Thesis

SGLT2 Inhibitors in Heart Failure: A Systematic Review of Therapeutic Effects Across Ejection Fraction and Diabetic Status

submitted by

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Acknowledgements

This diploma thesis, titled *"SGLT2 Inhibitors in Heart Failure: A Systematic Review of Therapeutic Effects Across Ejection Fraction and Diabetic Status"*, focuses on the use of SGLT2 inhibitors in patients with heart failure, with particular attention to their efficacy in both diabetic and non-diabetic populations. It was conducted at the Department of Pharmacology under the supervision of Dr. Reham Atallah and Univ.-Prof. Dr. Akos Heinemann.

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Zusammenfassung

Hintergrund

Herzinsuffizienz stellt eine der führenden Ursachen für Morbidität und Mortalität weltweit dar. Natrium-Glukose-Kotransporter 2 (SGLT2)-Inhibitoren, ursprünglich als Antidiabetika entwickelt, haben sich in den letzten Jahren als potenziell krankheitsmodifizierende Therapieoption bei Herzinsuffizienz etabliert, unabhängig von der Ejektionsfraktion oder dem Vorliegen eines Diabetes mellitus.

Zielsetzung

Ziel dieser systematischen Übersichtsarbeit war es, den aktuellen Stand der Evidenz zur Wirksamkeit von SGLT2-Inhibitoren bei erwachsenen Patientinnen und Patienten mit Herzinsuffizienz zusammenzufassen. Dabei wurden Unterschiede in der Wirkung zwischen heart failure with reduced ejection fraction (HFrEF) und heart failure with preserved ejection fraction (HFpEF) sowie bei Patient:innen mit und ohne Diabetes untersucht.

Methoden

Die Literatursuche wurde gemäß PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)-Kriterien in PubMed durchgeführt. Es wurden randomisierte kontrollierte Studien (RCTs) aus dem Zeitraum 2020–2025 eingeschlossen, die SGLT2-Inhibitoren mit Placebo oder Standardtherapie bei Herzinsuffizienz verglichen und mindestens einen der vordefinierten Endpunkte berichteten (Gesamtmortalität, kardiovaskuläre Mortalität, kardiovaskuläre Ereignisse, Hospitalisierung aufgrund von Herzinsuffizienz, Lebensqualität). Die Risikoanalyse erfolgte anhand von Version 2 of the Cochrane Risk-of-Bias tool (RoB2).

Ergebnisse

Sieben RCTs mit insgesamt über 20.000 Patient:innen wurden in die qualitative Synthese eingeschlossen. Der konsistenteste therapeutische Effekt zeigte sich in der signifikanten Reduktion von Hospitalisierungen bei Herzinsuffizienz, sowohl bei HFrEF als auch HFpEF, unabhängig vom Diabetesstatus. Verbesserungen der Lebensqualität, erhoben mit dem Kansas City Cardiomyopathy Questionaire (KCCQ), wurden in mehreren Studien dokumentiert. Ein moderater Trend zur Senkung der Gesamt- und kardiovaskulären Mortalität war vor allem bei HFrEF nachweisbar, blieb bei HFpEF jedoch uneinheitlich. Die Wirkung war auch bei nicht-

diabetischen Patient:innen erkennbar, was auf einen Mechanismus jenseits der glykämischen Kontrolle hinweist.

Schlussfolgerung

SGLT2-Inhibitoren stellen eine wirksame und breit anwendbare Therapieoption bei Herzinsuffizienz dar. Ihre Wirkung erstreckt sich über verschiedene Subtypen der Erkrankung sowie unabhängig vom Vorliegen eines Diabetes. Die Ergebnisse dieser Übersichtsarbeit stärken die Rolle von SGLT2-Inhibitoren als krankheitsmodifizierende Substanzen und unterstreichen ihr Potenzial in der klinischen Praxis.

Abstract

Background

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a novel therapeutic option in heart failure (HF), originally introduced for the management of type 2 diabetes. Recent evidence has highlighted their cardiovascular and renal benefits in both diabetic and non-diabetic patients with HF. However, their efficacy across the full spectrum of HF phenotypes, particularly in regard to key clinical outcomes, remains an area of active investigation.

Aims and Objectives

This systematic review aims to evaluate the effects of SGLT2 inhibitors on major clinical outcomes, namely all-cause mortality, cardiovascular mortality, hospitalization for heart failure, cardiovascular events, and quality of life (QoL), in adult patients with HF, stratified by ejection fraction phenotype and diabetic status.

Methods

A systematic PubMed search was conducted for randomized controlled trials (RCTs) published between January 2020 and March 2025. Inclusion was limited to primary RCTs examining SGLT2 inhibitors versus placebo or standard therapy in adult patients with HF. Data extraction and analysis were performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, and bias was assessed using Version 2 of the Cochrane Risk-of-Bias tool (RoB2). Seven high-quality RCTs met all inclusion criteria and were included in the final synthesis.

Results

Seven RCTs were included: DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved, DAPA HFpEF, EMPA-TROPISM and SUGAR-DM-HF, each targeting distinct population stratified by ejection fraction phenotype and/or diabetes status. SGLT2 inhibitors demonstrated a consistent reduction in HF-related hospitalizations across both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) populations. A modest improvement in all-cause and cardiovascular mortality was observed, primarily in HFrEF patients. Improvements in QoL were also reported in several trials. Notably, these benefits extended to patients without diabetes, suggesting a mechanism

of action beyond glycemic control. The findings were supported by recent meta-analyses, which further emphasized a class effect across diverse patient subgroups.

Conclusion

This review supports the use of SGLT2 inhibitors as a disease-modifying therapy in heart failure, independent of left ventricular ejection fraction or diabetic status. Their consistent benefit in reducing hospitalizations, along with potential effects on mortality and QoL, positions them as a foundational treatment in the evolving landscape of HF management.

Publication

At the time of submission, this thesis had not been published.

Index

List of Abbreviations

Abbreviation	Full Description
CI	Confidence Interval
CKD	Chronic Kidney Disease
DKA	Diabetic Ketoacidosis
eGFR	Estimated Glomerular Filtration Rate
HF	Heart Failure
HFmrEF	Heart Failure with Mildly Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
HHF	Hospitalization for Heart Failure
HR	Hazard Ratio
KCCQ-CS	Kansas City Cardiomyopathy Questionnaire Clinical Summary Score
LVEF	Left Ventricular Ejection Fraction
MeSH	Medical Subjects Heading
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
NYHA	New York Heart Association
QoL	Quality of Life
RAAS	Renin Angiotensin Aldosterone System
RCT	Randomized Controlled Trial
RoB2	Cochrane Risk of Bias Assessment, Version 2
SGLT1	Sodium-Glucose Cotransporter 1
SGLT2	Sodium-Glucose Cotransporter 2
T2DM	Type 2 Diabetes Mellitus
TmG	Maximum Transport Capacity
UGT	UDP-Glucuronosyltransferase

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1. Introduction

1.1. Clinical Background of Heart Failure

1.1.1. Definitions and Classifications

Heart failure (HF) is not a singular disease entity, but a clinical syndrome defined by typical symptoms such as dyspnea, fatigue, and peripheral edema, often accompanied by objective signs including elevated jugular venous pressure, pulmonary rales, or peripheral swelling (1, 2). These manifestations result from structural or functional abnormalities of the heart, which impair cardiac output and/or elevate intracardiac pressures, particularly under exertion. While myocardial dysfunction, either systolic, diastolic, or both, is the most frequent underlying mechanism, valvular disease, pericardial pathology, and arrhythmias may also contribute to the development of HF (1, 3).

Globally, over 64 million people are currently living with HF, with prevalence increasing significantly with age (4). Despite substantial advances in cardiovascular care, the five-year mortality rate remains around 50%, comparable to that of many cancers (4). HF also imposes a significant burden on health systems, accounting for up to 2% of total healthcare expenditure in high-income countries (4).

HF is traditionally classified into different phenotypes based on left ventricular ejection fraction (LVEF), which serves as a surrogate marker of systolic function (1, 5). This classification emerged from early clinical trials, which demonstrated significant therapeutic benefits in patients with LVEF ≤40% (1). Although LVEF is a continuous parameter and can vary between observers, especially when assessed by echocardiography, it still plays a key role in the diagnosis and management of HF (1, 6). Based on specific LVEF ranges, current guidelines distinguish between distinct HF subtypes, as originally defined by Paulus et al (3).

HF with reduced ejection fraction (HFrEF) is defined as LVEF of 40% or less and reflects a clear impairment in the pumping function of the left ventricle (1, 6). An LVEF between 41% and 49% is referred to as HF with mildly reduced ejection fraction (HFmrEF) (1, 5). This

term has replaced the older term “mid-range”, patients in this range (LVEF 41-49%) have demonstrated treatment responses to sodium-glucose cotransporter 2 (SGLT2) inhibitors comparable to those observed in HFrEF, as evidenced by trials such as DELIVER and EMPEROR-Preserved (7, 8).

In contrast, patients with an LVEF of 50% or higher, who also present with signs and symptoms of HF, along with structural heart abnormalities or elevated natriuretic peptides, are diagnosed with HF with preserved ejection fraction (HFpEF) (1). This phenotype is particularly relevant in elderly, often female patients with comorbidities such as hypertension, obesity, or type 2 diabetes (T2DM), a clinical profile frequently observed in major trials such as DELIVER and EMPEROR-Preserved (7, 8).

The prevalence of HF phenotypes is not equally distributed (7, 8). According to data from the European Society of Cardiology (ESC) Long-Term Registry and original registry publications, approximately 60% of patients have HFrEF, 24% have HFmrEF, and 16% have HFpEF (1, 9).

In addition to the structural classification based on left ventricular function, the New York Heart Association (NYHA) functional classification is widely used to assess symptom severity and exercise tolerance in patients with HF (1, 10). It ranges from class I, indicating no limitation of physical activity, to class IV, describing symptoms at rest (1, 10). Although not based on cardiac imaging, the NYHA classification remains a key tool in clinical practice and is frequently employed as an inclusion criterion in clinical trials, with its prognostic validity supported by observational studies (1, 11). **Table 1** provides a structured overview of the NYHA classification, which categorizes the severity of HF symptoms based on physical activity tolerance.

Table 1: NYHA classification of HF by symptom severity and functional limitation.
Adapted from the European Society of Cardiology guidelines (1).

Class I	No symptoms or restrictions during daily physical activity; patients can perform normal exertion without experiencing shortness of breath, fatigue, or palpitations.
Class II	Mild limitation of physical activity; patients are asymptomatic at rest but experience symptoms such as breathlessness, fatigue, or palpitations during regular exertion.
Class III	Noticeable limitation of physical activity; patients remain symptom-free at rest but experience discomfort even with less-than-ordinary activity.
Class IV	Inability to perform any physical activity without discomfort; symptoms may occur even at rest and intensify with minimal exertion.

Abbreviations: NYHA = New York Heart Association; HF = heart failure.

