative data exist. Neither DAPA-CKD [17] nor EMPA-KIDNEY [6] directly compared dapagliflozin and empagliflozin, limiting conclusions about superiority. Study design differences, including eGFR thresholds, albuminuria levels, and proportions of non-diabetic participants, may confound indirect comparisons. Dapagliflozin strongly reduces hard renal outcomes in proteinuric CKD, while empagliflozin shows robust efficacy with potentially more uniform effects on albuminuria across CKD populations.

In hypertensive non-diabetic proteinuria CKD, both agents are supported by high-quality trials (DAPA-CKD and EMPA-KIDNEY) [6,17]. The current literature favours a class effect rather than the clear superiority of any single agent.

Dapagliflozin vs Empagliflozin dose response

Dapagliflozin and empagliflozin show dose-dependent pharmacodynamic effects. The clinical dose–response is modest beyond standard therapeutic doses [60]. Both agents inhibit SGLT2 in the proximal renal tubules, raising urinary glucose excretion, promoting natriuresis, and lowering plasma glucose [3]. Early trials of dapagliflozin showed reductions in HbA1c, fasting plasma glucose, and body weight at doses of 2.5-10 mg daily. Ferrannini et al. [61] found maximal glycaemic efficacy at 10 mg, with limited benefit at higher exposures. Similarly, Häring et al. reported reductions in HbA1c of 10 mg and 25 mg in response to lower doses, supporting current therapeutic choices [62]. Large cardiovascular outcome trials reinforced efficacy at standard dosing. DECLARE–TIMI 58 [4] used dapagliflozin 10 mg daily, showing reductions in heart failure hospitalization and renal events. EMPA-REG OUTCOME [3] used empagliflozin 10 mg or 25 mg daily, reporting substantial reductions in cardiovascular mortality and heart failure hospitalization. These trials did not show clear superiority of higher doses, suggesting effective SGLT2 inhibition is key to cardiovascular and renal protection.

Dapagliflozin vas Empagliflozin in managing non-traditional risk factors

Non-traditional risk factors play a key role in the development and progression of cardiovascular and renal diseases among patients with type 2 diabetes mellitus and chronic kidney disease [63]. Sodium–glucose cotransporter-2 (SGLT2) inhibitors, particularly Dapagliflozin and Empagliflozin, have demonstrated clinically important benefits beyond glycaemic control. Evidence from the EMPA-REG OUTCOME trial [3] revealed that empagliflozin significantly reduced cardiovascular mortality and heart failure hospitalizations despite relatively modest reductions in glycated haemoglobin, indicating additional defensive mechanisms [3]. Likewise, the DAPA-HF (5) and DAPA-CKD [17] trials showed that dapagliflozin reduced the risk of worsening heart failure and progression of chronic kidney disease in both diabetic and non-diabetic individuals [17]. These benefits are attributed to multiple pleiotropic effects including reduction of intraglomerular hypertension through restoration of tubule-glomerular feedback, causing decreased albuminuria and renal fibrosis. SGLT2 inhibitors have also been associated with reduced systemic inflammation [64], oxidative stress [64], serum uric acid concentrations [64], visceral adiposity [64], and arterial stiffness [64], all of which are recognized non-traditional cardiovascular risk factors. Additionally, improved myocardial energy utilization and enhanced renal oxygenation may add further to their significant cardiorenal protective effects, independent of glucose-lowering effects [65].

Conclusion

In clinical practice, dapagliflozin and empagliflozin are widely used SGLT2 inhibitors with comparable cardio-renal benefits, though there are nuances. Empagliflozin reduced cardiovascular mortality in EMPA-REG OUTCOME, particularly in patients with ASCVD. Dapagliflozin, supported by DAPA-CKD and DECLARE-TIMI 58, provides evidence across CKD and heart failure, including non-diabetic patients.

Dapagliflozin is often used for CKD or heart failure phenotypes, while empagliflozin is preferred for secondary prevention of ASCVD. Safety profiles are similar with genital mycotic infections and volume depletion as the main adverse effects. SGLT2 inhibitors are key therapies in cardiometabolic and reno-cardiovascular care.

References

1. Morris David (2022) The evolving role of SGLT2 inhibitors. Journal of Diabetes Nursing 26: 3.
2. Wright Ernest M (2021) SGLT2 inhibitors: physiology and pharmacology. Kidney 360, 2(12): 2027-2037.
3. Zinman B, Wanner C, Lachin JM, et al. (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine 373(22): 2117–2128.
4. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, et al. (2019) Dapagliflozin and cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine 380(4): 347-357.
5. Mcmurray, John JV, et al. (2019) Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine 381(21): 1995-2008.
6. Empa-Kidney Collaborative Group (2023) Empagliflozin in patients with chronic kidney disease. New England Journal of Medicine 388(2): 117-127.
7. Yang Ting, Zhou Ying, CUI Yimin (2024) Urinary tract infections and genital mycotic infections associated with SGLT-2 inhibitors: an analysis of the FDA Adverse Event Reporting System. Expert Opinion on Drug Safety 23(8): 1035-1040.
8. Wright, Ernest M (2021) SGLT2 inhibitors: physiology and pharmacology. Kidney 360 2(12): 2027-2037.
9. Wright, Ernest M (2013) Glucose transport families SLC5 and SLC50. Molecular aspects of medicine 34(2-3): 183-196.
10. Wang, Xiaoxin X, et al. (2017) SGLT2 protein expression is increased in human diabetic nephropathy: SGLT2 protein inhibition decreases renal lipid accumulation, inflammation, and the development of nephropathy in diabetic mice. Journal of Biological Chemistry 292(13): 5335-5348.
11. Abdul-Ghani, Muhammad A, Defronzo, Ralph A, Norton, Luke (2013) Novel hypothesis to explain why SGLT2 inhibitors inhibit only 30–50% of filtered glucose load in humans. Diabetes 62(10): 3324-3328.
12. Akunjee, Munaza M, et al. (2025) SGLT2 inhibitors use in kidney disease: what did we learn? American Journal of Physiology-Endocrinology and Metabolism 328(6): E856-E868.
13. Shao, Shih-Chieh, et al. (2019) Comparative risk evaluation for cardiovascular events associated with dapagliflozin vs. empagliflozin in real-world type 2 diabetes patients: a multi-institutional cohort study. Cardiovascular diabetology 18(1): 120.
14. Saeed, Mujahid A, Narendran, Parth (2014) Dapagliflozin for the treatment of type 2 diabetes: a review of the literature. Drug design, development and therapy pp. 2493-2505.
15. Vaduganathan, Muthiah, et al. (2021) Applicability of US food and drug administration labeling for dapagliflozin to patients with heart failure with reduced ejection fraction in US clinical practice: the get with the guidelines–heart failure (GWTG-HF) registry. JAMA cardiology 6(3): 267-275.
16. Kurata, Yu, Nangaku, Masaomi (2022) Dapagliflozin for the treatment of chronic kidney disease. Expert Review of Endocrinology & Metabolism 17(4): 275-291.
17. Heerspink, Hiddo JL, et al. (2020) Dapagliflozin in patients with chronic kidney disease. New England Journal of Medicine 383(15): 1436-1446.
18. COX, Zachary L et al. (2024) Efficacy and safety of dapagliflozin in patients with acute heart failure. Journal of the American College of Cardiology 83(14): 1295-1306.
19. Anderson, John E, Wright JR, Eugene E, Shaefer JR, Charles F (2017) Empagliflozin: role in treatment options for patients with type 2 diabetes mellitus. Diabetes Therapy 8(1): 33-53.