1.1.2. Pathophysiological Mechanisms of HF

HFrEF is primarily characterized by impaired left ventricular contractility, resulting in systolic dysfunction, progressive ventricular dilation, and a reduction in ejection fraction (1). The condition often follows myocardial damage, such as that caused by ischemia or inflammation (12). These changes activate neurohormonal systems including the Renin-Angiotensin-Aldosterone System (RAAS) and the sympathetic nervous system, which initially compensate but ultimately contribute to further myocardial remodeling and deterioration (12).

In contrast, HFpEF is defined by preserved systolic function but impaired diastolic relaxation and compliance. Patients typically exhibit increased ventricular stiffness, delayed myocardial relaxation, and elevated filling pressures. The pathogenesis involves systemic inflammation, endothelial dysfunction, and myocardial fibrosis, often driven by comorbidities such as hypertension, diabetes, or obesity. Unlike in HFrEF, cardiac output at rest is often maintained but becomes insufficient during physical activity due to impaired filling dynamics (13). While both conditions result in similar symptoms, most notably exertional dyspnea, their distinct pathophysiological profiles have important implications for diagnosis and therapeutic strategies (13).

1.1.3. Evidence-Based Treatment in HFrEF and Therapeutic Challenges in HFpEF

Evidence-based therapies have been shown to improve both symptoms and prognosis in patients with HFrEF, whereas no such outcome benefit has yet been established for HFpEF (1).
Due to their distinct pathophysiological mechanisms, treatment outcomes differ; however, both HFrEF and HFpEF show increasing incidence and remain associated with high mortality (4).

The pharmacological management of HF depends largely on the patient's ejection fraction. For individuals with HFrEF, four major drug classes have demonstrated significant reductions in both mortality and hospitalization risk and are therefore recommended as standard therapy.

These include:

1. RAAS inhibitors (either angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor–neprilysin inhibitors)
2. beta-blockers
3. mineralocorticoid receptor antagonists
4. SGLT2 inhibitors.

Diuretics may be added to relieve symptoms in patients with signs of fluid overload, although they have not been shown to improve long-term outcomes (1).

In contrast, the evidence base for patients with HFpEF has remained limited for many years (1). Most pharmacological strategies used in this group have failed to consistently improve survival or reduce HF hospitalizations. As a result, the treatment of HFpEF has historically focused on symptom control and the management of comorbidities, such as hypertension, atrial fibrillation, or diabetes. This lack of effective, evidence-based therapy for HFpEF has long been recognized as a major unmet clinical need (1, 8).

The publication of the EMPEROR-Preserved trial in 2021 marked a turning point by demonstrating that the SGLT2 inhibitor empagliflozin significantly reduced the composite endpoint of cardiovascular death or HF hospitalization in patients with HFpEF (8). These

findings provided the first robust evidence of benefit for a pharmacological agent in this population (8).

1.2. Introduction to SGLT2 Inhibitors and Their Mechanism of Action

1.2.1. Pharmacological Background and Role in Type 2 Diabetes

SGLT2 inhibitors represent a novel class of oral antidiabetic drugs that lower blood glucose by promoting urinary glucose excretion, independent of insulin secretion or action (14). This insulin-independent mechanism offers key therapeutic advantages, including a low intrinsic risk of hypoglycaemia (14). In clinical trials, SGLT2 inhibitors have consistently demonstrated meaningful reductions in Haemoglobin A1c (HbA1c), body weight, and systolic blood pressure in patients with T2DM (14-16).

Dapagliflozin was the first highly selective SGLT2 inhibitor approved by the European Medicines Agency (EMA) in 2012 for use as monotherapy or in combination with other antidiabetic agents in cases of insufficient glycaemic control (14). Its glycaemic benefits are evident across different treatment regimens, including as an add-on therapy to metformin, sulfonylureas, or insulin (14). In addition to improving fasting and postprandial glucose levels, dapagliflozin therapy leads to sustained weight reduction, primarily via loss of fat mass, as demonstrated by dual-energy X-ray absorptiometry (DEXA) assessments (14, 17).

While SGLT2 inhibitors were originally developed as antidiabetic agents, large cardiovascular outcome trials unexpectedly revealed a profound benefit in patients with HF. Subgroup analyses from trials such as EMPA-REG OUTCOME and the CANVAS Program demonstrated that the reduction in hospitalizations for HF and cardiovascular death was not limited to individuals with established HF but extended to those without a prior diagnosis. This led to the hypothesis that many participants may have had undiagnosed HFpEF or HFrEF, thus broadening the therapeutic potential of SGLT2 inhibitors beyond glycemic control (18-20).

1.2.2. Molecular Mechanisms of SGLT2 Inhibitors

SGLT2 inhibitors act by blocking glucose and sodium reabsorption in the proximal renal tubule, leading to glycosuria and natriuresis (16). This results in osmotic diuresis, which lowers intravascular volume and subsequently reduces both cardiac preload and afterload (16). Additionally, the natriuretic effect contributes to a decrease in systolic blood pressure and alleviates glomerular hyperfiltration, offering renoprotective benefits, especially in patients with concomitant kidney disease (16).

Beyond their glucose-lowering properties, SGLT2 inhibitors exert a range of pleiotropic effects (16). These include improved myocardial energy efficiency through enhanced ketone utilization, reduction of pro-inflammatory cytokines, attenuation of oxidative stress, and antifibrotic actions in cardiac tissue (16). Collectively, these mechanisms support hemodynamic stabilization and myocardial protection, which may explain the significant reductions in HF hospitalizations and cardiovascular mortality observed in clinical outcome trials (16).

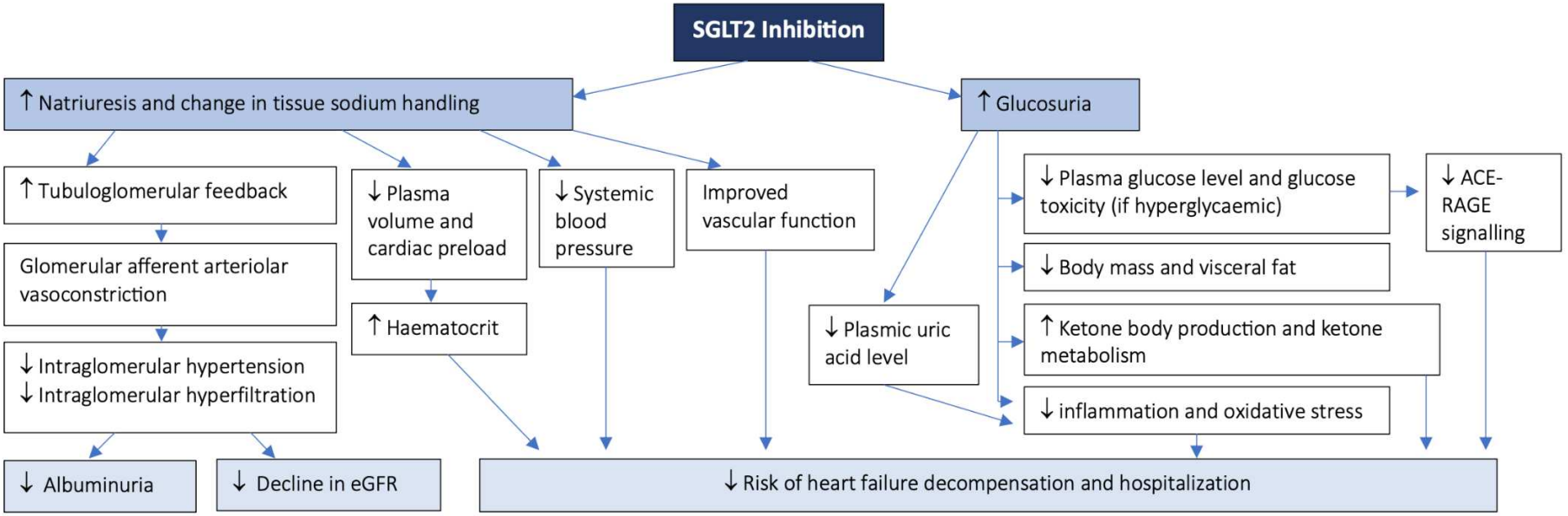


Figure 1: Effects of SGLT2 inhibition (1). Figure 1 describes the integrated effects of SGLT2 inhibitors likely to produce cardiovascular and renal benefits. Abbreviations: ACE = angiotensin-converting enzyme; RAGE = receptor for advanced glycation endproducts, eGFR = estimated glomerular filtration rate.

1.2.3. Clinical Pharmacology and Safety Profile of SGLT2 Inhibitors

Several SGLT2 inhibitors have been developed for clinical use in recent years. The most widely studied agents include dapagliflozin, empagliflozin, ertugliflozin and canagliflozin**.** These drugs share a common mechanism of action but differ in their pharmacokinetic properties, approved indications, and supporting clinical trial data.

1.2.3.1. Pharmacodynamics

SGLT2 inhibitors exert their glucose-lowering effect by enhancing urinary glucose excretion. This occurs through a reduction in both the renal threshold for glucose reabsorption and the maximum transport capacity (TmG) for filtered glucose (15). Under normal physiological conditions, glucose is freely filtered in the glomerulus and nearly completely reabsorbed in the proximal tubule. SGLT2, located in the S1 segment of the proximal tubule, is responsible for reabsorbing approximately 90% of the filtered glucose load, while sodium-glucose cotransporter 1 (SGLT1), found in the more distal S2/S3 segments, accounts for the remaining 10% (21). The driving force for this active reabsorption is a sodium gradient established by the Na^+/K^+ Adenosintriphosphatase (ATPase) on the basolateral membrane. The glucose is subsequently transported into the bloodstream via glucose transporter 1 (GLUT1) and glucose transporter 2 (GLUT2) (15, 22).

In individuals with T2DM, increased expression of SGLT2 has been observed, leading to an elevation of the TmG and enhanced renal glucose reabsorption, thereby worsening hyperglycemia (23, 24). SGLT2 inhibitors reverse this maladaptive response by decreasing TmG and lowering the threshold for glucose reabsorption. For example, dapagliflozin has been shown to reduce TmG by over 50% and lower the threshold for glycosuria from approximately 180 mg/dL to between 40 and 80 mg/dL (21, 25-27).

Despite SGLT2's role in reabsorbing 90% of filtered glucose, SGLT2 inhibitors only increase urinary glucose excretion by about 80 g/day, or less than 50% of the filtered glucose load (21). This is due to the compensatory activity of SGLT1, which remains functionally intact and reabsorbs a significant portion of glucose downstream when SGLT2 is inhibited (21). Thus, SGLT2 inhibition alone does not lead to complete glycosuria, but the observed pharmacodynamic effect is nonetheless clinically relevant and reproducible (21).

Beyond their glucosuric effect, SGLT2 inhibitors exert a range of clinically relevant pharmacodynamic actions that extend to the cardiovascular and renal systems. These agents have consistently demonstrated blood pressure–lowering effects, typically reducing systolic blood pressure by 3–5 mmHg, likely through natriuresis, osmotic diuresis and reduced arterial stiffness (28). Additionally, SGLT2 inhibitors are associated with modest reductions in body weight and serum uric acid levels, further contributing to their cardiometabolic benefits (29).

From a cardiovascular standpoint, SGLT2 inhibitors improve cardiac function by decreasing preload and afterload, reducing intravascular volume, and possibly modulating myocardial energetics (30). These hemodynamic effects are complemented by anti-inflammatory and antifibrotic mechanisms observed in experimental studies (16, 31). Notably, large-scale randomized controlled trials (RCTs) such as DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved have shown significant reductions in the risk of cardiovascular death or hospitalization for HF, irrespective of diabetes status (8, 31, 32).

Regarding nephroprotection, SGLT2 inhibitors reduce intraglomerular pressure via tubuloglomerular feedback, stabilize estimated glomerular filtration rate (eGFR) decline and decrease albuminuria (33). These effects have been confirmed across multiple trials and are thought to be independent of glycemic control (33, 34). The multifaceted pharmacodynamic profile of SGLT2 inhibitors thus underpins their expanding role in the management of HF and chronic kidney disease (CKD) (35).

1.2.3.2. Pharmacokinetics

To illustrate the pharmacokinetic properties of SGLT2 inhibitors, empagliflozin was selected as a representative compound (36). This choice is justified by the fact that empagliflozin is one of the most extensively studied agents within this drug class and has been investigated in a wide range of clinical settings. Its pharmacokinetic profile is considered typical for SGLT2 inhibitors and provides a reliable basis for general understanding (36). Key parameters such as absorption, half-life, metabolism and excretion are well characterized and reflect class-wide features that are relevant for clinical use (36).

Empagliflozin is rapidly absorbed from the gastrointestinal tract following oral administration, with peak plasma concentrations typically occurring within 1.5 to 3 hours (36). After reaching peak levels, plasma concentrations decline in a two-phase manner,

initially through rapid distribution, followed by slower elimination. Across the tested dose range from 2.5 to 100 mg, both systemic exposure and peak concentrations increased in an approximately linear, dose-proportional fashion (36).

The drug exhibits extensive binding to plasma proteins, primarily albumin, with a binding rate consistently reported to be over 85%, which supports its stable pharmacokinetic profile across therapeutic doses (34). Empagliflozin undergoes limited hepatic metabolism, with glucuronidation to inactive metabolites representing the major biotransformation route. Oxidative metabolism via cytochrome P450 (CYP450) enzymes plays only a minor role, thus minimizing the risk for drug–drug interactions, as already observed in clinical trials (29, 35).

Steady-state pharmacokinetics of empagliflozin are achieved by day five of repeated dosing, with trough plasma levels remaining stable from day five through day eight (36). At steady state, the concentration–time curve closely resembles that of the single-dose profile, supporting linear and time-independent kinetics (36). The terminal elimination half-life varies depending on dose and steady-state status but typically ranges between 10 and 18 hours, which supports once-daily dosing in clinical practice (36).

Drug accumulation is modest, with up to 23% increase in steady-state levels compared to single-dose administration (36). Renal clearance contributes to the elimination pathway, with values ranging from approximately 15 to 29 mL/min following a single dose and increasing to around 23 to 34 mL/min at steady state (36). The overall similarity between single-dose and steady-state pharmacokinetics confirms that Empagliflozin exhibits predictable and linear behavior over time (36).

1.2.3.3. Adverse Effects

To maintain consistency with the preceding sections, empagliflozin will again serve as the reference compound for the discussion of adverse effects, contraindications, and drug interactions. Its extensive clinical evaluation and regulatory documentation make it a suitable representative of the SGLT2 inhibitor class for illustrating safety-related considerations.

Empagliflozin is generally well tolerated, yet several adverse effects warrant clinical attention. Among the most frequently reported are genital infections, particularly vulvovaginitis and balanitis, which are more common in female patients and are usually mild to moderate in severity, responding well to standard treatment (36-38). Urinary tract

infections have also been observed, including severe cases such as pyelonephritis and urosepsis, as well as rare instances of Fournier's gangrene (37, 39). Patients frequently report increased urination and thirst due to the osmotic diuretic effect of glucosuria, and should be instructed to seek prompt medical attention if symptoms become severe or persistent (37). Persistent glucosuria may interfere with urine glucose testing but does not indicate poor glycemic control (37).

Volume depletion is a key safety concern with SGLT2 inhibitors, particularly in elderly patients or those receiving diuretics or antihypertensives (37, 40). It may manifest as symptomatic hypotension or dizziness and has been observed more frequently in patients aged 75 years or older (37, 40). Osmotic diuresis is the likely mechanism, and careful monitoring of blood pressure and hydration status is essential (37). Temporary treatment discontinuation is recommended prior to major surgery or during severe illness. Increases in hematocrit and mild electrolyte imbalances have also been reported (37).

One of the most serious and rare complications associated with SGLT2 inhibitors is diabetic ketoacidosis (DKA), which can occur even in the absence of significant hyperglycemia or with only moderately elevated glucose levels and has been reported even in non-diabetic individuals. Atypical symptoms such as nausea, abdominal pain, fatigue, or dyspnea should prompt immediate evaluation and discontinuation of treatment if DKA is suspected. This is particularly important in high-risk patients, including those with reduced insulin secretion (e.g., latent autoimmune diabetes in adults (known as LADA), history of pancreatitis), prolonged fasting, or acute illness (37). DKA requires immediate drug discontinuation and medical intervention.

Another, although very rare, adverse event is Fournier's gangrene, a necrotizing soft tissue infection of the perineum requiring urgent surgical treatment (37). While a potential class effect has not been confirmed, an increased risk of lower limb amputation has been observed in the CANVAS trial with canagliflozin, whereas such a risk was not consistently reported for empagliflozin or dapagliflozin (41). This risk was particularly elevated in patients with peripheral artery disease, prior amputations, or diabetic neuropathy (39). Therefore, appropriate foot care is recommended (37, 42).

1.2.3.4. Drug Interactions

Empagliflozin can potentiate the diuretic effect when co-administered with loop or thiazide diuretics, potentially increasing the risk of dehydration and hypotension (37). Additionally, co-administration with insulin or insulin secretagogues such as sulfonylureas may elevate the risk of hypoglycemia, and dosage adjustments should be considered (37).

From a pharmacokinetic perspective, empagliflozin is predominantly metabolized via UDP-glucuronosyltransferase (UGT)-mediated glucuronidation (37). While interactions with UGT enzyme inhibitors (e.g., probenecid) or inducers (e.g., rifampicin) may influence plasma levels of empagliflozin, although these changes are not typically of clinical relevance (37). Moreover, empagliflozin is a substrate for several transporters, including organic anion transporter 3 (OAT3), organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1/1B3), P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). However, no significant interactions have been observed with commonly prescribed concomitant medications (37).

1.2.3.5. Contraindications

Empagliflozin is contraindicated in patients with significantly impaired kidney function, specifically those with an eGFR below 30 mL/min/1.73 m^2, individuals with end-stage renal disease, or patients requiring dialysis, as its safety and efficacy in these groups have not been established (37). Additionally, its use is contraindicated in persons with known hypersensitivity to Empagliflozin or to any component of the drug formulation, including excipients such as lactose monohydrate, microcrystalline cellulose, and hydroxypropylcellulose (37).

Additional precautions include potential for liver injury, elevated hematocrit levels, and reduced glycemic efficacy in patients with impaired renal function (37, 43). Finally, due to the presence of lactose, empagliflozin is contraindicated in patients with rare hereditary disorders such as galactose intolerance or lactase deficiency (37).

1.2.4. Regulatory Status and Approved Indications

Empagliflozin has been authorized in the European Union as an oral antidiabetic agent and is available under the brand name Jardiance. Initially approved for the treatment of adults with T2DM to improve glycemic control, its indications have since been expanded based on clinical evidence (37).

Currently, Empagliflozin is also approved for the treatment of adults with symptomatic chronic HF, regardless of ejection fraction, in order to reduce the risk of cardiovascular death and hospitalization for HF. In addition, it is indicated to delay the progression of kidney disease in adult patients with T2DM and existing CKD (37).

Dapagliflozin, marketed as Forxiga, is similarly approved for HFrEF and HFpEF, CKD, and T2DM in the European Union (EMC, 2024). Both empagliflozin and dapagliflozin are used at a recommended dose of 10 mg once daily.

Ertugliflozin, marketed as Steglatro, is currently only approved for the treatment of T2DM (44). Canagliflozin, marketed as Invokana, is not approved for use in the European Union but has marketing authorization for T2DM in other regions. Its use is contraindicated in patients at high risk of amputation (39).

Table 2: **Overview of selected SGLT2 inhibitors including trade names, dosing, clinical indications (as of 2025) and remarks on clinical evidence.** Data are based on high-quality trials including DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved and CANVAS (7, 8, 31, 41, 45).

Agent	Trade Name	EU Indications (2025)	HF Dosage	Clinical Notes
Dapagliflozin	Forxiga	HFrEF, HFpEF, CKD, T2DM	10mg once daily	Effective down to eGFR ≥25 mL/min; DELIVER trial supported HFpEF use
Empagliflozin	Jardiance	HFrEF, HFpEF, T2DM	10mg once daily	Broad evidence from EMPEROR trials; well tolerated
Ertugliflozin	Steglatro	T2DM only	-	Not approved for HF; T2DM only

Canagliflozin	Invokana	Not approved in EU	-	CANVAS: linked to amputation risk; not approved for HF

Abbreviations: HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; T2DM = type 2 diabetes mellitus; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

1.3. Evidence Development and Landmark Trials

Over the last decade, a substantial body of clinical evidence has accumulated, demonstrating the cardiovascular benefits of SGLT2 inhibitors (16). Initially developed for glycaemic control in T2DM, these agents have shown robust effects in reducing hospitalizations for HF and cardiovascular death across a range of patient populations (32). The unexpected cardiovascular efficacy observed in early diabetes trials prompted a paradigm shift and led to the design of large-scale RCTs in patients with established HF (46). Four pivotal trials, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved and DELIVER, form the cornerstone of current clinical understanding and guideline recommendations (1).

The DAPA-HF trial**,** published in 2019, was the first dedicated HF trial to evaluate the efficacy of a SGLT2 inhibitor in patients with HFrEF (32). This double-blind RCT enrolled 4,744 patients with LVEF ≤40%, NYHA class II–IV, and elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, a biomarker reflecting cardiac wall stress that is widely used to assess the severity and prognosis of HF (32). Importantly, approximately 55% of participants did not have T2DM, allowing for a robust analysis of glycaemia-independent effects. Treatment with dapagliflozin 10 mg daily significantly reduced the risk of worsening HF or cardiovascular death compared to placebo (hazard ratio [HR] 0.74; 95% confidence interval [CI], 0.65–0.85; $p < 0.001$). The benefit was consistent across diabetic and non-diabetic subgroups, establishing for the first time that SGLT2 inhibition conferred clinical benefit beyond glucose lowering (32).