20. Packer, Milton, et al. (2020) Cardiovascular and renal outcomes with empagliflozin in heart failure. New England Journal of Medicine 383(15): 1413-1424.
21. Anker, Stefan D et al. (2021) Empagliflozin in heart failure with a preserved ejection fraction. New England Journal of Medicine 385(16): 1451-1461.
22. Larkin, Howard D (2026) FDA expands empagliflozin heart failure indication. 2022. FDA Expands Empagliflozin Heart Failure Indication | Diabetes | JAMA | JAMA Network.
23. Jafar, Tazeen H (2021) FDA approval of dapagliflozin for chronic kidney disease: a remarkable achievement? The Lancet 398(10297): 283-284.
24. Grempler R et al. (2012) Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. Diabetes, Obesity and Metabolism 14(1): 83-90.
25. Wright Ernest M, Loo Donald DF, Hirayama, Bruce A (2011) Biology of human sodium glucose transporters. Physiological reviews 91(2): 733-794.
26. Johnston, Rhona, et al. (2017) Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health Technology Assessment 21(2): 1-218.
27. KU, Eu Jeong, et al. (2019) Empagliflozin versus dapagliflozin in patients with type 2 diabetes inadequately controlled with metformin, glimepiride and dipeptidyl peptide 4 inhibitors: a 52-week prospective observational study. Diabetes research and clinical practice 151: 65-73.
28. Reed, James W (2016) Impact of sodium–glucose cotransporter 2 inhibitors on blood pressure. Vascular Health and Risk Management pp. 393-405.
29. De Albuquerque Rocha, Natalia, et al. (2018) Effects of sodium glucose co-transporter 2 inhibitors on the kidney. Diabetes and Vascular Disease Research 15(5): 375-386.
30. Bonnesen, Kasper, et al. (2025) Effectiveness of empagliflozin vs dapagliflozin for kidney outcomes in type 2 diabetes. JAMA internal medicine 185(3): 314-323.
31. Engström, Arvid, et al. (2024) Comparative cardiovascular and renal effectiveness of empagliflozin and dapagliflozin: Scandinavian cohort study. European Heart Journal-Cardiovascular Pharmacotherapy 10(5): 432-443.
32. Lega, Iliana C, et al. (2019) Sodium glucose cotransporter 2 inhibitors and risk of genital mycotic and urinary tract infection: a population-based study of older women and men with diabetes. Diabetes, Obesity and Metabolism 21(11): 2394-2404.
33. Ogawa, Wataru; Sakaguchi, Kazuhiko (2015) Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. Journal of diabetes investigation 7(2): 135.
34. Zaccardi, Francesco, et al. (2016) Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes, Obesity and Metabolism 18(8): 783-794.
35. Bajaj, Mandeep, et al. (2026) cardiovascular disease and Risk Management: Standards of Care in Diabetes. Diabetes Care, 2026.
36. Meunier-Mcvey, Natasha (2021) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur heart J 42(36): 3599-3726.
37. De Boer, Ian H, et al. (2022) Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and kidney disease: Improving Global Outcomes (KDIGO). Diabetes care 45(12): 3075-3090.
38. Alnsasra, Hilmi, et al. (2023) Effect of dapagliflozin versus empagliflozin on cardiovascular death in patients with heart failure across the spectrum of ejection fraction: cost per outcome analysis. American Journal of Cardiovascular Drugs