Following this, the EMPEROR-Reduced trial**,** published in 2020, confirmed and extended these findings. In this trial, 3,730 patients with symptomatic HFrEF (LVEF ≤40%) were randomized to receive empagliflozin 10mg daily or placebo in addition to optimal medical therapy. Empagliflozin significantly reduced the combined risk of cardiovascular death or hospitalization for HF (HR 0.75; 95% CI, 0.65–0.86; $p < 0.001$), with a notable reduction in

first and recurrent hospitalizations. Consistent with DAPA-HF, the effect was observed in both diabetic and non-diabetic patients, underscoring the class-wide cardioprotective effects of SGLT2 inhibitors (31).

While the DAPA-HF and EMPEROR-Reduced trials established the role of SGLT2 inhibitors in HFrEF, their efficacy in HFpEF remained uncertain. This gap was addressed by the EMPEROR-Preserved trial**,** published in 2021. The trial included 5,988 patients with HF symptoms and LVEF >40%, making it the first major RCT to target the HFpEF population. Empagliflozin 10 mg daily led to a significant reduction in the composite primary outcome of cardiovascular death or hospitalization for HF (HR 0.79; 95% CI, 0.69–0.90; $p < 0.001$), driven primarily by fewer hospitalizations. Although the reduction in cardiovascular mortality alone was not statistically significant, the trial provided the first robust evidence of benefit for any pharmacological therapy in HFpEF (8).

Building upon these findings, the DELIVER trial**,** published in 2022, evaluated dapagliflozin in a similar HFpEF patient population with LVEF >40%. Enrolling over 6,200 patients, the trial demonstrated an 18% relative risk reduction in the composite endpoint of worsening HF or cardiovascular death (HR 0.82; 95% CI, 0.73–0.92; $p < 0.001$). Unlike EMPEROR-Preserved, DELIVER showed consistent efficacy across the full spectrum of LVEF, including in patients with HFmrEF. These results further solidified the indication of SGLT2 inhibitors in a broader HF population, regardless of ejection fraction (7).

Despite the overall consistent results, several important differences and limitations across these major trials warrant attention. The trials varied in key aspects including inclusion criteria, baseline LVEF thresholds, diabetic status, and definitions of primary endpoints (1). For instance, DELIVER and EMPEROR-Preserved included patients with ejection fractions as low as 41%, potentially introducing overlap with HFmrEF (7, 8). Moreover, some studies, such as EMPEROR-Preserved, excluded patients with recent hospitalization (8). Additionally, while all trials confirmed reductions in HF hospitalizations, the impact on all-cause and cardiovascular mortality was more variable, particularly in HFpEF, where statistical significance was often not reached (7, 8).

Collectively, these landmark trials have established SGLT2 inhibitors as a foundational therapy in chronic HF, regardless of ejection fraction or diabetes status (1). Nevertheless, important gaps persist in the understanding of long-term outcomes, subgroup-specific effects,

and real-world applicability, especially concerning quality of life (QoL) measures, acute HF presentations, and patients without overt metabolic comorbidities (8, 16).

1.4. Scientific Gap and Rationale

Over the past years, large RCTs have established the efficacy of SGLT2 inhibitors in HF (32). However, none of these trials were designed with a primary focus on comparing outcomes between diabetic and non-diabetic subgroups**,** which represents a major gap in the evidence base (31, 32). While subgroup analyses in DAPA-HF and EMPEROR-Reduced suggested consistent benefits across glycemic status, these observations remained secondary findings rather than prespecified targets of investigation (46).

Furthermore, although SGLT2 inhibitors have been tested in both HFrEF and HFpEF populations, there is a lack of integrated analysis across the full spectrum of ejection fraction (1). To date, trials like EMPEROR-Preserved and DELIVER have primarily focused on HFpEF but often did not stratify results according to diabetic status, and existing meta-analyses typically remain phenotype-specific (7, 8). This leaves unresolved questions about whether diabetic status modifies treatment effects across EF subtypes (1).

In addition, key outcomes such as QoL and cardiovascular death were either secondary endpoints or not consistently powered across trials, especially in HFpEF cohorts, where mortality benefits failed to reach statistical significance (7, 8). Consequently, clinicians must extrapolate these results for broader patient populations, introducing uncertainty into guideline recommendations and real-world prescribing practices (1, 46).

Therefore, a comprehensive, systematic review comparing clinical outcomes of SGLT2 inhibitors by diabetic status in both HFrEF and HFpEF is timely and essential. Such a synthesis enhances evidence-based decision-making by clarifying whether benefits extend equivalently to non-diabetic patients and across ejection fraction phenotypes, thus informing future guideline updates and optimizing individualized patient care (1, 46).

1.5. Aim and Research Question

Building upon identified knowledge gaps, this review utilizes a structured PICO framework to evaluate whether SGLT2 inhibitors improve key clinical outcomes including all-cause

mortality, cardiovascular mortality, hospitalization for HF, major cardiovascular events, and patient-reported QoL, in adult patients with HF, both with reduced and preserved ejection fraction, and whether these effects differ between diabetic and non-diabetic individuals. The primary hypothesis is that these cardioprotective benefits are consistent across glycemic subgroups and ejection fraction phenotypes, supporting a unified therapeutic approach. This analysis aims to generate robust, diabetes-stratified evidence to inform future recommendations and optimize personalized care.

2.Methods

2.1. Study Design and Protocol

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines and was in accordance with the framework of the Medical University of Graz and the principles of good scientific practice. Although not registered in the Prospective Register of Systematic Review Protocols (PROSPERO) due to institutional policy, all methodological procedures were defined a priori to ensure transparency and reduce the risk of bias.

2.2. PICO-Framework

The PICO model is a well-established framework in evidence-based medicine used to structure clinically relevant and answerable research questions. The acronym PICO stands for Population, Intervention, Comparison, and Outcome. By clearly defining these four core elements, the model facilitates a systematic and transparent approach to literature searching, eligibility assessment, and study synthesis.

In this systematic review, the PICO framework served as the conceptual foundation for both the formulation of the research question and the definition of the inclusion and exclusion criteria. The resulting clinical question was structured as follows:

- **Population (P):** Adult patients (≥18 years) diagnosed with HF, including those with HFrEF and/or HFpEF, with or without concomitant T2DM.
- **Intervention (I):** Treatment with SGLT2 inhibitors, specifically dapagliflozin, empagliflozin, and ertugliflozin.
- **Comparison (C):** Placebo or standard guideline-directed medical therapy.
- **Outcomes (O):** Clinically relevant endpoints including all-cause mortality, cardiovascular mortality, cardiovascular events (e.g., myocardial infarction or stroke), hospitalizations due to HF, and patient-reported QoL.

2.3. Search Strategy

A systematic literature search was conducted exclusively in the PubMed database to identify relevant studies published between January 1, 2020, and May 9, 2025. The search was executed on May 9, 2025, at 09:54 AM Central European Time (CET). PubMed was selected due to its comprehensive indexing of biomedical research, its robust MeSH (Medical Subject Headings) structure, and its widespread use within the academic environment of the Medical University of Graz. Only peer-reviewed, full-text studies published in English were considered. Conference abstracts and preprints were excluded.
Search terms included a combination of MeSH terms and free-text keywords, as follows:

- "Heart Failure" [MeSH] OR "HFrEF" OR "HFpEF"
- AND "Sodium-Glucose Transporter 2 Inhibitors" [MeSH] OR "SGLT2 inhibitors" OR "dapagliflozin" OR "empagliflozin" OR "ertugliflozin"
- AND "Mortality" OR "Hospitalization" OR "Cardiovascular Events" OR "Quality of Life"
- AND "Randomized Controlled Trial" [Publication Type] OR "RCT

2.3.1. Eligibility Criteria

Table 3: Eligibility Criteria used for study selection.

Inclusion Criteria	Exclusion Criteria
▪ RCTs ▪ Adult patients (≥18 years) with HFrEF and/or HFpEF, with or without diabetes ▪ SGLT2 inhibitors versus placebo or standard therapy ▪ Reporting at least one relevant outcome ▪ Published in English between 2020 and 2025	▪ Non-RCT designs (e.g., observational studies, systematic reviews ▪ Studies exclusively targeting CKD ▪ Lack of a comparator group ▪ Interim results or duplicate reports

Abbreviations: RCT = randomized controlled trial; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; CKD = chronic kidney disease.

2.4. Study Selection

The initial PubMed search yielded 121 records. Following the removal of duplicates, titles and abstracts were screened for relevance based on the pre-specified PICO criteria. Screening and eligibility assessment were performed solely by the author, which is appropriate given the scope of a single-author academic thesis. Screening consistency was ensured by adhering to a structured and pre-defined eligibility framework.

For screening and data management, a comprehensive Excel spreadsheet was created, capturing the following variables: PMID, Author (Year), Title, Journal, Study Design, Population, HF type, Diabetes subgroup, Follow-up, SGLT2 inhibitor, Control group, outcomes (mortality, cardiovascular events, hospitalization and QoL), further outcomes, result summary, Cochrane Risk of Bias 2 (RoB2) analysis, evidence level, inclusion/exclusion decision, justification, synthesis inclusion, main trial status, analysis type, and notes.

Table 4: Screenshot of the structured Excel spreadsheet used for study selection and data extraction.

	PMID Number	Author (Year)	Title	Journal	Study Desig	Population	rEF/HFpEF	etes Subgr	low-up Dura	GLT2 Inhibit	ontrol Grou	- All-cause	Cardiovascu	Cardiovasc	hes - Hospit	hes - Quality	ther Outco	sults Summ	Analysis (R	vidence Lev	lusion YES/	Justification	sion (qualit	Main trial	nalysis type	Notes
2	39923808	Yu-Min Lin et	Comparative	European H	Systematic	151,789 pa	Included he	Yes; stratifi	Varies acro	Multiple (e.	Placebo or	Not separat	Reduced sig	MACE signi	Reduction i	Not assesse	Analysis inc	Both SGLT2	Low risk of	High for M/	YES	The meta-a	exclusion	Not applica	Systematic Review and	

The spreadsheet was developed to ensure systematic screening and documentation based on the PICO framework. Key variables included study identifiers, population characteristics, intervention details, HF phenotype, diabetes status, outcomes, and risk of bias assessments using the RoB2 tool.

Following title and abstract screening, 43 studies were selected for full-text review. Five studies fulfilled all predefined inclusion criteria and were directly included in the qualitative synthesis:

1. **DAPA-HF**
2. **DAPA-HFpEF**
3. **EMPEROR-Preserved**
4. **SUGAR-DM-HF**
5. **EMPA-TROPISM**

During the final validation phase, two additional primary studies, DELIVER and EMPEROR-Reduced, were identified through backward citation tracking of frequently cited secondary literature. These studies had not been retrieved through the initial PubMed search due to indexing limitations but were reassessed and met all inclusion criteria. Their inclusion was essential to ensure completeness and adequate representation of the evidence base on SGLT2 inhibitors in HF. This comprehensive selection strategy, combining both database search and manual citation tracking, ensured a methodologically rigorous synthesis, consistent with PRISMA 2020 guidelines and principles of good scientific practice.

Common reasons for exclusion included: secondary or post-hoc analysis (n = 37), dual SGLT1/SGLT2 inhibition (n = 1), and methodological incompatibility with the defined synthesis approach. The study selection process is depicted in the PRISMA flowchart in **Figure 2**.

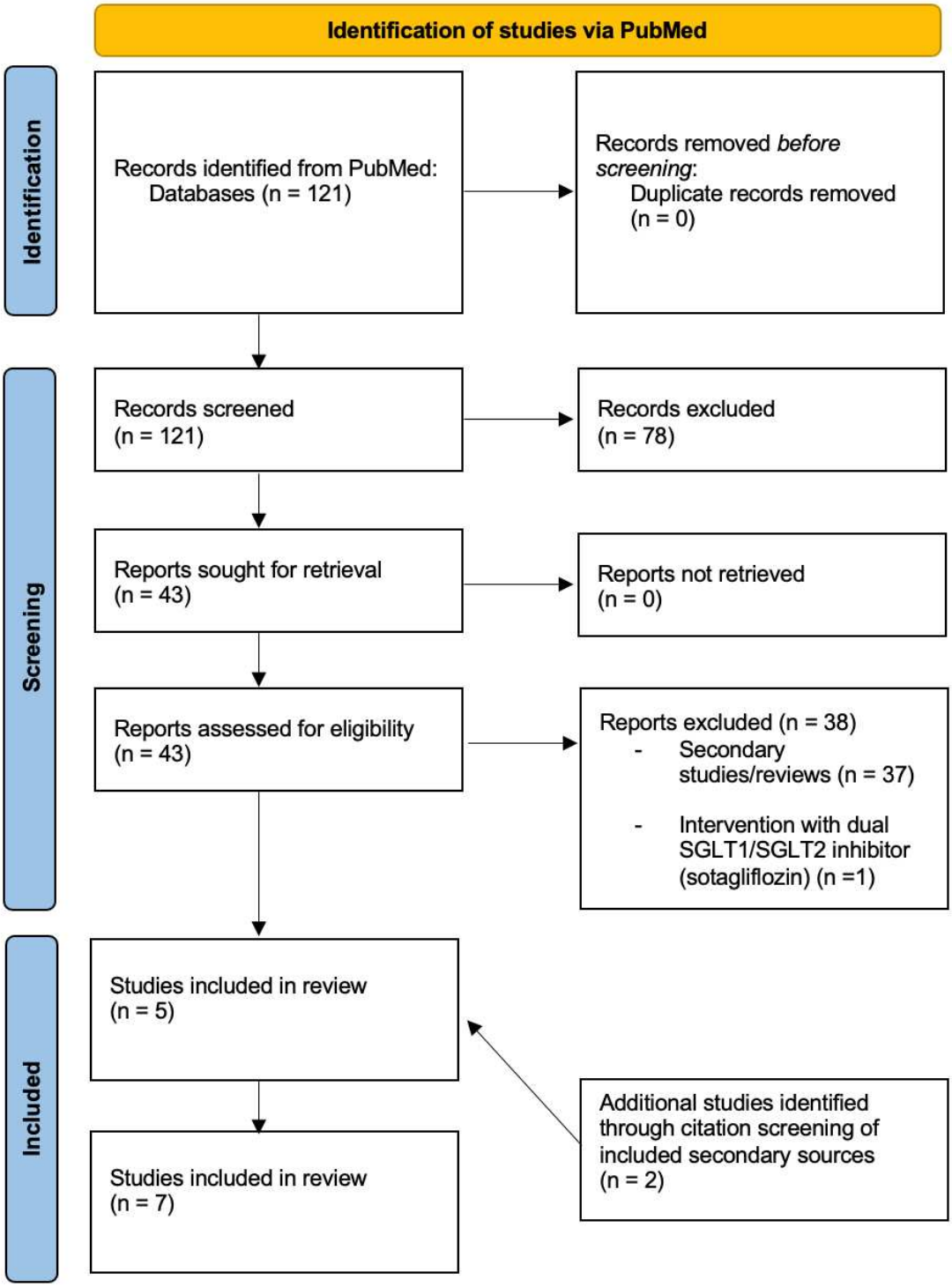


Figure 2: PRISMA 2020 flow diagram for the selection of studies included in this review. The diagram illustrates the systematic screening process from database search (n = 121) to final inclusion (n = 7). Two additional studies were manually identified through backward citation tracking and included following confirmation of eligibility upon reassessment. Source: Own illustration, Diagram generated with the PRISMA Flow Diagram Generator (*https://prisma.shinyapps.io/prisma-flowdiagram/*).

2.5. Data Extraction

Data extraction was conducted using the structured Excel form described previously. Extracted fields included bibliographic details, sample characteristics, intervention and comparator, HF and diabetes classification, outcome data, follow-up period, RoB2 ratings, and overall evidence level.

2.6. Risk of Bias Assessment

Risk of bias was assessed using the RoB2 tool, evaluating five domains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) outcome measurement, and (5) selection of reported results. Each domain was rated as “low risk,” “some concerns,” or “high risk.”

The randomization process was judged as low risk in studies with adequate sequence generation and concealed allocation. Deviations from intended interventions were rated based on blinding and protocol adherence; open-label designs typically resulted in "some concerns." Missing data were assessed based on attrition balance and imputation strategies. Outcome measurement was evaluated for blinding and consistency; adjudicated or blinded endpoints received a “low risk” rating. Selective reporting was considered low risk when trial protocols were available or reported outcomes aligned with prespecified registrations.

2.7. Data Synthesis

Due to substantial clinical and methodological heterogeneity (e.g., differences in populations, endpoints and outcome definitions), a meta-analysis was not feasible. Therefore, a qualitative synthesis was conducted. Studies were grouped by HF phenotype (HFrEF vs. HFpEF), diabetes status (where applicable), and reported clinical outcomes. Results are summarized narratively and supported by structured tables and figures in the Results section.

2.7.1. Use of AI-based Assistance

For language-related tasks such as spelling correction, grammar refinement, and stylistic clarity, AI-based tools, including ChatGPT, were used during the preparation of this thesis. All scientific content, analyses, and interpretations were conducted independently and critically by the author.

2.7.2. Technical Tools and Visualizations

The PRISMA 2020 flow diagram was generated using the official web-based PRISMA tool (*https://prisma.shinyapps.io/prisma-flowdiagram/*), ensuring standardized and transparent documentation of the study selection process in accordance with international reporting guidelines. Additional figures and tables throughout the thesis were created using Microsoft Word, Microsoft Excel, and ChatGPT for layout support and automated formatting assistance.

3.Results

3.1. Study Selection and Characteristics

A total of seven RCTs were included in this qualitative synthesis, following a structured screening process based on PRISMA 2020 guidelines. All studies met the predefined eligibility criteria in terms of population, intervention, comparison, outcomes, and study design (PICO framework), as outlined in the Methods section.

The included studies collectively enrolled over 20,000 adult patients with HF across varying ejection fraction profiles and diabetes status. They investigated the effects of different SGLT2 inhibitors, most commonly dapagliflozin and empagliflozin, on a range of clinically relevant outcomes, including all-cause mortality, cardiovascular mortality, HF hospitalizations, cardiovascular events, and patient-reported QoL.

Key characteristics of the included trials, including study design, sample size, HF phenotype, diabetes stratification, follow-up duration, and primary endpoints, are summarized in **Table 5.**

Table 5: Summary of RCTs investigating SGLT2 Inhibitors in Heart Failure Patients with and without Type 2 Diabetes. SOURCE (7, 8, 31, 32, 45, 47, 48).

Study	Author (Year)	Population	HF Phenotype	Diabetes Status	SGLT2 Inhibitor	Follow Up	Primary Outcomes	Main result	Risk of Bias(RoB2)
DAPA-HFpEF	Nassif et al. (2021)	N=324, NYHA II–IV, LVEF ≥45%	HFpEF	With & without T2DM	Dapagliflozin (10 mg daily)	12 weeks	KCCQ-CS score difference	Increase of 5.8 pts KCCQ-CS vs placebo (p=0.001)	Low
DAPA-HF	McMurray et al. (2019)	N=4744, NYHA II–IV, LVEF ≤40%	HFrEF	With & without T2DM	Dapagliflozin (10 mg daily)	Median 18.2 months	CV death or worsening HF (HHF or urgent IV therapy)	26% relative reduction, primary outcome (HR 0.74, p<0.001)	Low
EMPEROR-Reduced	Packer et al. (2020)	N=3730, NYHA II–IV, LVEF ≤40%	HFrEF	With & without T2DM	Empagliflozin (10 mg daily)	Median 16 months	CV death or HHF	Decrease of 25% primary outcome (HR 0.75, p<0.001)	Low
DELIVER	Solomon et al. (2022)	N=6263, NYHA II–IV, LVEF >40%	HFmrEF & HFpEF	With & without T2DM	Dapagliflozin (10 mg daily)	Median 2.3 years	CV death or worsening HF	18% relative reduction, primary outcome (HR 0.82, p<0.001)	Low
EMPEROR-Preserved	Anker et al. (2021)	N=5988, NYHA II–IV, LVEF >40%	HFmrEF & HFpEF	With & without T2DM	Empagliflozin (10 mg daily)	Median 26.2 months	CV death or HHF	21% relative reduction, primary outcome (HR 0.79, p<0.001)	Low
EMPA-TROPISM	Santos-Gallego et al. (2021)	N=84, NYHA II-III, LVEF < 50%	HFrEF	No T2DM	Empagliflozin (10 mg daily)	6 months	Change of LV end-diastolic volume and LV end-systolic volume	Improved LV volumes, LVEF, exercise capacity, and QoL	Low
SUGAR-DM-HF	Lee et al (2021).	N=105, NYHA II-IV, LVEF ≤ 40%	HFrEF	T2DM & 21.9% prediabetes	Empagliflozin (10 mg daily)	36 weeks	Change in LV volumes (LVESVi, LVEDVi) and NT-proBNP	Significant reductions in LV volumes and NT-proBNP	Low

Abbreviations: HF = heart failure; SGLT2 inhibitor = sodium-glucose cotransporter 2; RoB2 = Cochraine Risk of Bias Tool; version 2; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mildly

reduced ejection fraction; CV = cardiovascular; HHF = hospitalization for heart failure; NYHA = Yew York Heart Association; LEVEF = left ventricular ejection fraction; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; T2DM = type 2 diabetes mellitus; KCCQ-CS = Kansas City Cardiomyopathy Questionnaire Clinical Summary; NT-proBNP = N-terminal pro B-type natriuretic peptide; IV = intravenous; HR = hazard ratio.

3.2. Effects on Primary Outcomes

The effects of SGLT2 inhibitors on the five primary outcomes defined in the PICO framework including all-cause mortality, cardiovascular mortality, cardiovascular events, hospitalization for HF, and QoL, are summarized below. The results are presented separately for each outcome based on data from all seven included RCTs. Where applicable, HR and 95% CI are provided to illustrate the direction and magnitude of the effects.