23(3): 323-328.
39. Gourzoulidis, George, et al (2021) Cost-effectiveness of Empagliflozin compared with Dapagliflozin for the treatment of patients with type 2 diabetes mellitus and established cardiovascular disease in Greece. Clinical Drug Investigation 41(4): 371-380.
40. Roddick, Alistair J, et al. (2023) UK Kidney Association clinical practice guideline: sodium-glucose co-transporter-2 (SGLT-2) inhibition in adults with kidney disease 2023 update. BMC nephrology 24(1): 310.
41. Singh, Ajay K, Farag, Youssef MK; Agarwal, Rajiv (2023) Empagliflozin in patients with chronic kidney disease. New England Journal of Medicine 388(24): 2301.
42. León-Jiménez, David, et al. (2025) Kidney hemodynamic effects of sodium-glucose cotransporter 2 inhibitors in diabetes: physiology and clinical implications. Clinical kidney journal 18(1): sfae370.
43. Solomon, Scott D, et al. (2022) Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. New England Journal of Medicine 387(12): 1089-1098.
44. Vander Aart-Vander Beek, Annemarie B, De Boer, Rudolf A, Heerspink, Hiddo JL (2022) Kidney and heart failure outcomes associated with SGLT2 inhibitor use. Nature Reviews Nephrology 18(5): 294-306.
45. Halimi S, Vergès B (2014) Adverse effects and safety of SGLT-2 inhibitors. Diabetes & metabolism, 40(6): S28-S34.
46. Dutta, Siddhartha, et al. (2022) Euglycemic diabetic ketoacidosis associated with SGLT2 inhibitors: a systematic review and quantitative analysis. Journal of Family medicine and primary care 11(3): 927-940.
47. Bersoff-Matcha, Susan J et al. (2019) Fournier gangrene associated with sodium–glucose cotransporter-2 inhibitors: a review of spontaneous postmarketing cases. Annals of internal medicine 170(11): 764-769.
48. Maliha, Georg, Townsend, Raymond R (2015) SGLT2 inhibitors: their potential reduction in blood pressure. Journal of the American Society of Hypertension 9(1): 48-53.
49. Neal, Bruce, et al. (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. New England Journal of Medicine 377(7): 644-657.
50. Fralick, Michael, et al. (2021) Identifying risk factors for diabetic ketoacidosis associated with SGLT2 inhibitors: a nationwide cohort study in the USA. Journal of General Internal Medicine 36(9): 2601-2607.
51. Fioretto, Paola, et al. (2018) Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): The Derive Study. Diabetes, Obesity and Metabolism 20(11): 2532-2540.
52. Trial, Define-HF (2019) Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction. Circulation 140(18): 042929.
53. James S et al. (2024) Dapagliflozin in myocardial infarction without diabetes or heart failure. NEJM Evid 3: EVIDoa2300286. Přejít k původnímu zdroji... Přejít na PubMed.
54. Packer, Milton, et al. (2020) Cardiovascular and renal outcomes with empagliflozin in heart failure. New England Journal of Medicine 383(15): 1413-1424.
55. Anker, Stefan D, et al. (2021) Empagliflozin in heart failure with a preserved ejection fraction. New England Journal of Medicine 385(16): 1451-1461.
56. Verma, Subodh, et al. (2019) Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial. Circulation 140(21): 1693-1702.
57. Tromp, Jasper, et al. (2024) Treatment effects of empagliflozin in hospitalized heart failure patients across the range of left ventricular ejection fraction–Results from the EMPULSE trial. European journal of heart failure 26(4): 963-970.
58. Zelniker, Thomas A, et al. (2019) SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. The lancet 393(10166): 31-39.
59. Cherney, David ZI, et al. (2020) Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. The lancet Diabetes & endocrinology 8(7): 582-593.
60. Heise, Tim, et al. (2013) Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising doses of empagliflozin in patients with type 2 diabetes mellitus. Diabetes therapy 4(2): 331-345.
61. Bailey CJ et al. (2015) Efficacy and safety of dapagliflozin monotherapy in people with type 2 diabetes: a randomized double-blind placebo-controlled 102-week trial. Diabetic Medicine 32(4): 531-541.
62. Häring, Hans-Ulrich, et al. (2014) Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes care 37(6): 1650-1659.
63. Wang, Lina, et al. (2023) Non-traditional risk factors as contributors to cardiovascular disease. Reviews in Cardiovascular Medicine 24(5): 134.
64. Bonora, Benedetta Maria, Avogaro, Angelo, Fadini, Gian Paolo (2020) Extraglycemic effects of SGLT2 inhibitors: a review of the evidence. Diabetes, Metabolic Syndrome and Obesity pp. 161-174.
65. Vallon, Volker, Verma, Subodh (2021) Effects of SGLT2 inhibitors on kidney and cardiovascular function. Annual review of physiology 83(1): 503-528.