3.2.1. All-Cause Mortality

The impact of SGLT2 inhibitors on all-cause mortality was evaluated in several of the included RCTs. Notably, three major studies, DAPA-HF, EMPEROR-Reduced, and DELIVER, explicitly reported this endpoint as part of their prespecified secondary outcomes.

In the DAPA-HF trial, treatment with dapagliflozin resulted in a statistically significant reduction in all-cause mortality compared to placebo. The event rate was 11.6% in the dapagliflozin group versus 13.9% in the placebo group, corresponding to (HR 0.83; 95% CI 0.71–0.97, $p < 0.05$) (32).

Similarly, the EMPEROR-Reduced trial demonstrated a favorable effect of empagliflozin on all-cause mortality in patients with HFrEF. Although the reduction was not statistically significant, the observed effect (HR 0.92; 95% CI 0.77–1.10), indicating a trend toward benefit (31).

In patients with HFpEF or HFmrEF, the DELIVER trial assessed all-cause mortality as a key secondary endpoint. The study found a non-significant difference between dapagliflozin and placebo (HR 0.94; 95% CI: 0.83–1.07) (7).

Across the included trials, reductions in all-cause mortality were observed primarily in patients with HFrEF, with the most pronounced effect seen in the DAPA-HF trial. Subgroup analysis in DAPA-HF, EMPEROR-Reduced and DELIVER suggested that the overall cardiovascular benefits of SGLT2 inhibitors were consistent in patients with and without

T2DM, although dedicated subgroup analyses of all-cause mortality alone were not always reported. In trials enrolling patients with HFpEF or HFmrEF, no statistically significant differences in all-cause mortality were reported.

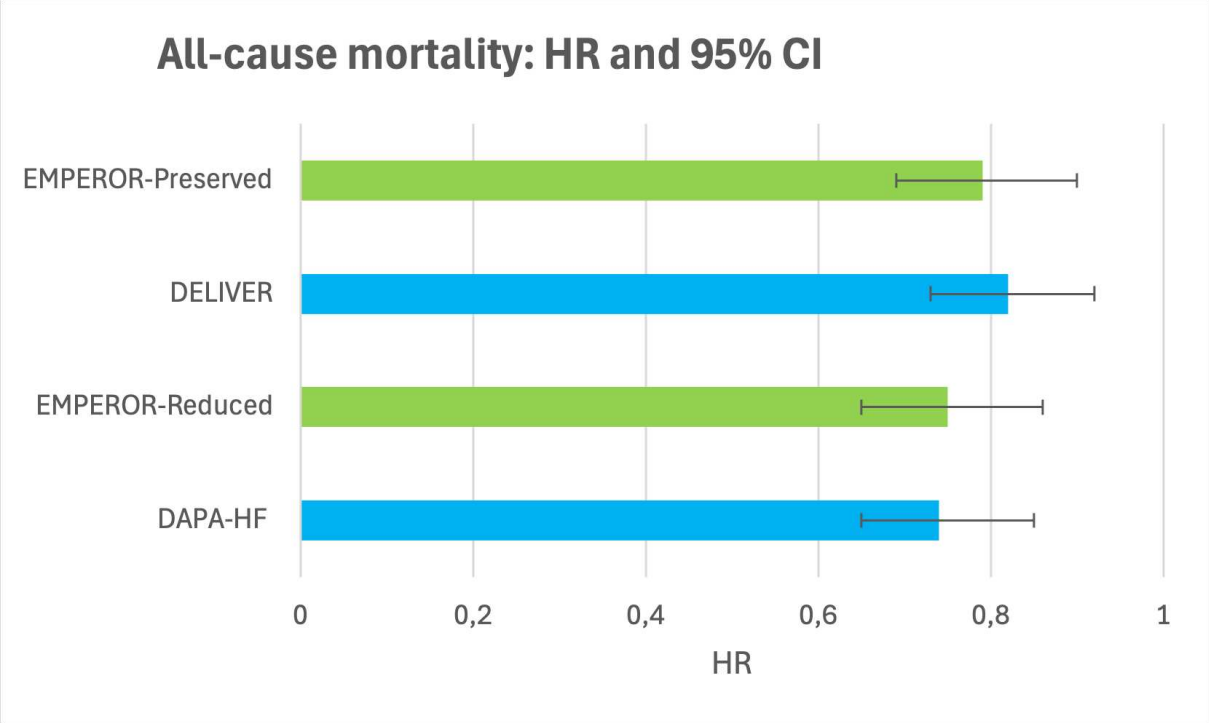


Figure 3: **All-cause mortality outcomes from four randomized controlled trials evaluating SGLT2 inhibitors in HF.** Shown are HR with 95% CI for all-cause mortality from the DAPA-HF, EMPEROR-Reduced, DELIVER, and EMPEROR-Preserved trials. Data are stratified by compound (dapagliflozin vs. empagliflozin). A HR below 1 indicates a reduction in mortality risk compared to placebo. Studies are grouped by HF phenotype: DAPA-HF and EMPEROR-Reduced enrolled patients with HFrEF; DELIVER and EMPEROR-Preserved enrolled patients with HFpEF. Source: Data extracted from (7, 8, 31, 32). Abbreviations: HR = hazard ratio; CI = confidence interval; HF = heart failure.

3.2.2. Cardiovascular Mortality

Cardiovascular mortality was reported as a predefined outcome in the majority of the included trials. In patients with HFrEF, both the DAPA-HF and EMPEROR-Reduced trials demonstrated clinically relevant reductions in the risk of cardiovascular death with SGLT2 inhibitor therapy.

In the DAPA-HF trial, dapagliflozin significantly reduced cardiovascular death compared to placebo, with an event rate of 9.6% versus 11.5%, corresponding to (HR 0.82; 95% CI: 0.69–0.98) (32). In the EMPEROR-Reduced trial, the use of empagliflozin was associated with a numerically lower rate of cardiovascular death (10.0% vs. 10.8%), though the result did not reach statistical significance (HR 0.92; 95% CI**:** 0.75–1.12) (31).

Among patients with preserved HFpEF or HFmrEF, cardiovascular mortality outcomes were less pronounced. The EMPEROR-Preserved trial observed a lower cardiovascular death rate of 7.3% in the empagliflozin group versus 8.2% in the placebo group (HR 0.91; 95% CI: 0.76–1.09), although this difference was not statistically significant(8). Similarly, in the DELIVER trial, dapagliflozin reduced cardiovascular mortality (HR 0.88; 95% CI: 0.74–1.05), which again did not reach statistical significance (7).

Across the included trials, reductions in cardiovascular mortality were more pronounced in patients with HFrEF, particularly in the DAPA-HF trial, while findings in HFpEF and HFmrEF populations showed numerically favorable but statistically non-significant trends. Although formal subgroup analysis by diabetes status were not uniformly reported across all studies, the available data did not indicate a consistent interaction between diabetes status and the effect of SGLT2 inhibitors on cardiovascular mortality.

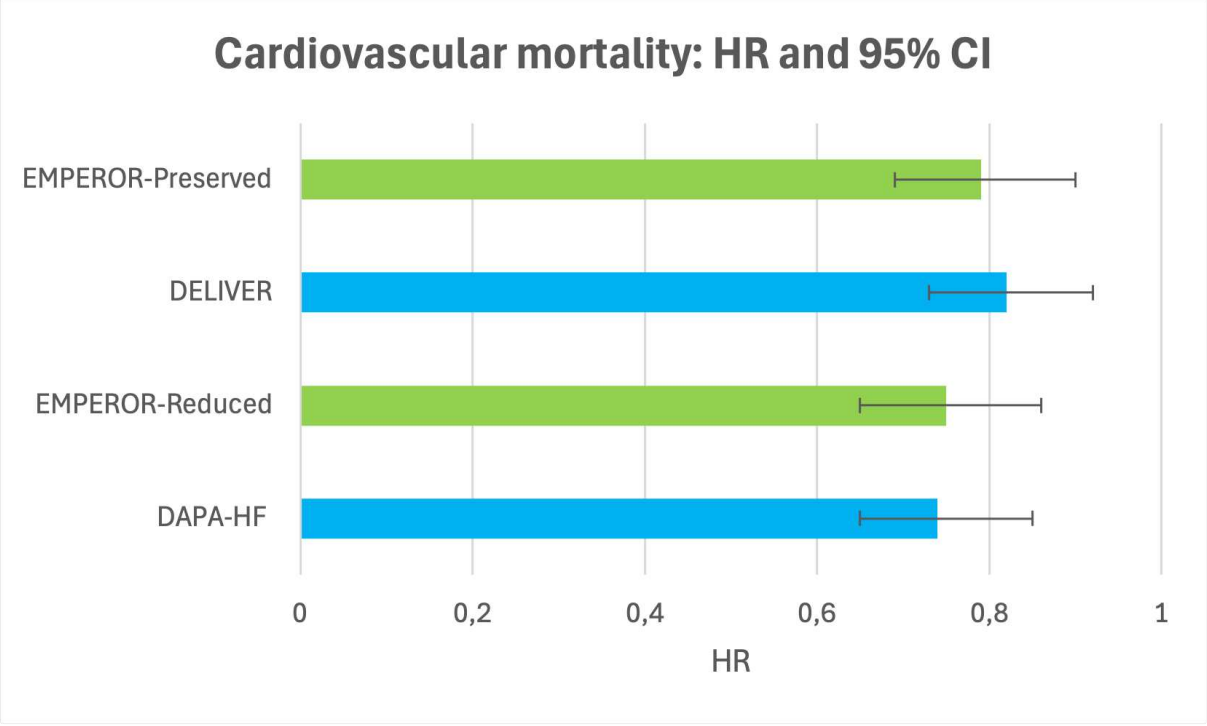


Figure 4: Cardiovascular mortality outcomes from four randomized controlled trials evaluating SGLT2 inhibitors in patients with HF. Shown are HR with 95% CI for cardiovascular mortality from the DAPA-HF, EMPEROR-Reduced, DELIVER, and EMPEROR-Preserved trials. The HR is shown on the X-axis; values <1 indicate reduced risk with SGLT2 inhibition versus placebo. Data are stratified by compound (dapagliflozin vs. empagliflozin). No additional subgroup analysis by diabetes status is shown; HF phenotype classification follows each trial's inclusion criteria. Source: Data extracted from (5, 22, 24, 25). Abbreviations: HR = hazard ratio; CI = confidence interval; HF = heart failure.

3.2.3. Cardiovascular Events

Among the seven included trials, cardiovascular events were variably defined and reported, often as components of composite primary endpoints. The most comprehensive data derive from the large-scale trials DELIVER, EMPEROR-Preserved, EMPEROR-Reduced and DAPA-HF, all of which included either “cardiovascular death or worsening HF” or similar endpoints (7, 8, 31, 32).

In the DELIVER trial, dapagliflozin was associated with an 18% relative risk reduction in the composite of cardiovascular death or worsening HF (HR 0.82; 95% CI 0.73–0.92; $p<0.001$), reflecting a statistically significant benefit (7). Similar findings were reported in the EMPEROR-Preserved trial, where empagliflozin significantly reduced the risk of the same composite endpoint by 21% (HR 0.79; 95% CI 0.69–0.90; $p<0.001$) (8).

In patients with HFrEF, the DAPA-HF trial reported a 26% relative reduction in the risk of cardiovascular death or worsening HF events, including urgent intravenous therapy or hospitalization (HR 0.74; 95% CI 0.65–0.85; $p<0.001$), indicating a statistically significant benefit (32). The EMPEROR-Reduced trial demonstrated a 25% relative risk reduction in the composite outcome of cardiovascular death or HF hospitalization (HR 0.75; 95% CI 0.65–0.86; $p<0.001$), confirming statistical significance (31).

The DAPA-HFpEF study, a short-term trial focused on QoL outcomes, did not report cardiovascular event rates as a primary outcome (45). Likewise, the EMPA-TROPISM and SUGAR-DM-HF trials emphasized surrogate structural endpoints and did not provide specific data on composite cardiovascular event rates (47, 48).

Overall, across the large trials enrolling patients with both preserved and reduced ejection fraction, SGLT2 inhibitors consistently reduced the incidence of cardiovascular event composites that included cardiovascular death and clinical worsening of HF.

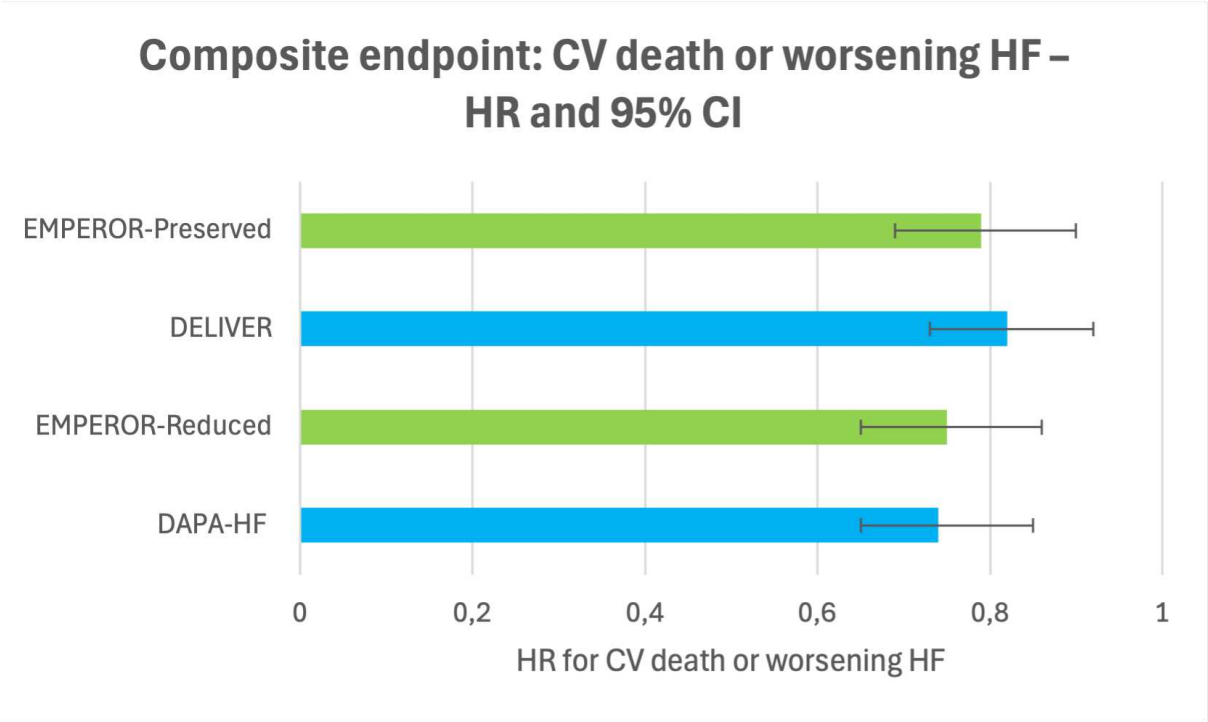


Figure 5: Composite cardiovascular endpoint outcomes from four large randomized controlled trials investigating SGLT2 inhibitors in HF. Displayed are HR with 95% CI for the combined outcome of cardiovascular death or worsening HF, reported in the DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and DELIVER trials. Results are stratified by compound (dapagliflozin vs. empagliflozin). An HR below 1 indicates a reduced risk of the composite event compared to placebo. Source: Data derived from (5, 22, 24, 25). Abbreviations: HR = hazard ratio; CI = confidence interval; HF = heart failure; CV = cardiovascular.

3.2.4. Hospitalization for HF

As the reported HR for HF hospitalization are largely derived from the composite endpoint of cardiovascular death or worsening HF, already visualized in Section 3.2.3, no separate figure is presented.

Hospitalization for HF (HHF) was consistently assessed as part of the primary composite endpoint in five of the seven included RCTs. These data provide robust evidence across varying HF phenotypes and patient populations.

In patients with HFrEF, the DAPA-HF trial showed that dapagliflozin significantly reduced the composite risk of cardiovascular death or worsening HF, which included first hospitalization or urgent intravenous (IV) therapy, by 26% (HR 0.74; 95% CI 0.65–0.85; $p<0.001$) (32). Similarly, the EMPEROR-Reduced trial significantly demonstrated a 25%

relative reduction in the composite of cardiovascular death or HHF with empagliflozin (HR 0.75; 95% CI 0.65–0.86; p<0.001) (31).

In the EMPEROR-Preserved trial, empagliflozin led to a 21% reduction in the combined endpoint of cardiovascular death or HHF (HR 0.79; 95% CI 0.69–0.90; p<0.001)(8). The DELIVER trial reported an 18% risk reduction in the composite of cardiovascular death or worsening HF (HR 0.82; 95% CI 0.73–0.92; p<0.001), which included HHF as a key event (7).

Although hospitalization was not a primary endpoint in the DAPA-HFpEF trial, EMPA-TROPISM or SUGAR-DM-HF, no additional HHF-specific data were reported from these studies.

Overall, across the large-scale trials, SGLT2 inhibitors demonstrated a statistically significant consistent reduction in HF–related hospitalizations, irrespective of ejection fraction status or diabetes presence.

3.2.5. Quality of Life

QoL was evaluated in three of the seven included RCTs using patient-reported outcome measures, primarily the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS).

The DAPA-HFpEF trial assessed the effect of dapagliflozin on QoL over a 12-week period. In this trial, patients receiving dapagliflozin experienced a statistically significant improvement in the KCCQ-CSS compared to placebo, with a mean difference of +5.8 points (p=0.001) (45). This change exceeded the minimal clinically important difference threshold, suggesting a measurable symptom relief from the patient perspective.

In the EMPA-TROPISM trial, conducted in HFrEF patients without diabetes, empagliflozin treatment over six months led to significant improvements in functional capacity and QoL. Patients receiving empagliflozin showed a mean increase of 21 points in the KCCQ-12 score compared to 2 points in the placebo group ($p < 0.001$), exceeding the threshold for a clinically meaningful difference and indicating a robust improvement in patient-perceived health status. (47).

The SUGAR-DM-HF did not find significant improvements in QoL-specific endpoints such as the KCCQ-TSS, but documented favorable changes in surrogate functional parameters, including NT-proBNP levels and left ventricular volumes, which may indirectly reflect symptom relief (48).

Taken together, findings from the DAPA-HFpEF and EMPA-TROPISM trials suggest that SGLT2 inhibitors may significantly improve patient-reported QoL in HF, particularly over short to medium follow-up periods. These beneficial effects were demonstrated in patients with both preserved and reduced ejection fraction and across diabetic and non-diabetic populations.

3.3. Subgroup Outcomes

A key objective of this systematic review was to examine whether the cardiovascular benefits of SGLT2 inhibitors differ between patients with and without T2DM. Across the included studies, subgroup analyses consistently demonstrated that the beneficial effects of SGLT2 inhibition were largely independent of baseline glycemic status.

In patients with HFrEF, both the DAPA-HF and EMPEROR-Reduced trials reported nearly identical treatment effects in patients with and without T2DM. In DAPA-HF, the HRs for the composite endpoint of cardiovascular death or worsening HF were 0.75 in patients with diabetes and 0.73 in those without, with no significant interaction (p for interaction = 0.80) (45). Similarly, EMPEROR-Reduced reported HRs of 0.72 vs. 0.78, further supporting a glucose-independent mechanism of action (31, 32).

Among patients with HFpEF or HFmrEF, similar consistency was observed. The DELIVER trial demonstrated identical treatment effects in both diabetic and non-diabetic subgroups (HR 0.83 for both), indicating no evidence of heterogeneity with respect of diabetic status while EMPEROR-Preserved showed comparable reductions (HR 0.81 in diabetics vs. 0.78 in non-diabetics) (7, 8).

Evidence from quality-of-life–focused trials further support this conclusion. In DAPA-HFpEF, significant improvements in KCCQ scores were observed in both groups, although numerically greater among non-diabetic participants (45). The EMPA-TROPISM trial, which enrolled exclusively non-diabetic patients with HFrEF, demonstrated significant reverse cardiac remodeling and functional improvement with empagliflozin, including reductions in

left ventricular volumes and mass, increased ejection fraction, and enhanced exercise capacity and QoL compared to placebo (47).

Conversely, the SUGAR-DM-HF trial included only individuals with T2DM or prediabetes (48). While it lacked a non-diabetic comparator group and did not demonstrate significant differences in clinical outcomes, it still offered complementary evidence through improvements in surrogate parameters such as left ventricular volumes and NT-proBNP levels in hyperglycemic populations (48).

Collectively, these findings underscore the consistent efficacy of SGLT2 inhibitors regardless of diabetes status, reinforcing their use across the full spectrum of patients with HF.

3.4. Risk of Bias

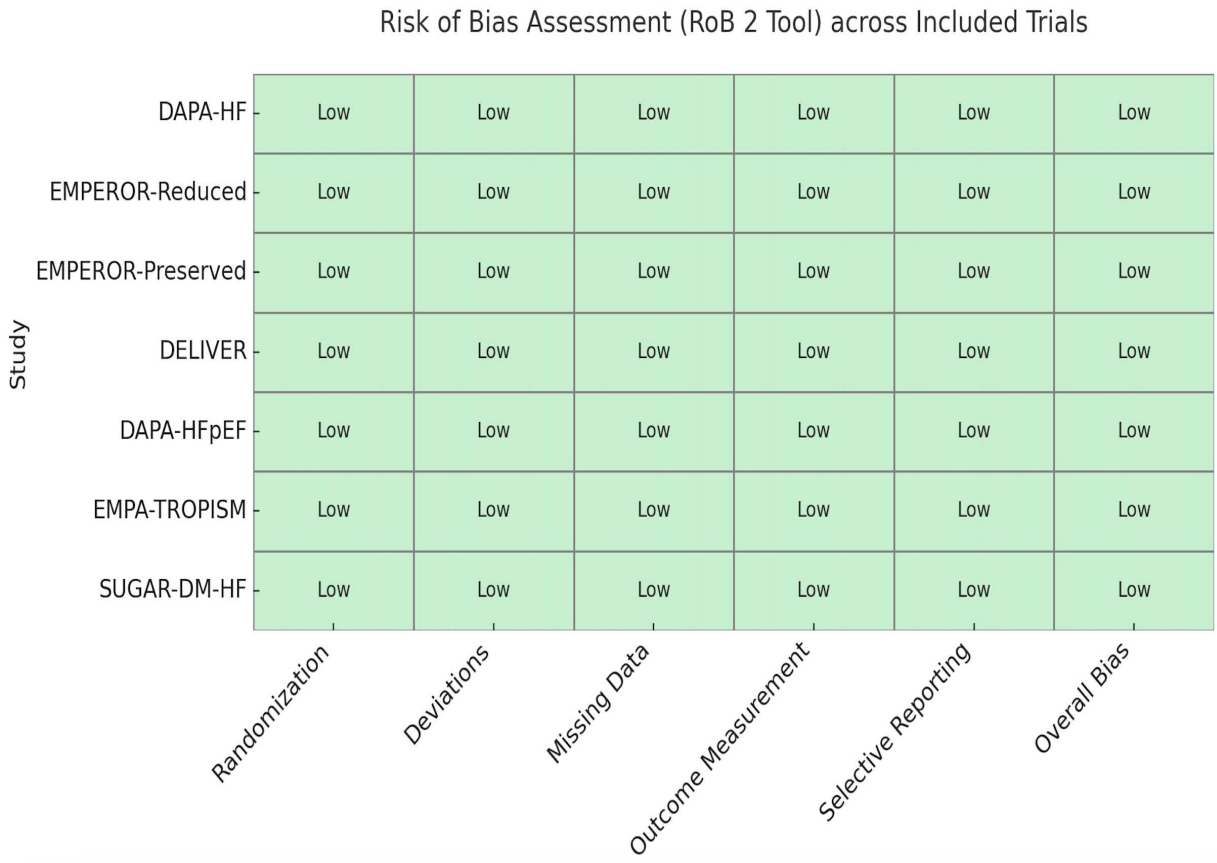
All seven studies included in this review were assessed for risk of bias using the RoB 2 tool, which evaluates five key domains: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

Across all included trials, the overall risk of bias was judged to be low. Randomization methods were adequately described and implemented, with appropriate allocation concealment. No major concerns were identified regarding deviations from intended interventions, and protocol adherence was consistently high. No trial was judged to have a high risk of bias in any domain, and most were rated as low risk across all five categories, justifying the overall low-risk judgment.

Outcome data were reported comprehensively, with minimal loss to follow-up and transparent handling of missing values. Outcome measures relied on validated endpoints and were applied uniformly across treatment groups. Moreover, all studies adhered to pre-specified protocols or trial registries, and no indications of selective reporting were found.

A summary of domain-level risk of bias judgments is presented in **Table 6**. These findings confirm the overall methodological rigor of the included studies and support the validity of the synthesized results presented in this review.

Table 5: Risk of bias assessment using the Cochrane RoB 2 Tool across all included randomized controlled trials. Each domain was rated as 'Low' risk. No study exhibited concerns for bias in any assessed category. Source: (5, 22, 24, 25, 28-30)



Abbreviations: RoB2 = Cochraine Risk of Bias Tool; version 2; HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

4.Discussion

4.1 Principal Findings

This systematic review provides a consolidated overview of the current evidence on the efficacy of SGLT2 inhibitors in adult patients with HF, differentiated by ejection fraction phenotype and diabetic status. Across the seven included RCTs, the primary therapeutic signal was a consistent reduction in HF–related hospitalizations. This effect was observed across both HFrEF and HFpEF populations and was independent of diabetic status, suggesting a class effect that transcends traditional treatment boundaries (7, 8, 31, 32, 45, 47, 48).

While mortality outcomes were less uniformly affected, a modest trend toward improved all-cause and cardiovascular mortality was observed in patients with HFrEF. These benefits, however, were not consistently reproduced in the HFpEF subgroup, underscoring the need for cautious interpretation. Improvements in patient-reported QoL, though evaluated in fewer studies, aligned with the clinical outcome data and further support the therapeutic value of SGLT2 inhibitors in this setting (7, 8, 31, 32, 45, 47, 48).

Crucially, the observed effects extended to patients without diabetes, confirming that the cardiovascular benefits of SGLT2 inhibitors are not contingent on glycemic modulation. Taken together, the findings of this review reinforce the role of SGLT2 inhibition as a disease-modifying strategy in HF and highlight its potential applicability across a broad clinical spectrum, irrespective of ejection fraction or glycemic status (7, 8, 31, 32, 45, 47, 48)

4.2. Interpretation and Comparison with Existing Evidence

The findings of this systematic review align closely with recent meta-analyses that evaluated the efficacy of SGLT2 inhibitors across diverse HF phenotypes. A 2022 meta-analysis including patients with HFpEF and HFmrEF demonstrated a significant reduction in the composite endpoint of cardiovascular mortality or HF hospitalization, irrespective of diabetic status (49). This supports the notion of a consistent class effect, even in patient populations where traditional HF therapies have historically shown limited efficacy.

In particular, the effect size for hospitalization reduction reported in that meta-analysis was in the same range as observed in the present synthesis, further reinforcing the robustness of this therapeutic benefit across different ejection fraction categories. While the effect on mortality remained more pronounced in HFrEF populations, the directionality of the findings was consistent across subgroups, mirroring the trends identified in our included RCTs (49).

Another meta-analysis focusing on major cardiovascular and renal outcomes across a broad range of clinical trials confirmed a reduction in HF–related events with SGLT2 inhibitors and highlighted that these effects were largely independent of glycemic control (50). This supports the mechanistic rationale for their use in non-diabetic patients and strengthens the argument that the cardiovascular benefits of SGLT2 inhibition extend beyond glucose lowering.

Taken together, these secondary sources validate the overall conclusions drawn from the primary trials included in this review and provide additional support for the use of SGLT2 inhibitors across the full spectrum of HF phenotypes, irrespective of underlying diabetic status.

4.3. Subgroup Analysis and Clinical Implications

A consistent finding across the included RCTs was the efficacy of SGLT2 inhibitors in reducing HF–related hospitalizations, irrespective of left ventricular ejection fraction phenotype or diabetes status. However, the magnitude and consistency of benefit varied between subgroups**,** warranting a closer examination of these differential effects.

In patients with HFrEF**,** the evidence base was particularly robust, with trials such as DAPA-HF and EMPEROR-Reduced demonstrating significant reductions in both hospitalization and cardiovascular mortality. These effects were largely consistent across age groups, NYHA functional classes, and glycemic status, indicating a broad therapeutic applicability of SGLT2 inhibitors in this population. In contrast, while HFpEF patients also experienced reductions in HF hospitalizations, the impact on mortality outcomes was less conclusive, with studies like DELIVER and EMPEROR-Preserved showing non-significant trends rather than statistically robust mortality effects (7, 8, 31, 32, 45, 47, 48).

Importantly, several trials included patients without diabetes, affirming the hypothesis that the cardiovascular benefits of SGLT2 inhibitors are not solely mediated by glycemic control

mechanisms. This finding expands the therapeutic scope of these agents to non-diabetic HF populations**,** aligning with emerging clinical guideline recommendations.

From a practical standpoint, these subgroup findings suggest that SGLT2 inhibitors should be considered a foundational therapy in HFrEF, regardless of diabetic status. In HFpEF, they represent a promising adjunctive treatment**,** particularly for reducing the burden of recurrent hospitalizations. The inclusion of elderly patients, women, and individuals with comorbid conditions such as CKD in many of the included trials also supports the generalizability of these findings to typical clinical populations**.**

Taken together, the subgroup analyses highlight the need for phenotype-specific expectations when initiating SGLT2 inhibitor therapy. While a mortality benefit is more likely in HFrEF**,** meaningful improvements in symptom burden and hospitalization risk can be anticipated in both HF phenotypes. These insights should guide shared decision-making, particularly when prioritizing therapies in patients with complex comorbidity profiles or uncertain glycemic status.

4.4. Strengths and Limitations

This systematic review offers several strengths. It includes only recent RCTs that clearly differentiate between HFrEF and HFpEF, enabling a detailed analysis of treatment effects across HF phenotypes. The consistent reporting of clinically meaningful outcomes such as mortality, hospitalization and QoL enhances the relevance of the findings. Importantly, the inclusion of both diabetic and non-diabetic patients reflects the evolving therapeutic role of SGLT2 inhibitors beyond glycemic control.

However, the absence of a meta-analysis limits the ability to quantify effect sizes or assess statistical heterogeneity. Outcome definitions, follow-up durations, and baseline characteristics varied between studies, which may affect comparability. Moreover, certain outcomes, such as QoL, were assessed in only a subset of trials. Potential publication bias and missed studies due to search limitations cannot be excluded. Lastly, while study quality was assessed using the RoB2 tool, some domains remained unclear, and no individual patient data were analyzed.

4.5. Future Research Needs

Despite the growing body of evidence supporting the use of SGLT2 inhibitors in HF, several areas remain insufficiently addressed. Most notably, while current trials have demonstrated clear benefits in HFrEF and increasingly in HFpEF, further research is needed to clarify the mechanisms underlying these effects, particularly in patients with HFpEF, where mortality reductions remain inconsistent.

Future studies should aim to identify which subgroups derive the greatest benefit**,** such as by stratifying outcomes by sex, age, renal function, and comorbidity profiles. Individual patient data meta-analyses or dedicated trials focusing on underrepresented populations could help refine treatment recommendations and optimize clinical decision-making.

Additionally, while improvements in QoL have been reported, data are limited to a few trials. Further research should systematically assess patient-reported outcomes using standardized instruments across broader populations and time frames.

Another important gap concerns the long-term safety and durability of SGLT2 inhibitors in non-diabetic HF patients. Although current data suggest a favorable profile, observational studies and longer-term follow-up are required to confirm sustained benefits and monitor rare adverse effects.

Finally, comparative studies between SGLT2 inhibitors and other cornerstone therapies, or their combination, could help clarify optimal sequencing or synergy within guideline-directed medical therapy.

5. Conclusion

This systematic review demonstrates that SGLT2 inhibitors effectively reduce hospitalizations for HF across a broad patient population, including those with HFrEF and HFpEF, and irrespective of diabetic status. While mortality benefits are more consistent in HFrEF, improvements in QoL and symptom burden were observed in both phenotypes. These findings support the use of SGLT2 inhibitors as a cornerstone in HF therapy and highlight their expanding role beyond glucose control. Further research is needed to optimize patient selection and explore long-term outcomes.

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